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(54) Title: T-CELL DEPLETING THERAPIES

(57) Abstract: Provided herein are methods of depleting T cells for therapeutic uses, including administration of anti-CD2 or anti-CD5 antibody drugs conjugates (ADCs) for treatment. Provided are anti-CD2 ADCs or anti-CD5 ADCs 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 can be used to deplete populations of CD2+ or CD5+ cells, such as CD2+ or CD5+ cancer cells or CD2+ or CD5+ immune cells, and can also be used to prepare a patient for hematopoietic stem cell transplantation or solid organ transplantation.

T-CELL DEPLETING THERAPIES

Related Applications

This application claims the benefit of priority to U.S. Provisional Patent Appln. No.
5 62/857,744, filed on June 5, 2019, the contents of which are incorporated by reference herein.

Sequence Listing

The instant application contains a Sequence Listing which has been submitted
electronically in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety.
10 Said ASCII copy, created on June 3, 2020, is named M103034_2170WO_SL.txt and is
91,817 bytes in size.

Background

15 T cells are a type of lymphocyte which develop in the thymus and play an important role in
the immune response. While T cells are an essential part of the immune system, aberrant T cell
activity can cause disease in a patient. For example, graft versus host disease (GVHD) is caused
primarily by donor T cells in the graft that elicit an immune response, resulting in host tissue
damage. Other examples of aberrant T cell activity resulting in disease include T cell associated
20 cancers, such as T cell lymphoma. Therapies targeting T cells remain a challenge in the art.

Summary

There is currently a need for T cell targeting compositions and methods for treating
disorders of the hematopoietic system, such as autoimmune disorders, as well as compositions
25 and methods for promoting the engraftment of exogenous hematopoietic stem cell grafts such that
the multi-potency and hematopoietic functionality of these cells is preserved following
transplantation.

Provided herein are T cell targeting compositions and methods for the direct treatment of
various disorders of the hematopoietic system, metabolic disorders, cancers, and autoimmune
30 diseases, among others. The compositions and methods disclosed herein target immune cells for
conditioning a human patient for a hematopoietic stem cell transplantation for treatment of a
disease such as, but not limited to, blood cancer or an autoimmune disease.

In one aspect, provided herein are methods of depleting T cells in a subject having an
autoimmune disease, said method comprising administering an effective amount of either an anti-
35 CD5 antibody drug conjugate (ADC) or an anti-CD2 ADC to a subject having an autoimmune
disease, wherein the ADC comprises an anti-CD5 antibody, or antigen-binding fragment thereof,
or an anti-CD2 antibody, or antigen-binding fragment thereof, conjugated to a cytotoxin via a
linker.

In one embodiment, the effective amount is an amount sufficient to substantially deplete endogenous CD5+ or CD2+ T cells in the thymus of the subject.

In one embodiment, the subject has multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus (SLE), or systemic sclerosis (SSc).

5 In another aspect, provided herein are methods of treating a subject having steroid-refractory graft versus host disease (GVHD) or at risk for developing GVHD, said method comprising administering an anti-CD2 ADC or an anti-CD5 ADC to the subject having steroid-refractory GVHD, such that the steroid refractory GVHD is treated, wherein the ADC comprises an anti-CD5 antibody, or antigen-binding fragment thereof, or an anti-CD2 antibody, or antigen-binding fragment thereof, conjugated to a cytotoxin via a linker.

In one embodiment, the steroid refractory GVHD is steroid refractory acute GVHD.

In one embodiment, the subject previously received an allogeneic HSC transplant.

In one embodiment, the subject has steroid refractory acute GVHD Grade 2 to Grade 4 (Mount Sinai acute GVHD International Consortium (MAGIC) criteria). In one embodiment, the GVHD grade is decreased by one grade according to the MAGIC criteria following administration of the anti-CD2 ADC or anti-CD5 ADC.

In other aspects, provided herein are methods of treating a subject having a T cell malignancy, said method comprising administering an effective amount of an anti-CD2 ADC or an anti-CD5 ADC to the subject, wherein the ADC comprises an anti-CD5 antibody, or antigen-binding fragment thereof, or an anti-CD2 antibody, or antigen-binding fragment thereof, conjugated to a cytotoxin via a linker.

In one embodiment, the T cell malignancy is a lymphoma. In certain embodiments, the T cell malignancy is T-cell acute lymphoblastic lymphoma (T-ALL), T-cell large granular lymphocyte (LGL) leukemia, human T-cell leukemia virus type 1-positive (HTLV-1+), adult T-cell leukemia/lymphoma (ATL), T-cell prolymphocytic leukemia (T-PLL), or peripheral T-cell lymphoma (PTCLs).

In one embodiment, the T cell malignancy is a relapsed, refractory T cell malignancy.

In one embodiment, the ADC comprises a humanized antibody or a human antibody. In one embodiment, the antibody has an isotype selected from the group consisting of IgG, IgA, IgM, IgD, and IgE. In certain embodiments, the IgG isotype is an IgG1 or an IgG4.

In some embodiments, the ADC is an anti-CD5 ADC (e.g., 5D7 conjugated to amatoxin).

In some embodiments, the ADC is an anti-CD2 ADC.

In one aspect, described herein are T cell targeting compositions and methods for conditioning a patient, such as a human patient, prior to receiving hematopoietic stem cell transplant therapy so as to promote the engraftment of hematopoietic stem cell grafts. The patient may be one that is suffering from an autoimmune disease or one or more blood disorders, such as, cancer, hemoglobinopathy, or other hematopoietic pathology, and is thus in need of

hematopoietic stem cell transplantation.

As described herein, hematopoietic stem cells are capable of differentiating into a multitude of cell types in the hematopoietic lineage, and can be administered to a patient in order to populate or re-populate a cell type that is deficient in the patient.

5 In certain aspects, compositions described herein feature antibody-drug conjugates (ADCs) that bind T cells, specifically CD2 or CD5, as well as methods of administering the same to a patient so as to (i) directly treat a blood disorder, such as an autoimmune disease, by selectively depleting a population of immune cells that express CD2 or CD5, such as an autoreactive T cell, B cell or natural killer (NK) cell, and/or to (ii) deplete a population of T cells, B cells or NK cells prior
10 to administration of a hematopoietic stem cell transplant to the patient, thereby reducing the likelihood of hematopoietic stem cell graft rejection. The former activity enables the direct treatment of a wide range of autoimmune disorders, as CD2 or CD5 may be expressed by a T cell, B cell or NK cell that cross-reacts with, and mounts an inappropriate immune response against, a self antigen. Administration of an anti-CD2 antibody-drug conjugate or anti-CD5 antibody-drug
15 conjugate, to a patient in this case can cause depletion of a population of CD2+ (or CD5+) autoimmune cells, such as T cells, B cells or NK cells that cross-react with one or more self antigens, thereby treating the autoimmune pathology. The latter activity facilitates the generation of an environment that is conducive to hematopoietic stem cell engraftment, as T cells, B cells and/or NK cells that cross-react with one or more non-self antigens expressed by a hematopoietic
20 stem cell (e.g., non-self MHC antigens) can mount an immune response against transplanted hematopoietic stem cells and thus promote graft rejection. In this latter case, patients suffering from a disorder such as cancer, an autoimmune disease, or other condition of the hematopoietic system can subsequently be administered a hematopoietic stem cell transplant in order, for instance, to repopulate one or more populations of blood cells that is defective or depleted in the
25 patient. Also provided herein are methods of treating a variety of hematopoietic conditions, such as sickle cell anemia, thalassemia, Fanconi anemia, Wiskott-Aldrich syndrome, adenosine deaminase deficiency-severe combined immunodeficiency, metachromatic leukodystrophy, Diamond-Blackfan anemia and Schwachman-Diamond syndrome, human immunodeficiency virus infection, and acquired immune deficiency syndrome, as well as cancers and autoimmune
30 diseases, among others.

In certain aspects, described herein is a method of depleting T cells in a subject in need thereof, said method comprising administering an effective amount of an anti-CD5 or an anti-CD2 antibody drug conjugate (ADC) to a subject in need thereof, wherein the subject is undergoing or prior to the subject receiving an hematopoietic stem cell (HSC) transplant or a solid organ
35 transplant, and wherein the ADC comprises an anti-CD5 or an anti-CD2 antibody conjugated to a cytotoxin via a linker.

In one embodiment, in instances where the effective amount of an anti-CD5 or an anti-CD2 antibody drug conjugate (ADC) is administered to a subject in need thereof prior to the subject receiving an hematopoietic stem cell (HSC) transplant or a solid organ transplant, the method further comprises administering to the subject an HSC transplant or a solid organ transplant.

5 In one embodiment, the HSC transplant is an autologous HSC transplant.

In one embodiment, the HSC transplant is administered to the subject after the level of the ADC has substantially cleared from the blood of the subject.

In one embodiment, the HSC or solid organ transplant is administered to the subject between 1 hour and 7 days after the level of the ADC has substantially cleared from the blood of the subject. In another embodiment, the HSC or solid organ transplant is administered to the subject between 6 hours and 3 days after the level of the ADC has substantially cleared from the blood of the subject. In still another embodiment, the HSC or solid organ transplant is administered to the subject between 12 hours and 36 days after the level of the ADC has substantially cleared from the blood of the subject.

15 In one embodiment, the HSC or solid organ transplant is administered to the subject about 24 hours after the ADC has substantially cleared from the blood of the subject, wherein the ADC comprises an anti-CD5 or an anti-CD2 antibody conjugated to a cytotoxin via a linker.

In certain aspects, provided herein is a method of depleting T cells in a subject having an autoimmune disease, said method comprising administering an effective amount of an anti-CD5 or an anti-CD2 antibody drug conjugate (ADC) to a subject having an autoimmune disease, wherein the ADC comprises an anti-CD5 or an anti-CD2 antibody conjugated to a cytotoxin via a linker. In one embodiment, the subject has multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus (SLE), or systemic sclerosis (SSc).

25 In one embodiment, the effective amount is an amount sufficient to substantially deplete endogenous CD5+ or CD2+ T cells in the thymus of the subject.

In other aspects, provided herein is a method of treating a subject having steroid-refractory graft versus host disease (GVHD, said method comprising administering an anti-CD2 or an anti-CD5 ADC to the subject having steroid-refractory GVHD, such that the steroid refractory GVHD is treated, wherein the ADC comprises an anti-CD5 or an anti-CD2 antibody conjugated to a cytotoxin via a linker. In one embodiment, the steroid refractory GVHD is steroid refractory acute GVHD. In one embodiment, the subject previously received an allogeneic HSC transplant. In one embodiment, the subject has steroid refractory acute GVHD Grade 2 to Grade 4 (Mount Sinai acute GVHD International Consortium (MAGIC) criteria). In one embodiment, the GVHD grade is decreased by one grade according to the MAGIC criteria following administration of the anti-CD2 or anti-CD5 ADC.

35 In further aspects, provided herein is a method of treating a subject having a T cell malignancy, said method comprising administering an effective amount of an anti-CD2 or an anti-

CD5 ADC to the subject, wherein the ADC comprises an anti-CD5 or an anti-CD2 antibody conjugated to a cytotoxin via a linker. In one embodiment, the T cell malignancy is a lymphoma. In one embodiment, the T cell malignancy is T-cell acute lymphoblastic lymphoma (T-ALL), T-cell large granular lymphocyte (LGL) leukemia, human T-cell leukemia virus type 1-positive (HTLV-1*), adult T-cell leukemia/lymphoma (ATL), T-cell prolymphocytic leukemia (T-PLL), or peripheral T-cell lymphoma (PTCLs). In one embodiment, the T cell malignancy is a relapsed, refractory T cell malignancy.

In one embodiment, the ADC comprises a humanized antibody or a human antibody.

In another embodiment, the antibody has an isotype selected from the group consisting of IgG, IgA, IgM, IgD, and IgE. In one embodiment, the IgG isotype is an IgG1 or an IgG4.

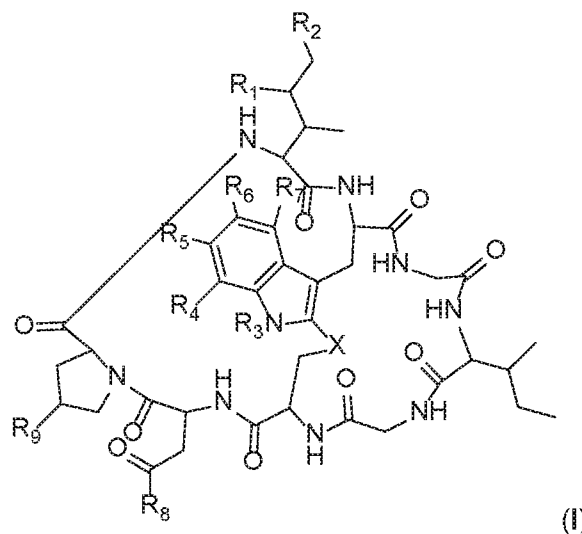
In one embodiment, the ADC is an anti-CD5 ADC.

In one embodiment, the ADC is an anti-CD2 ADC.

In one embodiment, 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, or an indolinobenzodiazepine dimer.

In one embodiment, the cytotoxin is an RNA polymerase inhibitor. In one embodiment, the RNA polymerase inhibitor is an RNA polymerase II inhibitor. In one embodiment, the RNA polymerase inhibitor is an amatoxin.

In one embodiment, the ADC is represented by the formula Ab-Z-L-Am, wherein Ab is the anti-CD5 or anti-CD2 antibody or antigen-binding fragment thereof, L is a linker, Z is a chemical moiety, and Am an amatoxin represented by formula (I)



wherein R₁ is H, OH, OR_A, or OR_C;

R₂ 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 $NR_C R_D$;

R_9 is H, OH, OR_C , or OR_D ;

5 X is -S-, -S(O)-, or -SO₂-;

R_C is -L-Z;

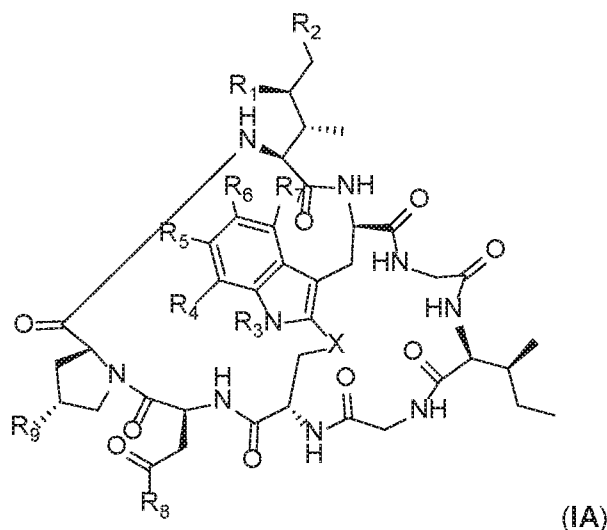
R_D is optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₂-C₆ heteroalkynyl, optionally substituted cycloalkyl, optionally substituted 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 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.

20 In one embodiment, Am-L-Z is represented by formula (IA).



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

R_2 is H, OH, OR_B , or OR_C ;

25 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 $NR_C R_D$;

R_9 is H, OH, OR_C , or OR_D ;

X is -S-, -S(O)-, or -SO₂-;

R_C is -L-Z;

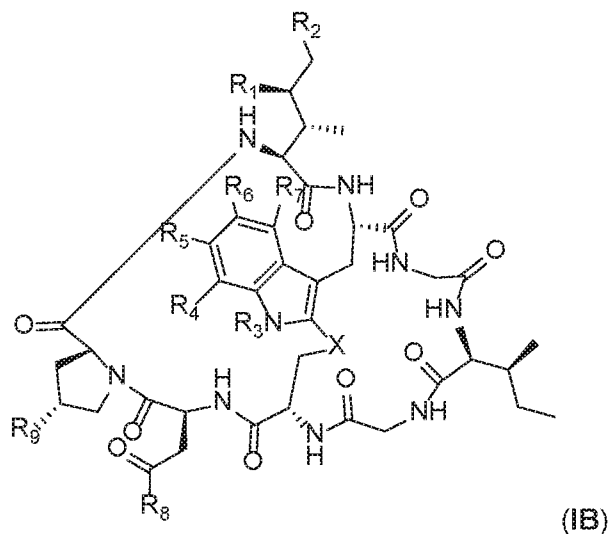
5 R_D is optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₂-C₆ heteroalkynyl, optionally substituted cycloalkyl, optionally substituted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

10 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 dipeptide, -C(=O)-, a peptide, or a combination thereof;

15 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.

In one embodiment, Am-L-Z is represented by formula (IB).



20 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 ;

25 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 $NR_C R_D$;

R_9 is H, OH, OR_C , or OR_D ;

X is -S-, -S(O)-, or -SO₂-;

R_C is -L-Z;

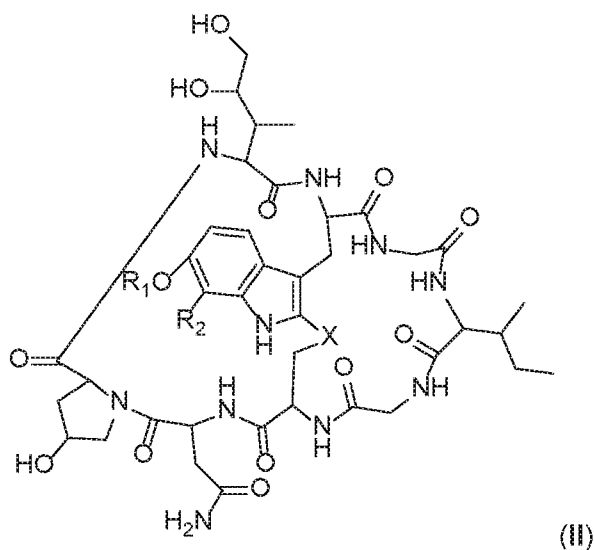
R_D is optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₂-C₆ heteroalkynyl, optionally substituted cycloalkyl, optionally substituted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

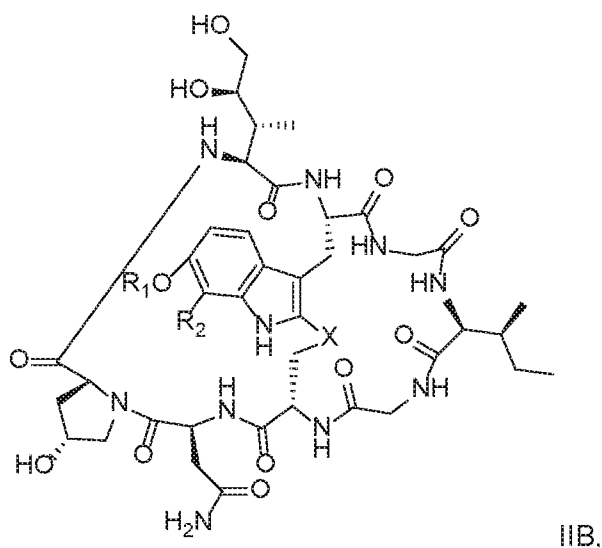
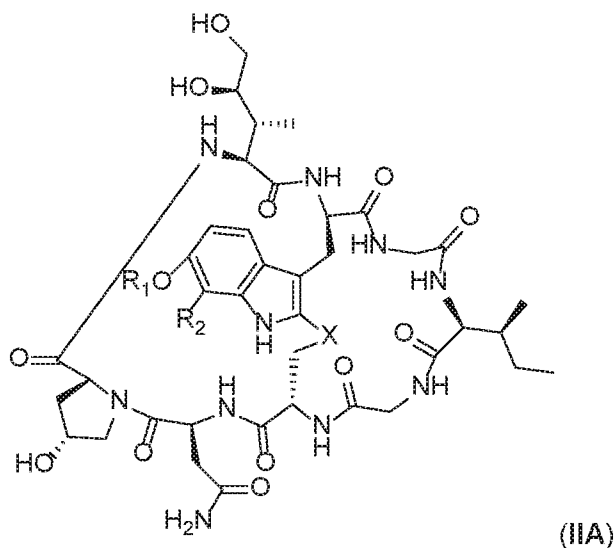
L is optionally substituted C₁-C₆ alkylene, optionally substituted C₁-C₆ heteroalkylene, optionally substituted C₂-C₆ alkenylene, optionally substituted C₂-C₆ heteroalkenylene, optionally substituted C₂-C₆ alkynylene, optionally substituted C₂-C₆ heteroalkynylene, optionally substituted cycloalkylene, optionally substituted heterocycloalkylene, optionally substituted arylene, optionally substituted heteroarylene, a 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.

In one embodiment, the ADC 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)





wherein X is S, SO, or SO₂;

5 R₁ is H or a linker covalently bound to the antibody or antigen-binding fragment thereof through a chemical moiety 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

10 R₂ is H or a linker covalently bound to the antibody or antigen-binding fragment thereof through a chemical moiety 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;

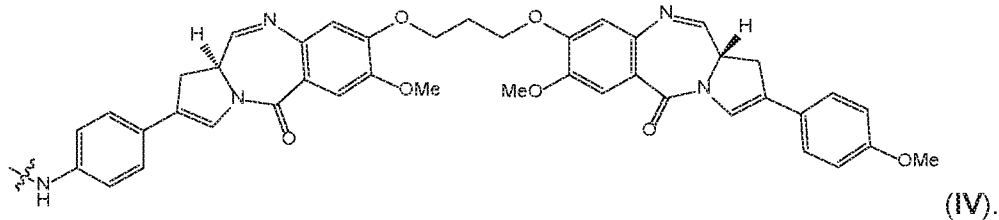
wherein when R₁ is H, R₂ is the linker, and when R₂ is H, R₁ is the linker.

In one embodiment, the cytotoxin of the ADC is which is a maytansinoid, e.g., DM1 or DM4.

15 In one embodiment, the cytotoxin of the ADC is an auristatin, e.g., monomethyl auristatin E (MMAE) or monomethyl auristatin F (MMAF).

In one embodiment, the cytotoxin of the ADC is an anthracycline, e.g., daunorubicin, doxorubicin, epirubicin, or idarubicin.

In one embodiment, the cytotoxin of the ADC is a pyrrolobenzodiazepine dimer derivative represented by formula (IV)



In one embodiment, the ADC is internalized by a CD5+ or a CD2+ immune cell following administration to the patient.

In one embodiment, the subject is a human.

In one embodiment, the anti-CD5 antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises SEQ ID NO: 288, and a light chain variable region that comprises SEQ ID NO: 289.

In one embodiment, the anti-CD5 antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises SEQ ID NO: 291, and a light chain variable region that comprises SEQ ID NO: 290.

Brief Description of the Figures

Fig. 1 graphically depicts the results of an *in vitro* cell line binding assay in which each of the indicated anti-CD2 antibodies or a negative control (i.e., mlgG1) was incubated with MOLT-4 cells (i.e., a human T lymphoblast cell line) followed by incubation of a fluorophore-conjugated anti-IgG antibody. Signal was detected through flow cytometry and is indicated as the geometric mean fluorescence intensity (y-axis) as a function of anti-CD2 antibody concentration (x-axis).

Fig. 2 graphically depicts the results of an *in vitro* primary cell binding assay in which the indicated anti-CD2 antibody (RPA-2.10) or a negative control (i.e., mlgG1) was incubated with primary human T-cells followed by incubation of a fluorophore-conjugated anti-IgG antibody. Signal was detected through flow cytometry and is indicated as the geometric mean fluorescence intensity (y-axis) as a function of anti-CD2 antibody concentration (x-axis).

Figs. 3A and 3B graphically depict results of an *in vitro* T cell killing assay including an anti-CD2-amanitin ADC (i.e., RPA-2.10-AM or "CD2 AM") having an interchain conjugated amanitin with an average drug-to-antibody ratio of 6 (Fig. 3A) or a site-specific conjugated amanitin drug-to-antibody ratio of 2 (Fig. 3B). In Fig. 3A, the anti-CD2-ADC T-cell killing analysis is shown in comparison to an unconjugated anti-CD2 antibody (i.e., "CD2 Naked"). In Fig. 3B, the anti-CD2 antibody the results are shown in comparison to an anti-CD2 antibody having a H435A mutation that decreases the half-life of the antibody. The results show the number of viable T-cells (y-axis) as a function of ADC (CD2 RPA-2.10 AM, CD2 D265C.H435A AM) or unconjugated antibody (CD2 RPA-2.10) concentration (x-axis) as assessed using flow cytometry.

Fig. 4 graphically depicts results of an *in vitro* natural killer (NK) cell killing assay including an anti-CD2-amanitin ADC (i.e., RPA-2.10-AM or "CD2 AM") having an interchain conjugated amanitin with drug-to-antibody ratio of 6. The results show the levels of viable NK-cells (y-axis) as a function of ADC (CD2-AM) or control antibody (i.e., hlgG1, hlgG1-amanitin ("hlgG1-AM")) concentration (x-axis) as assessed using a CellTiter Glo assay.

Figs. 5A and 5B graphically depict the results of an *in vivo* T-cell depletion assay showing the absolute levels of T-cells (CD3+ cells; y-axis) in the peripheral blood (Fig. 5A) and bone marrow (Fig. 5B) of humanized NSG mice 7 days after a single administration of 0.3 mg/kg, 1 mg/kg, or 3 mg/kg of an anti-CD2-amanitin ADC (i.e., RPA-2.10-AM) having an interchain drug-to-antibody ratio of 6. For comparison, Figs. 5A and 5B also show the level of T-cell depletion following treatment of humanized NSG mice with 25 mg/kg Ab1 (an unconjugated anti-CD2 antibody) or with the indicated controls (i.e., 25 mg/kg anti-CD52 antibody (clone YTH34.5); 3 mg/kg hlgG1-amanitan ADC ("hlgG1-AM"), 25 mg/kg hlgG1, or PBS).

Figs. 6A-6C graphically depict the results of an *in vivo* T-cell depletion assay showing the absolute levels of T-cells (CD3+ cells; y-axis) in the peripheral blood (Fig. 6A), bone marrow (Fig. 6B), and thymus (Fig. 6C) of humanized NSG mice 7 days after a single administration of 1 mg/kg or 3 mg/kg of an anti-CD2-amanitin ADC (i.e., RPA-2.10-AM) having a site-specific drug-to-antibody ratio of about 2. For comparison, Figs. 6A-6C also show the level of T-cell depletion following treatment of humanized NSG mice with 3 mg/kg of an unconjugated anti-CD2 antibody or with the indicated controls (i.e., 3 mg/kg hlgG1-amanitan-ADC ("hlgG1-AMC") or PBS).

Fig. 7 graphically depicts the results of an *in vitro* cell line binding assay in which each of the indicated anti-CD5 antibodies or a negative control (i.e., mlgG1) was incubated with MOLT-4 cells (i.e., a human T lymphoblast cell line) followed by incubation of a fluorophore-conjugated anti-IgG antibody. Signal was detected through flow cytometry and is indicated as the geometric mean fluorescence intensity (y-axis) as a function of anti-CD5 antibody concentration (x-axis).

Fig. 8 graphically depicts the results of an *in vitro* primary cell binding assay in which each of the indicated anti-CD5 antibodies or a negative control (i.e., hlgG1) was incubated with primary human T-cells followed by incubation of a fluorophore-conjugated anti-IgG antibody. Signal was detected through flow cytometry and is indicated as the geometric mean fluorescence intensity (y-axis) as a function of anti-CD5 antibody concentration (x-axis).

Figs. 9A and 9B graphically depict results of an *in vitro* T cell killing assay including an anti-CD5-amanitin ADC (i.e., 5D7-AM or "CD5 AM") having an interchain conjugated amanitin with an average drug-to-antibody ratio (DAR) of 6 (Fig. 9A) or a site-specific conjugated amanitin DAR of 2 (Fig. 9B). In Fig. 9A, the anti-CD5-ADC T-cell killing analysis is shown in comparison to an unconjugated anti-CD5 5D7 antibody (i.e., "CD5 Naked"). In Fig. 9B, the anti-CD5 antibody the results are shown in comparison to an anti-CD5 5D7 antibody having a H435A mutation that decreases the half life of the antibody (i.e., "CD5 Fast 1/2 Life AM"). The results show the number

of viable T-cells (y-axis) as a function of ADC (CD5 5D7 AM, CD5 5D7 D265C.H435A AM) or unconjugated antibody (CD5 5D7) concentration (x-axis) as assessed using flow cytometry.

Figs. 10A and 10B graphically depict the results of an *in vivo* T-cell depletion assay showing the absolute levels of T-cells (CD3+ cells; y-axis) in the peripheral blood (Fig. 10A) and bone marrow (Fig. 10B) of humanized NSG mice 7 days after a single administration of 0.3 mg/kg, 1 mg/kg, or 3 mg/kg of an anti-CD5 5D7-amanitin ADC (i.e., CD5 5D7-AM) having an interchain DAR of 6. For comparison, Figs. 10A-10B also show the level of T-cell depletion following treatment of humanized NSG mice with the indicated controls (i.e., 25 mg/kg anti-CD52 antibody; 3 mg/kg hlgG1-amanitin ADC (i.e., hlgG1-AM), 25 mg/kg hlgG1, or PBS).

Figs. 11A-11C graphically depict the results of an *in vivo* T-cell depletion assay showing the absolute levels of T-cells (CD3+ cells; y-axis) in the peripheral blood (Fig. 11A), bone marrow (Fig. 11B), and thymus (Fig. 11C) of humanized NSG mice 7 days after a single administration of 1 mg/kg or 3 mg/kg of an anti-CD5 5D7-amanitin ADC (i.e., 5D7-AM) having a site-specific DAR of 2. For comparison, Figs. 11A-11C also show the level of T-cell depletion following treatment of humanized NSG mice with 3 mg/kg of an unconjugated anti-CD5 antibody or with the indicated controls (i.e., 3 mg/kg hlgG1-amanitan-ADC ("hlgG1-AM") or PBS).

Figs. 12A and 12B graphically depict the results of depletion assays showing that an anti-CD5 ADC (CD5-AM) and an anti-CD2 ADC (CD2-AM) are both capable of depleting Th1 and Th17 cell subsets in polarizing conditions. Fig. 12A shows that the anti-CD5 ADC (CD5-AM) and the anti-CD2 ADC (CD2-AM) were both able to deplete Th1 cells at an IC50 of 2.73 pM, as indicated by the drop in IFN γ signal, indicating depletion of Th1 cells; the isotype control antibody was unable to deplete Th1 cells. Similarly, Fig. 12B shows that the anti-CD5 ADC (CD5-AM) and the anti-CD2 ADC (CD2-AM) were able to deplete Th17 cells at an IC50 of 2.53 pM, as indicated by the drop in IL-17 signal, indicating depletion of Th17 cells; the isotype control antibody was unable to deplete Th17 cells.

Figs. 13A to 13D graphically depict the results of an *in vivo* survival study showing that an anti-CD5 ADC (CD5-AM) extends survival in T-cell acute lymphoblastic leukemia. As shown in Fig. 13A and Fig. 13C, an anti-CD5 ADC (CD5-AM) or an anti-CD2 ADC (CD2-AM), respectively, was able to extend survival by more than 20 days compared to isotype and vehicle controls. Moreover, survival conferred by a single dose of the anti-CD5 ADC (CD5-AM) or the anti-CD2 ADC (CD2-AM) appeared comparable to a commercial chemotherapeutic (Ara-C) (Fig. 13A and Fig. 13C, respectively). As shown in Fig. 13B and Fig. 13D, CD5 ADC (CD5-AM) or an anti-CD2 ADC (CD2-AM), respectively, also decreased tumor burden in mice as compared to isotype and vehicle controls.

Figs. 14A and 14B graphically depict the results of an *in vivo* study showing that an anti-CD5 ADC prevents acute GvHD in a xeno model. As shown in Fig. 14A, slight body weight loss was seen in mice treated with the anti-CD5-ADC (CD5-AM), however, recovery was observed by

Day 13 post transplant. As shown in Fig. 14B, anti-CD5-ADC (CD5-AM) conferred a sustained survival of 80% in this model.

Detailed Description

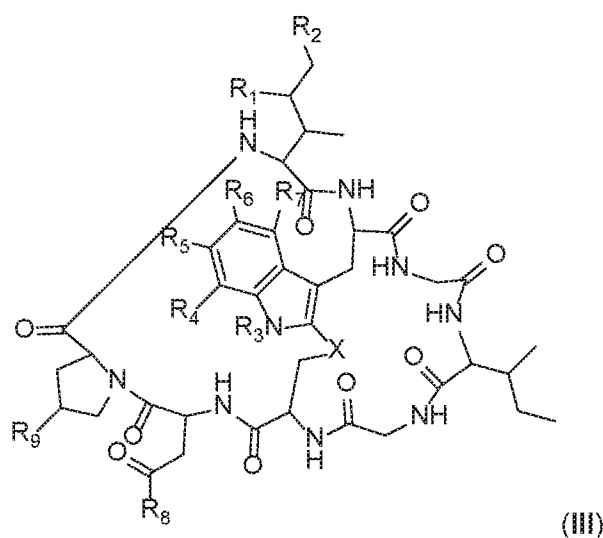
Compositions and methods described herein are based, at least in part, on the discovery that antibody drug conjugates (ADCs) that bind CD2 (also referred to as T cell surface antigen, LFA-2, and LFA-3 receptor) or that bind CD5 (also referred to as Lymphocyte antigen T1/Leu-1) can be used as therapeutic agents to (i) directly treat cancers and autoimmune diseases characterized by CD2+ cells or CD5+ cells and (ii) promote the engraftment of transplanted hematopoietic stem cells in a patient in need of transplant therapy by depleting populations of immune cells that cross-react with, and mount an immune response against, hematopoietic stem cell grafts (e.g., by cross-reacting with non-self MHC antigens expressed by the hematopoietic stem cell graft). These therapeutic activities can arise, for instance, by the binding of anti-CD2 or anti-CD5 antibody drug conjugates, such as a cancer cell, autoimmune cell, or immune cell that cross-reacts with a non-self hematopoietic stem cell antigen (e.g., a non-self MHC antigen), thereby inducing death of the bound cell. In the case of depleting a population of cancer cells or autoimmune cells, the anti-CD2 ADC or the anti-CD5 ADC, can be used to directly treat a cancer or autoimmune disease, such as a cancer autoimmune disease described herein. In the case of depleting a population of immune cells that cross-react with a non-self hematopoietic stem cell antigen, the anti-CD2 ADC or the anti-CD5 ADC can be used to prevent or reduce the likelihood of graft rejection in a patient that is suffering from a stem cell disorder, cancer, or autoimmune disease and that is undergoing hematopoietic stem cell transplant therapy. In such instances, the depletion of CD2+ immune cells or CD5+ immune cells that cross-react with one or more non-self hematopoietic stem cell antigens (e.g., one or more non-self MHC antigens) enables the successful engraftment of transplanted hematopoietic stem cells within the transplant recipient. As the transplanted cells engraft, they can home to hematopoietic tissue, where productive hematopoiesis can then ensue. The transplanted hematopoietic stem cells can subsequently give rise to a population of cells that is deficient or defective in the transplant recipient, such as 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. In this way, anti-CD2 ADCs or anti-CD5 ADCs can be used to promote the successful engraftment of hematopoietic stem cells in a patient, such as human patient suffering from a stem cell disorder described herein.

Definitions

As used herein, the term “about” refers to a value that is within 10% above or below the value being described. For example, the term “about 5 nM” indicates a range of from 4.5 nM to 5.5 nM.

As used herein, the term “amatoxin” refers to a member of the amatoxin family of peptides produced by *Amanita phalloides* mushrooms, a synthetic amatoxin, a variant amatoxin, or a derivative thereof, such as a variant or derivative thereof capable of inhibiting RNA polymerase II activity. Also included are synthetic amatoxins (see, e.g., US Patent No. 9676702, incorporated by reference herein). As described herein, amatoxins may be conjugated to an antibody, or antigen-binding fragment thereof, for instance, by way of a linker moiety (L) (thus forming a conjugate (also referred to as an antibody drug conjugate (ADC))). Exemplary methods of amatoxin conjugation and linkers useful for such processes are described below and are known in the art. Exemplary linker-containing amatoxins useful for conjugation to an antibody, or antigen-binding fragment, in accordance with the compositions and methods are also described herein.

In certain embodiments, amatoxins useful in conjunction with the compositions and methods described herein include compounds according to formula (III) below, α -amanitin, β -amanitin, γ -amanitin, ϵ -amanitin, amanin, amaninamide, amanullin, amanullinic acid, or proamanullin. Formula (III) is as follows:



wherein R_1 is H, OH, or OR_A ;

R_2 is H, OH, or OR_B ;

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 or R_D ;

R_4 is H, OH, OR_D , or R_D ;

R_5 is H, OH, OR_D , or R_D ;

R_6 is H, OH, OR_D , or R_D ;

R_7 is H, OH, OR_D , or R_D ;

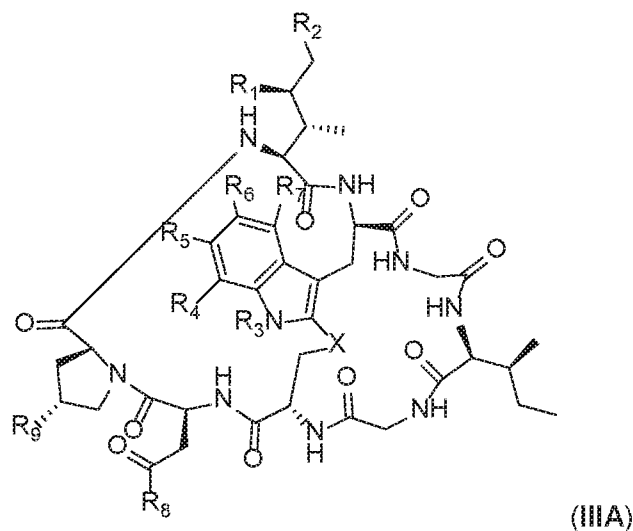
R_8 is OH, NH_2 , or OR_D ;

R_9 is H, OH, or OR_D ;

X is -S-, -S(O)-, or -SO₂-; and

- 5 R_D is optionally substituted alkyl (e.g., C₁-C₆ alkyl), optionally substituted heteroalkyl (e.g., C₁-C₆ heteroalkyl), optionally substituted alkenyl (e.g., C₂-C₆ alkenyl), optionally substituted heteroalkenyl (e.g., C₂-C₆ heteroalkenyl), optionally substituted alkynyl (e.g., C₂-C₆ alkynyl), optionally substituted heteroalkynyl (e.g., C₂-C₆ heteroalkynyl), optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl,
10 or a peptide.

For instance, in one embodiment, amatoxins useful in conjunction with the compositions and methods described herein include compounds according to formula (IIIA), below:



- 15 wherein R_1 is H, OH, or OR_A ;

R_2 is H, OH, or OR_B ;

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 or R_D ;

- 20 R_4 is H, OH, OR_D , or R_D ;

R_5 is H, OH, OR_D , or R_D ;

R_6 is H, OH, OR_D , or R_D ;

R_7 is H, OH, OR_D , or R_D ;

R_8 is OH, NH_2 , or OR_D ;

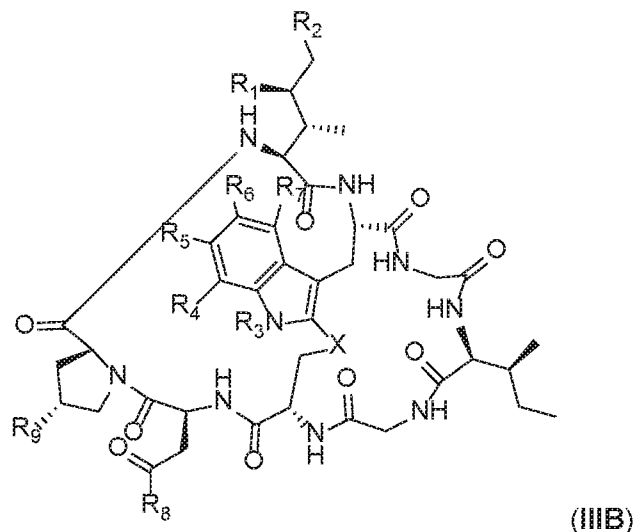
- 25 R_9 is H, OH, or OR_D ;

X is -S-, -S(O)-, or -SO₂-; and

R_D is optionally substituted alkyl (e.g., C₁-C₆ alkyl), optionally substituted heteroalkyl (e.g., C₁-C₆ heteroalkyl), optionally substituted alkenyl (e.g., C₂-C₆ alkenyl), optionally substituted

heteroalkenyl (e.g., C₂-C₆ heteroalkenyl), optionally substituted alkynyl (e.g., C₂-C₆ alkynyl), optionally substituted heteroalkynyl (e.g., C₂-C₆ heteroalkynyl), optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or a peptide.

- 5 In one embodiment, amatoxins useful in conjunction with the compositions and methods described herein also include compounds according to formula (IIIB), below:



wherein R₁ is H, OH, or OR_A;

- 10 R₂ is H, OH, or OR_B;

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;

R₃ is H or R_D;

R₄ is H, OH, OR_D, or R_D;

- 15 R₅ is H, OH, OR_D, or R_D;

R₆ is H, OH, OR_D, or R_D;

R₇ is H, OH, OR_D, or R_D;

R₈ is OH, NH₂, or OR_D;

R₉ is H, OH, or OR_D;

- 20 X is -S-, -S(O)-, or -SO₂-; and

R_D is optionally substituted alkyl (e.g., C₁-C₆ alkyl), optionally substituted heteroalkyl (e.g., C₁-C₆ heteroalkyl), optionally substituted alkenyl (e.g., C₂-C₆ alkenyl), optionally substituted heteroalkenyl (e.g., C₂-C₆ heteroalkenyl), optionally substituted alkynyl (e.g., C₂-C₆ alkynyl), optionally substituted heteroalkynyl (e.g., C₂-C₆ heteroalkynyl), optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, or a dipeptide.

As described herein, amatoxins may be conjugated to an antibody, or an antigen-binding fragment thereof, for instance, by way of a linker moiety. Exemplary methods of amatoxin

conjugation and linkers useful for such processes are described in the section entitled "Linkers for chemical conjugation," as well as in Table 2, below. Exemplary linker-containing amatoxins useful for conjugation to an anti-CD2 antibody, or an antigen-binding fragment or an anti-CD5 antibody, or an antigen-binding fragment thereof, in accordance with the compositions and methods described herein are shown in structural formulas (I), (IA), (IB), (II), (IIA), and (IIB), recited herein.

As used herein, the term "antibody" refers to an immunoglobulin molecule that specifically binds to, or is immunologically reactive with, a particular antigen. Examples of antibodies include monoclonal and otherwise modified forms of antibodies, including but not limited to chimeric antibodies, humanized antibodies, heteroconjugate antibodies (e.g., bispecific, trispecific and quad-specific antibodies, diabodies, triabodies, and tetrabodies), and antigen binding fragments of antibodies, including, for example, Fab', F(ab')₂, Fab, Fv, IgG, and scFv fragments. Unless otherwise indicated, the term "antibody" (Ab) is meant to include both intact molecules, as well as antibody fragments (including, for example, Fab and F(ab')₂ fragments) that are capable of specifically binding to a target protein. As used herein, the Fab and F(ab')₂ fragments refer to antibody fragments that lack the Fc fragment of an intact antibody. Examples of these antibody fragments are described herein.

Generally, antibodies comprise heavy and light chains containing antigen binding regions. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH, and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxyl-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies can mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (C1q) of the classical complement system.

The antibodies used herein are generally isolated or recombinant. "Isolated," when used herein refers to a polypeptide, e.g., an antibody, that has been separated and/or recovered from a cell or cell culture from which it was expressed. Thus, an "isolated antibody," refers to an antibody which is substantially free of other antibodies having different antigenic specificities. For instance, an isolated antibody that specifically binds to CD2 or CD5 is substantially free of antibodies that specifically bind antigens other than CD2 or CD5, respectively.

The term "antigen-binding fragment," as used herein, refers to a molecule other than an intact antibody that comprises a portion of an intact antibody and that binds the antigen to which the intact antibody binds. The antigen-binding function of an antibody can be performed by fragments of a full-length antibody. The antibody fragments can be, for example, a Fv, Fab, Fab', F(ab')₂, scFv, diabody, a triabody, single chain antibody molecules (e.g., scFv), an affibody, a nanobody, an aptamer, or a domain antibody. Examples of binding fragments encompassed of the term "antigen-binding fragment" of an antibody include, but are not limited to: (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L, and C_H1 domains; (ii) a F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and C_H1 domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a dAb including V_H and V_L domains; (vi) a dAb fragment that consists of a V_H domain (see, e.g., Ward et al., Nature 341:544-546, 1989); (vii) a dAb which consists of a V_H or a V_L domain; (viii) an isolated complementarity determining region (CDR); and (ix) a combination of two or more (e.g., two, three, four, five, or six) isolated CDRs which may optionally be joined by a synthetic linker. Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules (known as single chain Fv (scFv); see, for example, Bird et al., Science 242:423-426, 1988 and Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883, 1988). These antibody fragments can be obtained using conventional techniques known to those of skill in the art, and the fragments can be screened for utility in the same manner as intact antibodies. Antigen-binding fragments can be produced by recombinant DNA techniques, enzymatic or chemical cleavage of intact immunoglobulins, or, in certain cases, by chemical peptide synthesis procedures known in the art.

As used herein, the term "anti-CD2 antibody" or "an antibody that binds to CD2" refers to an antibody that specifically binds to CD2. An antibody "which binds" an antigen of interest, *i.e.*, CD2, is one capable of binding that antigen with sufficient affinity such that the antibody is useful in targeting a cell expressing the antigen. In a preferred embodiment, the antibody specifically binds to human CD2 (hCD2). CD2 is found on the cell surface of immune cells, such as T cells. The amino acid sequence of human CD2 to which an anti-CD2 antibody (or anti-CD2 conjugate) would bind is described below in SEQ ID NO: 13. An "anti-CD2 antibody drug conjugate" or an "anti-CD2 ADC" refers to an ADC comprising an anti-CD2 antibody.

As used herein, the term "anti-CD5 antibody" or "an antibody that binds to CD5" refers to an antibody that specifically binds to CD5. An antibody "which binds" an antigen of interest, *i.e.*, CD5, is one capable of binding that antigen with sufficient affinity such that the antibody is useful in targeting a cell expressing the antigen. In a preferred embodiment, the antibody specifically binds to human CD5 (hCD5), the amino acid sequence of which is described in SEQ ID NO: 286. An

"anti-CD5 antibody drug conjugate" or an "anti-CD5 ADC" refers to an ADC comprising an anti-CD5 antibody.

As used herein, the term "bispecific antibody" refers to, a hybrid antibody having two different antigen binding sites. Bispecific antibodies are a species of multispecific antibody and may be produced by a variety of methods including, but not limited to, fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai and Lachmann, 1990, Clin. Exp. Immunol. 79:315-321; Kostelny et al., 1992, J. Immunol. 148:1547-1553. The two binding sites of a bispecific antibody will bind to two different epitopes, which may reside on the same or different protein targets. For instance, one of the binding specificities can be directed towards a T cell surface antigen, such as CD2 or CD5, the other can be for a different T cell surface antigen or another cell surface protein, such as a receptor or receptor subunit involved in a signal transduction pathway that potentiates cell growth, among others.

As used herein, the term "complementarity determining region" (CDR) refers to a hypervariable region found both in the light chain and the heavy chain variable domains of an antibody. The more highly conserved portions of variable domains are referred to as framework regions (FRs). The amino acid positions that delineate a hypervariable region of an antibody can vary, depending on the context and the various definitions known in the art. Some positions within a variable domain may be viewed as hybrid hypervariable positions in that these positions can be deemed to be within a hypervariable region under one set of criteria while being deemed to be outside a hypervariable region under a different set of criteria. One or more of these positions can also be found in extended hypervariable regions. The antibodies described herein may contain modifications in these hybrid hypervariable positions. The variable domains of native heavy and light chains each comprise four framework regions that primarily adopt a β -sheet configuration, connected by three CDRs, which form loops that connect, and in some cases form part of, the β -sheet structure. The CDRs in each chain are held together in close proximity by the framework regions in the order FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4 and, with the CDRs from the other antibody chains, contribute to the formation of the target binding site of antibodies (see Kabat et al., Sequences of Proteins of Immunological Interest, National Institute of Health, Bethesda, MD., 1987). As used herein, numbering of immunoglobulin amino acid residues is performed according to the immunoglobulin amino acid residue numbering system of Kabat et al., unless otherwise indicated.

As used herein, the terms "condition" and "conditioning" refer to processes by which a patient is prepared for receipt of a transplant, e.g., a transplant of hematopoietic stem cells (HSCs). Such procedures promote the engraftment of a hematopoietic stem cell transplant (for instance, as inferred from a sustained increase in the quantity of viable hematopoietic stem cells within a blood sample isolated from a patient following a conditioning procedure and subsequent hematopoietic stem cell transplantation. According to the methods described herein, a patient

may be conditioned for hematopoietic stem cell transplant therapy by administration to the patient of an antibody or antigen-binding fragment thereof capable of binding an antigen expressed by T cells, such as CD2 or CD5. As described herein, the anti-CD2 antibody or the anti-CD5 antibody may be covalently conjugated to a cytotoxin so as to form an antibody-drug conjugate (ADC).

Administration of an antibody, antigen-binding fragment thereof, or antibody-drug conjugate capable of binding one or more of the foregoing antigens to a patient in need of hematopoietic stem cell transplant therapy can promote the engraftment of a hematopoietic stem cell graft, for example, by selectively depleting endogenous immune cells, such as CD2+ T cells (e.g., CD4+ and/or CD8+ T cells) and/or CD2+ NK cells (or CD5+ T cells (e.g., CD4+ and/or CD8+ T cells), CD5+ B cells, and/or CD5+ NK cells) that cross-react with one or more non-self antigens expressed by a hematopoietic stem cell (e.g., one or more non-self MHC antigens). This selective depletion of immune cells in turn prevents or reduces the likelihood of graft rejection following transplantation of an exogenous (for instance, an autologous, allogeneic, or syngeneic) hematopoietic stem cell graft.

As used herein, the term "conjugate" refers to a compound formed by the chemical bonding of a reactive functional group of one molecule, such as an antibody or antigen-binding fragment thereof, with an appropriately reactive functional group of another molecule, such as a cytotoxin described herein. Conjugates may include a linker between the two molecules (e.g., an anti-CD2 antibody and a cytotoxin; or an anti-CD5 antibody and a cytotoxin) bound to one another. Examples of linkers that can be used for the formation of a conjugate include peptide-containing linkers, such as those that contain naturally occurring or non-naturally occurring amino acids, such as D-amino acids. Linkers can be prepared using a variety of strategies described herein and known in the art. Depending on the reactive components therein, a linker may be cleaved, for example, by enzymatic hydrolysis, photolysis, hydrolysis under acidic conditions, hydrolysis under basic conditions, oxidation, disulfide reduction, nucleophilic cleavage, or organometallic cleavage (see, for example, Leriche et al., *Bioorg. Med. Chem.*, 20:571-582, 2012). Notably, the term "conjugate" (when referring to a compound) is also referred to interchangeably herein as a "drug conjugate", "antibody drug conjugate" or "ADC".

As used herein, the term "coupling reaction" refers to a chemical reaction in which two or more substituents suitable for reaction with one another react so as to form a chemical moiety that joins (e.g., covalently) the molecular fragments bound to each substituent. Coupling reactions include those in which a reactive substituent bound to a fragment that is a cytotoxin, such as a cytotoxin known in the art or described herein, reacts with a suitably reactive substituent bound to a fragment that is an antibody, antigen-binding fragment thereof, or antibody, such as an antibody, antigen-binding fragment thereof, or antibody specific for CD2 or CD5 known in the art or described herein. Examples of suitably reactive substituents include a nucleophile/electrophile pair (e.g., a thiol/haloalkyl pair, an amine/carbonyl pair, or a thiol/ α,β -unsaturated carbonyl pair, among others), a diene/dienophile pair (e.g., an azide/alkyne pair, among others), and the like. Coupling reactions include, without limitation,

thiol alkylation, hydroxyl alkylation, amine alkylation, amine condensation, amidation, esterification, disulfide formation, cycloaddition (e.g., [4+2] Diels-Alder cycloaddition, [3+2] Huisgen cycloaddition, among others), nucleophilic aromatic substitution, electrophilic aromatic substitution, and other reactive modalities known in the art or described herein.

5 As used herein, "CRU (competitive repopulating unit)" refers to a unit of measure of long-term engrafting stem cells, which can be detected after in-vivo transplantation.

As used herein, "drug-to-antibody ratio" or "DAR" refers to the number of cytotoxins, e.g., amatoxin, attached to the antibody of an ADC. The DAR of an ADC can range from 1 to 8, although higher loads are also possible depending on the number of linkage sites on an antibody.
10 Thus, in certain embodiments, an ADC described herein has a DAR of about 1, 2, 3, 4, 5, 6, 7, or 8.

As used herein, the term "donor" refers to a human or animal from which one or more cells are isolated prior to administration of the cells, or progeny thereof, into a recipient. The one or more cells may be, for example, a population of hematopoietic stem cells.

15 As used herein, the term "diabody" refers to a bivalent antibody containing two polypeptide chains, in which each polypeptide chain includes V_H and V_L domains joined by a linker that is too short (e.g., a linker composed of five amino acids) to allow for intramolecular association of V_H and V_L domains on the same peptide chain. This configuration forces each domain to pair with a complementary domain on another polypeptide chain so as to form a homodimeric structure.
20 Accordingly, the term "triabody" refers to trivalent antibodies comprising three peptide chains, each of which contains one V_H domain and one V_L domain joined by a linker that is exceedingly short (e.g., a linker composed of 1-2 amino acids) to permit intramolecular association of V_H and V_L domains within the same peptide chain. In order to fold into their native structures, peptides configured in this way typically trimerize so as to position the V_H and V_L domains of neighboring peptide chains spatially
25 proximal to one another (see, for example, Holliger et al., Proc. Natl. Acad. Sci. USA 90:6444-48, 1993).

As used herein, a "dual variable domain immunoglobulin" ("DVD-Ig") refers to an antigen binding protein that combines the target-binding variable domains of two antibodies by way of linkers to create a tetravalent, dual-targeting single agent (see, for example, Gu et al., Meth.
30 Enzymol., 502:25-41, 2012).

The term "effective amount" refers to the amount of a therapeutic agent, e.g., an anti-CD5 ADC or an anti-CD2 ADC, needed to prevent or alleviate at least one or more signs or symptoms of pain, and relates to a sufficient amount of a composition to provide the desired effect, e.g., to treat a subject having cancer. An effective amount would also include an amount sufficient to
35 prevent or delay the development of a symptom of the disease, alter the course of a symptom of the disease (for example but not limited to, slow the progression of a symptom of the disease), or reverse a symptom of the disease.

As used herein, the term "endogenous" describes a substance, such as a molecule, cell, tissue, or organ (e.g., a hematopoietic stem cell or a cell of hematopoietic lineage, such as a megakaryocyte, thrombocyte, platelet, erythrocyte, mast cell, myeloblast, basophil, neutrophil, eosinophil, microglial cell, granulocyte, monocyte, osteoclast, antigen-presenting cell, macrophage, dendritic cell, natural killer cell, T lymphocyte (e.g., a CD4+ or CD8+ T lymphocyte), or B lymphocyte) that is found naturally in a particular organism, such as a human patient, for instance, a human patient undergoing hematopoietic stem cell transplant therapy as described herein.

As used herein, the term "engraftment potential" is used to refer to the ability of hematopoietic stem and progenitor cells to repopulate a tissue, whether such cells are naturally circulating or are provided by transplantation. The term encompasses all events surrounding or leading up to engraftment, such as tissue homing of cells and colonization of cells within the tissue of interest. The engraftment efficiency or rate of engraftment can be evaluated or quantified using any clinically acceptable parameter as known to those of skill in the art and can include, for example, assessment of competitive repopulating units (CRU); incorporation or expression of a marker in tissue(s) into which stem cells have homed, colonized, or become engrafted; or by evaluation of the progress of a subject through disease progression, survival of hematopoietic stem and progenitor cells, or survival of a recipient. Engraftment can also be determined by measuring white blood cell counts in peripheral blood during a post-transplant period. Engraftment can also be assessed by measuring recovery of marrow cells by donor cells in a bone marrow aspirate sample.

As used herein, the term "excipient" refers to a substance formulated alongside the active ingredient of a medication. They may be included, for example, for the purpose of long-term stabilization, or to confer a therapeutic enhancement on the active ingredient in the final dosage form.

As used herein, the term "exogenous" describes a substance, such as a molecule, cell, tissue, or organ (e.g., a T cell, hematopoietic stem cell, or a cell of hematopoietic lineage, such as a megakaryocyte, thrombocyte, platelet, erythrocyte, mast cell, myeloblast, basophil, neutrophil, eosinophil, microglial cell, granulocyte, monocyte, osteoclast, antigen-presenting cell, macrophage, dendritic cell, natural killer cell, T lymphocyte, or B lymphocyte) that is not found naturally in a particular organism, such as a human patient. Exogenous substances include those that are provided from an external source to an organism or to cultured matter extracted therefrom.

As used herein, the term "framework region" or "FW region" includes amino acid residues that are adjacent to the CDRs of an antibody or antigen-binding fragment thereof. FW region residues may be present in, for example, human antibodies, humanized antibodies, monoclonal antibodies, antibody fragments, Fab fragments, single chain antibody fragments, scFv fragments, antibody domains, and bispecific antibodies, among others.

The terms "full length antibody" and "intact antibody" are used herein interchangeably to refer to an antibody in its substantially intact form, and not an antibody fragment as defined herein. In one embodiment, an ADC described herein comprises an intact antibody, e.g., an anti-CD5 or anti-CD2 intact antibody. Thus, for an IgG antibody, an intact antibody comprises two heavy chains each comprising a variable region, a constant region and an Fc region, and two light chains each comprising a variable region and a constant region. More specifically, an intact IgG comprises two light chains each comprising a light chain variable region (VL) and a light chain constant region (CL), and comprises two heavy chains each comprising a heavy chain variable region (VH) and three heavy chain constant regions (CH1, CH2, and CH3). CH2 and CH3 represent the Fc region of the heavy chain.

As used herein, the term "hematopoietic stem cells" ("HSCs") refers to immature blood cells having the capacity to self-renew and to differentiate into mature blood cells comprising diverse lineages including but not limited to granulocytes (e.g., promyelocytes, neutrophils, eosinophils, basophils), erythrocytes (e.g., reticulocytes, erythrocytes), thrombocytes (e.g., megakaryoblasts, platelet producing megakaryocytes, platelets), monocytes (e.g., monocytes, macrophages), dendritic cells, microglia, osteoclasts, and lymphocytes (e.g., NK cells, B cells and T cells). Such cells may include CD34⁺ cells. CD34⁺ cells are immature cells that express the CD34 cell surface marker. In humans, CD34⁺ cells are believed to include a subpopulation of cells with the stem cell properties defined above, whereas in mice, HSCs are CD34⁻. In addition, HSCs also refer to long term repopulating HSCs (LT-HSC) and short term repopulating HSCs (ST-HSC). LT-HSCs and ST-HSCs are differentiated, based on functional potential and on cell surface marker expression. For example, human HSCs are CD34⁺, CD38⁻, CD45RA⁻, CD90⁺, CD49F⁺, and lin⁻ (negative for mature lineage markers, including CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11B, CD19, CD20, CD56, and CD235A). In mice, bone marrow LT-HSCs are CD34⁻, SCA-1⁺, C-kit⁺, CD135⁻, Slamf1/CD150⁺, CD48⁻, and lin⁻ (negative for mature lineage markers, including Ter119, CD11b, Gr1, CD3, CD4, CD8, B220, and IL7ra), whereas ST-HSCs are CD34⁺, SCA-1⁺, C-kit⁺, CD135⁻, Slamf1/CD150⁺, and lin⁻ (negative for mature lineage markers, including Ter119, CD11b, Gr1, CD3, CD4, CD8, B220, and IL7ra). In addition, ST-HSCs are less quiescent and more proliferative than LT-HSCs under homeostatic conditions. However, LT-HSC have greater self-renewal potential (i.e., they survive throughout adulthood, and can be serially transplanted through successive recipients), whereas ST-HSCs have limited self-renewal (i.e., they survive for only a limited period of time, and do not possess serial transplantation potential). Any of these HSCs can be used in the methods described herein. ST-HSCs are particularly useful because they are highly proliferative and thus, can more quickly give rise to differentiated progeny.

As used herein, the term "hematopoietic stem cell functional potential" refers to the functional properties of hematopoietic stem cells which include 1) multi-potency (which refers to the ability to differentiate into multiple different blood lineages including, but not limited to,

granulocytes (e.g., promyelocytes, neutrophils, eosinophils, basophils), erythrocytes (e.g., reticulocytes, erythrocytes), thrombocytes (e.g., megakaryoblasts, platelet producing megakaryocytes, platelets), monocytes (e.g., monocytes, macrophages), dendritic cells, microglia, osteoclasts, and lymphocytes (e.g., NK cells, B cells and T cells), 2) self-renewal (which refers to the ability of hematopoietic stem cells to give rise to daughter cells that have equivalent potential as the mother cell, and further that this ability can repeatedly occur throughout the lifetime of an individual without exhaustion), and 3) the ability of hematopoietic stem cells or progeny thereof to be reintroduced into a transplant recipient whereupon they home to the hematopoietic stem cell niche and re-establish productive and sustained hematopoiesis.

As used herein, the terms "Major histocompatibility complex antigens" ("MHC", also referred to as "human leukocyte antigens" ("HLA") in the context of humans) refer to proteins expressed on the cell surface that confer a unique antigenic identity to a cell. MHC/HLA antigens are target molecules that are recognized by T cells and NK cells as being derived from the same source of hematopoietic stem cells as the immune effector cells ("self") or as being derived from another source of hematopoietic reconstituting cells ("non-self"). Two main classes of HLA antigens are recognized: HLA class I and HLA class II. HLA class I antigens (A, B, and C in humans) render each cell recognizable as "self," whereas HLA class II antigens (DR, DP, and DQ in humans) are involved in reactions between lymphocytes and antigen presenting cells. Both have been implicated in the rejection of transplanted organs. An important aspect of the HLA gene system is its polymorphism. Each gene, MHC class I (A, B and C) and MHC class II (DP, DQ and DR) exists in different alleles. HLA alleles are designated by numbers and subscripts. For example, two unrelated individuals may carry class I HLA-B, genes B5, and Bw41, respectively. Allelic gene products differ in one or more amino acids in the α and/or β domain(s). Large panels of specific antibodies or nucleic acid reagents are used to type HLA haplotypes of individuals, using leukocytes that express class I and class II molecules. The genes commonly used for HLA typing are the six MHC Class I and Class II proteins, two alleles for each of HLA-A; HLA-B and HLA-DR. The HLA genes are clustered in a "super-locus" present on chromosome position 6p21, which encodes the six classical transplantation HLA genes and at least 132 protein coding genes that have important roles in the regulation of the immune system as well as some other fundamental molecular and cellular processes. The complete locus measures roughly 3.6 Mb, with at least 224 gene loci. One effect of this clustering is that "haplotypes", i.e. the set of alleles present on a single chromosome, which is inherited from one parent, tend to be inherited as a group. The set of alleles inherited from each parent forms a haplotype, in which some alleles tend to be associated together. Identifying a patient's haplotypes can help predict the probability of finding matching donors and assist in developing a search strategy, because some alleles and haplotypes are more common than others and they are distributed at different frequencies in different racial and ethnic groups.

As used herein, the term "HLA-matched" refers to a donor-recipient pair in which none of the HLA antigens are mismatched between the donor and recipient, such as a donor providing a hematopoietic stem cell graft to a recipient in need of hematopoietic stem cell transplant therapy. HLA-matched (i.e., where all of the 6 alleles are matched) donor-recipient pairs have a decreased risk of graft rejection, as endogenous T cells and NK cells are less likely to recognize the incoming graft as foreign, and are thus less likely to mount an immune response against the transplant.

As used herein, the term "HLA-mismatched" refers to a donor-recipient pair in which at least one HLA antigen, in particular with respect to HLA-A, HLA-B and HLA-DR, is mismatched between the donor and recipient, such as a donor providing a hematopoietic stem cell graft to a recipient in need of hematopoietic stem cell transplant therapy. In some embodiments, one haplotype is matched and the other is mismatched. HLA-mismatched donor-recipient pairs may have an increased risk of graft rejection relative to HLA-matched donor-recipient pairs, as endogenous T cells and NK cells are more likely to recognize the incoming graft as foreign in the case of an HLA-mismatched donor-recipient pair, and such T cells and NK cells are thus more likely to mount an immune response against the transplant.

As used herein, the term "human antibody" refers to an antibody having antibody regions such as variable and constant regions or domains which correspond substantially to human germline immunoglobulin sequences. A human antibody can be produced in a human cell line (for example, by recombinant expression) or by a non-human animal or a prokaryotic or eukaryotic cell that is capable of expressing functionally rearranged human immunoglobulin (such as heavy chain and/or light chain) genes. When a human antibody is a single chain antibody, it can include a linker peptide that is not found in native human antibodies. For example, an Fv can contain a linker peptide, such as two to about eight glycine or other amino acid residues, which connects the variable region of the heavy chain and the variable region of the light chain. Such linker peptides are considered to be of human origin. Human antibodies can be made by a variety of methods known in the art including phage display methods using antibody libraries derived from human immunoglobulin sequences. Human antibodies can also be produced using transgenic mice that are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes (see, for example, PCT Publication Nos. WO1998/24893; WO1992/01047; WO1996/34096; WO1996/33735; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598). In one embodiment, a human antibody is made using recombinant methods such that the glycosylation pattern of the antibody is different than an antibody having the same sequence if it were to exist in nature.

As used herein, the term "humanized" antibody refers to a chimeric antibody generally comprising amino acid sequences from non-human CDRs and human framework regions. In one embodiment, a humanized antibody is a human antibody (recipient antibody) in which residues

from the CDRs of the recipient are replaced by residues from the CDRs of a non-human species (donor antibody) such as mouse, rat, rabbit, or nonhuman primate having the desired specificity, affinity, and/or capacity. In general, a humanized antibody contains substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin. All or substantially all of the FW regions may also be those of a human immunoglobulin sequence. The humanized antibody can also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin consensus sequence. Methods of antibody humanization are known in the art and have been described, for example, in Riechmann et al., Nature 332:323-327, 1988; U.S. Patent Nos: 5,530,101; 5,585,089; 5,693,761; 5,693,762; and 6,180,370.

As used herein, the term "immune cell" refers to a cell of the immune system that participates in the mounting and maintaining of an innate or adaptive immune response. Immune cells include lymphocytes that contain a receptor that specifically binds, and mounts an immune response against, an antigen of interest, such as a self antigen in the case of an autoimmune cell. Exemplary immune cells include mast cells, basophils, neutrophils, eosinophils, microglia, granulocytes, monocytes, antigen-presenting cells, macrophages, dendritic cells, natural killer cells, T lymphocytes, and B lymphocytes.

