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IMMUNOMODULATORY ANTIBODY-DRUG CONJUGATES

Abstract

The present disclosure provides, inter alia, antibody-drug conjugates that are useful in treating various diseases such as cancer.

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Background/Summary

REFERENCE TO THE SEQUENCE LISTING

[0001] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled SGENE.010WO.xml created on Apr. 26, 2023, which is 954,186 bytes in size. The information in the electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

BACKGROUND

Field

[0002] The present invention relates to the fields of chemistry and medicine. More particularly, the present invention relates to antibody-drug conjugates, compositions, their preparation, and their use as therapeutic agents.

Description of the Related Art

[0003] The cGAS-STING pathway is an innate immune pathway that recognizes intracellular DNA and triggers a type I interferon and inflammatory cytokine response that is important for both anti-viral and anti-tumor immunity. Upon DNA binding, cGMP-AMP synthase (cGAS) produces cGAMP, which is the endogenous ligand of STING. See, e.g., Villanueva, *Nat. Rev. Drug Disc.* 2019: 18; 15. At the molecular level, upon activation by cGAMP, the transmembrane STING dimer translocates from the endoplasmic reticulum to the Golgi apparatus, ultimately recruiting TANK-binding kinase 1 (TBK1) and the transcription factor interferon regulatory factor 3 (IRF3), leading to induction of type I interferons (IFNs) and an inflammatory response. See Konno, et al., *Cell* 2013: 155; 688-698. This innate immune pathway must be tightly regulated as excessive cGAS-STING activity has been linked to various autoimmune and inflammatory disorders. See Barber, *Nat. Rev. Immunol.* 2015: 15; 760-770; see also, Liu, et al., *N. Engl. J. Med.* 2014: 371; 507-518.

[0004] Exogenous STING agonists can help to overcome the immunosuppressive tumor microenvironment by activating an immune response against a tumor, resulting in tumor regression. See Sun, et al., *Science* 2013: 6121; 786-791; see also, Corrales and Gajewski, *Clinc. Cancer Res.* 2015: 21; 4774-4779. Examples include nucleotide-based STING agonists, which are, like the endogenous ligands, cyclic di-nucleotides. These compounds are typically charged and hydrophilic, susceptible to enzymatic degradation, and have poor bioavailability and pharmacokinetics. Thus, there remains a need for STING agonists with improved pharmacological properties that avoid systemic cytokine induction.

SUMMARY

[0005] Some embodiments described herein relate to antibody-drug conjugates (ADCs) that can elicit a localized immune response to target cells, and hence, exhibit reduced off-target toxicity, such as that observed with systemically administered immunostimutory compounds.

[0006] Some embodiments provide an antibody-drug conjugate (ADC) comprising: [0007] an antigen-binding protein or antigen-binding fragment thereof (e.g., an antibody); and [0008] a compound of Formula (I) as described herein; [0009] wherein the compound of Formula (I) is conjugated to the antigen-binding protein or antigen-binding fragment thereof via a succinimide or hydrolyzed succinimide covalently linked to a sulfur atom of a cysteine residue of the antigen-binding protein or antigen-binding fragment thereof.

[0010] Some embodiments provide an antibody-drug conjugate (ADC) having the formula:

Ab-(S*-M.sup.1-(D)).sub.p

wherein: [0011] Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody); [0012] each S* is a sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof; [0013] M.sup.1 is a succinimide or a hydrolyzed succinimide;

[0014] subscript p is an integer from 2 to 8; and [0015] each (D) is a Drug-Linker Unit of Formula (I), as described herein.
[0016] In some embodiments, Formula (I) has the structure:
##STR00001##
wherein variable groups R.sup.1, R.sup.2, R.sup.3, X.sup.A, and X.sup.B are as defined herein.
[0017] Some embodiments provide a compound of Formula (II):
##STR00002##
wherein M, L, R.sup.1, R.sup.2, R.sup.3, X.sup.A, and X.sup.B are as defined herein.
[0018] Some embodiments provide an antibody-drug conjugate having the structure:
##STR00003## [0019] wherein Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody), S* is the sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof, subscript p is an integer from 2 to 8, and the remaining variable groups are as defined herein. In some embodiments, Ab binds CD228. In some embodiments, Ab binds αvβ6. In some embodiments, Ab binds B7-H4.
[0020] Some embodiments provide an antibody-drug conjugate having the structure:
##STR00004## [0021] wherein Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody), S* is the sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof, subscript p is an integer from 2 to 8, and the remaining variable groups are as defined herein. In some embodiments, Ab binds CD228. In some embodiments, Ab binds αvβ6. In some embodiments, Ab binds B7-H4.
[0022] Some embodiments provide an antibody-drug conjugate having the structure:
##STR00005## [0023] wherein Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody), S* is the sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof, subscript p is an integer from 2 to 8, and the remaining variable groups are as defined herein. In some embodiments, Ab binds CD228. In some embodiments, Ab binds αvβ6. In some embodiments, Ab binds B7-H4.
[0024] Some embodiments provide an antibody-drug conjugate (ADC) having the formula:

Ab-(S*-(D′)).sub.p
wherein: [0025] Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody); [0026] each S* is a sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof; [0027] D′ is a Drug-Linker unit that is a radical of the compound of Formula (IV), as described herein; and [0028] subscript p is an integer from 2 to 8.
[0029] In some embodiments, Formula (IV) has the structure:
##STR00006##
wherein the variables are as defined herein.
[0030] Some embodiments provide an antibody-drug conjugate having the structure:
##STR00007##
wherein Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody), S* is the sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof, subscript p is an integer from 2 to 8, and the remaining variable groups are as defined herein. In some embodiments, Ab binds CD228. In some embodiments, Ab binds αvβ6. In some embodiments, Ab binds B7-H4.
[0031] Some embodiments provide an antibody-drug conjugate having the structure:
##STR00008## [0032] wherein Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody), S* is the sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof, subscript p is an integer from 2 to 8, and the remaining variable groups are as defined herein. In some embodiments, Ab binds CD228. In some embodiments, Ab binds αvβ6. In some embodiments, Ab binds B7-H4.
[0033] Some embodiments provide a compound of Formula (III):

##STR00009##
wherein the variables are as defined herein.
[0034] Some embodiments provide a compound having the structure of Formula (V):
##STR00010##
wherein the variables are as defined herein.
[0035] Some embodiments provide a composition comprising a distribution of ADCs as described herein.
[0036] Some embodiments provide a method of treating cancer in a subject in need thereof, comprising administering a therapeutically effective amount of an ADC composition, as described herein, to the subject.
[0037] Some embodiments provide a method of treating cancer in a subject in need thereof, comprising administering a therapeutically effective amount of an ADC, as described herein, to the subject.
[0038] Some embodiments provide a method of inducing an anti-tumor immune response in a subject in need thereof, comprising administering a therapeutically effective amount of an ADC composition, as described herein, to the subject.
[0039] Some embodiments provide a method of inducing an anti-tumor immune response in a subject in need thereof, comprising administering a therapeutically effective amount of an ADC, as described herein, to the subject.

Description

BRIEF DESCRIPTION OF THE DRAWINGS
[0040] FIG. **1** illustrates the response of THP1-Dual™ cells (also referred to as THP1 dual reporter cells) to various small molecule STING agonists.
[0041] FIG. **2** illustrates the response of wild type (WT) and STING-deficient murine bone marrow-derived macrophages to various small molecule STING agonists.
[0042] FIG. **3** illustrates the response of THP1 dual reporter cells to ADCs comprising a non-binding or targeted antibody conjugated to either compound 11 (cleavable linker with compound 1), compound 12 (non-cleavable linker with compound 12a), or compounds 13 or 14 (cleavable linkers with compound 12a).
[0043] FIG. **4** illustrates the response of THP1 dual reporter cells to compound 12 (non-cleavable linker with compound 12a) and compound 16 (cysteine adduct of compound 12 and free drug released from ADCs containing compound 12).
[0044] FIG. **5** illustrates the response of THP1 dual reporter cells to compounds 12a and 15b as a free drug or conjugated to a non-binding or targeted antibody (ADC of compounds 12 and 15) following incubation for 48 hours.
[0045] FIGS. **6**A and **6**B illustrate the response of SU-DHL-1 lymphoma cells to ADCs comprising a non-binding, antigen C-targeted or PD-L1-targeted antibody conjugated to compound 11 (cleavable linker with compound 1). Both cytokine production (MIP-1α) (FIG. **6**A) and viability (FIG. **6**B) are plotted.
[0046] FIG. **7** illustrates the response of THP1 dual reporter cells cultured alone or co-cultured with HEK 293T cells engineered to express target antigen C to ADCs comprising an antigen C-targeted mAb with a hIgG1 LALAPG backbone conjugated to compounds 12, 13, or 14.
[0047] FIG. **8** illustrates the bystander activity of ADCs comprising either an EphA2-targeted mAb or a non-binding mAb with a mIgG2a WT or LALAPG backbone conjugated to compound 12 using Renca cancer cells and THP1 dual reporter cells.
[0048] FIGS. **9**A-**9**C illustrate RFP+ MDA-MB-468 tumor cell killing (FIG. **9**A) and immune activation (CD8 T cell counts, FIG. **9**B; IP-10 production, FIG. **9**C) in response to treatment of

tumor cell and peripheral blood mononuclear cell (PBMC) co-cultures with compound 16 or conjugates consisting of a non-binding mAb or B7-H4-targeted mAb with a WT or LALAKA Fc backbone conjugated to compound 12. FIG. **9**A: RFP+ tumor cell confluence (96 hours); FIG. **9**B: CD8+ T cell counts (48 hours); FIG. **9**C IP-10 secretion (48 hours).

[0049] FIG. **10** illustrates RFP+ MDA-MB-468 tumor cell killing in response to treatment of tumor cell and peripheral blood mononuclear cell (PBMC) co-cultures with compound 16 or conjugates consisting of a αvβ6 or B7-H4-targeted mAb with a WT or LALAKA Fc backbone conjugated to compound 12. RFP+ tumor cell confluence at 96 hours is plotted.

[0050] FIG. **11** illustrates RFP+ HCT15 tumor cell killing in response to treatment of tumor cell and peripheral blood mononuclear cell (PBMC) co-cultures with compound 16 or conjugates of ααvβ6-targeted mAb with a WT Fc backbone conjugated to compound 12. RFP+ tumor cell confluence at 72 hours is plotted.

[0051] FIG. **12** illustrates RFP+ HT1080 tumor cell killing in response to treatment of tumor cell and peripheral blood mononuclear cell (PBMC) co-cultures with compound 16 or conjugates consisting of a non-binding mAb or CD228-targeted mAb with a WT Fc backbone conjugated to compound 12. RFP+ tumor cell confluence at 96 hours is plotted.

[0052] FIG. **13** illustrates RFP+ HT1080 tumor cell killing in response to treatment of tumor cell and peripheral blood mononuclear cell (PBMC) co-cultures with compound 16 or conjugates consisting of a non-binding mAb or CD228-targeted mAb with a WT or LALAKA Fc backbone conjugated to compound 12. RFP+ tumor cell confluence at 96 hours is plotted.

[0053] FIGS. **14**A and **14**B illustrate the response to q7dx3 ADC dosing (3 weekly doses) in a Renca tumor mouse model to evaluate various ADCs comprising a non-binding or EphA2-targeted mAb with a mIgG2a LALAPG backbone conjugated to compound 11 (dosed intraperitoneally), or compound 1 or (E)-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-(3-morpholinopropoxy)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazole-5-carboxamide tris(2,2,2-trifluoroacetate) (Compound A, a reference compound, dosed intravenously). FIG. **14**A: tumor growth; FIG. **14**B: % weight change.

[0054] FIGS. **15**A and **15**B illustrate the response to q7dx3 ADC dosing (3 weekly doses) in a Renca tumor mouse model to evaluate various ADCs comprising a non-binding or EphA2-targeted mAb with a mIgG2a LALAPG backbone conjugated to compounds 11 or 12 (dosed intraperitoneally). FIG. **15**A: tumor growth; FIG. **15**B: % weight change.

[0055] FIGS. **16**A and **16**B illustrate the response to q7dx3 ADC dosing (3 weekly doses) in a Renca tumor mouse model, which is engineered to express a human protein, to evaluate various ADCs comprising a non-binding or EphA2-targeted mAb with either a mIgG2a wild type (WT) or a mIgG2a LALAPG backbone conjugated to compounds 12 or 15. FIG. **16**A: tumor growth; FIG. **16**B: % weight change.

[0056] FIG. **17** illustrates the response to q7dx3 dosing (3 weekly doses, intraperitoneally) in a Renca tumor mouse model to evaluate the ADC comprising an EphA2-targeted mAb with a mIgG2a LALAPG backbone conjugated to compound 12 or unconjugated compound 12a.

[0057] FIG. **18** illustrates the response to q7dx3 dosing (3 weekly doses) of various compounds in a Renca tumor model to evaluate a PD-L1-targeted mAb, and various ADCs comprising a non-binding, PD-L1-targeted or antigen C-targeted mAb conjugated to compound 11.

[0058] FIG. **19** illustrates the response to q7dx3 dosing (3 weekly doses) of various compounds in a CT26 tumor model to evaluate unconjugated compound 1, a PD-L1-targeted mAb, and various ADCs comprising a non-binding, antigen C, PD-L1, or EphA2-targeted mAb conjugated to compound 11.

[0059] FIGS. **20**A-D illustrate the response to q7dx3 (3 weekly doses) or a single dose of ADC, as indicated, in a MC38 tumor model to evaluate various ADCs comprising a non-binding or EphA2-targeted mAb with a mIgG2a LALAPG backbone conjugated to compound 12. Mice that achieved

complete tumor regression in response to ADC treatment were rechallenged with MC38 tumor cells and tumor growth was monitored. FIG. **20**A: tumor growth (wild type (WT) mice); FIG. **20**B: % weight change (WT mice); FIG. **20**C: tumor growth (STING-deficient Tmem173.sup.gt mice); FIG. **20**D: tumor growth following MC38 tumor rechallenge.

[0060] FIGS. **21**A and **21**B illustrate the response to q7dx3 mAb or ADC dosing (3 weekly doses indicated by the arrow heads) in a 4T1 tumor model to evaluate various ADCs comprising a non-binding or EphA2-targeted mAb with a mIgG2a LALAPG backbone conjugated to compound 12. FIG. **21**A: tumor growth; FIG. **21**B: % weight change.

[0061] FIGS. **22**A and **22**B illustrates the response to q7dx3 ADC dosing (3 weekly doses) in a Renca tumor mouse model, in which Renca tumor cells are engineered to express murine B7-H4, to evaluate various ADCs comprising a non-binding or B7-H4-targeted mAb with either a mIgG2a wild type (WT) or a mIgG2a LALAKA or LALAPG backbone conjugated to compound 12. FIG. **22**A: tumor growth; FIG. **22**B: % weight change.

[0062] FIGS. **23**A and **23**B illustrate the response to q7dx3 ADC dosing (3 weekly doses) or a single dose, as indicated, in an EMT6 tumor mouse model, in which EMT6 tumor cells are engineered to express murine B7-H4, to evaluate various ADCs comprising a non-binding or B7-H4-targeted mAb with either a mIgG2a wild type (WT) or a mIgG2a LALAKA backbone conjugated to compound 12. FIG. **23**A: tumor growth; FIG. **23**B: % weight change.

[0063] FIG. **24** illustrates the response to q7dx3 ADC dosing (3 weekly doses) or a single dose, as indicated, in an CT26 tumor mouse model, in which CT26 tumor cells are engineered to express murine αvβ6, to evaluate various ADCs comprising a non-binding or αvβ6-targeted mAb with either a mIgG2a wild type (WT) or a mIgG2a LALAKA backbone conjugated to compound 12.

[0064] FIG. **25** illustrates the response to a single ADC dose (intraperitoneally) or q4dx3 compound A (3 doses 4 days apart, intravenously) in an LL2 tumor mouse model, in which LL2 tumor cells are engineered to express human CD228, to evaluate various ADCs comprising a non-binding or CD228-targeted mAb with hIgG1 wild type (WT) backbone conjugated to compound 12.

[0065] FIG. **26** illustrates the response to a q4dx2 ADC dosing (2 doses 4 days apart, intraperitoneally) and/or q4dx3 anti-PD1 mAb dosing (3 doses 4 days apart, intraperitoneally) in an LL2 tumor mouse model, in which LL2 tumor cells are engineered to express human CD228, to evaluate various ADCs comprising a non-binding or CD228-targeted mAb with hIgG1 wild type (WT) backbone conjugated to compound 12 as a monotherapy or in combination with a PD-1-targeted mAb.