As used herein, patients that are "in need of" a hematopoietic stem cell transplant, include patients that exhibit a defect or deficiency in one or more blood cell types, as well as patients having a stem cell disorder. Hematopoietic stem cells generally exhibit 1) multi-potency, and can thus differentiate into multiple different blood lineages including, but not limited to, granulocytes (e.g., promyelocytes, neutrophils, eosinophils, basophils), erythrocytes (e.g., reticulocytes, erythrocytes), thrombocytes (e.g., megakaryoblasts, platelet producing megakaryocytes, platelets), monocytes (e.g., monocytes, macrophages), dendritic cells, microglia, osteoclasts, and lymphocytes (e.g., NK cells, B cells and T cells), 2) self-renewal, and can thus give rise to daughter cells that have equivalent potential as the mother cell, and 3) the ability to be reintroduced into a transplant recipient whereupon they home to the hematopoietic stem cell niche and re-establish productive and sustained hematopoiesis. Hematopoietic stem cells can thus be administered to a patient defective or deficient in one or more cell types of the hematopoietic lineage in order to re-constitute the defective or deficient population of cells in vivo. For example, the patient may be suffering from cancer, and the deficiency may be caused by administration of a chemotherapeutic agent or other medicament that depletes, either selectively or non-specifically, the cancerous cell population. Additionally or alternatively, the patient may be suffering from a non-malignant hemoglobinopathy that may cause a defect or deficiency in one or more blood cell types, such as sickle cell anemia, thalassemia, Fanconi anemia, and Wiskott-Aldrich syndrome. The subject may be one that is suffering from adenosine deaminase severe combined immunodeficiency (ADA SCID), HIV/AIDS, metachromatic leukodystrophy, Diamond-Blackfan

anemia, and Schwachman-Diamond syndrome. The subject may have or be affected by an inherited blood disorder (e.g., sickle cell anemia) or an autoimmune disorder. Additionally or alternatively, the subject may have or be affected by a malignancy (e.g., a T-cell malignancy), such as a malignancy selected from the group consisting of hematologic cancers (e.g., leukemia, lymphoma, multiple myeloma, or myelodysplastic syndrome) and neuroblastoma. In some embodiments, the subject has or is otherwise affected by a metabolic disorder. For example, the subject may suffer or otherwise be affected by a metabolic disorder selected from the group consisting of glycogen storage diseases, mucopolysaccharidoses, Gaucher's Disease, Hurlers Disease, sphingolipidoses, metachromatic leukodystrophy, or any other diseases or disorders which may benefit from the treatments and therapies disclosed herein and including, without limitation, severe combined immunodeficiency, Wiscott-Aldrich syndrome, hyper immunoglobulin M (IgM) syndrome, Chediak-Higashi disease, hereditary lymphohistiocytosis, osteopetrosis, osteogenesis imperfecta, storage diseases, thalassemia major, sickle cell disease, systemic sclerosis, systemic lupus erythematosus, multiple sclerosis, juvenile rheumatoid arthritis and those diseases, or disorders described in "Bone Marrow Transplantation for Non-Malignant Disease," ASH Education Book, 1:319-338 (2000), the disclosure of which is incorporated herein by reference in its entirety as it pertains to pathologies that may be treated by administration of hematopoietic stem cell transplant therapy. Additionally or alternatively, a patient "in need of" a hematopoietic stem cell transplant may be one that is or is not suffering from one of the foregoing pathologies, but nonetheless exhibits a reduced level (e.g., as compared to that of an otherwise healthy subject) of one or more endogenous cell types within the hematopoietic lineage, such as 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. One of skill in the art can readily determine whether one's level of one or more of the foregoing cell types, or other blood cell type, is reduced with respect to an otherwise healthy subject, for instance, by way of flow cytometry and fluorescence activated cell sorting (FACS) methods, among other procedures, known in the art.

The term "isolated" when used in the context of a protein, e.g., an antibody, refers to a protein that by virtue of its origin or source of derivation is not associated with naturally associated components that accompany it in its native state; is substantially free of other proteins from the same species; is expressed by a cell from a different species; or does not occur in nature. Thus, a protein that is chemically synthesized or synthesized in a cellular system different from the cell from which it naturally originates will be "isolated" from its naturally associated components. A protein may also be rendered substantially free of naturally associated components by isolation, using protein purification techniques well known in the art.

The term "monoclonal antibody" or "mAb" refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical and/or bind to the same epitope, except for possible variant antibodies, *e.g.*, naturally occurring mutations or variants arising during production of a monoclonal antibody preparation, where such variants may be present in minor amounts. In contrast to polyclonal antibody preparations that typically include different antibodies directed against different determinants (epitopes), each mAb is directed against a single determinant on the antigen. The modifier "monoclonal" is not to be construed as requiring production of the antibody by any particular method.

As used herein, the term "patient at risk for GVHD" refers to a patient with one or more factors for developing GVHD. Risk factors include, but are not limited to, an allogeneic donor transplant (*e.g.*, transplantation of hematopoietic stem cells from a bone marrow transplant), including mismatched human leucocyte antigen (HLA) donor and sex mismatched donor, T cell replete stem cell transplant; donor and recipient age; presence of cytomegalovirus (CMV) or CMV antibodies in transplant donor or host; increased dose of total-body irradiation (TBI); conditioning regimen intensity; acute GVHD prophylaxis; lack of protective environments; splenectomy; immunoglobulin use; underlying disease; ABO compatibility; prior exposure to herpes viruses; donor blood transfusions; performance score; antibiotic gut decontamination; and post-allogeneic transplant blood transfusions.

As used herein, the term "patient at risk for an autoimmune disease" refers to a patient with one or more risk factors for developing an autoimmune disease. Risk factors include, but are not limited to, age (young to middle aged), sex (female), ethnicity (African American, American Indian, or Latino), family history of autoimmune diseases, exposure to environmental agents, previous infection, chronic inflammation, and donor transplantation (*e.g.*, transplantation of hematopoietic stem cells from a bone marrow transplant).

As used herein, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions and/or dosage forms, which are suitable for contact with the tissues of a subject, such as a mammal (*e.g.*, a human) without excessive toxicity, irritation, allergic response and other problem complications commensurate with a reasonable benefit/risk ratio.

As used herein, the term "pharmaceutical composition" means a mixture containing a therapeutic compound to be administered to a subject, such as a mammal, *e.g.*, a human, in order to prevent, treat or control a particular disease or condition affecting the mammal, such as an autoimmune disorder, cancer, or blood disorder, among others, *e.g.*, as described herein.

As used herein, the term "recipient" refers to a patient that receives a transplant, such as a transplant containing a population of hematopoietic stem cells. The transplanted cells administered to a recipient may be, *e.g.*, autologous, syngeneic, or allogeneic cells.

As used herein, the term "rejection" in the context of a transplant, such as a hematopoietic stem cell graft, refers to the process by which a recipient mounts an immune response against an incoming transplant, thereby reducing the ability of the transplanted matter (e.g., hematopoietic stem cells) to persist in the recipient. Rejection of a transplanted graft, such as a hematopoietic stem cell graft, can be quantified, for instance, by measuring the quantity or concentration of transplanted cells in various samples isolated from a patient at distinct time points following transplantation. A finding that the quantity or concentration of transplanted cells in samples isolated from the patient diminishes over time, for instance, by about 20%, about 25%, about 30%, about 35%, about 40%, about 56%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or more, indicates that the patient is suffering from graft rejection. Conversely, a finding that the quantity or concentration of transplanted cells in samples isolated from the patient remains stable over time, for instance, by being diminished by less than about 20%, about 15%, about 10%, about 5%, or fewer, indicates that the patient is not suffering from graft rejection. Alternatively, graft rejection can be quantified by measuring the quantity or concentration of immune cells, such as T cells and/or NK cells, that cross-react with MHC antigens expressed by the transplanted cells in various samples isolated from a patient at distinct time points following transplantation. A finding that the quantity or concentration of immune cells, such as T cells and/or NK cells, that cross-react with MHC antigens expressed by the transplanted cells in samples isolated from the patient increases over time, for instance, by about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 56%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 100%, about 200%, about 300%, or more, indicates that the patient is suffering from graft rejection. Conversely, a finding that the quantity or concentration of immune cells, such as T cells and/or NK cells, that cross-react with MHC antigens expressed by the transplanted cells in samples isolated from the patient diminishes over time, for instance, by about 20%, about 25%, about 30%, about 35%, about 40%, about 56%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or more, indicates that the patient is not suffering from graft rejection.

As used herein, the term "sample" refers to a specimen (e.g., blood, blood component (e.g., serum or plasma), urine, saliva, amniotic fluid, cerebrospinal fluid, tissue (e.g., placental or dermal), pancreatic fluid, chorionic villus sample, and cells) taken from a subject.

As used herein, the term "scFv" refers to a single chain Fv antibody in which the variable domains of the heavy chain and the light chain from an antibody have been joined to form one chain. scFv fragments contain a single polypeptide chain that includes the variable region of an antibody light chain (V_L) (e.g., CDR-L1, CDR-L2, and/or CDR-L3) and the variable region of an antibody heavy chain (V_H) (e.g., CDR-H1, CDR-H2, and/or CDR-H3) separated by a linker. The linker that joins the V_L and V_H regions of a scFv fragment can be a peptide linker composed of

proteinogenic amino acids. Alternative linkers can be used so as to increase the resistance of the scFv fragment to proteolytic degradation (for example, linkers containing D-amino acids), in order to enhance the solubility of the scFv fragment (for example, hydrophilic linkers such as polyethylene glycol-containing linkers or polypeptides containing repeating glycine and serine residues), to improve the biophysical stability of the molecule (for example, a linker containing cysteine residues that form intramolecular or intermolecular disulfide bonds), or to attenuate the immunogenicity of the scFv fragment (for example, linkers containing glycosylation sites). It will also be understood by one of ordinary skill in the art that the variable regions of the scFv molecules described herein can be modified such that they vary in amino acid sequence from the antibody molecule from which they were derived. For example, nucleotide or amino acid substitutions leading to conservative substitutions or changes at amino acid residues can be made (e.g., in CDR and/or framework residues) so as to preserve or enhance the ability of the scFv to bind to the antigen recognized by the corresponding antibody.

The terms "specific binding" or "specifically binds" in reference to the interaction of an antibody, or antibody fragment, with a second chemical species, means that the interaction is dependent upon the presence of a particular structure (e.g., an antigenic determinant or epitope) on the chemical species; for example, an antibody recognizes and binds to a specific protein structure rather than to proteins generally. If an antibody is specific for epitope "A", the presence of a molecule containing epitope A (or free, unlabeled A), in a reaction containing labeled "A" and the antibody, will reduce the amount of labeled A bound to the antibody. In one embodiment, an antibody specifically binds to a target, e.g., CD2 or CD5, if the antibody has a K_D for the target of at least about 10^{-4} M, about 10^{-5} M, about 10^{-6} M, about 10^{-7} M, about 10^{-8} M, about 10^{-9} M, about 10^{-10} M, about 10^{-11} M, about 10^{-12} M, or less (less meaning a number that is less than 10^{-12} , e.g. 10^{-13}). In one embodiment, the term "specific binding to CD2" or "specifically binds to CD2," as used herein, refers to an antibody or that binds to CD2 and has a dissociation constant (K_D) of 1.0×10^{-7} M or less, as determined by surface plasmon resonance. In another embodiment, the term "specific binding to CD5" or "specifically binds to CD5," as used herein, refers to an antibody or that binds to CD5 and has a dissociation constant (K_D) of 1.0×10^{-7} M or less, as determined by surface plasmon resonance. In one embodiment, K_D is determined according to standard bio-layer interferometry (BLI). It shall be understood, however, that the antibody may be capable of specifically binding to two or more antigens which are related in sequence. For example, in one embodiment, an antibody can specifically bind to both human and a non-human (e.g., mouse or non-human primate) orthologs of CD2. In another embodiment, an antibody can specifically bind to both human and a non-human (e.g., mouse or non-human primate) orthologs of CD5. Specific binding can also refer to an ADC, which comprises an antibody.

As used herein, the terms "subject" and "patient" refer to a mammal, such as a human, that receives treatment for a particular disease or condition as described herein. For instance, a

patient, such as a human patient, may be one that is suffering from an autoimmune disease described herein, and may be administered an anti-CD2 antibody-drug conjugate or an anti-CD5 antibody-drug conjugate described herein so as to (i) deplete a population of autoimmune cells (e.g., a population of autoimmune CD2+ T cells and/or NK cells; or a population of autoimmune CD5+ T cells, B cells, and/or NK cells) and/or (ii) deplete a population of CD2+ immune cells (e.g., CD2+ T cells and/or NK cells) or to deplete a population of CD5+ immune cells (e.g., CD5+ T cells, B cells, and/or NK cells) that cross-react with a non-self antigen expressed by hematopoietic stem cells (e.g., a non-self MHC antigen expressed by a hematopoietic stem cell graft), thereby preventing or reducing the likelihood of graft rejection prior to hematopoietic stem cell transplant therapy.

As used herein, the phrase "substantially cleared from the blood" refers to a point in time following administration of a therapeutic agent (such as an anti-CD2 ADC or an anti-CD5 ADC) to a patient when the concentration of the therapeutic agent in a blood sample isolated from the patient is such that the therapeutic agent is not detectable by conventional means (for instance, such that the therapeutic agent is not detectable above the noise threshold of the device or assay used to detect the therapeutic agent). A variety of techniques known in the art can be used to detect antibodies, or antibody fragments, such as ELISA-based detection assays known in the art or described herein. Additional assays that can be used to detect antibodies, and antibody fragments, include immunoprecipitation techniques and immunoblot assays, among others known in the art.

As used herein, the phrase "stem cell disorder" broadly refers to any disease, disorder, or condition that may be treated or cured by conditioning a subject's target tissues, for instance, by ablating an endogenous T cell population in a target tissue,) and/or by engrafting or transplanting stem cells in a subject's target tissues. For example, Type I diabetes patients have been shown to be cured by hematopoietic stem cell transplant and may benefit from conditioning in accordance with the compositions and methods described herein. Additional disorders that can be treated using the compositions and methods described herein include, without limitation, sickle cell anemia, thalassemias, Fanconi anemia, Wiskott-Aldrich syndrome, ADA SCID, HIV/AIDS, metachromatic leukodystrophy, Diamond-Blackfan anemia, and Schwachman-Diamond syndrome. The subject may have or be affected by an inherited blood disorder (e.g., sickle cell anemia) or an autoimmune disorder. Additionally or alternatively, the subject may have or be affected by a malignancy, such as a malignancy selected from the group consisting of hematologic cancers (e.g., leukemia, lymphoma, multiple myeloma, or myelodysplastic syndrome) and neuroblastoma. In some embodiments, the subject has or is otherwise affected by a metabolic disorder. For example, the subject may suffer or otherwise be affected by a metabolic disorder selected from the group consisting of glycogen storage diseases, mucopolysaccharidoses, Gaucher's Disease, Hurlers Disease, sphingolipidoses, metachromatic leukodystrophy, or any other diseases or

disorders which may benefit from the treatments and therapies disclosed herein and including, without limitation, severe combined immunodeficiency, Wiscott-Aldrich syndrome, hyper immunoglobulin M (IgM) syndrome, Chediak-Higashi disease, hereditary lymphohistiocytosis, osteopetrosis, osteogenesis imperfecta, storage diseases, thalassemia major, sickle cell disease, systemic sclerosis, systemic lupus erythematosus, multiple sclerosis, juvenile rheumatoid arthritis and those diseases, or disorders described in "Bone Marrow Transplantation for Non-Malignant Disease," ASH Education Book, 1:319-338 (2000), the disclosure of which is incorporated herein by reference in its entirety as it pertains to pathologies that may be treated by administration of hematopoietic stem cell transplant therapy.

As used herein, the term "transfection" refers to any of a wide variety of techniques commonly used for the introduction of exogenous DNA into a prokaryotic or eukaryotic host cell, such as electroporation, lipofection, calcium- phosphate precipitation, DEAE- dextran transfection and the like.

As used herein, the terms "treat" or "treatment" refer to therapeutic measures, in which the object is to prevent, cure, slow down, lessen an undesired physiological change or halt progression of a diagnosed condition or disorder in order to promote a beneficial phenotype in the patient being treated. Beneficial or desired clinical results depend on the disorder being treated and can include, but are not limited to, a reduction in tumor burden, a reduction in the quantity of autoimmune cells present in a sample isolated from the patient, such as a population of CD2+ T cells and/or NK cells (or a population of CD5+ T cells, B cells, and/or NK cells) that cross-react with a self antigen in the case of treating an autoimmune disorder directly, or a non-self antigen expressed by hematopoietic stem cells (e.g., a non-self MHC antigen) prior to hematopoietic stem cell transplantation in the case of treating an autoimmune disease by administration an anti-CD2 ADC or an anti-CD5 ADC, and a hematopoietic stem cell graft. Additional beneficial results include an increase in the cell count or relative concentration of hematopoietic stem cells in a patient in need of a hematopoietic stem cell transplant following conditioning therapy and subsequent administration of an exogenous hematopoietic stem cell graft to the patient. Beneficial results of therapy described herein may also include an increase in the cell count or relative concentration of one or more cells of hematopoietic lineage, such as a megakaryocyte, thrombocyte, platelet, erythrocyte, mast cell, myeloblast, basophil, neutrophil, eosinophil, microglial cell, granulocyte, monocyte, osteoclast, antigen-presenting cell, macrophage, dendritic cell, natural killer cell, T lymphocyte, or B lymphocyte, following conditioning therapy and subsequent hematopoietic stem cell transplant therapy. In certain embodiments, a patient is diagnosed with a disorder and then treated with the therapeutic agent, e.g., an anti-CD5 ADC. In other embodiments, a patient is at risk for developing a disorder, e.g., GVHD, so is treated as a preventative measure in order to reduce the risk of developing the disorder or lessen the symptoms of the disorder.

As used herein, the terms "variant" and "derivative" are used interchangeably and refer to naturally-occurring, synthetic, and semi-synthetic analogues of a compound, peptide, protein, or other substance described herein. A variant or derivative of a compound, peptide, protein, or other substance described herein may retain or improve upon the biological activity of the original material.

As used herein, the term "vector" includes a nucleic acid vector, such as a plasmid, a DNA vector, a plasmid, a RNA vector, virus, or other suitable replicon. Expression vectors described herein may contain a polynucleotide sequence as well as, for example, additional sequence elements used for the expression of proteins and/or the integration of these polynucleotide sequences into the genome of a mammalian cell. Certain vectors that can be used for the expression of antibodies and antibody fragments used herein include plasmids that contain regulatory sequences, such as promoter and enhancer regions, which direct gene transcription. Other useful vectors for expression of antibodies and antibody fragments contain polynucleotide sequences that enhance the rate of translation of these genes or improve the stability or nuclear export of the mRNA that results from gene transcription. These sequence elements may include, for example, 5' and 3' untranslated regions and a polyadenylation signal site in order to direct efficient transcription of the gene carried on the expression vector. The expression vectors described herein may also contain a polynucleotide encoding a marker for selection of cells that contain such a vector. Examples of a suitable marker include genes that encode resistance to antibiotics, such as ampicillin, chloramphenicol, kanamycin, and nourseothricin.

As used herein, the term "alkyl" refers to a straight- or branched-chain alkyl group having, for example, from 1 to 20 carbon atoms in the chain. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and the like.

As used herein, the term "alkylene" refers to a straight- or branched-chain divalent alkyl group. The divalent positions may be on the same or different atoms within the alkyl chain. Examples of alkylene include methylene, ethylene, propylene, isopropylene, and the like.

As used herein, the term "heteroalkyl" refers to a straight or branched-chain alkyl group having, for example, from 1 to 20 carbon atoms in the chain, and further containing one or more heteroatoms (e.g., oxygen, nitrogen, or sulfur, among others) in the chain.

As used herein, the term "heteroalkylene" refers to a straight- or branched-chain divalent heteroalkyl group. The divalent positions may be on the same or different atoms within the heteroalkyl chain. The divalent positions may be one or more heteroatoms.

As used herein, the term "alkenyl" refers to a straight- or branched-chain alkenyl group having, for example, from 2 to 20 carbon atoms in the chain. Examples of alkenyl groups include vinyl, propenyl, isopropenyl, butenyl, tert-butenyl, hexenyl, and the like.

As used herein, the term "alkenylene" refers to a straight- or branched-chain divalent

alkenyl group. The divalent positions may be on the same or different atoms within the alkenyl chain. Examples of alkenylene include ethenylene, propenylene, isopropenylene, butenylene, and the like.

As used herein, the term "heteroalkenyl" refers to a straight- or branched-chain alkenyl group having, for example, from 2 to 20 carbon atoms in the chain, and further containing one or more heteroatoms (e.g., oxygen, nitrogen, or sulfur, among others) in the chain.

As used herein, the term "heteroalkenylene" refers to a straight- or branched-chain divalent heteroalkenyl group. The divalent positions may be on the same or different atoms within the heteroalkenyl chain. The divalent positions may be one or more heteroatoms.

As used herein, the term "alkynyl" refers to a straight- or branched-chain alkynyl group having, for example, from 2 to 20 carbon atoms in the chain. Examples of alkynyl groups include propargyl, butynyl, pentynyl, hexynyl, and the like.

As used herein, the term "alkynylene" refers to a straight- or branched-chain divalent alkynyl group. The divalent positions may be on the same or different atoms within the alkynyl chain.

As used herein, the term "heteroalkynyl" refers to a straight- or branched-chain alkynyl group having, for example, from 2 to 20 carbon atoms in the chain, and further containing one or more heteroatoms (e.g., oxygen, nitrogen, or sulfur, among others) in the chain.

As used herein, the term "heteroalkynylene" refers to a straight- or branched-chain divalent heteroalkynyl group. The divalent positions may be on the same or different atoms within the heteroalkynyl chain. The divalent positions may be one or more heteroatoms.

As used herein, the term "cycloalkyl" refers to a monocyclic, or fused, bridged, or spiro polycyclic ring structure that is saturated and has, for example, from 3 to 12 carbon ring atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[3.1.0]hexane, and the like.

As used herein, the term "cycloalkylene" refers to a divalent cycloalkyl group. The divalent positions may be on the same or different atoms within the ring structure. Examples of cycloalkylene include cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, and the like.

As used herein, the term "heterocycloalkyl" refers to a monocyclic, or fused, bridged, or spiro polycyclic ring structure that is saturated and has, for example, from 3 to 12 ring atoms per ring structure selected from carbon atoms and heteroatoms selected from, e.g., nitrogen, oxygen, and sulfur, among others. The ring structure may contain, for example, one or more oxo groups on carbon, nitrogen, or sulfur ring members. Examples of heterocycloalkyls include by way of example and not limitation dihydropyridyl, tetrahydropyridyl (piperidyl), tetrahydrothiophenyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, tetrahydrofuranyl, tetrahydropyranyl, bis-tetrahydropyranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, piperazinyl, quinuclidinyl, and morpholinyl.

As used herein, the term "heterocycloalkylene" refers to a divalent heterocycloalkyl group. The divalent positions may be on the same or different atoms within the ring structure.

As used herein, the term "aryl" refers to a monocyclic or polycyclic aromatic ring system containing, for example, from 6 to 19 carbon atoms. Aryl groups include, but are not limited to, phenyl, fluorenyl, naphthyl, and the like. The divalent positions may be one or more heteroatoms.

As used herein, the term "arylene" refers to a divalent aryl group. The divalent positions may be on the same or different atoms.

As used herein, the term "heteroaryl" refers to a monocyclic heteroaromatic, or a bicyclic or a tricyclic fused-ring heteroaromatic group in which one or more ring atoms is a heteroatom, e.g., nitrogen, oxygen, or sulfur. Heteroaryl groups include pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, 3H-indolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, quinoliziny, quinazolinyl, pthalazinyl, quinoxaliny, cinnoliny, naphthyridiny, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolyl, isoquinolyl, tetrazolyl, 5,6,7,8-tetrahydroquinolyl, 5,6,7,8-tetrahydroisoquinolyl, purinyl, pteridinyl, carbazolyl, xanthenyl, benzoquinolyl, and the like.

As used herein, the term "heteroarylene" refers to a divalent heteroaryl group. The divalent positions may be on the same or different atoms. The divalent positions may be one or more heteroatoms.

Unless otherwise constrained by the definition of the individual substituent, the foregoing chemical moieties, such as "alkyl", "alkylene", "heteroalkyl", "heteroalkylene", "alkenyl", "alkenylene", "heteroalkenyl", "heteroalkenylene", "alkynyl", "alkynylene", "heteroalkynyl", "heteroalkynylene", "cycloalkyl", "cycloalkylene", "heterocycloalkyl", "heterocycloalkylene", "aryl", "arylene", "heteroaryl", and "heteroarylene" groups can optionally be substituted with, for example, from 1 to 5 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkyl aryl, alkyl heteroaryl, alkyl cycloalkyl, alkyl heterocycloalkyl, amino, ammonium, acyl, acyloxy, acylamino, aminocarbonyl, alkoxycarbonyl, ureido, carbamate, aryl, heteroaryl, sulfinyl, sulfonyl, alkoxy, sulfanyl, halogen, carboxy, trihalomethyl, cyano, hydroxy, mercapto, nitro, and the like. Typical substituents include, but are not limited to, -X, -R, -OH, -OR, -SH, -SR, NH₂, -NHR, -N(R)₂, -N⁺(R)₃, -CX₃, -CN, -OCN, -SCN, -NCO, -NCS, -NO, -NO₂, -N₃, -NC(=O)H, -NC(=O)R, -C(=O)H, -C(=O)R, -C(=O)NH₂, -C(=O)N(R)₂, -SO₃⁻, -SO₃H, -S(=O)₂R, -OS(=O)₂OR, -S(=O)₂NH₂, -S(=O)₂N(R)₂, -S(=O)R, -OP(=O)(OH)₂, -OP(=O)(OR)₂, -P(=O)(OR)₂, -PO₃, -PO₃H₂, -C(=O)X, -C(=S)R, -CO₂H, -CO₂R, -CO₂⁻, -C(=S)OR, -C(=O)SR, -C(=S)SR, -C(=O)NH₂, -C(=O)N(R)₂, -C(=S)NH₂, -C(=S)N(R)₂, -C(=NH)NH₂, and -C(=NR)N(R)₂; wherein each X is independently selected for each occasion from F, Cl, Br, and I; and each R is independently selected for each occasion from alkyl, aryl, heterocycloalkyl or heteroaryl, protecting group and

prodrug moiety. Wherever a group is described as "optionally substituted," that group can be substituted with one or more of the above substituents, independently for each occasion. The substitution may include situations in which neighboring substituents have undergone ring closure, such as ring closure of vicinal functional substituents, to form, for instance, lactams, lactones, cyclic anhydrides, acetals, hemiacetals, thioacetals, amins, and hemiaminals, formed by ring closure, for example, to furnish a protecting group.

It is to be understood that certain radical naming conventions can include either a mono-radical or a di-radical, depending on the context. For example, where a substituent requires two points of attachment to the rest of the molecule, it is understood that the substituent is a di-radical. For example, a substituent identified as alkyl that requires two points of attachment includes di-radicals such as $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, and the like. Other radical naming conventions clearly indicate that the radical is a di-radical such as "alkylene," "alkenylene," "arylene," "heterocycloalkylene," and the like.

Wherever a substituent is depicted as a di-radical (*i.e.*, has two points of attachment to the rest of the molecule), it is to be understood that the substituent can be attached in any directional configuration unless otherwise indicated.

Anti-CD2 Antibody Drug Conjugates

Compositions and methods described herein are based in part on the discovery that anti-CD2 ADCs can be used to treat cancers and autoimmune diseases directly, for instance, due to the ability of such agents to kill CD2⁺ cancer cells (e.g., CD2⁺ leukemic cells) and CD2⁺ autoimmune cells (e.g., CD2⁺ autoimmune T cells and/or NK cells). In particular, an anti-CD2 antibody is conjugated to a cytotoxin via a linker. Thus, where anti-CD2 antibodies are described, conjugates thereof are also contemplated unless otherwise indicated.

Compositions and methods described herein are also based in part on the discovery that ADCs capable of binding CD2 can be used as therapeutic agents to promote the engraftment of transplanted hematopoietic stem cells in a patient in need of transplant therapy by preventing or reducing the likelihood of immune cell-mediated graft rejection. For instance, anti-CD2 antibodies, and antigen binding fragments, can bind cell-surface CD2 expressed by immune cells such as T cells or NK cells that cross-react with, and mount an immune response against, one or more non-self hematopoietic stem cell antigens, such as one or more non-self MHC antigens expressed by the hematopoietic stem cells. The binding of such antibodies, and antigen-binding fragments, to hematopoietic stem cell-specific CD2⁺ immune cells can induce death of the bound immune cell, for instance, by antibody-dependent cell-mediated cytotoxicity or by the action of a cytotoxic agent that is conjugated to the antibody, or the antigen-binding fragment thereof. The depletion of a population of CD2⁺ immune cells that cross-react with non-self hematopoietic stem cells can thus facilitate the engraftment of hematopoietic stem cell transplants in a patient in need thereof by

attenuating the ability of the recipient's immune system to mount an immune response against the incoming graft. In this way, a patient suffering from a stem cell disorder, cancer, autoimmune disease, or other blood disorder described herein can be treated, as a hematopoietic stem cell transplant can be provided to a subject in order to repopulate a lineage of cells that is defective and/or deficient in the subject. The subject may be deficient in a population of cells due to, for instance, chemotherapy that has been administered to the subject with the aim of eradicating cancerous cells but that has, in the process, depleted healthy hematopoietic cells as well.

For example, in certain embodiments provided are compositions and methods of promoting the engraftment of transplanted hematopoietic stem cells by administration of an antibody, or an antigen-binding fragment thereof, capable of binding an antigen expressed by T cells. This administration can cause the selective depletion of a population of endogenous T cells, such as CD4+ and CD8+ T cells. This selective depletion of T cells can, in turn, prevent graft rejection following transplantation of an exogenous (for instance, an autologous, allogeneic, or syngeneic) hematopoietic stem cell graft. For instance, the selective depletion of CD4+ and/or CD8+ T cells using an anti-CD2 antibody, antigen-binding fragment, antibody-drug conjugate, or antibody-drug conjugate as described herein can attenuate a T cell-mediated immune response that may occur against a transplanted hematopoietic stem cell graft. Compositions and methods disclosed herein are also based in part on the discovery that antibodies, and antigen-binding fragments thereof, capable of binding CD2 can be administered to a patient in need of hematopoietic stem cell transplant therapy in order to promote the survival and engraftment potential of transplanted hematopoietic stem cells.

Engraftment of hematopoietic stem cell transplants due to the administration of anti-CD2 antibodies, or antigen-binding fragments thereof, can manifest in a variety of empirical measurements. For instance, engraftment of transplanted hematopoietic stem cells can be evaluated by assessing the quantity of competitive repopulating units (CRU) present within the bone marrow of a patient following administration of an antibody or antigen-binding fragment thereof capable of binding CD2 and subsequent administration of a hematopoietic stem cell transplant. Additionally, one can observe engraftment of a hematopoietic stem cell transplant by incorporating a reporter gene, such as an enzyme that catalyzes a chemical reaction yielding a fluorescent, chromophoric, or luminescent product, into a vector with which the donor hematopoietic stem cells have been transfected and subsequently monitoring the corresponding signal in a tissue into which the hematopoietic stem cells have homed, such as the bone marrow. One can also observe hematopoietic stem cell engraftment by evaluation of the quantity and survival of hematopoietic stem and progenitor cells, for instance, as determined by fluorescence activated cell sorting (FACS) analysis methods known in the art. Engraftment can also be determined by measuring white blood cell counts in peripheral blood during a post-transplant

period, and/or by measuring recovery of marrow cells by donor cells in a bone marrow aspirate sample.

The sections that follow provide a description of antibodies, or antigen-binding fragments thereof, that can be administered to a patient in need of hematopoietic stem cell transplant therapy in order to promote engraftment of hematopoietic stem cell grafts, as well as methods of administering such therapeutics to a patient prior to hematopoietic stem cell transplantation.

Anti-CD2 Antibodies

Compositions and methods described herein include an antibody, or fragment thereof, that specifically binds to human CD2. Human CD2 is also referred to as T-cell Surface Antigen T11/Leu-5, T11, CD2 antigen (p50), and Sheep Red Blood Cell Receptor (SRBC). CD2 is expressed on T cells. Two isoforms of human CD2 have been identified. Isoform 1 contains 351 amino acids is described in Seed, B. et al. (1987) 84: 3365-69 (see also Sewell et al. (1986) 83: 8718-22) and below (NCBI Reference Sequence: NP_001758.2):

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msfpckfvas fllifnvssk gavskeitna letwgalgqd inldipsfgm sddiddikwe
ktsdkkkiaq frkeketfke kdtyklfkng tlkikhktd dqdiykvsy dtkgknvlek
ifdlkigerv skpkiswtci nttltcevmn gtdpelnyq dgkhlklsqr vithkwttsl
sakfkctagn kvskessvep vscpekgldi yliigicggg sllmvfvall vfyitkrkkq
rsrrndeele trahrivatee rgrkphqipa stpqnpatsq hpppppghrs qapshrp PPP
ghrvqhqpqk rppapsgtqv hqqkgpplpr prvpkpphg aaenslspss n (SEQ ID NO: 13)
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A second isoform of CD2 is 377 amino acids and is identified herein as NCBI Reference Sequence: NP_001315538.1.

T cells and NK cells have been shown to express CD2, which is a cell adhesion molecule and specific marker for such lymphocytes. For instance, CD2 interacts with other adhesion molecules, such as lymphocyte function-associated antigen-3 (LFA-3/CD58), to potentiate T cell activation. Antibodies and antigen-binding fragments thereof capable of binding CD2 may suppress T cell activation and T cell-mediated immune responses against hematopoietic stem cell grafts, for example, by inhibiting the interaction between CD2 and LFA-3. Antibodies and antigen-binding fragments thereof that bind to this cell-surface antigen can be identified using techniques known in the art and described herein, including immunization, computational modeling techniques, and in vitro selection methods, such as the phage display and cell-based display platforms described below.

Described herein are antibodies, and antigen-binding fragments thereof, that specifically bind to a CD2 polypeptide, e.g., a human CD2 polypeptide, and uses thereof. In an exemplary embodiment, the antibody, or antigen-binding fragment thereof, that specifically binds to a CD2 polypeptide comprises a heavy chain variable region and a light chain variable region.

In one embodiment, the heavy chain variable region comprises one or more complementarity determining regions (CDRs). In one embodiment, the heavy chain variable

region comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:1. In one embodiment, the heavy chain variable region comprises a VH CDR2 comprising the amino acid sequence of SEQ ID NO:2. In one embodiment, the heavy chain variable region comprises a VH CDR3 comprising the amino acid sequence of SEQ ID NO:3. In one embodiment, the heavy chain variable region comprises one or more VH CDRs selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3. In one embodiment, the heavy chain variable region comprises two or more VH CDRs selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3. In one embodiment, the heavy chain variable region comprises a VH CDR1 comprising SEQ ID NO:1, a VH CDR2 comprising SEQ ID NO:2, and a VH CDR3 comprising SEQ ID NO:3.

In one embodiment, the light chain variable region comprises one or more complementarity determining regions (CDRs). In one embodiment, the light chain variable region comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:4. In one embodiment, the light chain variable region comprises a VL CDR2 comprising the amino acid sequence of SEQ ID NO:5. In one embodiment, the light chain variable region comprises a VL CDR3 comprising the amino acid sequence of SEQ ID NO:6. In one embodiment, the light chain variable region comprises one or more VL CDRs selected from the group consisting of SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6. In one embodiment, the light chain variable region comprises two or more VL CDRs selected from the group consisting of SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6. In one embodiment, the light chain variable region comprises a VL CDR1 comprising SEQ ID NO:4, a VL CDR2 comprising SEQ ID NO:5, and a VL CDR3 comprising SEQ ID NO:6.

In an exemplary embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises a VH CDR1 comprising SEQ ID NO:1, a VH CDR2 comprising SEQ ID NO:2, and a VH CDR3 comprising SEQ ID NO:3, and a light chain variable region that comprises a VL CDR1 comprising SEQ ID NO:4, a VL CDR2 comprising SEQ ID NO:5, and a VL CDR3 comprising SEQ ID NO:6.

In certain embodiments, one or more of the CDRs (i.e., one or more heavy chain CDRs having SEQ ID NOs: 1-3, and/or one or more light chain CDRs having SEQ ID NOs: 4-6) can comprise a conservative amino acid substitution (or 2, 3, 4, or 5 amino acid substitutions) while retaining the CD2 specificity of the antibody (i.e., specificity similar to an antibody, or antigen-binding fragment thereof, comprising heavy chain CDRs of SEQ ID NOs: 1 to 3, and light chain CDRs of SEQ ID NOs: 4 to 6).

In one embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 7. In another embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises an amino acid sequence having at least 95% identity to SEQ ID NO: 7, e.g., at least 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 7. In certain

embodiments, an antibody comprises a modified heavy chain (HC) variable region comprising an HC variable domain comprising SEQ ID NO: 7, or a variant of SEQ ID NO: 7, which variant (i) differs from SEQ ID NO: 7 in 1, 2, 3, 4 or 5 amino acids substitutions, additions or deletions; (ii) differs from SEQ ID NO: 7 in at most 5, 4, 3, 2, or 1 amino acids substitutions, additions or deletions; (iii) differs from SEQ ID NO: 7 in 1-5, 1-3, 1-2, 2-5 or 3-5 amino acids substitutions, additions or deletions and/or (iv) comprises an amino acid sequence that is at least about 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 7, wherein in any of (i)-(iv), an amino acid substitution may be a conservative amino acid substitution or a non-conservative amino acid substitution; and wherein the modified heavy chain variable region can have an enhanced biological activity relative to the heavy chain variable region of SEQ ID NO: 7, while retaining the CD2 binding specificity of the antibody, i.e. has a binding specificity similar to an antibody, or antigen-binding fragment thereof, comprising SEQ ID NO: 7. In one embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that differs from the amino acid sequence set forth in SEQ ID NO: 7 at one, two, three or four amino acids. For example, the antibody, or antigen-binding fragment thereof, can comprise a heavy chain variable region that differs from the amino acid sequence set forth in SEQ ID NO: 7 at one, two, three, or four of positions 12, 13, 28, and/or 48. In one embodiment, the heavy chain variable region differs from the amino acid sequence set forth in SEQ ID NO: 7 at positions 12, 13, 28, and 48. In one embodiment, the heavy chain variable region comprises one, two, three, or four of the following substitutions with respect to the sequence set forth in SEQ ID NO: 7: K12Q; K13R; T28I; and M48V. In one embodiment, the heavy chain variable region comprises the substitutions K12Q; K13R; T28I; and M48V with respect to SEQ ID NO: 7.

In one embodiment, the antibody, or antigen-binding fragment thereof, comprises a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 8. In another embodiment, the antibody, or antigen-binding fragment thereof, comprises a light chain variable region that comprises an amino acid sequence having at least 95% identity to SEQ ID NO: 8, e.g., at least 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 8. In certain embodiments, an antibody comprises a modified light chain (LC) variable region comprising an LC variable domain comprising SEQ ID NO: 8, or a variant of SEQ ID NO: 8, which variant (i) differs from SEQ ID NO: 8 in 1, 2, 3, 4 or 5 amino acids substitutions, additions or deletions; (ii) differs from SEQ ID NO: 8 in at most 5, 4, 3, 2, or 1 amino acids substitutions, additions or deletions; (iii) differs from SEQ ID NO: 8 in 1-5, 1-3, 1-2, 2-5 or 3-5 amino acids substitutions, additions or deletions and/or (iv) comprises an amino acid sequence that is at least about 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 8, wherein in any of (i)-(iv), an amino acid substitution may be a conservative amino acid substitution or a non-conservative amino acid substitution; and wherein the modified light chain variable region can have an enhanced biological activity relative to the light chain variable region of SEQ ID NO: 8, while retaining the CD2 binding

specificity of the antibody, i.e., has a binding specificity similar to an antibody, or antigen-binding fragment thereof, comprising SEQ ID NO:8.

In an exemplary embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises an amino acid sequence having at least 95% identity to SEQ ID NO: 7, e.g., at least about 95%, about 96%, about 97%, about 98%, about 99%, or 100% identity to SEQ ID NO: 7, and a light chain variable region that comprises an amino acid sequence having at least about 95% identity to SEQ ID NO:8, e.g., at least about 95%, about 96%, about 97%, about 98%, about 99%, or 100% identity to SEQ ID NO:8. In one embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises SEQ ID NO: 7, and a light chain variable region that comprises SEQ ID NO:8. In one embodiment, the antibody is an Ab1 antibody that comprises a heavy chain variable region comprising SEQ ID NO:7, and a light chain variable region comprising SEQ ID NO:8.

In one embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO:9. In another embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises an amino acid sequence having at least 95% identity to SEQ ID NO:9, e.g., at least about 95%, about 96%, about 97%, about 98%, about 99%, or 100% identity to SEQ ID NO:9. In an exemplary embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises an amino acid sequence having at least 95% identity to SEQ ID NO:9, e.g., at least about 95%, about 96%, about 97%, about 98%, about 99%, or 100% identity to SEQ ID NO:9, and a light chain variable region that comprises an amino acid sequence having at least about 95% identity to SEQ ID NO:10, e.g., at least about 95%, about 96%, about 97%, about 98%, about 99%, or 100% identity to SEQ ID NO:10. In one embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises SEQ ID NO:9, and a light chain variable region that comprises SEQ ID NO:10. In one embodiment, the antibody is an Ab1a antibody that comprises a heavy chain variable region comprising SEQ ID NO:9, and a light chain variable region comprising SEQ ID NO:10.

In one embodiment, the heavy chain variable region comprises one or more complementarity determining regions (CDRs). In one embodiment, the heavy chain variable region comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:14. In one embodiment, the heavy chain variable region comprises a VH CDR2 comprising the amino acid sequence of SEQ ID NO:15. In one embodiment, the heavy chain variable region comprises a VH CDR3 comprising the amino acid sequence of SEQ ID NO:16. In one embodiment, the heavy chain variable region comprises one or more VH CDRs selected from the group consisting of SEQ ID NO:14, SEQ ID NO:15, and SEQ ID NO:16. In one embodiment, the heavy chain variable region comprises two or more VH CDRs selected from the group consisting of SEQ ID NO:14,

SEQ ID NO:15, and SEQ ID NO:16. In one embodiment, the heavy chain variable region comprises a VH CDR1 comprising SEQ ID NO:14, a VH CDR2 comprising SEQ ID NO:15, and a VH CDR3 comprising SEQ ID NO:16.

5 In one embodiment, the heavy chain variable region comprises one or more complementarity determining regions (CDRs). In one embodiment, the heavy chain variable region comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:14. In one embodiment, the heavy chain variable region comprises a VH CDR2 comprising the amino acid sequence of SEQ ID NO:15. In one embodiment, the heavy chain variable region comprises a VH CDR3 comprising the amino acid sequence of SEQ ID NO:17. In one embodiment, the heavy chain variable region comprises one or more VH CDRs selected from the group consisting of SEQ ID NO:14, SEQ ID NO:15, and SEQ ID NO:17. In one embodiment, the heavy chain variable region comprises two or more VH CDRs selected from the group consisting of SEQ ID NO:14, SEQ ID NO:15, and SEQ ID NO:17. In one embodiment, the heavy chain variable region comprises a VH CDR1 comprising SEQ ID NO:14, a VH CDR2 comprising SEQ ID NO:15, and a
15 VH CDR3 comprising SEQ ID NO:17.

In one embodiment, the light chain variable region comprises one or more complementarity determining regions (CDRs). In one embodiment, the light chain variable region comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:18. In one embodiment, the light chain variable region comprises a VL CDR2 comprising the amino acid sequence of SEQ ID NO:19. In
20 one embodiment, the light chain variable region comprises a VL CDR3 comprising the amino acid sequence of SEQ ID NO:20. In one embodiment, the light chain variable region comprises one or more VL CDRs selected from the group consisting of SEQ ID NO:18, SEQ ID NO:19, and SEQ ID NO:20. In one embodiment, the light chain variable region comprises two or more VL CDRs selected from the group consisting of SEQ ID NO:18, SEQ ID NO:19, and SEQ ID NO:20. In one
25 embodiment, the light chain variable region comprises a VL CDR1 comprising SEQ ID NO:18, a VL CDR2 comprising SEQ ID NO:19, and a VL CDR3 comprising SEQ ID NO:20.

In an exemplary embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises a VH CDR1 comprising SEQ ID NO:14, a VH CDR2 comprising SEQ ID NO:15, and a VH CDR3 comprising SEQ ID NO:16, and a light chain variable
30 region that comprises a VL CDR1 comprising SEQ ID NO:18, a VL CDR2 comprising SEQ ID NO:19, and a VL CDR3 comprising SEQ ID NO:20.

In an exemplary embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises a VH CDR1 comprising SEQ ID NO:14, a VH CDR2 comprising SEQ ID NO:15, and a VH CDR3 comprising SEQ ID NO:17, and a light chain variable
35 region that comprises a VL CDR1 comprising SEQ ID NO:18, a VL CDR2 comprising SEQ ID NO:19, and a VL CDR3 comprising SEQ ID NO:20.

In certain embodiments, one or more of the CDRs (i.e., one or more heavy chain CDRs having SEQ ID NOs: 14-17, and/or one or more light chain CDRs having SEQ ID NOs: 18-19) can comprise a conservative amino acid substitution (or 2, 3, 4, or 5 amino acid substitutions) while retaining the CD2 specificity of the antibody (i.e., specificity similar to an antibody, or antigen-binding fragment thereof, comprising heavy chain CDRs of SEQ ID NOs: 14 to 16, and light chain CDRs of SEQ ID NOs: 18 to 20; or comprising heavy chain CDRs of SEQ ID NOs: 14, 15, 17, and light chain CDRs of SEQ ID NOs: 18 to 20).

In one embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 21. In another embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises an amino acid sequence having at least about 95% identity to SEQ ID NO: 21, e.g., at least about 95%, about 96%, about 97%, about 98%, about 99%, or 100% identity to SEQ ID NO: 21. In certain embodiments, an antibody comprises a modified heavy chain (HC) variable region comprising an HC variable domain comprising SEQ ID NO: 21, or a variant of SEQ ID NO: 21, which variant (i) differs from SEQ ID NO: 21 in 1, 2, 3, 4 or 5 amino acids substitutions, additions or deletions; (ii) differs from SEQ ID NO: 21 in at most 5, 4, 3, 2, or 1 amino acids substitutions, additions or deletions; (iii) differs from SEQ ID NO: 21 in 1-5, 1-3, 1-2, 2-5 or 3-5 amino acids substitutions, additions or deletions and/or (iv) comprises an amino acid sequence that is at least about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98% or about 99% identical to SEQ ID NO: 21, wherein in any of (i)-(iv), an amino acid substitution may be a conservative amino acid substitution or a non-conservative amino acid substitution; and wherein the modified heavy chain variable region can have an enhanced biological activity relative to the heavy chain variable region of SEQ ID NO: 21, while retaining the CD2 binding specificity of the antibody, i.e. has a binding specificity similar to an antibody, or antigen-binding fragment thereof, comprising SEQ ID NO: 21.

In one embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 22. In another embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises an amino acid sequence having at least about 95% identity to SEQ ID NO: 22, e.g., at least about 95%, about 96%, about 97%, about 98%, about 99%, or 100% identity to SEQ ID NO: 22. In certain embodiments, an antibody comprises a modified heavy chain (HC) variable region comprising an HC variable domain comprising SEQ ID NO: 21, or a variant of SEQ ID NO: 22, which variant (i) differs from SEQ ID NO: 22 in 1, 2, 3, 4 or 5 amino acids substitutions, additions or deletions; (ii) differs from SEQ ID NO: 22 in at most 5, 4, 3, 2, or 1 amino acids substitutions, additions or deletions; (iii) differs from SEQ ID NO: 22 in 1-5, 1-3, 1-2, 2-5 or 3-5 amino acids substitutions, additions or deletions and/or (iv) comprises an amino acid sequence that is at least about 75%, about 80%, about 85%, about 90%, about 95%, about 96%,

about 97%, about 98% or about 99% identical to SEQ ID NO: 22, wherein in any of (i)-(iv), an amino acid substitution may be a conservative amino acid substitution or a non-conservative amino acid substitution; and wherein the modified heavy chain variable region can have an enhanced biological activity relative to the heavy chain variable region of SEQ ID NO: 22, while retaining the CD2 binding specificity of the antibody, i.e. has a binding specificity similar to an antibody, or antigen-binding fragment thereof, comprising SEQ ID NO: 22.

In one embodiment, the antibody, or antigen-binding fragment thereof, comprises a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO:23. In another embodiment, the antibody, or antigen-binding fragment thereof, comprises a light chain variable region that comprises an amino acid sequence having at least about 95% identity to SEQ ID NO:23, e.g., at least about 95%, about 96%, about 97%, about 98%, about 99%, or 100% identity to SEQ ID NO:23. In certain embodiments, an antibody comprises a modified light chain (LC) variable region comprising an LC variable domain comprising SEQ ID NO: 23, or a variant of SEQ ID NO: 23, which variant (i) differs from SEQ ID NO: 23 in 1, 2, 3, 4 or 5 amino acids substitutions, additions or deletions; (ii) differs from SEQ ID NO: 23 in at most 5, 4, 3, 2, or 1 amino acids substitutions, additions or deletions; (iii) differs from SEQ ID NO: 23 in 1-5, 1-3, 1-2, 2-5 or 3-5 amino acids substitutions, additions or deletions and/or (iv) comprises an amino acid sequence that is at least about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98% or about 99% identical to SEQ ID NO: 23, wherein in any of (i)-(iv), an amino acid substitution may be a conservative amino acid substitution or a non-conservative amino acid substitution; and wherein the modified light chain variable region can have an enhanced biological activity relative to the light chain variable region of SEQ ID NO:23, while retaining the CD2 binding specificity of the antibody, i.e., has a binding specificity similar to an antibody, or antigen-binding fragment thereof, comprising SEQ ID NO:23.

In an exemplary embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises an amino acid sequence having at least 95% identity to SEQ ID NO: 21, e.g., at least about 95%, about 96%, about 97%, about 98% or about 99%, or 100% identity to SEQ ID NO: 21, and a light chain variable region that comprises an amino acid sequence having at least about 95% identity to SEQ ID NO:23, e.g., at least about 95%, about 96%, about 97%, about 98% or about 99%, or 100% identity to SEQ ID NO:23. In one embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises SEQ ID NO: 21, and a light chain variable region that comprises SEQ ID NO:23.

In an exemplary embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises an amino acid sequence having at least about 95% identity to SEQ ID NO: 22, e.g., at least about 95%, about 96%, about 97%, about 98% or about 99%, or 100% identity to SEQ ID NO: 22, and a light chain variable region that comprises an amino

acid sequence having at least about 95% identity to SEQ ID NO:23, e.g., ., at least about 95%, about 96%, about 97%, about 98% or about 99%, or 100% identity to SEQ ID NO:23. In one embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises SEQ ID NO: 22, and a light chain variable region that comprises SEQ ID

Anti-CD2 antibodies that can be used in conjunction with the compositions and methods described herein include those that have one or more, or all, of the following CDRs:

- a. a CDR-H1 having the amino acid sequence EYYMY (SEQ ID NO: 1);
- b. a CDR-H2 having the amino acid sequence RIDPEDGSIDYVEKFKK (SEQ ID NO: 2);
- c. a CDR-H3 having the amino acid sequence GKFNYRFAY (SEQ ID NO: 3);
- d. a CDR-L1 having the amino acid sequence RSSQSLLHSSGNTYLN (SEQ ID NO: 4);
- e. a CDR-L2 having the amino acid sequence LVSKLES (SEQ ID NO: 5); and
- f. a CDR-L3 having the amino acid sequence MQFTHYPYT (SEQ ID NO: 6).

Antibodies and antigen-binding fragments thereof containing the foregoing CDR sequences are described, e.g., in US Patent No. 6,849,258, the disclosure of which is incorporated herein by reference as it pertains to anti-CD2 antibodies and antigen-binding fragments thereof.

The antibodies and fragments thereof disclosed in US Patent Nos. 5,730,979; 5,817,311;

5,951,983; and 7,592,006; such as LO-CD2a, BTI-322, and antibodies produced by the hybridoma cell line deposited as ATCC Deposit No. HB 11423 (e.g., antibodies or antigen-binding fragments thereof containing one or more, or all, of the CDR sequences of antibody LO-CD2a isolated from the hybridoma cell line deposited as ATCC Deposit No. HB 11423) can be used in conjunction with the compositions and methods disclosed herein. Exemplary antibodies that may be used in conjunction with the compositions and methods described herein include humanized antibodies containing one or more, or all, of the CDR sequences of an antibody isolated from the hybridoma cell line deposited as ATCC Deposit No. HB 11423, such as MEDI-507. MEDI-507 is a humanized anti-CD2 monoclonal antibody that contains the CDR-H and CDR-L sequences of (a) through (f) above, and is described in Branco et al., Transplantation 68:1588-1596 (1999). MEDI-507 is additionally described in WO99/03502A1 and WO1994/020619A1; U.S. Patent Nos. US7,592,006, US6,849,258, US5,951,983, US5,817,311, and US5,730,979; and U.S. Patent Publication Nos. US2011/0280868, US2004/0265315 and 2011/0091453, the disclosures of each of which are incorporated herein by reference as they pertain to anti-CD2 antibodies and antigen-binding fragments thereof, such as the anti-CD2 antibody MEDI-507. In one embodiment, the anti-CD2 antibody is Siplizumab, or an antigen-binding fragment thereof.

The disclosures of the foregoing scientific journal article and US Patents are incorporated herein by reference as they pertain to anti-CD2 antibodies and antigen-binding fragments thereof.

Other anti-CD2 antibodies that can be used in conjunction with the compositions and methods described herein include, for instance, anti-CD2 antibodies that are described in US Patent Nos. 6,541,611 and 7,250,167, the disclosures of each of which are incorporated herein by reference as they pertain to anti-CD2 antibodies and antigen-binding fragments thereof, such as the anti-CD2 antibody LO-CD2b and antibodies produced by the hybridoma cell line deposited as ATCC Deposit No. PTA-802. Exemplary antibodies that may be used in conjunction with the compositions and methods described herein include humanized antibodies containing one or more, or all, of the CDR sequences of an antibody isolated from the hybridoma cell line deposited as ATCC Deposit No. PTA-802.

Other anti-CD2 antibodies that can be used in conjunction with the compositions and methods described herein include, for instance, anti-CD2 antibodies that are described in US Patent Nos. 5,795,572 and 5,807,734, the disclosures of each of which are incorporated herein by reference as they pertain to anti-CD2 antibodies and antigen-binding fragments thereof, such as the anti-CD2 antibody produced by hybridoma cell line deposited as ATCC Deposit No. HB 69277. For instance, anti-CD2 antibodies and antigen-binding fragments thereof that may be used in conjunction with the compositions and methods described herein include those that contain a hinge region having an amino acid sequence of EPKSSDKTHTSPSP (SEQ ID NO: 287), such as scFv fragments containing a hinge region having the amino acid sequence of EPKSSDKTHTSPSP (SEQ ID NO: 287). The incorporation of a hinge region having the amino acid sequence of SEQ ID NO: 287 can be beneficial, as this hinge motif has been mutated relative to wild-type hinge region sequences so as to eliminate potentially reactive cysteine residues that may promote undesirable oxidative dimerization of a single-chain antibody fragment, such as a scFv fragment.

Other anti-CD2 antibodies that can be used in conjunction with the compositions and methods described herein include, for instance, anti-CD2 antibodies that are described in US Patent No. 6,764,688, such as the anti-CD2 antibody TS2/18 and antibodies produced by hybridoma cell line deposited as ATCC Deposit No. HB-195. The disclosure of US Patent No. 6,764,688 is incorporated herein by reference as it pertains to anti-CD2 antibodies and antigen-binding fragments thereof.

Other anti-CD2 antibodies that can be used in conjunction with the compositions and methods described herein include, for instance, anti-CD2 antibodies that are described in US Patent Nos. 6,162,432, 6,558,662, 7,408,039, 7,332,157, 7,638,121, 7,939,062, and 7,115,259, US Patent Application Publication No. 2006/0084107, 2014/0369974, 2002/0051784, and 2013/0183322, and PCT Publication No. WO1992/016563, the disclosures of each of which are incorporated herein by reference as they pertain to anti-CD2 antibodies and antigen binding fragments thereof.

Antibodies and fragments thereof for use in conjunction with the methods described herein

include variants of those antibodies described above, such as antibody fragments that contain or lack an Fc domain, as well as humanized variants of non-human antibodies described herein and antibody-like protein scaffolds (e.g., ¹⁰Fn3 domains) containing one or more, or all, of the CDRs or equivalent regions thereof of an antibody, or an antibody fragment, described herein. Exemplary antigen-binding fragments of the foregoing antibodies include 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, among others.

In one embodiment, the anti-CD2 antibody or binding fragment thereof, comprises a modified Fc region, wherein said modified Fc region comprises at least one amino acid modification relative to a wild-type Fc region, such that said molecule has an altered affinity for or binding to an FcγR (FcγR). Certain amino acid positions within the Fc region are known through crystallography studies to make a direct contact with FcγR. Specifically amino acids 234-239 (hinge region), amino acids 265-269 (B/C loop), amino acids 297-299 (C'/E loop), and amino acids 327-332 (F/G) loop. (see Sonderrmann et al., 2000 Nature, 406: 267-273). The antibodies described herein may comprise variant Fc regions comprising modification of at least one residue that makes a direct contact with an FcγR based on structural and crystallographic analysis. In one embodiment, the Fc region of the anti-CD2 antibody (or fragment thereof) comprises an amino acid substitution at amino acid 265 according to the EU index as in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, NH1, MD (1991), expressly incorporated herein by references. The "EU index as in Kabat" refers to the numbering of the human IgG1 EU antibody. In one embodiment, the Fc region comprises a D265A mutation. In one embodiment, the Fc region comprises a D265C mutation. In some embodiments, the Fc region of the antibody (or fragment thereof) comprises an amino acid substitution at amino acid 234 according to the EU index as in Kabat. In one embodiment, the Fc region comprises a L234A mutation. In some embodiments, the Fc region of the anti-CD2 antibody (or fragment thereof) comprises an amino acid substitution at amino acid 235 according to the EU index as in Kabat. In one embodiment, the Fc region comprises a L235A mutation. In yet another embodiment, the Fc region comprises a L234A and L235A mutation. In a further embodiment, the Fc region comprises a D265C, L234A, and L235A mutation. In yet a further embodiment, the Fc region comprises a D265C, L234A, L235A, and H435A mutation. In a further embodiment, the Fc region comprises a D265C and H435A mutation.

The antibodies used herein may be further engineered to further modulate antibody half-life by introducing additional Fc mutations, such as those described for example in (Dall'Acqua et al. (2006) J Biol Chem 281: 23514-24), (Zalevsky et al. (2010) Nat Biotechnol 28: 157-9), (Hinton et al. (2004) J Biol Chem 279: 6213-6), (Hinton et al. (2006) J Immunol 176: 346-56), (Shields et al. (2001) J Biol Chem 276: 6591-604), (Petkova et al. (2006) Int Immunol 18: 1759-69), (Datta-

Mannan et al. (2007) Drug Metab Dispos 35: 86-94), (Vaccaro et al. (2005) Nat Biotechnol 23: 1283-8), (Yeung et al. (2010) Cancer Res 70: 3269-77) and (Kim et al. (1999) Eur J Immunol 29: 2819-25), and include positions 250, 252, 253, 254, 256, 257, 307, 376, 380, 428, 434 and 435. Exemplary mutations that may be made singularly or in combination are T250Q, M252Y, 1253A, S254T, T256E, P257I, T307A, D376V, E380A, M428L, H433K, N434S, N434A, N434H, N434F, H435A and H435R mutations.

In some embodiments, the anti-CD2 antibody or antigen-binding fragment thereof is conjugated to a cytotoxin (e.g., amatotoxin) by way of a cysteine residue in the Fc domain of the antibody or antigen-binding fragment thereof. In some embodiments, the cysteine residue is introduced by way of a mutation in the Fc domain of the antibody or antigen-binding fragment thereof. For instance, the cysteine residue may be selected from the group consisting of Cys118, Cys239, and Cys265. In one embodiment, the Fc region of the anti-CD2 antibody (or fragment thereof) comprises an amino acid substitution at amino acid 265 according to the EU index as in Kabat. In one embodiment, the Fc region comprises a D265C mutation. In one embodiment, the Fc region comprises a D265C and a H435A mutation.

Thus, in one embodiment, the Fc region comprises a mutation resulting in a decrease in half life. An antibody having a short half life may be advantageous in certain instances where the antibody is expected to function as a short-lived therapeutic, e.g., the conditioning step described herein where the antibody is administered followed by HSCs. Ideally, the antibody would be substantially cleared prior to delivery of the HSCs, which may also generally express CD2 but are not the target of the anti-CD2 antibody, unlike the endogenous stem cells. In one embodiment, the Fc region comprises a mutation at position 435 (EU index according to Kabat). In one embodiment, the mutation is an H435A mutation.

The foregoing anti-CD2 antibodies, or antigen-binding fragments thereof, can be used in various aspects set forth herein, including, for example, in methods for depletion of CD2+ cells in a human subject. The foregoing anti-CD2 antibodies, or antigen-binding fragments thereof, can also be conjugated to an agent, e.g., a cytotoxin, for example, an amatotoxin, as described herein.

Anti-CD5 Antibody Drug Conjugates

The present disclosure is also based in part on the discovery that anti-CD5 antibodies, or antigen-binding fragments thereof, or anti-CD5 ADCs can be used to treat cancers, such as T-cell malignancies, and autoimmune diseases directly, for instance, due to the ability of such agents to kill CD5+ cancer cells (e.g., CD5+ leukemic cells) and CD5+ autoimmune cells (e.g., CD5+ autoimmune T cells, B cells, and/or NK cells). Further, anti-CD5 ADCs can be used to treat patients at risk for graft versus host disease (GVHD)

In particular, an anti-CD5 antibody described herein is conjugated to a cytotoxin via a linker. Thus, where anti-CD5 antibodies are described, conjugates thereof are also contemplated

unless otherwise indicated.

Aspects of the disclosure described herein are additionally based in part on the discovery that antibodies, or antigen-binding fragments thereof, capable of binding CD5 can be used as therapeutic agents to promote the engraftment of transplanted hematopoietic stem cells in a patient in need of transplant therapy by preventing or reducing the likelihood of immune cell-mediated graft rejection. For instance, anti-CD5 antibodies, and antigen binding fragments, can bind cell-surface CD5 expressed by immune cells such as T cells, B cells, or NK cells that cross-react with, and mount an immune response against, non-self hematopoietic stem cell antigens, such as non-self MHC antigens expressed by a hematopoietic stem cell graft. The binding of such antibodies, and antigen-binding fragments, to hematopoietic stem cell-specific CD5+ immune cells can induce death of the bound immune cell, for instance, by antibody-dependent cell-mediated cytotoxicity or by the action of a cytotoxic agent that is conjugated to the antibody, or the antigen-binding fragment thereof.. The depletion of a population of CD5+ immune cells that cross-react with non-self hematopoietic stem cells can thus facilitate the engraftment of hematopoietic stem cell transplants in a patient in need thereof by attenuating the ability of the recipient's immune system to mount an immune response against the incoming graft. In this way, a patient suffering from a stem cell disorder, cancer, autoimmune disease, or other blood disorder described herein can be treated, as a hematopoietic stem cell transplant can be provided to a subject in order to repopulate a lineage of cells that is defective and/or deficient in the subject. The subject may be deficient in a population of cells due to, for instance, chemotherapy that has been administered to the subject with the aim of eradicating cancerous cells but that has, in the process, depleted healthy hematopoietic cells as well.

For example, described herein are compositions and methods for promoting the engraftment of transplanted hematopoietic stem cells by administration of an antibody, or an antigen-binding fragment thereof, or ADC capable of binding an antigen expressed by T cells. This administration can cause the selective depletion of a population of endogenous T cells, such as CD4+ and CD8+ T cells. This selective depletion of T cells can, in turn, prevent graft rejection following transplantation of an exogenous (for instance, an autologous, allogeneic, or syngeneic) hematopoietic stem cell graft. For instance, the selective depletion of CD4+ and/or CD8+ T cells using an anti-CD5 antibody, antigen-binding fragment, antibody-drug conjugate, or antibody-drug conjugate as described herein can attenuate a T cell-mediated immune response that may occur against a transplanted hematopoietic stem cell graft. Compositions and methods disclosed herein are based in part on the discovery that antibodies, and antigen-binding fragments thereof, capable of binding CD5 can be administered to a patient in need of hematopoietic stem cell transplant therapy in order to promote the survival and engraftment potential of transplanted hematopoietic stem cells.

Engraftment of hematopoietic stem cell transplants due to the administration of anti-CD5 antibodies, or antigen-binding fragments thereof, can manifest in a variety of empirical measurements. For instance, engraftment of transplanted hematopoietic stem cells can be evaluated by assessing the quantity of competitive repopulating units (CRU) present within the bone marrow of a patient following administration of an antibody or antigen-binding fragment thereof capable of binding CD5 and subsequent administration of a hematopoietic stem cell transplant. Additionally, one can observe engraftment of a hematopoietic stem cell transplant by incorporating a reporter gene, such as an enzyme that catalyzes a chemical reaction yielding a fluorescent, chromophoric, or luminescent product, into a vector with which the donor hematopoietic stem cells have been transfected and subsequently monitoring the corresponding signal in a tissue into which the hematopoietic stem cells have homed, such as the bone marrow. One can also observe hematopoietic stem cell engraftment by evaluation of the quantity and survival of hematopoietic stem and progenitor cells, for instance, as determined by fluorescence activated cell sorting (FACS) analysis methods known in the art. Engraftment can also be determined by measuring white blood cell counts in peripheral blood during a post-transplant period, and/or by measuring recovery of marrow cells by donor cells in a bone marrow aspirate sample.

The sections that follow provide a description of antibodies, or antigen-binding fragments thereof, that can be administered to treat an autoimmune disease, cancer, treat or prevent graft versus host disease (GVHD), or to treat a patient in need of hematopoietic stem cell transplant therapy in order to promote engraftment of hematopoietic stem cell grafts, as well as methods of administering such therapeutics to a patient prior to hematopoietic stem cell transplantation.

Anti-CD5 Antibodies

Compositions and methods described herein include an antibody, or fragment thereof, that specifically binds to human CD5. Human CD5 is also referred to as LEU1 or T1. Human CD5 is a type-I transmembrane glycoprotein found on the surface of thymocytes, T lymphocytes and a subset of B lymphocytes. Two isoforms of human CD5 have been identified. Isoform 1 contains 438 amino acids and is described in Jones. et al. (1988) *Nature* 323 (6086), 346-349 and below (NCBI Reference Sequence: NP_001333385.1):

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MVCSQSWGRS SKQWEDPSQASKVCQRLNCG VPLSLGPFLV TYTPQSSIICYGQL
GSFSNCSHSRNDMCHS LGLTCLEPQKTTPTTRPPPTTTPEPTAPP RLQLVAQSGG
QHCAGVVEFYSGSLGGTISY EAQDKTQDLE NFLCNNLQCG SFLKHLPETE AGRAQDPGEP
REHQPLPIQWKIQNSSCTSL EHCFRKIKPQ KSGRVLALLC SGFQPKVQSR LVGGSSICEG
TVEVRQGAQWAALCDSSSAR SSLRWEEVCR EQQCGSVNSY RVLDA GDPTS RGLFCPHQKL
SQCHELWERN SYCKKV FVTCQDPNPAGLAAGTVASIILAL VLLVLLVVC GPLAYKKLVK

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KFRQKKQRQWIGPTGMNQNM SFHRNHTATV RSHAENPTAS HVDNEYSQPP RNSHLSAYPA
LEGALHRSSMQPDNSSDSY DLHGAQRL (SEQ ID NO: 286)

T cells have been shown to express CD5, which is a cell adhesion molecule and has been
implicated both in the proliferative response of activated T cells and in T cell helper function. It has
also been shown to function as a receptor, delivering co-stimulatory signals to T cells by
interacting with CD72, a cell surface protein exclusive to B cells. Antibodies, or antigen-binding
fragments thereof, that bind CD5 may suppress T cell activation and T cell-mediated immune
responses against hematopoietic stem cell grafts, for example, by inhibiting the interaction
between CD5 and CD72. Antibodies, and antigen-binding fragments thereof, that bind CD5 can
also be used to kill CD5+ T cells directly, for instance, by conjugating the antibody, or antigen-
binding fragment thereof, to a cytotoxin (such as a cytotoxin described herein or known in the art)
or by using an unconjugated antibody, or antigen-binding fragment thereof, capable of recruiting
complement proteins to the T cell.

Additionally, subsets of activated B cells have been shown to express CD5, and this
expression pattern is particularly common among autoreactive B cells (Werner-Favre et al.,
European Journal of Immunology 19:1209-1231 (1989), the disclosure of which is incorporated
herein by reference in its entirety). CD5 has also been shown to be expressed by subsets of NK
cells; particularly among patients that have multiple myeloma have been shown to harbor
populations of low density CD5+ (CD5LOW+) NK cells, and this surface antigen has been
implicated in NK cell activation (Ishiyama et al., Anticancer Research 14:725-730 (1994), the
disclosure of which is incorporated herein by reference in its entirety). Antibodies, or antigen-
binding fragments thereof, that specifically bind CD5 can thus be used to attenuate the activation
of B cells and NK cells. Antibodies, or antigen-binding fragments thereof, that bind CD5 can also
be used to kill CD5+ B cells and NK cells directly, for instance, by conjugating the antibody, or
antigen-binding fragment thereof, to a cytotoxin (such as a cytotoxin described herein or known in
the art) or by using an unconjugated antibody, or antigen-binding fragment thereof, capable of
recruiting complement proteins to the B cell or NK cell.

Disclosed herein are antibodies, and antigen-binding fragments thereof, that specifically
bind to a CD5 polypeptide, e.g., a human CD5 polypeptide, and uses thereof. In an exemplary
embodiment, the antibody, or antigen-binding fragment thereof, that specifically binds to a CD5
polypeptide comprises a heavy chain variable region and a light chain variable region.

In one embodiment, the heavy chain variable region comprises one or more
complementarity determining regions (CDRs). In one embodiment, the heavy chain variable
region comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 42. In one
embodiment, the heavy chain variable region comprises a VH CDR2 comprising the amino acid
sequence of SEQ ID NO: 43. In one embodiment, the heavy chain variable region comprises a

VH CDR3 comprising the amino acid sequence of SEQ ID NO: 44. In one embodiment, the heavy chain variable region comprises one or more VH CDRs selected from the group consisting of SEQ ID NO: 42, SEQ ID NO: 43, and SEQ ID NO: 44. In one embodiment, the heavy chain variable region comprises two or more VH CDRs selected from the group consisting of SEQ ID NO: 42, SEQ ID NO: 43, and SEQ ID NO: 44. In one embodiment, the heavy chain variable region comprises a VH CDR1 comprising SEQ ID NO: 42, a VH CDR2 comprising SEQ ID NO: 43, and a VH CDR3 comprising SEQ ID NO: 44.

In one embodiment, the light chain variable region comprises one or more complementarity determining regions (CDRs). In one embodiment, the light chain variable region comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 45. In one embodiment, the light chain variable region comprises a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 46. In one embodiment, the light chain variable region comprises a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 47. In one embodiment, the light chain variable region comprises one or more VL CDRs selected from the group consisting of SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47. In one embodiment, the light chain variable region comprises two or more VL CDRs selected from the group consisting of SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47. In one embodiment, the light chain variable region comprises a VL CDR1 comprising SEQ ID NO: 45, a VL CDR2 comprising SEQ ID NO: 46, and a VL CDR3 comprising SEQ ID NO: 46.

In an exemplary embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises a VH CDR1 comprising SEQ ID NO: 42, a VH CDR2 comprising SEQ ID NO: 43, and a VH CDR3 comprising SEQ ID NO: 44, and a light chain variable region that comprises a VL CDR1 comprising SEQ ID NO: 45, a VL CDR2 comprising SEQ ID NO: 46, and a VL CDR3 comprising SEQ ID NO: 47.

In certain embodiments, one or more of the CDRs (*i.e.*, one or more heavy chain CDRs having SEQ ID NOs: 42-44, and/or one or more light chain CDRs having SEQ ID NOs: 45-47) can comprise a conservative amino acid substitution (or 2, 3, 4, or 5 amino acid substitutions) while retaining the CD5 specificity of the antibody (*i.e.*, specificity similar to an antibody, or antigen-binding fragment thereof, comprising heavy chain CDRs of SEQ ID NOs: 42 to 44, and light chain CDRs of SEQ ID NOs: 45 to 47).

In certain embodiments, the anti-CD5 antibody, or antigen binding fragment thereof, is murine antibody 5D7, or a humanized version thereof. Murine antibody 5D7 binds to human CD5 and is described in US Patent Publication No. 20008/0245027, the contents of which relating to the antibody sequences disclosed therein are incorporated by reference herein. SEQ ID Nos: 54 to 59 described in Table 5 correspond to the CDRs of murine anti-CD5 antibody 5D7. A humanized version of anti-CD5 antibody 5D7 is described in SEQ ID NO: 282 (humanized heavy chain variable region) and SEQ ID NO: 283 (humanized light chain variable region). In one embodiment, the ADCs and uses thereof described herein include an antibody comprising the

CDRs set forth in SEQ ID Nos: 54 to 59. In one embodiment, the ADCs and uses thereof described herein include an antibody comprising the heavy and light chain variable regions as set forth in SEQ ID Nos: 282 and 283, respectively.

In one embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy
5 chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 282. In another embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises an amino acid sequence having at least 95% identity to SEQ ID NO: 282, *e.g.*, at least 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 282. In certain embodiments, an antibody comprises a modified heavy chain (HC) variable region
10 comprising an HC variable domain comprising SEQ ID NO: 282, or a variant of SEQ ID NO: 282, which variant (i) differs from SEQ ID NO: 282 in 1, 2, 3, 4 or 5 amino acids substitutions, additions or deletions; (ii) differs from SEQ ID NO: 282 in at most 5, 4, 3, 2, or 1 amino acids substitutions, additions or deletions; (iii) differs from SEQ ID NO: 282 in 1-5, 1-3, 1-2, 2-5 or 3-5 amino acids substitutions, additions or deletions and/or (iv) comprises an amino acid sequence that is at least
15 about 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 282, wherein in any of (i)-(iv), an amino acid substitution may be a conservative amino acid substitution or a non-conservative amino acid substitution; and wherein the modified heavy chain variable region can have an enhanced biological activity relative to the heavy chain variable region of SEQ ID NO: 282, while retaining the CD5 binding specificity of the antibody, *i.e.* has a binding specificity similar
20 to an antibody, or antigen-binding fragment thereof, comprising SEQ ID NO: 282.

In one embodiment, the antibody, or antigen-binding fragment thereof, comprises a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 283. In another embodiment, the antibody, or antigen-binding fragment thereof, comprises a light chain variable region that comprises an amino acid sequence having at least 95% identity to SEQ ID
25 NO: 283, *e.g.*, at least 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 283. In certain embodiments, an antibody comprises a modified light chain (LC) variable region comprising an LC variable domain comprising SEQ ID NO: 283, or a variant of SEQ ID NO: 283, which variant (i) differs from SEQ ID NO: 283 in 1, 2, 3, 4 or 5 amino acids substitutions, additions or deletions; (ii) differs from SEQ ID NO: 283 in at most 5, 4, 3, 2, or 1 amino acids substitutions, additions or deletions; (iii) differs from SEQ ID NO: 283 in 1-5, 1-3, 1-2, 2-5 or 3-5 amino acids
30 substitutions, additions or deletions and/or (iv) comprises an amino acid sequence that is at least about 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 283, wherein in any of (i)-(iv), an amino acid substitution may be a conservative amino acid substitution or a non-conservative amino acid substitution; and wherein the modified light chain variable region can
35 have an enhanced biological activity relative to the light chain variable region of SEQ ID NO: 283, while retaining the CD5 binding specificity of the antibody, *i.e.*, has a binding specificity similar to an antibody, or antigen-binding fragment thereof, comprising SEQ ID NO: 283.

In an exemplary embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises an amino acid sequence having at least 95% identity to SEQ ID NO: 282, e.g., at least 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 282, and a light chain variable region that comprises an amino acid sequence having at least 95% identity to SEQ ID NO: 283, e.g., at least 95%, 96%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 283. In one embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises SEQ ID NO: 282, and a light chain variable region that comprises SEQ ID NO: 283.

In one embodiment, the anti-CD5 antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises SEQ ID NO: 288, and a light chain variable region that comprises SEQ ID NO: 289.

In one embodiment, the anti-CD5 antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises SEQ ID NO: 291, and a light chain variable region that comprises SEQ ID NO: 290.

In another embodiment, the anti-CD5 antibody, or antigen-binding fragment thereof, can contain a heavy chain variable region that comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 54. In one embodiment, the heavy chain variable region comprises a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 55. In one embodiment, the heavy chain variable region comprises a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 56. In one embodiment, the heavy chain variable region comprises one or more VH CDRs selected from the group consisting of SEQ ID NO: 54, SEQ ID NO: 55, and SEQ ID NO: 56. In one embodiment, the heavy chain variable region comprises two or more VH CDRs selected from the group consisting of SEQ ID NO: 54, SEQ ID NO: 55, and SEQ ID NO: 56. In one embodiment, the heavy chain variable region comprises a VH CDR1 comprising SEQ ID NO: 54, a VH CDR2 comprising SEQ ID NO: 55, and a VH CDR3 comprising SEQ ID NO: 56.

In one embodiment, the light chain variable region comprises one or more complementarity determining regions (CDRs). In one embodiment, the light chain variable region comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 57. In one embodiment, the light chain variable region comprises a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 58. In one embodiment, the light chain variable region comprises a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 59. In one embodiment, the light chain variable region comprises one or more VL CDRs selected from the group consisting of SEQ ID NO: 57, SEQ ID NO: 58, and SEQ ID NO: 59. In one embodiment, the light chain variable region comprises two or more VL CDRs selected from the group consisting of SEQ ID NO: 57, SEQ ID NO: 58, and SEQ ID NO: 59. In one embodiment, the light chain variable region comprises a VL CDR1 comprising SEQ ID NO: 57, a VL CDR2 comprising SEQ ID NO: 58, and a VL CDR3 comprising SEQ ID NO: 59.

In an exemplary embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region that comprises a VH CDR1 comprising SEQ ID NO: 54, a VH CDR2 comprising SEQ ID NO: 55, and a VH CDR3 comprising SEQ ID NO: 56, and a light chain variable region that comprises a VL CDR1 comprising SEQ ID NO: 57, a VL CDR2 comprising SEQ ID NO: 58, and a VL CDR3 comprising SEQ ID NO: 59.

In certain embodiments, one or more of the CDRs (*i.e.*, one or more heavy chain CDRs having SEQ ID NOs: 54-56, and/or one or more light chain CDRs having SEQ ID NOs: 57-59) can comprise a conservative amino acid substitution (or 2, 3, 4, or 5 amino acid substitutions) while retaining the CD5 specificity of the antibody (*i.e.*, specificity similar to an antibody, or antigen-binding fragment thereof, comprising heavy chain CDRs of SEQ ID NOs: 54 to 56, and light chain CDRs of SEQ ID NOs: 57 to 59).

Antibodies and antigen-binding fragments thereof capable of binding CD5 antigen can be identified using techniques known in the art and described herein, such as by immunization, computational modeling techniques, and in vitro selection methods, such as the phage display and cell-based display platforms described below.

Anti-CD5 antibodies that can be used in conjunction with the compositions and methods described herein include those that have one or both of the following variable regions, or an amino acid sequence having at least 85% sequence identity thereto (*e.g.*, an amino acid sequence having 85%, 90%, 95%, 97%, 98%, 99%, or more, sequence identity thereto):

a V_L having the amino acid sequence

DIQMTQSPSSMSASLGDRVITICRASQDINSYLSWFQQKPGKSPKTLIYRANRL
VDGVPSRFSGSGSGTDYTLTISSLQYEDFGIYYCQQYDESPWTFGGGTKLEIK
(SEQ ID NO: 26); and

a V_H having the amino acid sequence

QIQLVQSGPGLKKPGGSRISCAASGYTFTNYGMNWWKQAPGKGLRWMGWI
NTHTGEPTYADDFKGRFTFSLDTSKSTAYLQINSLRAEDTATYFCTRRGYDWY
FDVWGQGTTTVTVSS (SEQ ID NO: 27).

Antibodies and antigen-binding fragments thereof containing the foregoing V_L and V_H sequences are described, *e.g.*, in US Patent No. 5,869,619, the disclosure of which is incorporated herein by reference as it pertains to anti-CD5 antibodies and antigen-binding fragments thereof, such as the he1 antibody. In some embodiments, the anti-CD5 antibody or antigen-binding fragment thereof includes the V_L and V_H chains of SEQ ID NO: 26 and SEQ ID NO: 27. In some embodiments, the anti-CD5 antibody or antigen-binding fragment thereof includes the CDRs contained in the V_L and V_H chains of SEQ ID NO: 26 and SEQ ID NO: 27. In some embodiments, the anti-CD5 antibody or antigen-binding fragment thereof includes the CDRs contained in the V_L and V_H chains of SEQ ID NO: 26 and SEQ ID NO: 27 and the remainder of the V_L and V_H

sequences have at least 85% sequence identity (e.g., 85%, 90%, 95%, 97%, 98%, 99%, or greater sequence identity) to the V_L and V_H sequences of SEQ ID NO: 26 and SEQ ID NO: 27.

In some embodiments, the anti-CD5 antibody or antigen-binding fragment thereof includes the following CDRs:

- 5 a CDR-H1 having the amino acid sequence GYTFTNY (SEQ ID NO: 28);
- a CDR-H2 having the amino acid sequence NTHTGE (SEQ ID NO: 29);
- a CDR-H3 having the amino acid sequence RGYDWYFDV (SEQ ID NO: 30);
- a CDR-L1 having the amino acid sequence RASQDINSYLS (SEQ ID NO: 31);
- a CDR-L2 having the amino acid sequence RANRLVD (SEQ ID NO: 32); and
- 10 a CDR-L3 having the amino acid sequence QQYDESPWT (SEQ ID NO: 33).

Additional anti-CD5 antibodies that can be used in conjunction with the compositions and methods described herein include those that have one or both of the following variable regions, or an amino acid sequence having at least 85% sequence identity thereto (e.g., an amino acid sequence having 85%, 90%, 95%, 97%, 98%, 99%, or more, sequence identity thereto):

- 15 a V_L having the amino acid sequence
DIQMTQSPSSLSASVGDRVTITCRASQDINSYLSWFQQKPGKAPKTLIYRANRL
ESGVPSRFSGSGSGTDYTLTIS SLQYEDFGIYYCQQYDESPWTFGGGTKLEIK
(SEQ ID NO: 34); and
- a V_H having the amino acid sequence
20 EIQLVQSGGGLVKPGGSRISCAASGYTFTNYGMNWWVRQAPGKGLEWMGWI
NTHYGEPTYADSFKGTRTFSLDDSKNTAYLQINSLRAEDTAVYFCTRRGYDW
YFDVWGQGGTTVTVSS (SEQ ID NO: 35).

Antibodies and antigen-binding fragments thereof containing the foregoing V_L and V_H sequences are described, e.g., in US Patent No. 5,869,619, the disclosure of which is incorporated
25 herein by reference as it pertains to anti-CD5 antibodies and antigen-binding fragments thereof, such as the he3 antibody. In some embodiments, the anti-CD5 antibody or antigen-binding fragment thereof includes the CDRs contained in the V_L and V_H chains of the antibody that includes the V_L and V_H chains of SEQ ID NO:28 and SEQ ID NO: 29. In some embodiments, the anti-CD5 antibody or antigen-binding fragment thereof includes the CDRs contained in the V_L and
30 V_H chains of SEQ ID NO:28 and SEQ ID NO: 29 and the remainder of the V_L and V_H sequences have at least 85% sequence identity (e.g., 85%, 90%, 95%, 97%, 98%, 99%, or greater sequence identity) to the V_L and V_H sequences of SEQ ID NO:28 and SEQ ID NO: 29.

In some embodiments, the anti-CD5 antibody or antigen-binding fragment thereof includes the following CDRs:

- 35 a CDR-H1 having the amino acid sequence GYTFTNY (SEQ ID NO: 36);
- a CDR-H2 having the amino acid sequence NTHYGE (SEQ ID NO: 37);
- a CDR-H3 having the amino acid sequence RRGYDWYFDV (SEQ ID NO: 38);

a CDR-L1 having the amino acid sequence RASQDINSYLS (SEQ ID NO: 39);
a CDR-L2 having the amino acid sequence RANRLES (SEQ ID NO: 40); and
a CDR-L3 having the amino acid sequence QQYDESPWT (SEQ ID NO: 41).

Antibodies and antigen-binding fragments thereof containing the foregoing CDR sequences
5 are described, e.g., in US Patent No. 5,869,619, the disclosure of which is incorporated herein by
reference as it pertains to anti-CD5 antibodies and antigen-binding fragments thereof.

Other anti-CD5 antibodies that can be used in conjunction with the compositions and
methods described herein include, for instance, anti-CD5 antibodies that are described in US
Patent Nos. 5,821,123; 5,766,886; 5,770,196; 7,153,932; 5,621,083; 6,649,742; 6,146,631;
10 5,756,699; 5,744,580; 6,376,217; 5,837,491; and 6,146,850, the disclosures of each of which are
incorporated herein by reference as they pertain to anti-CD5 antibodies and antigen-binding
fragments thereof.

Other anti-CD5 antibodies that can be used in conjunction with the compositions and
methods described herein include, for instance, those produced by the hybridoma cell line
15 deposited as ATCC CRL 8000 (anti-CD5 murine antibody OKT1). Such antibodies are described
in US Patent Nos. 4,515,894; 4,657,760; and 4,363,799, the disclosures of each of which are
incorporated herein by reference as they pertain to anti-CD5 antibodies and antigen-binding
fragments thereof.

Still other anti-CD5 antibodies that can be used in conjunction with the compositions and
20 methods described herein include anti-CD5 antibodies that are described in US Patent No.
8,679,500 and WO 2010/145895, such as the anti-CD5 antibody MAT 304. The disclosures of US
Patent No. 8,679,500 and WO 2010/145895, including the sequences, are incorporated herein by
reference as it pertains to anti-CD5 antibodies and antigen-binding fragments thereof.

Other anti-CD5 antibodies that can be used in conjunction with the compositions and
25 methods described herein include, for instance, anti-CD5 antibodies that are described in US
Patent No 4,675,386 (produced by hybridoma deposited under ATCC accession number CRL-
8023), and also in Manske et al. (*J Immunol* 136:4721-4728 (1986)), Shawler et al. (*Cancer Res*
44:5921-5927 (1984)), Royston et al. (*Blood* 54 Suppl. 1:106a-106a (1979)), and Royston et al. (*J*
Immunol 125:725-731 (1980)), such as the anti-CD5 antibody T-101. The disclosure of US Patent
30 No 4,675,386 are incorporated herein by reference as it pertains to anti-CD5 antibodies and
antigen-binding fragments thereof.

Other anti-CD5 antibodies that can be used in conjunction with the compositions and
methods described herein include, for instance, those produced by the hybridoma cell line
deposited as ATCC HB9285 (anti-CD5 conjugate zolimomab aritox – antibody linked to the A
35 chain of the ricin protein). Such antibodies are described in WO1989006968; Henslee-Downey et
al., *Transplantation* 61:738-45, 1996; Henslee et al., *Transplant. Proc.* 21:3004-3007, 1989;

Przepiorka et al., Ther. Immunol. 1:77-82, 1994, the disclosures of each of which are incorporated herein by reference as they pertain to anti-CD5 antibodies and antigen-binding fragments thereof.

Additional anti-CD5 antibodies that can be used in conjunction with the compositions and methods described herein include anti-CD5 antibodies that are described in US Application No. US20110250203 and WO 2010/022737. See also the teachings of Koefoed et al., Br. J. Haematol, 2013 ("Koefoed et al."). The disclosures of US20110250203 and WO 2010/022737 and Koefoed et al. are incorporated herein by reference as it pertains to anti-CD5 antibodies and antigen-binding fragments thereof.

Anti-CD5 antibodies that can be used in conjunction with the compositions and methods described herein include those that have one or more, or all, of the following CDRs:

- a CDR-H1 having the amino acid sequence GYSITSGYY (SEQ ID NO: 42);
- a CDR-H2 having the amino acid sequence ISYSGFT (SEQ ID NO: 43);
- a CDR-H3 having the amino acid sequence AGDRTGSWFAY (SEQ ID NO: 44);
- a CDR-L1 having the amino acid sequence QDISNY (SEQ ID NO: 45);
- a CDR-L2 having the amino acid sequence ATS (SEQ ID NO: 46); and
- a CDR-L3 having the amino acid sequence LQYASYPFT (SEQ ID NO: 47).

Antibodies and antigen-binding fragments thereof containing the foregoing CDR sequences are described, e.g., in US Patent No. 8,679,500, the disclosure of which is incorporated herein by reference as it pertains to anti-CD5 antibodies and antigen-binding fragments thereof.

Anti-CD5 antibodies that can be used in conjunction with the compositions and methods described herein include those that have one or more, or all, of the following CDRs:

- a CDR-H1 having the amino acid sequence GYIFTNYG (SEQ ID NO: 48);
- a CDR-H2 having the amino acid sequence INTYNGEP (SEQ ID NO: 49);
- a CDR-H3 having the amino acid sequence ARGDYGYEDY (SEQ ID NO: 50);
- a CDR-L1 having the amino acid sequence QGISNY (SEQ ID NO: 51);
- a CDR-L2 having the amino acid sequence YTS (SEQ ID NO: 52); and
- a CDR-L3 having the amino acid sequence QQYSKLPWT (SEQ ID NO: 53).

Antibodies and antigen-binding fragments thereof containing the foregoing CDR sequences are described, e.g., in US Patent No. 8,679,500.

Anti-CD5 antibodies that can be used in conjunction with the compositions and methods described herein include those that have one or more, or all, of the following CDRs:

- a CDR-H1 having the amino acid sequence FSLSTSGMG (SEQ ID NO: 54);
- a CDR-H2 having the amino acid sequence WWDDD (SEQ ID NO: 55);
- a CDR-H3 having the amino acid sequence RRATGTGFDY (SEQ ID NO: 56);
- a CDR-L1 having the amino acid sequence QDVGTA (SEQ ID NO: 57);
- a CDR-L2 having the amino acid sequence WTSTRHT (SEQ ID NO: 58); and
- a CDR-L3 having the amino acid sequence YNSYNT (SEQ ID NO: 59).

Antibodies and antigen-binding fragments thereof containing the foregoing CDR sequences are described, e.g., in US Patent Application Publication No. 2008/0254027, the disclosure of which is incorporated herein by reference as it pertains to anti-CD5 antibodies and antigen-binding fragments thereof.

5 Other anti-CD5 antibodies that can be used in conjunction with the compositions and methods described herein include, for instance, anti-CD5 antibodies that are described in PCT Application Publication No. WO1992/014491, such as the anti-CD5 antibodies produced by hybridoma cell line deposited at the Institut Pasteur under No. 1-1025 on January 10, 1991. The disclosure of PCT Application Publication No. WO1992/014491 is incorporated herein by reference
10 as it pertains to anti-CD5 antibodies and antigen-binding fragments thereof.

 Other anti-CD5 antibodies that can be used in conjunction with the compositions and methods described herein include, for instance, anti-CD5 antibodies that are described in US Patent Nos. 6,010,902 and 7,192,736, US Patent Application Publication Nos. 2011/0250203 and 2017/0129128, and PCT Application Publication Nos. WO2016/172606; WO1994/023747; and
15 WO1996/041608; the disclosures of each of which are incorporated herein by reference as they pertain to anti-CD5 antibodies and antigen binding fragments thereof.

 In some embodiments, the anti-CD5 antibodies that can be used in conjunction with the compositions and methods described herein include those that contain a combination of CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 regions set forth in Table 1, below.

20

Table 1.

Ab No.	Name	CDRH1	SEQ ID NO:	CDRH2	SEQ ID NO:	CDRH3	SEQ ID NO:
1	1D8	SGYSFTGYTM	60	LINPYNGGTT	61	CARDYYGSSPFDYW	62
2	3I21	SGYSFTDYTM	63	LINPYNGGTM	64	CARDNYGSSPFDYW	65
3	4H10	SGYSFTGYTM	66	LINPYNGGTM	67	CARDNYGSSPYFDYW	68
4	8J23	SGYSFTGYTM	69	LINPYNGGTM	70	CARDNYGSSPYFDYW	71
5	5O4	SGYSFTGYTM	72	LINPYNGGTT	73	CARDYYGSSPFDYW	74
6	4H2	SGTFSNYAM	75	SISSGGNTF	76	CVRYYYGVTYWYFDVW	77
7	5G2	SGTFFSSYAM	78	SISSGGSTY	79	CVRYYYGIRYVYFDVW	80
8	8G8	SGYSFTAYNI	81	SIDPYYGDTK	82	CARRMITMGDWYFDVW	83
9	6M4	SGYSFTAYSM	84	SIDPYYGDTK	85	CARRMITTGDWYFDVW	86
10	2E3	SGYTFTNFAI	87	LISSNSGDVS	88	CARHYGAHNYFDYW	89
11	4E24	SGYTFTNFAI	90	LISTSSGDVS	91	CARHYGANNYFDYW	92
12	4F10	SGYTFTNFAI	93	LISSNSGDVS	94	CARHYGAHNYFDYW	95
13	7J9	SGYTFTNFAI	96	LISSNSGDVS	97	CARHYGAHNYFDYW	98
14	7P9	SGFNIKDTYM	99	RIDPANGNTK	100	CAREENYVGYTYFDYW	101
15	8E24	SGYSFTSYWM	102	MIHPDSETR	103	CARWGDHDDAMDFW	104
16	6L18	SGFSLTNYDV	105	VIWSGGNTD	106	CARNHGDGYFNWYFDVW	107
17	7H7	SGFSLTNYDV	108	VIWSGGNTD	109	CARNHGDGYNNWYFDVW	110
18	1E7	SGTFSNYGM	111	AINSGDITY	112	CARGTAWFTYW	113
19	8J21	SGYSFTGYTM	114	LINPYNGGTR	115	CARDGDDGWDIDVW	116
20	7I11	SGYIFANYGM	117	WINTYTGEPT	118	CARRGTYWHFDVW	119
21	8M9	SGYNFTNYGM	120	WINTYTGEPT	121	CARRGSYWHFDVW	122
22	1P21	SGYTFTNYGM	123	WINTYTGEPT	124	CARRSTLVFDYW	125
23	2H11	SGYTFTDYYI	126	WIYPGGGNTN	127	CARNGYWYFDVW	128
24	3M22	SGYTFTDYYI	129	WIYPGGGNTN	130	CARNGYWYFDVW	131
25	5M6	SGNTFTNFYL	132	CIYPGNVTK	133	CAKEGDYDGTAYFDYW	134
26	5H8	SGYTFTNYGM	135	WINTYTGEPT	136	CARRRDGNFDYW	137
27	7I19	SEFTFSNYAM	138	TISSGGSYTY	139	CVRHGYFDVW	140
28	1A20	SGYTFTSYRM	141	RIDPYDSGTH	142	CAFYDYGAYW	143
29	8E15	SGFNIKDTYM	144	RIDPANGNTK	145	CASYDPDYW	146
30	8C10	SGYSFTDYTM	147	LINPYNGGTR	148	CARDTTATYFDYW	149
31	3P16	SGYMFTNHGM	150	WINTYTGEPT	151	CARRVATYFDVW	152
32	4F3	SGYMFTNYGM	153	WINTYTGEPT	154	CTRRSHITLDYW	155

33	5M24	SGYIFTNYGM	156	WINTYTGEPT	157	CARRRTTAFDYW	158
34	5O24	SGFNIKDYI	159	WIDPENGRTE	160	CNNGNYVRHYYFDYW	161
35	7B16	SGYTFINYGM	162	WINTYTGEPT	163	CTRRREITFDYW	164
36	1E8	SGYTFTDYFI	165	EIYPGSSNTY	166	CARSGISPFTYW	167
37	2H16	SGYIFTGYNI	168	AVYPGNGDTS	169	CAKYDRFFASW	170

Ab No.	Name	CDRL1	SEQ ID NO:	CDRL2	SEQ ID NO:	CDRL3	SEQ ID NO:
1	1D8	SQGISNHL	171	YFTSS	172	CQQYSNLPYTF	173
2	3I21	SQGIRNYL	174	YFTSS	175	CQQYSNLPYTF	176
3	4H10	SQGISNHL	177	YFTSS	178	CQQYSNLPYTF	179
4	8J23	SQGINNLY	180	YYTSS	181	CQQYSKIPYTC	182
5	5O4	SQGISNHL	183	YFTSS	184	CQQYSNLPYTF	185
6	4H2	SQSVHDHGD SYM	186	YAASN	187	CQQNYEDPTF	188
7	5G2	SQSVDDYDGD SYM	189	YAASN	190	CQQSNEDPTF	191
8	8G8	SQDISNYL	192	YYTSR	193	CQQGDALPWF	194
9	6M4	SQDISTYL	195	FYTSR	196	CQQGNLPTF	197
10	2E3	TSSISSYL	198	YGTSN	199	CQQWSSRPPTF	200
11	4E24	NSSVSSSYL	201	YGTSN	202	CQQYSGYPLTF	203
12	4F10	TSSISSYL	204	YGTSN	205	CQQYSDYPLTF	206
13	7J9	TSSISSYL	207	YGTSN	208	CQQRSYFPPTF	209
14	7P9	SENIYYNL	210	YNANS	211	CKQVYDVPPTF	212
15	8E24	SENIYGYF	213	YNAKT	214	CQHHYGTPTF	215
16	6L18	SQDINNYI	216	HYTST	217	CLQYDNLWTF	218
17	7H7	SQDINKYI	219	HYTST	220	CLQYDNLWTF	221
18	1E7	SENIYSYL	222	YNAKT	223	CQHHYGYPTF	224
19	8J21	SQGIRNYL	225	YHTST	226	CQQYSNLPITF	227
20	7I11	SQDVRTDV	228	YSASF	229	CQQHYTSPWTF	230
21	8M9	SQDVITAV	231	YSASY	232	CQQHYSTPWF	233
22	1P21	SQSIGTSI	234	KSASE	235	CQQSNRWPLTF	236
23	2H11	SSQSLLNQKNYL	237	YWAST	238	CQNDYDYPYTF	239
24	3M22	SSSVSSSYL	240	YSTSN	241	CHQYHRSPLTF	242
25	5M6	SENIYYNL	243	YNANS	244	CQQTDFVPTF	245
26	5H8	SQTIGTSI	246	KNASE	247	CQQNSWPLTY	248
27	7I19	SQSLLYSSDQKNYL	249	YWAST	250	CQQYNYPLTF	251
28	1A20	NSSVSYM	252	YDTSK	253	CQQWSSNPPTF	254
29	8E15	SENIYYNL	255	YNANS	256	CKQAYDVPTF	257
30	8C10	SSSLSYM	258	YDTSN	259	CQQWSSFPPTF	260
31	3P16	SQRIGTSM	261	KSASE	262	CQQNSWPLTF	263
32	4F3	SQSIGTSI	264	KSASE	265	CQQNSWPLTF	266
33	5M24	SQNIIGTSI	267	KDASE	268	CQQSDSWPLTF	269
34	5O24	ISSVSYM	270	YATSN	271	CQQWSSNPRTF	272

35	7B16	SQTIATSI	273	KNASE	274	CQQSNSWPLTF	275
36	1E8	SQSLVHSNGNTYL	276	YKVSN	277	CWQNTHFPQTF	278
37	2H16	NESVEYSGTSLM	279	SAASN	280	CQQSRQVPLTF	281

Antibodies and antigen-binding fragments thereof containing the foregoing CDR sequences of Table 1 are described, e.g., in US Patent Application Publication No. 2011/0250203, the disclosure of which is incorporated herein by reference as it pertains to anti-CD5 antibodies and antigen binding fragments thereof.

Antibodies and fragments thereof for use in conjunction with the compositions and methods described herein include variants of those antibodies described above, such as antibody fragments that contain or lack an Fc domain, as well as humanized variants of non-human antibodies described herein and antibody-like protein scaffolds (e.g., ¹⁰Fn3 domains) containing one or more, or all, of the CDRs or equivalent regions thereof of an antibody, or an antibody fragment, described herein. Exemplary antigen-binding fragments of the foregoing antibodies include 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, among others.

The foregoing anti-CD5 antibodies, or antigen-binding fragments thereof, can be used in various aspects set forth herein, including, for example, in methods for depletion of CD5+ cells in a human subject. The foregoing anti-CD5 antibodies, or antigen-binding fragments thereof, can also be conjugated to an agent, e.g., a cytotoxin, for example, an amatoxin, as described herein. Additional anti-CD5 antibodies that may be used in aspects of the compositions and methods described herein are described in U.S. Patent No. 8,679,500, U.S. Patent Application Publication No. US2011/0250203, and U.S. Patent Application Publication No. US2008/0254027, the entire contents of each of which are incorporated herein by reference. Additional anti-CD5 antibodies which may be used in aspects of compositions and methods described herein include, for example, monoclonal antibody T101 described by Dillman et al., J. Clin. Oncol. (1984), 2(8):881-891, and monoclonal antibody Leu-1 described by Miller et al., Blood (1983), 62(5):988-95.

In one embodiment, the anti-CD5 antibody or binding fragment thereof, comprises a modified Fc region, wherein said modified Fc region comprises at least one amino acid modification relative to a wild-type Fc region, such that said molecule has an altered affinity for or binding to an FcγR (FcγR). Certain amino acid positions within the Fc region are known through crystallography studies to make a direct contact with FcγR. Specifically, amino acids 234-239 (hinge region), amino acids 265-269 (B/C loop), amino acids 297-299 (C'/E loop), and amino acids 327-332 (F/G) loop. (see Sondermann et al., 2000 Nature, 406: 267-273). The antibodies described herein may comprise variant Fc regions comprising modification of at least one residue that makes a direct contact with an FcγR based on structural and crystallographic analysis. In one embodiment, the Fc region of the anti-CD5 antibody (or fragment thereof) comprises an amino acid substitution at amino acid 265 according to the EU index as in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, NH1, MD (1991), expressly incorporated herein by references. The "EU index as in Kabat" refers to the numbering of the

human IgG1 EU antibody. In one embodiment, the Fc region comprises a D265A mutation. In one embodiment, the Fc region comprises a D265C mutation. In some embodiments, the Fc region of the antibody (or fragment thereof) comprises an amino acid substitution at amino acid 234 according to the EU index as in Kabat. In one embodiment, the Fc region comprises a L234A mutation. In some embodiments, the Fc region of the anti-CD5 antibody (or fragment thereof) comprises an amino acid substitution at amino acid 235 according to the EU index as in Kabat. In one embodiment, the Fc region comprises a L235A mutation. In yet another embodiment, the Fc region comprises a L234A and L235A mutation. In a further embodiment, the Fc region comprises a D265C, L234A, and L235A mutation. In yet a further embodiment, the Fc region comprises a D265C, L234A, L235A, and H435A mutation. In a further embodiment, the Fc region comprises a D265C and H435A mutation.

The antibodies used in the compositions and methods described herein may be further engineered to further modulate antibody half-life by introducing additional Fc mutations, such as those described for example in (Dall'Acqua et al. (2006) J Biol Chem 281: 23514-24), (Zalevsky et al. (2010) Nat Biotechnol 28: 157-9), (Hinton et al. (2004) J Biol Chem 279: 6213-6), (Hinton et al. (2006) J Immunol 176: 346-56), (Shields et al. (2001) J Biol Chem 276: 6591-604), (Petkova et al. (2006) Int Immunol 18: 1759-69), (Datta-Mannan et al. (2007) Drug Metab Dispos 35: 86-94), (Vaccaro et al. (2005) Nat Biotechnol 23: 1283-8), (Yeung et al. (2010) Cancer Res 70: 3269-77) and (Kim et al. (1999) Eur J Immunol 29: 2819-25), and include positions 250, 252, 253, 254, 256, 257, 307, 376, 380, 428, 434 and 435. Exemplary mutations that may be made singularly or in combination are T250Q, M252Y, I253A, S254T, T256E, P257I, T307A, D376V, E380A, M428L, H433K, N434S, N434A, N434H, N434F, H435A and H435R mutations.

In some embodiments, the anti-CD5 antibody or antigen-binding fragment thereof is conjugated to a cytotoxin (e.g., amatoxin) by way of a cysteine residue in the Fc domain of the antibody or antigen-binding fragment thereof. In some embodiments, the cysteine residue is introduced by way of a mutation in the Fc domain of the antibody or antigen-binding fragment thereof. For instance, the cysteine residue may be selected from the group consisting of Cys118, Cys239, and Cys265. In one embodiment, the Fc region of the anti-CD5 antibody (or fragment thereof) comprises an amino acid substitution at amino acid 265 according to the EU index as in Kabat. In one embodiment, the Fc region comprises a D265C mutation. In one embodiment, the Fc region comprises a D265C and a H435A mutation.

Thus, in one embodiment, the Fc region comprises a mutation resulting in a decrease in half life. An antibody having a short half life may be advantageous in certain instances where the antibody is expected to function as a short-lived therapeutic, e.g., the conditioning step described herein where the antibody is administered followed by HSCs. Ideally, the antibody would be substantially cleared prior to delivery of the HSCs, which may also generally express CD5 but are not the target of the anti-CD5 antibody, unlike the endogenous stem cells. In one embodiment, the

Fc region comprises a mutation at position 435 (EU index according to Kabat). In one embodiment, the mutation is an H435A mutation.

The foregoing anti-CD5 antibodies, or antigen-binding fragments thereof, can be used in various aspects set forth herein, including, for example, in methods for depletion of CD5+ cells in a human subject. The foregoing anti-CD5 antibodies, or antigen-binding fragments thereof, can also be conjugated to an agent, e.g., a cytotoxin, for example, an amatoxin, as described herein.

Methods of Identifying Anti-CD2 and Anti-CD5 Antibodies

Methods for high throughput screening of libraries of antibodies, or antibody fragments, that bind CD2 or CD5 can be used to identify and affinity mature agents useful for conditioning a patient (e.g., a human patient) in need of hematopoietic stem cell therapy and/or for directly treating a cancer or autoimmune disease as described herein. Such methods include in vitro display techniques known in the art, such as phage display, bacterial display, yeast display, mammalian cell display, ribosome display, mRNA display, and cDNA display, among others. The use of phage display to isolate antibodies, or antigen-binding fragments, that bind biologically relevant molecules has been reviewed, for example, in Felici et al., *Biotechnol. Annual Rev.* 1:149-183, 1995; Katz, *Annual Rev. Biophys. Biomol. Struct.* 26:27-45, 1997; and Hoogenboom et al., *Immunotechnology* 4:1-20, 1998, the disclosures of each of which are incorporated herein by reference as they pertain to in vitro display techniques. Randomized combinatorial peptide libraries have been constructed to select for polypeptides that bind cell surface antigens as described in Kay, *Perspect. Drug Discovery Des.* 2:251-268, 1995 and Kay et al., *Mol. Divers.* 1:139-140, 1996, the disclosures of each of which are incorporated herein by reference as they pertain to the discovery of antigen-binding molecules. Proteins, such as multimeric proteins, have been successfully phage-displayed as functional molecules (see, for example, EP 0349578; EP 4527839; and EP 0589877, as well as Chiswell and McCafferty, *Trends Biotechnol.* 10:80-84 1992, the disclosures of each of which are incorporated herein by reference as they pertain to the use of in vitro display techniques for the discovery of antigen-binding molecules. In addition, functional antibody fragments, such as Fab and scFv fragments, have been expressed in in vitro display formats (see, for example, McCafferty et al., *Nature* 348:552- 554, 1990; Barbas et al., *Proc. Natl. Acad. Sci. USA* 88:7978-7982, 1991; and Clackson et al., *Nature* 352:624-628, 1991, the disclosures of each of which are incorporated herein by reference as they pertain to in vitro display platforms for the discovery of antigen-binding molecules). These techniques, among others, can be used to identify and improve the affinity of antibodies, or antibody fragments, that bind CD2 or CD5 that can in turn be used to deplete CD2+ T cells and/or NK cells (or CD5+ T cells, B cells and/or NK cells) in a patient (e.g., a human patient) in need of hematopoietic stem cell transplant therapy and/or suffering from cancer or an autoimmune disease described herein.

Additional techniques can be used to identify antibodies, and antigen-binding fragments thereof, that bind CD2 or CD5 on the surface of a cell (e.g., a T cell, B cell or NK cell) and that are internalized by the cell, for instance, by receptor-mediated endocytosis. For example, the in vitro display techniques described above can be adapted to screen for antibodies, and antigen-binding fragments thereof, that bind CD2 or CD5 on the surface of a T cell, B cell or NK cell and that are subsequently internalized. Phage display represents one such technique that can be used in conjunction with this screening paradigm. To identify antibodies, and fragments thereof, that bind CD2 or CD5 and are subsequently internalized by T cells, B cells and/or NK cells, one of skill in the art can use the phage display techniques described in Williams et al., *Leukemia* 19:1432-1438, 2005, the disclosure of which is incorporated herein by reference in its entirety. For example, using mutagenesis methods known in the art, recombinant phage libraries can be produced that encode antibodies, antibody fragments, such as scFv fragments, Fab fragments, diabodies, triabodies, and ¹⁰Fn3 domains, among others, or antibodies that contain randomized amino acid cassettes (e.g., in one or more, or all, of the CDRs or equivalent regions thereof or an antibody or antibody fragment). The framework regions, hinge, Fc domain, and other regions of the antibodies or antibody fragments may be designed such that they are non-immunogenic in humans, for instance, by virtue of having human germline antibody sequences or sequences that exhibit only minor variations relative to human germline antibodies.

Using phage display techniques described herein or known in the art, phage libraries containing randomized antibodies, or antibody fragments, covalently bound to the phage particles can be incubated with CD2 antigen or CD5 antigen, for instance, by first incubating the phage library with blocking agents (such as, for instance, milk protein, bovine serum albumin, and/or IgG so as to remove phage encoding antibodies, or fragments thereof, that exhibit non-specific protein binding and phage that encode antibodies or fragments thereof that bind Fc domains, and then incubating the phage library with a population of T cells, B cells or NK cells that are CD2+ (or CD5+). The phage library can be incubated with the T cells, B cells or NK cells for a time sufficient to allow CD2-specific antibodies, or antigen-binding fragments thereof (or CD5-specific antibodies, or antigen-binding fragments thereof), to bind cell-surface CD2 or CD5 and to subsequently be internalized by the T cells, B cells or NK cells (e.g., from 30 minutes to 6 hours at 4° C, such as 1 hour at 4° C). Phage containing antibodies, or fragments thereof, that do not exhibit sufficient affinity for CD2 or CD5 so as to permit binding to, and internalization by, T cells or NK cells can subsequently be removed by washing the cells, for instance, with cold (4° C) 0.1 M glycine buffer at pH 2.8. Phage bound to antibodies, or fragments thereof, that have been internalized by the T cells, B cells and/or NK cells can be identified, for instance, by lysing the cells and recovering internalized phage from the cell culture medium. The phage can then be amplified in bacterial cells, for example, by incubating bacterial cells with recovered phage in 2xYT medium using methods known in the art. Phage recovered from this medium can then be characterized, for

instance, by determining the nucleic acid sequence of the gene(s) encoding the antibodies, or fragments thereof, inserted within the phage genome. The encoded antibodies, or fragments thereof, can subsequently be prepared de novo by chemical synthesis (for instance, of antibody fragments, such as scFv fragments) or by recombinant expression (for instance, of full-length antibodies).

An exemplary method for in vitro evolution of anti-CD2 antibodies or anti-CD5 antibodies for use with the compositions and methods described herein is phage display. Phage display libraries can be created by making a designed series of mutations or variations within a coding sequence for the CDRs of an antibody or the analogous regions of an antibody-like scaffold (e.g., the BC, CD, and DE loops of ^{10} Fn3 domains). The template antibody-encoding sequence into which these mutations are introduced may be, for example, a naive human germline sequence. These mutations can be performed using standard mutagenesis techniques known in the art. Each mutant sequence thus encodes an antibody corresponding to the template save for one or more amino acid variations. Retroviral and phage display vectors can be engineered using standard vector construction techniques known in the art. P3 phage display vectors along with compatible protein expression vectors can be used to generate phage display vectors for antibody diversification.

The mutated DNA provides sequence diversity, and each transformant phage displays one variant of the initial template amino acid sequence encoded by the DNA, leading to a phage population (library) displaying a vast number of different but structurally related amino acid sequences. Due to the well-defined structure of antibody hypervariable regions, the amino acid variations introduced in a phage display screen are expected to alter the binding properties of the binding peptide or domain without significantly altering its overall molecular structure.

In a typical screen, a phage library may be contacted with and allowed to bind CD2 or CD5 or an epitope thereof. To facilitate separation of binders and non-binders, it is convenient to immobilize the target on a solid support. Phage bearing a CD2-binding moiety or a CD5-binding moiety can form a complex with the target on the solid support, whereas non-binding phage remain in solution and can be washed away with excess buffer. Bound phage can then be liberated from the target by changing the buffer to an extreme pH (pH 2 or pH 10), changing the ionic strength of the buffer, adding denaturants, or other known means.

The recovered phage can then be amplified through infection of bacterial cells, and the screening process can be repeated with the new pool that is now depleted in non-binding antibodies and enriched for antibodies that bind CD2 or CD5. The recovery of even a few binding phage is sufficient to amplify the phage for a subsequent iteration of screening. After a few rounds of selection, the gene sequences encoding the antibodies or antigen-binding fragments thereof derived from selected phage clones in the binding pool are determined by conventional methods, thus revealing the peptide sequence that imparts binding affinity of the phage to the target. During

the panning process, the sequence diversity of the population diminishes with each round of selection until desirable peptide-binding antibodies remain. The sequences may converge on a small number of related antibodies or antigen-binding fragments thereof. An increase in the number of phage recovered at each round of selection is an indication that convergence of the library has occurred in a screen.

Another method for identifying anti-CD2 antibodies or anti-CD5 antibodies includes using humanizing non-human antibodies that bind CD2 or CD5, for instance, according to the following procedure. Non-human antibodies that bind CD2 or CD5 can be humanized, for instance, according to the following procedure. Consensus human antibody heavy chain and light chain sequences are known in the art (see e.g., the "VBASE" human germline sequence database; Kabat et al. Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242, 1991; Tomlinson et al., J. Mol. Biol. 227:776-798, 1992; and Cox et al., Eur. J. Immunol. 24:827-836, 1994, the disclosures of each of which are incorporated herein by reference as they pertain to consensus human antibody heavy chain and light chain sequences. Using established procedures, one of skill in the art can identify the variable domain framework residues and CDRs of a consensus antibody sequence (e.g., by sequence alignment). One can substitute one or more CDRs of the heavy chain and/or light chain variable domains of consensus human antibody with one or more corresponding CDRs of a non-human antibody that binds CD2 or CD5 in order to produce a humanized antibody. This CDR exchange can be performed using gene editing techniques described herein or known in the art.

One example of a variable domain of a consensus human antibody contains the heavy chain variable domain

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYAMSWVRQAPGKGLEWVAVISENGSDTYADS
VKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCARDRGGA¹VS²YFDVWGQGT³LVTVSS (SEQ ID

NO: 11) and the light chain variable domain

DIQMTQSPSSLSASVGDRVTITCRASQDVSSYLAWYQQKPGKAPKLLIYAASSLES¹GVPSRFSGS
GSGTDFTLT²ISS³LQPEDFATYYCQ⁴QYNSL⁵LPYTFGQGT⁶KVEIKRT (SEQ ID NO: 12), identified in

US Patent No. 6,054,297, the disclosure of which is incorporated herein by reference as it pertains to human antibody consensus sequences. The CDRs in the above sequences are shown in bold.

To produce humanized antibodies, one can recombinantly express a polynucleotide encoding the above consensus sequence in which one or more variable region CDRs have been replaced with one or more variable region CDR sequences of a non-human antibody that binds CD2 or CD5. As the affinity of the antibody for CD2 or CD5 is determined primarily by the CDR sequences, the resulting humanized antibody is expected to exhibit an affinity for CD2 or CD5 that is about the same as that of the non-human antibody from which the humanized antibody was derived. Methods of determining the affinity of an antibody for a target antigen include, for

instance, ELISA-based techniques described herein and known in the art, as well as surface plasmon resonance, fluorescence anisotropy, and isothermal titration calorimetry, among others.

The internalizing capacity of the prepared antibodies, or fragments thereof, can be assessed, for instance, using radionuclide internalization assays known in the art. For example, anti-CD2
 5 antibodies, or fragments thereof (or anti-CD5 antibodies, or fragments thereof), identified using in vitro display techniques described herein or known in the art can be functionalized by incorporation of a radioactive isotope, such as ^{18}F , ^{75}Br , ^{77}Br , ^{122}I , ^{123}I , ^{124}I , ^{125}I , ^{129}I , ^{131}I , ^{211}At , ^{67}Ga , ^{111}In , ^{99}Tc , ^{169}Yb , ^{186}Re , ^{64}Cu , ^{67}Cu , ^{177}Lu , ^{77}As , ^{72}As , ^{86}Y , ^{90}Y , ^{89}Zr , ^{212}Bi , ^{213}Bi , or ^{225}Ac . For instance, radioactive halogens, such as ^{18}F , ^{75}Br , ^{77}Br , ^{122}I , ^{123}I , ^{124}I , ^{125}I , ^{129}I , ^{131}I , ^{211}At , can be incorporated into antibodies, or
 10 fragments thereof, using beads, such as polystyrene beads, containing electrophilic halogen reagents (e.g., Iodination Beads, Thermo Fisher Scientific, Inc., Cambridge, MA). Radiolabeled antibodies, or fragments thereof, can be incubated with T cells, B cells and/or NK cells for a time sufficient to permit internalization (e.g., from 30 minutes to 6 hours at 4°C , such as 1 hour at 4°C). The cells can then be washed to remove non-internalized antibodies, or fragments thereof, (e.g., using cold (4°C) 0.1 M
 15 glycine buffer at pH 2.8). Internalized antibodies, or fragments thereof, can be identified by detecting the emitted radiation (e.g., γ -radiation) of the resulting T cells, B cells and/or NK cells in comparison with the emitted radiation (e.g., γ -radiation) of the recovered wash buffer.

For recombinant production of an anti-CD2 antibody or an anti-CD5 antibody, nucleic acid encoding an antibody, e.g., as described above, is isolated and inserted into one or more vectors for
 20 further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

Suitable host cells for cloning or expression of antibody-encoding vectors include prokaryotic or eukaryotic cells described herein. For example, antibodies may be produced in bacteria, in particular
 25 when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria, see, e.g., U.S. Pat. Nos. 5,648,237, 5,789,199, and 5,840,523. (See also Charlton, *Methods in Molecular Biology*, Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, N.J., 2003), pp. 245-254, describing expression of antibody fragments in *E. coli*.) After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

30 Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, e.g., in Graham et al., *J. Gen Virol.* 36:59 (1977)); baby hamster kidney cells (BHK); mouse sertoli cells (TM4 cells as described, e.g., in Mather, *Biol. Reprod.* 23:243-251 (1980));
 35 monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK; buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells, as described, e.g., in

Mather et al., *Annals N.Y. Acad. Sci.* 383:44-68 (1982); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR- CHO cells (Urlaub et al., *Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, see, e.g., Yazaki and Wu, *Methods in Molecular Biology*, Vol. 248 (B. K. C. Lo, ed., Humana Press, Totowa, N.J.), pp. 255-268 (2003). In one embodiment, the host cell is eukaryotic, e.g. a Chinese Hamster Ovary (CHO) cell or lymphoid cell (e.g., Y0, NS0, Sp20 cell).

Antibody-Drug Conjugates (ADCs)

Anti-CD5 or CD2 antibody drug conjugates that can be used in the methods described herein include an anti-CD5 or an anti-CD2 antibody conjugated to a cytotoxin via a linker. Anti-CD5 antibodies and anti-CD2 antibodies that can be used in the ADCs described herein are known in the art and described above. Cytotoxins, linkers, and methods of conjugation are described below.

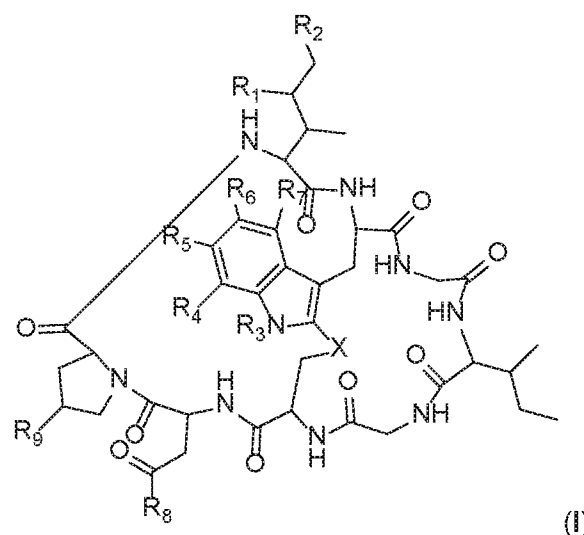
Cytotoxins

Antibodies, and antigen-binding fragments thereof, described herein (e.g., antibodies, antigen-binding fragments, that recognize and bind CD2 or CD5) can be conjugated to a cytotoxin, such as pseudomonas exotoxin A, deBouganin, diphtheria toxin, an amatoxin, such as α -amanitin, 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, or another cytotoxic compound described herein or known in the art in order to (i) directly treat a cancer or autoimmune disease described herein or (ii) deplete endogenous immune cells so as to prevent or reduce the likelihood of rejection of hematopoietic stem cells upon transplantation into a patient (e.g., a human patient) in need of hematopoietic stem cell transplant therapy. In some embodiments, the cytotoxic molecule is conjugated to an internalizing antibody, or antigen-binding fragment thereof, such that following the cellular uptake of the antibody, or antigen-binding fragment, the cytotoxin may access its intracellular target and kill endogenous T cells, B cells and/or NK cells. Suitable cytotoxins suitable for use with the compositions and methods described herein include DNA-intercalating agents, (e.g., anthracyclines), agents capable of disrupting the mitotic spindle apparatus (e.g., vinca alkaloids, maytansine, maytansinoids, and derivatives thereof), RNA polymerase inhibitors (e.g., an amatoxin, such as α -amanitin, and derivatives thereof), agents capable of disrupting protein biosynthesis (e.g., agents that exhibit rRNA N-glycosidase activity, such as saporin and ricin A-chain), among others known in the art.

In some embodiments, the cytotoxin of the antibody-drug conjugate is an RNA polymerase inhibitor. In some embodiments, the RNA polymerase inhibitor is an amatoxin or derivative thereof.

In some embodiments, the cytotoxin is an amatoxin or a derivative thereof, such as α -amanitin, β -amanitin, γ -amanitin, ϵ -amanitin, amanin, amaninamide, amanullin, amanullinic acid, and proamanullin. Structures of the various naturally occurring amatoxins are represented by formula III, and are disclosed in, e.g., Zanotti et al., *Int. J. Peptide Protein Res.* 30, 1987, 450-459.

In one embodiment, the cytotoxin is an amanitin. For instance, the antibodies, or antigen-binding fragments, described herein may be bound to an amatotoxin so as to form a conjugate 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 is an amatotoxin. Many positions on amatotoxins or derivatives thereof can serve as the position to covalently bond the linking moiety L, and, hence the antibodies or antigen-binding fragments thereof. For instance, the antibodies, and antigen-binding fragments, described herein may be bound to an amatotoxin so as to form a conjugate 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 amatotoxin. In some embodiments, Am-L-Z is represented by formula (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 :

R₄ is H, OH, OR_C, OR_D, R_C, or R_D;

R_5 is H, OH, OR_C, OR_D, R_C, or R_D;

R_6 is H, OH, OR_C , OR_D , R_C , or R_D ;

R_7 is H, OH, OR_C , OR_D , R_C , or R_D ;

R_8 is OH, NH_2 , OR_C , OR_D , NHR_C , or $NR_C R_D$.

R_9 is H, OH, OR_C , or OR_D ;

X is -S-, -S(O)-, or -SO₂-;

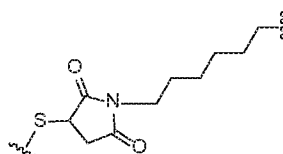
R_C is -L-Z;

R_D is optionally substituted alkyl (e.g., C₁-C₆ alkyl), optionally substituted heteroalkyl (e.g., C₁-C₆ heteroalkyl), optionally substituted alkenyl (e.g., C₂-C₆ alkenyl), optionally substituted heteroalkenyl (e.g., C₂-C₆ heteroalkenyl), optionally substituted alkynyl (e.g., C₂-C₆ alkynyl), optionally substituted heteroalkynyl (e.g., C₂-C₆ heteroalkynyl), optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

L is a linker, such as optionally substituted alkylene (e.g., C₁-C₆ alkylene), optionally substituted heteroalkylene (C₁-C₆ heteroalkylene), optionally substituted alkenylene (e.g., C₂-C₆ alkenylene), optionally substituted heteroalkenylene (e.g., C₂-C₆ heteroalkenylene), optionally substituted alkynylene (e.g., C₂-C₆ alkynylene), optionally substituted heteroalkynylene (e.g., C₂-C₆ heteroalkynylene), optionally substituted cycloalkylene, optionally substituted heterocycloalkylene, optionally substituted arylene, optionally substituted heteroarylene, a dipeptide, -C(=O)-, a peptide, or a combination thereof; and

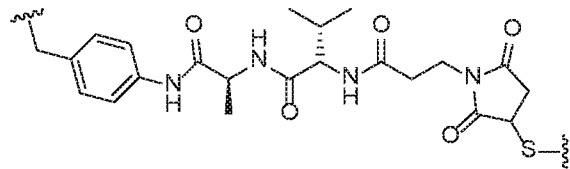
Z is a chemical moiety formed from a coupling reaction between a reactive substituent present on L and a reactive substituent present within an antibody, or antigen-binding fragment thereof, that binds CD2 or CD5.

In some embodiments, Am contains exactly one R_C substituent. In some embodiments, the linker comprises a -(CH)_{2n}- unit, where n is an integer from 2-6. In some embodiments, the linker includes -((CH₂)_n where n is 6. In some embodiments, L-Z is

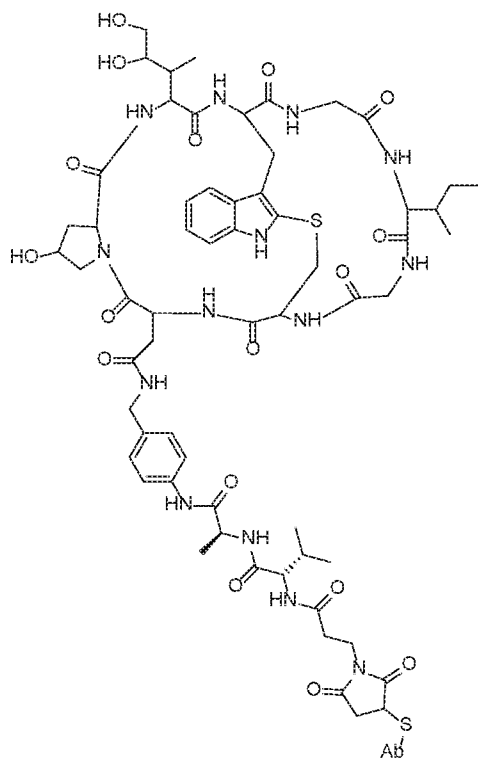


where S is a sulfur atom which represents the reactive substituent present within an antibody, or antigen-binding fragment thereof, that binds CD117 (e.g., from the -SH group of a cysteine residue).

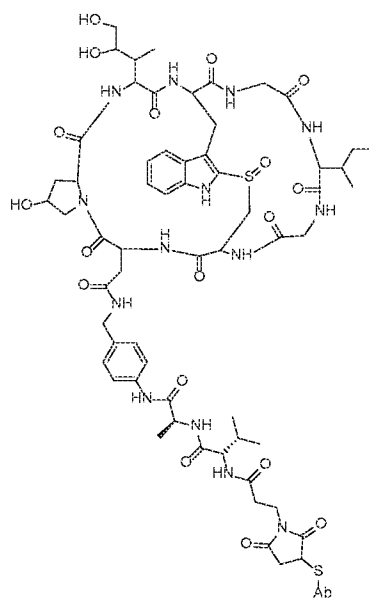
In some embodiments, L-Z is



In some embodiments, Am-L-Z-Ab is

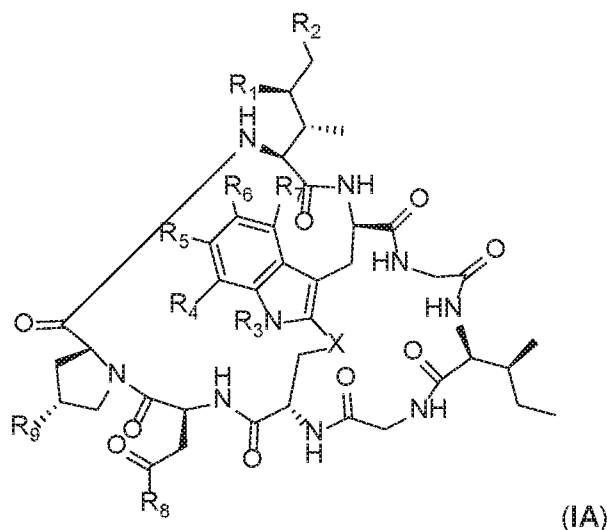


In some embodiments, Am-L-Z-Ab is



5

In some embodiments, Am-L-Z is represented by formula (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 heterocyclolalkyl group;

R_3 is H, R_C , or R_D ;

R_4 is H, OH, OR_C , OR_D , R_C , or R_D ;

R_5 is H, OH, OR_C , OR_D , R_C , or R_D ;

R_6 is H, OH, OR_C , OR_D , R_C , or R_D ;

R_7 is H, OH, OR_C , OR_D , R_C , or R_D ;

R_8 is OH, NH_2 , OR_C , OR_D , NHR_C , or $NR_C R_D$;

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 alkyl (e.g., C_1 - C_6 alkyl), optionally substituted heteroalkyl (e.g., C_1 - C_6 heteroalkyl), optionally substituted alkenyl (e.g., C_2 - C_6 alkenyl), optionally substituted heteroalkenyl (e.g., C_2 - C_6 heteroalkenyl), optionally substituted alkynyl (e.g., C_2 - C_6 alkynyl), optionally substituted heteroalkynyl (e.g., C_2 - C_6 heteroalkynyl), optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

L is a linker, such as optionally substituted alkylene (e.g., C_1 - C_6 alkylene), optionally substituted heteroalkylene (C_1 - C_6 heteroalkylene), optionally substituted alkenylene (e.g., C_2 - C_6 alkenylene), optionally substituted heteroalkenylene (e.g., C_2 - C_6 heteroalkenylene), optionally substituted alkynylene (e.g., C_2 - C_6 alkynylene), optionally substituted heteroalkynylene (e.g., C_2 - C_6 heteroalkynylene), optionally substituted cycloalkylene, optionally substituted heterocycloalkylene, optionally substituted arylene, optionally substituted heteroarylene; a dipeptide, $-C(=O)-$, a peptide, a disulfide, a hydrazone, a $-(CH_2CH_2O)_p-$ group, wherein p is an integer from 1-6, a $((CH_2)_mO)$

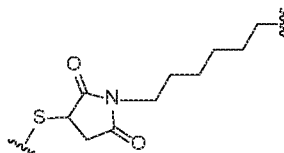
$n(\text{CH}_2)_m$ — group, where n and each m are each independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; or a combination thereof;

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

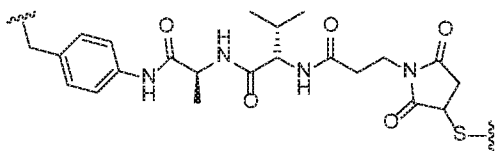
5 thereof, that binds CD2 or CD5; and

wherein Am contains exactly one R_C substituent.

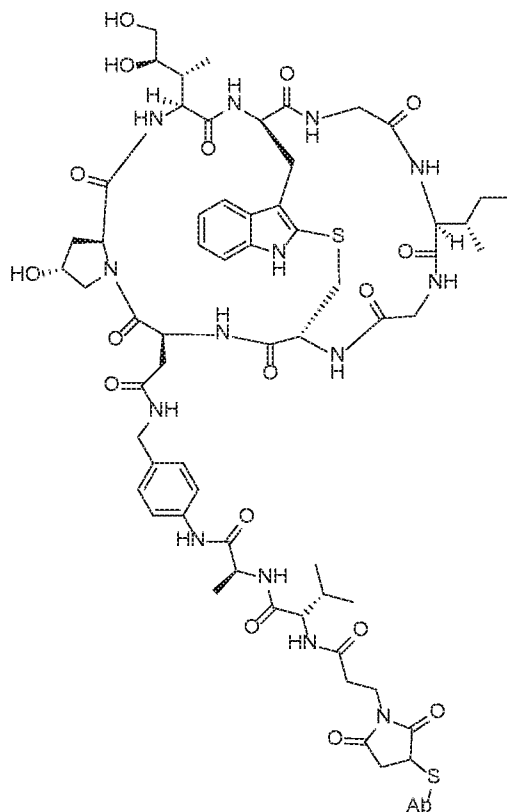
In some embodiments, the linker includes $-(\text{CH}_2)_n$ where n is 6. In some embodiments, $L-Z$ is



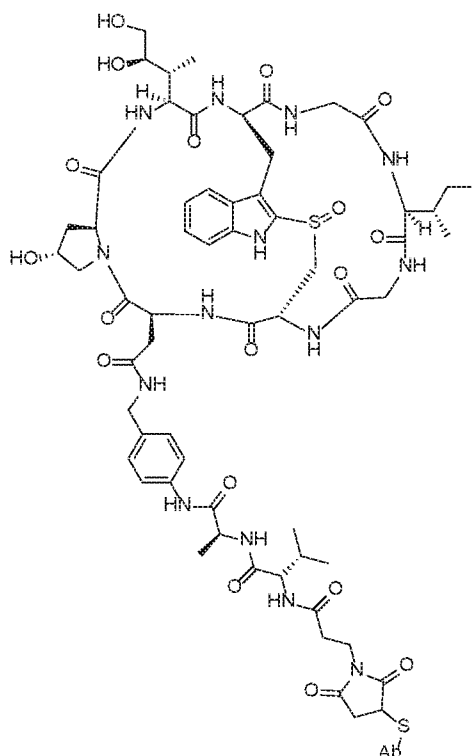
10 In some embodiments, $L-Z$ is



In some embodiments, Am-L-Z-Ab is

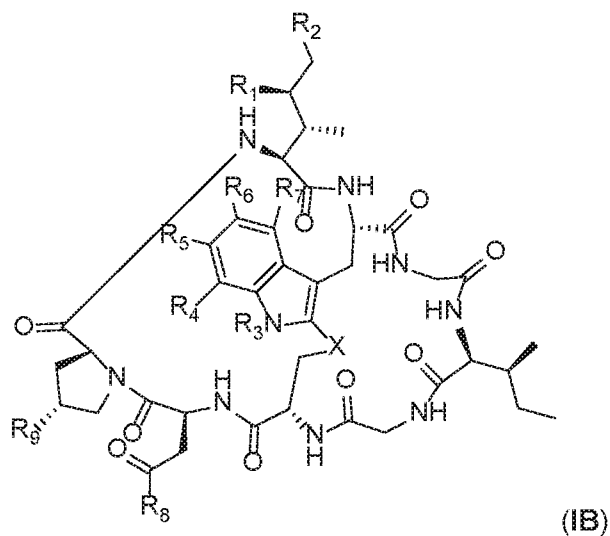


In some embodiments, Am-L-Z-Ab is



In some embodiments, Am-L-Z is represented by formula (IB)

5



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

R_2 is H, OH, OR_B , or OR_C ;

10 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 is H, OH, OR_C , OR_D , R_C , or R_D ;

R_5 is H, OH, OR_C , OR_D , R_C , or R_D ;

R_6 is H, OH, OR_C , OR_D , R_C , or R_D ;

R_7 is 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 ;

5 R_9 is H, OH, OR_C , or OR_D ;

X is -S-, -S(O)-, or -SO₂-;

R_C is -L-Z;

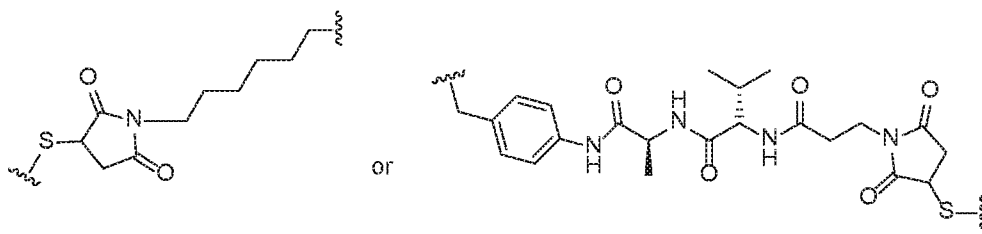
R_D is optionally substituted alkyl (e.g., C₁-C₆ alkyl), optionally substituted heteroalkyl (e.g., C₁-C₆ heteroalkyl), optionally substituted alkenyl (e.g., C₂-C₆ alkenyl), optionally substituted heteroalkenyl (e.g., C₂-C₆ heteroalkenyl), optionally substituted alkynyl (e.g., C₂-C₆ alkynyl), optionally substituted heteroalkynyl (e.g., C₂-C₆ heteroalkynyl), optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

L is a linker, such as optionally substituted alkylene (e.g., C₁-C₆ alkylene), optionally substituted heteroalkylene (C₁-C₆ heteroalkylene), optionally substituted alkenylene (e.g., C₂-C₆ alkenylene), optionally substituted heteroalkenylene (e.g., C₂-C₆ heteroalkenylene), optionally substituted alkynylene (e.g., C₂-C₆ alkynylene), optionally substituted heteroalkynylene (e.g., C₂-C₆ heteroalkynylene), optionally substituted cycloalkylene, optionally substituted heterocycloalkylene, optionally substituted arylene, optionally substituted heteroarylene, a dipeptide, -C(=O)-, a peptide, a disulfide, a hydrazone, a -(CH₂CH₂O)_p- group, wherein p is an integer from 1-6, a ((CH₂)_mO)_n(CH₂)_m- group, where n and each m are each independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; or a combination thereof;

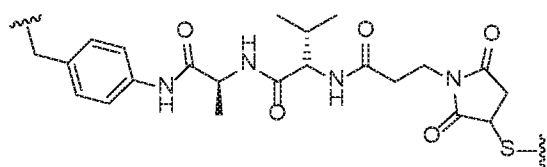
Z is a chemical moiety formed from a coupling reaction between a reactive substituent present on L and a reactive substituent present within an antibody, or antigen-binding fragment thereof, that binds CD2 or CD5; and

wherein Am contains exactly one R_C substituent.