[0066] FIGS. **27**A and **27**B illustrate the response to a q4dx2 ADC dosing (2 doses 4 days apart, intraperitoneally) and/or q7dx3 Compound A dosing (3 doses 7 days apart, intravenously) in an LL2 tumor mouse model, in which LL2 tumor cells are engineered to express human CD228. ADCs comprised a CD228-targeted mAb with hIgG1 or mIgG2a wild type (WT) Fc backbone conjugated to compound 12. FIG. **27**A: tumor growth; FIG. **27**B: % weight change.

[0067] FIGS. **28**A and **28**B illustrate the response to a q7dx3 ADC dosing (3 doses 7 days apart, intravenously or intraperitoneally as indicated) in an LL2 tumor mouse model, in which LL2 tumor cells are engineered to express human CD228. ADCs comprised a non-binding mAb, EphA2-targeted mAb, or CD228-targeted mAb with a mIgG2a wild type (WT) or LALAKA backbone conjugated to compound 12. FIG. **28**A: tumor growth; FIG. **28**B: % weight change.

[0068] FIG. **29** illustrates the pharmacokinetic profile of an ADC comprising a [deglycosylated]non-binding mAb conjugated to compound 12 following administration to male C57BL/6 mice.

[0069] FIG. **30** illustrates the antitumor activity in response to a single dose (intravenous (i.v.) or intraperitoneal (i.p.), as indicated) of ADCs comprising a CD228-targeted mAb with a hIgG1 wild type (WT) Fc backbone conjugated to compound 12, 13, or 14 in an LL2 tumor mouse model in which LL2 tumor cells are engineered to express human CD228.

[0070] FIG. **31** illustrates the pharmacokinetic profile of a single dose (intravenous or intraperitoneal, as indicated) of ADCs comprising a CD228-targeted mAb with a hIgG1 wild type (WT) Fc backbone conjugated to compound 12, 13, or 14 in an LL2 tumor mouse model in which LL2 tumor cells are engineered to express human CD228.
[0071] FIG. **32** illustrates the antitumor activity in response to a single 1, 5, or 10 mg/kg dose (intravenous) of ADCs comprising a CD228-targeted mAb with a hIgG1 wild type (WT) Fe backbone conjugated to compound 12 in an LL2 tumor mouse model in which LL2 tumor cells are engineered to express human CD228.
[0072] FIG. **33** illustrates the pharmacokinetic profile of a single dose (intravenous) of ADCs comprising a CD228-targeted mAb with a hIgG1 wild type (WT) Fc backbone conjugated to compound 12 in an LL2 tumor mouse model in which LL2 tumor cells are engineered to express human CD228.
[0073] FIG. **34** illustrates the antitumor activity in response to a single 3 mg/kg dose (intraperitoneal) of various ADCs comprising a B7-H4 or αvβ6-targeted mAb conjugated to compound 12 in the MDAMB468 xenograft mouse model of breast cancer.
[0074] FIG. **35** illustrates RFP+ HT1080 tumor cell killing in response to treatment of tumor cell and peripheral blood mononuclear cell (PBMC) co-cultures with conjugates consisting of a CD228-targeted mAb with a WT or LALAKA Fc backbone conjugated to compound 11, 12, 13, 14, or 25. The ratio of RFP+ tumor cells at 120 hours relative to 0 hours is plotted.

DETAILED DESCRIPTION

[0075] Provided herein are antibody-drug conjugates (ADCs) that can elicit a localized immune response to target cells, and hence, reduced off-target toxicity, for example, as compared to the toxicity often observed with systemic administration of immunostimutory compounds, such as STING agonists. The in vivo toxicity of such compounds is often linked to systemic immune activation, resulting in both on- and off-target immune responses. The ADCs described herein include STING agonists as the drug payload to provide localized, selective induction of immune activation. See, e.g., Milling, et al., *Adv. Drug Deliv. Rev.* 2017: 114; 79-101; see also, Hu, et al., *EBioMedicine* 2019: 41; 497-508. This approach can deliver specific STING activation, as well as localized immune cell recruitment, while reducing systemic immune activation and its concomitant adverse effects.

Definitions

[0076] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present application; other, suitable methods and materials known in the art in some aspects of this disclosure are also used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entireties. In case of conflict, the present specification, including definitions, will control. When trade names are used herein, the trade name includes the product formulation, the generic drug, and the active pharmaceutical ingredient(s) of the trade name product, unless otherwise indicated by context.
[0077] The terms “a,” “an,” or “the” as used herein not only include aspects with one member, but also include aspects with more than one member. For instance, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a linker” includes reference to one or more such linkers, and reference to “the cell” includes reference to a plurality of such cells.
[0078] The term “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation, for example, within experimental variability and/or statistical experimental error, and thus the number or numerical range may vary up to ±10% of the stated number or numerical range. In reference to an ADC composition comprising a

distribution of ADCs as described herein, the average number of conjugated STING agonist compounds to an antibody in the composition can be an integer or a non-integer, particularly when the antibody is to be partially loaded. Thus, the term “about” recited prior to an average drug loading value is intended to capture the expected variations in drug loading within an ADC composition. The term “antigen-binding protein or an antigen-binding fragment thereof” as used herein refers to a peptide, polypeptide, protein, or fragment of a protein that has the ability to bind to a desired target antigen. Antigen-binding protein or an antigen-binding fragment thereof include antibodies, intact antibodies, and antibody fragments. In some aspects, the desired target antigen is CD228 or a fragment of CD228. In some aspects, the specified target antigen is αvβ6 or a fragment of αvβ6. In some aspects, the specified target antigen is B7-H4 or a fragment of B7-H4.

[0079] The term “antibody” as used herein covers intact monoclonal antibodies, polyclonal antibodies, monospecific antibodies, multispecific antibodies (e.g., bispecific antibodies), including intact antibodies and antigen binding antibody fragments, and reduced forms thereof in which one or more of the interchain disulfide bonds are disrupted, that exhibit the desired biological activity and provided that the antigen binding antibody fragments have the requisite number of attachment sites for the desired number of attached groups, such as a linker (L), as described herein. In some aspects, the linkers are attached via a succinimide or hydrolyzed succinimide to the sulfur atoms of cysteine residues of reduced interchain disulfide bonds and/or cysteine residues introduced by genetic engineering. The native form of an antibody is a tetramer and characterized by two identical pairs of immunoglobulin chains, each pair having one light chain and one heavy chain. In each pair, the light and heavy chain variable domains (VL and VH) are together primarily responsible for binding to an antigen. The light chain and heavy chain variable domains contains a framework region interrupted by three hypervariable regions, also called “complementarity determining regions” or “CDRs.” In some embodiments, the light chain and heavy chains also contain constant regions that are recognized by and interact with the immune system. (see, e.g., Janeway et al., 2001, *Immuno. Biology,* 5th Ed., *Garland Publishing*, New York). An antibody includes any isotype (e.g., IgG, IgE, IgM, IgD, and IgA) or subclass (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) thereof. The antibody is derivable from any suitable species. In some aspects, the antibody is of human or murine origin, and in some aspects the antibody is a human, humanized or chimeric antibody. In some aspects, antibodies are fucosylated to varying extents or afucosylated.

[0080] An “intact antibody” is one which comprises an antigen-binding variable region as well as light chain constant domains (C.sub.L) and heavy chain constant domains, C.sub.H1, C.sub.H2, C.sub.H3 and C.sub.H4, as appropriate for the antibody class. The constant domains are either native sequence constant domains (e.g., human native sequence constant domains) or amino acid sequence variants thereof.

[0081] An “antibody fragment” comprises a portion of an intact antibody, comprising the antigen-binding or variable region thereof. Antibody fragments of the present disclosure include at least one cysteine residue (natural or engineered) that provides a site for attachment of a linker and/or linker-drug compound. In some aspects, an antibody fragment includes Fab, Fab′, or F(ab′).sub.2.

[0082] As used herein the term “engineered cysteine residue” or “eCys residue” refers to a cysteine amino acid or a derivative thereof that is incorporated into an antibody. In some aspects, one or more eCys residues are incorporated into an antibody, and typically, the eCys residues are incorporated into either the heavy chain or the light chain of an antibody. Generally, incorporation of an eCys residue into an antibody is performed by mutagenizing a nucleic acid sequence of a parent antibody to encode for one or more amino acid residues with a cysteine or a derivative thereof. Suitable mutations include replacement of a desired residue in the light or heavy chain of an antibody with a cysteine or a derivative thereof, incorporation of an additional cysteine or a derivative thereof at a desired location in the light or heavy chain of an antibody, as well as adding an additional cysteine or a derivative thereof to the N- and/or C-terminus of a desired heavy or light chain of an amino acid. Further information can be found in U.S. Pat. No. 9,000,130, the contents

of which are incorporated herein in its entirety. Derivatives of cysteine (Cys) include but are not limited to beta-2-Cys, beta-3-Cys, homocysteine, and N-methyl cysteine.
[0083] In some aspects, the antibodies of the present disclosure include those having one or more engineered cysteine (eCys) residues. In some aspects, derivatives of cysteine (Cys) include, but are not limited to beta-2-Cys, beta-3-Cys, homocysteine, and N-methyl cysteine.
[0084] An “antigen” is an entity to which an antibody specifically binds.
[0085] The terms “CD228,” “melanotransferrin,” “MELTF,” “p97” and “MF12” are used interchangeably herein, and, unless otherwise specified, include any naturally occurring variants (e.g., splice variants, allelic variants), isoforms, and vertebrate species homologs of human CD228. The term encompasses “full length,” unprocessed CD228 as well as any form of CD228 that results from processing within a cell. The amino acid sequence of an exemplary human CD228 is provided in Uniprot #P08582. CD228 is a glycosylphosphatidylinositol-anchored glycoprotein and was first identified as a 97-kDa cell-surface marker for malignant melanoma cells. CD228 is overexpressed on a majority of clinical melanoma isolates and is also observed on many human carcinomas. CD228 has been shown to be expressed in a variety of cancers.
[0086] The terms “αvβ6,” “αvβ6,” “αvβ6,” “ανα6,” “alpha-v beta-6,” or “P6” are used interchangeably herein, and, unless otherwise specified, include any naturally occurring variants (e.g., splice variants, allelic variants), isoforms, and vertebrate species homologs of human αvβ6. The term encompasses “full length,” unprocessed αvβ6 as well as any form of αvβ6 that results from processing within a cell. An exemplary P6 human sequence is assigned GenBank accession number AAA36122. An exemplary αv human sequence is assigned NCBI NP_002201.1. αvβ6 is a cell adhesion receptor that binds extracellular matrix proteins such as fibronectin. αvβ6 is composed of an alpha v subunit and a beta 6 subunit, and is upregulated in multiple cancers, including non-small cell lung cancer (NSCLC). NSCLC is the most common type of lung cancer. In the past year, over 200,000 people were diagnosed with lung cancer, which is the leading cause of cancer death.
[0087] The terms “B7-H4,” “B7X,” “B7H4,” “B7S1,” “B7h.5,” “VCTN1,” or “PRO1291” are used interchangeably herein, and, unless otherwise specified, include any naturally occurring variant (e.g. splice variants, allelic variants), isoforms, and vertebrate species homologs of human B7-H4. The term encompasses “full length,” unprocessed B7-H4 as well as any form of B7-14 that results from processing within a cell. The amino acid sequence of an exemplary human B7-14 is provided in Uniprot #Q7Z7D3. B7-H4 is an immune regulatory molecule that shares homology with other B7 family members, including PD-L1. Human B7-H4 is encoded by VTCN1. It is a type I transmembrane protein comprised of both IgV and IgC ectodomains. While B7-H4 expression in healthy tissues is relatively limited at the protein level, B7-H4 is expressed in several solid tumors such as gynecological carcinomas of the breast, ovary, and endometrium. Expression of B7-H4 in tumors tends to correlate with poor prognosis. The receptor for B7-H4 is unknown, but it is believed to be expressed on T cells. B7-H4 is believed to directly inhibit T cell activity.
[0088] The terms “specific binding” and “specifically binds” mean that the antibody or antibody fragment thereof will bind, in a selective manner, with its corresponding target antigen and not with a multitude of other antigens. Typically, the antibody or antibody fragment binds with an affinity of at least about 1×10.sup.−7 M, for example, 10.sup.−8 M to 10.sup.−9 M, 10.sup.−10 M, 10.sup.−4 M, or 10.sup.−12 M and binds to the predetermined antigen with an affinity that is at least two-fold greater than its affinity for binding to a non-specific antigen (e.g., BSA, casein) other than the predetermined antigen or a closely-related antigen.
[0089] The term “amino acid” as used herein, refers to natural and non-natural, and proteogenic amino acids. Exemplary amino acids include, but are not limited to alanine, arginine, aspartic acid, asparagine, histidine, glycine, glutamic acid, glutamine, phenylalanine, lysine, leucine, serine, tyrosine, threonine, isoleucine, proline, tryptophan, valine, cysteine, methionine, ornithine, β-alanine, citrulline, serine methyl ether, aspartate methyl ester, glutamate methyl ester, homoserine

methyl ether, and N,N-dimethyl lysine.
[0090] A “sugar moiety” as used herein, refers to a monovalent radical of monosaccharide, for example, a pyranose or a furanose. A sugar moiety may comprise a hemiacetal or a carboxylic acid (from oxidation of the pendant —CH.sub.2OH group). In some aspects, the sugar moiety is in the β-D conformation. In some aspects, the sugar moiety is a glucose, glucuronic acid, or mannose group.
[0091] The term “inhibit” or “inhibition of” means to reduce by a measurable amount, or to prevent entirely (e.g., 100% inhibition).
[0092] The term “therapeutically effective amount” refers to an amount of an ADC as described herein that is effective to treat a disease or disorder in a mammal. In the case of cancer, the therapeutically effective amount of the ADC provides one or more of the following biological effects: reduction of the number of cancer cells; reduction of tumor size; inhibition of cancer cell infiltration into peripheral organs; inhibition of tumor metastasis; inhibition, to some extent, of tumor growth; and/or relief, to some extent, of one or more of the symptoms associated with the cancer. For cancer therapy, efficacy, in some aspects, is measured by assessing the time to disease progression (TTP) and/or determining the response rate (RR).
[0093] Unless otherwise indicated or implied by context, the term “substantial” or “substantially” refers to a majority, i.e. >50% of a population, of a mixture, or a sample, typically more than 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%.
[0094] The terms “intracellularly cleaved” and “intracellular cleavage” refer to a metabolic process or reaction occurring inside a cell, in which the cellular machinery acts on the ADC or a fragment thereof, to intracellularly release free drug from the ADC, or other degradant products thereof. The moieties resulting from that metabolic process or reaction are thus intracellular metabolites.
[0095] The terms “cancer” and “cancerous” refer to or describe the physiological condition or disorder in mammals that is typically characterized by unregulated cell growth. A “tumor” comprises multiple cancerous cells.
[0096] “Subject” as used herein refers to an individual to which an ADC is administered. Examples of a “subject” include, but are not limited to, a mammal such as a human, rat, mouse, guinea pig, non-human primate, pig, goat, cow, horse, dog, cat, bird and fowl. Typically, a subject is a rat, mouse, dog, non-human primate, or human. In some aspects, the subject is a human.
[0097] The terms “treat” or “treatment,” unless otherwise indicated or implied by context, refer to therapeutic treatment and prophylactic measures to prevent relapse, wherein the object is to inhibit an undesired physiological change or disorder, such as, for example, the development or spread of cancer. For purposes of the present disclosure, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. “Treatment” in some aspects also means prolonging survival as compared to expected survival if not receiving treatment.
[0098] In the context of cancer, the term “treating” includes any or all of: inhibiting growth of cancer cells or of a tumor; inhibiting replication of cancer cells, lessening of overall tumor burden or decreasing the number of cancer cells, and ameliorating one or more symptoms associated with the disease.
[0099] The term “salt,” as used herein, refers to organic or inorganic salts of a compound, such as a Drug Unit (D), a linker such as those described herein, or an ADC. In some aspects, the compound contains at least one amino group, and accordingly acid addition salts can be formed with the amino group. Exemplary salts include, but are not limited to, sulfate, trifluoroacetate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate,

ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, and pamoate (i.e., 1,1′-methylene-bis-(2-hydroxy-3-naphthoate)) salts. A salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion, or other counterion. In some aspects, the counterion is any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a salt has one or more than one charged atom in its structure. In instances where there are multiple charged atoms as part of the salt, multiple counter ions can be present. Hence, a salt can have one or more charged atoms and/or one or more counterions. A "pharmaceutically acceptable salt" is one that is suitable for administration to a subject as described herein and in some aspects includes salts as described by P. H. Stahl and C. G. Wermuth, editors, Handbook of Pharmaceutical Salts: Properties, Selection and Use, Weinheim/Zurich:Wiley-VCH/VHCA, 2002, the list for which is specifically incorporated by reference in its entirety.