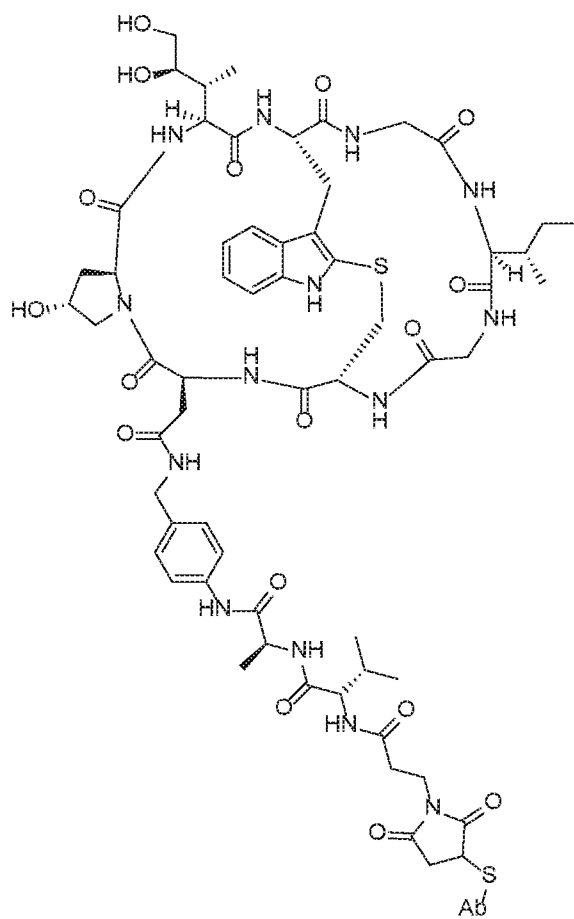
In some embodiments, the linker L and the chemical moiety Z, taken together as L-Z, is



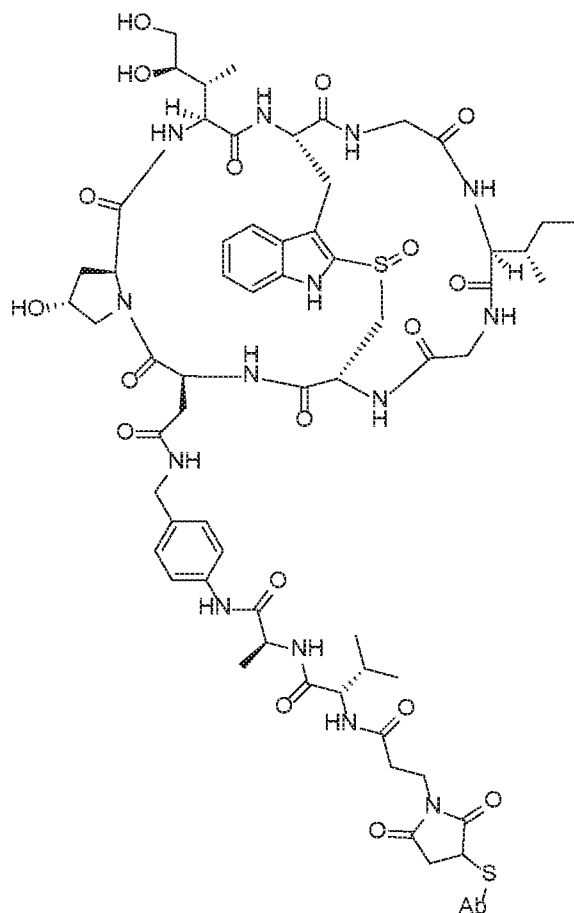
In some embodiments, L-Z is



In some embodiments, Am-L-Z-Ab is



In some embodiments, Am-L-Z-Ab is



In some embodiments, 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:



5

wherein Y is $-\text{C}(=\text{O})-$, $-\text{C}(=\text{S})-$, $-\text{C}(=\text{NR}_E)-$, or $-\text{C}(\text{R}_E\text{R}_{E'})-$; 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 .

10

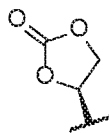
In some embodiments, Am-L-Z is represented by formula (IA) or formula (IB),

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

15



R_3 is H or R_C ;

R_4 is H, OH, OR_C , OR_D , R_C , or R_D ;

R_5 is H, OH, OR_C , OR_D , R_C , or R_D ;

5 R_6 is H, OH, OR_C , OR_D , R_C , or R_D ;

R_7 is H, OH, OR_C , OR_D , R_C , or R_D ;

R_8 is OH, NH_2 , OR_C , or NHR_C ;

R_9 is H or OH; and

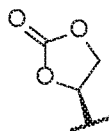
wherein X, R_C and R_D are each as defined above.

10 In some embodiments, Am-L-Z is represented by formula (IA) or formula (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 , together with the oxygen atoms to which they are bound, combine to form:



15 R_3 is H or R_C ;

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

R_6 and R_7 are each H;

R_8 is OH, NH_2 , OR_C , or NHR_C ;

R_9 is H or OH; and

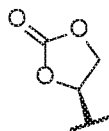
20 wherein X and R_C are as defined above.

In some embodiments, Am-L-Z is represented by formula (IA) or formula (IB),

wherein 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:



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

R_5 is OR_C ;

R_8 is OH or NH_2 ;

R_9 is H or OH; and

30 wherein R_C is as defined above. Such amatoxin conjugates are described, for example, in US Patent Application Publication No. 2016/0002298, the disclosure of which is incorporated

herein by reference in its entirety.

In some embodiments, Am-L-Z is represented by formula (IA) or formula (IB),

wherein R₁ and R₂ are each independently H or OH;

R₃ is R_C;

5 R₄, R₆, and R₇ are each H;

R₅ is H, OH, or OC₁-C₆ alkyl;

R₈ is OH or NH₂;

R₉ is H or OH; and

10 wherein X and R_C are as defined above. Such amatoxin conjugates are described, for example, in US Patent Application Publication No. 2014/0294865, the disclosure of which is incorporated herein by reference in its entirety.

In some embodiments, Am-L-Z is represented by formula (IA) or formula (IB),

wherein R₁ and R₂ are each independently H or OH;

R₃, R₆, and R₇ are each H;

15 R₄ and R₅ are each independently H, OH, OR_C, or R_C;

R₈ is OH or NH₂;

R₉ is H or OH; and

20 wherein X and R_C are as defined above. Such amatoxin conjugates are described, for example, in US Patent Application Publication No. 2015/0218220, the disclosure of which is incorporated herein by reference in its entirety.

In some embodiments, Am-L-Z is represented by formula (IA) or formula (IB),

wherein R₁ and R₂ are each independently H or OH;

R₃, R₆, and R₇ are each H;

R₄ and R₅ are each independently H or OH;

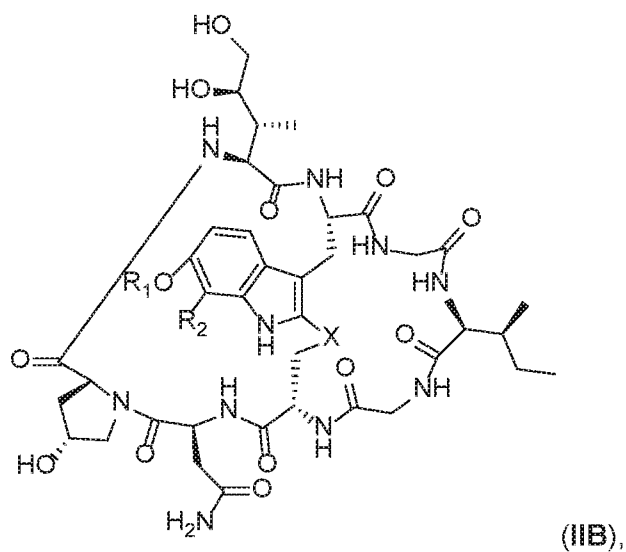
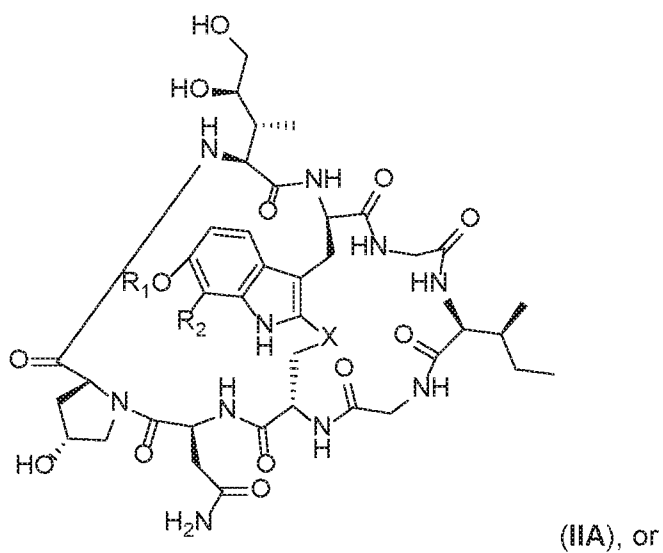
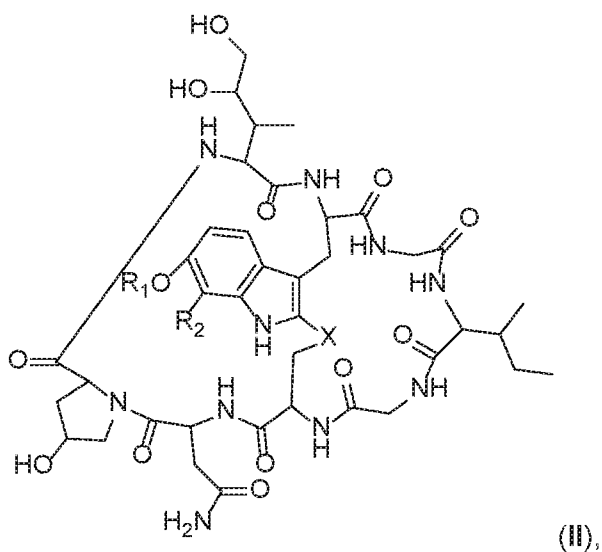
25 R₈ is OH, NH₂, OR_C, or NHR_C;

R₉ is H or OH; and

wherein R_C is as defined above. Such amatoxin conjugates are described, for example, in US Patent Nos. 9,233,173 and 9,399,681, as well as in US 2016/0089450, the disclosures of each of which are incorporated herein by reference in their entirety.

30 Additional amatoxins that may be used for conjugation to an antibody, or antigen-binding fragment thereof, in accordance with the compositions and methods described herein are described, for example, in WO 2016/142049; WO 2016/071856; and WO 2017/046658, the disclosures of each of which are incorporated herein by reference in their entirety.

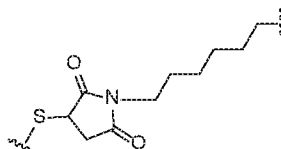
In some embodiments, Am-L-Z is represented by formula (II), formula (IIA), or formula (IIB)



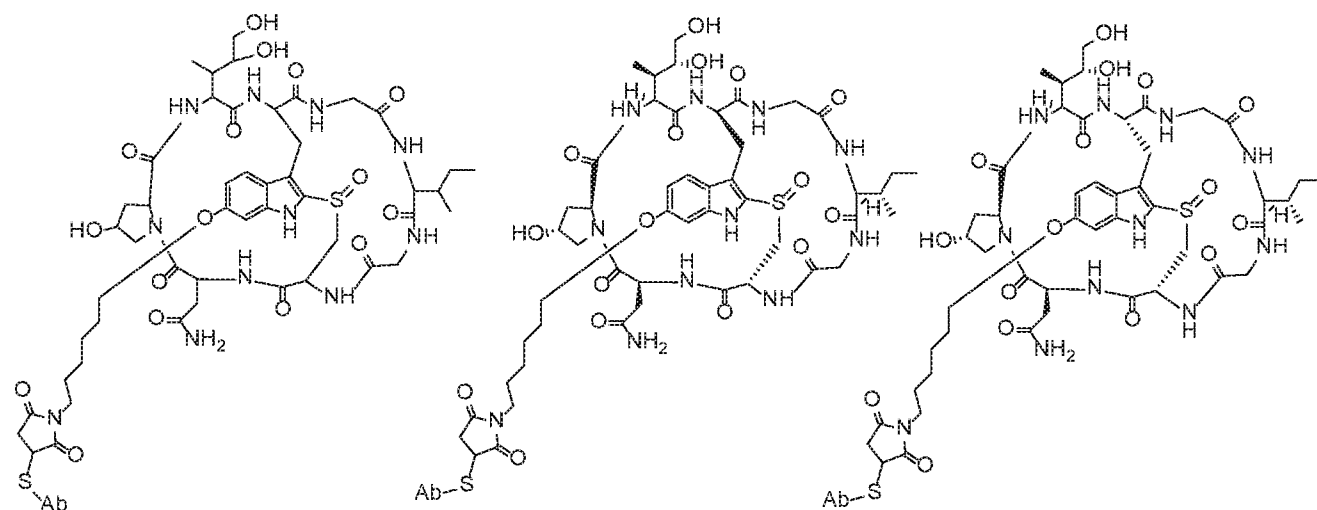
5 wherein X is S, SO, or SO₂; R₁ is H or a linker covalently bound to the antibody or antigen-binding fragment thereof through a chemical moiety Z, formed from a coupling reaction between a reactive substituent present on the linker and a reactive substituent present within an antibody, or

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 moiety 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.

In some embodiments, the linker includes a $-(CH_2)_n-$ unit, where n is an integer from 2-6. In some embodiments, R_1 is the linker and R_2 is H, and the linker and chemical moiety, together as L-Z, is



In some embodiments, Am-L-Z-Ab is one of:

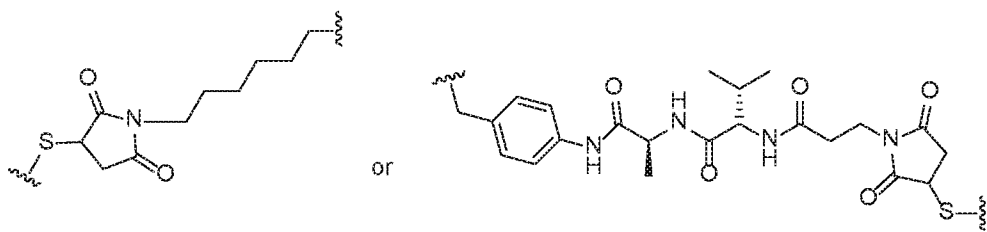


In some embodiments, the cytotoxin is an α -amanitin. In some embodiments, the α -amanitin is a compound of formula III. In some embodiments, the α -amanitin of formula III is attached to an antibody, or antigen-binding fragment thereof, that binds CD2 or CD5 via a linker L. The linker L may be attached to the α -amanitin of formula III at any one of several possible positions (e.g., any of R^1 - R^9) to provide an α -amanitin-linker conjugate of formula I, IA, IB, II, IIA, or IIB. In some embodiments, the linker is attached at position R^1 . In some embodiments, the linker is attached at position R^2 . In some embodiments, the linker is attached at position R^3 . In some embodiments, the linker is attached at position R^4 . In some embodiments, the linker is attached at position R^5 . In some embodiments, the linker is attached at position R^6 . In some embodiments, the linker is attached at position R^7 . In some embodiments, the linker is attached at position R^8 . In some embodiments, the linker is attached at position R^9 . In some embodiments, the linker includes a hydrazine, a disulfide, a thioether or a dipeptide. In some embodiments, the linker includes a dipeptide selected from Val-Ala and Val-Cit. In some embodiments, the linker includes a

para-aminobenzyl group (PAB). In some embodiments, the linker includes the moiety PAB-Cit-Val. In some embodiments, the linker includes the moiety PAB-Ala-Val. In some embodiments, the linker includes a $-(C=O)(CH_2)_n-$ unit, wherein n is an integer from 1-6

In some embodiments, the linker includes a $-(CH_2)_n-$ unit, where n is an integer from 2-

6. In some embodiments, the linker is $-PAB-Cit-Val-((C=O)(CH_2)_n)-$. In some embodiments, the linker is $-PAB-Ala-Val-((C=O)(CH_2)_n)-$. In some embodiments, the linker L and the chemical moiety Z, taken together as L-Z, is



Antibodies, and antigen-binding fragments, for use with the compositions and methods described herein can be conjugated to an amatoxin, such as α -amanitin or a variant thereof, using conjugation techniques known in the art or described herein. For instance, antibodies, and antigen-binding fragments thereof, that recognize and bind CD2 or CD5 can be conjugated to an amatoxin, such as α -amanitin or a variant thereof, as described in US 2015/0218220, the disclosure of which is incorporated herein by reference as it pertains, for example, to amatoxins, such as α -amanitin and variants thereof, as well as covalent linkers that can be used for covalent conjugation. . Synthetic methods of making amatoxins are described in, for example, U.S. Patent No. 9,676,702, which is incorporated by reference herein with respect to the synthetic methods disclosed therein.

Antibodies, or antigen-binding fragments, for use with the compositions and methods described herein can be conjugated to an amatoxin, such as α -amanitin or a variant thereof, using conjugation techniques known in the art or described herein. For instance, antibodies, or antigen-binding fragments thereof, that recognize and bind CD2 or CD5 can be conjugated to an amatoxin, such as α -amanitin or a variant thereof, as described in US 2015/0218220, the disclosure of which is incorporated herein by reference as it pertains, for example, to amatoxins, such as α -amanitin and variants thereof, as well as covalent linkers that can be used for covalent conjugation.

Exemplary antibody- drug conjugates useful in conjunction with the methods described herein may be formed by the reaction of an antibody, or an antigen-binding fragment thereof, with an amatoxin that is conjugated to a linker containing a substituent suitable for reaction with a reactive residue on the antibody, or the antigen-binding fragment thereof. Amatoxins that are conjugated to a linker containing a substituent suitable for reaction with a reactive residue on the antibody, or antigen-binding fragment thereof, described herein include, without limitation, 7'C-(4-(6-(maleimido)hexanoyl)piperazin-1-yl)-amatoxin; 7'C-(4-(6-(maleimido)hexanamido)piperidin-1-yl)-amatoxin; 7'C-(4-(6-(6-(maleimido)hexanamido)hexanoyl)piperazin-1-yl)-amatoxin; 7'C-(4-(4-

- ((maleimido)methyl)cyclohexanecarbonyl)piperazin-1-yl)-amatoxin; 7'C-(4-(6-(4-
 ((maleimido)methyl)cyclohexanecarboxamido)hexanoyl)piperazin-1-yl)-amatoxin; 7'C-(4-(2-(6-
 (maleimido)hexanamido)ethyl)piperidin-1-yl)-amatoxin; 7'C-(4-(2-(6-(6-
 (maleimido)hexanamido)hexanamido)ethyl)piperidin-1-yl)-amatoxin; 7'C-(4-(2-(4-
 5 ((maleimido)methyl)cyclohexanecarboxamido)ethyl)piperidin-1-yl)-amatoxin; 7'C-(4-(2-(6-(4-
 ((maleimido)methyl)cyclohexanecarboxamido)hexanamido)ethyl)piperidin-1-yl)-amatoxin; 7'C-(4-
 (2-(3-carboxypropanamido)ethyl)piperidin-1-yl)-amatoxin; 7'C-(4-(2-(2-
 bromoacetamido)ethyl)piperidin-1-yl)-amatoxin; 7'C-(4-(2-(3-(pyridin-2-
 yldisulfanyl)propanamido)ethyl)piperidin-1-yl)-amatoxin; 7'C-(4-(2-(4-
 10 (maleimido)butanamido)ethyl)piperidin-1-yl)-amatoxin; 7'C-(4-(2-(maleimido)acetyl)piperazin-1-yl)-
 amatoxin; 7'C-(4-(3-(maleimido)propanoyl)piperazin-1-yl)-amatoxin; 7'C-(4-(4-
 (maleimido)butanoyl)piperazin-1-yl)-amatoxin; 7'C-(4-(2-(6-(4-
 ((maleimido)methyl)cyclohexanecarboxamido)hexanamido)ethyl)piperidin-1-yl)-amatoxin; 7'C-(3-
 ((6-(maleimido)hexanamido)methyl)pyrrolidin-1-yl)-amatoxin; 7'C-(3-((6-(6-
 15 (maleimido)hexanamido)hexanamido)methyl)pyrrolidin-1-yl)-amatoxin; 7'C-(3-((4-
 ((maleimido)methyl)cyclohexanecarboxamido)methyl)pyrrolidin-1-yl)-amatoxin; 7'C-(3-((6-((4-
 (maleimido)methyl)cyclohexanecarboxamido)hexanamido)methyl)pyrrolidin-1-yl)-amatoxin; 7'C-(4-
 (2-(6-(2-(aminooxy)acetamido)hexanamido)ethyl)piperidin-1-yl)-amatoxin; 7'C-(4-(2-(4-(2-
 (aminooxy)acetamido)butanamido)ethyl)piperidin-1-yl)-amatoxin; 7'C-(4-(4-(2-
 20 (aminooxy)acetamido)butanoyl)piperazin-1-yl)-amatoxin; 7'C-(4-(6-(2-
 (aminooxy)acetamido)hexanoyl)piperazin-1-yl)-amatoxin; 7'C-((4-(6-
 (maleimido)hexanamido)piperidin-1-yl)methyl)-amatoxin; 7'C-((4-(2-(6-
 (maleimido)hexanamido)ethyl)piperidin-1-yl)methyl)-amatoxin; 7'C-((4-(6-
 (maleimido)hexanoyl)piperazin-1-yl)methyl)-amatoxin; (R)-7'C-((3-((6-
 25 (maleimido)hexanamido)methyl)pyrrolidin-1-yl)methyl)-amatoxin; (S)-7'C-((3-((6-
 (maleimido)hexanamido)methyl)pyrrolidin-1-yl)methyl)-amatoxin; 7'C-((4-(2-(6-(6-
 (maleimido)hexanamido)hexanamido)ethyl)piperidin-1-yl)methyl)-amatoxin; 7'C-((4-(2-(4-
 ((maleimido)methyl)cyclohexanecarboxamido)ethyl)piperidin-1-yl)methyl)-amatoxin; 7'C-((4-(2-(6-
 (4-((maleimido)methyl)cyclohexanecarboxamido)hexanamido)ethyl)piperidin-1-yl)methyl)-
 30 amatoxin; 7'C-((4-(2-(6-(maleimido)hexanamido)ethyl)piperazin-1-yl)methyl)-amatoxin; 7'C-((4-(2-
 (6-(6-(maleimido)hexanamido)hexanamido)ethyl)piperazin-1-yl)methyl)-amatoxin; 7'C-((4-(2-(4-
 ((maleimido)methyl)cyclohexanecarboxamido)ethyl)piperazin-1-yl)methyl)-amatoxin; 7'C-((4-(2-(6-
 (4-((maleimido)methyl)cyclohexanecarboxamido)hexanamido)ethyl)piperazin-1-yl)methyl)-
 amatoxin; 7'C-((3-((6-(6-(maleimido)hexanamido)hexanamido)-S-methyl)pyrrolidin-1-yl)methyl)-
 35 amatoxin; 7'C-((3-((6-(6-(maleimido)hexanamido)hexanamido)-R-methyl)pyrrolidin-1-yl)methyl)-
 amatoxin; 7'C-((3-((4-((maleimido)methyl)cyclohexanecarboxamido)-S-methyl)pyrrolidin-1-
 yl)methyl)-amatoxin; 7'C-((3-((4-((maleimido)methyl)cyclohexanecarboxamido)-R-

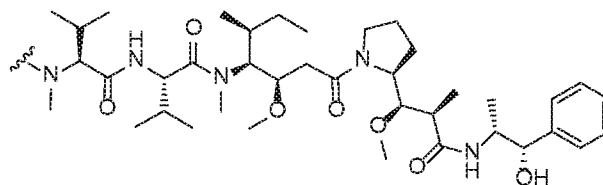
methyl)pyrrolidin-1-yl)methyl)-amatoxin; 7'C-((3-((6-(4-
 ((maleimido)methyl)cyclohexanecarboxamido)hexanamido)methyl)pyrrolidin-1-yl)methyl)-
 amatoxin; 7'C-((4-(2-(3-carboxypropanamido)ethyl)piperazin-1-yl)methyl)-amatoxin; 7'C-((4-(6-(6-
 (maleimido)hexanamido)hexanoyl)piperazin-1-yl)methyl)-amatoxin; 7'C-((4-(6-(4-
 5 ((maleimido)methyl)cyclohexanecarboxamido)hexanoyl)piperazin-1-yl)methyl)-amatoxin; 7'C-((4-
 (2-(maleimido)acetyl)piperazin-1-yl)methyl)-amatoxin; 7'C-((4-(3-(maleimido)propanoyl)piperazin-
 1-yl)methyl)-amatoxin; 7'C-((4-(4-(maleimido)butanoyl)piperazin-1-yl)methyl)-amatoxin; 7'C-((4-(2-
 (2-(maleimido)acetamido)ethyl)piperidin-1-yl)methyl)-amatoxin; 7'C-((4-(2-(4-
 (maleimido)butanamido)ethyl)piperidin-1-yl)methyl)-amatoxin; 7'C-((4-(2-(6-(4-
 10 ((maleimido)methyl)cyclohexanecarboxamido)hexanamido)ethyl)piperidin-1-yl)methyl)-amatoxin;
 7'C-((3-((6-(maleimido)hexanamido)methyl)azetidin-1-yl)methyl)-amatoxin; 7'C-((3-(2-(6-
 (maleimido)hexanamido)ethyl)azetidin-1-yl)methyl)-amatoxin; 7'C-((3-((4-
 ((maleimido)methyl)cyclohexanecarboxamido)methyl)azetidin-1-yl)methyl)-amatoxin; 7'C-((3-(2-(4-
 ((maleimido)methyl)cyclohexanecarboxamido)ethyl)azetidin-1-yl)methyl)-amatoxin; 7'C-((3-(2-(6-(4-
 15 ((maleimido)methyl)cyclohexanecarboxamido)hexanamido)ethyl)azetidin-1-yl)methyl)-amatoxin;
 7'C-(((2-(6-(maleimido)-N-methylhexanamido)ethyl)(methyl)amino)methyl)-amatoxin; 7'C-(((4-(6-
 (maleimido)-N-methylhexanamido)butyl)(methyl)amino)methyl)-amatoxin; 7'C-(((2-(2-(6-
 (maleimido)hexanamido)ethyl)aziridin-1-yl)methyl)-amatoxin; 7'C-(((2-(2-(6-(4-
 ((maleimido)methyl)cyclohexanecarboxamido)hexanamido)ethyl)aziridin-1-yl)methyl)-amatoxin;
 20 7'C-((4-(6-(6-(2-(aminooxy)acetamido)hexanamido)hexanoyl)piperazin-1-yl)methyl)-amatoxin; 7'C-
 ((4-(1-(aminooxy)-2-oxo-6,9,12,15-tetraoxa-3-azaheptadecan-17-oyl)piperazin-1-yl)methyl)-
 amatoxin; 7'C-((4-(2-(2-(aminooxy)acetamido)acetyl)piperazin-1-yl)methyl)-amatoxin; 7'C-((4-(3-(2-
 (aminooxy)acetamido)propanoyl)piperazin-1-yl)methyl)-amatoxin; 7'C-((4-(4-(2-
 (aminooxy)acetamido)butanoyl)piperazin-1-yl)methyl)-amatoxin; 7'C-((4-(2-(6-(2-
 25 (aminooxy)acetamido)hexanamido)ethyl)piperidin-1-yl)methyl)-amatoxin; 7'C-((4-(2-(2-(2-
 (aminooxy)acetamido)acetamido)ethyl)piperidin-1-yl)methyl)-amatoxin; 7'C-((4-(2-(4-(2-
 (aminooxy)acetamido)butanamido)ethyl)piperidin-1-yl)methyl)-amatoxin; 7'C-((4-(20-(aminooxy)-
 4,19-dioxo-6,9,12,15-tetraoxa-3,18-diazaicosyl)piperidin-1-yl)methyl)-amatoxin; 7'C-(((2-(6-(2-
 (aminooxy)acetamido)-N-methylhexanamido)ethyl)(methyl)amino)methyl)-amatoxin; 7'C-(((4-(6-(2-
 30 (aminooxy)acetamido)-N-methylhexanamido)butyl)(methyl)amino)methyl)-amatoxin; 7'C-((3-((6-(4-
 ((maleimido)methyl)cyclohexanecarboxamido)hexanamido)methyl)pyrrolidin-1-yl)-S-methyl)-
 amatoxin; 7'C-((3-((6-(4-((maleimido)methyl)cyclohexanecarboxamido)hexanamido)-R-
 methyl)pyrrolidin-1-yl)methyl)-amatoxin; 7'C-((4-(2-(2-bromoacetamido)ethyl)piperazin-1-
 yl)methyl)-amatoxin; 7'C-((4-(2-(2-bromoacetamido)ethyl)piperidin-1-yl)methyl)-amatoxin; 7'C-((4-
 35 (2-(3-(pyridine-2-yl)disulfanyl)propanamido)ethyl)piperidin-1-yl)methyl)-amatoxin; 6'O-(6-(6-
 (maleimido)hexanamido)hexyl)-amatoxin; 6'O-(5-(4-
 ((maleimido)methyl)cyclohexanecarboxamido)pentyl)-amatoxin; 6'O-(2-((6-(maleimido)hexyl)oxy)-

2-oxoethyl)-amatoxin; 6'O-((6-(maleimido)hexyl)carbamoyl)-amatoxin; 6'O-((6-(4-
 ((maleimido)methyl)cyclohexanecarboxamido)hexyl)carbamoyl)-amatoxin; 6'O-(6-(2-
 bromoacetamido)hexyl)-amatoxin; 7'C-(4-(6-(azido)hexanamido)piperidin-1-yl)-amatoxin; 7'C-(4-
 (hex-5-ynoylamino)piperidin-1-yl)-amatoxin; 7'C-(4-(2-(6-(maleimido)hexanamido)ethyl)piperazin-
 1-yl)-amatoxin; 7'C-(4-(2-(6-(6-(maleimido)hexanamido)hexanamido)ethyl)piperazin-1-yl)-
 amatoxin; 6'O-(6-(6-(11,12-didehydro-5,6-dihydro-dibenz[b,f]azocin-5-yl)-6-oxohexanamido)hexyl)-
 amatoxin; 6'O-(6-(hex-5-ynoylamino)hexyl)-amatoxin; 6'O-(6-(2-(aminooxy)acetyl-amido)hexyl)-
 amatoxin; 6'O-((6-aminooxy)hexyl)-amatoxin; and 6'O-(6-(2-iodoacetamido)hexyl)-amatoxin. The
 foregoing linkers, among others useful in conjunction with the compositions and methods
 described herein, are described, for example, in US Patent Application Publication No.
 2015/0218220, the disclosure of which is incorporated herein by reference in its entirety.

Anti-CD5 or CD2 antibodies and antigen-binding fragments thereof, including those described
 herein, can be conjugated to a cytotoxin that is an auristatin (U.S. Pat. Nos. 5,635,483; 5,780,588).
 Auristatins are anti-mitotic agents that interfere with microtubule dynamics, GTP hydrolysis, and
 nuclear and cellular division (Woyke et al (2001) Antimicrob. Agents and Chemother. 45(12):3580-
 3584) and have anticancer (U.S. Pat. No. 5,663,149) and antifungal activity (Pettit et al (1998)
 Antimicrob. Agents Chemother. 42:2961-2965). (U.S. Pat. Nos. 5,635,483; 5,780,588). The auristatin
 drug moiety may be attached to the antibody through the N (amino) terminus or the C (carboxyl)
 terminus of the peptidic drug moiety (WO 02/088172).

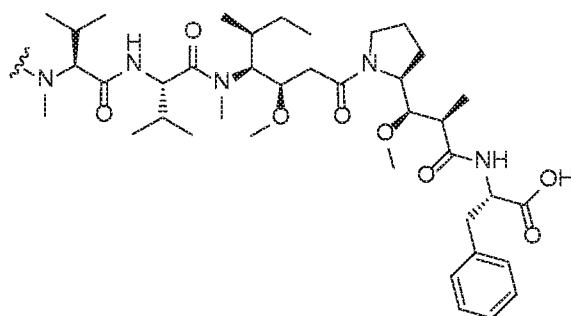
Exemplary auristatin embodiments include the N-terminus linked monomethylauristatin drug
 moieties DE and DF, (MMAE and MMAF, respectively), disclosed in Senter et al, Proceedings of the
 American Association for Cancer Research, Volume 45, Abstract Number 623, presented Mar. 28,
 2004, the disclosure of which is herein incorporated by reference in its entirety.

An exemplary auristatin embodiment is MMAE, wherein the wavy line indicates the point of
 covalent attachment to the linker of an antibody-linker conjugate (-L-Z-Ab or -L-Z', as described
 herein),



wherein the wavy line indicates the point of covalent attachment to the linker of an antibody-
 drug or drug-linker conjugate (-L-Z-Ab or -L-Z', as described herein).

Another exemplary auristatin embodiment is MMAF:



wherein the wavy line indicates the point of covalent attachment to the linker of an antibody-linker conjugate (-L-Z-Ab or -L-Z', as described herein), as disclosed in US 2005/0238649.

5 Auristatins may be prepared according to the methods of: U.S. Pat. No. 5,635,483; U.S. Pat. No. 5,780,588; Pettit et al (1989) J. Am. Chem. Soc. 111:5463-5465; Pettit et al (1998) Anti-Cancer Drug Design 13:243-277; Pettit, G. R., et al. Synthesis, 1996, 719-725; Pettit et al (1996) J. Chem. Soc. Perkin Trans. 15:859-863; and Doronina (2003) Nat. Biotechnol. 21(7):778-784.

10 Maytansinoids

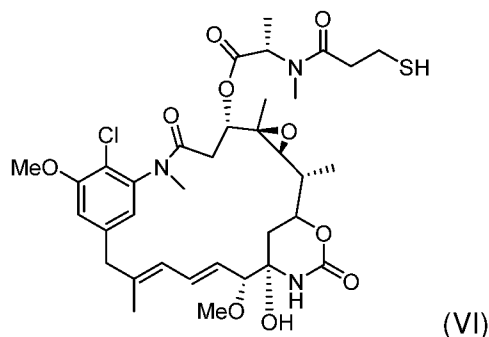
Anti-CD5 or CD2 antibodies and antigen-binding fragments thereof described herein can be conjugated to a cytotoxin that is a microtubule binding agent. In some embodiments, the microtubule binding agent is a maytansine, a maytansinoid or a maytansinoid analog. Maytansinoids are mitotic inhibitors which bind microtubules and act by inhibiting tubulin polymerization. Maytansine was first isolated from the east African shrub Maytenus serrata (U.S. Pat. No. 3,896,111). Subsequently, it was discovered that certain microbes also produce maytansinoids, such as maytansinol and C-3 maytansinol esters (U.S. Pat. No. 4,151,042). Synthetic maytansinol and derivatives and analogues thereof are disclosed, for example, in U.S. Pat. Nos. 4,137,230; 4,248,870; 4,256,746; 4,260,608; 15 4,265,814; 4,294,757; 4,307,016; 4,308,268; 4,308,269; 4,309,428; 4,313,946; 4,315,929; 4,317,821; 4,322,348; 4,331,598; 4,361,650; 4,364,866; 4,424,219; 4,450,254; 4,362,663; and 4,371,533. Maytansinoid drug moieties are attractive drug moieties in antibody drug conjugates because they are: (i) relatively accessible to prepare by fermentation or chemical modification, derivatization of fermentation products, (ii) amenable to derivatization with functional groups suitable for conjugation 20 through the non-disulfide linkers to antibodies, (iii) stable in plasma, and (iv) effective against a variety of tumor cell lines.

Examples of suitable maytansinoids include esters of maytansinol, synthetic maytansinol, and maytansinol analogs and derivatives. Included herein are any cytotoxins that inhibit microtubule formation and that are highly toxic to mammalian cells, as are maytansinoids, maytansinol, and 30 maytansinol analogs, and derivatives.

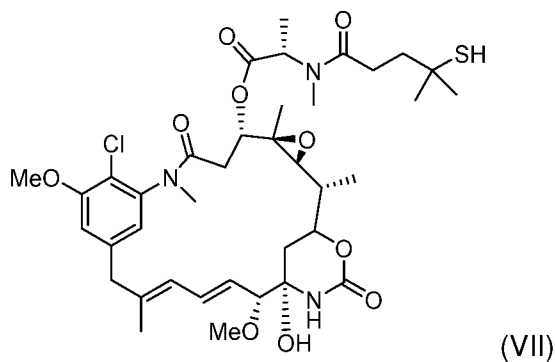
Examples of suitable maytansinol esters include those having a modified aromatic ring and

those having modifications at other positions. Such suitable maytansinoids are disclosed in U.S. Pat. Nos. 4,137,230; 4,151,042; 4,248,870; 4,256,746; 4,260,608; 4,265,814; 4,294,757; 4,307,016; 4,308,268; 4,308,269; 4,309,428; 4,313,946; 4,315,929; 4,317,821; 4,322,348; 4,331,598; 4,361,650; 4,362,663; 4,364,866; 4,424,219; 4,450,254; 4,322,348; 4,362,663; 4,371,533; 5,208,020; 5,416,064; 5,475,092; 5,585,499; 5,846,545; 6,333,410; 7,276,497; and 7,473,796, the disclosures of each of which are incorporated herein by reference as they pertain to maytansinoids and derivatives thereof.

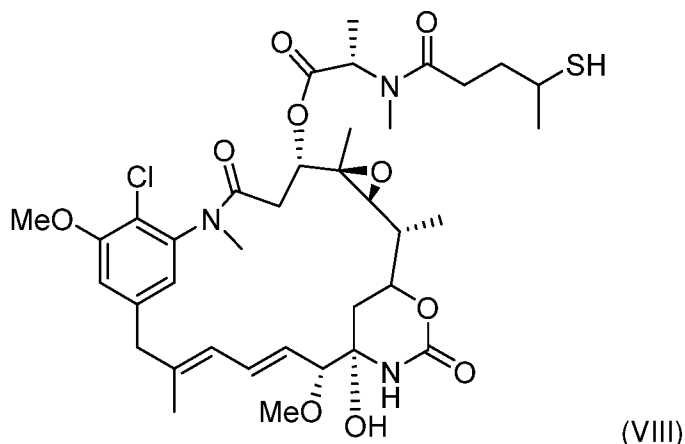
In some embodiments, the antibody-drug conjugates (ADCs) of the present disclosure utilize the thiol-containing maytansinoid (DM1), formally termed N^{2'}-deacetyl-N^{2'}-(3-mercapto-1-oxopropyl)-maytansine, as the cytotoxic agent. DM1 is represented by the following structural formula VI:



In another embodiment, the conjugates of the present invention utilize the thiol-containing maytansinoid N^{2'}-deacetyl-N^{2'}-(4-methyl-4-mercapto-1-oxopentyl)-maytansine (e.g., DM4) as the cytotoxic agent. DM4 is represented by the following structural formula VII:



Another maytansinoid comprising a side chain that contains a sterically hindered thiol bond is N^{2'}-deacetyl-N^{2'}-(4-mercapto-1-oxopentyl)-maytansine (termed DM3), represented by the following structural formula VII:



Each of the maytansinoids taught in U.S. Pat. Nos. 5,208,020 and 7,276,497, can also be used in the conjugates of the present disclosure. In this regard, the entire disclosure of 5,208,020 and 7,276,497 is incorporated herein by reference.

Many positions on maytansinoids can serve as the position to covalently bond the linking moiety and, hence the antibodies or antigen-binding fragments thereof (-L-Z-Ab or -L-Z', as described herein). For example, the C-3 position having a hydroxyl group, the C-14 position modified with hydroxymethyl, the C-15 position modified with hydroxy and the C-20 position having a hydroxy group are all expected to be useful. In some embodiments, the C-3 position serves as the position to covalently bond the linker moiety, and in some particular embodiments, the C-3 position of maytansinol serves as the position to covalently bond the linking moiety. There are many linking groups known in the art for making antibody-maytansinoid conjugates, including, for example, those disclosed in U.S. Pat. Nos. 5,208,020, 6,441,163, and EP Patent No. 0425235 B1; Chari et al., Cancer Research 52:127-131 (1992); and U.S. 2005/0169933 A1, the disclosures of which are hereby expressly incorporated by reference. Additional linking groups are described and exemplified herein.

The present invention also includes various isomers and mixtures of maytansinoids and conjugates. Certain compounds and conjugates of the present invention may exist in various stereoisomeric, enantiomeric, and diastereomeric forms. Several descriptions for producing such antibody-maytansinoid conjugates are provided in U.S. Pat. Nos. 5,208,020; 5,416,064; 6,333,410; 6,441,163; 6,716,821; and 7,368,565, each of which is incorporated herein in its entirety.

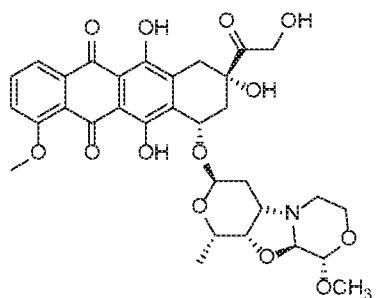
Anthracyclines

In other embodiments, anti-CD5 or CD2 antibodies and antigen-binding fragments thereof described herein can be conjugated to a cytotoxin that is an anthracycline molecule. Anthracyclines are antibiotic compounds that exhibit cytotoxic activity. Studies have indicated that anthracyclines may operate to kill cells by a number of different mechanisms including: 1)

intercalation of the drug molecules into the DNA of the cell thereby inhibiting DNA-dependent nucleic acid synthesis; 2) production by the drug of free radicals which then react with cellular macromolecules to cause damage to the cells or 3) interactions of the drug molecules with the cell membrane [see, e.g., C. Peterson et al., "Transport And Storage Of Anthracycline In
 5 Experimental Systems And Human Leukemia" in Anthracycline Antibiotics In Cancer Therapy; N.R. Bachur, "Free Radical Damage" id. at pp.97-102]. Because of their cytotoxic potential anthracyclines have been used in the treatment of numerous cancers such as leukemia, breast carcinoma, lung carcinoma, ovarian adenocarcinoma and sarcomas [see e.g., P.H- Wiernik, in Anthracycline: Current Status And New Developments p 11]. Commonly used anthracyclines
 10 include doxorubicin, epirubicin, idarubicin and daunomycin. In some embodiments, the cytotoxin is an anthracycline selected from the group consisting of daunorubicin, doxorubicin, epirubicin, and idarubicin. Representative examples of anthracyclines include, but are not limited to daunorubicin (Cerubidine; Bedford Laboratories), doxorubicin (ADRIAMYCIN®; Bedford Laboratories; also referred to as doxorubicin hydrochloride, hydroxy-daunorubicin, and RUBEX®), epirubicin
 15 (ELLENCE®; Pfizer), and idarubicin (IDAMYCIN®; Pfizer Inc.)

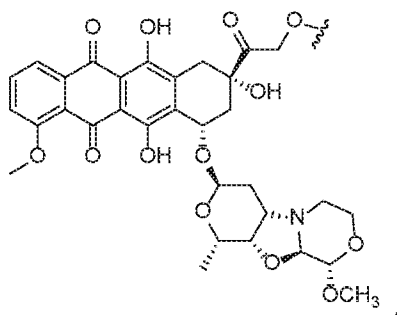
The anthracycline analog, doxorubicin (ADRIAMYCIN®) is thought to interact with DNA by intercalation and inhibition of the progression of the enzyme topoisomerase II, which unwinds DNA for transcription. Doxorubicin stabilizes the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being resealed and thereby stopping the
 20 process of replication. Doxorubicin and daunorubicin (DAUNOMYCIN) are prototype cytotoxic natural product anthracycline chemotherapeutics (Sessa et al., (2007) Cardiovasc. Toxicol. 7:75-79).

One non-limiting example of a suitable anthracycline for use herein is PNU-159682 ("PNU"). PNU exhibits greater than 3000-fold cytotoxicity relative to the parent nemorubicin (Quintieri et al., Clinical Cancer Research 2005, 11, 1608-1617). PNU is represented by structural
 25 formula:



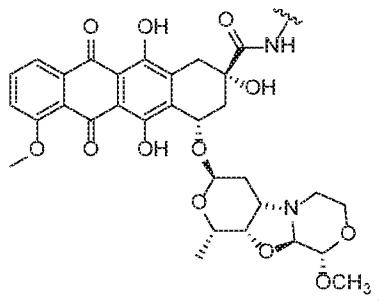
Multiple positions on anthracyclines such as PNU can serve as the position to covalently bond the linking moiety and, hence the bispecific binding agents as described herein. For example, linkers may be introduced through modifications to the hydroxymethyl ketone side chain.

In some embodiments, the cytotoxin is a PNU derivative represented by structural formula:



wherein the wavy line indicates the point of covalent attachment to the linker of the ADC as described herein.

In some embodiments, the cytotoxin is a PNU derivative represented by structural formula:



5

wherein the wavy line indicates the point of covalent attachment to the linker of the ADC as described herein.

Benzodiazepine Cytotoxins

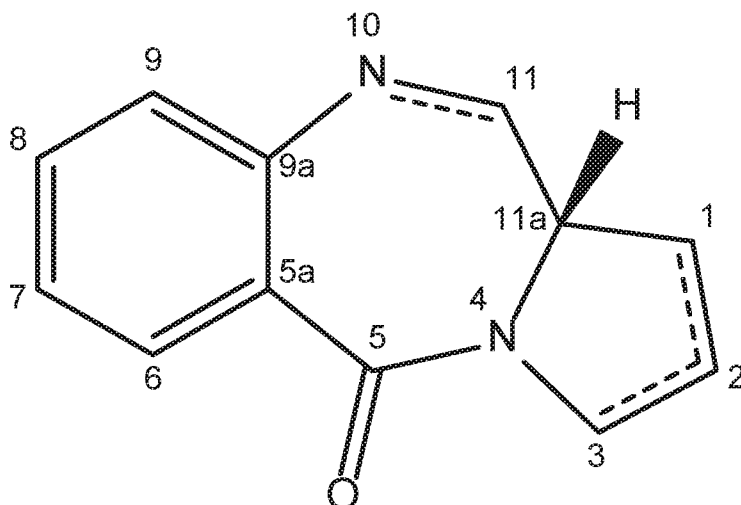
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Anti-CD45 antibodies, and antigen-binding fragments thereof, as described herein (including e.g., bispecific and biparatopic antibodies) can be conjugated to a cytotoxin comprising a benzodiazepine moiety, such as a PBD or an IGN, as described herein.

Pyrrolobenzodiazepines (PBDs)

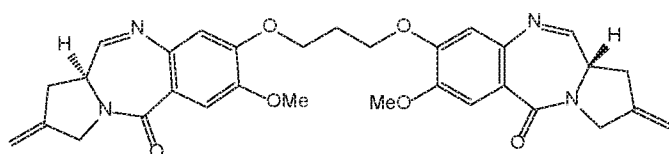
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PBDs are of the general structure:



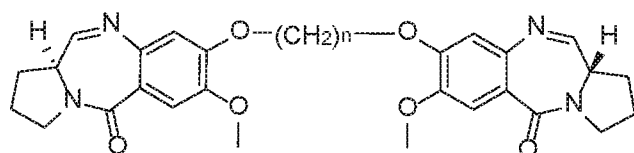
They differ in the number, type and position of substituents, in both their aromatic ("A") rings and pyrrolo ("C") rings, and in the degree of saturation of the C ring. In the diazepine B-ring there is either an imine (N=C), a carbinolamine (NH-CH(OH)), or a carbinolamine methyl ether (NH-CH(OMe)) at the N10-C11 position. This position is the electrophilic moiety responsible for DNA alkylation. All of the known natural product PBDs have an (S)-configuration at the chiral C11a position which provides them with a right-handed twist when viewed from the C ring towards the A ring. This provides the appropriate three-dimensional shape for isohelicity with the minor groove of B-form DNA, leading to a tight fit at the binding site (Kohn, In *Antibiotics III*. Springer-Verlag, New York, pp. 3-11 (1975); Hurley and Needham-VanDevanter, *Acc. Chem. Res.*, 19, 230-237 (1986)). The ability of PBDs to form adducts in the minor groove enables them to interfere with DNA processing, resulting in anti-tumor activity.

It has been previously disclosed that the biological activity of these molecules can be potentiated by joining two PBD units together through their C8-hydroxyl functionalities via a flexible alkylene linker (Bose, D. S., et al., *J. Am. Chem. Soc.*, 114, 4939-4941 (1992); Thurston, D. E., et al., *J. Org. Chem.*, 61, 8141-8147 (1996)). The PBD dimers are thought to form sequence-selective DNA lesions, such as the palindromic 5'-Pu-GATC-Py-3' inter-strand cross-link (Smellie, M., et al., *Biochemistry*, 42, 8232-8239 (2003); Martin, C., et al., *Biochemistry*, 44, 4135-4147) which is thought to be mainly responsible for their biological activity. An advantageous dimeric pyrrolobenzodiazepine compound has been described by Gregson et al. (*Chem. Commun.* 1999, 797-798; "compound 1", and by Gregson et al. (*J. Med. Chem.* 2001, 44, 1161-1174; "compound 4a"). This compound, also known as SG2000, is of the structural formula:



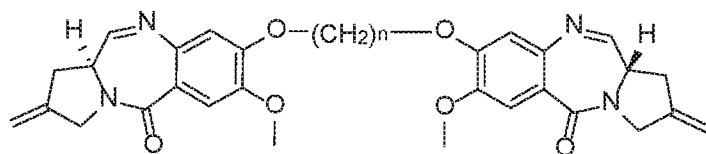
Generally, modifications to the pyrrolidine alkene moiety provide the handle with which to covalently bond the linking moiety and, hence the antibodies or antigen-binding fragments thereof (-L-Z' and -L-Z-Ab, respectively, as described herein). Alternatively, a linker may be attached at position N10.

In some embodiments, the cytotoxin is a pyrrolobenzodiazepine dimer represented by the structural formula:



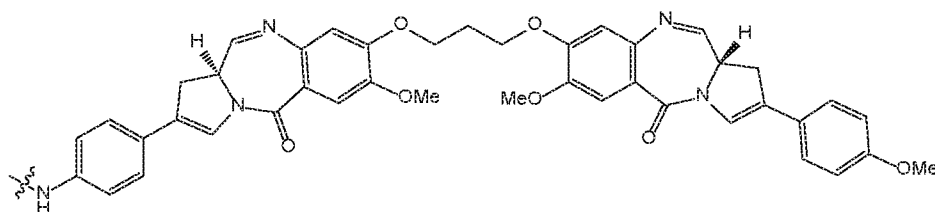
wherein n is an integer from 2 to 5. The compound of this formula wherein n is 3 is known as DSB-120 (Bose et al., *J. Am. Chem. Soc.* 1992, 114, 4939-4941).

In some embodiments, the cytotoxin is a pyrrolobenzodiazepine dimer represented by the structural formula:



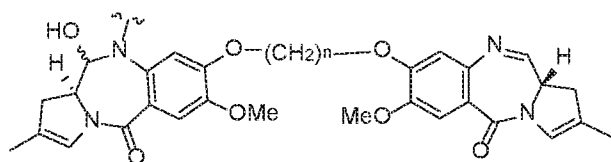
wherein n is an integer from 2 to 5. The compound of this formula wherein n is 3 is known as SJG-136 (Gregson et al., J. Med. Chem. 2001, 44, 737 – 748). The compound of this formula wherein n is 5 is known as DRG-16 (Gregson et al., Med. Chem. 2004;47:1161–1174).

In some embodiments, the cytotoxin is a pyrrolobenzodiazepine dimer represented by the structural formula:



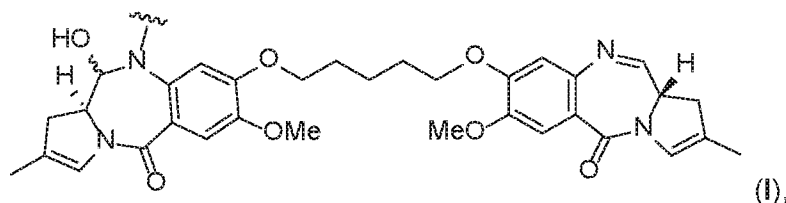
wherein the wavy line indicates the point of covalent attachment to the linker of the ADC as described herein. ADCs based on this PBD are disclosed in, for example, Sutherland et al., Blood 2013 122:1455-1463, which is incorporated by reference herein in its entirety.

In some embodiments, the cytotoxin is a PBD dimer represented by the structural formula:



wherein n is 3 or 5, and wherein the wavy line indicates the point of covalent attachment to the linker of the ADC as described herein.

In some embodiments, the cytotoxin is a PBD dimer represented by the structural formula (I) below:



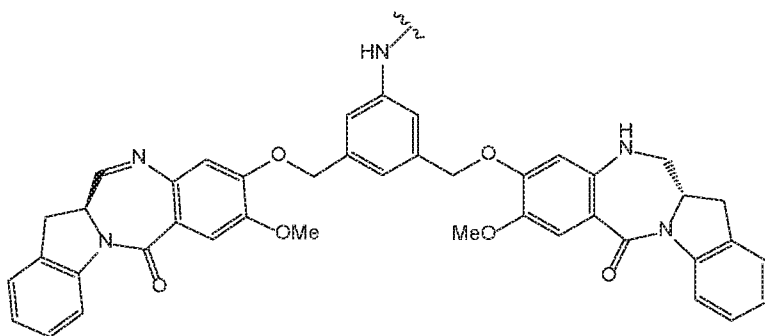
wherein the wavy line indicates the point of covalent attachment to the linker of the ADC as described herein.

Indolinobenzodiazepines (IGNs)

In some embodiments, the antibodies, or antigen-binding fragments thereof, that bind CD45 as described herein can be conjugated to a cytotoxin that is an indolinobenzodiazepine ("IGN") or a cytotoxin that comprises an IGN. In some embodiments, the IGN cytotoxin is an
 5 indolinobenzodiazepine dimer or an indolinobenzodiazepine pseudodimer.

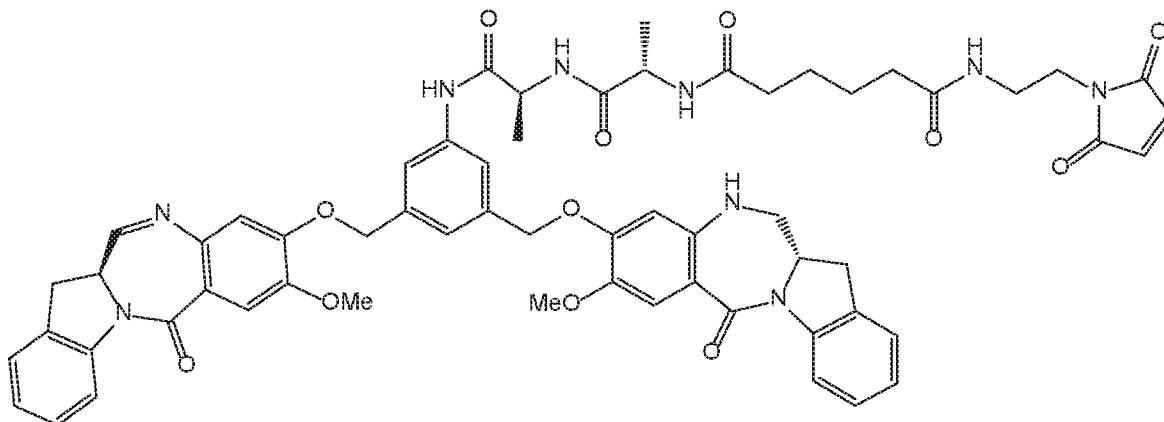
Indolinobenzodiazepine dimers represent a relatively new chemical class of cytotoxins with high *in vitro* potency (low pM range IC₅₀ values) towards cancer cells. Similar to the PBD dimer SJG-136, IGN dimers bind to the minor groove of DNA, and covalently bind to guanine residues via the
 10 two imine functionalities in the dimer, resulting in crosslinking of the DNA. An IGN dimer (IGN 6; replacing the methylene groups of the PBD moiety with phenyl rings) demonstrated ~10-fold higher potency *in vitro* as compared to SJG-136, possibly due to faster rate of adduct formation with DNA IGN (see, e.g., Miller et al., "A New Class of Antibody-Drug Conjugates with Potent DNA Alkylating Activity" Mol. Cancer Ther. 2016, 15(8), 1870-1878). In contrast, IGN pseudodimers comprise a
 15 single reactive indolinobenzodiazepine imine; the second indolinobenzodiazepine in the dimeric cytotoxin is present in reduced (amine) form. Accordingly, IGN pseudodimers alkylate DNA through the single imine moiety present in the dimer, and do not crosslink DNA.

In some embodiments, the cytotoxin is an IGN pseudodimer having a structure of formula:



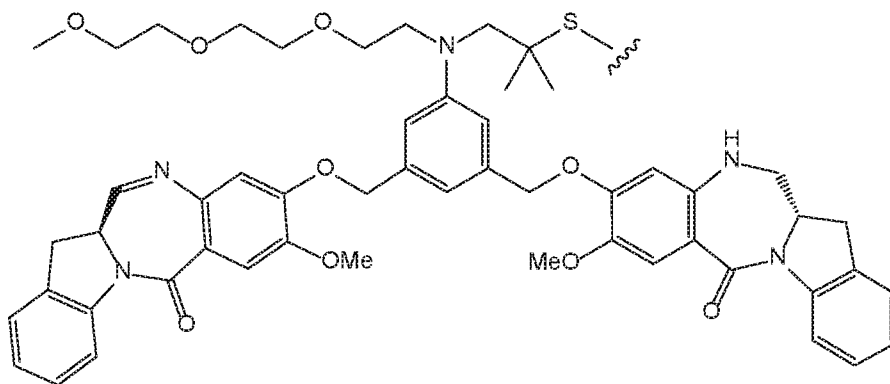
wherein the wavy line indicates the attachment point of the linker.

In some embodiments, the cytotoxin-linker conjugate, prior to conjugation to the antibody and including the reactive substituent Z', taken together as Cy-L-Z', has the structure:



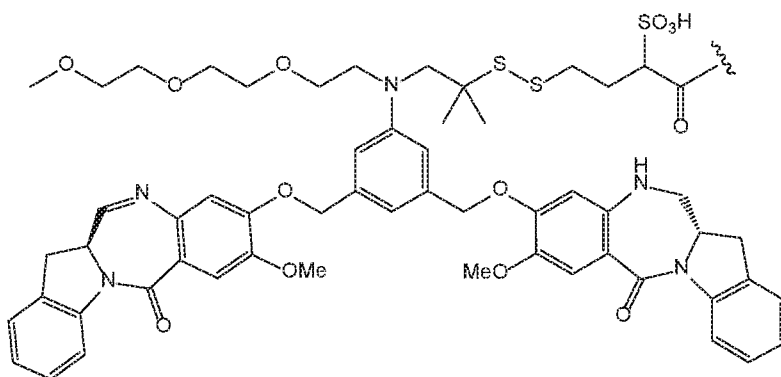
This cytotoxin-linker conjugate is referred to herein as DGN549, and is present in the ADC IMGN632, both of which are disclosed in, for example, International Patent Application Publication No. WO2017004026, which is incorporated by reference herein.

In some embodiments, the cytotoxin is an indolinobenzodiazepine pseudodimer having a structure of formula:



wherein the wavy line indicates the attachment point of the linker. This IGN pseudodimer cytotoxin is referred to herein as DGN462, disclosed in, for example, U.S. Patent Application Publication No. 20170080102, which is incorporated by reference herein.

In some embodiments, the cytotoxin-linker conjugate, prior to conjugation to the antibody and including the chemical moiety Z, taken together as Cy-L-Z, has the structure:



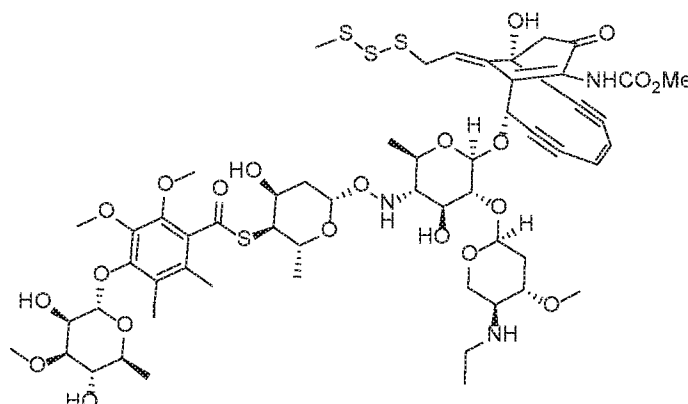
wherein the wavy line indicates the point of attachment to the antibody (e.g., an anti-CD45 antibody or fragment thereof). This cytotoxin-linker conjugate is present in the ADC IMGN779, disclosed in, for example, U.S. Patent Application Publication No. 20170080102, previously incorporated by reference herein.

Calicheamicin

In other embodiments, the antibodies and antigen-binding fragments thereof described herein can be conjugated to a cytotoxin that is an enediyne antitumor antibiotic (e.g., calicheamicins, ozogamicin). The calicheamicin family of antibiotics are capable of producing double-stranded DNA

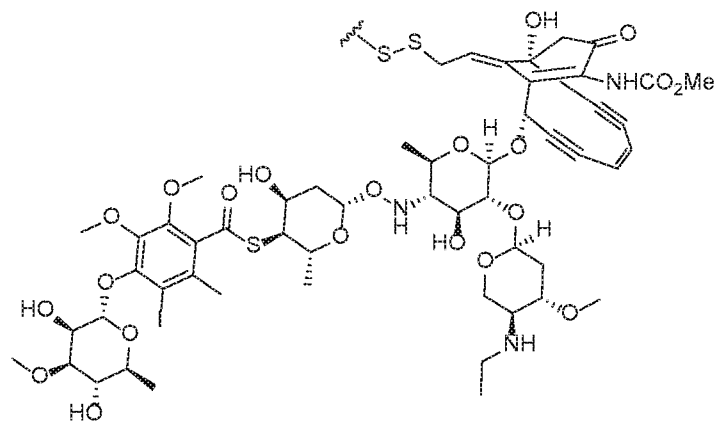
breaks at sub-picomolar concentrations. For the preparation of conjugates of the calicheamicin family, see U.S. Pat. Nos. 5,712,374; 5,714,586; 5,739,116; 5,767,285; 5,770,701; 5,770,710; 5,773,001; and 5,877,296 (all to American Cyanamid Company). Structural analogues of calicheamicin which may be used include, but are not limited to, those disclosed in, for example, Hinman et al., Cancer Research 53:3336-3342 (1993), Lode et al., Cancer Research 58:2925-2928 (1998), and the aforementioned U.S. patents to American Cyanamid.

An exemplary calicheamicin is designated γ_1 , which is herein referenced simply as gamma, and has the structural formula:



In some embodiments, the calicheamicin is a gamma-calicheamicin derivative or an N-acetyl gamma-calicheamicin derivative. Structural analogues of calicheamicin which may be used include, but are not limited to, those disclosed in, for example, Hinman et al., Cancer Research 53:3336-3342 (1993), Lode et al., Cancer Research 58:2925-2928 (1998), and the aforementioned U.S. patents. Calicheamicins contain a methyltrisulfide moiety that can be reacted with appropriate thiols to form disulfides, at the same time introducing a functional group that is useful in attaching a calicheamicin derivative to a bispecific binding agent as described herein, via a linker. For the preparation of conjugates of the calicheamicin family, see U.S. Pat. Nos. 5,712,374; 5,714,586; 5,739,116; 5,767,285; 5,770,701; 5,770,710; 5,773,001; and 5,877,296 (all to American Cyanamid Company). Structural analogues of calicheamicin which may be used include, but are not limited to, those disclosed in, for example, Hinman et al., Cancer Research 53:3336-3342 (1993), Lode et al., Cancer Research 58:2925-2928 (1998), and the aforementioned U.S. patents to American Cyanamid.

In some embodiments, the cytotoxin of the ADC as disclosed herein is a calicheamicin disulfide derivative represented by the formula:

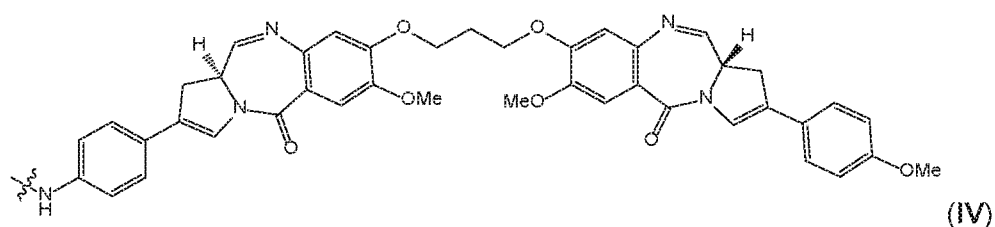


wherein the wavy line indicates the attachment point of the linker.

Additional cytotoxins that can be conjugated to antibodies, and antigen-binding fragments thereof, that recognize and bind CD2 or CD5 for use in directly treating a cancer, autoimmune condition, or for conditioning a patient (e.g., a human patient) in preparation for hematopoietic stem cell transplant therapy include, without limitation, 5-ethynyluracil, abiraterone, acylfulvene, adecypenol, adozelesin, aldesleukin, altretamine, ambamustine, amidox, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, andrographolide, angiogenesis inhibitors, antarelix, anti-dorsalizing morphogenetic protein-1, antiandrogen, prostatic carcinoma, antiestrogen, antineoplaston, antisense oligonucleotides, aphidicolin glycinate, apoptosis gene modulators, apoptosis regulators, apurinic acid, asulacrinc, atamestane, atrimustine, axinastatin 1, axinastatin 2, axinastatin 3, azasetron, azatoxin, azatyrosine, baccatin III derivatives, balanol, batimastat, BCR/ABL antagonists, benzochlorins, benzoylstauroporine, beta lactam derivatives, beta-alanine, betadex, betulinic acid, bFGF inhibitors, bicalutamide, bisantrene, bisaziridinylspermine, bisnafide, bistratene A, bizelesin, brequinar, bleomycin A2, bleomycin B2, brosimone, budotin, buthionine sulfoximine, calcipotriol, calphostin C, camptothecin derivatives (e.g., 10-hydroxy-camptothecin), capecitabine, carboxamide-amino-triazole, carboxyamidotriazole, carzelesin, casein kinase inhibitors, castanospermine, cecropin B, cetorelix, chlorins, chloroquinoline sulfonamide, cicaprost, cis-porphyrin, cladribine, clomifene and analogues thereof, clotrimazole, collismycin A, collismycin B, combretastatin A4, combretastatin analogues, conagenin, crambescidin 816, crisnatol, cryptophycin 8, cryptophycin A derivatives, curacin A, cyclopentantraquinones, cycloplatin, cypemycin, cytarabine, cytosine arabinoside, cytosine deoxyaraboside, dacarbazine, dasatinib, decitabine, dehydrodidemnin B, 2'-deoxycoformycin (DCF), deslorelin, dexifosfamide, dextrazoxane, dexverapamil, diaziquone, didemnin B, didox, diethylnorspermine, dihydro-5-azacytidine, dihydrotaxol, dioxamycin, diphenyl spiromustine, discodermolide, docosanol, dolasetron, doxorubicin, droloxifen, dronabinol, duocarmycin SA, ebselen, ecomustine, edelfosine, edrecolomab, eflornithine, elemene, emitefur, epothilones, epothilones, epristeride, estramustine and analogues thereof, etoposide, etoposide 4'-phosphate (also referred to as etopofos), exemestane, fadrozole, fazarabine, fenretinide, filgrastim, finasteride, flavopiridol, fluzelastine, fluasterone, fludarabine, fluorodaunorubicin hydrochloride, forfenimex,

formestane, fostriecin, fotemustine, gadolinium texaphyrin, gallium nitrate, galocitabine, ganirelix, gelatinase inhibitors, gemcitabine, glutathione inhibitors, hepsulfam, homoharringtonine (HHT), hypericin, ibandronic acid, idoxifene, idramantone, ilmofofosine, ilomastat, imidazoacridones, imiquimod, immunostimulant peptides, iobenguane, iododoxorubicin, ipomeanol, irinotecan, iroplact, irsogladine, isobengazole, jasplakinolide, kahalalide F, lamellarin-N triacetate, lanreotide, leinamycin, lenograstim, lentinan sulfate, leptolstatin, letrozole, lipophilic platinum compounds, lissoclinamide 7, lobaplatin, lometrexol, lonidamine, losoxantrone, loxoribine, lurtotecan, lutetium texaphyrin, lysofylline, masoprocol, maspin, matrix metalloproteinase inhibitors, menogaril, mnerbarone, meterelin, methioninase, metoclopramide, MIF inhibitor, ifepristone, miltefosine, mirimostim, mithracin, mitoguazone, mitolactol, mitomycin and analogues thereof, mitonafide, mitoxantrone, mofarotene, molgramostim, mycaperoxide B, myriaporone, N-acetyldinaline, N-substituted benzamides, nafarelin, nagrestip, napavin, naphterpin, nartograstim, nedaplatin, nemorubicin, neridronic acid, nilutamide, nisamycin, nitrullyn, octreotide, okicenone, onapristone, ondansetron, oracin, ormaplatin, oxaliplatin, oxaunomycin, paclitaxel and analogues thereof, palauamine, palmitoylrhizoxin, pamidronic acid, panaxytriol, panomifene, parabactin, pazelliptine, pegaspargase, peldesine, pentosan polysulfate sodium, pentostatin, pentozole, perflubron, perfosfamide, phenazinomycin, picibanil, pirarubicin, piritrexim, podophyllotoxin, porfiromycin, purine nucleoside phosphorylase inhibitors, raltitrexed, rhizoxin, rogletimide, rohitukine, rubiginone B1, ruboxyl, safingol, saintopin, sarcophytol A, sargramostim, sobuzoxane, sonermin, sparfosic acid, spicamycin D, spiromustine, stipiamide, sulfinosine, tallimustine, tegafur, temozolomide, teniposide, thaliblastine, thiocoraline, tirapazamine, topotecan, topsentin, tricinibine, trimetrexate, veramine, vinorelbine, vinxaltine, vorozole, zeniplatin, and zilascorb, among others.

In some embodiments, the cytotoxin is a pyrrolobenzodiazepine dimer represented by formula (IV):



A variety of linkers can be used to conjugate antibodies, and antigen-binding fragments, described herein that recognize and bind CD2 or CD5, with a cytotoxic molecule.

The term "Linker" as used herein means a divalent chemical moiety comprising a covalent bond or a chain of atoms that covalently attaches an anti-CD5 or CD2 antibody or fragment thereof (Ab) to a drug moiety (D) to form antibody-drug conjugates of the present disclosure (ADCs; Ab-Z-L-D, where D is a cytotoxin). Suitable linkers have two reactive termini, one for conjugation to an antibody and the other for conjugation to a cytotoxin. The antibody conjugation reactive terminus of the linker (reactive moiety, Z) is typically a site that is capable of

conjugation to the antibody through a cysteine thiol or lysine amine group on the antibody, and so is typically a thiol-reactive group such as a double bond (as in maleimide) or a leaving group such as a chloro, bromo, iodo, or an R-sulfanyl group, or an amine-reactive group such as a carboxyl group; while the antibody conjugation reactive terminus of the linker is typically a site that is capable of conjugation to the cytotoxin through formation of an amide bond with a basic amine or carboxyl group on the cytotoxin, and so is typically a carboxyl or basic amine group. When the term "linker" is used in describing the linker in conjugated form, one or both of the reactive termini will be absent (such as reactive moiety Z, having been converted to chemical moiety Z) or incomplete (such as being only the carbonyl of the carboxylic acid) because of the formation of the bonds between the linker and/or the cytotoxin, and between the linker and/or the antibody or antigen-binding fragment thereof. Such conjugation reactions are described further herein below.

A variety of linkers can be used to conjugate the antibodies, or antibody fragments described herein to a cytotoxic molecule. In some embodiments, the linker is cleavable under intracellular conditions, such that cleavage of the linker releases the drug unit from the antibody in the intracellular environment. In yet other embodiments, the linker unit is not cleavable and the drug is released, for example, by antibody degradation. The linkers useful for the present ADCs are preferably stable extracellularly, prevent aggregation of ADC molecules and keep the ADC freely soluble in aqueous media and in a monomeric state. Before transport or delivery into a cell, the ADC is preferably stable and remains intact, i.e. the antibody remains linked to the drug moiety. The linkers are stable outside the target cell and may be cleaved at some efficacious rate inside the cell. An effective linker will: (i) maintain the specific binding properties of the antibody; (ii) allow intracellular delivery of the conjugate or drug moiety; (iii) remain stable and intact, i.e. not cleaved, until the conjugate has been delivered or transported to its targeted site; and (iv) maintain a cytotoxic, cell-killing effect or a cytostatic effect of the cytotoxic moiety. Stability of the ADC may be measured by standard analytical techniques such as mass spectroscopy, HPLC, and the separation/analysis technique LC/MS. Covalent attachment of the antibody and the drug moiety requires the linker to have two reactive functional groups, i.e. bivalency in a reactive sense. Bivalent linker reagents which are useful to attach two or more functional or biologically active moieties, such as peptides, nucleic acids, drugs, toxins, antibodies, haptens, and reporter groups are known, and methods have been described their resulting conjugates (Hermanson, G. T. (1996) Bioconjugate Techniques; Academic Press: New York, p. 234-242).

Suitable cleavable linkers include those that may be cleaved, for instance, by enzymatic hydrolysis, photolysis, hydrolysis under acidic conditions, hydrolysis under basic conditions, oxidation, disulfide reduction, nucleophilic cleavage, or organometallic cleavage (see, for example, Leriche et al., Bioorg. Med. Chem., 20:571-582, 2012, the disclosure of which is incorporated herein by reference as it pertains to linkers suitable for covalent conjugation).

Linkers hydrolyzable under acidic conditions include, for example, hydrazones, semicarbazones, thiosemicarbazones, cis-aconitic amides, orthoesters, acetals, ketals, or the like. (See, e.g., U.S. Pat. Nos. 5,122,368; 5,824,805; 5,622,929; Dubowchik and Walker, 1999, Pharm. Therapeutics 83:67-123; Neville et al., 1989, Biol. Chem. 264:14653-14661, the disclosure of each of which is incorporated herein by reference in its entirety as it pertains to linkers suitable for covalent conjugation. Such linkers are relatively stable under neutral pH conditions, such as those in the blood, but are unstable at below pH 5.5 or 5.0, the approximate pH of the lysosome.

Linkers cleavable under reducing conditions include, for example, a disulfide. A variety of disulfide linkers are known in the art, including, for example, those that can be formed using SATA (N-succinimidyl-S-acetylthioacetate), SPDP (N-succinimidyl-3-(2-pyridyldithio)propionate), SPDB (N-succinimidyl-3-(2-pyridyldithio)butyrate) and SMPT (N-succinimidyl-oxycarbonyl-alpha-methyl-alpha-(2-pyridyl-dithio)toluene), SPDB and SMPT (See, e.g., Thorpe et al., 1987, Cancer Res. 47:5924-5931; Wawrzynczak et al., In Immunoconjugates: Antibody Conjugates in Radioimaging and Therapy of Cancer (C. W. Vogel ed., Oxford U. Press, 1987. See also U.S. Pat. No. 4,880,935, the disclosure of each of which is incorporated herein by reference in its entirety as it pertains to linkers suitable for covalent conjugation.

Examples of linkers useful for the synthesis of drug-antibody conjugates include those that contain electrophiles, such as Michael acceptors (e.g., maleimides), activated esters, electron-deficient carbonyl compounds, and aldehydes, among others, suitable for reaction with nucleophilic substituents present within antibodies or antigen-binding fragments, such as amine and thiol moieties. For instance, linkers suitable for the synthesis of drug-antibody conjugates include, without limitation, succinimidyl 4-(N-maleimidomethyl)-cyclohexane-L-carboxylate (SMCC), N-succinimidyl iodoacetate (SIA), sulfo-SMCC, *m*-maleimidobenzoyl-*N*-hydroxysuccinimidyl ester (MBS), sulfo-MBS, and succinimidyl iodoacetate, among others described, for instance, Liu et al., 18:690-697, 1979, the disclosure of which is incorporated herein by reference as it pertains to linkers for chemical conjugation. Additional linkers include the non-cleavable maleimidocaproyl linkers, which are particularly useful for the conjugation of microtubule-disrupting agents such as auristatins, are described by Doronina et al., Bioconjugate Chem. 17:14-24, 2006, the disclosure of which is incorporated herein by reference as it pertains to linkers for chemical conjugation. Additional linkers suitable for the synthesis of drug-antibody conjugates as described herein include those capable of releasing a cytotoxin by a 1,6-elimination process, (a "self-immolative" group), such as *p*-aminobenzyl alcohol (PABC), 6-maleimidoheptanoic acid, pH-sensitive carbonates, and other reagents described in Jain et al., Pharm. Res. 32:3526-3540, 2015, the disclosure of which is incorporated herein by reference in its entirety. In some embodiments, the linker includes a self-immolative group such as the aforementioned PAB or PABC (para-aminobenzyloxycarbonyl), which are disclosed in, for example, Carl et al., J. Med. Chem. (1981) 24:479-480; Chakravarty et al (1983) J. Med. Chem. 26:638-644;

US 6214345; US20030130189; US20030096743; US6759509; US20040052793; US6218519; US6835807; US6268488; US20040018194; W098/13059; US20040052793; US6677435; US5621002; US20040121940; W02004/032828). Other such chemical moieties capable of this process ("self-immolative linkers") include methylene carbamates and heteroaryl groups such as aminothiazoles, aminoimidazoles, aminopyrimidines, and the like. Linkers containing such heterocyclic self-immolative groups are disclosed in, for example, U.S. Patent Publication Nos. 20160303254 and 20150079114, and U.S. Patent No. 7,754,681; Hay et al. (1999) Bioorg. Med. Chem. Lett. 9:2237; US 2005/0256030; de Groot et al (2001) J. Org. Chem. 66:8815-8830; and US 7223837.

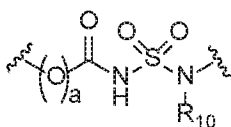
Linkers susceptible to enzymatic hydrolysis can be, e.g., a peptide-containing linker that is cleaved by an intracellular peptidase or protease enzyme, including, but not limited to, a lysosomal or endosomal protease. One advantage of using intracellular proteolytic release of the therapeutic agent is that the agent is typically attenuated when conjugated and the serum stabilities of the conjugates are typically high. In some embodiments, the peptidyl linker is at least two amino acids long or at least three amino acids long. Exemplary amino acid linkers include a dipeptide, a tripeptide, a tetrapeptide or a pentapeptide. Examples of suitable peptides include those containing amino acids such as Valine, Alanine, Citrulline (Cit), Phenylalanine, Lysine, Leucine, and Glycine. Amino acid residues which comprise an amino acid linker component include those occurring naturally, as well as minor amino acids and non-naturally occurring amino acid analogs, such as citrulline. Exemplary dipeptides include valine-citrulline (vc or val-cit) and alanine-phenylalanine (af or ala-phe). Exemplary tripeptides include glycine-valine-citrulline (gly-val-cit) and glycine-glycine-glycine (gly-gly-gly). In some embodiments, the linker includes a dipeptide such as Val-Cit, Ala-Val, or Phe-Lys, Val-Lys, Ala-Lys, Phe-Cit, Leu-Cit, Ile-Cit, Phe-Arg, or Trp-Cit. Linkers containing dipeptides such as Val-Cit or Phe-Lys are disclosed in, for example, U.S. Pat. No. 6,214,345, the disclosure of which is incorporated herein by reference in its entirety as it pertains to linkers suitable for covalent conjugation. In some embodiments, the linker includes a dipeptide selected from Val-Ala and Val-Cit. In some embodiments, a dipeptide is used in combination with a self-immolative linker.

Linkers suitable for conjugating the antibodies, or antibody fragments, described herein to a cytotoxic molecule include those capable of releasing a cytotoxin by a 1,6-elimination process. Chemical moieties capable of this elimination process include the *p*-aminobenzyl (PAB) group, 6-maleimidoheptanoic acid, pH-sensitive carbonates, and other reagents as described in Jain et al., Pharm. Res. 32:3526-3540, 2015, the disclosure of which is incorporated herein by reference in its entirety, and particularly as it pertains to linkers suitable for covalent conjugation.

In some embodiments, the linker includes a "self-immolative" group such as the aforementioned PAB or PABC (para-aminobenzylloxycarbonyl), which are disclosed in, for example, Carl et al., J. Med. Chem. (1981) 24:479-480; Chakravarty et al (1983) J. Med. Chem. 26:638-644; US

6214345; US20030130189; US20030096743; US6759509; US20040052793; US6218519; US6835807; US6268488; US20040018194; W098/13059; US20040052793; US6677435; US5621002; US20040121940; W02004/032828). Other such chemical moieties capable of this process ("self-immolative linkers") include methylene carbamates and heteroaryl groups such as aminothiazoles, aminoimidazoles, aminopyrimidines, and the like. Linkers containing such heterocyclic self-immolative groups are disclosed in, for example, U.S. Patent Publication Nos. 20160303254 and 20150079114, and U.S. Patent No. 7,754,681; Hay et al. (1999) Bioorg. Med. Chem. Lett. 9:2237; US 2005/0256030; de Groot et al (2001) J. Org. Chem. 66:8815-8830; and US 7223837. In some embodiments, a dipeptide is used in combination with a self-immolative linker.

Suitable linkers may contain groups having solubility enhancing properties. Linkers including the $(\text{CH}_2\text{CH}_2\text{O})_p$ unit (polyethylene glycol, PEG), for example, can enhance solubility, as can alkyl chains substituted with amino, sulfonic acid, phosphonic acid or phosphoric acid residues. Linkers including such moieties are disclosed in, for example, U.S. Patent Nos. 8,236,319 and 9,504,756, the disclosure of each of which is incorporated herein by reference as it pertains to linkers suitable for covalent conjugation. Further solubility enhancing groups include, for example, acyl and carbamoyl sulfamide groups, having the structure:



wherein a is 0 or 1; and

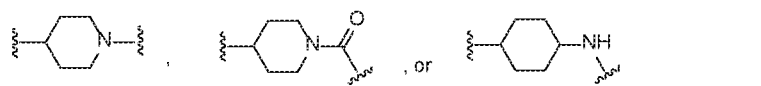
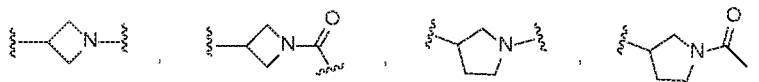
R^{10} is selected from the group consisting of hydrogen, C_1 - C_{24} alkyl groups, C_3 - C_{24} cycloalkyl groups, C_1 - C_{24} (hetero)aryl groups, C_1 - C_{24} alkyl(hetero)aryl groups and C_1 - C_{24} (hetero)arylalkyl groups, the C_1 - C_{24} alkyl groups, C_3 - C_{24} cycloalkyl groups, C_2 - C_{24} (hetero)aryl groups, C_3 - C_{24} alkyl(hetero)aryl groups and C_3 - C_{24} (hetero)arylalkyl groups, each of which may be optionally substituted and/or optionally interrupted by one or more heteroatoms selected from O, S and $\text{NR}^{11}\text{R}^{12}$, wherein R^{11} and R^{12} are independently selected from the group consisting of hydrogen and C_1 - C_4 alkyl groups; or R^{10} is a cytotoxin, wherein the cytotoxin is optionally connected to N via a spacer moiety. Linkers containing such groups are described, for example, in U.S. Patent No. 9,636,421 and U.S. Patent Application Publication No. 2017/0298145, the disclosures of which are incorporated herein by reference as they pertain to linkers suitable for covalent conjugation to cytotoxins and antibodies or antigen-binding fragments thereof.

In some embodiments, the linker may include one or more of a hydrazine, a disulfide, a thioether, a dipeptide, a *p*-aminobenzyl (PAB) group, a heterocyclic self-immolative group, an optionally substituted C_1 - C_6 alkyl, an optionally substituted C_1 - C_6 heteroalkyl, an optionally substituted C_2 - C_6 alkenyl, an optionally substituted C_2 - C_6 heteroalkenyl, an optionally substituted C_2 - C_6 alkynyl, an optionally substituted C_2 - C_6 heteroalkynyl, an optionally substituted C_3 - C_6

cycloalkyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, a solubility enhancing group, acyl, $-(C=O)-$, or $-(CH_2CH_2O)_p-$ group, wherein p is an integer from 1-6. One of skill in the art will recognize that one or more of the groups listed may be present in the form of a bivalent (diradical) species, e.g., C_1-C_6 alkylene and the like.

5 In some embodiments, the linker L comprises the moiety $^*-L_1L_2-^{**}$, wherein:

L_1 is absent or is $-(CH_2)_mNR^{13}C(=O)-$, $-(CH_2)_mNR^{13}-$, $-(CH_2)_mX_3(CH_2)_m-$,



L_2 is absent or is $-(CH_2)_m-$, $-NR^{13}(CH_2)_m-$, $-(CH_2)_mNR^{13}C(=O)(CH_2)_m-$, $-X_4-$,

$(CH_2)_mNR^{13}C(=O)X_4-$, $-(CH_2)_mNR^{13}C(=O)-$, $-((CH_2)_mO)_n(CH_2)_m-$, $-((CH_2)_mO)_n(CH_2)_mX_3(CH_2)_m-$,

10 $NR^{13}((CH_2)_mO)_nX_3(CH_2)_m-$, $-NR^{13}((CH_2)_mO)_n(CH_2)_mX_3(CH_2)_m-$, $-X_1X_2C(=O)(CH_2)_m-$,

$(CH_2)_m(O(CH_2)_m)_n-$, $-(CH_2)_mNR^{13}(CH_2)_m-$, $-(CH_2)_mNR^{13}C(=O)(CH_2)_mX_3(CH_2)_m-$,

$(CH_2)_mC(=O)NR^{13}(CH_2)_mNR^{13}C(=O)(CH_2)_m-$, $-(CH_2)_mC(=O)-$, $-(CH_2)_mNR^{13}(CH_2)_mC(=O)X_2X_1C(=O)-$,

$-(CH_2)_mX_3(CH_2)_mC(=O)X_2X_1C(=O)-$, $-(CH_2)_mC(=O)NR^{13}(CH_2)_m-$,

$(CH_2)_mC(=O)NR^{13}(CH_2)_mX_3(CH_2)_m-$, $-(CH_2)_mX_3(CH_2)_mNR^{13}C(=O)(CH_2)_m-$,

15 $(CH_2)_mX_3(CH_2)_mC(=O)NR^{13}(CH_2)_m-$, $-(CH_2)_mO)_n(CH_2)_mNR^{13}C(=O)(CH_2)_m-$,

$(CH_2)_mC(=O)NR^{13}(CH_2)_m(O(CH_2)_m)_n-$, $-(CH_2)_m(O(CH_2)_m)_nC(=O)-$, $-(CH_2)_mNR^{13}(CH_2)_mC(=O)-$,

$(CH_2)_mC(=O)NR^{13}(CH_2)_mNR^{13}C(=O)-$, $-(CH_2)_m(O(CH_2)_m)_nX_3(CH_2)_m-$, $-(CH_2)_mX_3((CH_2)_mO)_n(CH_2)_m-$,

$(CH_2)_mX_3(CH_2)_mC(=O)-$, $-(CH_2)_mC(=O)NR^{13}(CH_2)_mO)_n(CH_2)_mX_3(CH_2)_m-$,

$(CH_2)_mX_3(CH_2)_m(O(CH_2)_m)_nNR^{13}C(=O)(CH_2)_m-$, $-(CH_2)_mX_3(CH_2)_m(O(CH_2)_m)_nC(=O)-$,

20 $(CH_2)_mX_3(CH_2)_m(O(CH_2)_m)_n-$, $-(CH_2)_mC(=O)NR^{13}(CH_2)_mC(=O)-$,

$(CH_2)_mC(=O)NR^{13}(CH_2)_m(O(CH_2)_m)_nC(=O)-$, $-((CH_2)_mO)_n(CH_2)_mNR^{13}C(=O)(CH_2)_m-$,

$(CH_2)_mC(=O)NR^{13}(CH_2)_mC(=O)NR^{13}(CH_2)_m-$, $-(CH_2)_mNR^{13}C(=O)(CH_2)_mNR^{13}C(=O)(CH_2)_m-$

$(CH_2)_mX_3(CH_2)_mC(=O)NR^{13}-$, $-(CH_2)_mC(=O)NR^{13}-$, $-(CH_2)_mX_3-$, $-C(R^{13})_2(CH_2)_m-$, $-(CH_2)_mC(R^{13})_2NR^{13}-$,

$-(CH_2)_mC(=O)NR^{13}(CH_2)_mNR^{13}-$, $-(CH_2)_mC(=O)NR^{13}(CH_2)_mNR^{13}C(=O)NR^{13}-$,

25 $(CH_2)_mC(=O)X_2X_1C(=O)-$, $-C(R^{13})_2(CH_2)_mNR^{13}C(=O)(CH_2)_m-$,

$(CH_2)_mC(=O)NR^{13}(CH_2)_mC(R^{13})_2NR^{13}-$, $-C(R^{13})_2(CH_2)_mX_3(CH_2)_m-$, $-(CH_2)_mX_3(CH_2)_mC(R^{13})_2NR^{13}-$,

$C(R^{13})_2(CH_2)_mOC(=O)NR^{13}(CH_2)_m-$, $-(CH_2)_mNR^{13}C(=O)O(CH_2)_mC(R^{13})_2NR^{13}-$,

$(CH_2)_mX_3(CH_2)_mNR^{13}-$, $-(CH_2)_mX_3(CH_2)_m(O(CH_2)_m)_nNR^{13}-$, $-(CH_2)_mNR^{13}-$,

$(CH_2)_mC(=O)NR^{13}(CH_2)_m(O(CH_2)_m)_nNR^{13}-$, $-(CH_2)_m(O(CH_2)_m)_nNR^{13}-$, $-(CH_2CH_2O)_n(CH_2)_m-$,

30 $(CH_2)_m(OCH_2CH_2)_n-$, $-(CH_2)_mO(CH_2)_m-$, $-(CH_2)_mS(=O)_2-$, $-(CH_2)_mC(=O)NR^{13}(CH_2)_mS(=O)_2-$,

$(CH_2)_mX_3(CH_2)_mS(=O)_2-$, $-(CH_2)_mX_2X_1C(=O)-$, $-(CH_2)_m(O(CH_2)_m)_nC(=O)X_2X_1C(=O)-$,

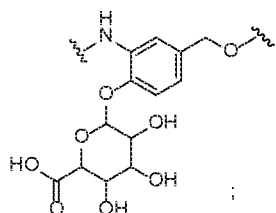
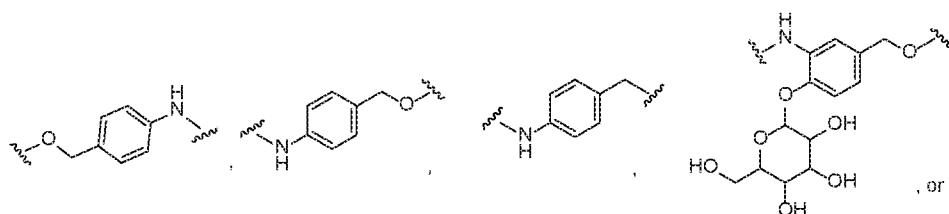
$(CH_2)_m(O(CH_2)_m)_nX_2X_1C(=O)-$, $-(CH_2)_mX_3(CH_2)_mX_2X_1C(=O)-$, $-(CH_2)_mX_3(CH_2)_m(O(CH_2)_m)_nX_2X_1$

$C(=O)-$, $-(CH_2)_mX_3(CH_2)_mC(=O)NR^{13}(CH_2)_mNR^{13}C(=O)-$, $-(CH_2)_mX_3(CH_2)_mC(=O)NR^{13}(CH_2)_mC(=O)-$,
 $-(CH_2)_mX_3(CH_2)_mC(=O)NR^{13}(CH_2)_m(O(CH_2)_m)_nC(=O)-$, $-(CH_2)_mC(=O)X_2X_1C(=O)NR^{13}(CH_2)_m-$,
 $(CH_2)_mX_3(O(CH_2)_m)_nC(=O)-$, $-(CH_2)_mNR^{13}C(=O)((CH_2)_mO)_n(CH_2)_m-$,
 $(CH_2)_m(O(CH_2)_m)_nC(=O)NR^{13}(CH_2)_m-$, $-(CH_2)_mNR^{13}C(=O)NR^{13}(CH_2)_m-$ or $-$

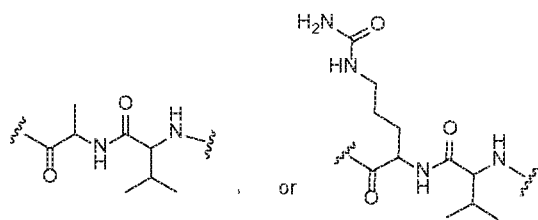
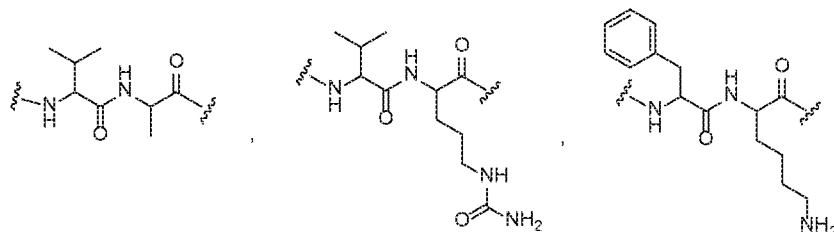
5 $(CH_2)_mX_3(CH_2)_mNR^{13}C(=O)-$;

wherein

X_1 is

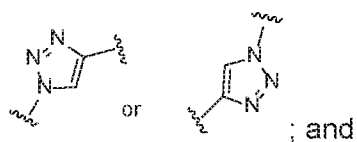


X_2 is

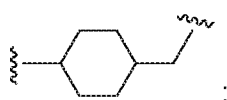


10

X_3 is



X_4 is



15

wherein

R^{13} is independently selected for each occasion from H and C_1 - C_6 alkyl;

m is independently selected for each occasion from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10;

n is independently selected for each occasion from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14; and

wherein the single asterisk (*) indicates the attachment point to the cytotoxin (e.g., an amatoxin), and the double asterisk (**) indicates the attachment point to the reactive substituent Z' or chemical moiety Z, with the proviso that L_1 and L_2 are not both absent.

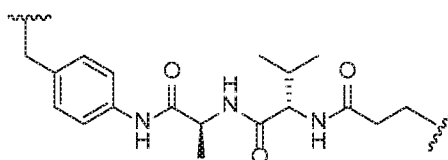
In some embodiments, the linker includes a p-aminobenzyl group (PAB). In some embodiments, the p-aminobenzyl group is disposed between the cytotoxic drug and a protease cleavage site in the linker. In some embodiments, the p-aminobenzyl group is part of a p-aminobenzylloxycarbonyl unit. In some embodiments, the p-aminobenzyl group is part of a p-aminobenzylamido unit.

In some embodiments, the linker comprises 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.

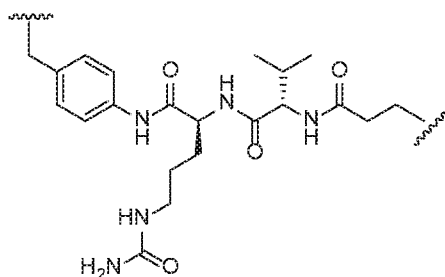
In some embodiments, the linker comprises a combination of one or more of a peptide, oligosaccharide, $-(CH_2)_p-$, $-(CH_2CH_2O)_p-$, PAB, Val-Cit-PAB, Val-Ala-PAB, Val-Lys(Ac)-PAB, Phe-Lys-PAB, Phe-Lys(Ac)-PAB, D-Val-Leu-Lys, Gly-Gly-Arg, Ala-Ala-Asn-PAB, or Ala-PAB.

In some embodiments, the linker comprises a $-(C=O)(CH_2)_p-$ unit, wherein p is an integer from 1-6.

In one specific embodiment, the linker comprises the structure:



wherein the wavy lines indicate attachment points to the cytotoxin and the reactive moiety Z'. In another specific embodiment, the linker comprises the structure:

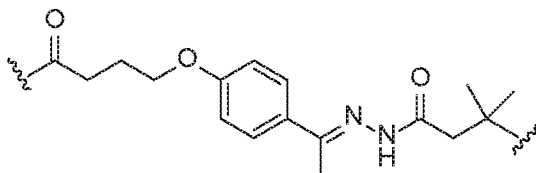


wherein the wavy lines indicate attachment points to the cytotoxin and the reactive moiety Z'. Such PAB-dipeptide-propionyl linkers are disclosed in, e.g., Patent Application Publication No. WO2017/149077, which is incorporated by reference herein in its entirety. Further, the cytotoxins disclosed in WO2017/149077 are incorporated by reference herein.

In certain embodiments, the linker of the ADC is maleimidocaproyl-Val-Ala-para-aminobenzyl (mc-Val-Ala-PAB).

In certain embodiments, the linker of the ADC is maleimidocaproyl-Val-Cit-para-aminobenzyl (mc-vc-PAB).

5 In some embodiments, the linker comprises



In some embodiments, the linker comprises MCC (4-[N-maleimidomethyl]cyclohexane-1-carboxylate).

10 It will be recognized by one of skill in the art that any one or more of the chemical groups, moieties and features disclosed herein may be combined in multiple ways to form linkers useful for conjugation of the antibodies and cytotoxins as disclosed herein. Further linkers useful in conjunction with the compositions and methods described herein, are described, for example, in U.S. Patent Application Publication No. 2015/0218220, the disclosure of which is incorporated herein by reference in its entirety.

15 Linkers suitable for use herein further may include one or more groups selected from C₁-C₆ alkylene, C₁-C₆ heteroalkylene, C₂-C₆ alkenylene, C₂-C₆ heteroalkenylene, C₂-C₆ alkynylene, C₂-C₆ heteroalkynylene, C₃-C₆ cycloalkylene, heterocycloalkylene, arylene, heteroarylene, and combinations thereof, each of which may be optionally substituted. Non-limiting examples of such groups include (CH₂)_n, (CH₂CH₂O)_n, and -(C=O)(CH₂)_n- units, wherein n is an integer from 1-6,
20 independently selected for each occasion.

In some embodiments, the linker may include one or more of a hydrazine, a disulfide, a thioether, a dipeptide, a *p*-aminobenzyl (PAB) group, a heterocyclic self-immolative group, an optionally substituted C₁-C₆ alkyl, an optionally substituted C₁-C₆ heteroalkyl, an optionally substituted C₂-C₆ alkenyl, an optionally substituted C₂-C₆ heteroalkenyl, an optionally substituted C₂-C₆ alkynyl, an optionally substituted C₂-C₆ heteroalkynyl, an optionally substituted C₃-C₆ cycloalkyl, an optionally substituted heterocycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, acyl, -(C=O)-, or -(CH₂CH₂O)_n- group, wherein n is an integer from 1-6. One of skill in the art will recognize that one or more of the groups listed may be present in the form of a bivalent (diradical) species, *e.g.*, C₁-C₆ alkylene and the like.

30 In some embodiments, the linker includes a *p*-aminobenzyl group (PAB). In one embodiment, the *p*-aminobenzyl group is disposed between the cytotoxic drug and a protease cleavage site in the linker. In one embodiment, the *p*-aminobenzyl group is part of a *p*-aminobenzylloxycarbonyl unit. In one embodiment, the *p*-aminobenzyl group is part of a *p*-aminobenzylamido unit.

In some embodiments, the linker comprises 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.

In some embodiments, the linker comprises a combination of one or more of a peptide, oligosaccharide, $-(CH_2)_n-$, $-(CH_2CH_2O)_n-$, 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.

In some embodiments, the linker comprises a $-(C=O)(CH_2)_n-$ unit, wherein n is an integer from 1-6.

In some embodiments, the linker comprises a $-(CH_2)_n-$ unit, wherein n is an integer from 2 to 6.

In certain embodiments, the linker of the ADC is N-beta-maleimidopropyl-Val-Ala-para-aminobenzyl (BMP-Val-Ala-PAB).

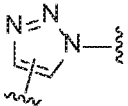
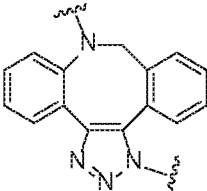
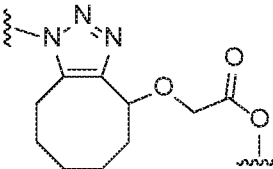
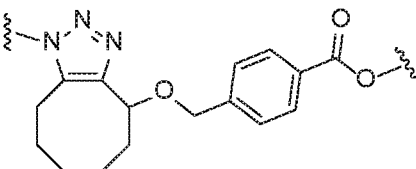
Linkers that can be used to conjugate an antibody, or an antigen-binding fragment thereof, to a cytotoxic agent include those that are covalently bound to the cytotoxic agent on one end of the linker and, on the other end of the linker, contain a chemical moiety formed from a coupling reaction between a reactive substituent present on the linker and a reactive substituent present within the antibody, or an antigen-binding fragment thereof, that binds CD2 or CD5. Reactive substituents that may be present within an antibody, or an antigen-binding fragment thereof, that binds CD2 or CD5 include, without limitation, hydroxyl moieties of serine, threonine, and tyrosine residues; amino moieties of lysine residues; carboxyl moieties of aspartic acid and glutamic acid residues; and thiol moieties of cysteine residues, as well as propargyl, azido, haloaryl (e.g., fluoroaryl), haloheteroaryl (e.g., fluoroheteroaryl), haloalkyl, and haloheteroalkyl moieties of non-naturally occurring amino acids.

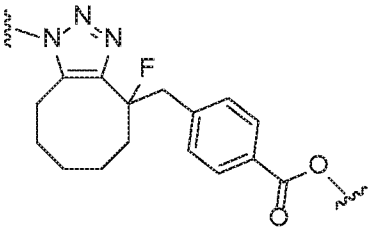
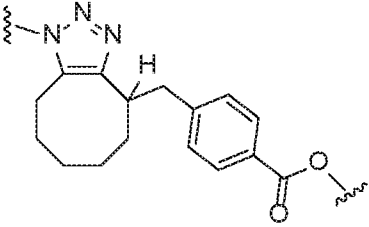
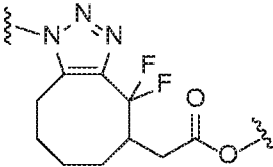
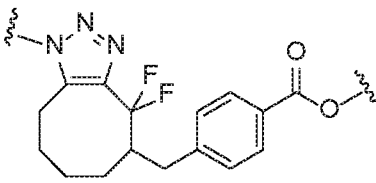
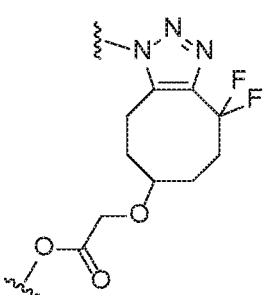
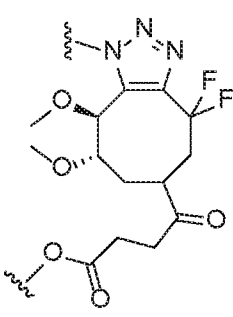
Examples of linkers useful for the synthesis of drug-antibody conjugates include those that contain electrophiles, such as Michael acceptors (e.g., maleimides), activated esters, electron-deficient carbonyl compounds, and aldehydes, among others, suitable for reaction with nucleophilic substituents present within antibodies or antigen-binding fragments, such as amine and thiol moieties. For instance, linkers suitable for the synthesis of drug-antibody conjugates include, without limitation, succinimidyl 4-(N-maleimidomethyl)-cyclohexane-L-carboxylate (SMCC), N-succinimidyl iodoacetate (SIA), sulfo-SMCC, *m*-maleimidobenzoyl-*N*-hydroxysuccinimidyl ester (MBS), sulfo-MBS, and succinimidyl iodoacetate, among others described, for instance, Liu et al., 18:690-697, 1979, the disclosure of which is incorporated herein by reference as it pertains to linkers for chemical conjugation. Additional linkers include the non-cleavable maleimidocaproyl linkers, which are particularly useful for the conjugation of microtubule-disrupting agents such as auristatins, are described by Doronina et al., Bioconjugate Chem. 17:14-24, 2006, the disclosure of which is incorporated herein by reference as it pertains to linkers for chemical conjugation.

It will be recognized by one of skill in the art that any one or more of the chemical groups, moieties and features disclosed herein may be combined in multiple ways to form linkers useful for conjugation of the antibodies and cytotoxins as disclosed herein. Further linkers useful in conjunction with the compositions and methods described herein, are described, for example, in U.S. Patent Application Publication No. 2015/0218220, the disclosure of which is incorporated herein by reference in its entirety.

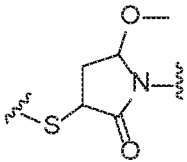
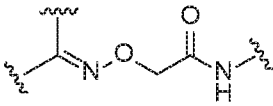
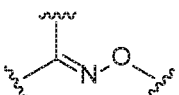
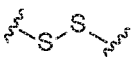
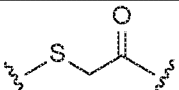
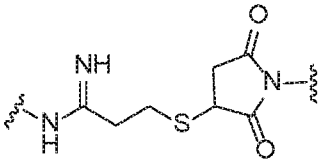
Linkers useful for conjunction with the antibody-drug conjugates described herein include, without limitation, linkers containing chemical moieties Z formed by coupling reactions as depicted in Table 2, below. Wavy lines designate points of attachment to the antibody, or antigen-binding fragment, and the cytotoxic molecule.

Table 2. Exemplary chemical moieties formed by coupling reactions in the formation of antibody-drug conjugates

Exemplary Coupling Reactions	Chemical Moiety Z Formed by Coupling Reactions
[3+2] Cycloaddition	
[3+2] Cycloaddition	
[3+2] Cycloaddition, Esterification	
[3+2] Cycloaddition, Esterification	

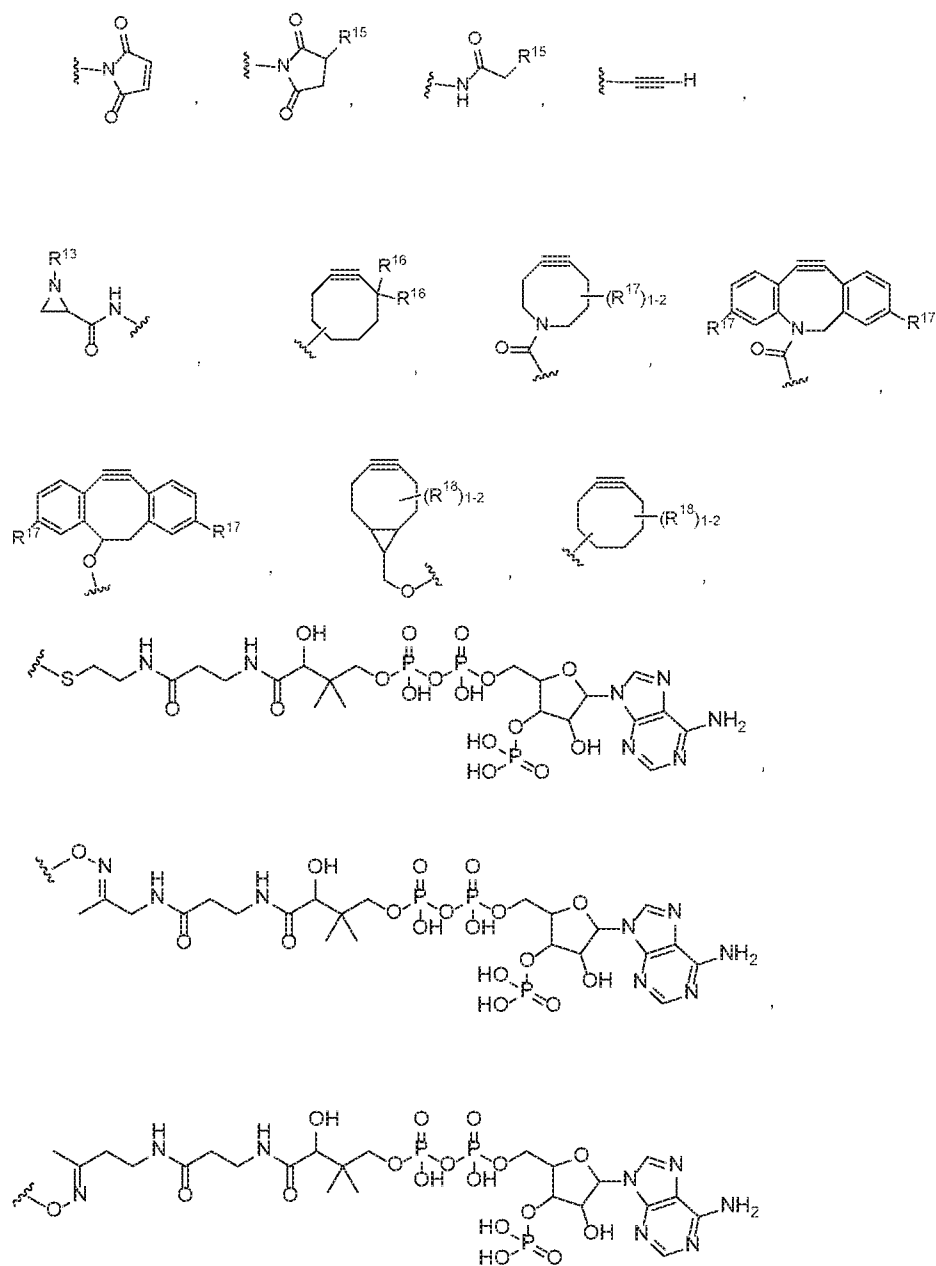
[3+2] Cycloaddition, Esterification	
[3+2] Cycloaddition, Esterification	
[3+2] Cycloaddition, Esterification	
[3+2] Cycloaddition, Esterification	
[3+2] Cycloaddition, Esterification	
[3+2] Cycloaddition, Esterification	

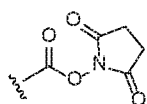
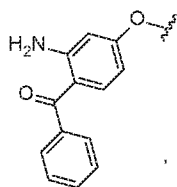
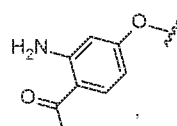
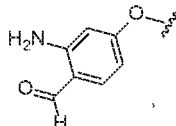
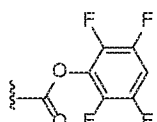
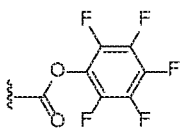
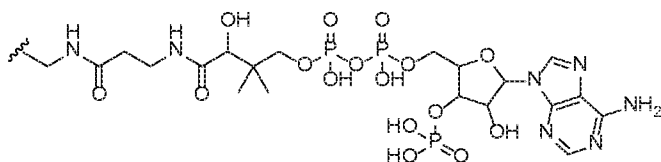
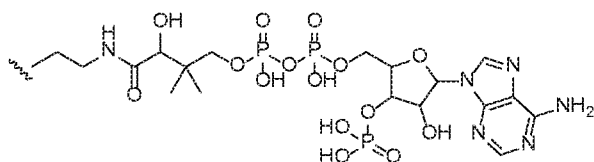
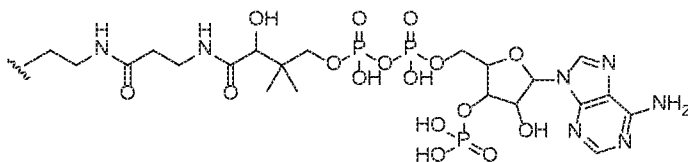
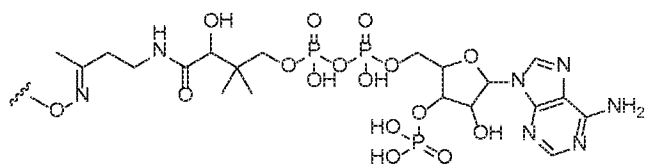
[3+2] Cycloaddition, Esterification	
[3+2] Cycloaddition, Esterification	
[3+2] Cycloaddition, Esterification	
[3+2] Cycloaddition, Etherification	
[3+2] Cycloaddition	
Michael addition	

Michael addition	
Imine condensation, Amidation	
Imine condensation	
Disulfide formation	
Thiol alkylation	
Condensation, Michael addition	

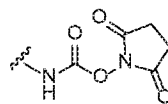
One of skill in the art will recognize that a reactive substituent Z attached to the linker and a reactive substituent on the antibody or antigen-binding fragment thereof, are engaged in the covalent coupling reaction to produce the chemical moiety Z, and will recognize the reactive substituent Z. Therefore, antibody-drug conjugates useful in conjunction with the methods described herein may be formed by the reaction of an antibody, or antigen-binding fragment thereof, with a linker or cytotoxin-linker conjugate, as described herein, the linker or cytotoxin-linker conjugate including a reactive substituent Z, suitable for reaction with a reactive substituent on the antibody, or antigen-binding fragment thereof, to form the chemical moiety Z.

In some embodiments, Z' is $-NR^{13}C(=O)CH=CH_2$, $-N_3$, $-SH$, $-S(=O)_2(CH=CH_2)$, $-(CH_2)_2S(=O)_2(CH=CH_2)$, $-NR^{13}S(=O)_2(CH=CH_2)$, $-NR^{13}C(=O)CH_2R^{14}$, $-NR^{13}C(=O)CH_2Br$, $-NR^{13}C(=O)CH_2I$, $-NHC(=O)CH_2Br$, $-NHC(=O)CH_2I$, $-ONH_2$, $-C(O)NHNH_2$, $-CO_2H$, $-NH_2$, $-NH(C=O)$, $-NC(=S)$,





, or



;

wherein

R^{13} is independently selected for each occasion from H and C_1 - C_6 alkyl;

5 R^{14} is $-S(CH_2)_nCHR^{15}NHC(=O)R^{13}$;

R^{15} is R^{13} or $-C(=O)OR^{13}$;

R^{16} is independently selected for each occasion from H, C_1 - C_6 alkyl, F, Cl, and $-OH$;

R^{17} is independently selected for each occasion from H, C_1 - C_6 alkyl, F, Cl, $-NH_2$, $-OCH_3$, $-OCH_2CH_3$, $-N(CH_3)_2$, $-CN$, $-NO_2$ and $-OH$; and

10 R^{18} is independently selected for each occasion from H, C_1 - C_6 alkyl, F, benzyloxy substituted with $-C(=O)OH$, benzyl substituted with $-C(=O)OH$, C_1 - C_4 alkoxy substituted with $-C(=O)OH$, and C_1 - C_4 alkyl substituted with $-C(=O)OH$;

m is independently selected for each occasion from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10; and n is independently selected for each occasion from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14.

As depicted in Table 2, examples of suitably reactive substituents on the linker and antibody or antigen-binding fragment thereof include a nucleophile/electrophile pair (e.g., a thiol/haloalkyl pair, an amine/carbonyl pair, or a thiol/ α,β -unsaturated carbonyl pair, and the like), a diene/dienophile pair (e.g., an azide/alkyne pair, or a diene/ α,β -unsaturated carbonyl pair, among others), and the like. Coupling reactions between the reactive substituents to form the chemical moiety Z include, without limitation, thiol alkylation, hydroxyl alkylation, amine alkylation, amine or hydroxylamine condensation, hydrazine formation, amidation, esterification, disulfide formation, cycloaddition (e.g., [4+2] Diels-Alder cycloaddition, [3+2] Huisgen cycloaddition, among others), nucleophilic aromatic substitution, electrophilic aromatic substitution, and other reactive modalities known in the art or described herein. Preferably, the linker contains an electrophilic functional group for reaction with a nucleophilic functional group on the antibody, or antigen-binding fragment thereof.

Reactive substituents that may be present within an antibody, or antigen-binding fragment thereof, as disclosed herein include, without limitation, nucleophilic groups such as (i) N-terminal amine groups, (ii) side chain amine groups, e.g. lysine, (iii) side chain thiol groups, e.g. cysteine, and (iv) sugar hydroxyl or amino groups where the antibody is glycosylated. Reactive substituents that may be present within an antibody, or antigen-binding fragment thereof, as disclosed herein include, without limitation, hydroxyl moieties of serine, threonine, and tyrosine residues; amino moieties of lysine residues; carboxyl moieties of aspartic acid and glutamic acid residues; and thiol moieties of cysteine residues, as well as propargyl, azido, haloaryl (e.g., fluoroaryl), haloheteroaryl (e.g., fluoroheteroaryl), haloalkyl, and haloheteroalkyl moieties of non-naturally occurring amino acids. In some embodiments, the reactive substituents present within an antibody, or antigen-binding fragment thereof as disclosed herein include, are amine or thiol moieties. Certain antibodies have reducible interchain disulfides, i.e. cysteine bridges. Antibodies may be made reactive for conjugation with linker reagents by treatment with a reducing agent such as DTT (dithiothreitol). Each cysteine bridge will thus form, theoretically, two reactive thiol nucleophiles. Additional nucleophilic groups can be introduced into antibodies through the reaction of lysines with 2-iminothiolane (Traut's reagent) resulting in conversion of an amine into a thiol. Reactive thiol groups may be introduced into the antibody (or fragment thereof) by introducing one, two, three, four, or more cysteine residues (e.g., preparing mutant antibodies comprising one or more non-native cysteine amino acid residues). U.S. Pat. No. 7,521,541 teaches engineering antibodies by introduction of reactive cysteine amino acids.

In some embodiments, the reactive moiety Z attached to the linker is a nucleophilic group which is reactive with an electrophilic group present on an antibody. Useful electrophilic groups on

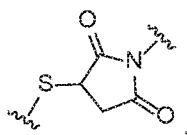
an antibody include, but are not limited to, aldehyde and ketone carbonyl groups. The heteroatom of a nucleophilic group can react with an electrophilic group on an antibody and form a covalent bond to the antibody. Useful nucleophilic groups include, but are not limited to, hydrazide, oxime, amino, hydroxyl, hydrazine, thiosemicarbazone, hydrazine carboxylate, and arylhydrazide.

In some embodiments, Z is the product of a reaction between reactive nucleophilic substituents present within the antibodies, or antigen-binding fragments thereof, such as amine and thiol moieties, and a reactive electrophilic substituent Z. For instance, Z may be a Michael acceptor (e.g., maleimide), activated ester, electron-deficient carbonyl compound, or an aldehyde, among others.

In some embodiments, the ADC comprises an anti-CD2 antibody or an anti-CD5 antibody conjugated to an amatoxin of any of formulae I, IA, IB, II, IIA, or IIB as disclosed herein via a linker and a chemical moiety Z. In some embodiments, the linker includes a dipeptide. In some embodiments, the linker includes a dipeptide selected from Val-Ala and Val-Cit. In some embodiments, the linker includes a para-aminobenzyl group (PAB). In some embodiments, the linker includes the moiety PAB-Cit-Val. In some embodiments, the linker includes the moiety PAB-Ala-Val. In some embodiments, the linker includes a $-(C=O)(CH_2)_n-$ unit, wherein n is an integer from 1-6. In some embodiments, the linker is $-PAB-Cit-Val-(C=O)(CH_2)_n-$.

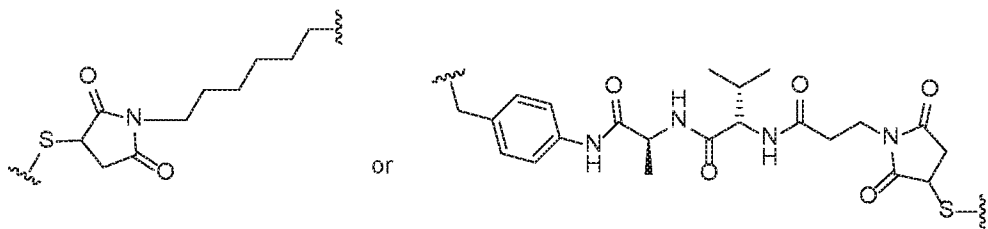
In some embodiments, the linker includes a $-(CH_2)_n-$ unit, where n is an integer from 2-6. In some embodiments, the linker is $-PAB-Cit-Val-(C=O)(CH_2)_n-$. In some embodiments, the linker is $-PAB-Ala-Val-(C=O)(CH_2)_n-$. In some embodiments, the linker is $-(CH_2)_n-$. In some embodiments, the linker is $-(CH_2)_n-$, wherein n is 6.

In some embodiments, the chemical moiety Z is selected from Table 2. In some embodiments, the chemical moiety Z is



where S is a sulfur atom which represents the reactive substituent present within an antibody, or antigen-binding fragment thereof, that binds CD2 or CD5 (e.g., from the -SH group of a cysteine residue).

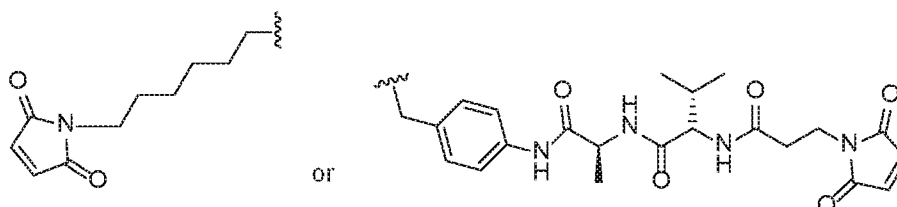
In some embodiments, the linker L and the chemical moiety Z, taken together as L-Z, is



One of skill in the art will recognize the linker- reactive substituent group structure, prior to conjugation with the antibody or antigen binding fragment thereof, includes a maleimide as the

group Z. The foregoing linker moieties and amatoxin-linker conjugates, among others useful in conjunction with the compositions and methods described herein, are described, for example, in U.S. Patent Application Publication No. 2015/0218220 and Patent Application Publication No. WO2017/149077, the disclosure of each of which is incorporated herein by reference in its entirety.

In some embodiments, the linker- reactive substituent group structure, prior to conjugation with the antibody or antigen binding fragment thereof, is:



Preparation of Antibody-Drug Conjugates

In the ADCs of formula I as disclosed herein, an antibody or antigen binding fragment thereof is conjugated to one or more cytotoxic drug moieties (D), e.g. about 1 to about 20 drug moieties per antibody, through a linker L and a chemical moiety Z as disclosed herein. The ADCs of the present disclosure may be prepared by several routes, employing organic chemistry reactions, conditions, and reagents known to those skilled in the art, including: (1) reaction of a reactive substituent of an antibody or antigen binding fragment thereof with a bivalent linker reagent to form Ab-Z-L as described herein above, followed by reaction with a drug moiety D; or (2) reaction of a reactive substituent of a drug moiety with a bivalent linker reagent to form D-L-Z, followed by reaction with a reactive substituent of an antibody or antigen binding fragment thereof as described herein above to form an ADC of formula D-L-Z-Ab, such as Am-Z-L-Ab. Additional methods for preparing ADC are described herein.

In another aspect, the antibody or antigen binding fragment thereof has one or more lysine residues that can be chemically modified to introduce one or more sulfhydryl groups. The ADC is then formed by conjugation through the sulfhydryl group's sulfur atom as described herein above. The reagents that can be used to modify lysine include, but are not limited to, N-succinimidyl S-acetylthioacetate (SATA) and 2-Iminoethiolane hydrochloride (Traut's Reagent).

In another aspect, the antibody or antigen binding fragment thereof can have one or more carbohydrate groups that can be chemically modified to have one or more sulfhydryl groups. The ADC is then formed by conjugation through the sulfhydryl group's sulfur atom as described herein above.

In yet another aspect, the antibody can have one or more carbohydrate groups that can be oxidized to provide an aldehyde (-CHO) group (see, for e.g., Laguzza, et al., J. Med. Chem. 1989, 32(3), 548-55). The ADC is then formed by conjugation through the corresponding aldehyde as described herein above. Other protocols for the modification of proteins for the attachment or

association of cytotoxins are described in Coligan et al., Current Protocols in Protein Science, vol. 2, John Wiley & Sons (2002), incorporated herein by reference.

Methods for the conjugation of linker-drug moieties to cell-targeted proteins such as antibodies, immunoglobulins or fragments thereof are found, for example, in U.S. Pat. No. 5,208,020; U.S.

5 Pat. No. 6,441,163; WO2005037992; WO2005081711; and WO2006/034488, all of which are hereby expressly incorporated by reference in their entirety.

Alternatively, a fusion protein comprising the antibody and cytotoxic agent may be made, e.g., by recombinant techniques or peptide synthesis. The length of DNA may comprise respective regions encoding the two portions of the conjugate either adjacent one another or separated by a
10 region encoding a linker peptide which does not destroy the desired properties of the conjugate.

Methods of Treatment

Anti-CD2 or anti-CD5 ADCs can be used to target T cells in the thymus of a patient where
15 the T cell specific ADCs can be used to deplete endogenous T cells and "reboot" the subject's immune system.

In vivo T cell depletion is commonly achieved using chemotherapy, such as anti-thymocyte globulin (ATG). The present methods achieve T cell depletion while leaving the subject's immune system intact. T cell depletion can be used to treat a subject who has had or is planning to
20 undergo hematopoietic stem cell (HSC) transplantation, such as autologous HSC transplantation.

As described herein, hematopoietic stem cell transplant therapy can be administered to a subject in need of treatment so as to populate or re-populate one or more blood cell types. Hematopoietic stem cells generally exhibit multi-potency, and can thus differentiate into multiple different blood lineages including, but not limited to, granulocytes (e.g., promyelocytes,
25 neutrophils, eosinophils, basophils), erythrocytes (e.g., reticulocytes, erythrocytes), thrombocytes (e.g., megakaryoblasts, platelet producing megakaryocytes, platelets), monocytes (e.g., monocytes, macrophages), dendritic cells, microglia, osteoclasts, and lymphocytes (e.g., NK cells, B-cells and T-cells). Hematopoietic stem cells are additionally capable of self-renewal, and can thus give rise to daughter cells that have equivalent potential as the mother cell, and also feature
30 the capacity to be reintroduced into a transplant recipient whereupon they home to the hematopoietic stem cell niche and re-establish productive and sustained hematopoiesis.

Hematopoietic stem cells can thus be administered to a patient defective or deficient in one or more cell types of the hematopoietic lineage in order to re-constitute the defective or deficient population of cells *in vivo*, thereby treating the pathology associated with the defect or depletion in
35 the endogenous blood cell population. The compositions and methods described herein can thus be used to treat a non-malignant hemoglobinopathy (e.g., a hemoglobinopathy selected from the group consisting of sickle cell anemia, thalassemia, Fanconi anemia, aplastic anemia, and Wiskott-Aldrich syndrome). Additionally or alternatively, the compositions and methods described

herein can be used to treat an immunodeficiency, such as a congenital immunodeficiency. Additionally or alternatively, the compositions and methods described herein can be used to treat an acquired immunodeficiency (e.g., an acquired immunodeficiency selected from the group consisting of HIV and AIDS). The compositions and methods described herein can be used to
5 treat a metabolic disorder (e.g., a metabolic disorder selected from the group consisting of glycogen storage diseases, mucopolysaccharidoses, Gaucher's Disease, Hurlers Disease, sphingolipidoses, and metachromatic leukodystrophy).

Additionally or alternatively, the compositions and methods described herein can be used to treat a malignancy or proliferative disorder, such as a hematologic cancer, myeloproliferative
10 disease. In the case of cancer treatment, the compositions and methods described herein may be administered to a patient prior to hematopoietic stem cell transplantation therapy in order to deplete a population of immune cells that cross-react with, and mount an immune response against, non-self hematopoietic stem cells, such as those expressing one or more non-self MHC antigens. This serves to prevent or reduce the likelihood of rejection of the transplanted
15 hematopoietic stem cell grafts, allowing the transplanted hematopoietic stem cells to home to a stem cell niche and establish productive hematopoiesis. This, in turn, can re-constitute a population of cells depleted during cancer cell eradication, such as during systemic chemotherapy. Exemplary hematological cancers that can be treated using the compositions and methods described herein include, without limitation, acute myeloid leukemia, acute lymphoid leukemia,
20 chronic myeloid leukemia, chronic lymphoid leukemia, multiple myeloma, diffuse large B-cell lymphoma, and non-Hodgkin's lymphoma, as well as other cancerous conditions, including neuroblastoma.

Anti-CD2 or anti-CD5 antibody drug conjugates (ADCs) can be used to treat disorders associated with aberrant T cell activity. For example, an anti-CD2 ADC or an anti-CD5 ADC can
25 be used to treat a T cell malignancy (e.g., lymphomas that affect T cells), where an effective amount of an anti-CD2 or an anti-CD5 ADC is administered to a subject having a T cell malignancy to reduce the growth or proliferation, of the malignant T cells. A "T cell malignancy" is a cancer that forms in T cells. In particular, the methods disclosed herein may be used to treat a patient having a T cell malignancy associated with CD5+ expression.. In certain embodiments,
30 Malignant T-cells express CD5+ such that treatment with an anti-CD5 ADC targets and depletes the malignant T-cells, resulting in a therapeutic benefit. In certain embodiments, the T cell malignancy is relapsed, refractory T cell malignancy. Examples of T cell malignancies that can be treated using the methods disclosed herein include T-cell acute lymphoblastic lymphoma (T-ALL; also called precursor T-lymphoblastic leukemia or T-cell acute lymphocytic leukemia), T-cell large
35 granular lymphocyte (LGL) leukemia, human T-cell leukemia virus type 1-positive (HTLV-1*), adult T-cell leukemia/lymphoma (ATL), T-cell prolymphocytic leukemia (T-PLL), and peripheral T-cell lymphoma (PTCLs).

In certain embodiments, an anti-CD2 ADC or an anti-CD5 ADC may be used to treat a human patient having a T cell lymphoma. Examples of T cell lymphomas that may be treated using the methods and compositions disclosed herein include, but are not limited to, T cell Systemic EBV+ T-cell lymphoma of childhood, extranodal NK-/T-cell lymphoma, nasal type, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, indolent T-cell, lymphoproliferative disorder of the GI tract, hepatosplenic T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, mycosis fungoides, Sézary syndrome, primary cutaneous CD30+ T-cell, lymphoproliferative disorders (e.g., Lymphomatoid papulosis, Primary cutaneous anaplastic large cell lymphoma), primary cutaneous $\gamma\delta$ T-cell lymphoma, primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma, primary cutaneous acral CD8+ T-cell lymphoma, primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder, angioimmunoblastic T-cell lymphoma, follicular T-cell lymphoma, nodal peripheral T-cell lymphoma with TFH phenotype, anaplastic large-cell lymphoma (ALK+), anaplastic large-cell lymphoma (ALK-), and breast implant-associated anaplastic large-cell lymphoma.

In some embodiments, a human patient having a T-cell malignancy is treated by administering an anti-CD5 ADC, e.g., an anti-CD5 antibody conjugated to an amatoxin described herein via a linker.

In some embodiments, a human patient having a T-cell malignancy is treated by administering an anti-CD2 ADC, e.g., an anti-CD2 antibody conjugated to an amatoxin described herein via a linker.

Additional diseases that can be treated with the compositions and methods described herein include, without limitation, 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.

Anti-CD5 or CD2 ADCs described herein may be used to induce solid organ transplant tolerance. For instance, the compositions and methods described herein may be used to deplete or ablate a population of immune cells prior to hematopoietic stem cell transplantation. Following such depletion of cells from the target tissues, a population of stem or progenitor cells from an organ donor (e.g., hematopoietic stem cells from the organ donor) may be administered to the transplant recipient, and following the engraftment of such stem or progenitor cells, a temporary or stable mixed chimerism may be achieved, thereby enabling long-term transplant organ tolerance without the need for further immunosuppressive agents. The likelihood of rejection of the transplanted graft can be reduced, or rejection may be prevented altogether, by administration of an anti-CD2 ADC or an anti-CD5 ADC. In this way, the compositions and methods described herein may be used to induce transplant tolerance in a solid organ transplant recipient (e.g., a

kidney transplant, lung transplant, liver transplant, and heart transplant, among others). The compositions and methods described herein are well-suited for use in connection the induction of solid organ transplant tolerance, for instance, because a low percentage temporary or stable donor engraftment is sufficient to induce long-term tolerance of the transplanted organ.

5 In addition, the compositions and methods described herein can be used to treat cancers directly, such as cancers characterized by cells that are CD2+ or CD5+. For instance, the compositions and methods described herein can be used to treat leukemia, particularly in patients that exhibit CD2+ or CD5+ leukemic cells. By depleting CD2+ or CD5+ cancerous cells, such as leukemic cells, the compositions and methods described herein can be used to treat various
10 cancers directly. Exemplary cancers that may be treated in this fashion include hematological cancers, such as acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphoid leukemia, multiple myeloma, diffuse large B-cell lymphoma, and non-Hodgkin's lymphoma,

In addition, the compositions and methods described herein can be used to treat
15 autoimmune disorders. The methods and compositions disclosed herein can also be used to substantially deplete endogenous CD5+ or CD2+ T cells in the thymus of a subject having an autoimmune disease, such as, but not limited to, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus (SLE), or systemic sclerosis (SSc). For instance, an antibody, or antigen-binding fragment thereof, can be administered to a subject, such as a human patient suffering from
20 an autoimmune disorder, so as to kill a CD2+ or CD5+ immune cell. The CD2+ or CD5+ immune cell may be an autoreactive lymphocyte, such as a T-cell that expresses a T-cell receptor that specifically binds, and mounts an immune response against, a self antigen. By depleting self-reactive, CD2+ cells or CD5+ cells, the compositions and methods described herein can be used to treat autoimmune pathologies, such as those described below. Additionally or alternatively, the
25 compositions and methods described herein can be used to treat an autoimmune disease by depleting a population of endogenous hematopoietic stem cells prior to hematopoietic stem cell transplantation therapy, in which case the transplanted cells can home to a niche created by the endogenous cell depletion step and establish productive hematopoiesis. This, in turn, can re-constitute a population of cells depleted during autoimmune cell eradication.