[0100] The term "tautomer," as used herein refers to compounds whose structures differ markedly in arrangement of atoms, but which exist in easy and rapid equilibrium, and it is to be understood that, in some cases, compounds provided herein are depicted as different tautomers, and when compounds have tautomeric forms, all tautomeric forms are intended to be within the scope of the disclosure, and the naming of the compounds does not exclude any tautomer.

[0101] The term "halo" or "halogen" refers to fluoro, chloro, bromo, or iodo (e.g., in some aspects, fluoro or chloro).

[0102] The term "alkyl" refers to an unsubstituted methyl or straight chain or branched, saturated hydrocarbon having the indicated number of carbon atoms (e.g., "C.sub.1-C.sub.4 alkyl," "C.sub.1-C.sub.6 alkyl," "C.sub.1-C.sub.8 alkyl," or "C.sub.1-C.sub.10" alkyl have from 1 to 4, to 6, 1 to 8, or 1 to 10 carbon atoms, respectively) and is derived by the removal of one hydrogen atom from the parent alkane. Representative "C.sub.1-C.sub.8 alkyl" groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl and n-octyl: while branched C.sub.1-C.sub.8 alkyls include, but are not limited to, isopropyl, sec-butyl, isobutyl, tert-butyl, isopentyl, and 2-methylbutyl.

[0103] The term "alkylene" refers to methylene or a bivalent unsubstituted saturated branched or straight chain hydrocarbon of the stated number of carbon atoms (e.g., a C.sub.1-C.sub.6 alkylene has from 1 to 6 carbon atoms) and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of the parent alkane. In some aspects, alkylene groups are substituted with 1-6 fluoro groups, for example, on the carbon backbone (as —CHF— or —CF.sub.2—) or on terminal carbons of straight chain or branched alkylenes (such as —CHF.sub.2 or —CF.sub.3). Alkylene radicals include but are not limited to: methylene (—CH.sub.2—), ethylene (—CH.sub.2CH.sub.2—), n-propylene (—CH.sub.2CH.sub.2CH.sub.2—), n-propylene (—CH.sub.2CH.sub.2CH.sub.2—), n-butylene (—CH.sub.2CH.sub.2CH.sub.2CH.sub.2—), difluoromethylene (—CF.sub.2—), tetrafluoroethylene (—CF.sub.2CF.sub.2—), and the like.

[0104] The term "alkenyl" refers to an unsubstituted straight chain or branched, hydrocarbon having at least one carbon-carbon double bond and the indicated number of carbon atoms (e.g., "C.sub.2-C.sub.8 alkenyl" or "C.sub.2-C.sub.10" alkenyl have from 2 to 8 or 2 to 10 carbon atoms, respectively). When the number of carbon atoms is not indicated, the alkenyl group has from 2 to 6 carbon atoms.

[0105] The term "alkynyl" refers to an unsubstituted straight chain or branched, hydrocarbon having at least one carbon-carbon triple bond and the indicated number of carbon atoms (e.g., "C.sub.2-C.sub.8 alkynyl" or "C.sub.2-C.sub.10" alkynyl have from 2 to 8 or 2 to 10 carbon atoms, respectively). When the number of carbon atoms is not indicated, the alkynyl group has from 2 to 6 carbon atoms.

[0106] The term "heteroalkyl" refers to a stable straight or branched chain saturated hydrocarbon having the stated number of total atoms and at least one (e.g., 1 to 15) heteroatom selected from the

group consisting of O, N, Si and S. In some aspects, the carbon and heteroatoms of the heteroalkyl group are oxidized (e.g., to form ketones, N-oxides, sulfones, and the like) and in some aspects, the nitrogen atoms are quaternized. The heteroatom(s) are placed at any interior position of the heteroalkyl group and/or at the position at which the heteroalkyl group is attached to the remainder of the molecule. In some aspects, heteroalkyl groups are substituted with 1-6 fluoro groups, for example, on the carbon backbone (as —CHF— or —CF.sub.2—) or on terminal carbons of straight chain or branched heteroalkyls (such as —CHF.sub.2 or —CF.sub.3). Examples of heteroalkyl groups include, but are not limited to, —CH.sub.2—CH.sub.2—O—CH.sub.3, —CH.sub.2—CH.sub.2—NH—CH.sub.3, —CH.sub.2—CH.sub.2—N(CH.sub.3).sub.2, —C(═O)—NH—CH.sub.2—CH.sub.2—NH—CH.sub.3, —C(═O)—N(CH.sub.3)—CH.sub.2—CH.sub.2—N(CH.sub.3).sub.2, —C(═O)—NH—CH.sub.2—CH.sub.2—NH—C(═O)—CH.sub.2—CH.sub.3, —C(═O)—N(CH.sub.3)—CH.sub.2—CH.sub.2—N(CH.sub.3)—C(═O)—CH.sub.2—CH.sub.3, —O—CH.sub.2—CH.sub.2—CH.sub.2—NH(CH.sub.3), —O—CH.sub.2—CH.sub.2—CH.sub.2—N(CH.sub.3).sub.2, —O—CH.sub.2—CH.sub.2—CH.sub.2—NH—C(═O)—CH.sub.2—CH.sub.3, —O—CH.sub.2—CH.sub.2—CH.sub.2—N(CH.sub.3)—C(═O)—CH.sub.2—CH.sub.3, —CH.sub.2—CH.sub.2—CH.sub.2—NH(CH.sub.3), —O—CH.sub.2—CH.sub.2—CH.sub.2—N(CH.sub.3).sub.2, —CH.sub.2—CH.sub.2—CH.sub.2—NH—C(═O)—CH.sub.2—CH.sub.3, —CH.sub.2—CH.sub.2—CH.sub.2—N(CH.sub.3)—C(═O)—CH.sub.2—CH.sub.3, —CH.sub.2—S—CH.sub.2—CH.sub.3, —CH.sub.2—CH.sub.2—S(O)—CH.sub.3, —NH—CH.sub.2—CH.sub.2—NH—C(═O)—CH.sub.2—CH.sub.3, —CH.sub.2—CH.sub.2—S(O).sub.2—CH.sub.3, —CH.sub.2—CH.sub.2—O—CF.sub.3, and —Si(CH.sub.3).sub.3. In some aspects, up to two heteroatoms are consecutive, such as, for example, —CH.sub.2—NH—OCH.sub.3 and —CH.sub.2—O—Si(CH.sub.3).sub.3. A terminal polyethylene glycol (PEG) moiety is a type of heteroalkyl group.

[0107] The term “heteroalkylene” refers to a bivalent unsubstituted straight or branched group derived from heteroalkyl (as defined herein). Examples of heteroalkylene groups include, but are not limited to, —CH.sub.2—CH.sub.2—O—CH.sub.2—, —CH.sub.2—CH.sub.2—O—CF.sub.2—, —CH.sub.2—CH.sub.2—NH—CH.sub.2—, —C(═O)—NH—CH.sub.2—CH.sub.2—NH—CH.sub.2—, —C(═O)—N(CH.sub.3)—CH.sub.2—CH.sub.2—N(CH.sub.3)—CH.sub.2—, —C(═O)—NH—CH.sub.2—CH.sub.2—NH—C(═O)—CH.sub.2—CH.sub.2—, —C(═O)—N(CH.sub.3)—CH.sub.2—CH.sub.2—N(CH.sub.3)—C(═O)—CH.sub.2—CH.sub.2—, —O—CH.sub.2—CH.sub.2—CH.sub.2—NH—CH.sub.2—, —O—CH.sub.2—CH.sub.2—CH.sub.2—N(CH.sub.3)—CH.sub.2—, —O—CH.sub.2—CH.sub.2—CH.sub.2—NH—C(═O)—CH.sub.2—CH.sub.2—, —O—CH.sub.2—CH.sub.2—CH.sub.2—N(CH.sub.3)—C(═O)—CH.sub.2—CH.sub.2—, —CH.sub.2—CH.sub.2—CH.sub.2—NH—CH.sub.2—, —CH.sub.2—CH.sub.2—CH.sub.2—N(CH.sub.3)—CH.sub.2—, —CH.sub.2—CH.sub.2—CH.sub.2—NH—C(═O)—CH.sub.2—CH.sub.2—, —CH.sub.2—CH.sub.2—CH.sub.2—N(CH.sub.3)—C(═O)—CH.sub.2—CH.sub.2—, —CH.sub.2—CH.sub.2—NH—C(═O)—, —CH.sub.2—CH.sub.2—N(CH.sub.3)—CH.sub.2—, —CH.sub.2—CH.sub.2—N.sup.+(CH.sub.3).sub.2—, —NH—CH.sub.2—CH.sub.2(NH.sub.2)—CH.sub.2—, and —NH—CH.sub.2—CH.sub.2(NHCH.sub.3)—CH.sub.2—. A bivalent polyethylene glycol (PEG) moiety is a type of heteroalkylene group.

[0108] The term “alkoxy” refers to an alkyl group, as defined herein, which is attached to a molecule via an oxygen atom. For example, alkoxy groups include, but are not limited to methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, sec-butoxy, tert-butoxy, n-pentoxy and n-hexoxy.

[0109] The term “alkylthio” refers to an alkyl group, as defined herein, which is attached to a molecule via a sulfur atom. For example, alkythio groups include, but are not limited to thiomethyl, thioethyl, thio-n-propyl, thio-iso-propyl, and the like.

[0110] The term “haloalkyl” refers to an unsubstituted straight chain or branched, saturated hydrocarbon having the indicated number of carbon atoms (e.g., “C.sub.1-C.sub.4 alkyl,” “C.sub.1-C.sub.6 alkyl,” “C.sub.1-C.sub.8 alkyl,” or “C.sub.1-C.sub.10” alkyl have from 1 to 4, to 6, 1 to 8,

or 1 to 10 carbon atoms, respectively) wherein at least one hydrogen atom of the alkyl group is replaced by a halogen (e.g., fluoro, chloro, bromo, or iodo). When the number of carbon atoms is not indicated, the haloalkyl group has from 1 to 6 carbon atoms. Representative C.sub.1-C.sub.6 haloalkyl groups include, but are not limited to, trifluoromethyl, 2,2,2-trifluoroethyl, and 1-chloroisopropyl.

[0111] The term "haloalkoxy" refers to a haloalkyl group, as defined herein, which is attached to a molecule via an oxygen atom. For example, haloalkoxy groups include, but are not limited to trifluoromethoxy, 2,2,2-trifluoroethoxy, and 1,1,1-trifluoro2-methylpropoxy.

[0112] The term "cycloalkyl" refers to a cyclic, saturated or partially unsaturated hydrocarbon having the indicated number of carbon atoms (e.g., "C.sub.3-8 cycloalkyl" or "C.sub.3-6" cycloalkyl have from 3 to 8 or 3 to 6 carbon atoms, respectively). When the number of carbon atoms is not indicated, the cycloalkyl group has from 3 to 6 carbon atoms. Cycloalkyl groups include bridged, fused, and spiro ring systems, and bridged bicyclic systems where one ring is aromatic and the other is unsaturated. Representative "C.sub.3-6 cycloalkyl" groups include, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0113] The term "aryl" refers to an unsubstituted monovalent carbocyclic aromatic hydrocarbon radical of 6-10 carbon atoms derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Aryl groups include, but are not limited to, phenyl, naphthyl, anthracenyl, biphenyl, and the like.

[0114] The term "heterocycle" refers to a saturated or partially unsaturated ring or a multiple condensed ring system, including bridged, fused, and spiro ring systems. In some aspects, heterocycles are described by the total number of atoms in the ring system, for example a 3-10 membered heterocycle has 3 to 10 total ring atoms. The term includes single saturated or partially unsaturated rings (e.g., 3, 4, 5, 6 or 7-membered rings) from about 1 to 6 carbon atoms and from about 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur in the ring. In some aspects, the ring is substituted with one or more (e.g., 1, 2 or 3) oxo groups and the sulfur and nitrogen atoms may also be present in their oxidized forms. Such rings include but are not limited to azetidinyl, tetrahydrofuranyl and piperidinyl. The term "heterocycle" also includes multiple condensed ring systems (e.g., ring systems comprising 2, 3 or 4 rings) wherein a single heterocycle ring (as defined above) is condensed with one or more heterocycles (e.g., decahydronapthyridinyl), carbocycles (e.g., decahydroquinolyl) or aryls. In some aspects, the rings of a multiple condensed ring system are connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. It is to be understood that the point of attachment of a multiple condensed ring system (as defined above for a heterocycle) can be at any position of the multiple condensed ring system including a heterocycle, aryl and carbocycle portion of the ring. It is also to be understood that the point of attachment for a heterocycle or heterocycle multiple condensed ring system can be at any suitable atom of the heterocycle or heterocycle multiple condensed ring system including a carbon atom and a heteroatom (e.g., a nitrogen). Exemplary heterocycles include, but are not limited to aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydrofuranyl, dihydrooxazolyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,2,3,4-tetrahydroquinolyl, benzoxazinyl, dihydrooxazolyl, chromanyl, 1,2-dihydropyridinyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, and 1,4-benzodioxanyl.

[0115] The term "heteroaryl" refers to an aromatic hydrocarbon ring system with at least one heteroatom within a single ring or within a fused ring system, selected from the group consisting of O, N and S. The ring or ring system has 4n+2 electrons in a conjugated π system where all atoms contributing to the conjugated π system are in the same plane. In some aspects, heteroaryl groups have 5-10 total ring atoms and 1, 2, or 3 heteroatoms (referred to as a "5-10 membered heteroaryl"). Heteroaryl groups include, but are not limited to, imidazole, triazole, thiophene, furan, pyrrole, benzimidazole, pyrazole, pyrazine, pyridine, pyrimidine, and indole.

[0116] The term “hydroxyl” refers to an —OH radical.
[0117] The term “cyano” refers to a —CN radical.
[0118] The term “carboxy” refers to a —C(═O)OH radical.
[0119] The term “oxo” refers to a ═O radical.
[0120] The term “succinimide” as used as part of an antibody-drug conjugate (ADC) refers to:
##STR00011##
where the wavy lines indicate attachment to a Drug-Linker Unit or antigen-binding protein or an antigen-binding fragment thereof.
[0121] The term “hydrolyzed succinimide” as used as part of an antibody-drug conjugate (ADC) refers to:
##STR00012##
where the wavy lines indicate attachment to a Drug-Linker Unit or antigen-binding protein or an antigen-binding fragment thereof.
[0122] The term “optionally substituted” indicates that the referenced moiety is unsubstituted or substituted with the indicated groups.
[0123] It will be appreciated by those skilled in the art that compounds of this disclosure having a chiral center may exist in and be isolated in optically active and racemic forms.
[0124] As used herein, the term “free drug” refers to a biologically active species that is not covalently attached to an antibody. Accordingly, free drug refers to any unconjugated compound, including a compound as it exists immediately upon cleavage from the ADC. In some aspects, the release mechanism is via a cleavable linker in the ADC, or via intracellular conversion or metabolism of the ADC. In some aspects, the free drug will be protonated and/or may exist as a charged moiety. The free drug is a pharmacologically active species which is capable of exerting the desired biological effect. In some aspects, the pharmacologically active species is the parent drug alone. In some aspects, the pharmacologically active species is the parent drug bonded to a component or vestige of the ADC (e.g., a component of the linker, succinimide, hydrolyzed succinimide, and/or antibody that has not undergone subsequent intracellular metabolism). In some aspects, free drug refers to a compound of Formula (I), as described herein, for example, wherein one or more of X.sup.B, Y, W, A, and M.sup.1 are absent. In some aspects, free drug refers to a compound of Formula (II), as described herein. In some aspects, free drug refers to a compound of Formula (II-A), as described herein. In some aspects, free drug refers to a compound of Formula (III), as described herein. In some aspects, free drug refers to a compound of Formula (IV), as described herein. In some aspects, free drug refers to a compound of Formula (V), as described herein.
[0125] As used herein, the term “Drug Unit” refers to the free drug that is conjugated to an antigen-binding protein or an antigen-binding fragment thereof in an ADC, as described herein. In some aspects, the Drug Unit includes all or portions of non-cleavable linking components that conjugate the drug to the antigen-binding protein or an antigen-binding fragment thereof.
[0126] As used herein, the term “Drug-Linker Unit” refers to a drug and linking components (whether cleavable or non-cleavable) that conjugate the drug to an antigen-binding protein or an antigen-binding fragment thereof.
[0127] As used herein, the term “antibody-drug conjugate” or simply “ADC” refers to an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody) conjugated to a Drug Unit as described herein. In some aspects, an antibody-drug conjugate typically binds to target antigen (e.g., CD228, αvβ6, or B7-H4) on a cell surface followed by internalization of the antibody-drug conjugate into the cell where the Drug Unit is released.
[0128] As used herein, the term “ADC composition” refers to a composition comprising a distribution of ADCs having different numbers of Drug Units conjugated to an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody).
Antibody-Drug Conjugate (ADC) Compounds