30 Autoimmune diseases that can be treated using the compositions and methods described herein include, without limitation, psoriasis, psoriatic arthritis, Type 1 diabetes mellitus (Type 1 diabetes), rheumatoid arthritis (RA), human systemic lupus (SLE), multiple sclerosis (MS), inflammatory bowel disease (IBD), lymphocytic colitis, acute disseminated encephalomyelitis (ADEM), Addison's disease, alopecia universalis, ankylosing spondylitis, antiphospholipid
35 antibody syndrome (APS), aplastic anemia, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease (AIED), autoimmune lymphoproliferative syndrome (ALPS), autoimmune oophoritis, Balo disease, Behcet's disease, bullous pemphigoid, cardiomyopathy,

Chagas' disease, chronic fatigue immune dysfunction syndrome (CFIDS), 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 (GBS), 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 (MCTD), myasthenia gravis, neuromyotonia, opsoclonus myoclonus syndrome (OMS), 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 (also known as "giant cell arteritis"), ulcerative colitis, collagenous colitis, uveitis, vasculitis, vitiligo, vulvodynia ("vulvar vestibulitis"), and Wegener's granulomatosis.

For instance, using the compositions and methods described herein, one of skill in the art can administer to a subject suffering from an autoimmune disorder an anti-CD2 ADC or an anti-CD5 ADC in a quantity sufficient to treat the autoimmune pathology. For instance, the subject may be suffering from scleroderma, multiple sclerosis, ulcerative colitis, Crohn's disease, and/or Type 1 diabetes. To ameliorate one or more of these conditions, a physician of skill in the art can prescribe and administer to the subject an anti-CD2 ADC or an anti-CD5 ADC. An anti-CD2 ADC or an anti-CD5 ADC can be used to deplete a population of endogenous, autoreactive CD2+ T cells or NK cells, or a population of endogenous, autoreactive CD5+ T cells, B cells or NK cells in a subject.

In some embodiments, an anti-CD5 ADC or an anti-CD2 ADC is used to deplete a subset of autoreactive CD5+ or CD2+ T cells, such as Th1 or Th17 cells. In some embodiments, an anti-CD5 antibody, or antigen-binding portion thereof, conjugated to an amatoxin can be used to deplete a Th1 or Th17 cell in a human subject having an autoimmune disease, such as, but not limited to, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus (SLE), or systemic sclerosis (SSc). In some embodiments, an anti-CD2 antibody, or antigen-binding portion thereof, conjugated to an amatoxin can be used to deplete a Th1 or Th17 cell in a human subject having an autoimmune disease, such as, but not limited to, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus (SLE), or systemic sclerosis (SSc). The role of T cell subsets, including Th1 and Th17 in autoimmunity is reviewed in, e.g., Hirahara and Nakayama, *Int. Immunol.* 28(4):163-171, 2016; Raphael et al., *Cytokine* 71(1):5-17, 2015; and Sun and Zhang, *Adv. Exp. Med. Biol.* 841:1-13, 2014, the teachings of which are incorporated by reference in their entireties.

In some embodiments, an anti-CD5 ADC or an anti-CD2 ADC is administered to a human patient having a Th1 mediated autoimmune disease, such as multiple sclerosis, for treatment. A “Th1 mediated autoimmune disease” is an autoimmune disease where detrimental Th1 lymphocyte activity is associated with the disease.

5 In other embodiments, an anti-CD5 ADC or an anti-CD2 ADC is administered to a human patient having a Th17 mediated autoimmune disease, such as multiple sclerosis, for treatment. A “Th17 mediated autoimmune disease” is an autoimmune disease where detrimental Th17 lymphocyte activity is associated with the disease. Examples of such diseases include, but are not limited to, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus (SLE), or systemic
10 sclerosis (SSc). The role of Th17 cells in inflammatory and autoimmune disease is described in Zambramo-Zaragoza *et al.* (2014) *Int J Inflam.*, vol, 2014, article ID 651503.

In preparation for therapy, the physician may assess the quantity or concentration of autoreactive T cells, B cells and/or NK cells in a sample isolated from a subject. This may be done, for instance, using FACS analysis techniques known in the art. One of skill in the art may
15 then administer to the subject an antibody, or fragment thereof, either alone or conjugated to a cytotoxin, so as to deplete the population of autoreactive T cells, B cells and/or NK cells. To evaluate the efficacy of the therapy, the physician may determine the quantity or concentration of autoreactive T cells, B cells and/or NK cells in a sample isolated from the patient at a time subsequent to the administration of the anti-CD2 ADC or an anti-CD5 ADC. A determination that
20 the quantity or concentration of autoreactive T cells, B cells and/or NK cells in a sample isolated from the subject following therapy relative to the quantity or concentration of T cells, B cells or NK cells prior to therapy provides an indication that the patient is responding to the anti-CD2 ADC or anti-CD5 ADC.

Antibody drug conjugates comprising anti-CD2 antibodies, or antigen-binding fragments
25 thereof (or anti-CD5 antibodies, or antigen-binding fragments thereof), can also be used in combination with CAR T therapy. Specifically, an effective amount of an anti-CD2 antibody drug conjugate (an anti-CD5 antibody drug conjugate) can be administered to a patient in need thereof prior to CAR T treatment in order to deplete native T cells. Depletion of native T cells expressing CD2 or CD5 using the methods and compositions described herein can provide for more effective
30 transfer of engineered T cells used in CAR T therapy.

The methods and compositions described herein can also be used to treat acute and chronic forms of graft versus host disease (GVHD), including steroid refractory GVHD, e.g., steroid refractory acute GVHD. GVHD is one of the main complications of transplantation, including allogeneic stem cell transplantation (SCT). The compositions disclosed herein may be used to
35 selectively target activated T cells in a patient who has received, is receiving, or will be receiving a transplant, such as a stem cell transplant. The anti-CD5 ADCs or the anti-CD2 ADCs described herein can be used to reduce the risk of GVHD by targeting and depleting CD5+ or CD2+ positive

cells in a human patient who has received, is receiving, or will be receiving a transplant, such as but not limited to, an HSC transplant.

In certain embodiments, the compositions and methods disclosed herein are for treating GVHD prior to appearance of symptoms of GVHD in a patient following a transplantation therapy, e.g., allogeneic HSCs. In some embodiments, the methods and compositions described herein can be used to treat steroid refractory GVHD. While GVHD can be controlled by high-dose steroids in many patients, some patients will become refractory to the steroid treatment, resulting in a poor prognosis. By depleting CD5+ T cells or CD2+ T cells using an antigen specific ADC, steroid refractory GVHD can be treated when steroids have failed. Improvements in GVHD (e.g., acute GVHD or steroid refractory acute GVHD) can be measured using the grading system provided by the Mount Sinai acute GVHD International Consortium (MAGIC) criteria. Thus, in one embodiment, administration of an effective amount of an anti-CD2 or an anti-CD5 ADC to a subject having GVHD (e.g., acute GVHD or steroid refractory acute GVHD) results in an improvement in the subject's MAGIC score.

Routes of Administration and Dosing

ADCs can be administered to a patient (e.g., a human patient in need of hematopoietic stem cell transplant therapy) in a variety of dosage forms. For instance, ADCs can be administered to a patient in need of hematopoietic stem cell transplant therapy and/or suffering from cancer or an autoimmune disease in the form of an aqueous solution, such as an aqueous solution containing one or more pharmaceutically acceptable excipients. Exemplary pharmaceutically acceptable excipients for use with the compositions and methods described herein are viscosity-modifying agents. The aqueous solution may be sterilized using techniques known in the art.

ADCs may be administered by a variety of routes, such as orally, transdermally, subcutaneously, intranasally, intravenously, intramuscularly, intraocularly, or parenterally. The most suitable route for administration in any given case will depend on the ADC administered, the patient, pharmaceutical formulation methods, administration methods (e.g., administration time and administration route), the patient's age, body weight, sex, severity of the diseases being treated, the patient's diet, and the patient's excretion rate.

The effective dose of an ADC can range, for example from about 0.001 to about 100 mg/kg (e.g., about 0.001 mg/kg to about 0.01 mg/kg, about 0.01 mg/kg to about 0.1 mg/kg, about 0.1 mg/kg to about 1 mg/kg, about 1 mg/kg to about 10 mg/kg, about 10 mg/kg to about 100 mg/kg) of body weight per single (e.g., bolus) administration, multiple administrations, or continuous administration, or to achieve an optimal serum concentration (e.g., a serum concentration of about 0.0001 to about 5000 µg/mL, about 0.0001-0.001 µg/mL, about 0.001-0.01 µg/mL, about 0.01-0.1 µg/mL, about 0.1-1 µg/mL, about 1-10 µg/mL, about 10-100 µg/mL, about 100-1000 µg/mL, about

1000-2000 µg/mL, about 2000-3000 µg/mL, or about 3000-5000 µg/mL) of the antibody, or an antigen-binding fragment thereof. The dose may be administered one or more times (e.g., about 2-10 times) per day, week, or month to a subject (e.g., a human) undergoing conditioning therapy in preparation for receipt of a hematopoietic stem cell transplant. The ADC can be administered to the patient at a time that optimally promotes engraftment of the exogenous hematopoietic stem cells, for instance, at a time that optimally depletes CD2+ (or CD5+) T cells, B cells or NK cells that cross-react with a non-self hematopoietic stem cell antigen (e.g., a non-self MHC antigen expressed by the hematopoietic stem cells) prior to hematopoietic stem cell transplantation. For example, anti-CD2 ADCs or anti-CD5 ADCs, may be administered to a patient undergoing hematopoietic stem cell transplant therapy from about 1 hour to about 1 week (e.g., about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 13 hours, about 14 hours, about 15 hours, about 16 hours, about 17 hours, about 18 hours, about 19 hours, about 20 hours, about 21 hours, about 22 hours, about 23 hours, about 24 hours, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 7 days; or about 1 to 3 days; about 1 to 4 days; about 12 hours to 3 days) or more prior to administration of the exogenous hematopoietic stem cell transplant. The half-life of the antibody may be between about 1 hour and about 24 hours (e.g., about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11, hours, about 12 hours, about 13 hours, about 14 hours, about 15 hours, about 16 hours, about 17 hours, about 18 hours, about 19 hours, about 20 hours, about 21 hours, about 22 hours, about 23 hours, or about 24 hours).

In one embodiment, an anti-CD2 ADC or an anti-CD5 ADC has a reduced half life (compared to an ADC comprising an antibody with wild type Fc region) where the Fc region of the antibody comprises an H435A mutation (numbering according to the EU index).

According to the methods disclosed herein, a physician of skill in the art can condition a patient, such as a human patient, so as to promote the engraftment of exogenous hematopoietic stem cell grafts prior to hematopoietic stem cell transplant therapy. To this end, a physician of skill in the art can administer to the human patient an antibody, or antigen-binding fragment thereof, capable of binding CD2 or CD5, such as an anti-CD2 ADC described herein. The antibody, or fragment thereof, may be covalently conjugated to a toxin, such as a cytotoxic molecule described herein or known in the art, or an Fc domain. For instance, an anti-CD2 ADC can be covalently conjugated to a cytotoxin, such as pseudomonas exotoxin A, deBouganin, diphtheria toxin, an amatoxin, such as α-amanitin, saporin, maytansine, a maytansinoid, an auristatin, an anthracycline, a calicheamicin, irinotecan, SN-38, a duocarmycin, a pyrrolobenzodiazepine, a pyrrolobenzodiazepine dimer, an indolinobenzodiazepine, an indolinobenzodiazepine dimer, or a variant thereof. This conjugation can be performed using covalent bond-forming techniques

described herein or known in the art. The antibody, antigen-binding fragment thereof, or antibody-drug conjugate can subsequently be administered to the patient, for example, by intravenous administration, prior to transplantation of exogenous hematopoietic stem cells (such as autologous, syngeneic, or allogeneic hematopoietic stem cells) to the patient.

5 An anti-CD2 or anti-CD5 antibody-drug conjugate can be administered in an amount sufficient to reduce the quantity of endogenous T cells, B cells, and/or NK cells such as bone marrow resident T cells, for example, by about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 10% to 90%, about 10% to 70%, about 10% to 60%, or more prior to hematopoietic stem cell transplant therapy. For
10 example, the anti-CD2 or anti-CD5 ADC can be administered in an amount sufficient to reduce the quantity of endogenous T cells, B cells, and/or NK cells, such as bone marrow resident T cells, for example, by about 10%-20%, by about 20-30%, by about 30-40%, by about 40-50%, by about 50-60%, by about 60-70%, by about 70%-80%, by about 80%-90%, by about 90%-95%, or more prior to hematopoietic stem cell transplant therapy. For example, the anti-CD2 or anti-CD5 antibody-
15 drug conjugate, can be administered in an amount sufficient to reduce the quantity of endogenous T cells, B cells, and/or NK cells, such as bone marrow resident T cells, for example, by at least about 10%, by at least about 20%, by at least about 30%, by at least about 40%, by at least about 50%, by at least about 60%, by at least about 70%, by at least about 80%, by at least about 90%, by at least about 95%, or more prior to hematopoietic stem cell transplant therapy. The reduction
20 in T cell count can be monitored using conventional techniques known in the art, such as by FACS analysis of cells expressing characteristic T cell surface antigens in a blood sample withdrawn from the patient at varying intervals during conditioning therapy. For instance, a physician of skill in the art can withdraw a bone marrow sample from the patient at various time points during conditioning therapy and determine the extent of endogenous T cell reduction by conducting a
25 FACS analysis to elucidate the relative concentrations of T cells in the sample using antibodies that bind to T cell marker antigens. According to some embodiments, when the concentration of T cells has reached a minimum value in response to conditioning therapy with an anti-CD2 or anti-CD5 antibody-drug conjugate, the physician may conclude the conditioning therapy, and may begin preparing the patient for hematopoietic stem cell transplant therapy.

30 The anti-CD2 or anti-CD5 antibody-drug conjugate, can be administered to the patient in an aqueous solution containing one or more pharmaceutically acceptable excipients, such as a viscosity-modifying agent. The aqueous solution may be sterilized using techniques described herein or known in the art. The antibody-drug conjugate, can be administered to the patient at a dosage of, for example, from about 0.001 mg/kg to about 100 mg/kg (e.g., about 0.001 mg/kg to
35 about 0.01 mg/kg, about 0.01 mg/kg to about 0.1 mg/kg, about 0.1 mg/kg to about 1 mg/kg, about 1 mg/kg to about 10 mg/kg, about 10 mg/kg to about 100 mg/kg) prior to administration of a hematopoietic stem cell graft to the patient. The antibody-drug conjugate, can be administered to

the patient at a time that optimally promotes engraftment of the exogenous hematopoietic stem cells, for instance, from about 1 hour to about 1 week (e.g., about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 13 hours, about 14 hours, about 15 hours, about 16 hours, about 17 hours, about 18 hours, about 19 hours, about 20 hours, about 21 hours, about 22 hours, about 23 hours, about 24 hours, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 7 days) or more prior to administration of the exogenous hematopoietic stem cell transplant.

Following the conclusion of conditioning therapy, the patient may then receive an infusion (e.g., an intravenous infusion) of exogenous hematopoietic stem cells, such as from the same physician that performed the conditioning therapy or from a different physician. The physician may administer the patient an infusion of autologous, syngeneic, or allogeneic hematopoietic stem cells, for instance, at a dosage of from about 1×10^3 to about 1×10^9 hematopoietic stem cells/kg (e.g., from about 1×10^3 hematopoietic stem cells to about 1×10^4 , from about 1×10^4 hematopoietic stem cells to about 1×10^5 , from about 1×10^5 hematopoietic stem cells to about 1×10^6 , from about 1×10^6 hematopoietic stem cells to about 1×10^7 , or from about 1×10^8 hematopoietic stem cells to about 1×10^9). The physician may monitor the engraftment of the hematopoietic stem cell transplant, for example, by withdrawing a blood sample from the patient and determining the increase in concentration of hematopoietic stem cells or cells of the hematopoietic lineage (such as 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) following administration of the transplant. This analysis may be conducted, for example, from about 1 hour to about 6 months, or more, following hematopoietic stem cell transplant therapy (e.g., about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 13 hours, about 14 hours, about 15 hours, about 16 hours, about 17 hours, about 18 hours, about 19 hours, about 20 hours, about 21 hours, about 22 hours, about 23 hours, about 24 hours, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, about 21 weeks, about 22 weeks, about 23 weeks, about 24 weeks, or more). A finding that the concentration of hematopoietic stem cells or cells of the hematopoietic lineage has increased (e.g., by about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 100%, about 200%, about

500%, or more) following the transplant therapy relative to the concentration of the corresponding cell type prior to transplant therapy provides one indication that treatment with the anti-CD2 or anti-CD5) antibody-drug conjugate, has successfully promoted engraftment of the transplanted hematopoietic stem cell graft.

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Examples

The following examples are put forth so as to provide those of ordinary skill in the art with a description of how the compositions and methods described herein may be used, made, and evaluated, and are intended to be purely exemplary and are not intended to limit the scope of what the inventors regard as their invention.

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Example 1: *In vitro* binding analysis of anti-CD2 antibodies.

To determine the binding characteristics of anti-CD2 antibodies RPA-2.10 mIgG1 and Ab1 hIgG1, antibody binding studies were performed at 25 degrees Celsius in 1x PBS supplemented with 0.1% w/v bovine serum albumin with a Pall ForteBio Octet Red96 using biolayer interferometry (BLI). The indicated purified human (Ab1-hIgG1) or murine (RPA-2.10 mIgG1) antibody was immobilized onto anti-human Fc biosensors (AHC; Pall ForteBio 18-5063) or anti-murine Fc biosensors (AMQ; Pall ForteBio 18-5090 and incubated with 50nM of purified human CD2 ectodomain (Sigma Aldrich and Catalog #5086). The apparent monovalent affinity (K_D), apparent association rate (K_{ON}), and apparent dissociation rate (K_{DIS}) were determined by local full fitting with a 1:1 binding model as calculated by ForteBio data analysis software version 10 of each IgG to purified human CD2 ectodomain are shown in Table 3.

20

Further characterization of anti-CD2 antibodies is provided in Examples 2 to 6.

25 Table 3: Binding kinetics of the indicated IgG to human CD2 ectodomain

Antibody	Conc. (nM)	Response (nm)	K_D (M)	K_{ON} (1/Ms)	K_{DIS} (1/s)	Full R^2
mRPA-2.10	50	0.1807	2.00E-09	8.60E+04	1.72E-04	0.9952
Ab1	50	0.0615	2.12E-09	1.36E+05	2.89E-04	0.9683

Example 2: *In vitro* cell line binding analysis of anti-CD2 antibodies

MOLT-4 cells (i.e., an immortalized human T lymphoblast cell line) were plated at 20,000 cells/well and stained with a titration of the indicated murine anti-CD2 antibodies (i.e., RPA-2.10, TS1/8, BH1, UMCD2, 1E7E8.G4, or LT2) for 2 hours at 4 °C. Secondary anti-mouse AF488 stain, at a constant amount, was added for 30 minutes at 4 °C. After washing, plates were run on a flow cytometer and binding of the indicated antibody (and the negative control, i.e., mIgG1) was determined based on geometric mean fluorescence intensity in the AF488 channel. Results from

30

these assays are provided in Fig. 1.

As shown in Fig. 1, the murine anti-CD2 antibodies RPA-2.10, TS1/8, BH1, UMCD2, 1E7E8.G4, and LT2 bind to human T lymphoblast cells (i.e. MOLT-4 cells), with an EC_{50} = 160 pM (RPA-2.10), 125 pM (TS 1/8), 639 pM (BH1), 151 pM (UMCD2), 134 pM (1E7E8), and 60 pM (LT2).

Example 3: *In vitro* primary cell binding analysis of anti-CD2 antibodies

Primary human T-cells were plated at 8×10^4 cells/well and stained with a titration of the murine anti-CD23 antibody RPA-2.10 for 2 hours at 37°C. Secondary anti-mouse or anti-human AF488 stain, relative to primary antibody, at a constant amount, was added for 30 minutes at 4 °C. After washing, plates were run on a flow cytometer and binding of the indicated antibody (and the negative control, i.e., mIgG1 or hIgG1) was determined based on geometric mean fluorescence intensity in the AF488 channel. Results from these assays are provided in Fig. 2.

As shown in Fig. 2, the murine anti-CD2 antibody RPA-2.10 binds to primary human T-cells with an EC_{50} = 1.84 pM (RPA-2.10).

Example 4. *In vitro* analysis of an anti-CD2-amanitin antibody drug conjugate (ADC) using an *in vitro* T-cell killing assay

The anti-CD2 antibody RPA 2.10 was conjugated to amanitin with a cleavable linker to form an anti-CD2-ADC. One anti-CD2-ADC was prepared from the murine anti-CD2 antibody RPA-2.10 having an average interchain drug-to-antibody ratio (DAR) of 6. A second anti-CD2-ADC having an average DAR of 2 was prepared using a human chimeric variant of RPA-2.10 conjugated to amanitin using site-specific conjugation. Further, a fast half-life variant of anti-CD2-ADC was generated through the introduction of a H435A mutation. Each anti-CD2-ADC was assessed using an *in vitro* T-cell killing assay.

Cryopreserved negatively-selected primary human T cells were thawed and stimulated with anti-CD3 antibodies and IL-2. At the start of the assay, 2×10^4 T cells were seeded per well of a 384 well plate and the indicated ADCs or non-conjugated anti-CD2 antibody were added to the wells at various concentrations between 0.003 nM and 30 nM before being placed in an incubator with 37 °C and 5% CO₂. Following five days of culture, cells were analyzed by flow cytometry. Cells were stained with a viability marker 7-AAD and run on a volumetric flow cytometer. Numbers of viable T-cells (Figs. 3A and 3B) were determined by FSC vs SSC and 7-AAD staining. A non-conjugated anti-CD2 antibody (RPA 2.10) served as a comparator (Fig. 3A).

As shown in Fig. 3A, anti-CD2-ADCs having an interchain drug-to-antibody ratio of 6 exhibited potent and specific killing of T cells (IC_{50} =5.0pM) whereas T cells remained viable in the presence of non-conjugated ("naked") anti-CD2 antibodies. As shown in Fig. 3B, human chimeric anti-CD2-ADCs having a site-specific drug-to-antibody ratio of 2 retained a potent level of T-cell

killing (IC₅₀=1.0pm) similar to that of the DAR 6 ADCs. Further, the fast-half life variant of the anti-CD2-ADCs (H435A) exhibited a similar level of T-cell killing (IC₅₀=6.3 pm; Fig. 3B) as an anti-CD2-ADC with WT half-life.

5 Example 5. *In vitro* analysis of an anti-CD2-amanitin antibody drug conjugate (ADC) using an *in vitro* T-cell killing assay

The anti-CD2 antibody RPA 2.10 was conjugated to amanitin with a cleavable linker to form an interchain anti-CD2-ADC with an average interchain drug-to-antibody ratio (DAR) of 6. The anti-CD2-ADC was assessed using an *in vitro* natural killer (NK)-cell killing assay.

10 Primary human CD56⁺ CD3⁻ NK cells were cultured with recombinant IL-2 and IL-15 for four days. At the start of the assay, 30,000 freshly isolated NK cells from a healthy human donor were seeded per well of a 384 well plate and the indicated ADC or control (i.e., IgG1 or IgG1-amanitin ADC) was added to the wells at various concentrations between 0.003 nm and 30 nm before being placed in an incubator with 37 °C and 5% CO₂. Following 4 days of culture, NK cell
15 viability was analyzed by a CellTiter-Glo assay (Fig. 4).

As shown in Fig. 4, anti-CD2-ADC exhibited potent killing of NK cells, with an IC₅₀ of 5.2 pM. The lack of complete killing by the anti-CD2-ADC is consistent with the fact that CD2 is only expressed on about 75% of NK cells.

20 Example 6. Analysis of T-cell Depletion using a hNSG Mouse Model

In vivo T-cell depletion assays were conducted using humanized NSG mice (Jackson Laboratories). An anti-CD2 antibody RPA 2.10 was conjugated to amanitin with a cleavable linker to form an anti-CD2-ADC. One anti-CD2-ADC was prepared with murine RPA 2.10 having an average interchain drug-to-antibody ratio (DAR) of 6 while another anti-CD2-ADC was prepared
25 with human chimeric RPA 2.10 having an average site-specific DAR of 2. Each anti-CD2-ADC (DAR6 and DAR2) was administered as a single intravenous injection (0.3 mg/kg, 1 mg/kg, or 3 mg/kg for DAR6 ADCs, and 1 mg/kg or 3 mg/kg for DAR2 ADCs) to the humanized mouse model. Peripheral blood cells, bone marrow, or thymic samples were collected on Day 7 and the absolute number of CD3⁺ T-cells was determined by flow cytometry (see Figs. 5A and 5B for DAR2 ADCs,
30 and 6A-6C for DAR6 ADCs).

As shown in, Figs. 5A-5B, humanized NSG mice treated with 0.3 mg/kg, 1 mg/kg, or 3 mg/kg interchain DAR6 anti-CD2-ADC exhibited potent T-cell depletion in peripheral blood or bone marrow while thymic T-cells were depleted following treatment with 3 mg/kg of DAR6 anti-CD2-ADC. For comparison, Figs. 5A and 5B also show the level of T-cell depletion following treatment
35 of humanized NSG mice with 25 mg/kg Ab1 (an unconjugated anti-CD2 antibody) or with the indicated controls (i.e., 25 mg/kg anti-CD52 antibody (clone YTH34.5); 3 mg/kg hIgG1-amanitan ADC ("hIgG1-AM"), 25 mg/kg hIgG1, or PBS).

As shown in, Figs. 6A-6C, humanized NSG mice treated with 1 mg/kg or 3 mg/kg site-specific DAR2 anti-CD2-ADC exhibited potent T-cell depletion in peripheral blood or bone marrow while thymic T-cells displayed about 59% depleted following treatment with 3 mg/kg of DAR2 anti-CD2-ADC. For comparison, Figs. 6A-6C also show the level of T-cell depletion following treatment of humanized NSG mice with 3 mg/kg of an unconjugated anti-CD2 antibody or with the indicated controls (i.e., 3 mg/kg hlgG1-amanitan-ADC ("hlgG1-AMC") or PBS).

Example 7: *In vitro* binding analysis of anti-CD5 antibodies.

To determine the binding characteristics of anti-CD5 antibody 5D7 hlgG1, antibody binding studies were performed at 25 degrees celsius in 1x PBS supplemented with 0.1% w/v bovine serum albumin with a Pall ForteBio Octet Red96 using biolayer interferometry (BLI). The purified human anti-CD5 antibody (5D7) was immobilized onto anti-human Fc biosensors (AHC; Pall ForteBio 18-5063) and incubated with 50nM of purified human CD5 ectodomain). The binding characteristics of anti-CD5 antibody 5D7 are shown in Table 4. Anti-human CD5 antibody 5D7 as used in Examples 7 to 11 is a humanized version of murine antibody 5D7 (see US 2008/0254027). The sequences of antibody 5D7 as used herein are described in SEQ ID Nos: 282 and 283 (heavy and light chain variable region amino acid sequences) and SEQ ID Nos: 54 to 59 (heavy and light chain CDRs).

Table 4: Binding kinetics of 5D7 to human CD5 ectodomain

Antibody	Conc. (nM)	Response (nm)	K _D (M)	K _{ON} (1/Ms)	K _{DIS} (1/s)	Full R ²
5D7	50	0.6696	1.41E-10	2.39E+05	3.36E-05	0.9996

Example 8: *In vitro* cell line binding analysis of anti-CD5 antibodies

MOLT-4 cells (i.e., an immortalized human T lymphoblast cell line) were plated at 20,000 cells/well and stained with a titration of the indicated murine anti-CD5 antibodies (i.e., L17F12, UCHT2, 205919, and CRIS-1) for 2 hours at 4 °C. Secondary anti-mouse AF488 stain, at a constant amount, was added for 30 minutes at 4 °C. After washing, plates were run on a flow cytometer and binding of the indicated antibody (and the negative control, i.e., mlgG1) was determined based on geometric mean fluorescence intensity in the AF488 channel. Results from these assays are provided in Fig. 7.

As shown in Fig.7, the murine anti-CD5 antibodies L17F12 (Thermo Fisher), UCHT2 (BioLegend), 205919 (Novus Biologicals), and CRIS-1 (Novus Biologicals) bound to human T lymphoblast cells (i.e. MOLT-4 cells), with an EC₅₀ = 207 pM (L17), 354 pM (UCH), 1350 pM (205), and 43 pM (CRIS).

Example 9: *In vitro* primary cell binding analysis of anti-CD5 antibodies

Primary human T-cells were plated at 8×10^4 cells/well and stained with a titration of the human anti-CD5 antibody 5D7 for 2 hours at 37°C. Secondary anti-mouse AF488 stain, at a constant amount, was added for 30 minutes at 4 °C. After washing, plates were run on a flow cytometer and binding of the anti-CD5 5D7 antibody (and the negative control, i.e., hlgG1) was determined based on geometric mean fluorescence intensity in the AF488 channel. Results from these assays are provided in Fig. 8.

As shown in Fig. 8, the anti-CD5 antibody 5D7 bound to primary human T-cells with an $EC_{50} = 3.0$ pM.

Example 10. *In vitro* analysis of an anti-CD5-amatoxin antibody drug conjugate (ADC) using an *in vitro* T-cell killing assay

The anti-CD5 antibody 5D7 was conjugated to an amatoxin (amanitin) with a cleavable linker to form an anti-CD5 5D7ADC. Anti-CD5 5D7-ADCs having a drug to antibody ratio (DAR) of about 6 (interchain DAR6) were tested, as well as anti-CD5 5D7-ADCs having a DAR of about 2 (prepared using site-specific conjugation via a D265C mutation). Further, a fast half-life variant of the anti-CD5 5D7-ADC was generated through the introduction of an H435A mutation within the Fc region.

Each anti-CD5 5D7-ADC was assessed using an *in vitro* human T-cell killing assay. Cryopreserved negatively-selected primary human T cells were thawed and stimulated with anti-CD3 antibodies and IL-2. At the start of the assay, 2×10^4 T cells were seeded per well of a 384 well plate and the indicated ADCs or non-conjugated anti-CD5 antibody were added to the wells at various concentrations between 0.003 nM and 30 nM before being placed in an incubator with 37 °C and 5% CO₂. Following five days of culture, cells were analyzed by flow cytometry. Cells were stained with a viability marker 7-AAD and run on a volumetric flow cytometer.

Numbers of viable T-cells (Figs. 9A and 9B) were determined by FSC vs SSC and 7-AAD. A non-conjugated anti-CD5 5D7 antibody served as a comparator (Fig. 9A).

As shown in Fig. 9A, anti-CD5 5D7-ADCs having a DAR of about 6 exhibited potent and specific killing of human T cells ($IC_{50}=3.7$ pM) whereas T cells remained viable in the presence of non-conjugated ("naked") anti-CD5 5D7 antibodies. As shown in Fig. 9B, ADCs having a site-specific (D265C) DAR of about 2 retained a potent level of T-cell killing ($IC_{50} = 5.0$ pM) similar to that of the DAR 6 ADCs. The fast-half life variant of the anti-CD5 5D7-ADC (H435A) exhibited a similar level of T-cell killing ($IC_{50}=4.9$ pM; Fig. 9B).

Example 11. Analysis of T-cell Depletion using a hNSG Mouse Model

In vivo T-cell depletion assays were conducted using humanized NSG mice (Jackson Laboratories). Anti-CD5 antibody 5D7 was conjugated to amatoxin (amanitin) with a cleavable

linker to form an anti-CD5 5D7-ADC. Anti-CD5 5D7-ADCs were prepared either as a DAR of about 6 or a DAR of about 2, as described above. Each anti-CD5 5D7ADC (DAR6 or DAR2) was administered as a single intravenous injection (0.3 mg/kg, 1 mg/kg, or 3 mg/kg for DAR6 ADCs, or 1 mg/kg or 3 mg/kg for DAR2 ADCs) to the humanized mouse. Peripheral blood cells, bone marrow, or thymic samples were collected on Day 7 and the absolute number of CD3+ T-cells was determined by flow cytometry (see Figs. 10A-10B for DAR2 ADCs, and 11A-11C for DAR6 ADCs).

As shown in, Figs. 10A-10B, humanized NSG mice treated with 0.3 mg/kg, 1 mg/kg, or 3 mg/kg DAR6 anti-CD5 5D7-ADCs exhibited potent T-cell depletion in peripheral blood or bone marrow while thymic T-cells were depleted following treatment with 1mg/kg or 3 mg/kg of DAR6 anti-CD5 5D7-ADCs. Negative controls used in this *in vivo* experiment included a human IgG1 not specific to CD5 (as a naked antibody (hulgG1) and conjugated to an amatoxin (hulgG1-AM). As described in Figures 10A to 10B, the hulgG1 naked and conjugated controls had no impact on T cell depletion in peripheral blood (Fig. 10A) and bone marrow (Fig. 10B) as these controls were comparable to the PBS control. An anti-CD52 antibody (antibody YTH34.5) was used as a control as well, and was also able to deplete peripheral and bone marrow T cells at a dose of 25 mg/kg.

As shown in, Figs. 11A-11C, humanized NSG mice treated with 1 mg/kg site or 3 mg/kg site-specific DAR2 anti-CD5 5D7-ADC exhibited potent T-cell depletion in peripheral blood, bone marrow, and thymic T-cells. In each of Figures 11A to 11C, naked antibody 5D7 was also used as a control. Antibody 5D7 was able to deplete peripheral T cells (relative to a non-specific human IgG1 control or PBS) as described in Figure 11A, but was unable to deplete either marrow T cells or thymic T cells whereas the 5D7-AM ADC was effective at depleting both marrow and thymic as described in Figures 11B and 11C.

Example 12. Anti-CD5 ADC Depletes Th1 and Th17 Cell Subsets in Polarizing Conditions

Th1 and Th17 have been implicated as playing a pathogenic role in a number of autoimmune diseases, such as MS and RA. To test the ability of anti-CD2 and anti-CD5 ADCs to deplete Th1 and Th17 cells, an *in vitro* assay was performed under polarizing conditions.

Primary human T-cells were cultured for 6 days in the presence of either an anti-CD2 or an anti-CD5 ADC in polarizing conditions. For Th1 differentiation, primary T-cells were cultured in the presence of aCD3, aCD28, rhIFN γ , IL-12, IL27, and aIL-4. For Th17 differentiation, primary T-cells were cultured in the presence of aCD3, aCD28, rhIL-5, IL-1B, TGF-B1, IL-23, aIL-4, and aIFN γ . The anti-CD5 ADC (also called CD5-AM) used in the experiment was an anti-CD5 antibody 5D7 conjugated to an amatoxin (represented by Formula (II)) via a non-cleavable maleimide linker. The sequences of antibody 5D7 as used herein are described in the sequence table (see table for 5D7 CDRs and humanized 5D7). The anti-CD2 ADC (also called CD2-AM) used in the experiment was antibody RPA-2.10 human IgG conjugated to an amatoxin (represented by Formula (II)) via a non-cleavable maleimide linker. Both the anti-CD2 antibody

and the anti-CD5 antibody contained mutations D265C and H435A (EU index). On Day 6, cells were simulated for 4 hours with PMA, ionomycin, transport inhibitor, and stained for intracellular IFN γ and IL-17.

As shown in Figs. 12A and 12B, the anti-CD5 ADC and the anti-CD2 ADC depleted Th1 and Th17 cells, respectively, at single-digit picomolar concentrations. Fig. 12A shows that the anti-CD5 ADC and the anti-CD2 ADC was able to deplete Th1 cells at an IC₅₀ of 2.73 pM, as indicated by the drop in IFN γ signal, indicating depletion of Th1 cells. The isotype control antibody was unable to deplete Th1 cells. Similarly, Fig. 12B shows that the anti-CD5 ADC and the anti-CD2 ADC were both able to deplete Th17 cells at an IC₅₀ of 2.53 pM, as indicated by the drop in IL-17 signal, indicating depletion of Th17 cells. Isotype control antibody was unable to deplete Th17 cells.

Example 13. Anti-CD5 ADC Extends Survival in T-ALL PDX Mouse Model

In this study, patient-derived xenograft (PDX) model of pre-T-cell acute lymphoblastic leukemia (T-ALL) was used to examine the efficacy of an anti-CD5 ADC and the efficacy of an anti-CD2 ADC on mouse survival as compared to isotype and vehicle controls. The cells of the xenograft express CD5⁺ and CD2⁺ (data not shown). The anti-CD5 ADC and the anti-CD2 ADC used in this example are both described in Example 12. When peripheral tumor burden in mice reached 5%, the mice were treated with a single dose of either the anti-CD2 ADC or the anti-CD5 ADC at a dose of 6 mg/kg.

As shown in Fig. 13A and 13C, the anti-CD5 ADC and anti-CD2 ADC, respectively, were both able to extend survival by more than 20 days compared to isotype and vehicle controls. Moreover, survival conferred by a single dose of anti-CD5 ADC or anti-CD2 ADC appeared comparable to the positive control (chemotherapeutic Ara-C) and markedly more effective than standard of care (dexamethasone) (Fig. 13A and Fig. 13C). As shown in Fig. 13B and Fig. 13D, the anti-CD5 ADC and the anti-CD2 ADC, respectively, also each decreased tumor burden in mice as compared to isotype and vehicle controls.

Example 14. Anti-CD5 ADC Prevents Acute GvHD in Xenograft Model

The following experiment determined the efficacy of an anti-CD5 ADC to prevent acute graft versus host disease (GVHD). The description of the anti-CD5 ADC is provided in Example 12.

Humanized NSG mice were irradiated one day prior (Day -1) to transplantation with peripheral blood mononuclear cells (PBMC) (Day 0). The following day, the mice were treated with a single dose of anti-CD5 ADC (6 mg/kg).

As shown in Fig. 14A, slight body weight loss (BWL) was seen in mice treated with anti-CD5-ADC, however, recovery was observed by Day 13 post transplant. As shown in Fig. 14B, anti-CD5-ADC conferred a sustained survival of 80% in this model.

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Table 5: Sequence Summary

Sequence Identifier	Description	Sequence
SEQ ID NO: 1	Ab1 CDR-H1	EYYMY
SEQ ID NO: 2	Ab1 CDR-H2	RIDPEDGSIDYVEKFKK
SEQ ID NO: 3	Ab1 CDR-H3	GKFNYRFAY
SEQ ID NO: 4	Ab1 CDR-L1	RSSQSLLHSSGNTYLN
SEQ ID NO: 5	Ab1 CDR-L2	LVSKLES
SEQ ID NO: 6	Ab1 CDR-L3	MQFTHYPYT
SEQ ID NO: 7	Ab1 Heavy chain variable region	QVQLVQSGAEVKKPGASVKVSCASGYTFTEYY MYWVRQAPGQGLELMGRIDPEDGSIDYVEKFKK KVTLTADTSSSTAYMELSSLTSDDTAVYYCARGK FNYRFAYWGQGTLLTVSS
SEQ ID NO: 8	Ab1 Light chain variable region	DVVMQTQSPPSLLVTLGQPASISCRSSQSLLHSSG NTYLNWLLQRPGQSPQPLIYLVSKLESGVPDRFS GSGSGTDFTLKISGVEAEDVGVYYCMQFTHYPYT FGQGTKLEIK
SEQ ID NO: 9	Ab1a Heavy chain variable region	QVQLVQSGAEVQRPGASVKVSCASGYIFTEYY MYWVRQAPGQGLELVGRIDPEDGSIDYVEKFKKK VTLTADTSSSTAYMELSSLTSDDTAVYYCARGKF NYRFAYWGQGTLLTVSS
SEQ ID NO: 10	Ab1a Light chain variable region	DVVMQTQSPPSLLVTLGQPASISCRSSQSLLHSSG NTYLNWLLQRPGQSPQPLIYLVSKLESGVPDRFS GSGSGTDFTLKISGVEAEDVGVYYCMQFTHYPYT FGQGTKLEIK
SEQ ID NO: 11	Consensus human Ab Heavy chain variable domain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYA MSWVRQAPGKGLEWVAIVSENGSDTYADSVKG RFTISRDDSKNTLYLQMNSLRAEDTAVYYCARDR GGAVSYFDVWGQGTLLTVSS
SEQ ID NO: 12	Consensus human Ab Light chain variable domain	DIQMTQSPSSLSASVGDRVTITCRASQDVSSYLA WYQQKPGKAPKLLIYAASSLESGVPSRFSGSGS GTDFTLTISLQPEDFATYYCQQYNLSLPYTFGQG TKVEIKRT
SEQ ID NO: 13	Human CD2 sequence	MSFPCKFVAS FLLIFNVSSK GAVSKEITNA LETWGALGQD INLDIPSFQM SDDIDDIKWE KTSDDKKIAQ FRKEKETFE KDTYKLFKNG TLKIKHLKTD DQDIYKVSII DTKGKNVLEK IFDLKIQERV SKPKISWTCI NTTLTCEVMN GTDPELNLYQ DGKHLKLSQR VITHKWTTSL SAFKCTAGN KVSKESSVEP VSCPEKGLDI

Sequence Identifier	Description	Sequence
		YLIIGICGGG SLLMVFVALL VFYITKRKKQ RSRRNDEELE TRAHRVATEE RGRKPHQIPA STPQNPATSQ HPPPPPGHRS QAPSHRPPPP GHRVQHQPQK RPPAPSGTQV HQQKGPPLPR PRVQPKPPHG AAENSLSPSS N
SEQ ID NO: 14	RPA-2.10 CDR-H1	GFTFSSY
SEQ ID NO: 15	RPA-2.10 CDR-H2	SGGGF
SEQ ID NO: 16	RPA-2.10 CDR-H3 Variant 1	SSYGEIMDY
SEQ ID NO: 17	RPA-2.10 CDR-H3 Variant 2	SSYGELMDY
SEQ ID NO: 18	RPA-2.10 CDR-L1	RASQRIGTSIH
SEQ ID NO: 19	RPA-2.10 CDR-L2	YASESIS
SEQ ID NO: 20	RPA-2.10 CDR-L3	QQSHGWPFTF
SEQ ID NO: 21	RPA-2.10 Heavy chain variable region Variant 1	EVKLVESGGGLVKPGGSLKLSCAASGFTFSSYDM SWVRQTPEKRLEWVASISGGGFLYYLDSVKGRFT ISRDNARNILYLHMTSLRSEDAMYYCARSSYGEI MDYWGQGTSTVTVSS
SEQ ID NO: 22	RPA-2.10 Heavy chain variable region Variant 2	EVKLVESGGGLVKPGGSLKLSCAASGFTFSSYDM SWVRQTPEKRLEWVASISGGGFLYYLDSVKGRFT ISRDNARNILYLHMTSLRSEDAMYYCARSSYGEI MDYWGQGTSTVTVSS
SEQ ID NO: 23	RPA-2.10 Light chain variable region	DILLTQSPAILSVPGERVVFSCRASQRIGTSIHWY QRTTGSPRLLIKYASESISGIPSRFSGSGSGTDF TLSINSVESEDVADYYCQQSHGWPFTFGGGTKLE IE
SEQ ID NO: 24	RPA-2.10 Heavy chain constant region	AKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFP EPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSV TVPSSTWPSETVTCNVAHPASSTKVDKKIVPRDC GCKPCICTVPEVSSVFIFPPKPKDVLITITPKVTC VVDISKDDPEVQFSWFVDDVEVHTAQTQPREE QFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAF PAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKV SLTCMITDFFPEDITVEWQWNGQPAENYKNTQPI MDTDGSYFVYSKLVQKSNWEAGNTFTCSVLHE GLHNHHTTEKSLSHSPGK
SEQ ID NO: 25	RPA-2.10 Light chain constant region	RADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPK DINVKWKIDGSERQNGVLNSWTDQDSKDSTYSM SSTLTTLTKDEYERHNSYTCEATHKTSTSPIVKSFN RNEC
SEQ ID NO: 26	Light chain variable region	DIQMTQSPSSMSASLGDRVTITCRASQDINSYLS WFQQKPGKSPKTLIYRANRLVDGVPSRFSGSGS GTDYTLTISSLQYEDFGIYYCQQYDESPWTFGGG TKLEIK

Sequence Identifier	Description	Sequence
SEQ ID NO: 27	Heavy chain variable region	QIQLVQSGPGLKKPGGSRISCAASGYTFTNYGM NWWKQAPGKGLRWGMWINHTHTGEPTYADDFKG RFTFSLDTSKSTAYLQINSLRAEDTATYFCTRRGY DWYFDVWGQGTTVTVSS
SEQ ID NO: 28	CDR-H1	GYTFTNY
SEQ ID NO: 29	CDR-H2	NHTHTGE
SEQ ID NO: 30	CDR-H3	RGYDWYFDV
SEQ ID NO: 31	CDR-L1	RASQDINSYLS
SEQ ID NO: 32	CDR-L2	RANRLVD
SEQ ID NO: 33	CDR-L3	QQYDESPWT
SEQ ID NO: 34	Light chain variable region	DIQMTQSPSSLSASVGDRVTITCRASQDINSYLSW FQQKPGKAPKTLIYRANRLESGVPSRFSGSGSGT DYTLTISSLQYEDFGIYYCQQYDESPWTFGGGTK LEIK
SEQ ID NO: 35	Heavy chain variable region	EIQLVQSGGGLVKPGGSRISCAASGYTFTNYGM NWWVRQAPGKGLEWMGMWINHTHYGEPTYADSFKG TRTFSLDDSKNTAYLQINSLRAEDTAVYFCTRRGY DWYFDVWGQGTTVTVSS
SEQ ID NO: 36	CDR-H1	GYTFTNY
SEQ ID NO: 37	CDR-H2	NHTHYGE
SEQ ID NO: 38	CDR-H3	RRGYDWYFDV
SEQ ID NO: 39	CDR-L1	RASQDINSYLS
SEQ ID NO: 40	CDR-L2	RANRLES
SEQ ID NO: 41	CDR-L3	QQYDESPWT
SEQ ID NO: 42	CDR-H1	GYSITSGYY
SEQ ID NO: 43	CDR-H2	ISYSGFT
SEQ ID NO: 44	CDR-H3	AGDRTGSWFAY
SEQ ID NO: 45	CDR-L1	QDISNY
SEQ ID NO: 46	CDR-L2	ATS
SEQ ID NO: 47	CDR-L3	LQYASYPFT
SEQ ID NO: 48	CDR-H1	GYIFTNYG
SEQ ID NO: 49	CDR-H2	INTYNGEP

Sequence Identifier	Description	Sequence
SEQ ID NO: 50	CDR-H3	ARGDYYGYEDY
SEQ ID NO: 51	CDR-L1	QGISNY
SEQ ID NO: 52	CDR-L2	YTS
SEQ ID NO: 53	CDR-L3	QQYSKLPWT
SEQ ID NO: 54	5D7 CDR-H1	FSLSTSGMG
SEQ ID NO: 55	5D7 CDR-H2	WWDDD
SEQ ID NO: 56	5D7 CDR-H3	RRATGTGFDY
SEQ ID NO: 57	5D7 CDR-L1	QDVGTA
SEQ ID NO: 58	5D7 CDR-L2	WTSTRHT
SEQ ID NO: 59	5D7 CDR-L3	YNSYNT
SEQ ID NOs: 60-281		See Table 1 for summary of SEQ ID NOs: 35-256
SEQ ID NO: 282	Humanized 5D7 Heavy chain variable region (CDRs in bold)	QVTLKESGPVLVKPTETLTCTFSGF SLSSTSGM GVGWIRQAPGKGLEWVAHI WWDDDVYYNPSLKS RLTITKDASKDQVSLKLSSVTAADTAVYYCVR RRRA TGTGFDYWGQGT LVTVSS
SEQ ID NO: 283	Humanized 5D7 Light chain variable region (CDRs in bold)	NIVMTQSPSSLSASVGDRVITCQAS QDVGTA VA WYQQKPDQSPKLLIY WTSTRHT GV PDRFTGSGS GTDFTLTISLQPEDATYFCHQY NSYNT FGSGTK LEIK
SEQ ID NO: 284	Consensus human Heavy chain variable domain (CDRs in bold)	EVQLVESGGGLVQPGGSLRLSCAAS GFTFSDYA MSWVRQAPGKGLEWVA ISENGSDTY ADSVKG RFTISRDDSKNTLYLQMNSLR AEDTAVYYCARDR GGAVSYFDVWGQGT LVTVSS
SEQ ID NO: 285	Consensus human Light chain variable domain (CDRs in bold)	DIQMTQSPSSLSASVGDRVITC RASQDVSSYLA WYQQKPGKAPKLLIYAASSLES GVPSRFSGSGS GTDFTLTISLQPEDFATYYC QQYNSLPYTFGQG TKVEIKRT
SEQ ID NO: 286	Human CD5 amino acid sequence	MVCSQSWGRS SKQWEDPSQA SKVCQRLNCG VPLSLGPFLV TYTPQSSIIC YGQLGSFSNCSHSRNDMCHS LGLTCLEPQK TTPPTTRPPP TTTPEPTAPP RLQLVAQSGG QHCAGVVEFYSGSLGGTISY EAQDKTQDLE NFLCNNLQCG SFLKHLPETE AGRAQDPGEP REHQPLPIQWKIQNSSCTSL EHCFRKIKPQ KSGRVLALLC SGFQPKVQSR LVGGSSICEG TVEVRQGAQWAALCDSSSAR SSLRWEEVCR EQQCGSVNSY RVLDAGDPTS RGLFCPHQKL SQCHELWERN SYCKKV FVTC QDPNPAGLAA GTVASIIAL VLLVLLVVC GPLAYKKLVK

Sequence Identifier	Description	Sequence
		KFRQKKQRQWIGPTGMNQNM SFHRNHTATV RSHAENPTAS HVDNEYSQPP RNSHLSAYPA LEGALHRSSMQPDNSSDSY DLHGAQRL
SEQ ID NO: 287	Hinge	EPKSSDKTHTSPPSP
SEQ ID NO: 288	Humanized 5D7 Heavy chain variable region (CDRs in bold)	QVTLKESGPALVKPTQTLTLTCTFSGF SLSTSGM GVGWIRQPPGKGLEWVAHI WWDDDVYYNPSLKS RLTITKDASKDQVVLMTNMDPVCTATYYC VRRR ATGTGFDYWGQGLTVVSS
SEQ ID NO: 289	Humanized 5D7 Light chain variable region (CDRs in bold)	NIVMTQSPPTLSLSPGERATLSCRAS QDVGTAVA WYQQKPDQSPKLLI WTSTRHTGVPDRFTGSGS GTDFTLTISRLEPEDFAVYFCHQ YNSYNTFGSGTK LEIK
SEQ ID NO: 290	MAT304 light chain variable region	DIQVTSQSPSSLSASLGERISLTCRTSQDISNYLNW FQQKPDGTFKRLIYATSSLDGVPKRFSGSGSGS DYSLTISSESEDFADYYCLQYASYPFTFGSGTKL EIK
SEQ ID NO: 291	MAT304 variable heavy chain	EVQLQESGPGLVKPSQTLSTCSVTGYSITSGYY WHWIRQFPGNKLEWMGYISYSGFTNYKTSLINRI SITHDTSENQFFLNLSVTTEDTATYYCAGDRTGS WFAYWGQGLTVVSA

Other Embodiments

All publications, patents, and patent applications mentioned in this specification are incorporated herein by reference to the same extent as if each independent publication or patent application was specifically and individually indicated to be incorporated by reference.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the invention that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the claims.

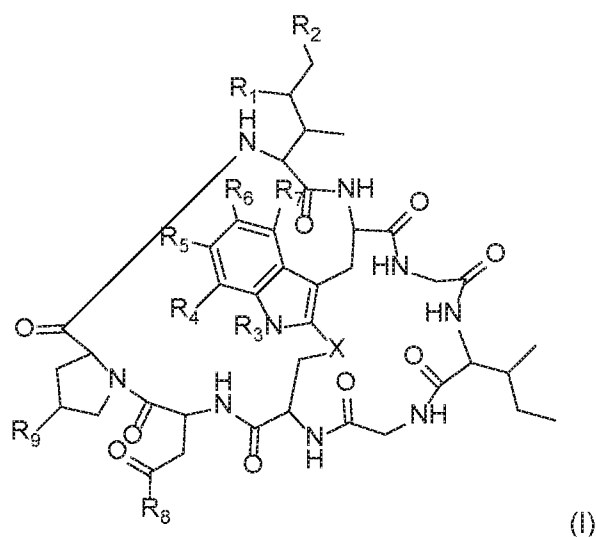
Other embodiments are within the claims.

CLAIMS

1. A method of depleting T cells in a subject having an autoimmune disease, said method comprising administering an effective amount of either an anti-CD5 antibody drug conjugate (ADC) or an anti-CD2 ADC to a subject having an autoimmune disease, wherein the ADC comprises an anti-CD5 antibody, or antigen-binding fragment thereof, or an anti-CD2 antibody, or antigen-binding fragment thereof, conjugated to a cytotoxin via a linker.
2. The method of claim 1, wherein the effective amount is an amount sufficient to substantially deplete endogenous CD5+ or CD2+ T cells in the thymus of the subject.
3. The method of claim 1 or 2, wherein the subject has multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus (SLE), or systemic sclerosis (SSc).
4. A method of treating a subject having steroid-refractory graft versus host disease (GVHD) or at risk for developing GVHD, said method comprising administering an anti-CD2 ADC or an anti-CD5 ADC to the subject having steroid-refractory GVHD, such that the steroid refractory GVHD is treated, wherein the ADC comprises an anti-CD5 antibody, or antigen-binding fragment thereof, or an anti-CD2 antibody, or antigen-binding fragment thereof, conjugated to a cytotoxin via a linker.
5. The method of claim 4, wherein the steroid refractory GVHD is steroid refractory acute GVHD.
6. The method of claim 4 or 5, wherein the subject previously received an allogeneic HSC transplant.
7. The method of claim 5 or 6, wherein the subject has steroid refractory acute GVHD Grade 2 to Grade 4 (Mount Sinai acute GVHD International Consortium (MAGIC) criteria).
8. The method of claim 7, wherein the GVHD grade is decreased by one grade according to the MAGIC criteria following administration of the anti-CD2 ADC or anti-CD5 ADC.
9. A method of treating a subject having a T cell malignancy, said method comprising administering an effective amount of an anti-CD2 ADC or an anti-CD5 ADC to the subject, wherein the ADC comprises an anti-CD5 antibody, or antigen-binding fragment thereof, or an anti-CD2 antibody, or antigen-binding fragment thereof, conjugated to a cytotoxin via a linker.

10. The method of claim 9, wherein the T cell malignancy is a lymphoma.
11. The method of claim 9, wherein the T cell malignancy is T-cell acute lymphoblastic lymphoma (T-ALL), T-cell large granular lymphocyte (LGL) leukemia, human T-cell leukemia virus type 1–positive (HTLV-1+), adult T-cell leukemia/lymphoma (ATL), T-cell prolymphocytic leukemia (T-PLL), or peripheral T-cell lymphoma (PTCLs).
12. The method of claim 10 or 11, wherein the T cell malignancy is a relapsed, refractory T cell malignancy.
13. The method of any one of claims 1 to 12, wherein the ADC comprises a humanized antibody or a human antibody.
14. The method of any one of claims 1 to 13, wherein the antibody has an isotype selected from the group consisting of IgG, IgA, IgM, IgD, and IgE.
15. The method of claim 14, wherein the IgG isotype is an IgG1 or an IgG4.
16. The method of any one of claims 1 to 15, wherein the ADC is an anti-CD5 ADC.
17. The method of any one of claims 1 to 15, wherein the ADC is an anti-CD2 ADC.
18. The method of any one of claims 1 to 17, wherein the cytotoxin is selected from the group consisting of pseudomonas exotoxin A, deBouganin, diphtheria toxin, an amatoin, saporin, maytansine, a maytansinoid, an auristatin, an anthracycline, a calicheamicin, irinotecan, SN-38, a duocarmycin, a pyrrolobenzodiazepine, a pyrrolobenzodiazepine dimer, an indolinobenzodiazepine, or an indolinobenzodiazepine dimer.
19. The method of any one of claims 1 to 17, wherein the cytotoxin is an RNA polymerase inhibitor.
20. The method of claim 19, wherein the RNA polymerase inhibitor is an RNA polymerase II inhibitor.
21. The method of claim 19, wherein the RNA polymerase inhibitor is an amatoin.

22. The method of any one of claims 1 to 17, wherein the ADC is represented by the formula Ab-Z-L-Am, wherein Ab is the anti-CD5 antibody or antigen-binding fragment thereof, L is a linker, Z is a chemical moiety, and Am an amatoxin represented by formula (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 $NR_C R_D$;

R_9 is H, OH, OR_C , or OR_D ;

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

R_C is $-L-Z$;

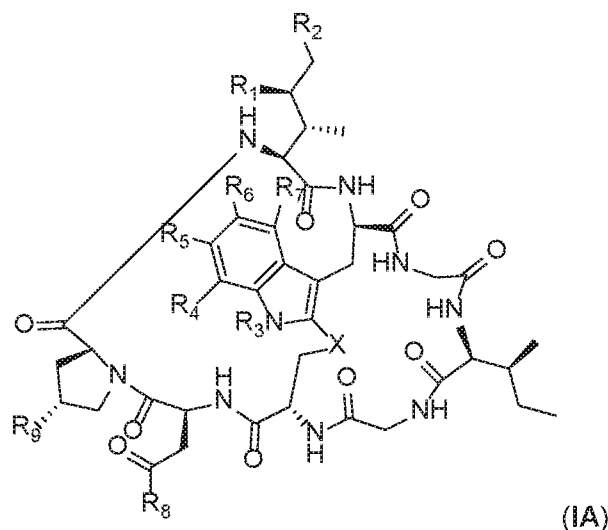
R_D is optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_2 - C_6 heteroalkynyl, optionally substituted cycloalkyl, 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

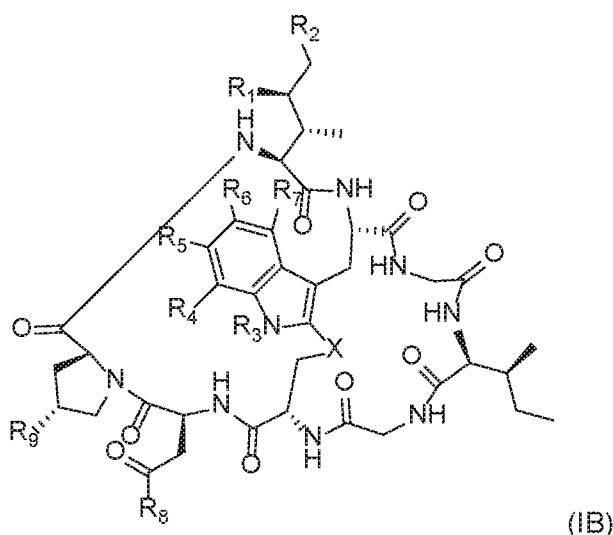
Z is a chemical moiety formed from a coupling reaction between a reactive substituent present on L and a reactive substituent present within the antibody or antigen-binding fragment thereof,

wherein Am comprises exactly one R_C substituent.

23. The method of claim 22, wherein Am-L-Z is represented by formula (IA).



24. The method of claim 23, wherein Am-L-Z is represented by formula (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;

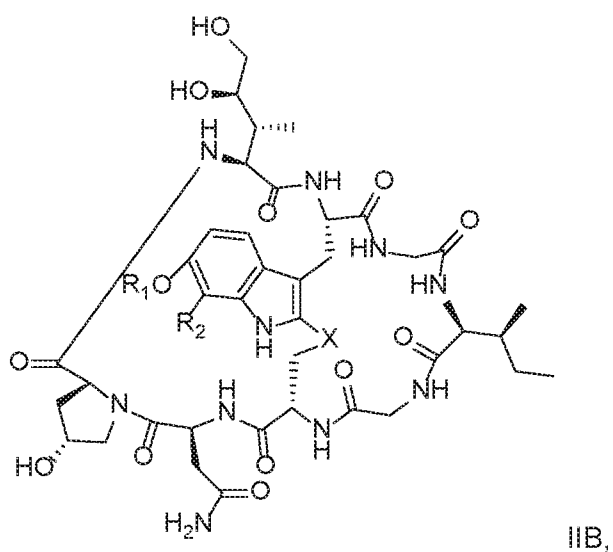
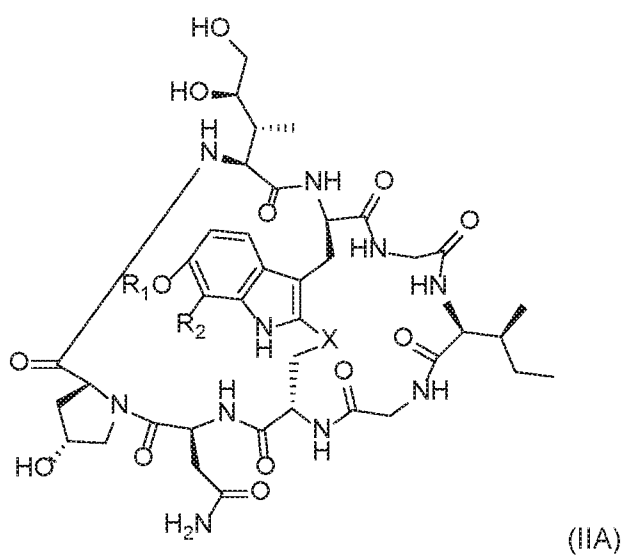
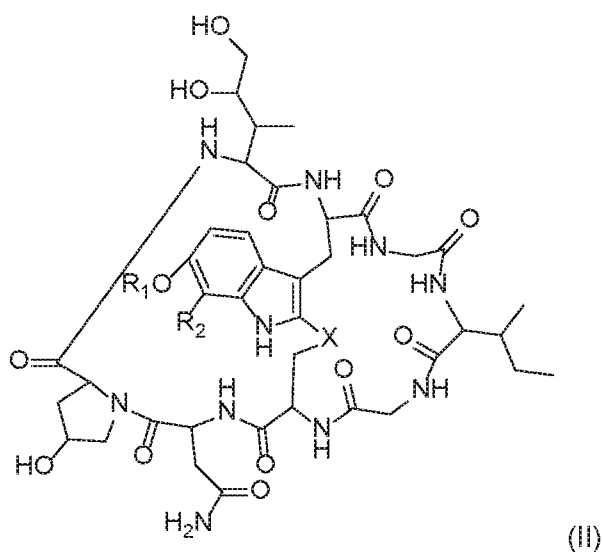
L is optionally substituted C_1 - C_6 alkylene, optionally substituted C_1 - C_6 heteroalkylene, optionally substituted C_2 - C_6 alkenylene, optionally substituted C_2 - C_6 heteroalkenylene, optionally substituted C_2 - C_6 alkynylene, optionally substituted C_2 - C_6 heteroalkynylene, optionally substituted 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.

25. The method of any one of claims 1 to 17, wherein the ADC 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)



wherein X is S, SO, or SO₂;

R₁ is H or a linker covalently bound to the antibody or antigen-binding fragment thereof through a chemical moiety 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

R₂ is H or a linker covalently bound to the antibody or antigen-binding fragment thereof through a chemical moiety 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 R₁ is H, R₂ is the linker, and when R₂ is H, R₁ is the linker.

26. The method of any one of claims 1 to 17, wherein the cytotoxin of the ADC is which is a maytansinoid.

27. The method of claim 26, wherein the maytansinoid is DM1 or DM4.

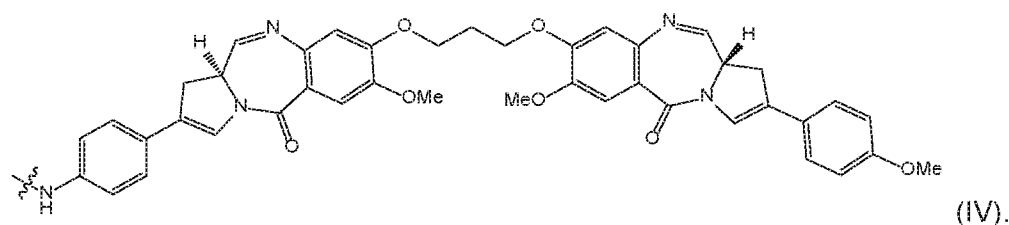
28. The method of any one of claims 1 to 17, wherein the cytotoxin of the ADC is an auristatin.

29. The method of claim 28, wherein the auristatin is monomethyl auristatin E (MMAE) or monomethyl auristatin F (MMAF).

30. The method of any one of claims 1 to 17, wherein the cytotoxin of the ADC is an anthracycline.

31. The method of claim 30, wherein the anthracycline is daunorubicin, doxorubicin, epirubicin, or idarubicin.

32. The method of any one of claims 1 to 17, wherein the cytotoxin of the ADC is a pyrrolobenzodiazepine dimer derivative represented by formula (IV)



33. The method of any one of claims 1 to 32, wherein the ADC is internalized by a CD5+ or a CD2+ immune cell following administration to the patient.

34. The method of any one of claims 1-32, wherein the ADC is internalized by a CD5+ immune cell following administration to the patient.
35. The method of any one of claims 1-32, wherein the ADC is internalized by a CD2+ immune cell following administration to the patient.
36. The method of claim 34, wherein the immune cell is a malignant T cell.
37. The method of any one of the preceding claims, wherein the subject is a human.
38. The method of any one of the preceding claims, wherein the anti-CD5 antibody, or antigen-binding portion thereof, comprises a heavy chain comprising a variable region as set forth in the amino acid sequence of SEQ ID NO: 282, and a light chain comprising a variable region comprising the amino acid sequence set forth in SEQ ID NO: 283.
39. The method of any one of the preceding claims, wherein the anti-CD5 antibody, or antigen-binding portion thereof, comprises a heavy chain comprising a variable region as set forth in the amino acid sequence of SEQ ID NO: 288, and a light chain comprising a variable region comprising the amino acid sequence set forth in SEQ ID NO: 289.
40. The method of any one of the preceding claims, wherein the anti-CD5 antibody, or antigen-binding portion thereof, comprises a heavy chain comprising a variable region as set forth in the amino acid sequence of SEQ ID NO: 291, and a light chain comprising a variable region comprising the amino acid sequence set forth in SEQ ID NO: 290.