[0129] Some embodiments provide an antibody-drug conjugate (ADC) comprising: [0130] an antigen-binding protein or antigen-binding fragment thereof; and [0131] a compound of Formula (I) as described herein; [0132] wherein the compound of Formula (I) is conjugated to the antigen-binding protein or antigen-binding fragment thereof via a succinimide or hydrolyzed succinimide covalently linked to a sulfur atom of a cysteine residue.
[0133] Some embodiments provide an antibody-drug conjugate (ADC) having the formula:

Ab-(S*-M.sup.1-(D)).sub.p [0134] wherein: [0135] Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody); [0136] each S* is a sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof; [0137] M.sup.1 is a succinimide or a hydrolyzed succinimide; [0138] subscript p is an integer from 2 to 8; and [0139] each (D) is a Drug-Linker Unit of Formula (I):
##STR00013## [0140] wherein: [0141]  custom-character represents covalent attachment of L to M.sup.1; [0142] R.sup.1 is hydrogen, hydroxyl, C.sub.1-6 alkoxy, —(C.sub.1-6 alkyl) C.sub.1-6 alkoxy, —(CH.sub.2).sub.n—NR.sup.AR.sup.B, or PEG2 to PEG4; [0143] each R.sup.2 and R.sup.3 are independently —CO.sub.2H, —(C═O).sub.m—NR.sup.CR.sup.D, or —(CH.sub.2)—NR.sup.ER.sup.F; [0144] each R.sup.A, R.sup.B, R.sup.C, R.sup.D, R.sup.E, and R.sup.F are independently hydrogen or C.sub.1-3 alkyl; [0145] each subscript n is independently an integer from 0 to 6; [0146] each subscript m is independently 0 or 1; [0147] each subscript q is an integer from 0 to 6; [0148] X.sup.A is —CH.sub.2—, —O—, —S—, —NH—, or —N(CH.sub.3)—; [0149] X.sup.B is absent or a 2-16 membered heteroalkylene; [0150] X.sup.B, M.sup.1, and L are each independently optionally substituted with a PEG Unit from PEG2 to PEG72; and [0151] L is an optional linker as described herein. When present, L is linked via a covalent bond to X.sup.B, or X.sup.A if X.sup.B is absent, as depicted in Formula (I). When L is absent, M.sup.1 is linked via a covalent bond to X.sup.B, or X.sup.A if X.sup.B is absent, as depicted in Formula (I).
[0152] In some embodiments, M.sup.1 is a succinimide. In some embodiments, M.sup.1 is a hydrolyzed succinimide. It will be understood that a hydrolyzed succinimide may exist in two regioisomeric form(s). Those forms are exemplified below for hydrolysis of M.sup.1 bonded to *S-Ab, wherein the structures representing the regioisomers from that hydrolysis are formula M.sup.1a and M.sup.1b; wherein the wavy lines adjacent to the bonds represent the covalent attachment to Formula (I).
##STR00014##
[0153] The M or M.sup.1 groups, when present, are capable of covalent attachment to an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody) to an A group, when present (or a W, Y, or X.sup.B group if subscript a and/or subscript w and/or subscript y are 0). In this regard an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody) has a functional group that can form a bond with a functional group of M or M.sup.1. In some embodiments, useful functional groups present on an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody), either naturally or via chemical manipulation include, but are not limited to, sulfhydryl (—SH), amino, hydroxyl, carboxy, and the anomeric hydroxyl group of a carbohydrate. In one aspect, the antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody) functional groups are sulfhydryl and amino. In some embodiments, sulfhydryl groups are generated by reduction of an intramolecular disulfide bond of an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody). Alternatively, in some embodiments, sulfhydryl groups are generated by reaction of an amino group of a lysine moiety of an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody) using 2-iminothiolane (Traut's reagent) or another sulfhydryl generating reagent. In some embodiments, M or M.sup.1 forms a bond with a sulfur atom of the antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody). In some embodiments, the sulfur atom is derived from a sulfhydryl group of the antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody).

[0154] In some embodiments, L has the formula -(A).sub.a-(W).sub.w—(Y).sub.y—, wherein: [0155] A is a C.sub.2-20 alkylene optionally substituted with 1-3 R.sup.a1; or a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R.sup.b1; [0156] each R.sup.a1 is independently selected from the group consisting of: C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, ═O, —NR.sup.d1R.sup.e1, —C(O)NR.sup.a1R.sup.e1, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl); [0157] each R.sup.b1 is independently selected from the group consisting of: C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, —NR.sup.d1R.sup.e1, —C(O)NR.sup.d1R.sup.e1°, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl); [0158] each R.sup.d1 and R.sup.e1 are independently hydrogen or C.sub.1-3 alkyl; [0159] W is from 1-12 amino acids or has the structure: ##STR00015## [0160] wherein Su is a Sugar moiety; [0161] —O.sup.A— represents a glycosidic bond; [0162] each R.sup.9 is independently hydrogen, halogen, —CN, or —NO.sub.2; [0163] W.sub.1 is absent or —O—C(═O)—; [0164] custom-character represents covalent attachment to A or M.sup.1; [0165] * represents covalent attachment to Y, X.sup.A, or X.sup.B in Formula (I); [0166] Y is a self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety; [0167] subscript a is 0 or 1; [0168] subscript y is 0 or 1; and [0169] subscript w is 0 or 1.

[0170] In some embodiments, R.sup.1 is hydrogen. In some embodiments, R.sup.1 is hydroxyl. In some embodiments, R.sup.1 is C.sub.1-6 alkoxy. In some embodiments, R.sup.1 is methoxy. In some embodiments, R.sup.1 is —(C.sub.1-6 alkyl)C.sub.1-6 alkoxy. In some embodiments, R.sup.1 is methoxyethyl. In some embodiments, R.sup.1 is PEG2 to PEG4.

[0171] In some embodiments, R.sup.1 is —(CH.sub.2).sub.n—NR.sup.AR.sup.B. In some embodiments, R.sup.A and R.sup.B are both hydrogen. In some embodiments, R.sup.A and R.sup.B are independently C.sub.1-3 alkyl. In some embodiments, one of R.sup.A and R.sup.B is hydrogen and the other of R.sup.A and R.sup.B is C.sub.1-3 alkyl. In some embodiments, the C.sub.1-3 alkyl is methyl. In some embodiments, each subscript n is 0. In some embodiments, each subscript n is 1. In some embodiments, each subscript n is 2. In some embodiments, each subscript n is 3, 4, 5, or 6.

[0172] In some embodiments, each R.sup.2 and R.sup.3 are independently —CO.sub.2H, —(C═O).sub.m—NR.sup.CR.sup.D, or (CH.sub.2).sub.q—NR.sup.ER.sup.F; and R.sup.2 and R.sup.3 are the same. In some embodiments, each R.sup.2 and R.sup.3 are independently —CO.sub.2H, —(C═O).sub.m—NR.sup.CR.sup.D, or —(CH.sub.2).sub.q—NR.sup.ER.sup.F; and R.sup.2 and R.sup.3 are different.

[0173] In some embodiments, R.sup.2 is —(C═O).sub.m—NR.sup.CR.sup.D. In some embodiments. R.sup.3 is —(C═O).sub.m—NR.sup.CR.sup.D. In some embodiments, R.sup.C and R.sup.D are both hydrogen. In some embodiments, R.sup.C and R.sup.D are each independently C.sub.1-3 alkyl. In some embodiments, the C.sub.1-3 alkyl is methyl. In some embodiments, one of R.sup.C and R.sup.D is hydrogen and the other of R.sup.C and R.sup.D is C.sub.1-3 alkyl. In some embodiments, each subscript m is 0. In some embodiments, each subscript m is 1.

[0174] In some embodiments, R.sup.2 is —(CH.sub.2).sub.q—NR.sup.ER.sup.F. In some embodiments, R.sup.3 is —(CH.sub.2).sub.q—NR.sup.ER.sup.F. In some embodiments, R.sup.E and R.sup.F are both hydrogen. In some embodiments, R.sup.E and R.sup.F are each independently C.sub.1-3 alkyl. In some embodiments, the C.sub.1-3 alkyl is methyl. In some embodiments, one of R.sup.E and R.sup.F is hydrogen and the other of R.sup.E and R.sup.F is C.sub.1-3 alkyl. In some embodiments, each subscript q is 0. In some embodiments, each subscript q is an integer from 1 to 6. In some embodiments, each subscript q is 1. In some embodiments, each subscript q is 2. In some embodiments, each subscript q is 3, 4, 5, or 6.

[0175] In some embodiments, R.sup.3 is —CO.sub.2H. In some embodiments, R.sup.2 is —CO.sub.2H.

[0176] In some embodiments, X.sup.A is —CH.sub.2—. In some embodiments, X.sup.A is —O—. In some embodiments, X.sup.A is —S—. In some embodiments, X.sup.A is —NH—. In some

embodiments, X.sup.A is —N(CH.sub.3)—.
[0177] In some embodiments, X.sup.B is a 2-16 membered heteroalkylene. In some embodiments, X.sup.B is a 2-12 membered heteroalkylene. In some embodiments, X.sup.B is a 2-10 membered heteroalkylene. In some embodiments, X.sup.B is a 2-8 membered heteroalkylene. In some embodiments, X.sup.B is a 4-8 membered heteroalkylene. In some embodiments, the heteroalkylene is straight chained. In some embodiments, the heteroalkylene is branched. In some embodiments, the heteroalkylene is branched, having 1-4 methyl groups. In some embodiments, the heteroalkylene is branched, having 1 or 2 methyl groups. In some embodiments, the heteroalkylene is substituted with 1-3 fluoro groups. In some embodiments, X.sup.B comprises one or two nitrogen atoms. In some embodiments, X.sup.B comprises one or two oxo groups. In some embodiments, X.sup.B comprises one nitrogen atom and one oxo group. In some embodiments, X.sup.B comprises two nitrogen atoms and two oxo groups. In some embodiments, X.sup.B comprises a carbamate.
[0178] In some embodiments, the covalent attachment of Y and X.sup.B comprises an amide. In some embodiments, the covalent attachment of Y and X.sup.B comprises a carbamate. In some embodiments, the covalent attachment of Y and X.sup.B comprises an ether.
[0179] In some embodiments, X.sup.B is
##STR00016##
wherein  custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L, when present, or M.sup.1. In some embodiments, X.sup.B is
##STR00017##
wherein  custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L, when present, or M.sup.1. In some embodiments, X.sup.B is
##STR00018##
wherein custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L, when present, or M.sup.1. In some embodiments, X.sup.B is
##STR00019##
wherein  custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L, when present, or M.sup.1. In some embodiments, X.sup.B is
##STR00020##
wherein  custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L, when present, or M.sup.1. In some embodiments, X.sup.B is
##STR00021##
wherein  custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L, when present, or M.sup.1.
[0180] In some embodiments, X.sup.B is selected from the group consisting of the structures below, wherein  custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L, when present, or M.sup.1.
##STR00022## ##STR00023##
[0181] In some embodiments, one of X.sup.B and L is substituted with a PEG Unit from PEG2 to PEG72, as described herein. In some embodiments, X.sup.B and L are each substituted with an independently selected PEG Unit from PEG2 to PEG72, as described herein. In some embodiments, each PEG Unit from PEG2 to PEG72 can range from PEG8 to PEG12, PEG12 to PEG24, or PEG36 to PEG72. In some embodiments, each PEG Unit from PEG2 to PEG72 is PEG8 to PEG24.
[0182] In some embodiments, X.sup.B and L are unsubstituted.
[0183] In some embodiments, R.sup.1 is methoxy; R.sup.2 and R.sup.3 are both —C(═O)NH.sub.2; and X.sup.A is —O—.
[0184] In some embodiments, L is absent and X.sup.A—X.sup.B-M.sup.1 is selected from the group consisting of:

##STR00024##
wherein custom-character represents covalent attachment to the remainder of Formula (I).
[0185] In some embodiments, X.sup.A—X.sup.B-L is selected from:
##STR00025##
wherein custom-character represents covalent attachment to the remainder of Formula (I).
[0186] In some embodiments, R.sup.1 is methoxy and R.sup.2 and R.sup.3 are both —C(═O)NH.sub.2. In some embodiments, X.sup.A is —O— and X.sup.B is
##STR00026##
wherein custom-character represents covalent attachment to X.sup.A and * represents covalent attachment to L, when present, or M.sup.1. In some embodiments, R.sup.1 is methoxy; R.sup.2 and R.sup.3 are both —C(═O)NH.sub.2; X.sup.A is —O—; and X.sup.B is
##STR00027##
wherein custom-character represents covalent attachment to X.sup.A and * represents covalent attachment to L, when present, or M.sup.1. In some embodiments, R.sup.1 is methoxy; R.sup.2 and R.sup.3 are both —C(═O)NH.sub.2; X.sup.A is —O—; X.sup.B is
##STR00028##
custom-character represents covalent attachment to X.sup.A and * represents covalent attachment to L; and subscript a and subscript y are both 0.
[0187] In some embodiments, X.sup.B is absent.
[0188] In some embodiments, subscript p is an integer from 2 to 8, from 2 to 6, from 2 to 4, from 4 to 8, or from 6 to 8. In some embodiments, subscript p is 2, 4, 6, or 8. In some embodiments, subscript p is 2. In some embodiments, subscript p is 4. In some embodiments, subscript p is 6. In some embodiments, subscript p is 8. In some alternative embodiments, subscript p is an integer from 1 to 16. Accordingly, in any of the structures shown here, subscript p may alternatively be defined to be an integer from 1 to 16.
[0189] In some embodiments, X.sup.B is absent and L is covalently attached to X.sup.A. In some embodiments, X.sup.B is absent and Y is covalently attached to X.sup.A. In some embodiments, X.sup.B is absent and Y is absent, and W is covalently attached to X.sup.A. In some embodiments, X.sup.B is absent, Y is absent, W is absent, and A is covalently attached to X.sup.A.
[0190] In some embodiments, X.sup.B is 2-16 membered heteroalkylene and L is covalently attached to X.sup.B. In some embodiments, X.sup.B is 2-16 membered heteroalkylene and Y is covalently attached to X.sup.B. In some embodiments, X.sup.B is 2-16 membered heteroalkylene, Y is absent, and W is covalently attached to X.sup.B. In some embodiments, X.sup.B is 2-16 membered heteroalkylene, Y is absent, W is absent, and A is covalently attached to X.sup.B.
[0191] In some embodiments, W.sub.1 is —OC(═O)— and subscript y is 1. In some embodiments, X.sup.A is —O— and X.sup.B and W.sub.1 are absent. In some embodiments, X.sup.A is NH or —O—, X.sup.B is absent, and W.sub.1 is —OC(═O). In some embodiments, X.sup.A is —N(CH.sub.3)—, X.sup.B is absent, and W.sub.1 is —OC(═O). In some embodiments, X.sup.A is —S—, X.sup.B is absent, and W.sub.1 is —OC(═O). In some embodiments, W.sub.1 is —OC(═O)— and X.sup.B is covalently attached to W via —O— or —NH—.
[0192] In some embodiments, A is covalently attached to M.sup.1. In some embodiments, when subscript a is 0, W is covalently attached to M.sup.1. In some embodiments, when subscript a is 0 and subscript w is 0, Y is covalently attached to M.sup.1. In some embodiments, when subscripts a, y, and w, are each 0, X.sup.B is covalently attached to M.sup.1.
[0193] In some embodiments, the ADC has the formula:
##STR00029##
wherein: [0194] Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody); [0195] each S* is a sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof; [0196] R.sup.1, R.sup.2, R.sup.3, X.sup.A, X.sup.B, and L are as defined above in connection with Formula (I); and each subscript p is independently an integer

from 2 to 8.
[0197] In some aspects, the ADC has the formula:
##STR00030## [0198] wherein: [0199] Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody); [0200] each S* is a sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof; [0201] R.sup.1, R.sup.2, R.sup.3, X.sup.A, X.sup.B, and L are as defined above in connection with Formula (I); and each subscript p is independently an integer from 2 to 8.
[0202] In some aspects, the ADC has the formula:
##STR00031## [0203] wherein: [0204] Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody); [0205] each S* is a sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof; [0206] R.sup.1, R.sup.2, R.sup.3, X.sup.A, X.sup.B, Y, W, and A are as defined above in connection with Formula (I); [0207] each subscript y is independently 0 or 1; [0208] each subscript w is independently 0 or 1; [0209] each subscript a is independently 0 or 1; and each subscript p is independently an integer from 2 to 8.
[0210] In some embodiments, the ADC has the formula:
##STR00032##
##STR00033## [0211] wherein: [0212] Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody); [0213] each S* is a sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof; [0214] R.sup.1, R.sup.2, R.sup.3, L.sup.A, R.sup.H, Y, W, and L.sup.B are as defined below in connection with Formula (II-A); [0215] each subscript y is independently 0 or 1; [0216] each subscript w is independently 0 or 1; and [0217] each subscript p is independently an integer from 2 to 8.
[0218] In some aspects, the ADC has the formula:
##STR00034## [0219] wherein: [0220] Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody); [0221] each S* is a sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof; [0222] R.sup.1, R.sup.2, R.sup.3, L.sup.A, R.sup.H, Y, W, and L.sup.B are as defined below in connection with Formula (II-A); [0223] each subscript y is independently 0 or 1; [0224] each subscript w is independently 0 or 1; and [0225] each subscript p is independently an integer from 2 to 8.
[0226] In some embodiments, the ADC has the formula:
##STR00035##
##STR00036## [0227] wherein: [0228] Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody); [0229] each S* is a sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof; [0230] R.sup.1, R.sup.2, R.sup.3, L.sup.A, R.sup.H, and L.sup.B are as defined below in connection with Formula (II-B); and [0231] each subscript p is independently an integer from 2 to 8.
[0232] In some aspects, the ADC has the formula:
##STR00037## [0233] wherein: [0234] Ab is an antibody; [0235] R.sup.1, R.sup.2, R.sup.3, L.sup.A, R.sup.H, and L.sup.B are as defined below in connection with Formula (II-B); and [0236] each subscript p is independently an integer from 2 to 8.
[0237] Some embodiments provide an antibody-drug conjugate (ADC) having the formula:

Ab-(S*-(D′)).sub.p
wherein: [0238] Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody); [0239] each S* is a sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof; [0240] D′ is a Drug-Linker Unit that is a radical of the compound of Formula (IV), as described below; and subscript p is an integer from 2 to 8.
[0241] In some embodiments, the radical of the compound of Formula (IV) comprises a radical in substituent M within Formula (IV). In some embodiments, the Drug-Linker Unit D′ has the structure:

##STR00038##
where *** indicates attachment to S* and the remaining variables are as defined below in connection with Formula (IV).
[0242] In some aspects, the Drug-Linker Unit D′ has the structure:
##STR00039##
where *** indicates attachment to S* and the remaining variables are as defined below in connection with Formula (IV).
[0243] In some embodiments, the ADC has the formula:
##STR00040## [0244] wherein: [0245] Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody); [0246] each S* is a sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof; [0247] each subscript p is independently an integer from 2 to 8; and the remaining variables are as defined below in connection with Formula (IV).
[0248] In some aspects, the ADC has the formula:
##STR00041## [0249] wherein: [0250] Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody); [0251] each S* is a sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof; [0252] each subscript p is independently an integer from 2 to 8; and [0253] the remaining variables are as defined below in connection with Formula (IV).
[0254] Some embodiments provide an antibody-drug conjugate (ADC) selected from the group consisting of:
##STR00042## ##STR00043## ##STR00044## ##STR00045## ##STR00046## ##STR00047## ##STR00048## ##STR00049## ##STR00050## ##STR00051## ##STR00052## ##STR00053## ##STR00054##
##STR00055## ##STR00056## ##STR00057## ##STR00058## ##STR00059## ##STR00060## ##STR00061## ##STR00062## ##STR00063##
and pharmaceutically acceptable salts thereof, [0255] wherein: [0256] Ab is an antigen-binding protein or an antigen-binding fragment thereof (e.g., an antibody); [0257] each S* is a sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof; and [0258] each subscript p is independently an integer from 2 to 8.
[0259] The structures shown above include all tautomeric forms. Thus, for example, the structure:
##STR00064##
is to be understood as encompassing the following tautomeric forms:
##STR00065## ##STR00066##
Antigen Binding Proteins and Fragments Thereof (e.g., Antibodies)
[0260] In some embodiments, an antibody is a polyclonal antibody. In some embodiments, an antibody is a monoclonal antibody. In some embodiments, an antibody is chimeric. In some embodiments, an antibody is humanized. In some embodiments, an antibody is fully human. In some embodiments, an antibody is an antigen binding fragment.
[0261] The term “monoclonal antibody” as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. The modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies and is not to be construed as requiring production of the antibody by any particular method.
[0262] Useful polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of immunized animals. Useful monoclonal antibodies are homogeneous populations of antibodies to a particular antigenic determinant (e.g., a cancer cell antigen, a protein, a peptide, a carbohydrate, a chemical, nucleic acid, or fragments thereof). In some embodiments, a monoclonal

antibody (mAb) to an antigen-of-interest is prepared by using any technique known in the art which provides for the production of antibody molecules by continuous cell lines in culture.

[0263] Useful monoclonal antibodies include, but are not limited to, human monoclonal antibodies, humanized monoclonal antibodies, or chimeric human-mouse (or other species) monoclonal antibodies. The antibodies include full-length antibodies and antigen binding fragments thereof. Human monoclonal antibodies may be made by any of numerous techniques known in the art (e.g., Teng et al., 1983, *Proc. Natl. Acad. Sci. USA.* 80:7308-7312; Kozbor et al., 1983, *Immunology Today* 4:72-79; and Olsson et al., 1982, Meth. Enzymol. 92:3-16).

[0264] In some embodiments, an antibody includes a functionally active fragment, derivative or analog of an antibody that binds specifically to target cells (e.g., cancer cell antigens) or other antibodies bound to cancer cells or matrix. In this regard, "functionally active" means that the fragment, derivative or analog is able to bind specifically to target cells. To determine which CDR sequences bind the antigen, synthetic peptides containing the CDR sequences are typically used in binding assays with the antigen by any binding assay method known in the art (e.g., the Biacore assay) (See, e.g., Kabat et al., 1991, *Sequences of Proteins of Immunological Interest*, Fifth Edition, National Institute of Health, Bethesda, Md; Kabat E et al., 1980, *J. Immunology* 125(3):961-969).

[0265] Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which are typically obtained using standard recombinant DNA techniques, are useful antibodies. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as for example, those having a variable region derived from a murine monoclonal and a constant region derived from a human immunoglobulin. See, e.g., U.S. Pat. Nos. 4,816,567; and 4,816,397, which are incorporated herein by reference in their entireties. Humanized antibodies are antibody molecules from non-human species having one or more CDRs from the non-human species and a framework region from a human immunoglobulin molecule. See, e.g., U.S. Pat. No. 5,585,089, which is incorporated herein by reference in its entirety. In some embodiments, such chimeric and humanized monoclonal antibodies is produced by recombinant DNA techniques known in the art, for example using methods described in International Publication No. WO 87/02671; European Patent Publication No. 0 184 187; European Patent Publication No. 0 171 496; European Patent Publication No. 0 173 494; International Publication No. WO 86/01533; U.S. Pat. No. 4,816,567; European Patent Publication No. 012 023; Berter et al., 1988, Science 240:1041-1043; Liu et al., 1987, Proc. Natl. Acad. Sci. USA 84:3439-3443; Liu et al., 1987, J. Immunol. 139:3521-3526; Sun et al., 1987, Proc. Natl. Acad. Sci. USA 84:214-218; Nishimura et al., 1987, Cancer. Res. 47:999-1005; Wood et al., 1985, Nature 314:446-449; and Shaw et al., 1988, J. Natl. Cancer Inst. 80:1553-1559; Morrison, 1985, Science 229:1202-1207; Oi et al., 1986, BioTechniques 4:214; U.S. Pat. No. 5,225,539; Jones et al., 1986, Nature 321: 522-525; Verhoeyan et al., 1988, Science 239:1534; and Beidler et al., 1988, J. Immunol. 141:4053-4060; each of which is incorporated herein by reference in its entirety.

[0266] In some embodiments, an antibody is a completely human antibody. In some embodiments, an antibody is produced using transgenic mice that are incapable of expressing endogenous immunoglobulin heavy and light chain genes, but which are capable of expressing human heavy and light chain genes.

[0267] In some embodiments, an antibody is an intact or fully-reduced antibody. The term 'fully-reduced' is meant to refer to an antibody in which all four inter-chain disulfide linkages have been reduced to provide eight thiols that can be attached to a linker (L).

[0268] In some embodiments, attachment to an antibody is via thioether, amine, or amide linkages from native and/or engineered cysteine, lysine, or methionine residues, or from an amino acid residue engineered to participate in a cycloaddition reaction (such as a click reaction) with the corresponding linker intermediate. See, e.g., Macrlc, et al., *PLOS One* 2019: 14(1); e0209860. In some embodiments, an antibody is an intact or fully-reduced antibody, or is an antibody bearing an

engineered cysteine, lysine, or methionine group that is modified with a functional group that can participate in, for example, click chemistry or other cycloaddition reactions for attachment of other components of the ADC as described herein (e.g., Diels-Alder reactions or other [3+2] or [4+2]cycloadditions).

[0269] Antibodies that bind specifically to a cancer cell antigen are available commercially or produced by any method known to one of skill in the art such as, e.g., chemical synthesis or recombinant expression techniques. The nucleotide sequences encoding antibodies that bind specifically to a cancer cell antigen are obtainable, e.g., from the GenBank database or similar database, literature publications, or by routine cloning and sequencing.

[0270] In some embodiments, the antibody is used for the treatment of a cancer (e.g., an antibody approved by the FDA and/or EMA). Antibodies that bind specifically to a cancer cell antigen are available commercially or produced by any method known to one of skill in the art such as, e.g., recombinant expression techniques. The nucleotide sequences encoding antibodies that bind specifically to a cancer cell antigen are obtainable, e.g., from the GenBank database or similar database, literature publications, or by routine cloning and sequencing.

[0271] In some embodiments, an antibody can bind specifically to a receptor or a receptor complex expressed on lymphocytes. The receptor or receptor complex can comprise an immunoglobulin gene superfamily member, a TNF receptor superfamily member, an integrin, a cytokine receptor, a chemokine receptor, a major histocompatibility protein, a lectin, or a complement control protein.

[0272] In some embodiments, an antibody can bind specifically to a cancer cell antigen. It will be understood that the antibody component in an ADC is an antibody in residue form such that "Ab" in the ADC structures described herein incorporates the structure of the antibody.

[0273] Non-limiting examples of antibodies that can be used for treatment of cancer and antibodies that bind specifically to tumor associated antigens are disclosed in Franke, A. E., Sievers, E. L., and Scheinberg, D. A., "Cell surface receptor-targeted therapy of acute myeloid leukemia: a review" *Cancer Biother Radiopharm.* 2000, 15, 459-76; Murray, J. L., "Monoclonal antibody treatment of solid tumors: a coming of age" *Semin Oncol.* 2000, 27, 64-70; Breitling, F., and Dubel, S., *Recombinant Antibodies*, John Wiley, and Sons, New York, 1998, each of which is hereby incorporated by reference in its entirety.

[0274] Embodiments of antibodies that bind to one or more of cancer cell antigens and immune cell antigens are provided below.

[0275] Non-limiting examples of target antigens and associated antibodies useful for the treatment of cancer and antibodies that bind specifically to cancer cell antigens (also called tumor antigens), include B7-DC (e.g., Catalog #PA5-20344); BCMA; B7-H3 (e.g., enoblituzumab, omburtamab, MGD009, MGC018, DS-7300); B7-H4 (e.g., Catalog #14-5949-82); B7-H6 (e.g., Catalog #12-6526-42); B7-H7; C.sub.5 complement (e.g., BCD-148; CAN106); CA-125; CA9 (e.g., girentuximab); CCR8 (e.g., JTX-1811); CLEC12A (e.g., tepoditamab); CSPG4 (e.g., U.S. Pat. No. 10,822,427); CCNB1; DDR1; de2-7 EGFR (e.g., MAb 806); DPEP1; DR4 (e.g., mapatumumab); endosialin (e.g., ontuxizumab); ENPP1; EPCAM (e.g., adecatumumab); EPHA2; ERBB2 (e.g., trastuzumab); ERBB3; ERVMER34_1; FAP (e.g., sibrotuzumab); FasL; FGFR2 (e.g., aprutumab); FGFR4 (e.g., MM-161); FLT3 (e.g., 4G8SDIEM); FBP; FucGM1 (e.g., BMS-986012); FZD8; G250; GAGE; GD2 (e.g., dinutuximab); gpNMB (e.g., glembatumumab); GPR87; GUCY2C (e.g., indusatumab); HAVCR2; IDO1; ITGB6; ITGB8; LICAM (e.g., JCAR023); MRC1 (e.g., ThermoFisher Catalog #12-2061-82); ML-IAP (e.g., 88C570, ThermoFisher Catalog #40958); NT5E (e.g., 7G2, ThermoFisher Catalog #41-0200); OY-TES1; p53; p53mutant; PAX5; PDPN (e.g., ThermoFisher Catalog #14-5381-82); VSIR (e.g., ThermoFisher Catalog #PA5-52493); Dectin2 (e.g., ThermoFisher Catalog #MA5-16250); PAX3 (e.g., GT1210, ThermoFisher Catalog #MA5-31583); Sialyl-Thomsen-nouveau-antigen (e.g., Eavarone et al. PLoS One, 2018; 13(7): e0201314); PDGFR-B (e.g., rinucumab); ADAM12 (e.g., Catalog #14139-1-AP); ADAM9 (e.g., IMGC936); AFP (e.g., ThermoFisher Catalog #PA5-25959); AGR2 (e.g., ThermoFisher Catalog

#PA5-34517); AKAP-4 (e.g., Catalog #PA5-52230); androgen receptor (e.g., ThermoFisher Catalog #MA5-13426); ALPP (e.g., Catalog #MA5-15652); CD44 (e.g., RG7356); AMHR2 (e.g., ThermoFisher Catalog #PA5-13902); ANTXR1 (e.g., Catalog #MA1-91702); ARTN (e.g., ThermoFisher Catalog #PA5-47063); av06; CA19-9 (e.g., AbGn-7; MVT-5873); carcinoembryonic antigen (e.g., arcitumomab; cergutuzumab; amunaleukin; labetuzumab); CD115 (e.g., axatilimab; cabiralizumab; emactuzumab); CD137 (e.g., ADG106; CTX-471); CD147 (e.g., gavilimomab; metuzumab); CD155 (e.g., U.S. Publication No. 2018/0251548); CD274 (e.g., adebrelimab; atezolizumab; garivulimab); CDCP1 (e.g., RG7287); CDH3 (e.g., PCA062); CDH6 (e.g., HKT288); CEACAM1; CEACAM6; CLDN18.1 (e.g., zolbetuximab); CLDN18.2 (e.g., zolbetuximab); CLPTM1L; CS-1 (e.g., tigatuzumab); GD3 (e.g., mitumomab); HLA-G (e.g., TTX-080); IL1RAP (e.g., nidanilimab); LAG-3 (e.g., encelimab); LY6G6D (e.g., PA5-23303); LYPD1 (e.g., ThermoFisher Catalog #PA5-26749); MAD-CT-2; MAGEA3 (e.g., ThermoFisher Catalog #60054-1-IG); MAGEA4 (e.g., Catalog #MA5-26117); MAGEC2 (e.g., ThermoFisher Catalog #PA5-64010); MLANA (e.g., Catalog #MA5-15237); MELTF (e.g., ThermoFisher Catalog #H00004241-M04A); MSLN (e.g., 5B2, Catalog #MA5-11918); MUC1 (e.g., MH1 (CT2), ThermoFisher Catalog #MA5-11202); MUC5AC (e.g., 45M1, Catalog #MA5-12178); MYCN (e.g., NCM-II 100, ThermoFisher Catalog #MA1-170); NCAM1 (e.g., ThermoFisher Catalog #MA5-11563); Nectin-4 (e.g., enfortumab); NY—BR-1 (e.g., NY—BR-1 No. 2, Catalog #MA5-12645); PSMA (e.g., BAY 2315497); PSA (e.g., ThermoFisher Catalog #PA1-38514; Daniels-Wells et al. *BMC Cancer,* 2013; 13:195); PSCA (e.g., AGS-1C4D4); PTK7 (e.g., cofetuzumab); PVRIG; Ras mutant (e.g., Shin et al. Sci Adv. 2020; 6(3):eaay2174); RET (e.g., WO2020210551); RGS5 (e.g., TF-TA503075); RhoC (e.g., ThermoFisher Catalog PA5-77866); ROR2 (e.g., BA3021); ROS1 (e.g., WO2019107671); SART3 (e.g., TF 18025-1-AP); SLC12A2 (e.g., ThermoFisher Catalog #13884-1-AP); SLC38A1 (e.g., ThermoFisher Catalog #12039-1-AP); SLC39A6 (e.g., ladiratuzumab); SLC44A4 (e.g., ASG-5ME); SLC7A11 (e.g., ThermoFisher Catalog #PA1-16893); SLITRK6 (e.g., sirtratumab); SSX2 (e.g., ThermoFisher Catalog #MA5-24971); survivin (e.g., PA1-16836); TACSTD2 (e.g., PA5-47074); TAG-72 (e.g., MA1-25956); TIGIT (e.g., etigilimab); TM4SF5 (e.g., 18239-1-AP); TMPRSS11D (e.g., PA5-30927); TNFRSF12 (e.g., BAY-356); TRAIL (e.g., Catalog #12-9927-42); Trem2 (e.g., PY314); TRP-2 (e.g., PA5-52736); uPAR (e.g., ATN-658); UPK1B (e.g., ThermoFisher Catalog #PA5-56863); UPK2 (e.g., ThermoFisher Catalog #PA5-60318); UPK3B (e.g., ThermoFisher Catalog #PA5-52696); VEGF (e.g., GNR-011); VEGFR2 (e.g., gentuximab); CD44 (e.g., RG7356); WT1 (e.g., ThermoFisher Catalog #MA5-32215); XAGE1 (e.g., ThermoFisher Catalog #PA5-46413); CTLA4 (e.g., ipilimumab); Sperm protein 17 (e.g., BS-5754R); TLR2/4/1 (e.g., tomaralimab); B7-1 (e.g., galiximab); ANXA1 (e.g., Catalog #71-3400); BCR-ABL; CAMPATH-1 (e.g., alemtuzumab; ALLO-647; ANT1034); CD123 (e.g., BAY-943; CSL360); CD19 (e.g., ALLO-501); CD20 (e.g., divozilimab; ibritumomab); CD30 (e.g., iratumumab); CD33 (e.g., lintuzumab; BI 836858; AMG 673); CD352 (e.g., SGN-CD352A); CD37 (e.g., lilotomab; GEN3009); CD40 (e.g., dacetuzumab; lucatumumab); CD45 (e.g., apamistamab); CD48 (e.g., SGN-CD48A); CXCR4 (e.g., ulocuplumab); ETV6-AML (e.g., Catalog #PA5-81865); ROR1 (e.g., cirmtuzumab); CD74 (e.g., milatuzumab); SIT1 (e.g., PA5-53825); SLAMF7 (e.g., Elotuzumab); Axl (e.g., BA3011; tilvestamab); Siglecs 1-16 (see, e.g., Angata et al. Trends Pharmacol Sci. 2015; 36(10): 645-660); SIRPa (e.g., Catalog #17-1729-42); SIRPg (e.g., PA5-104381); OX40 (e.g., ABM193); PROM1 (e.g., Catalog #14-1331-82); TMEM132A (e.g., Catalog #PA5-62524); TMEM40 (e.g., PA5-60636); PD-1 (e.g., balstilimab; budigalimab; geptanolimab); ALK (e.g., DLX521); CCR4 (e.g., AT008; mogamulizumab-kpkc); CD27 (e.g., varlilumab); CD278 (e.g., feladilimab; vopratelimab); CD32 (e.g., mAb 2B6); CD47 (e.g., letaplimab; magrolimab); and CD70 (e.g., cusatuzumab).

[0276] In some embodiments, an antibody can bind specifically to a cancer cell antigen associated with a solid tumor and/or a hematological cancer. Non-limiting examples of target antigens and associated antibodies that bind specifically to cancer cell antigens associated with a solid tumor

and/or a hematological cancer target antigen include Axl (e.g., BA3011; tilvestamab); B7-H3 (e.g., enoblituzumab, omburtamab, MGD009, MGC018, DS-7300); B7-H4 (e.g., Catalog #14-5949-82); B7-H6 (e.g., Catalog #12-6526-42); B7-H7; Siglecs 1-16 (see, e.g., Angata et al. Trends Pharmacol Sci. 2015; 36(10): 645-660); SIRPa (e.g., Catalog #17-1729-42); SIRPg (e.g., PA5-104381); OX40 (e.g., ABM193); PROM1 (e.g., Catalog #14-1331-82); TMEM132A (e.g., Catalog #PA5-62524); TMEM40 (e.g., PA5-60636); PD-1 (e.g., balstilimab; budigalimab; geptanolimab); ALK (e.g., DLX521); CCR4 (e.g., AT008; mogamulizumab-kpkc); CD27 (e.g., varlilumab); CD278 (e.g., feladilimab; vopratelimab); CD32 (e.g., mAb 2B6); CD47 (e.g., letaplimab; magrolimab); and CD70 (e.g., cusatuzumab).

[0277] In some embodiments, an antibody can bind specifically to a cancer cell antigen associated with a solid tumor. Non-limiting examples of target antigens and associated antibodies that bind specifically to solid-tumor-associated target antigens include PAX3 (e.g., GT1210, ThermoFisher Catalog #MA5-31583); Sialyl-Thomsen-nouveau-antigen (e.g., Eavarone et al. *PLoS One.* 2018; 13(7): e0201314); PDGFR-B (e.g., rinucumab); ADAM12 (e.g., Catalog #14139-1-AP); ADAM9 (e.g., IMGC936); AFP (e.g., ThermoFisher Catalog #PA5-25959); AGR2 (e.g., ThermoFisher Catalog #PA5-34517); AKAP-4 (e.g., Catalog #PA5-52230); androgen receptor (e.g., ThermoFisher Catalog #MA5-13426); ALPP (e.g., Catalog #MA5-15652); CD44 (e.g., RG7356); AMHR2 (e.g., ThermoFisher Catalog #PA5-13902); ANTXR1 (e.g., Catalog #MA1-91702); ARTN (e.g., ThermoFisher Catalog #PA5-47063); αvβ6; CA19-9 (e.g., AbGn-7; MVT-5873); carcinoembryonic antigen (e.g., arcitumomab; cergutuzumab; amunaleukin; labetuzumab); CD115 (e.g., axatilimab; cabiralizumab; emactuzumab); CD137 (e.g., ADG106; CTX-471); CD147 (e.g., gavilimomab; Metuzumab); CD155 (e.g., U.S. Publication No. 2018/0251548); CD274 (e.g., adebrelimab; atezolizumab; garivulimab); CDCP1 (e.g., RG7287); CDH3 (e.g., PCA062); CDH6 (e.g., HKT288); CEACAM1; CEACAM6); CLDN18.1 (e.g., zolbetuximab); CLDN18.2 (e.g., zolbetuximab); CLPTM1L; CS-1 (e.g., tigatuzumab); GD3 (e.g., mitumomab); HLA-G (e.g., TTX-080); IL1RAP (e.g., nidanilimab); LAG-3 (e.g., encelimab); LY6G6D (e.g., PA5-23303); LYPD1 (e.g., ThermoFisher Catalog #PA5-26749); MAD-CT-2; MAGEA3 (e.g., ThermoFisher Catalog #60054-1-IG); MAGEA4 (e.g., Catalog #MA5-26117); MAGEC2 (e.g., ThermoFisher Catalog #PA5-64010); MLANA (e.g., Catalog #MA5-15237); MELTF (e.g., ThermoFisher Catalog #H00004241-M04A); MSLN (e.g., 5B2, Catalog #MA5-11918); MUC1 (e.g., MH1 (CT2), ThermoFisher Catalog #MA5-11202); MUC5AC (e.g., 45M1, Catalog #MA5-12178); MYCN (e.g., NCM-II 100, ThermoFisher Catalog #MA1-170); NCAM1 (e.g., ThermoFisher Catalog #MA5-11563); Nectin-4 (e.g., enfortumab); NY—BR-1 (e.g., NY—BR-1 No. 2, Catalog #MA5-12645); PSMA (e.g., BAY 2315497); PSA (e.g., ThermoFisher Catalog #PA1-38514; Daniels-Wells et al. *BMC Cancer* 2013; 13:195); PSCA (e.g., AGS-1C.sub.4D4); PTK7 (e.g., cofetuzumab); PVRIG; Ras mutant (e.g., Shin et al. *Sci Adv.* 2020; 6(3):eaay2174); RET (e.g., WO2020210551); RGS5 (e.g., TF-TA503075); RhoC (e.g., ThermoFisher Catalog PA5-77866); ROR2 (e.g., BA3021); ROS1 (e.g., WO2019107671); SART3 (e.g., TF 18025-1-AP); SLC12A2 (e.g., ThermoFisher Catalog #13884-1-AP); SLC38A1 (e.g., ThermoFisher Catalog #12039-1-AP); SLC39A6 (e.g., ladiratuzumab); SLC44A4 (e.g., ASG-5ME); SLC7A11 (e.g., ThermoFisher Catalog #PA1-16893); SLITRK6 (e.g., sirtratumab); SSX2 (e.g., ThermoFisher Catalog #MA5-24971); survivin (e.g., PA1-16836); TACSTD2 (e.g., PA5-47074); TAG-72 (e.g., MA1-25956); TIGIT (e.g., etigilimab); TM4SF5 (e.g., 18239-1-AP); TMPRSS11D (e.g., PA5-30927); TNFRSF12 (e.g., BAY-356); TRAIL (e.g., Catalog #12-9927-42); Trem2 (e.g., PY314); TRP-2 (e.g., PA5-52736); uPAR (e.g., ATN-658); UPK1B (e.g., ThermoFisher Catalog #PA5-56863); UPK2 (e.g., ThermoFisher Catalog #PA5-60318); UPK3B (e.g., ThermoFisher Catalog #PA5-52696); VEGF (e.g., GNR-011); VEGFR2 (e.g., gentuximab); CD44 (e.g., RG7356); WT1 (e.g., ThermoFisher Catalog #MA5-32215); XAGE1 (e.g., ThermoFisher Catalog #PA5-46413); and CTLA4 (e.g., ipilimumab).

[0278] In some embodiments, an antibody can bind specifically to a cancer cell antigen associated

with a hematological cancer. Non-limiting examples of target antigens and associated antibodies that bind specifically to hematological cancer cell target antigens include Sperm protein 17 (e.g., BS-5754R); TLR2/4/1 (e.g., Tomaralimab); B7-1 (e.g., galiximab); ANXA1 (e.g., Catalog #71-3400); BCR-ABL; CAMPATH-1 (e.g., alemtuzumab; ALLO-647; ANT1034); CD123 (e.g., BAY-943; CSL360); CD19 (e.g., ALLO-501); CD20 (e.g., divozilimab; ibritumomab); CD30 (e.g., iratumumab); CD33 (e.g., lintuzumab; BI 836858; AMG 673); CD352 (e.g., SGN-CD352A); CD37 (e.g., lilotomab; GEN3009); CD40 (e.g., dacetuzumab; lucatumumab); CD45 (e.g., apamistamab); CD48 (e.g., SGN-CD48A); CXCR4 (e.g., ulocuplumab); ETV6-AML (e.g., Catalog #PA5-81865); ROR1 (e.g., cirmtuzumab); CD74 (e.g., milatuzumab); SIT1 (e.g., PA5-53825); and SLAMF7 (e.g., elotuzumab).

[0279] In some embodiments, an antibody is used that binds specifically to a target antigen (e.g., an antigen associated with a disease or disorder). Antibodies that bind specifically to a target antigen (e.g., an antigen associated with a disease or disorder) are available commercially or are produced by any method known to one of skill in the art such as, e.g., recombinant expression techniques. The nucleotide sequences encoding antibodies that bind specifically to a target antigen (e.g., an antigen associated with a disease or disorder) are obtainable, e.g., from the GenBank database or similar database, literature publications, or by routine cloning and sequencing.

[0280] Non-limiting examples of target antigens and associated antibodies that bind specifically to target antigens (e.g., an antigen associated with a disease or disorder, or an antigen associated with an immune cell) include CD163 (e.g., TBI 304H); TIGIT (e.g., etigilimab); DCSIGN (see, e.g., International Publication No. WO2018134389); IFNAR1 (e.g., faralimomab); ASCT2 (e.g., idactamab); ULBP1/2/3/4/5/6 (e.g., PA5-82302); CLDN1 (e.g., INSERM anti-Claudin-1); CLDN2 (see, e.g., International Publication No. WO2018123949); IL-21R (e.g., PF-05230900); DCIR; DCLK1 (see, e.g., International Publication No. WO2018222675); Dectin1 (see, e.g., U.S. Pat. No. 9,045,542); GITR (e.g., ragifilimab); ITGAV (e.g., abituzumab); LY9 (e.g., PA5-95601); MICA (e.g., 1E2C8, Catalog #66384-1-IG); MICB (e.g., Catalog #MA5-29422); NOX1 (e.g., Catalog #PA5-103220); CD2 (e.g., BTI-322; siplizumab); CD247 (e.g., AFM15); CD25 (e.g., basiliximab); CD28 (e.g., REGN5668); CD3 (e.g., otelixizumab; visilizumab); CD38 (e.g., felzartamab; AMG 424); CD3E (e.g., foralumab; teplizumab); CD5 (e.g., MAT 304; zolimomab aritox); ALPPL2 (e.g., Catalog #PA5-22336); B7-2 (e.g., Catalog #12-0862-82); B7-H3 (e.g., enoblituzumab, omburtamab, MGD009, MGC018, DS-7300); B7-H4 (e.g., Catalog #14-5949-82); B7-H6 (e.g., Catalog #12-6526-42); B7-H7; BAFF-R (e.g., Catalog #14-9117-82); BMPR2; BORIS; CD112 (see, e.g., U.S. Publication No. 20100008928); CD24 (see, e.g., U.S. Pat. No. 8,614,301); CD244 (e.g., R&D AF1039); CD30L (see, e.g., U.S. Pat. No. 9,926,373); CD3D; CD3G; CD79A (see, e.g., International Publication No. WO 2020252110); CD83 (e.g., CBT004); CD97; CDH17 (see, e.g., International Publication No. WO 2018115231); CLDN16; CLDN19; CYP1B1; DPEP3; DPP4; DSG2 (see, e.g., U.S. Pat. No. 10,836,823); EPHA receptors; epidermal growth factor; FAS; FGFR1 (e.g., RG7992); FGFR3 (e.g., vofatamab); FN1; FOLR1 (e.g., farletuzumab); FSHR; FZD5; GM2 (e.g., BIW-8962); GM3 (e.g., racotumomab); GPA33 (e.g., KRN330); GPC3 (e.g., codrituzumab); HAS3; HLA-E; HLA-F; HLA-DR; ICAM1; IFNAR2; IL13Ra2; IL-5R (e.g., benralizumab); KISSIR; LAMPi; LAYN; LCK; legumain; LILRB2; LILRB4; LMP2; MAD-CT-1; MAGEA1 (e.g., Catalog #MA5-11338); MerTk (e.g., DS5MMER, Catalog #12-5751-82); MFSD13A; hTERT; gp100; Fas-related antigen 1; a metalloproteinase; Mincle (e.g., OTI2A8, Catalog #TA505101); NA17; NY-ESO-1 (e.g., E978m, Catalog #35-6200); polysialic acid (see, e.g., Watzlawik et al. *J Nat Sci.* 2015; 1(8):e141); PR1; Sarcoma translocation breakpoints; SLC10A2 (e.g., ThermoFisher Catalog #PA5-18990); SLC17A2 (e.g., ThermoFisher Catalog #PA5-106752); SLC39A5 (e.g., ThermoFisher Catalog #MA5-27260); SLC6A15 (e.g., ThermoFisher Catalog #PA5-52586); SLC6A6 (e.g., ThermoFisher Catalog #PA5-53431); SLC7A5; and CALCR (see, e.g., International Publication No. WO 2015077826).

[0281] In some embodiments, an antibody can bind specifically to an antigen associated with

anemia. A non-limiting example of an antibody that binds specifically to an antigen associated with anemia includes CD163 (e.g., TBI 304H).

[0282] In some embodiments, an antibody can bind specifically to an antigen associated with a viral infection. Non-limiting examples of target antigens and associated antibodies that binds specifically to an antigen associated with a viral infection include DCSIGN (see, e.g., International Publication No. WO2018134389); IFNAR1 (e.g., faralimomab); ASCT2 (e.g., idactamab); ULBP1/2/3/4/5/6 (e.g., PA5-82302); and CLDN1 (e.g., INSERM anti-Claudin-1).

[0283] In some embodiments, an antibody can bind specifically to an antigen associated with an autoimmune disease. Non-limiting examples of target antigens and associated antibodies that bind specifically to an antigen associated with an autoimmune disease include CLDN2 (see, e.g., International Publication No. WO 2018123949); IL-21R (e.g., PF-05230900); DCIR; DCLK1 (see, e.g., WO2018222675); Dectin1 (see, e.g., U.S. Pat. No. 9,045,542); GITR (e.g., ragifilimab); ITGAV (e.g., abituzumab); LY9 (e.g., PA5-95601); MICA (e.g., 1E2C8, Catalog #66384-1-IG); MICB (e.g., Catalog #MA5-29422); NOX1 (e.g., Catalog #PA5-103220); CD2 (e.g., BTI-322; siplizumab); CD247 (e.g., AFM15); CD25 (e.g., basiliximab); CD28 (e.g., REGN5668); CD3 (e.g., otelixizumab; visilizumab); CD38 (e.g., felzartamab; AMG 424); CD3E (e.g., foralumab; teplizumab); and CD5 (e.g., MAT 304; zolimomab aritox).