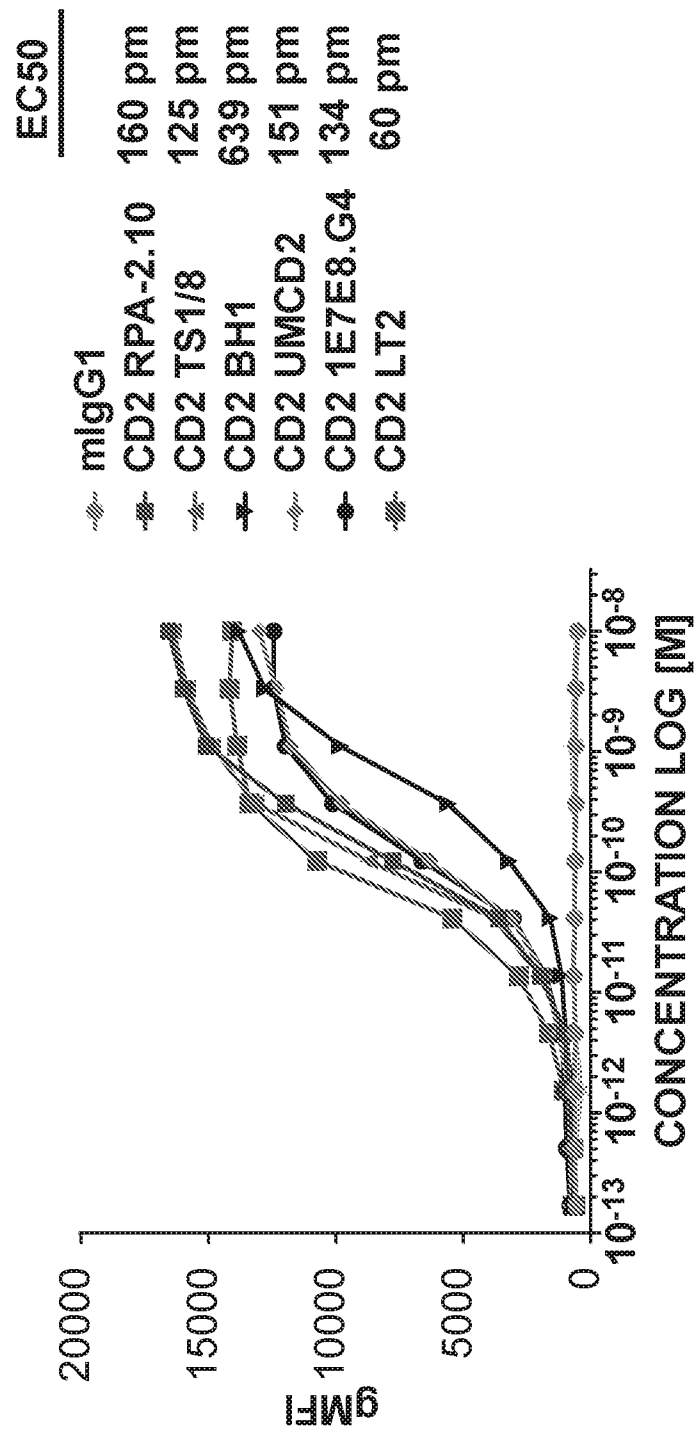


FIG. 1

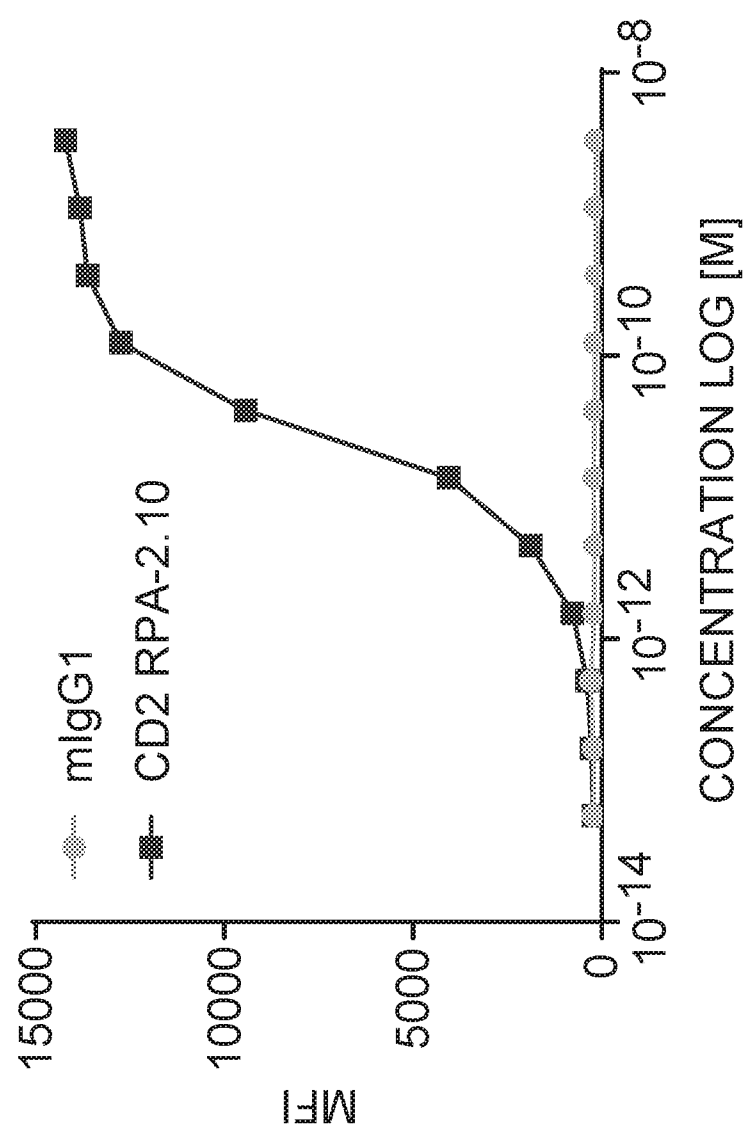


FIG. 2

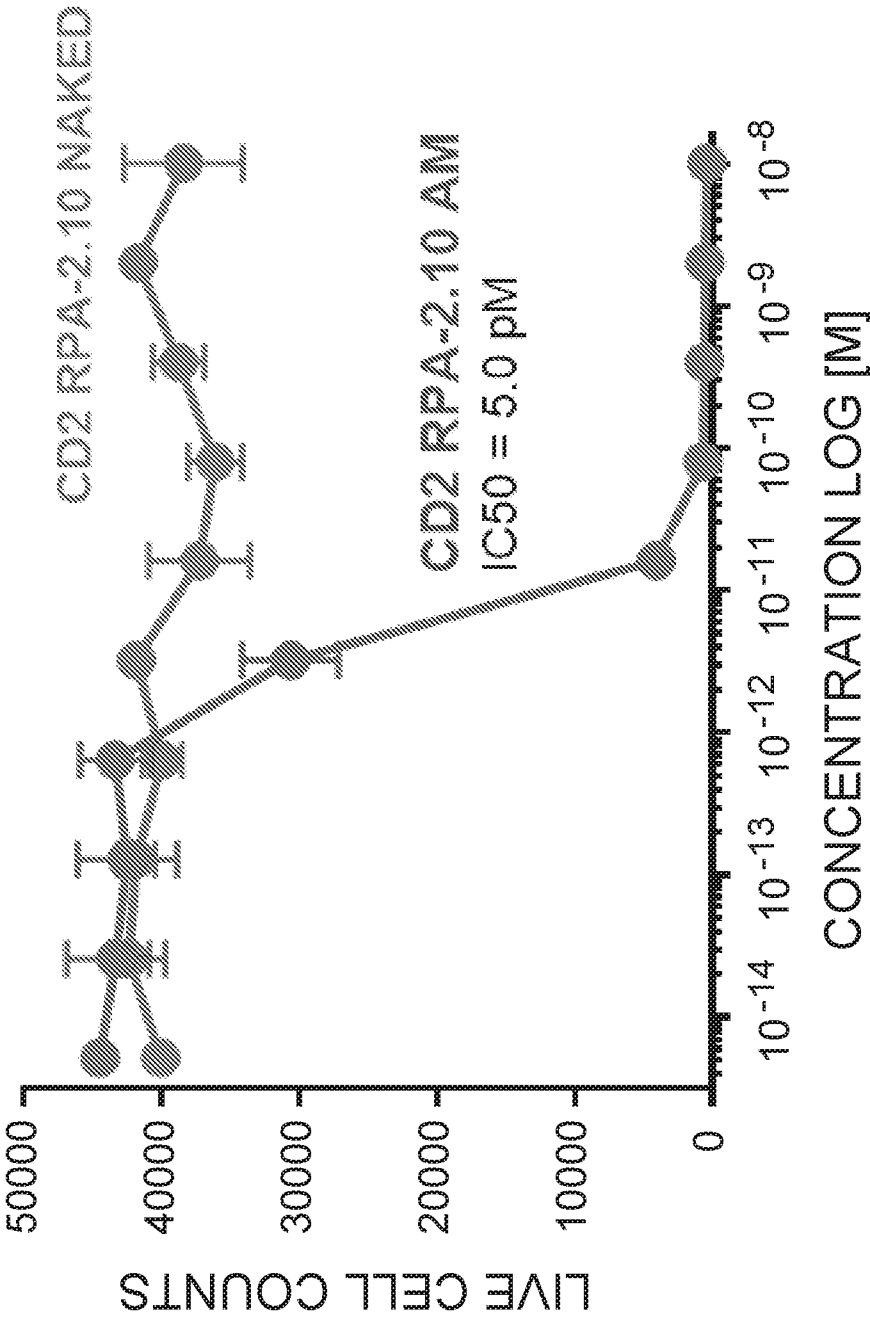


FIG. 3A

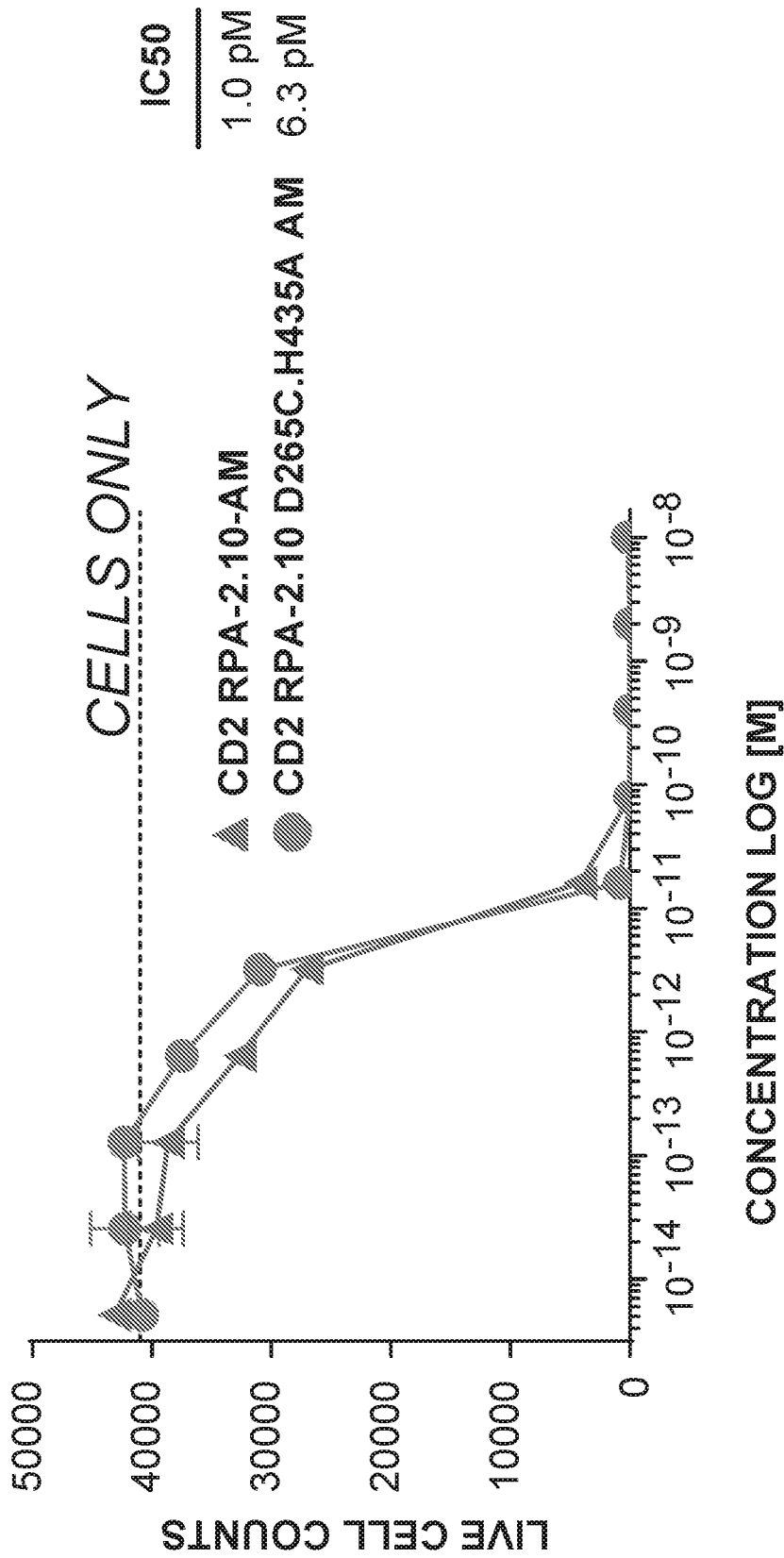


FIG. 3B

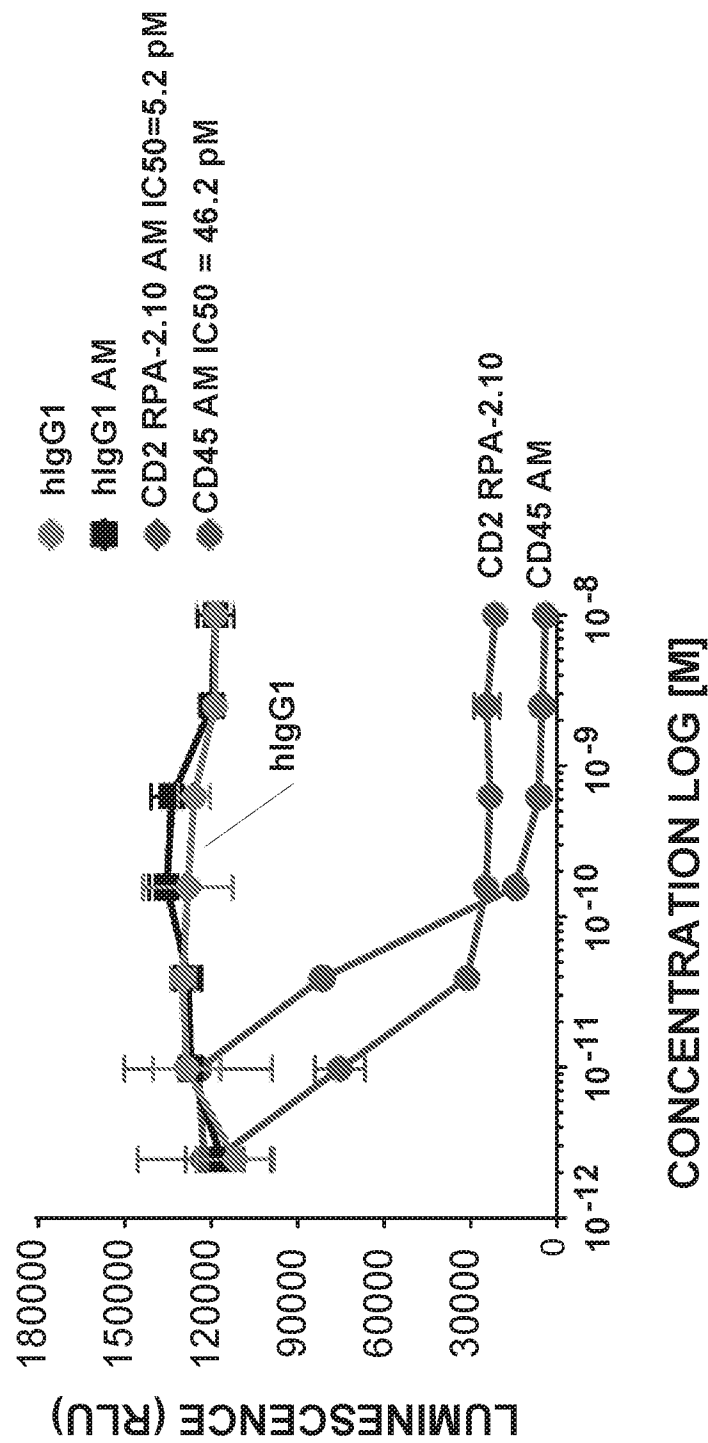


FIG. 4

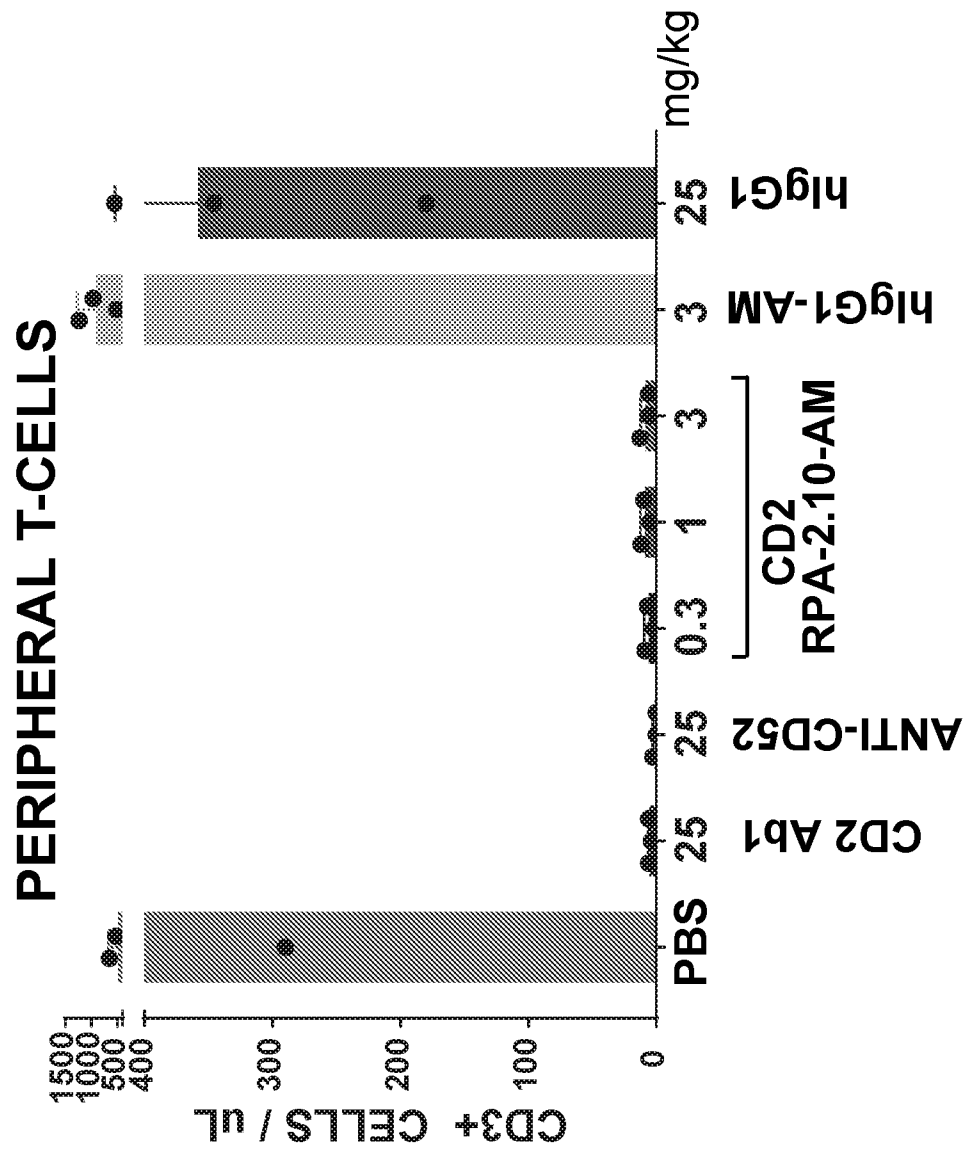


FIG. 5A

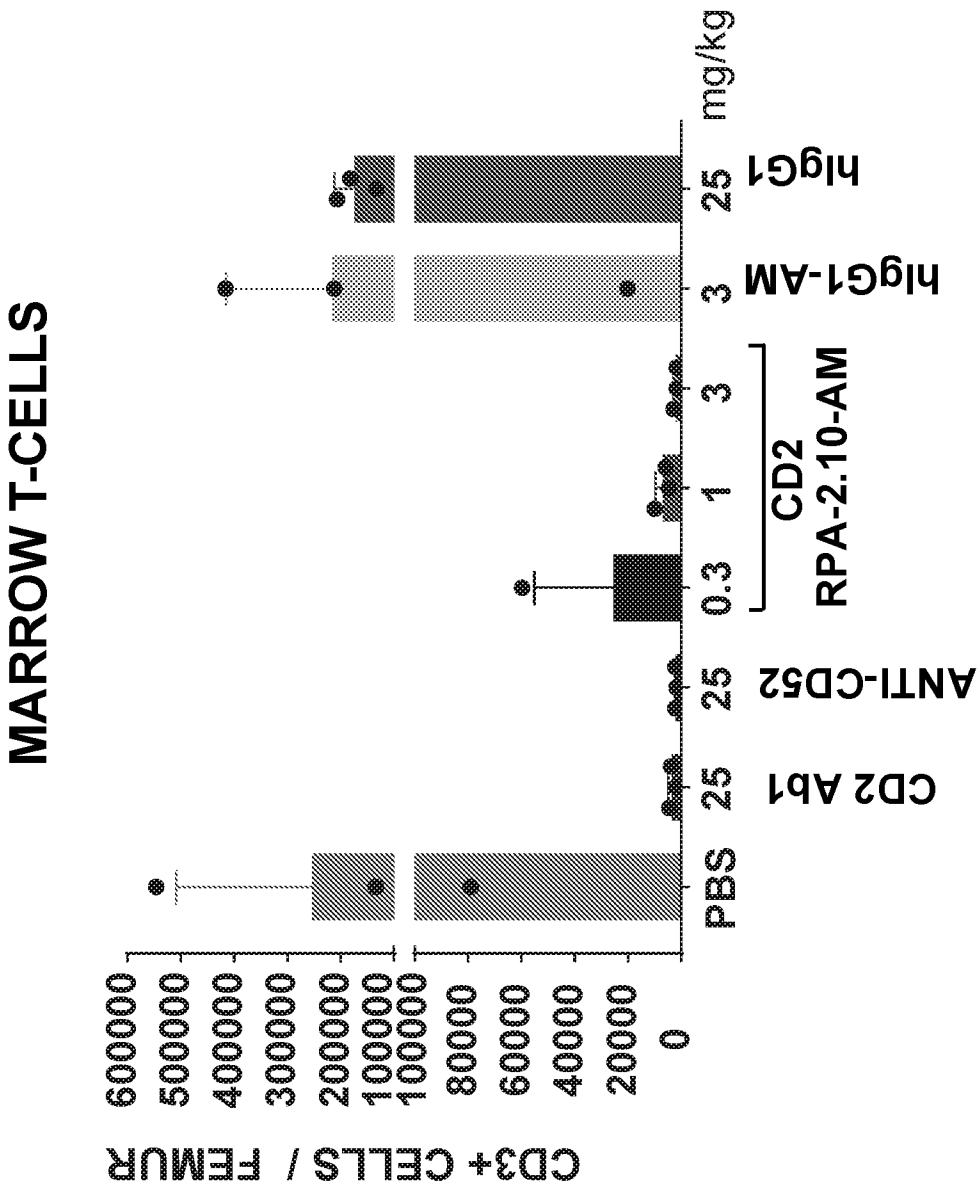


FIG. 5B

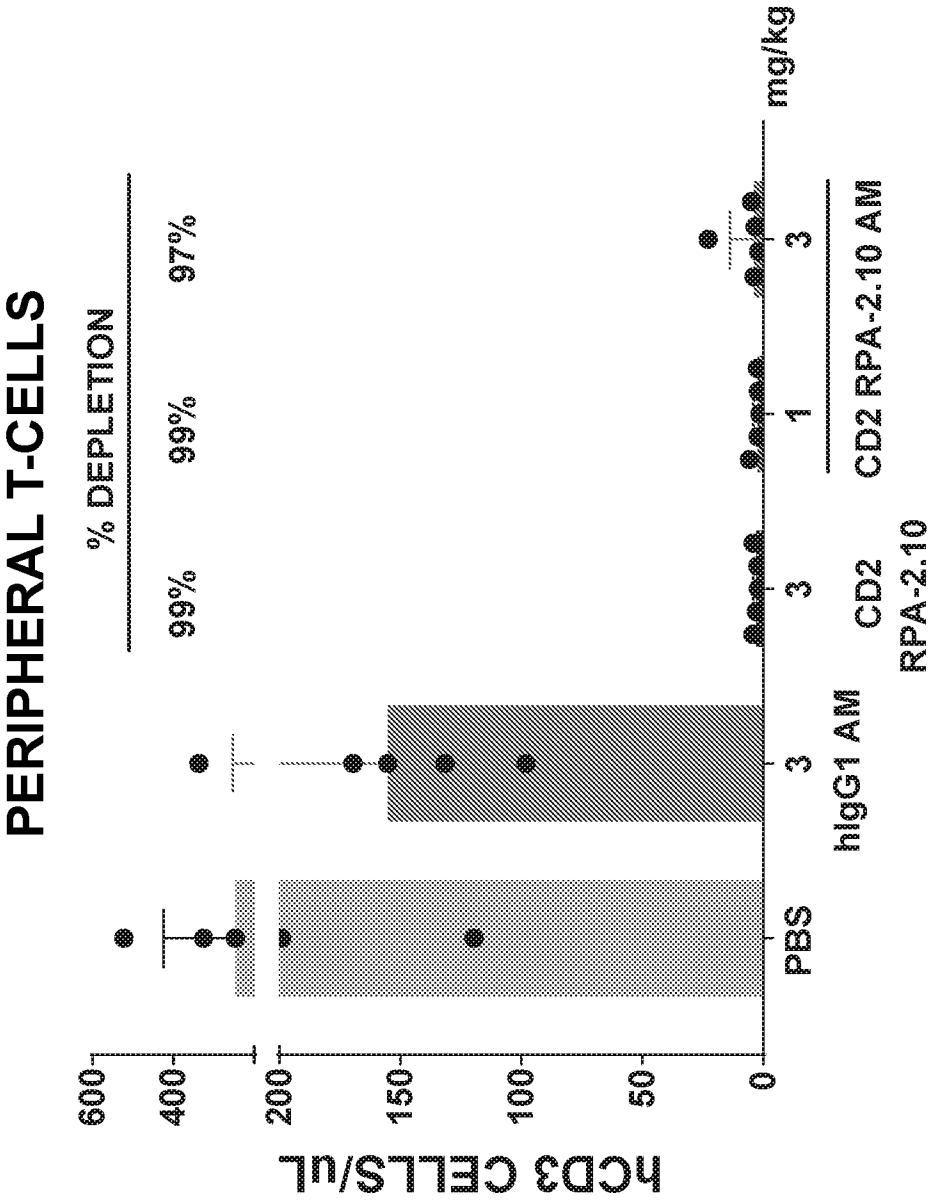


FIG. 6A

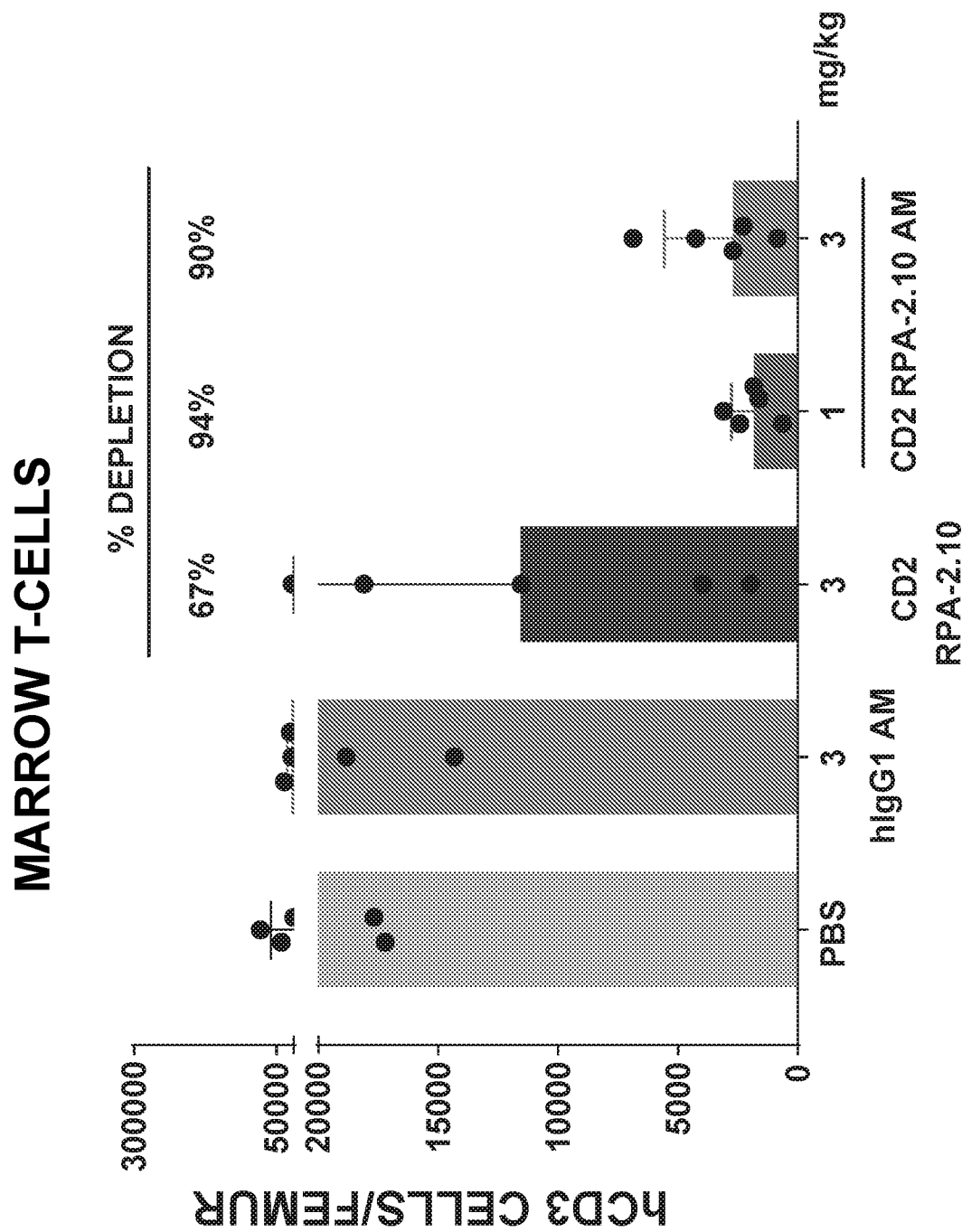


FIG. 6B

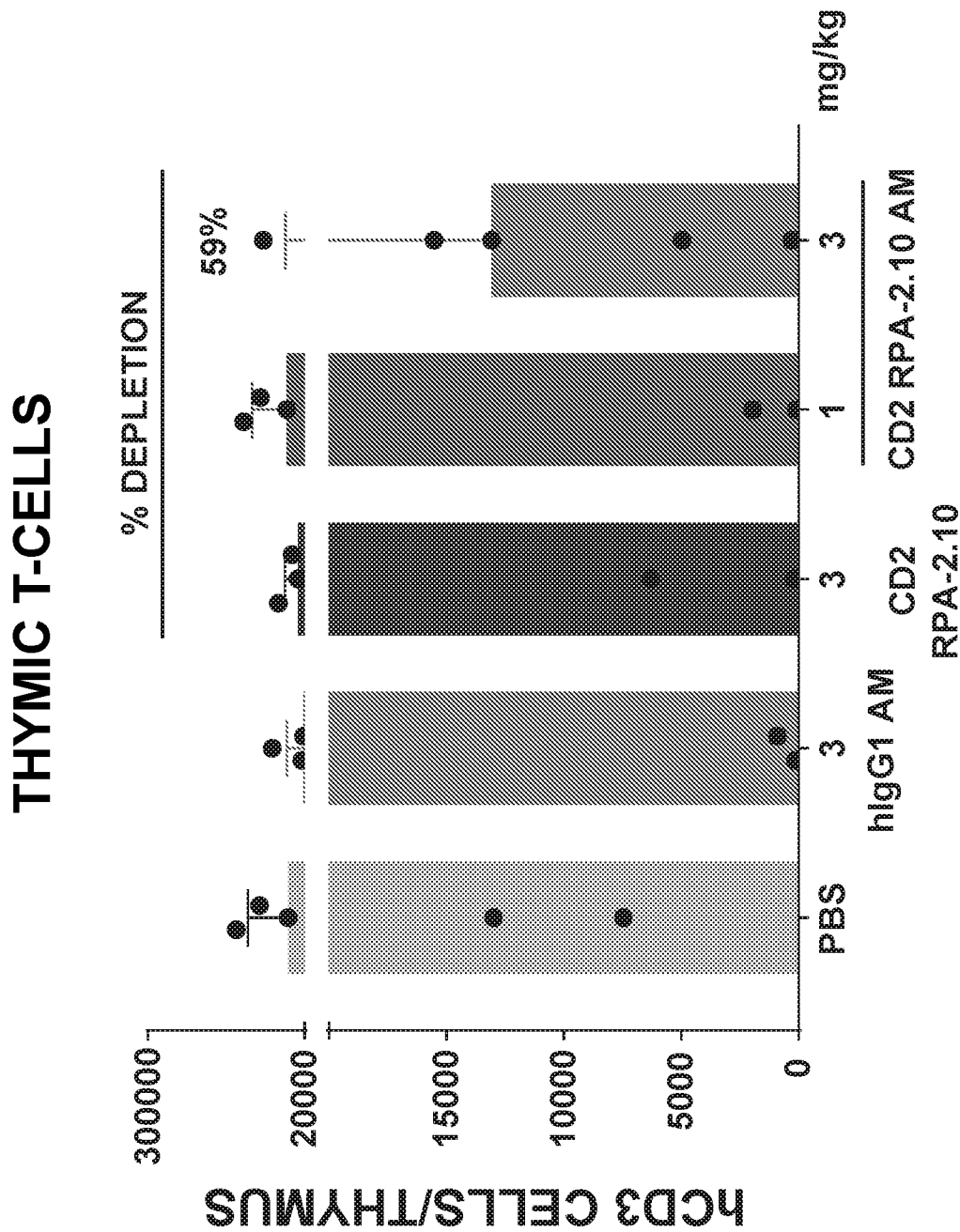


FIG. 6C

EC50

	mlgG1	
	CD5 L17F12	207 pM
	CD5 UCHT2	354 pM
	CD5 205919	1350 pM
	CD5 CRIS-1	43 pm

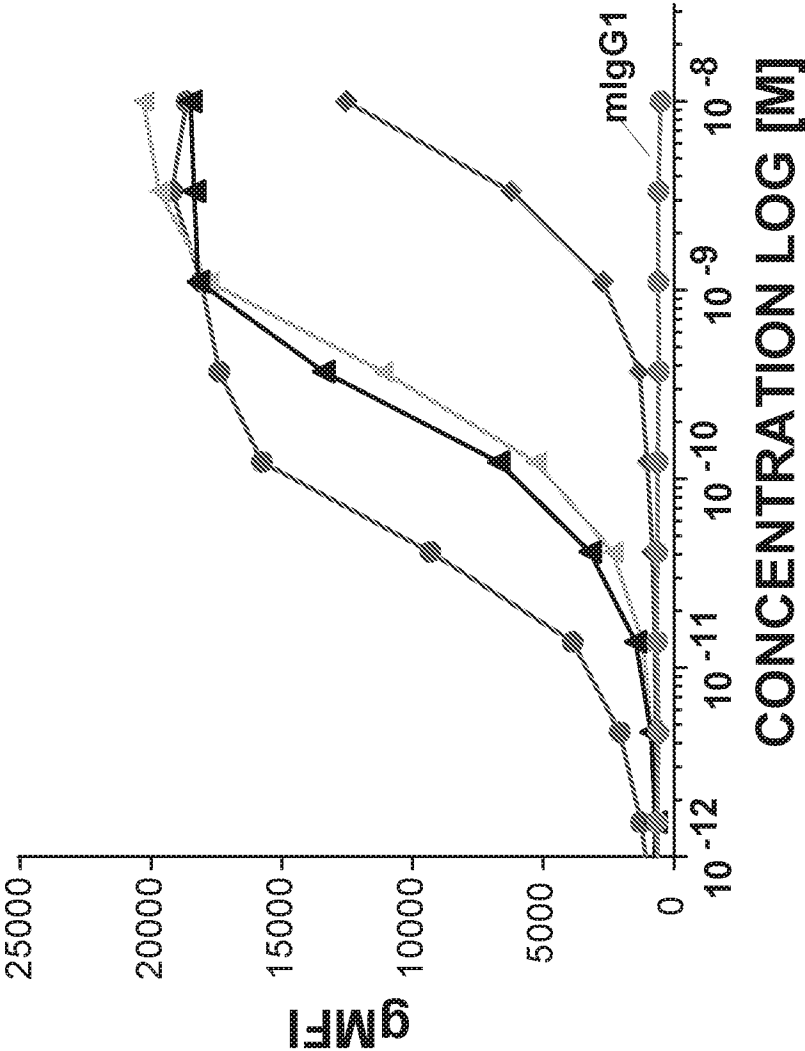


FIG. 7

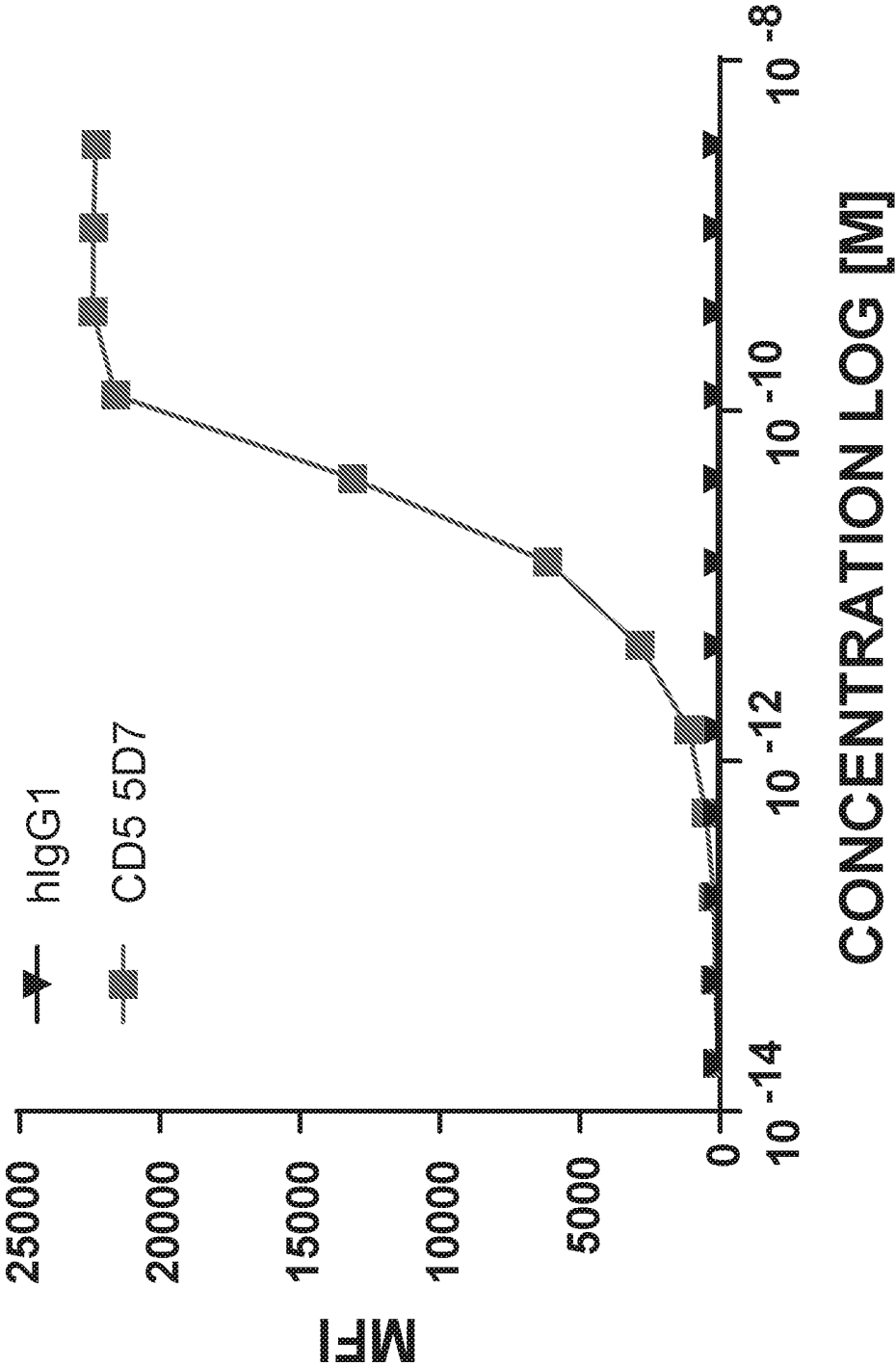


FIG. 8

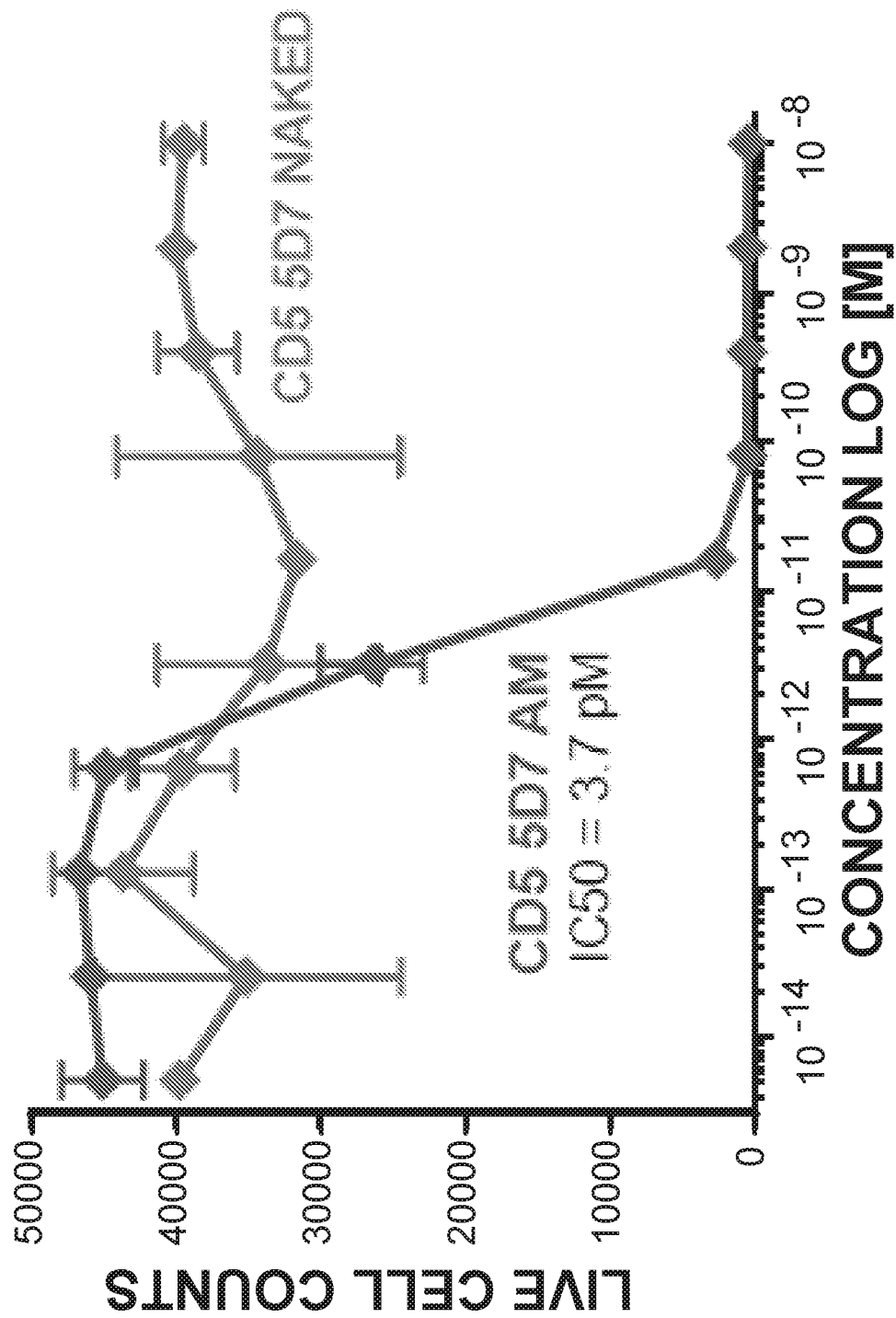


FIG. 9A

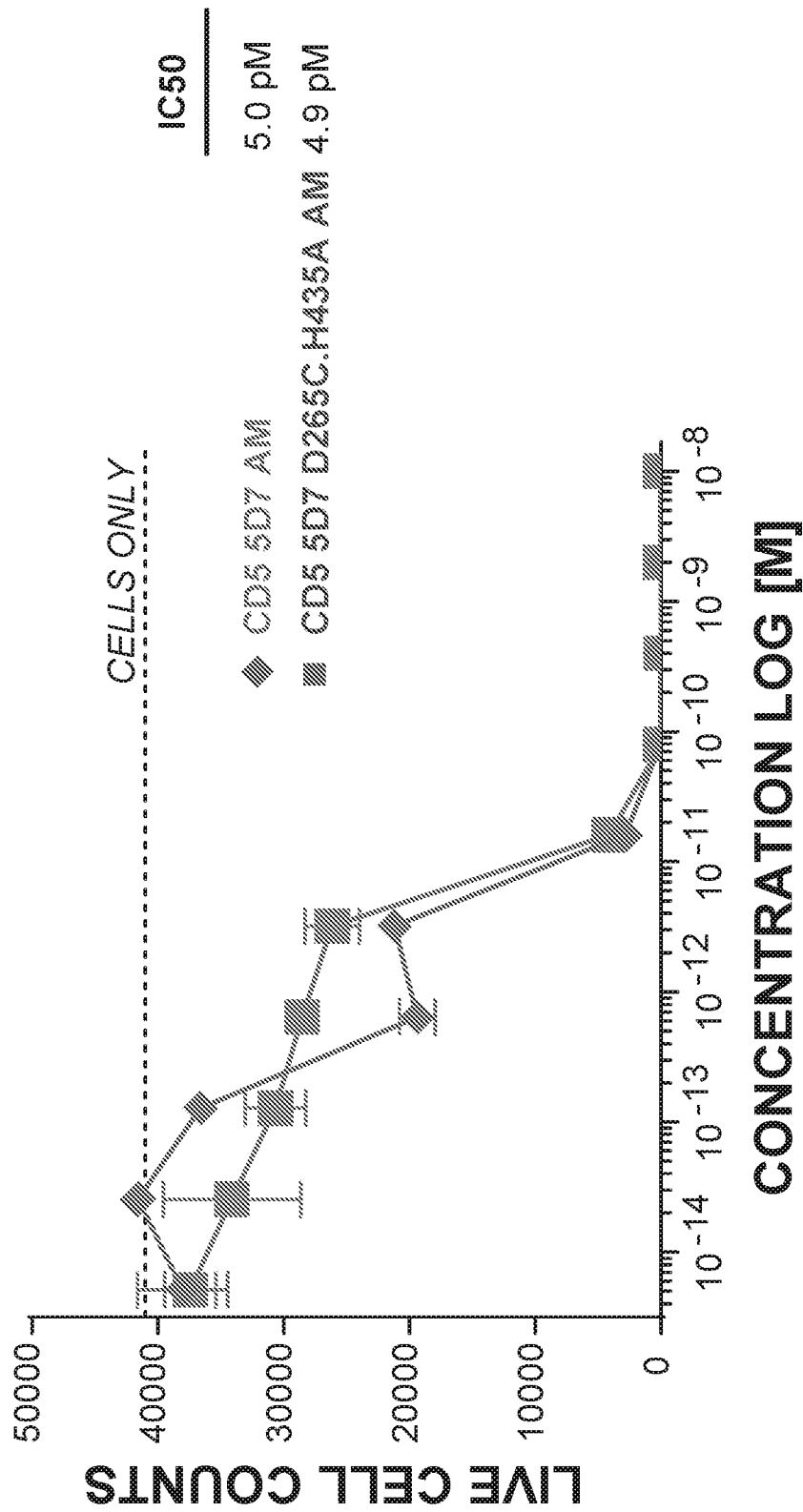


FIG. 9B

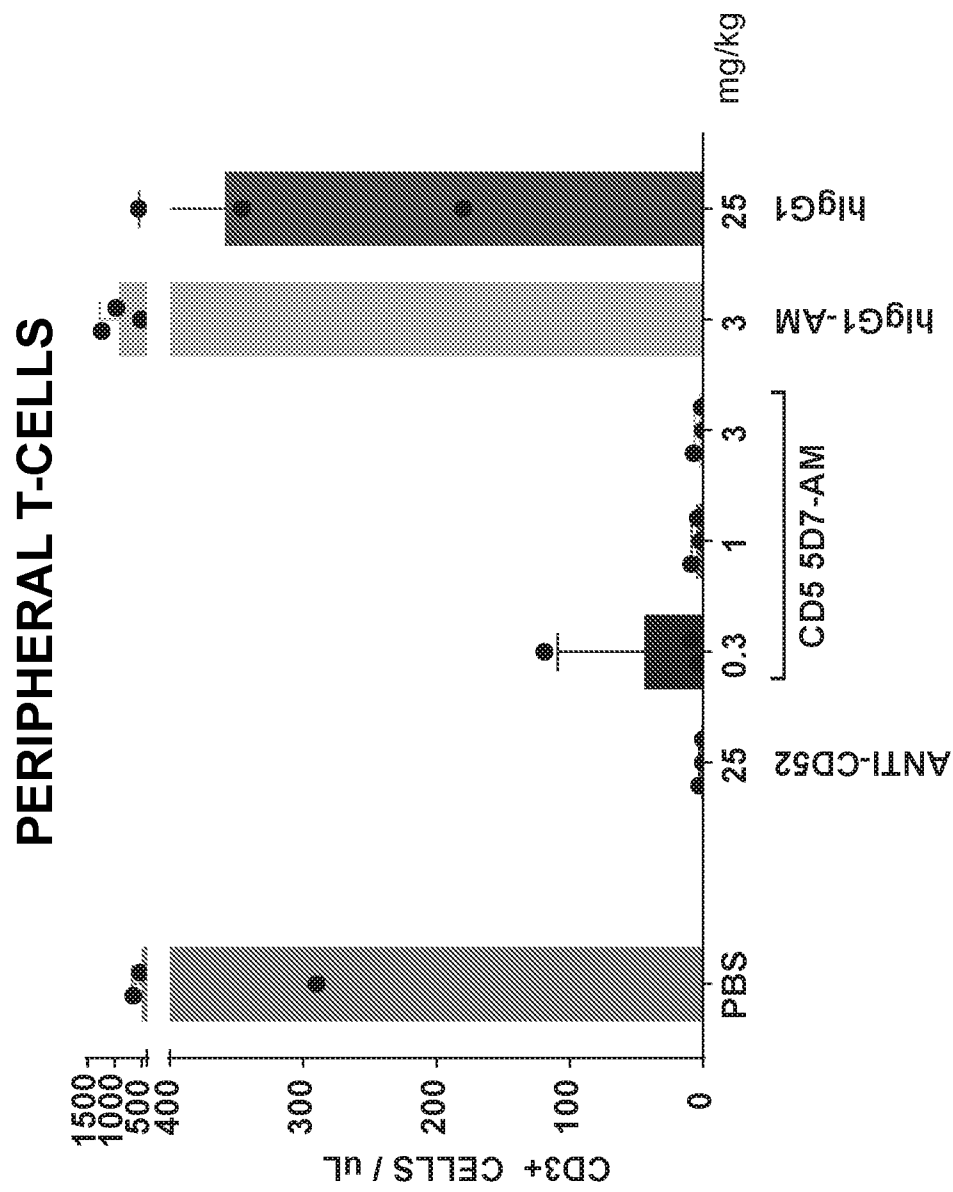


FIG. 10A

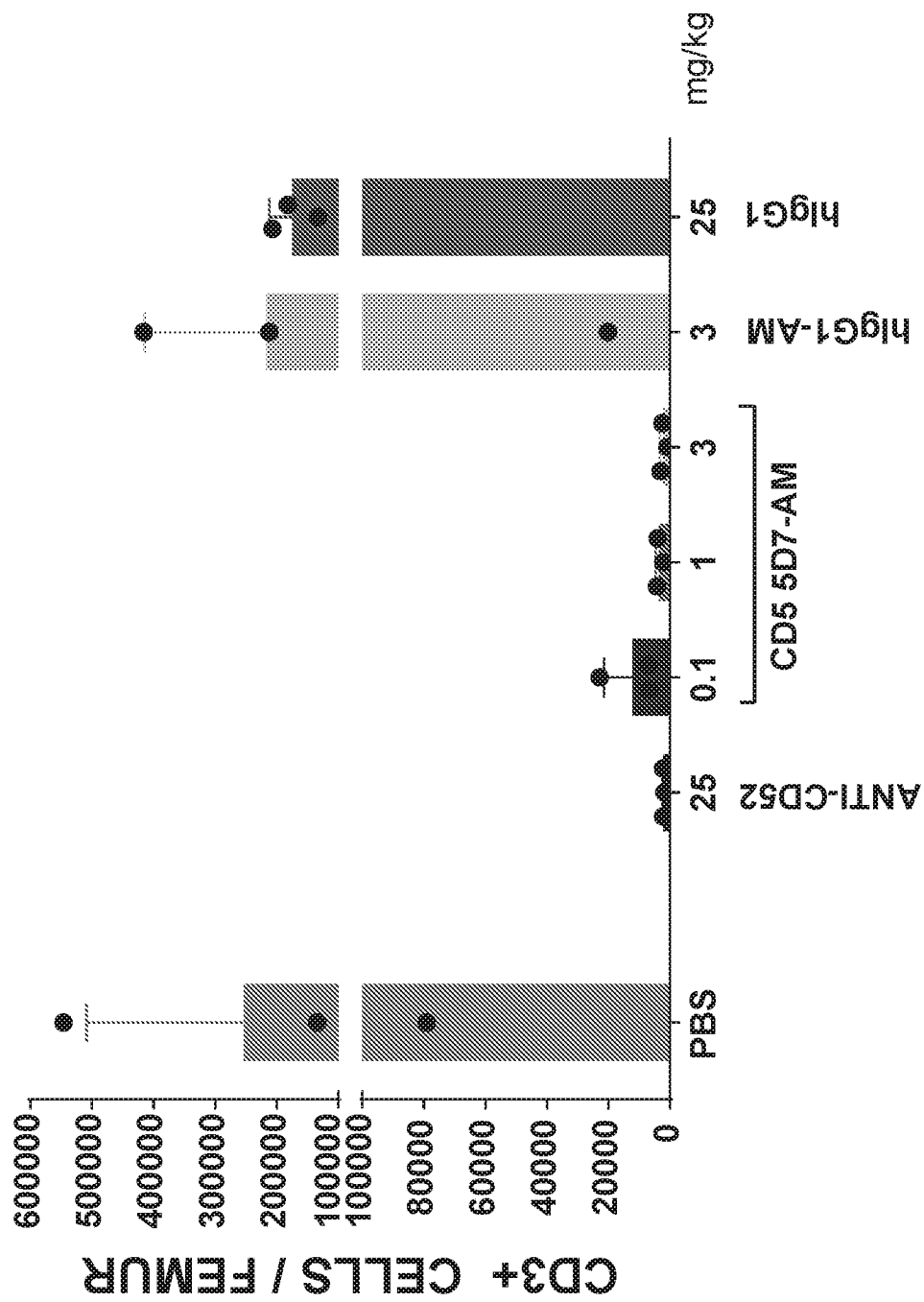


FIG. 10B

PERIPHERAL T-CELLS

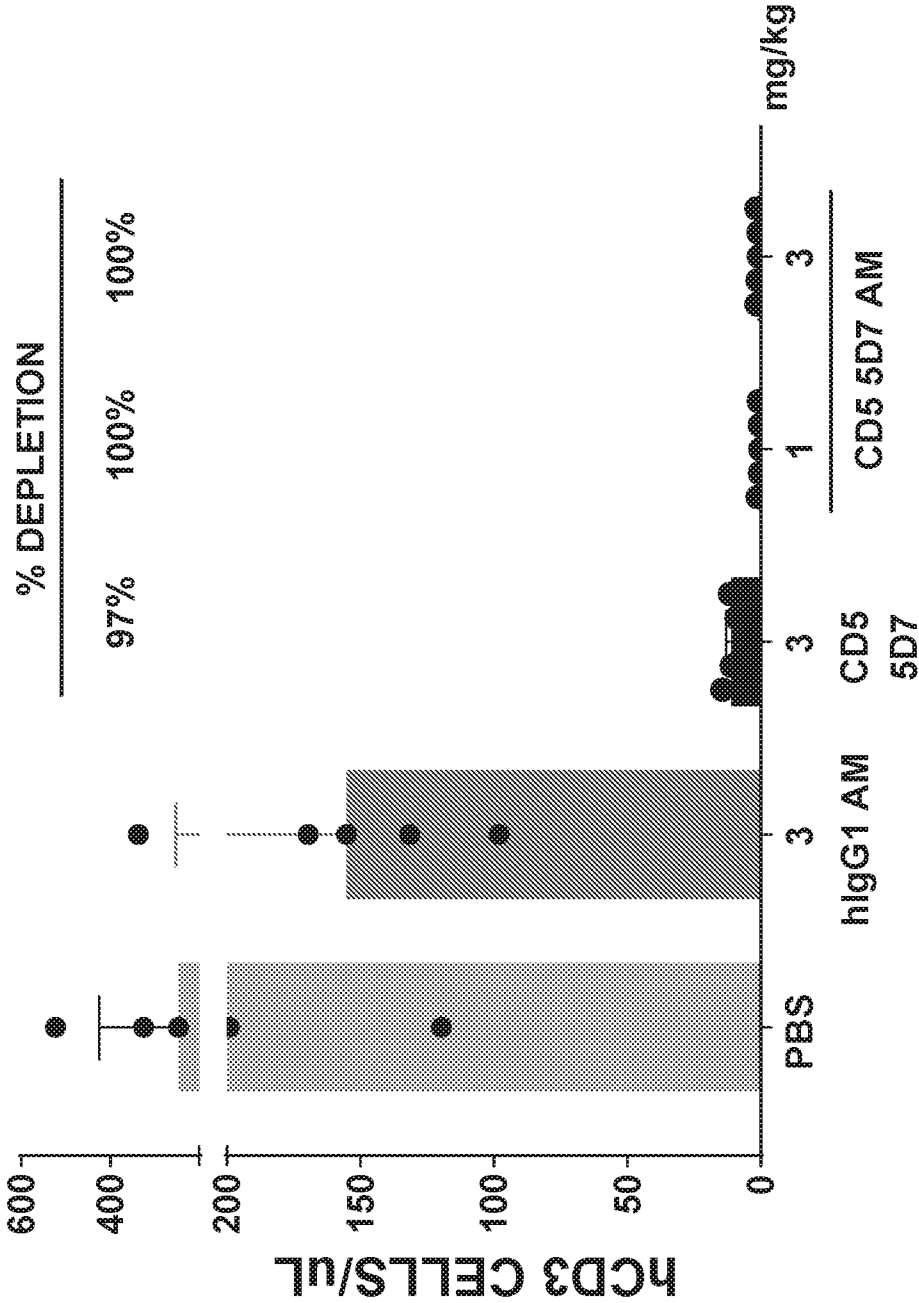


FIG. 11A

MARROW T-CELLS

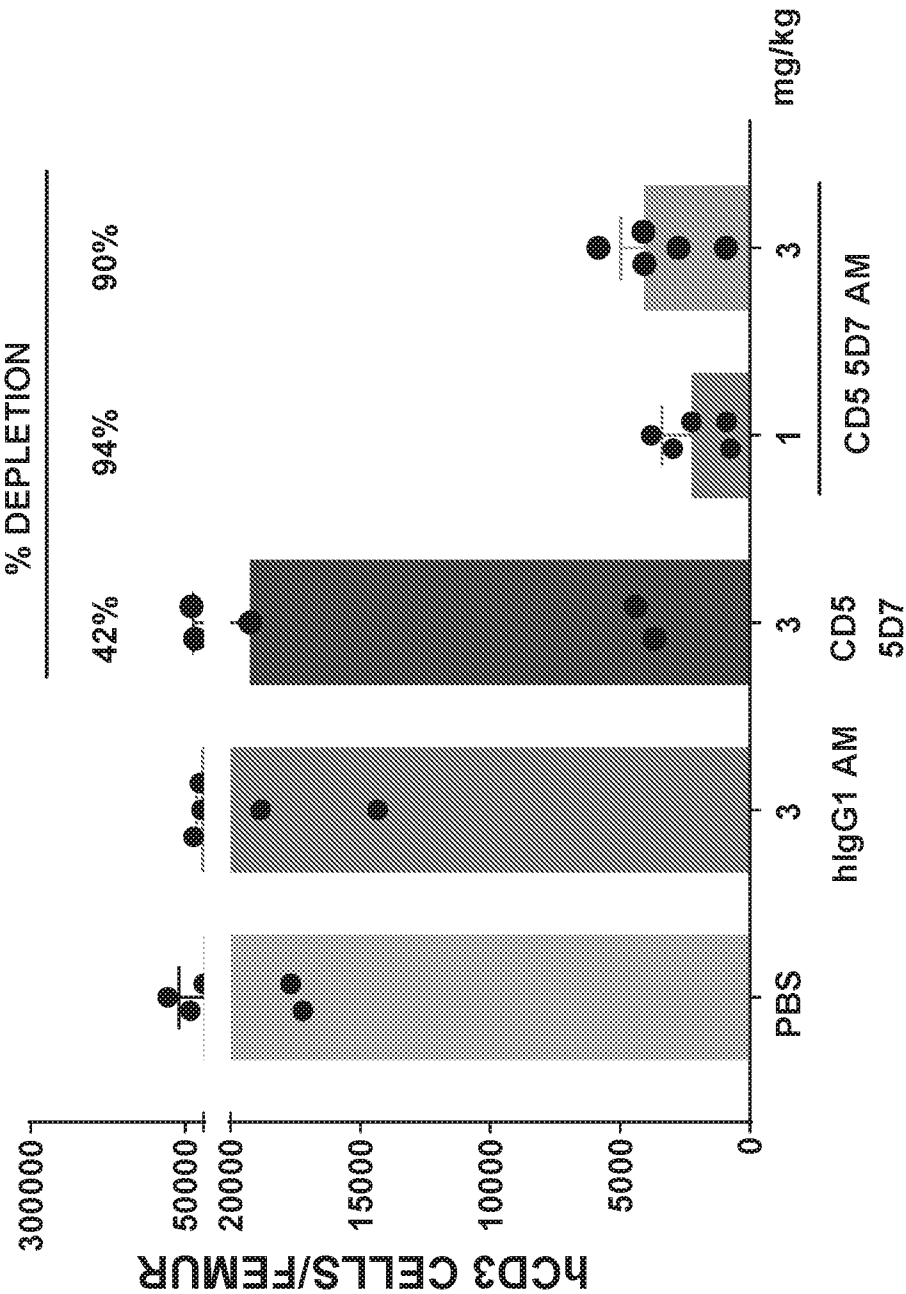


FIG. 11B

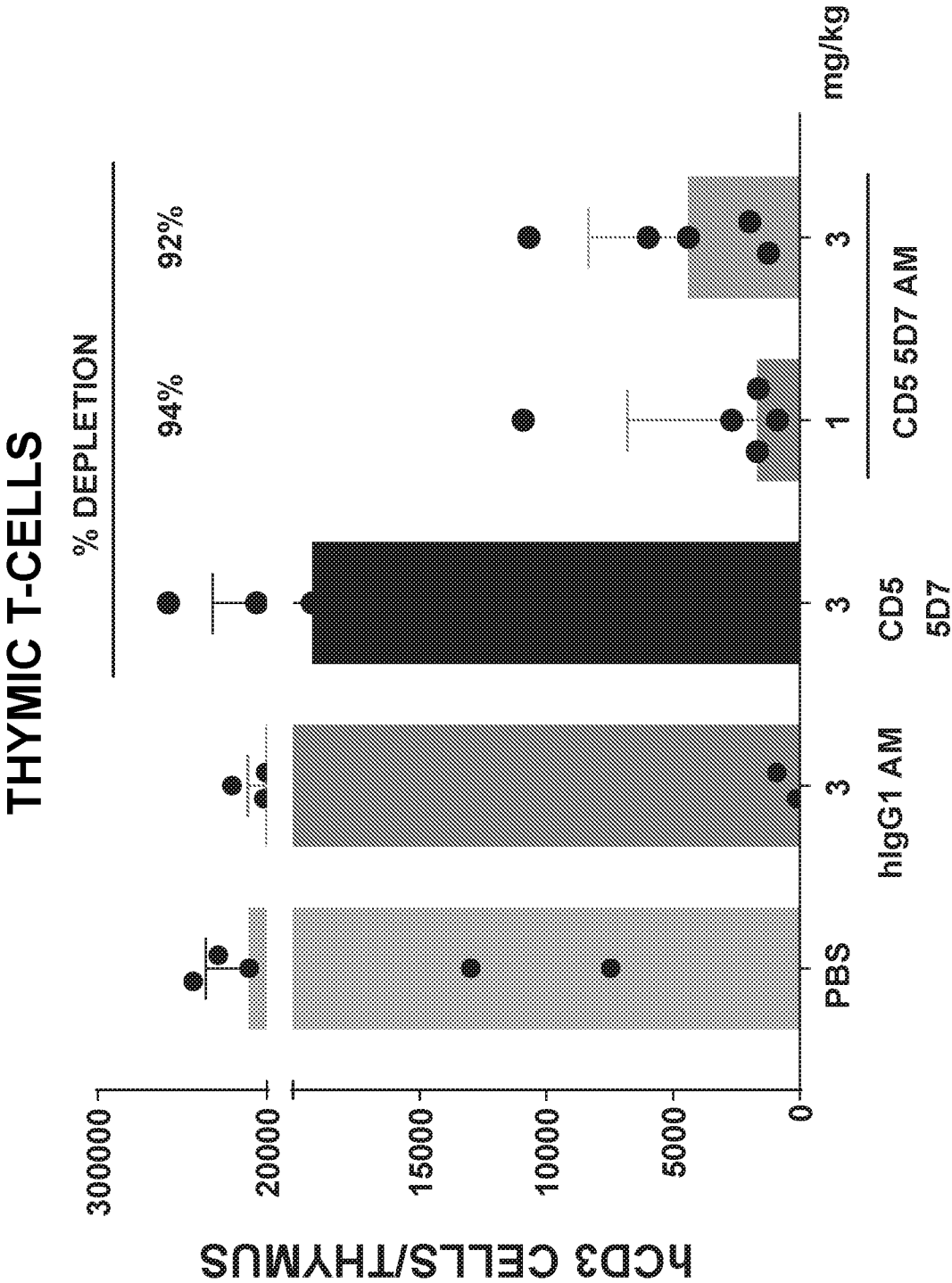


FIG. 11C

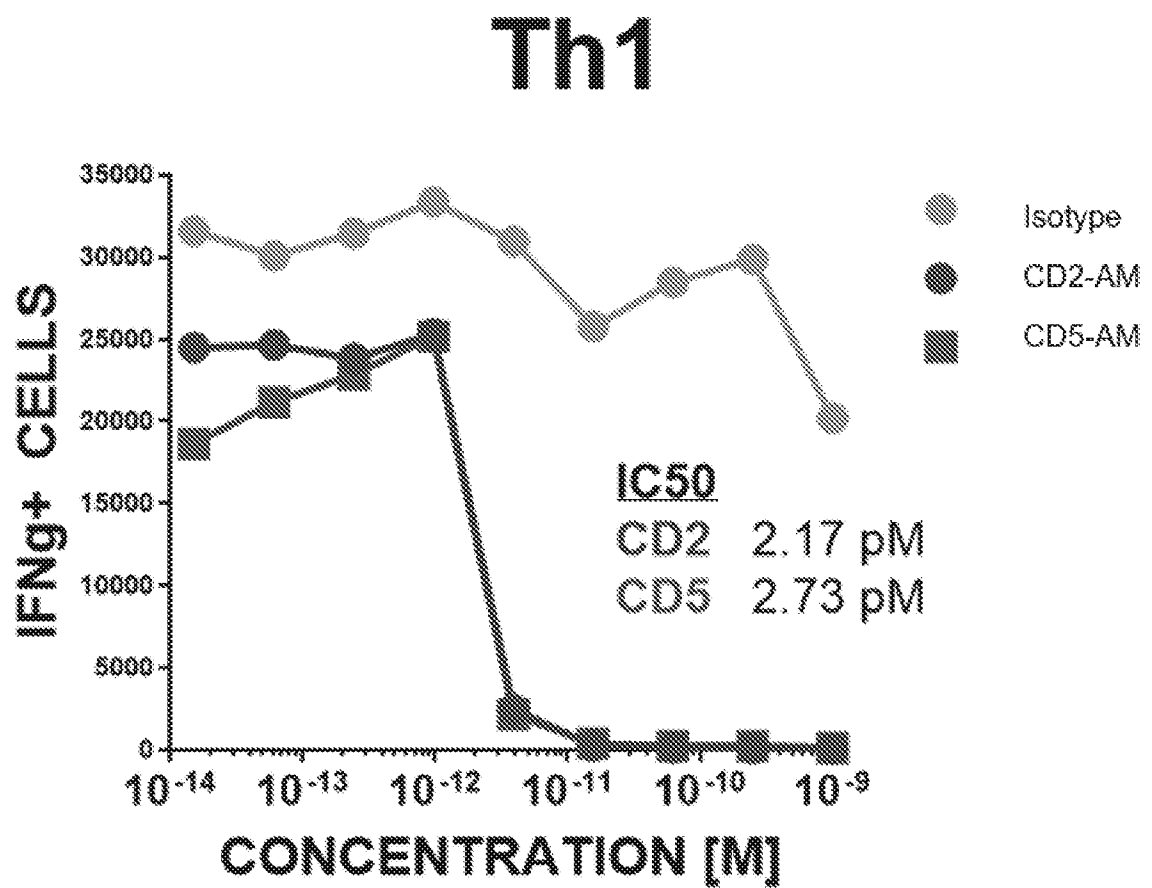


FIG. 12A

Th17

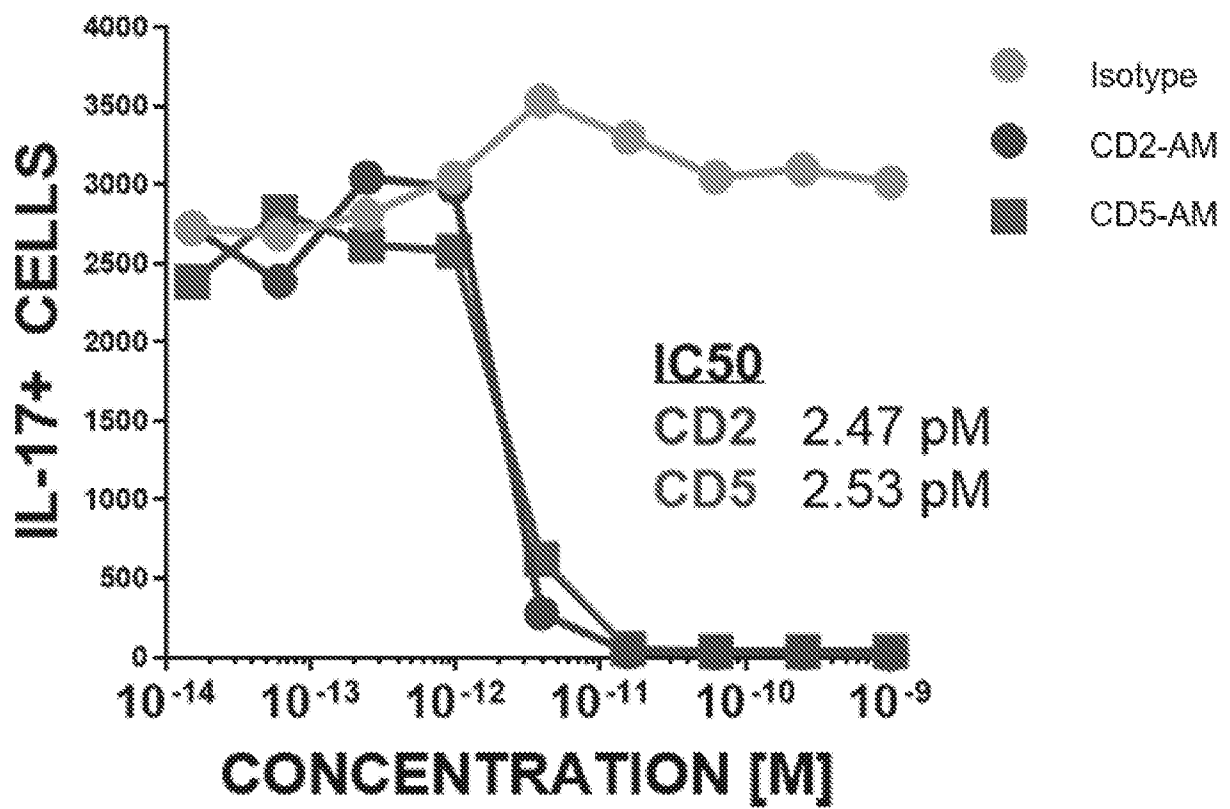


FIG. 12B

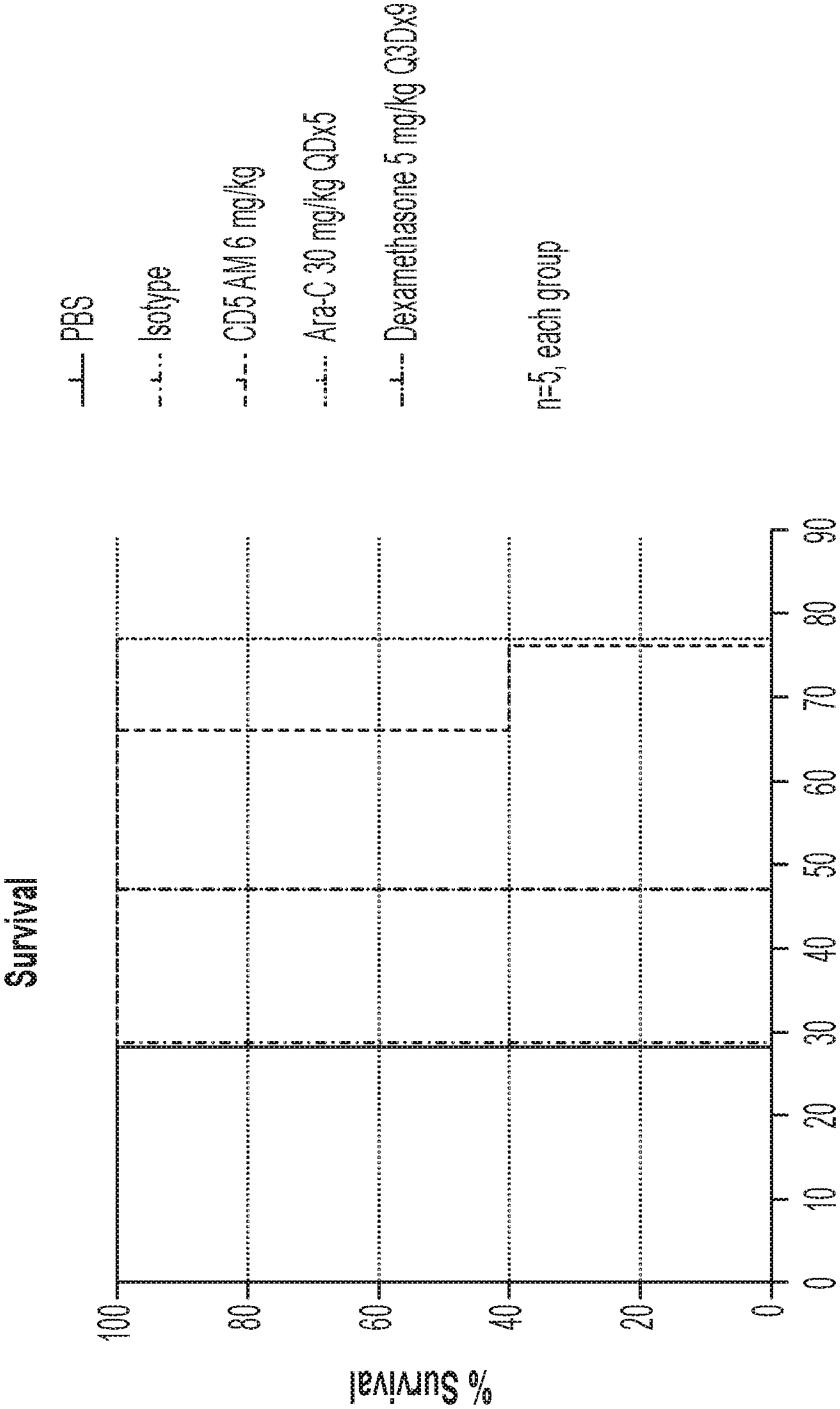


FIG. 13A

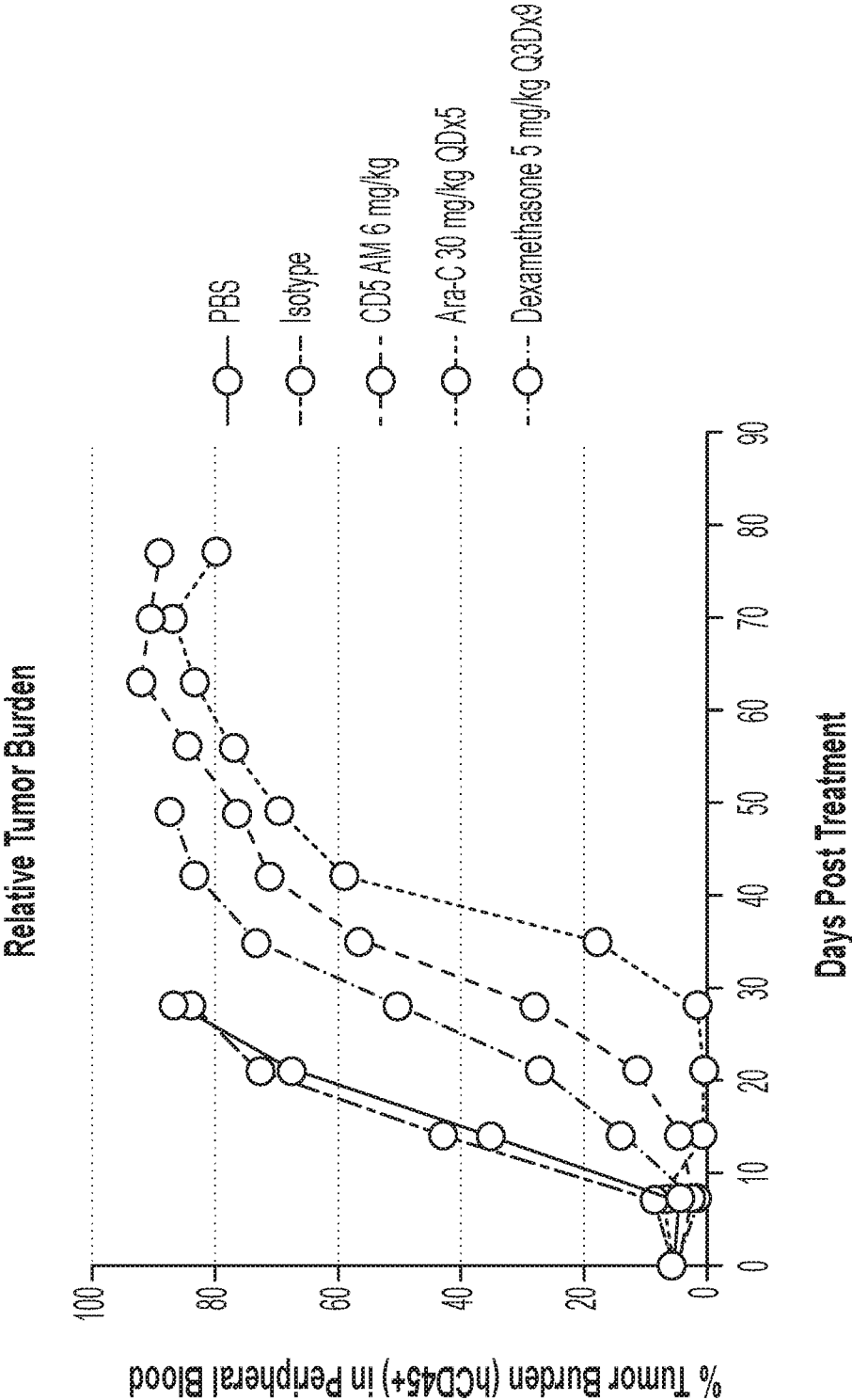


FIG. 13B

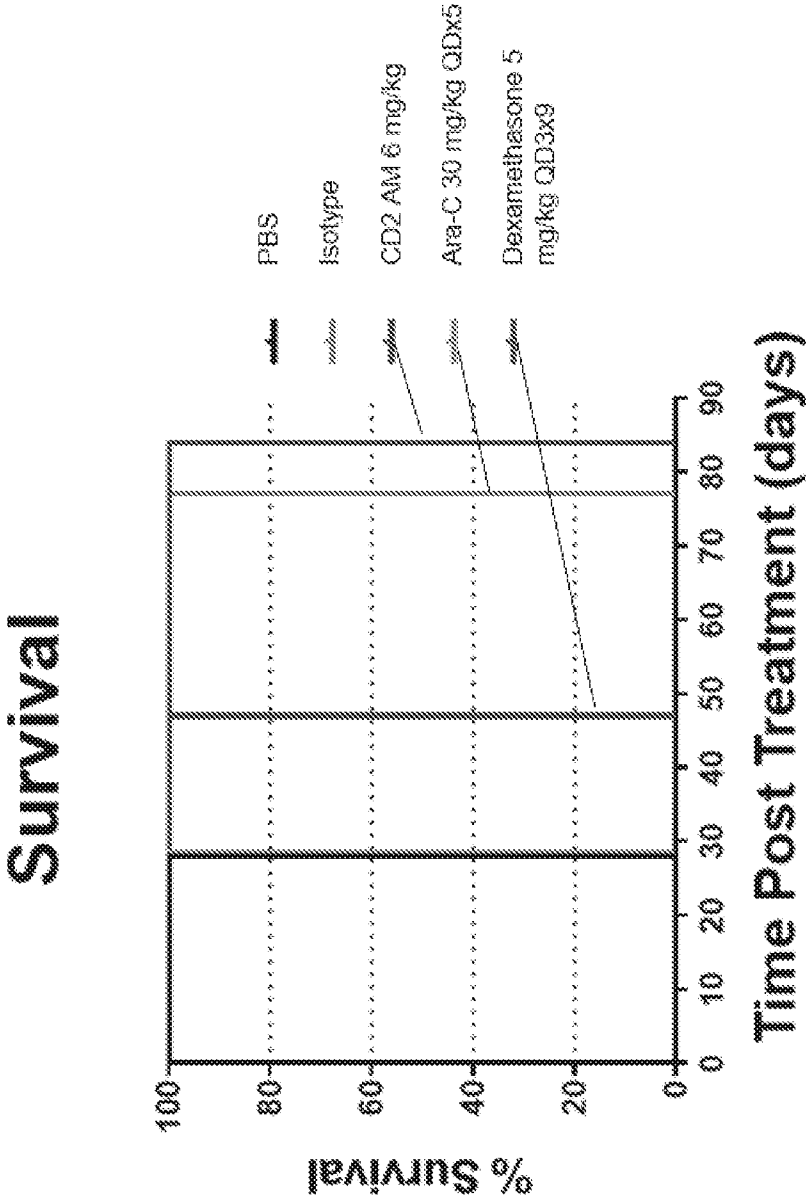


FIG. 13C

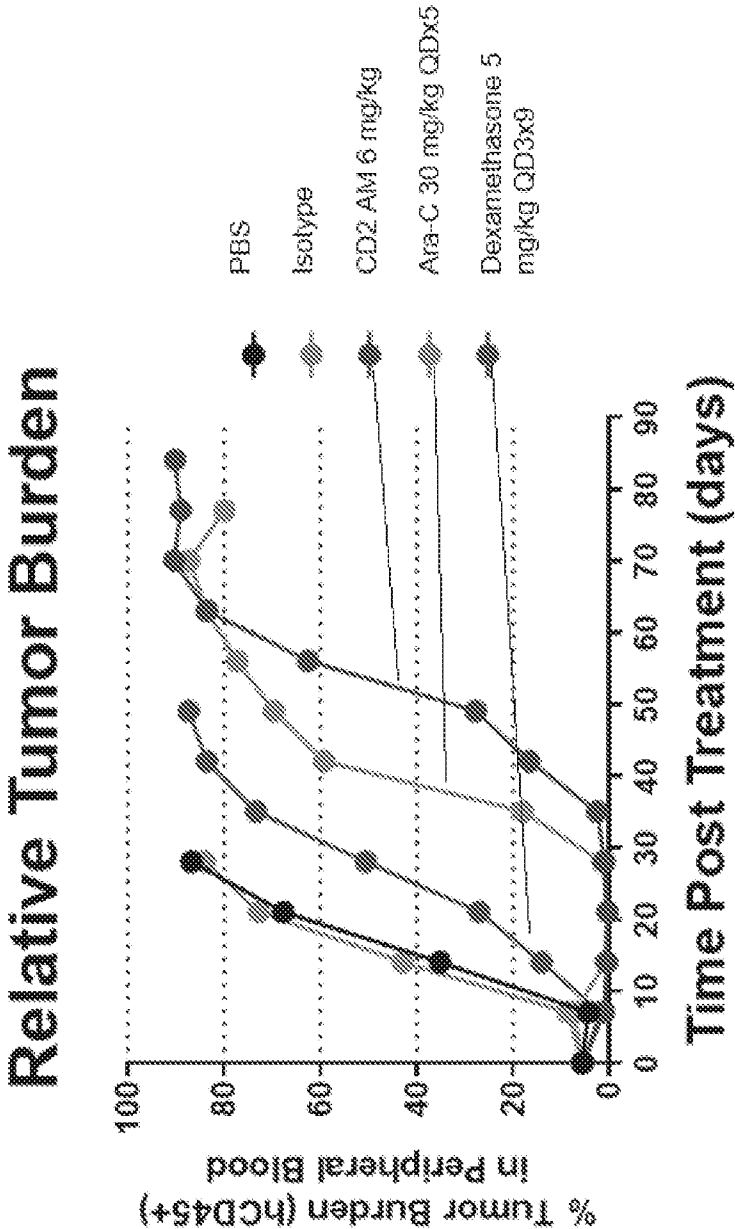


FIG. 13D

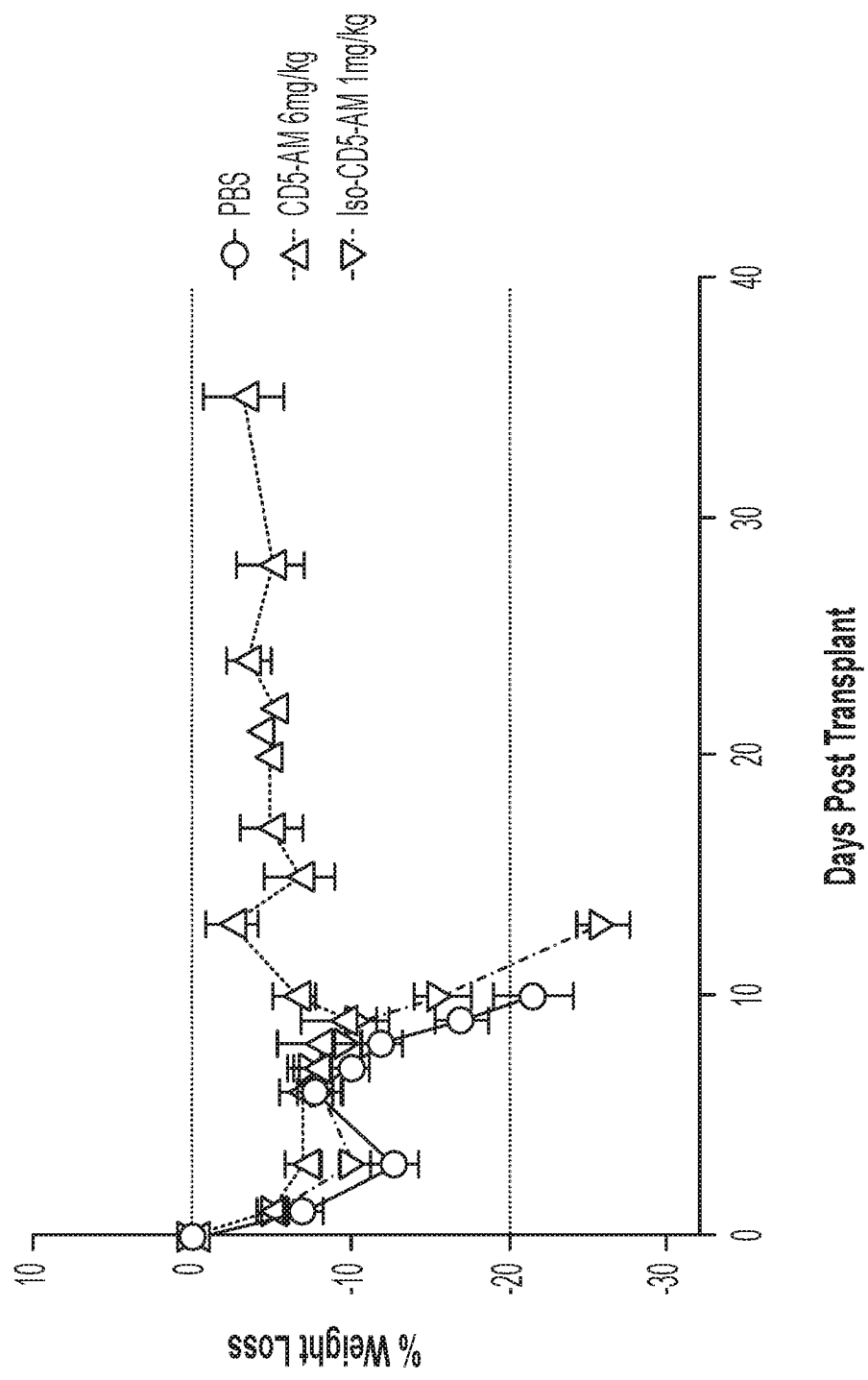


FIG. 14A

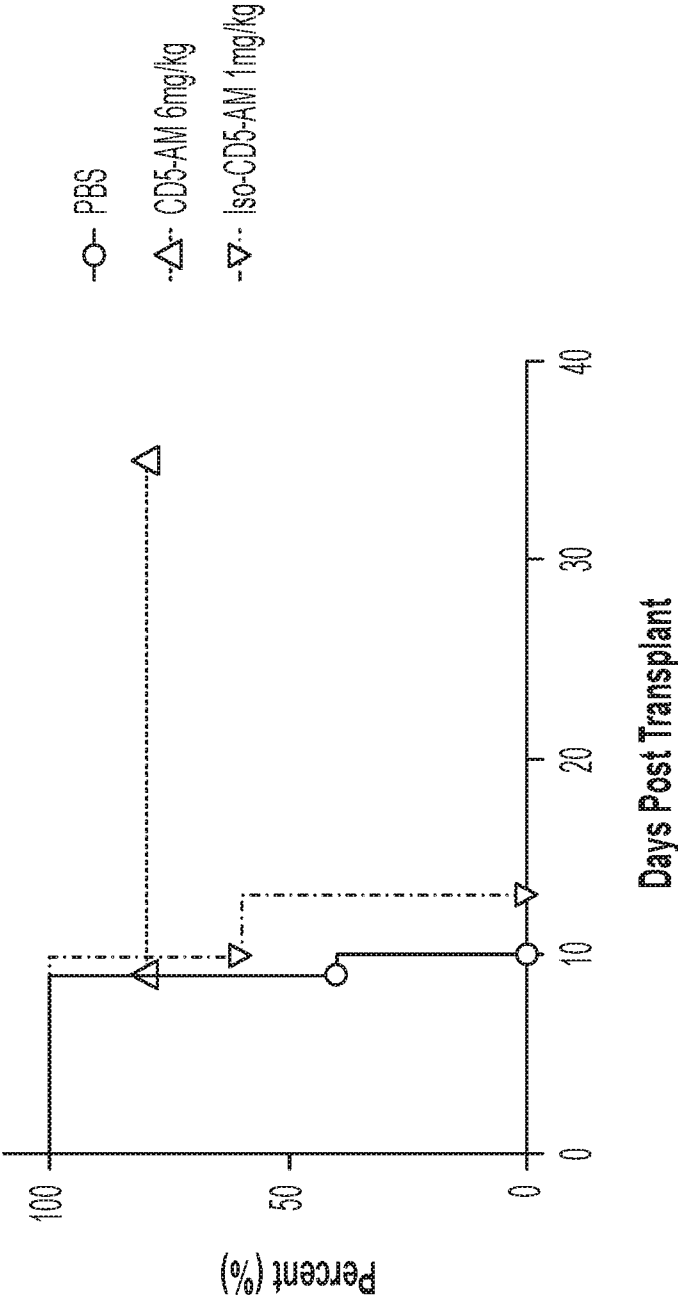


FIG. 14B

SEQUENCE LISTING

<110> MAGENTA THERAPEUTICS, INC.

<120> T-CELL DEPLETING THERAPIES

<130> M103034 2170W0

<140>

<141>

<150> 62/857,744

<151> 2019-06-05

<160> 287

<170> PatentIn version 3.5

<210> 1

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 1

Glu Tyr Tyr Met Tyr

1 5

<210> 2

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 2

Arg Ile Asp Pro Glu Asp Gly Ser Ile Asp Tyr Val Glu Lys Phe Lys

1 5 10 15

Lys

<210> 3

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 3

Gly Lys Phe Asn Tyr Arg Phe Ala Tyr
1 5

<210> 4

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 4

Arg Ser Ser Gln Ser Leu Leu His Ser Ser Gly Asn Thr Tyr Leu Asn
1 5 10 15

<210> 5

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 5

Leu Val Ser Lys Leu Glu Ser
1 5

<210> 6

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 6

Met Gln Phe Thr His Tyr Pro Tyr Thr
1 5

<210> 7

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 7

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Glu Tyr
20 25 30

Tyr Met Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Leu Met
35 40 45

Gly Arg Ile Asp Pro Glu Asp Gly Ser Ile Asp Tyr Val Glu Lys Phe
50 55 60

Lys Lys Lys Val Thr Leu Thr Ala Asp Thr Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Lys Phe Asn Tyr Arg Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 8

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 8

Asp Val Val Met Thr Gln Ser Pro Pro Ser Leu Leu Val Thr Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Ser Gly Asn Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Gln Pro Leu Ile Tyr Leu Val Ser Lys Leu Glu Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Gly Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Phe
85 90 95

Thr His Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 9

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 9

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Gln Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Glu Tyr
20 25 30

Tyr Met Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Leu Val
35 40 45

Gly Arg Ile Asp Pro Glu Asp Gly Ser Ile Asp Tyr Val Glu Lys Phe
50 55 60

Lys Lys Lys Val Thr Leu Thr Ala Asp Thr Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Lys Phe Asn Tyr Arg Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 10

<211> 112

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic
polypeptide

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Asp Val Val Met Thr Gln Ser Pro Pro Ser Leu Leu Val Thr Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Ser Gly Asn Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Gln Pro Leu Ile Tyr Leu Val Ser Lys Leu Glu Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Gly Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Phe
85 90 95

Thr His Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 11

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 11

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Glu Asn Gly Ser Asp Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Gly Ala Val Ser Tyr Phe Asp Val Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 12

<211> 109

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

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1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Leu Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105

<210> 13

<211> 351

<212> PRT

<213> Homo sapiens

<400> 13

Met Ser Phe Pro Cys Lys Phe Val Ala Ser Phe Leu Leu Ile Phe Asn
1 5 10 15

Val Ser Ser Lys Gly Ala Val Ser Lys Glu Ile Thr Asn Ala Leu Glu
20 25 30

Thr Trp Gly Ala Leu Gly Gln Asp Ile Asn Leu Asp Ile Pro Ser Phe
35 40 45

Gln Met Ser Asp Asp Ile Asp Asp Ile Lys Trp Glu Lys Thr Ser Asp
50 55 60

Lys Lys Lys Ile Ala Gln Phe Arg Lys Glu Lys Glu Thr Phe Lys Glu
65 70 75 80

Lys Asp Thr Tyr Lys Leu Phe Lys Asn Gly Thr Leu Lys Ile Lys His
85 90 95

Leu Lys Thr Asp Asp Gln Asp Ile Tyr Lys Val Ser Ile Tyr Asp Thr
100 105 110

Lys Gly Lys Asn Val Leu Glu Lys Ile Phe Asp Leu Lys Ile Gln Glu
115 120 125

Arg Val Ser Lys Pro Lys Ile Ser Trp Thr Cys Ile Asn Thr Thr Leu
130 135 140

Thr Cys Glu Val Met Asn Gly Thr Asp Pro Glu Leu Asn Leu Tyr Gln
145 150 155 160

Asp Gly Lys His Leu Lys Leu Ser Gln Arg Val Ile Thr His Lys Trp
165 170 175

Thr Thr Ser Leu Ser Ala Lys Phe Lys Cys Thr Ala Gly Asn Lys Val
180 185 190

Ser Lys Glu Ser Ser Val Glu Pro Val Ser Cys Pro Glu Lys Gly Leu
195 200 205

Asp Ile Tyr Leu Ile Ile Gly Ile Cys Gly Gly Gly Ser Leu Leu Met
210 215 220

Val Phe Val Ala Leu Leu Val Phe Tyr Ile Thr Lys Arg Lys Lys Gln
225 230 235 240

Arg Ser Arg Arg Asn Asp Glu Glu Leu Glu Thr Arg Ala His Arg Val
245 250 255

Ala Thr Glu Glu Arg Gly Arg Lys Pro His Gln Ile Pro Ala Ser Thr
260 265 270

Pro Gln Asn Pro Ala Thr Ser Gln His Pro Pro Pro Pro Pro Gly His
275 280 285

Arg Ser Gln Ala Pro Ser His Arg Pro Pro Pro Pro Gly His Arg Val
290 295 300

Gln His Gln Pro Gln Lys Arg Pro Pro Ala Pro Ser Gly Thr Gln Val
305 310 315 320

His Gln Gln Lys Gly Pro Pro Leu Pro Arg Pro Arg Val Gln Pro Lys
325 330 335

Pro Pro His Gly Ala Ala Glu Asn Ser Leu Ser Pro Ser Ser Asn
340 345 350

<210> 14
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 14
Gly Phe Thr Phe Ser Ser Tyr
1 5

<210> 15
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 15
Ser Gly Gly Gly Phe
1 5

<210> 16
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 16
Ser Ser Tyr Gly Glu Ile Met Asp Tyr
1 5

<210> 17
<211> 9
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 17

Ser Ser Tyr Gly Glu Leu Met Asp Tyr
1 5

<210> 18

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 18

Arg Ala Ser Gln Arg Ile Gly Thr Ser Ile His
1 5 10

<210> 19

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 19

Tyr Ala Ser Glu Ser Ile Ser
1 5

<210> 20

<211> 10

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 20

Gln Gln Ser His Gly Trp Pro Phe Thr Phe
1 5 10

<210> 21

<211> 117

<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 21

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Gly Gly Gly Phe Leu Tyr Tyr Leu Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Ile Leu Tyr Leu
65 70 75 80

His Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Ser Ser Tyr Gly Glu Ile Met Asp Tyr Trp Gly Gln Gly Thr Ser
100 105 110

Val Thr Val Ser Ser
115

<210> 22

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 22

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Gly Gly Gly Phe Leu Tyr Tyr Leu Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Ile Leu Tyr Leu
65 70 75 80

His Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Ser Ser Tyr Gly Glu Leu Met Asp Tyr Trp Gly Gln Gly Thr Ser
100 105 110

Val Thr Val Ser Ser
115

<210> 23

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 23

Asp Ile Leu Leu Thr Gln Ser Pro Ala Ile Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Arg Ile Gly Thr Ser
20 25 30

Ile His Trp Tyr Gln Gln Arg Thr Thr Gly Ser Pro Arg Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser
65 70 75 80

Glu Asp Val Ala Asp Tyr Tyr Cys Gln Gln Ser His Gly Trp Pro Phe
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Glu
100 105

<210> 24

<211> 324

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 24

Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala
1 5 10 15

Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu
50 55 60

Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val
65 70 75 80

Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
85 90 95

Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro
100 105 110

Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu
115 120 125

Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
130 135 140

Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
145 150 155 160

Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
165 170 175

Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
180 185 190

Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
195 200 205

Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
210 215 220

Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
225 230 235 240

Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
245 250 255

Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
260 265 270

Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn
275 280 285

Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
290 295 300

Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His
305 310 315 320

Ser Pro Gly Lys

<210> 25
<211> 107

<212> PRT
<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 25

Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu
1 5 10 15

Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe
20 25 30

Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg
35 40 45

Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu
65 70 75 80

Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser
85 90 95

Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
100 105

<210> 26

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 26

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Met Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Asn Ser Tyr
20 25 30

Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Tyr
65 70 75 80

Glu Asp Phe Gly Ile Tyr Tyr Cys Gln Gln Tyr Asp Glu Ser Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 27

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 27

Gln Ile Gln Leu Val Gln Ser Gly Pro Gly Leu Lys Lys Pro Gly Gly
1 5 10 15

Ser Val Arg Ile Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Arg Trp Met
35 40 45

Gly Trp Ile Asn Thr His Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Thr Phe Ser Leu Asp Thr Ser Lys Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Asn Ser Leu Arg Ala Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Thr Arg Arg Gly Tyr Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> 28
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<212> PRT
<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic
peptide

<400> 28
Gly Tyr Thr Phe Thr Asn Tyr
1 5

<210> 29
<211> 6
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<213> Artificial Sequence

<220>
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peptide

<400> 29
Asn Thr His Thr Gly Glu
1 5

<210> 30
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 30
Arg Gly Tyr Asp Trp Tyr Phe Asp Val
1 5

<210> 31
<211> 11
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<223> Description of Artificial Sequence: Synthetic peptide

<400> 31

Arg Ala Ser Gln Asp Ile Asn Ser Tyr Leu Ser
1 5 10

<210> 32

<211> 7

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 32

Arg Ala Asn Arg Leu Val Asp
1 5

<210> 33

<211> 9

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 33

Gln Gln Tyr Asp Glu Ser Pro Trp Thr
1 5

<210> 34

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 34

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Asn Ser Tyr
20 25 30

Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile
35 40 45

Tyr Arg Ala Asn Arg Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Tyr
65 70 75 80

Glu Asp Phe Gly Ile Tyr Tyr Cys Gln Gln Tyr Asp Glu Ser Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 35

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 35

Glu Ile Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Val Arg Ile Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr His Tyr Gly Glu Pro Thr Tyr Ala Asp Ser Phe
50 55 60

Lys Gly Thr Arg Thr Phe Ser Leu Asp Asp Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Ile Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Thr Arg Arg Gly Tyr Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly Gly
100 105 110

Thr Thr Val Thr Val Ser Ser
115

<210> 36

<211> 7

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic
peptide

<400> 36

Gly Tyr Thr Phe Thr Asn Tyr
1 5

<210> 37

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 37

Asn Thr His Tyr Gly Glu
1 5

<210> 38

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 38

Arg Arg Gly Tyr Asp Trp Tyr Phe Asp Val
1 5 10

<210> 39

<211> 11

<212> PRT
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<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 39

Arg Ala Ser Gln Asp Ile Asn Ser Tyr Leu Ser
1 5 10

<210> 40

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

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Arg Ala Asn Arg Leu Glu Ser
1 5

<210> 41

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 41

Gln Gln Tyr Asp Glu Ser Pro Trp Thr
1 5

<210> 42

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 42

Gly Tyr Ser Ile Thr Ser Gly Tyr Tyr
1 5

<210> 43
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<400> 43
Ile Ser Tyr Ser Gly Phe Thr
1 5

<210> 44
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<400> 44
Ala Gly Asp Arg Thr Gly Ser Trp Phe Ala Tyr
1 5 10

<210> 45
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 45
Gln Asp Ile Ser Asn Tyr
1 5

<210> 46
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
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<400> 46
Ala Thr Ser
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<210> 47
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
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peptide

<400> 47
Leu Gln Tyr Ala Ser Tyr Pro Phe Thr
1 5

<210> 48
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
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peptide

<400> 48
Gly Tyr Ile Phe Thr Asn Tyr Gly
1 5

<210> 49
<211> 8
<212> PRT
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<220>
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peptide

<400> 49
Ile Asn Thr Tyr Asn Gly Glu Pro
1 5

<210> 50
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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Ala Arg Gly Asp Tyr Tyr Gly Tyr Glu Asp Tyr
1 5 10

<210> 51

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 51

Gln Gly Ile Ser Asn Tyr

1 5

<210> 52

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 52

Tyr Thr Ser

1

<210> 53

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 53

Gln Gln Tyr Ser Lys Leu Pro Trp Thr

1 5

<210> 54

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 54
Phe Ser Leu Ser Thr Ser Gly Met Gly
1 5

<210> 55
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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peptide

<400> 55
Trp Trp Asp Asp Asp
1 5

<210> 56
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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peptide

<400> 56
Arg Arg Ala Thr Gly Thr Gly Phe Asp Tyr
1 5 10

<210> 57
<211> 6
<212> PRT
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<220>
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peptide

<400> 57
Gln Asp Val Gly Thr Ala
1 5

<210> 58
<211> 7
<212> PRT
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<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 58

Trp Thr Ser Thr Arg His Thr
1 5

<210> 59

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 59

Tyr Asn Ser Tyr Asn Thr
1 5

<210> 60

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 60

Ser Gly Tyr Ser Phe Thr Gly Tyr Thr Met
1 5 10

<210> 61

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 61

Leu Ile Asn Pro Tyr Asn Gly Gly Thr Thr
1 5 10

<210> 62

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 62

Cys	Ala	Arg	Asp	Tyr	Tyr	Gly	Ser	Ser	Pro	Asp	Phe	Asp	Tyr	Trp
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<210> 63

<211> 10

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 63

Ser	Gly	Tyr	Ser	Phe	Thr	Asp	Tyr	Thr	Met
1				5					10

<210> 64

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 64

Leu	Ile	Asn	Pro	Tyr	Asn	Gly	Gly	Thr	Met
1				5					10

<210> 65

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 65

Cys	Ala	Arg	Asp	Asn	Tyr	Gly	Ser	Ser	Pro	Asp	Phe	Asp	Tyr	Trp
1				5					10					15

<210> 66

<211> 10

<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 66

Ser	Gly	Tyr	Ser	Phe	Thr	Gly	Tyr	Thr	Met
1				5					10

<210> 67

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 67

Leu	Ile	Asn	Pro	Tyr	Asn	Gly	Gly	Thr	Met
1				5					10

<210> 68

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 68

Cys	Ala	Arg	Asp	Asn	Tyr	Gly	Ser	Ser	Pro	Tyr	Phe	Asp	Tyr	Trp
1				5					10					15

<210> 69

<211> 10

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 69

Ser	Gly	Tyr	Ser	Phe	Thr	Gly	Tyr	Thr	Met
1				5					10

<210> 70
<211> 10
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<400> 70
Leu Ile Asn Pro Tyr Asn Gly Gly Thr Met
1 5 10

<210> 71
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 71
Cys Ala Arg Asp Asn Tyr Gly Ser Ser Pro Tyr Phe Asp Tyr Trp
1 5 10 15

<210> 72
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 72
Ser Gly Tyr Ser Phe Thr Gly Tyr Thr Met
1 5 10

<210> 73
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 73
Leu Ile Asn Pro Tyr Asn Gly Gly Thr Thr
1 5 10

<210> 74
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 74
Cys Ala Arg Asp Tyr Tyr Gly Ser Ser Pro Asp Phe Asp Tyr Trp
1 5 10 15

<210> 75
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<400> 75
Ser Gly Phe Thr Phe Ser Asn Tyr Ala Met
1 5 10

<210> 76
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 76
Ser Ile Ser Ser Gly Gly Asn Thr Phe
1 5

<210> 77
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<400> 77

Cys Val Arg Tyr Tyr Tyr Gly Val Thr Tyr Trp Tyr Phe Asp Val Trp
1 5 10 15

<210> 78

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 78

Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
1 5 10

<210> 79

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 79

Ser Ile Ser Ser Gly Gly Ser Thr Tyr
1 5

<210> 80

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 80

Cys Val Arg Tyr Tyr Tyr Gly Ile Arg Tyr Trp Tyr Phe Asp Val Trp
1 5 10 15

<210> 81

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 81

Ser Gly Tyr Ser Phe Thr Ala Tyr Asn Ile
1 5 10

<210> 82

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 82

Ser Ile Asp Pro Tyr Tyr Gly Asp Thr Lys
1 5 10

<210> 83

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 83

Cys Ala Arg Arg Met Ile Thr Met Gly Asp Trp Tyr Phe Asp Val Trp
1 5 10 15

<210> 84

<211> 10

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic
peptide

<400> 84

Ser Gly Tyr Ser Phe Thr Ala Tyr Ser Met
1 5 10

<210> 85

<211> 10

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 85

Ser Ile Asp Pro Tyr Tyr Gly Asp Thr Lys
1 5 10

<210> 86

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 86

Cys Ala Arg Arg Met Ile Thr Thr Gly Asp Trp Tyr Phe Asp Val Trp
1 5 10 15

<210> 87

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 87

Ser Gly Tyr Thr Phe Thr Asn Phe Ala Ile
1 5 10

<210> 88

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 88

Leu Ile Ser Ser Asn Ser Gly Asp Val Ser
1 5 10

<210> 89

<211> 14

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 89

Cys	Ala	Arg	His	Tyr	Gly	Ala	His	Asn	Tyr	Phe	Asp	Tyr	Trp
1				5					10				

<210> 90

<211> 10

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 90

Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Phe	Ala	Ile
1				5					10

<210> 91

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 91

Leu	Ile	Ser	Thr	Ser	Ser	Gly	Asp	Val	Ser
1				5					10

<210> 92

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 92

Cys	Ala	Arg	His	Tyr	Gly	Ala	Asn	Asn	Tyr	Phe	Asp	Tyr	Trp
1				5					10				

<210> 93

<211> 10

<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 93

Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Phe	Ala	Ile
1				5					10

<210> 94

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 94

Leu	Ile	Ser	Ser	Asn	Ser	Gly	Asp	Val	Ser
1				5					10

<210> 95

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 95

Cys	Ala	Arg	His	Tyr	Gly	Ala	His	Asn	Tyr	Phe	Asp	Tyr	Trp
1				5					10				

<210> 96

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 96

Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Phe	Ala	Ile
1				5					10

<210> 97
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<400> 97
Leu Ile Ser Ser Asn Ser Gly Asp Val Ser
1 5 10

<210> 98
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 98
Cys Ala Arg His Tyr Gly Ala His Asn Tyr Phe Asp Tyr Trp
1 5 10

<210> 99
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 99
Ser Gly Phe Asn Ile Lys Asp Thr Tyr Met
1 5 10

<210> 100
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 100
Arg Ile Asp Pro Ala Asn Gly Asn Thr Lys
1 5 10

<210> 101
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 101
Cys Ala Arg Glu Glu Asn Tyr Tyr Gly Thr Tyr Tyr Phe Asp Tyr Trp
1 5 10 15

<210> 102
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 102
Ser Gly Tyr Ser Phe Thr Ser Tyr Trp Met
1 5 10

<210> 103
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 103
Met Ile His Pro Ser Asp Ser Glu Thr Arg
1 5 10

<210> 104
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 104

Cys Ala Arg Trp Gly Asp His Asp Asp Ala Met Asp Phe Trp
1 5 10

<210> 105
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 105
Ser Gly Phe Ser Leu Thr Asn Tyr Asp Val
1 5 10

<210> 106
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 106
Val Ile Trp Ser Gly Gly Asn Thr Asp
1 5

<210> 107
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 107
Cys Ala Arg Asn His Gly Asp Gly Tyr Phe Asn Trp Tyr Phe Asp Val
1 5 10 15

Trp

<210> 108
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 108

Ser Gly Phe Ser Leu Thr Asn Tyr Asp Val
1 5 10

<210> 109

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 109

Val Ile Trp Ser Gly Gly Asn Thr Asp
1 5

<210> 110

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 110

Cys Ala Arg Asn His Gly Asp Gly Tyr Tyr Asn Trp Tyr Phe Asp Val
1 5 10 15

Trp

<210> 111

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 111

Ser Gly Phe Thr Phe Ser Asn Tyr Gly Met
1 5 10

<210> 112
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 112
Ala Ile Asn Ser Asn Gly Asp Ile Thr Tyr
1 5 10

<210> 113
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 113
Cys Ala Arg Gly Thr Ala Trp Phe Thr Tyr Trp
1 5 10

<210> 114
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 114
Ser Gly Tyr Ser Phe Thr Gly Tyr Thr Met
1 5 10

<210> 115
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 115

Leu Ile Asn Pro Tyr Asn Gly Gly Thr Arg
1 5 10

<210> 116

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 116

Cys Ala Arg Asp Gly Asp Asp Gly Trp Asp Ile Asp Val Trp
1 5 10

<210> 117

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 117

Ser Gly Tyr Ile Phe Ala Asn Tyr Gly Met
1 5 10

<210> 118

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 118

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr
1 5 10

<210> 119

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 119

Cys Ala Arg Arg Gly Thr Tyr Trp His Phe Asp Val Trp
1 5 10

<210> 120

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 120

Ser Gly Tyr Asn Phe Thr Asn Tyr Gly Met
1 5 10

<210> 121

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 121

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr
1 5 10

<210> 122

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 122

Cys Ala Arg Arg Gly Ser Tyr Trp His Phe Asp Val Trp
1 5 10

<210> 123

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 123

Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Met
1 5 10

<210> 124

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 124

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr
1 5 10

<210> 125

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 125

Cys Ala Arg Arg Ser Thr Leu Val Phe Asp Tyr Trp
1 5 10

<210> 126

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 126

Ser Gly Tyr Thr Phe Thr Asp Tyr Tyr Ile
1 5 10

<210> 127

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 127

Trp	Ile	Tyr	Pro	Gly	Gly	Gly	Asn	Thr	Arg
1				5					10

<210> 128

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 128

Cys	Ala	Arg	Asn	Gly	Tyr	Trp	Tyr	Phe	Asp	Val	Trp
1				5					10		

<210> 129

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 129

Ser	Gly	Tyr	Thr	Phe	Thr	Asp	Tyr	Tyr	Ile
1				5					10

<210> 130

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 130

Trp	Ile	Tyr	Pro	Gly	Gly	Gly	Asn	Thr	Arg
1				5					10

<210> 131

<211> 12

<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 131

Cys Ala Arg Asn Gly Tyr Trp Tyr Phe Asp Val Trp
1 5 10

<210> 132

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 132

Ser Gly Asn Thr Phe Thr Asn Phe Tyr Leu
1 5 10

<210> 133

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 133

Cys Ile Tyr Pro Gly Asn Val Lys Thr Lys
1 5 10

<210> 134

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 134

Cys Ala Lys Glu Gly Asp Tyr Asp Gly Thr Ala Tyr Phe Asp Tyr Trp
1 5 10 15

<210> 135
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 135
Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Met
1 5 10

<210> 136
<211> 10
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<400> 136
Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr
1 5 10

<210> 137
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 137
Cys Ala Arg Arg Arg Asp Gly Asn Phe Asp Tyr Trp
1 5 10

<210> 138
<211> 10
<212> PRT
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<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 138
Ser Glu Phe Thr Phe Ser Asn Tyr Ala Met
1 5 10

<210> 139
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 139
Thr Ile Ser Ser Gly Gly Ser Tyr Thr Tyr
1 5 10

<210> 140
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<400> 140
Cys Val Arg His Gly Tyr Phe Asp Val Trp
1 5 10

<210> 141
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<400> 141
Ser Gly Tyr Thr Phe Thr Ser Tyr Arg Met
1 5 10

<210> 142
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 142

Arg Ile Asp Pro Tyr Asp Ser Gly Thr His
1 5 10

<210> 143

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 143

Cys Ala Phe Tyr Asp Gly Ala Tyr Trp
1 5

<210> 144

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 144

Ser Gly Phe Asn Ile Lys Asp Thr Tyr Met
1 5 10

<210> 145

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 145

Arg Ile Asp Pro Ala Asn Gly Asn Thr Lys
1 5 10

<210> 146

<211> 9

<212> PRT

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<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 146

Cys Ala Ser Tyr Asp Pro Asp Tyr Trp
1 5

<210> 147

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 147

Ser Gly Tyr Ser Phe Thr Asp Tyr Thr Met
1 5 10

<210> 148

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 148

Leu Ile Asn Pro Tyr Asn Gly Gly Thr Arg
1 5 10

<210> 149

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 149

Cys Ala Arg Asp Thr Thr Ala Thr Tyr Tyr Phe Asp Tyr Trp
1 5 10

<210> 150

<211> 10

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<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 150

Ser Gly Tyr Met Phe Thr Asn His Gly Met
1 5 10

<210> 151

<211> 10

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<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 151

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr
1 5 10

<210> 152

<211> 12

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 152

Cys Ala Arg Arg Val Ala Thr Tyr Phe Asp Val Trp
1 5 10

<210> 153

<211> 10

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<400> 153

Ser Gly Tyr Met Phe Thr Asn Tyr Gly Met
1 5 10

<210> 154

<211> 10

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<400> 154

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr
1 5 10

<210> 155

<211> 12

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<400> 155

Cys Thr Arg Arg Ser His Ile Thr Leu Asp Tyr Trp
1 5 10

<210> 156

<211> 10

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 156

Ser Gly Tyr Ile Phe Thr Asn Tyr Gly Met
1 5 10

<210> 157

<211> 10

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<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 157

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr
1 5 10

<210> 158

<211> 12

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<400> 158

Cys	Ala	Arg	Arg	Arg	Thr	Thr	Ala	Phe	Asp	Tyr	Trp
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<210> 159

<211> 10

<212> PRT

<213> Artificial Sequence

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<400> 159

Ser	Gly	Phe	Asn	Ile	Lys	Asp	Tyr	Tyr	Ile
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<210> 160

<211> 10

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 160

Trp	Ile	Asp	Pro	Glu	Asn	Gly	Arg	Thr	Glu
1				5					10

<210> 161

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 161

Cys	Asn	Asn	Gly	Asn	Tyr	Val	Arg	His	Tyr	Tyr	Phe	Asp	Tyr	Trp
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<210> 162
<211> 10
<212> PRT
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<400> 162
Ser Gly Tyr Thr Phe Ile Asn Tyr Gly Met
1 5 10

<210> 163
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<400> 163
Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr
1 5 10

<210> 164
<211> 12
<212> PRT
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Cys Thr Arg Arg Arg Glu Ile Thr Phe Asp Tyr Trp
1 5 10

<210> 165
<211> 10
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<400> 165
Ser Gly Tyr Thr Phe Thr Asp Tyr Phe Ile
1 5 10

<210> 166
<211> 10
<212> PRT
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<400> 166
Glu Ile Tyr Pro Gly Ser Ser Asn Thr Tyr
1 5 10

<210> 167
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<220>
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<400> 167
Cys Ala Arg Ser Gly Ile Ser Pro Phe Thr Tyr Trp
1 5 10

<210> 168
<211> 10
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<400> 168
Ser Gly Tyr Ile Phe Thr Gly Tyr Asn Ile
1 5 10

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<400> 169

Ala Val Tyr Pro Gly Asn Gly Asp Thr Ser
1 5 10

<210> 170

<211> 11

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peptide

<400> 170

Cys Ala Lys Tyr Asp Arg Phe Phe Ala Ser Trp
1 5 10

<210> 171

<211> 8

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<223> Description of Artificial Sequence: Synthetic
peptide

<400> 171

Ser Gln Gly Ile Ser Asn His Leu
1 5

<210> 172

<211> 5

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peptide

<400> 172

Tyr Phe Thr Ser Ser
1 5

<210> 173

<211> 11

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peptide

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1 5 10

<210> 174
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peptide

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Ser Gln Gly Ile Arg Asn Tyr Leu
1 5

<210> 175
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peptide

<400> 175
Tyr Phe Thr Ser Ser
1 5

<210> 176
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peptide

<400> 176
Cys Gln Gln Tyr Ser Asn Leu Pro Tyr Thr Phe
1 5 10

<210> 177
<211> 8
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<400> 177

Ser Gln Gly Ile Ser Asn His Leu
1 5

<210> 178

<211> 5

<212> PRT

<213> Artificial Sequence

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<400> 178

Tyr Phe Thr Ser Ser
1 5

<210> 179

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 179

Cys Gln Gln Tyr Ser Asn Leu Pro Tyr Thr Phe
1 5 10

<210> 180

<211> 8

<212> PRT

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<223> Description of Artificial Sequence: Synthetic peptide

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Ser Gln Gly Ile Asn Asn Tyr Leu
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<210> 181

<211> 5

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<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 181

Tyr Tyr Thr Ser Ser
1 5

<210> 182

<211> 11

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 182

Cys Gln Gln Tyr Ser Lys Ile Pro Tyr Thr Cys
1 5 10

<210> 183

<211> 8

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<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 183

Ser Gln Gly Ile Ser Asn His Leu
1 5

<210> 184

<211> 5

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<400> 184

Tyr Phe Thr Ser Ser
1 5

<210> 185

<211> 11

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<400> 185

Cys Gln Gln Tyr Ser Asn Leu Pro Tyr Thr Phe
1 5 10

<210> 186

<211> 12

<212> PRT

<213> Artificial Sequence

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<400> 186

Ser Gln Ser Val Asp His Asp Gly Asp Ser Tyr Met
1 5 10

<210> 187

<211> 5

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<213> Artificial Sequence

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<400> 187

Tyr Ala Ala Ser Asn
1 5

<210> 188

<211> 10

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<400> 188

Cys Gln Gln Asn Tyr Glu Asp Pro Thr Phe
1 5 10

<210> 189
<211> 12
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<400> 189
Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Met
1 5 10

<210> 190
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<212> PRT
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<400> 190
Tyr Ala Ala Ser Asn
1 5

<210> 191
<211> 10
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<400> 191
Cys Gln Gln Ser Asn Glu Asp Pro Thr Phe
1 5 10

<210> 192
<211> 8
<212> PRT
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<400> 192
Ser Gln Asp Ile Ser Asn Tyr Leu
1 5

<210> 193
<211> 5
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<400> 193
Tyr Tyr Thr Ser Arg
1 5

<210> 194
<211> 11
<212> PRT
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<220>
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<400> 194
Cys Gln Gln Gly Asp Ala Leu Pro Trp Thr Phe
1 5 10

<210> 195
<211> 8
<212> PRT
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<400> 195
Ser Gln Asp Ile Ser Thr Tyr Leu
1 5

<210> 196
<211> 5
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<213> Artificial Sequence

<220>
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<400> 196

Phe Tyr Thr Ser Arg
1 5

<210> 197
<211> 11
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<220>
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peptide

<400> 197
Cys Gln Gln Gly Asn Ser Leu Pro Phe Thr Phe
1 5 10

<210> 198
<211> 9
<212> PRT
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<220>
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peptide

<400> 198
Thr Ser Ser Ile Ser Ser Ser Tyr Leu
1 5

<210> 199
<211> 5
<212> PRT
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peptide

<400> 199
Tyr Gly Thr Ser Asn
1 5

<210> 200
<211> 11
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<220>
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peptide

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Cys Gln Gln Trp Ser Ser Arg Pro Pro Thr Phe
1 5 10

<210> 201
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<212> PRT
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peptide

<400> 201
Asn Ser Ser Val Ser Ser Ser Tyr Leu
1 5

<210> 202
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<212> PRT
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peptide

<400> 202
Tyr Gly Thr Ser Asn
1 5

<210> 203
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peptide

<400> 203
Cys Gln Gln Tyr Ser Gly Tyr Pro Leu Thr Phe
1 5 10

<210> 204
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<400> 204

Thr Ser Ser Ile Ser Ser Ser Tyr Leu
1 5

<210> 205

<211> 5

<212> PRT

<213> Artificial Sequence

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<400> 205

Tyr Gly Thr Ser Asn
1 5

<210> 206

<211> 11

<212> PRT

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 206

Cys Gln Gln Tyr Ser Asp Tyr Pro Leu Thr Phe
1 5 10

<210> 207

<211> 9

<212> PRT

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<400> 207

Thr Ser Ser Ile Ser Ser Ser Tyr Leu
1 5

<210> 208

<211> 5

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<400> 208

Tyr Gly Thr Ser Asn
1 5

<210> 209

<211> 11

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<400> 209

Cys Gln Gln Arg Ser Tyr Phe Pro Phe Thr Phe
1 5 10

<210> 210

<211> 8

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 210

Ser Glu Asn Ile Tyr Tyr Asn Leu
1 5

<210> 211

<211> 5

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 211

Tyr Asn Ala Asn Ser
1 5

<210> 212

<211> 11

<212> PRT
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<400> 212

Cys	Lys	Gln	Val	Tyr	Asp	Val	Pro	Phe	Thr	Phe
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<210> 213

<211> 8

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<400> 213

Ser	Glu	Asn	Ile	Tyr	Gly	Tyr	Phe
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<210> 214

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 214

Tyr	Asn	Ala	Lys	Thr
1			5	

<210> 215

<211> 11

<212> PRT

<213> Artificial Sequence

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<400> 215

Cys	Gln	His	His	Tyr	Gly	Thr	Pro	Phe	Thr	Phe
1				5					10	

<210> 216
<211> 8
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<400> 216
Ser Gln Asp Ile Asn Asn Tyr Ile
1 5

<210> 217
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<212> PRT
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<220>
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<400> 217
His Tyr Thr Ser Thr
1 5

<210> 218
<211> 10
<212> PRT
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<400> 218
Cys Leu Gln Tyr Asp Asn Leu Trp Thr Phe
1 5 10

<210> 219
<211> 8
<212> PRT
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<400> 219
Ser Gln Asp Ile Asn Lys Tyr Ile
1 5

<210> 220
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<400> 220
His Tyr Thr Ser Thr
1 5

<210> 221
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<400> 221
Cys Leu Gln Tyr Asp Asn Leu Trp Thr Phe
1 5 10

<210> 222
<211> 8
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Ser Glu Asn Ile Tyr Ser Tyr Leu
1 5

<210> 223
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<400> 223

Tyr Asn Ala Lys Thr
1 5

<210> 224
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peptide

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Cys Gln His His Tyr Gly Tyr Pro Tyr Thr Phe
1 5 10

<210> 225
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peptide

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Ser Gln Gly Ile Arg Asn Tyr Leu
1 5

<210> 226
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peptide

<400> 226
Tyr His Thr Ser Thr
1 5

<210> 227
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peptide

<400> 227

Cys Gln Gln Tyr Ser Asn Leu Pro Leu Thr Phe
1 5 10

<210> 228

<211> 8

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<223> Description of Artificial Sequence: Synthetic
peptide

<400> 228

Ser Gln Asp Val Arg Thr Asp Val
1 5

<210> 229

<211> 5

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<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 229

Tyr Ser Ala Ser Phe
1 5

<210> 230

<211> 11

<212> PRT

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peptide

<400> 230

Cys Gln Gln His Tyr Thr Ser Pro Trp Thr Phe
1 5 10

<210> 231

<211> 8

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<400> 231

Ser Gln Asp Val Ile Thr Ala Val
1 5

<210> 232

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 232

Tyr Ser Ala Ser Tyr
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<210> 233

<211> 11

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<400> 233

Cys Gln Gln His Tyr Ser Thr Pro Trp Thr Phe
1 5 10

<210> 234

<211> 8

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<400> 234

Ser Gln Ser Ile Gly Thr Ser Ile
1 5

<210> 235

<211> 5

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 235

Lys Ser Ala Ser Glu
1 5

<210> 236

<211> 11

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<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 236

Cys Gln Gln Ser Asn Arg Trp Pro Leu Thr Phe
1 5 10

<210> 237

<211> 12

<212> PRT

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<400> 237

Ser Ser Gln Ser Leu Leu Asn Gln Lys Asn Tyr Leu
1 5 10

<210> 238

<211> 5

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<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 238

Tyr Trp Ala Ser Thr
1 5

<210> 239

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<400> 239

Cys Gln Asn Asp Tyr Asp Tyr Pro Tyr Thr Phe
1 5 10

<210> 240

<211> 9

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<400> 240

Ser Ser Ser Val Ser Ser Ser Tyr Leu
1 5

<210> 241

<211> 5

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 241

Tyr Ser Thr Ser Asn
1 5

<210> 242

<211> 11

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 242

Cys His Gln Tyr His Arg Ser Pro Leu Thr Phe
1 5 10

<210> 243
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peptide

<400> 243
Ser Glu Asn Ile Tyr Tyr Asn Leu
1 5

<210> 244
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peptide

<400> 244
Tyr Asn Ala Asn Ser
1 5

<210> 245
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peptide

<400> 245
Cys Gln Gln Thr Phe Asp Val Pro Trp Thr Phe
1 5 10

<210> 246
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peptide

<400> 246
Ser Gln Thr Ile Gly Thr Ser Ile
1 5

<210> 247
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peptide

<400> 247
Lys Asn Ala Ser Glu
1 5

<210> 248
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peptide

<400> 248
Cys Gln Gln Ser Asn Ser Trp Pro Leu Thr Tyr
1 5 10

<210> 249
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peptide

<400> 249
Ser Gln Ser Leu Leu Tyr Ser Ser Asp Gln Lys Asn Tyr Leu
1 5 10

<210> 250
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peptide

<400> 250

Tyr Trp Ala Ser Thr
1 5

<210> 251
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peptide

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1 5 10

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peptide

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1 5

<210> 253
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peptide

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Tyr Asp Thr Ser Lys
1 5

<210> 254
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peptide

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Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe
1 5 10

<210> 255
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peptide

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Ser Glu Asn Ile Tyr Tyr Asn Leu
1 5

<210> 256
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peptide

<400> 256
Tyr Asn Ala Asn Ser
1 5

<210> 257
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peptide

<400> 257
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1 5 10

<210> 258
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<400> 258

Ser Ser Ser Leu Ser Tyr Met
1 5

<210> 259

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 259

Tyr Asp Thr Ser Asn
1 5

<210> 260

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 260

Cys Gln Gln Trp Ser Ser Phe Pro Pro Thr Phe
1 5 10

<210> 261

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 261

Ser Gln Arg Ile Gly Thr Ser Met
1 5

<210> 262

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 262

Lys Ser Ala Ser Glu
1 5

<210> 263

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 263

Cys Gln Gln Ser Asn Ser Trp Pro Leu Thr Phe
1 5 10

<210> 264

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 264

Ser Gln Ser Ile Gly Thr Ser Ile
1 5

<210> 265

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 265

Lys Ser Ala Ser Glu
1 5

<210> 266

<211> 11

<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 266

Cys Gln Gln Ser Asn Ser Trp Pro Leu Thr Phe
1 5 10

<210> 267

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 267

Ser Gln Asn Ile Gly Thr Ser Ile
1 5

<210> 268

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 268

Lys Asp Ala Ser Glu
1 5

<210> 269

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 269

Cys Gln Gln Ser Asp Ser Trp Pro Leu Thr Phe
1 5 10

<210> 270
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 270
Ile Ser Ser Val Ser Tyr Met
1 5

<210> 271
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 271
Tyr Ala Thr Ser Asn
1 5

<210> 272
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 272
Cys Gln Gln Trp Ser Ser Asn Pro Arg Thr Phe
1 5 10

<210> 273
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 273
Ser Gln Thr Ile Ala Thr Ser Ile
1 5

<210> 274
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 274
Lys Asn Ala Ser Glu
1 5

<210> 275
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 275
Cys Gln Gln Ser Asn Ser Trp Pro Leu Thr Phe
1 5 10

<210> 276
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 276
Ser Gln Ser Leu Val His Ser Asn Gly Asn Thr Tyr Leu
1 5 10

<210> 277
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 277

Tyr Lys Val Ser Asn
1 5

<210> 278
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 278
Cys Trp Gln Asn Thr His Phe Pro Gln Thr Phe
1 5 10

<210> 279
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 279
Asn Glu Ser Val Glu Tyr Ser Gly Thr Ser Leu Met
1 5 10

<210> 280
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 280
Ser Ala Ala Ser Asn
1 5

<210> 281
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 281

Cys Gln Gln Ser Arg Gln Val Pro Leu Thr Phe
1 5 10

<210> 282

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 282

Gln Val Thr Leu Lys Glu Ser Gly Pro Val Leu Val Lys Pro Thr Glu
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Gly Met Gly Val Gly Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu
35 40 45

Trp Val Ala His Ile Trp Trp Asp Asp Asp Val Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Ala Ser Lys Asp Gln Val
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Val Arg Arg Arg Ala Thr Gly Thr Gly Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 283

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 283

Asn Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Val Gly Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Trp Thr Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys His Gln Tyr Asn Ser Tyr Asn Thr
85 90 95

Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 284

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 284

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Glu Asn Gly Ser Asp Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Gly Ala Val Ser Tyr Phe Asp Val Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 285

<211> 109

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 285

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Leu Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105

<210> 286

<211> 438

<212> PRT

<213> Homo sapiens

<400> 286

Met Val Cys Ser Gln Ser Trp Gly Arg Ser Ser Lys Gln Trp Glu Asp
1 5 10 15

Pro Ser Gln Ala Ser Lys Val Cys Gln Arg Leu Asn Cys Gly Val Pro
20 25 30

Leu Ser Leu Gly Pro Phe Leu Val Thr Tyr Thr Pro Gln Ser Ser Ile
35 40 45

Ile Cys Tyr Gly Gln Leu Gly Ser Phe Ser Asn Cys Ser His Ser Arg
50 55 60

Asn Asp Met Cys His Ser Leu Gly Leu Thr Cys Leu Glu Pro Gln Lys
65 70 75 80

Thr Thr Pro Pro Thr Thr Arg Pro Pro Pro Thr Thr Thr Pro Glu Pro
85 90 95

Thr Ala Pro Pro Arg Leu Gln Leu Val Ala Gln Ser Gly Gly Gln His
100 105 110

Cys Ala Gly Val Val Glu Phe Tyr Ser Gly Ser Leu Gly Gly Thr Ile
115 120 125

Ser Tyr Glu Ala Gln Asp Lys Thr Gln Asp Leu Glu Asn Phe Leu Cys
130 135 140

Asn Asn Leu Gln Cys Gly Ser Phe Leu Lys His Leu Pro Glu Thr Glu
145 150 155 160

Ala Gly Arg Ala Gln Asp Pro Gly Glu Pro Arg Glu His Gln Pro Leu
165 170 175

Pro Ile Gln Trp Lys Ile Gln Asn Ser Ser Cys Thr Ser Leu Glu His
180 185 190

Cys Phe Arg Lys Ile Lys Pro Gln Lys Ser Gly Arg Val Leu Ala Leu
195 200 205

Leu Cys Ser Gly Phe Gln Pro Lys Val Gln Ser Arg Leu Val Gly Gly
210 215 220

Ser Ser Ile Cys Glu Gly Thr Val Glu Val Arg Gln Gly Ala Gln Trp
225 230 235 240

Ala Ala Leu Cys Asp Ser Ser Ser Ala Arg Ser Ser Leu Arg Trp Glu
245 250 255

Glu Val Cys Arg Glu Gln Gln Cys Gly Ser Val Asn Ser Tyr Arg Val
260 265 270

Leu Asp Ala Gly Asp Pro Thr Ser Arg Gly Leu Phe Cys Pro His Gln
275 280 285

Lys Leu Ser Gln Cys His Glu Leu Trp Glu Arg Asn Ser Tyr Cys Lys
290 295 300

Lys Val Phe Val Thr Cys Gln Asp Pro Asn Pro Ala Gly Leu Ala Ala
305 310 315 320

Gly Thr Val Ala Ser Ile Ile Leu Ala Leu Val Leu Leu Val Val Leu
325 330 335

Leu Val Val Cys Gly Pro Leu Ala Tyr Lys Lys Leu Val Lys Lys Phe
340 345 350

Arg Gln Lys Lys Gln Arg Gln Trp Ile Gly Pro Thr Gly Met Asn Gln
355 360 365

Asn Met Ser Phe His Arg Asn His Thr Ala Thr Val Arg Ser His Ala
370 375 380

Glu Asn Pro Thr Ala Ser His Val Asp Asn Glu Tyr Ser Gln Pro Pro
385 390 395 400

Arg Asn Ser His Leu Ser Ala Tyr Pro Ala Leu Glu Gly Ala Leu His
405 410 415

Arg Ser Ser Met Gln Pro Asp Asn Ser Ser Asp Ser Asp Tyr Asp Leu
420 425 430

His Gly Ala Gln Arg Leu
435

<210> 287

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 287

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser Pro Pro Ser Pro
1 5 10 15