[0284] In some embodiments, the antibody is a non-targeted antibody, for example, a non-binding or control antibody. In some embodiments, the antigen is CD30. In some embodiments, the antibody is an antibody or antigen-binding fragment that binds to CD30, such as described in International Patent Publication No. WO 02/43661. In some embodiments, the anti-CD30 antibody is cAC10, which is described in International Patent Publication No. WO 02/43661. cAC10 is also known as brentuximab. In some embodiments, the anti-CD30 antibody comprises the CDRs of cAC10. In some embodiments, the CDRs are as defined by the Kabat numbering scheme. In some embodiments, the CDRs are as defined by the Chothia numbering scheme. In some embodiments, the CDRs are as defined by the IMGT numbering scheme. In some embodiments, the CDRs are as defined by the AbM numbering scheme. In some embodiments, the anti-CD30 antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOs: 1, 2, 3, 4, 5, and 6, respectively. In some embodiments, the anti-CD30 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95% at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 8. In some embodiments, the anti-CD30 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 10 and a light chain comprising the amino acid sequence of SEQ ID NO: 11.

[0285] In some embodiments, an antibody provided herein binds to EphA2. In some embodiments, the antibody comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOs: 12, 13, 14, 15, 16, and 17, respectively. In some embodiments, the anti-EphA2 antibody comprises a heavy chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 18 and a light chain variable region comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 19. In some embodiments, the anti-EphA2 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 20 or SEQ ID NO: 21 and a light chain comprising the amino acid sequence of SEQ ID NO: 22. In some embodiments, the anti-EphA2 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 23 or SEQ ID NO: 24 and a light chain comprising the amino acid

sequence of SEQ ID NO: 25. In some embodiments, the anti-EphA2 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 26 or SEQ ID NO: 27 and a light chain comprising the amino acid sequence of SEQ ID NO: 28. In some embodiments, the antibody is h1C1 or 1C1.

[0286] In some embodiments, the target antigen of an ADC disclosed herein is CD228. In some embodiments, the antigen-binding protein or an antigen-binding fragment thereof is hL49 HALC hIgG1. In some embodiments, the antigen-binding protein or an antigen-binding fragment thereof comprises the following 6 CDRs: [0287] an CDR-11 comprising the amino acid sequence of SEQ ID NO: 29; [0288] an CDR-H2 comprising the amino acid sequence of SEQ ID NO: 30; [0289] an CDR-H3 comprising the amino acid sequence of SEQ ID NO: 31; [0290] an CDR-L1 comprising the amino acid sequence of SEQ ID NO: 32; [0291] an CDR-L2 comprising the amino acid sequence of SEQ ID NO: 33; and [0292] an CDR-L3 comprising the amino acid sequence of SEQ ID NO: 34.

[0293] In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises a VH and a VL, wherein the VH has at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 35 and the VL has at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 36. In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises a VH and a VL, wherein the VH comprises the amino acid sequence of SEQ ID NO: 35 and the VL comprises the amino acid sequence of SEQ ID NO: 36. In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises an HC comprising the amino acid sequence of SEQ ID NO: 37 or SEQ ID NO: 38 and an LC comprising the amino acid sequence of SEQ ID NO: 39. In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises an HC comprising the amino acid sequence of SEQ ID NO: 40 or SEQ ID NO: 41 and an LC comprising the amino acid sequence of SEQ ID NO: 42.

[0294] In some embodiments, the target antigen of an ADC disclosed herein is αvβ6. In some embodiments, the antigen-binding protein or antigen-binding fragment thereof is h2A2 HCLG hIgG1. In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises the following 6 CDRs: [0295] an CDR-H1 comprising the amino acid sequence of SEQ ID NO: 43; [0296] an CDR-H2 comprising the amino acid sequence of SEQ ID NO: 44; [0297] an CDR-H3 comprising the amino acid sequence of SEQ ID NO: 45; [0298] an CDR-L1 comprising the amino acid sequence of SEQ ID NO: 46; [0299] an CDR-L2 comprising the amino acid sequence of SEQ ID NO: 47; and [0300] an CDR-L3 comprising the amino acid sequence of SEQ ID NO: 48.

[0301] In some embodiments, the antigen binding protein or antigen-binding fragment thereof comprises a VH and a VL, wherein the VH has at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 49 and the VL has at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 50. In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises a VH and a VL, wherein the VH comprises the amino acid sequence of SEQ ID NO: 49 and the VL comprises the amino acid sequence of SEQ ID NO: 50. In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises an HC comprising the amino acid sequence of SEQ ID NO: 51 or SEQ ID NO: 52 and an LC comprising the amino acid sequence of SEQ ID NO: 53. In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises an HC comprising the amino acid sequence of SEQ ID NO: 54 or SEQ ID NO: 55 and an LC comprising the amino acid sequence of SEQ ID NO: 56.

[0302] In some embodiments, the target antigen of an ADC disclosed herein is B7-H4. In some embodiments, the antigen-binding protein or antigen-binding fragment thereof is B7H41001

hIgG1. In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises the following 6 CDRs: [0303] an CDR-H1 comprising the amino acid sequence of SEQ ID NO: 57; [0304] an CDR-H2 comprising the amino acid sequence of SEQ ID NO: 58; [0305] an CDR-H3 comprising the amino acid sequence of SEQ ID NO: 59; [0306] an CDR-L1 comprising the amino acid sequence of SEQ ID NO: 60; [0307] an CDR-L2 comprising the amino acid sequence of SEQ ID NO: 61; and [0308] an CDR-L3 comprising the amino acid sequence of SEQ ID NO: 62.

[0309] In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises a VH and a VL, wherein the VH has at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 63 and the VL has at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 64. In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises a VH and a VL, wherein the VH comprises the amino acid sequence of SEQ ID NO: 63 and the VL comprises the amino acid sequence of SEQ ID NO: 64. In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises an HC comprising the amino acid sequence of SEQ ID NO: 65 or SEQ ID NO: 66 and an LC comprising the amino acid sequence of SEQ ID NO: 67. In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises an HC comprising the amino acid sequence of SEQ ID NO: 68 or SEQ ID NO: 69 and an LC comprising the amino acid sequence of SEQ ID NO: 70.

[0310] In some embodiments, the antigen-binding protein or antigen-binding fragment thereof is selected from the group consisting of B7H4-15461, B7H4-20500, B7H4-20501, B7H4-20502.1, B7H4-22208, B7H4-15462, B7H4-22213, B7H4-15465, B7H4-20506, B7H4-15483, B7H4-20513, B7H4-22216, B7H4-15489, B7H4-20516, B7H4-15472, B7H4-15503, B7H4-15495, B7H4-15478, B7H4-15441, and B7H4-20496. In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises VH CDR1, VH CDR2, VH CDR3 and VL CDR1, VL CDR2, and VL CDR3 sequences selected from the group consisting of: [0311] (a) SEQ ID NOs: 71-76, respectively; [0312] (b) SEQ ID NOs: 79-84, respectively; [0313] (c) SEQ ID NOs: 87-92, respectively; [0314] (d) SEQ ID NOs: 95-100, respectively; [0315] (e) SEQ ID NOs: 103-108, respectively; [0316] (f) SEQ ID NOs: 111-116, respectively; [0317] (g) SEQ ID NOs: 119-124, respectively; [0318] (h) SEQ ID NOs: 127-132, respectively; [0319] (i) SEQ ID NOs: 135-140, respectively; [0320] (j) SEQ ID NOs: 143-148, respectively; [0321] (k) SEQ ID NOs: 151-156, respectively; [0322] (l) SEQ ID NOs: 159-164, respectively; [0323] (m) SEQ ID NOs: 167-172, respectively; [0324] (n) SEQ ID NOs: 175-180, respectively; [0325] (o) SEQ ID NOs: 183-188, respectively; [0326] (p) SEQ ID NOs: 191-196, respectively; [0327] (q) SEQ ID NOs: 199-204, respectively; [0328] (r) SEQ ID NOs: 207-212, respectively; [0329] (s) SEQ ID NOs: 215-220, respectively; and [0330] (t) SEQ ID NOs: 223-228, respectively.

[0331] In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises a VH and a VL, wherein the VH has at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 77, 85, 93, 101, 109, 117, 125, 133, 141, 149, 157, 165, 173, 181, 189, 197, 205, 213, 221, and 229 and the VL has at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174, 182, 190, 198, 206, 214, 222, and 230, respectively. In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises a VH and a VL, wherein the VH has an amino acid sequence selected from the group consisting of SEQ ID NOs: 77, 85, 93, 101, 109, 117, 125, 133, 141, 149, 157, 165, 173, 181, 189, 197, 205, 213, 221, and 229 and the VL has an amino acid sequence selected from the group consisting of SEQ ID NOs: 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174, 182, 190, 198, 206, 214, 222, and 230, respectively. In some embodiments, the antigen-binding

protein or antigen-binding fragment thereof comprises an HC comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, and 269 and an LC comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, and 270, respectively.

[0332] In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises CDR, VH, VL, HC, and LC sequences having at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence of SEQ ID NOs 271-1032. In some embodiments, the antigen-binding protein or antigen-binding fragment thereof comprises CDR, VH, VL, HC, and LC amino acid sequences according to SEQ ID NOs 271-1032.

[0333] In some embodiments, antigen binding proteins (ABPs), including antigen binding fragments thereof, (e.g., antibodies and antigen binding fragments thereof) that bind CD228, αvβ6, B7-H4, EphA2, or CD30 are provided herein. The antigen binding proteins and fragments contain an antigen binding domain that specifically binds to CD228, αvβ6, B7-H4, EphA2, or CD30, including to human CD228, αvβ6, B7-H4, EphA2, or CD30. In some embodiments, anti-CD228, anti-αvβ6, anti-B7-H4, anti-EphA2, or anti-CD30 antibody-drug conjugates (ADCs) comprise an anti-CD228, anti-αvβ6, anti-B7-H4, anti-EphA2, or anti-CD30 ABP as described above conjugated to a drug-linker described herein. In some embodiments, these anti-CD228 ADCs are used to treat CD228-expressing cancers such as melanoma, pancreatic cancer, mesothelioma, colorectal cancer, lung cancer, thyroid cancer, breast cancer, choliangiocarcinoma, esophageal cancer and head and neck cancer. In some embodiments, these anti-B7-H4 ADCs are used to treat B7-H4-expressing cancers such as breast cancer, ovarian cancer, lung cancer, endometrial cancer, cholangiocarcinoma, or gallbladder cancer. In some embodiments, these anti-αvβ6 ADCs are used to treat αvβ6-expressing cancers such as non-small cell lung cancer (NSCLC), head and neck cancer, esophageal cancer, breast cancer, ovarian cancer, bladder cancer, skin cancer (SCC), ovarian cancer, cervical cancer, gastric cancer, and pancreatic cancer. In some embodiments, these anti-CD30 ADCs are used to treat CD30-expressing diseases such as cancer, autoimmune diseases, and other infectious diseases. In further embodiments, these anti-CD30 ADCs are used to treat solid and liquid tumors, and autoimmune diseases such as HIV and AIDS. In some embodiments, these anti-EphA2 ADCs are used to treat EphA2-expressing cancers such as esophageal cancer, bladder cancer, renal cell carcinoma, colon cancer, ovarian cancer, endometrial cancer, cervical cancer, or melanoma.

TABLE-US-00001 TABLE OF SEQUENCES SEQ ID NO Description Sequence 1 cAC10 CDR- DYYIT H1 2 cAC10 CDR- WIYPGSGNTKYNEKFKG H2 3 cAC10 CDR- YGNYWFAY H3 4 cAC10 CDR- KASQSVDFDGDSYMN L1 5 cAC10 CDR- AASNLES L2 6 cAC10 CDR- QQSNEDPWT L3 7 cAC10 VH
QIQLQQSGPEVVKPGASVKISCKASGYTFTDYYITWVKQKPGQGLEWIGWIYPGSGNTKYNEK
FKGKATLTVDTSSSTAFMQLSSLTSEDTAVYFCANYGNYWFAYWGQGTQVTVSA 8
cAC10 VL
DIVLTQSPASLAVSLGQRATISCKASQSVDFDGDSYMNWYQQKPGQPPKVLIYAASNLESGIPA
RFSGSGSGTDFTLNIHPVEEEDAATYYCQQSNEDPWTFGGGTKLEIK 9 cAC10 HC
QIQLQQSGPEVVKPGASVKISCKASGYTFTDYYITWVKQKPGQGLEWIGWIYPGSGNTKYNEK
FKGKATLTVDTSSSTAFMQLSSLTSEDTAVYFCANYGNYWFAYWGQGTQVTVSAAST
KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGG
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK 10 cAC10 HC v2
QIQLQQSGPEVVKPGASVKISCKASGYTFTDYYITWVKQKPGQGLEWIGWIYPGSGNTKYNEK

FKGKATLTVDTSSSTAFMQLSSLTSEDTAVYFCANYGNYWFAYWGQGTQVTVSAAST
KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGG
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STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
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QQGNVFSCSVMHEALHNHYTQKSLSLSPG 11 cAC10 LC
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GIPARFSGSGSGTDFTLNIHPVEEEDAATYYCQQSNEDPWTFGGGTKLEIKR
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KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 12 h1C1 CDR-
HYMMA H1 13 h1C1 CDR- RIGPSGGPTHYADSVKG H2 14 h1C1 CDR-
YDSGYDYVAVAGPAEYFQH H3 15 h1C1 CDR- RASQSISTWLA L1 16 h1C1 CDR-
KASNLHT L2 17 hlC1 CDR- QQYNSYSRT L3 18 h1C1 VH
EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYMMAWVRQAPGKGLEWVSRIGPSGGPTHYAD
SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGYDSGYDYVAVAGPAEYFQHWGQGTL
VTVSS 19 h1C1 VL
DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQKPGKAPKLLIYKASNLHTGVPSRFSG
SGSGTEFSLTISGLQPDDFATYYCQQYNSYSRTFGQGTKVEIK 20 h1C1 HC
EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYMMAWVRQAPGKGLEWVSRIGPSGGPTHYAD
SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGYDSGYDYVAVAGPAEYFQHWGQGTL
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STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
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EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYMMAWVRQAPGKGLEWVSRIGPSGGPTHYAD
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DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQKPGKAPKLLIYKASNLHTGVPSRFSG
SGSGTEFSLTISGLQPDDFATYYCQQYNSYSRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGT
ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 23 h1C1 mIgG2a
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HC
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VTVSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQS
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PPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALP
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DFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGL
HNHHTTKSFSRTPGK 24 h1C1 mIgG2a
EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYMMAWVRQAPGKGLEWVSRIGPSGGPTHYAD
HC v2

SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGYDSGYDYVAVAGPAEYFQHWGQGTL
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DLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIF
PPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALP
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HNHHTTKSFSRTPG 25 h1C1 mκ LC
DIQMTQSPSSLSASVGDRVTITCRASQSISTWLAWYQQKPGKAPKLLIYKASNLHTGVPSRFSG
SGSGTEFSLTISGLQPDDFATYYCQQYNSYSRTFGQGTKVEIKRADAAPTVSIFPPSSEQLTSGG
ASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERIINS
YTCEATHKTSTSPIVKSFNRNEC 26 h1C1 mIgG2a
EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYMMAWVRQAPGKGLEWVSRIGPSGGPTHYAD
LALAPG HC
SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGYDSGYDYVAVAGPAEYFQHWGQGTL
VTVSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQS
DLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFI
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LHNHHTTKSFSRTPGK 27 h1C1 mIgG2a
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LALAPG HC
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LHNHHTTKSFSRTPG 28 h1C1
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LC
ASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNS
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YISDSGITYYNPSLKS CDR-H2 31 hL49 HA RTLATYYAMDY CDR-H3 32 hL49 LC
RASQSLVIISDGNTYLII CDR-L1 33 hL49 LC RVSNRFS CDR-L2 34 hL49 LC
SQSTHVPPT CDR-L3 35 hL49 HA VH
QVQLQESGPGLVKPSETLSLTCTVSGDSITSGYWNWIRQPPGKGLEYIGYISDSGITYYN
PSLKSRVTISRDTSKNQYSLKLSSVTAADTAVYYCARRTLATYYAMDYWGQGTLVTVSS 36
hL49 LC VL
DFVMTQSPLSLPVTLGQPASISCRASQSLVHSDGNTYLHWYQQRPGQSPRLLIYRVSNRFSGVP
DRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPPTFGQGTKLEIK 37 hL49 HA HC
QVQLQESGPGLVKPSETLSLTCTVSGDSITSGYWNWIRQPPGKGLEYIGYISDSGITYYNPSLKS
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FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP
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RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV

EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGK 38 hL49 HA HC
QVQLQESGPGLVKPSETLSLTCTVSGDSITSGYWNWIRQPPGKGLEYIGYISDSGITYYNPSLKS
v2
RVTISRDTSKNQYSLKLSSVTAADTAVYYCARRTLATYYAMDYWGQGTLVTVSSASTKGPSV
FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP
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SLSPG 39 hL49 LC LC
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LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE
KHKVYACEVTHQGLSSPVTKSFNRGEC 40 hL49 HA
QVQLQESGPGLVKPSETLSLTCTVSGDSITSGYWNWIRQPPGKGLEYIGYISDSGITYYNPSLKS
LALAKA HC
RVTISRDTSKNQYSLKLSSVTAADTAVYYCARRTLATYYAMDYWGQGTLVTVSSASTKGPSV
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174 B7H4-15489

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B7H4-20496
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GIIPIFGKAHYAQKFQG 01/PD-L1 CDR-H2 273 SG-559- KFHFVSGSPFGMDV 01/PD-L1
CDR-H3 274 SG-559- RASQSVSSYLA 01/PD-L1 CDR-L1 275 SG-559- DASNRAT 01/PD-L1
CDR-L2 276 SG-559- QQRSNWPT 01/PD-L1 CDR-L3 277 SG-559-
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DYGDYGMDY H3 282 h1F6 CDR- RASKSVSTSGYSFMH L1 283 h1F6 CDR- LASNLES
L2 284 h1F6 CDR- QHSREVPWT L3 285 h1F6 VH

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290 TROP2 CDR- WINTYTGEPTYTDDFKG H2 291 TROP2 CDR- GGFGSSYWYFDV H3
292 TROP2 CDR- KASQDVSIAVA L1 293 TROP2 CDR- SASYRYT L2 294 TROP2 CDR-
QQHYITPLT L3 295 TROP2 VH
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TAGMQ H1 298 TROP2 CDR- WINTHSGVPKYAEDFKG H2 299 TROP2 CDR-
SGFGSSYWYFDV H3 300 TROP2 CDR- KASQDVSTAVA L1 301 TROP2 CDR- SASYRYT
L2 302 TROP2 CDR- QQHYITPLT L3 303 TROP2 VH
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306 MICA CDR- YIEPYNVVPMYNPKFKG H2 307 MICA CDR- SGSSNFDY H3 308
MICA CDR- SASSSISSHYLH L1 309 MICA CDR- RTSNLAS L2 310 MICA CDR-
QQGSSLPLT L3 311 MICA VH
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314 MICA CDR- LIWYDGSNKFYGDSVKG H2 315 MICA CDR- EGSGHY H3 316
MICA CDR- RASQGISSALA L1 317 MICA CDR- DASSLES L2 318 MICA CDR-
QQFNSYPIT L3 319 MICA VH
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322 MICA CDR- YISPGGDYIYYADSVKG H2 323 MICA CDR- DRRHYGSYAMDY H3

324 MICA CDR- RSSKSLLHSNLNTYLY L1 325 MICA CDR- RMSNLAS L2 326 MICA CDR- MQHLEYPFT L3 327 MICA VH
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334 MICA CDR- QQVNRGAAIT L3 335 MICA VH
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EARGSYAFDI CDR-H3 340 ITGav/CD51 RASQSVSSYLA CDR-L1 341 ITGav/CD51
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H3 348 ITGav CDR- RASQDISNYLA L1 349 ITGav CDR- YTSKIHS L2 350 ITGav CDR-
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H1 354 gpA33 CDR- TIYYNGSTYYSPSLKS H2 355 gpA33 CDR- QGYDIKINIDV H3 356
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H1 362 IL1Rap CDR- RIYPGDGNTHYAQKFQG H2 363 IL1Rap CDR- GYLDPMDY H3
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CDR- QQYSILPWT L3 367 IL1Rap VH
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AQNLEIPRT CDR-L3 399 EpCAM VH
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AQNLELPRT CDR-L3 407 EpCAM VH
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EpCAM VL
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DYSMH CDR-H1 410 EpCAM WINTETGEPTYADDFKG CDR-H2 411 EpCAM TAVY CDR-
H3 412 EpCAM RASQEISVSLS CDR-L1 413 EpCAM ATSTLDS CDR-L2 414 EpCAM
LQYASYPWT CDR-L3 415 EpCAM VH
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H1 418 CD352 CDR- WINTYSGEPRYADDFKG H2 419 CD352 CDR- DYGRWYFDV H3
420 CD352 CDR- RASSSVSHMH L1 421 CD352 CDR- ATSNLAS L2 422 CD352 CDR-
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426 CS1 CDR-H2 EINPDSSTINYAPSLKD 427 CS1 CDR-H3 PDGNYWYFDV 428 CS1
CDR-L1 KASQDVGIAVA 429 CS1 CDR-L2 WASTRHT 430 CS1 CDR-L3 QQYSSYPYT
431 CS1 VH
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CS1 VL
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H1 434 CD38 CDR- AISGSGGGTYYADSVKG H2 435 CD38 CDR- DKILWFGEPVFDY H3
436 CD38 CDR- RASQSVSSYLA L1 437 CD38 CDR- DASNRAT L2 438 CD38 CDR-
QQRSNWPPT L3 439 CD38 VH
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440 CD38 VL
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GSGTDFTLTISSLEPEDFAVYYCQQRSNWPPTFGQGTKVEIKR 441 CD25 CDR- SYRMH
H1 442 CD25 CDR- YINPSTGYTEYNQKFKD H2 443 CD25 CDR- GGGVFDY H3 444
CD25 CDR- SASSSISYMH L1 445 CD25 CDR- TTSNLAS L2 446 CD25 CDR-
HQRSTYPLT L3 447 CD25 VH
QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYRMHWVRQAPGQGLEWIGYINPSTGYTEYNQ
KFKDKATITADESTNTAYMELSSLRSEDTAVYYCARGGGVFDYWGQGTLVTVSS 448
CD25 VL
DIQMTQSPSTLSASVGDRVTITCSASSSISYMHWYQQKPGKAPKLLIYTTSNLASGVPARFSGSG
SGTEFTLTISSLQPDDFATYYCHQRSTYPLTFGQGTKVEVK 449 ADAM9 SYWMH CDR-H1
450 ADAM9 EIIPINGHTNYNEKFKS CDR-H2 451 ADAM9 GGYYYYGSRDYFDY CDR-H3
452 ADAM9 KASQSVDYDGDSYMN CDR-L1 453 ADAM9 AASDLES CDR-L2 454 ADAM9
QQSHEDPFT CDR-L3 455 ADAM9 VH
QVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGEIIPINGHTNYNE
KFKSKATLTLDKSSSTAYMQLSSLASEDSAVYYCARGGYYYYGSRDYFDYWGQGTTLTVSS
456 ADAM9 VL
DIVLTQSPASLAVSLGQRATISCKASQSVDYDGDSYMNWYQQIPGQPPKLLIYAASDLESGIPA
RFSGSGSGTDFTLNIHPVEEEDAATYYCQQSHEDPFTFGGGTKLEIK 457 ADAM9 SYWMH
CDR-H1 458 ADAM9 EIIPIFGHTNYNEKFKS CDR-H2 459 ADAM9 GGYYYYPRQGFLDY
CDR-H3 460 ADAM9 KASQSVDYSGDSYMN CDR-L1 461 ADAM9 AASDLES CDR-L2 462
ADAM9 QQSHEDPFT CDR-L3 463 ADAM9 VH
EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYWMHWVRQAPGKGLEWVGEIIPIFGHTNYNEK
FKSRFTISLDNSKNTLYLQMGSLRAEDTAVYYCARGGYYYYPRQGFLDYWGQGTTVTVSS
464 ADAM9 VL
DIVMTQSPDSLAVSLGERATISCKASQSVDYSGDSYMNWYQQKPGQPPKLLIYAASDLESGIPA
RFSGSGSGTDFTLTISSLEPEDFATYYCQQSHEDPFTFGQGTKLEIK 465 CD59 CDR-
SYGMN H1 466 CD59 CDR- YISSSSSTIYYADSVKG H2 467 CD59 CDR- GPGMDV H3
468 CD59 CDR- KSSQSVLYSSNNKNYLA L1 469 CD59 CDR- WASTRES L2 470 CD59
CDR- QQYYSTPQLT L3 471 CD59 VH
QVQLQQSGGGVVQPGRSLGLSCAASGFTFSSYGMNWVRQAPGKGLEWVSYISSSSSTIYYADS
VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGPGMDVWGQGTTVTVS 472 CD59
VL
DIVLTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTRESGV

PDRFSGSGSGTDFTPAISSLQAEDVAVYYCQQYYSTPQLTFGGGTKVDIK 473 CD19 TSGMGVG (hBU12) CDR-H1 474 CD19 HIWWDDDKRYNPALKS (hBU12) CDR-H2 475 CD19 MELWSYYFDY (hBU12) CDR-H3 476 CD19 SASSSVSYMH (hBU12) CDR-L1 477 CD19 DTSKLAS (hBU12) CDR-L2 478 CD19 FQGSVYPFT (hBU12) CDR-L3 479 CD19 QVQLQESGPGLVKPSQTLSLTCTVSGGSISTSGMGVGWIRQHPGKGLEWIGHIWWDDDKRYNP (hBU12) VH ALKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARMELWSYYFDYWGQGTLVTVSS 480 CD19 EIVLTQSPATLSLSPGERATLSCSASSSVSYMHWYQQKPGQAPRLLIYDTSKLASGIPARFSGSG (hBU12) VL SGTDFTLTISSLEPEDVAVYYCFQGSVYPFTFGQGTKLEIKR 481 CD19 QVQLQESGPGLVKPSQTLSLTCTVSGGSISTSGMGVGWIRQHPGKGLEWIGHIWWDDDKR (hBU12) HC YNPALKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARMELWSYYFDYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK 482 CD19 EIVLTQSPATLSLSPGERATLSCSASSSVSYMHWYQQKPGQAPRLLIYDTSKLASGIPAR (hBU12) LC FSGSGSGTDFTLTISSLEPEDVAVYYCFQGSVYPFTFGQGTKLEIKRTVAAPSVFIFPPS DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 483 CD138 CDR- NYWIE H1 484 CD138 CDR- EILPGTGRTIYNEKFKG H2 485 CD138 CDR- RDYYGNFYYAMDY H3 486 CD138 CDR- SASQGINNYLN L1 487 CD138 CDR- YTSTLQS L2 488 CD138 CDR- QQYSKLPRT L3 489 CD138 VH QVQLQQSGSELMMPGASVKISCKATGYTFSNYWIEWVKQRPGHGLEWIGEILPGTGRTIY NEKFKGKATFTADISSNTVQMQLSSLTSEDSAVYYCARRDYYGNFYYAMDYWGQGTSVTVSS 490 CD138 VL DIQMTQSTSSLSASLGDRVTISCSASQGINNYLNWYQQKPDGTVELLIYYTSTLQSGVP SRFSGSGSGTDYSLTISNLEPEDIGTYYCQQYSKLPRTFGGGTKLEIK 491 CD166 CDR- TYGMGVG H1 492 CD166 CDR- NIWWSEDKHYSPSLKS H2 493 CD166 CDR- IDYGNDYAFTY H3 494 CD166 CDR- RSSKSLLHSNGITYLY L1 495 CD166 CDR- QMSNLAS L2 496 CD166 CDR- AQNLELPYT L3 497 CD166 VH QITLKESGPTLVKPTQTLTLTCTFSGFSLSTYGMGVGWIRQPPGKALEWLANIWWSEDKHYSPS LKSRLTITKDTSKNQVVLTITNVDPVDTATYYCVQIDYGNDYAFTYWGQGTLVTVSS 498 CD166 VL DIVMTQSPLSLPVTPGEPASISCRSSKSLLHSNGITYLYWYLQKPGQSPQLLIYQMSNLASGVPD RFSGSGSGTDFTLKISRVEAEDVGVYYCAQNLELPYTFGQGTKLEIK 499 CD56 CDR- SFGMH H1 500 CD56 CDR- YISSGSFTIYYADSVKG H2 501 CD56 CDR- MRKGYAMDY H3 502 CD56 CDR- RSSQIIITHSDGNTYLE L1 503 CD56 CDR- KVSNRFS L2 504 CD56 CDR- FQGSHVPHT L3 505 CD56 VH QVQLVESGGGVVQPGRSLRLSCAASGFTFSSFGMHWVRQAPGKGLEWVAYISSGSFTIYYADS VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARMRKGYAMDYWGQGTLVTVSS 506 CD56 VL DVVMTQSPLSLPVTLGQPASISCRSSQIIIHSDGNTYLEWFQQRPGQSPRRLIYKVSNRFSGVPDR FSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPHTFGQGTKVEIK 507 CD74 CDR- NYGVN H1 508 CD74 CDR- WINPNTGEPTFDDDFKG H2 509 CD74 CDR- SRGKNEAWFAY H3 510 CD74 CDR- RSSQSLVHRNGNTYLH L1 511 CD74 CDR-

TVSNRFS L2 512 CD74 CDR- SQSSHVPPT L3 513 CD74 VH
QVQLQQSGSELKKPGASVKVSCKASGYTFTNYGVNWIKQAPGQGLQWMGWINPNTGEPTFD
DDFKGRFAFSLDTSVSTAYLQISSLKADDTAVYFCSRSRGKNEAWFAYWGQGTLVTVSS
514 CD74 VL
DIQLTQSPLSLPVTLGQPASISCRSSQSLVHRNGNTYLHWFQQRPGQSPRLLIYTVSNRFSGVPD
RFSGSGSGTDFTLKISRVEAEDVGVYFCSQSSHVPPTFGAGTRLEIK 515 CEACAM5
TYWMS CDR-H1 516 CEACAM5 EIHPDSSTINYAPSLKD CDR-H2 517 CEACAM5
LYFGFPWFAY CDR-H3 518 CEACAM5 KASQDVGTSVA CDR-L1 519 CEACAM5
WTSTRHT CDR-L2 520 CEACAM5 QQYSLYRS CDR-L3 521 CEACAM5
EVQLVESGGGVVQPGRSLRLSCSASGFDFTTYWMSWVRQAPGKGLEWIGEIHPDSSTINYAPS
VH LKDRFTISRDNAKNTLFLQMDSLRPEDTGVYFCASLYFGFPWFAYWGQGTPVTVSS
522 CEACAM5
DIQLTQSPSSLSASVGDRVTITCKASQDVGTSVAWYQQKPGKAPKLLIYWTSTRHTGVPSRFSG
VL SGSGTDFTFTISSLQPEDIATYYCQQYSLYRSFGQGTKVEIK 523 CanAg CDR-
YYGMN H1 524 CanAg CDR- WIDTTTGEPTYAQKFQG H2 525 CanAg CDR-
RGPYNWYFDV H3 526 CanAg CDR- RSSKSLLHSNGNTYLY L1 527 CanAg CDR-
RMSNLVS L2 528 CanAg CDR- LQHLEYPFT L3 529 CanAg VH
QVQLVQSGAEVKKPGETVKISCKASDYTFTYYGMNWVKQAPGQGLKWMGWIDTTTGEPTYA
QKFQGRIAFSLETSASTAYLQIKSLKSEDTATYFCARRGPYNWYFDVWGQGTTVTVSS 530
CanAg VL
DIVMTQSPLSVPVTPGEPVSISCRSSKSLLHSNGNTYLYWFLQRPGQSPQLLIYRMSNLVSGVPD
RFSGSGSGTAFTLRISRVEAEDVGVYYCLQIILEYPFTFGPGTKLELK 531 DLL-3 CDR-
NYGMN H1 532 DLL-3 CDR- WINTYTGEPTYADDFKG H2 533 DLL-3 CDR-
IGDSSPSDY H3 534 DLL-3 CDR- KASQSVSNDVV L1 535 DLL-3 CDR- YASNRYT L2
536 DLL-3 CDR- QQDYTSPWT L3 537 DLL-3 VH
QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTY
ADDFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARIGDSSPSDYWGQGTLVTVSS 538
DLL-3 VL
EIVMTQSPATLSVSPGERATLSCKASQSVSNDVVWYQQKPGQAPRLLIYYASNRYTGIPA
RFSGSGSGTEFTLTISSLQSEDFAVYYCQQDYTSPWTFGQGTKLEIK 539 DPEP-3 SYWIE
CDR-H1 540 DPEP-3 EILPGSGNTYYNERFKD CDR-H2 541 DPEP-3 RAAAYYSNPEWFAY
CDR-H3 542 DPEP-3 TASSSVNSFYLH CDR-L1 543 DPEP-3 STSNLAS CDR-L2 544 DPEP-3
HQYHRSPYT CDR-L3 545 DPEP-3 VH
QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYWIEWVRQAPGQGLEWMGEILPGSGNTYYNE
RFKDRVTITADESTSTAYMELSSLRSEDTAVYYCARRAAAYYSNPEWFAYWGQGTLVTVSS
546 DPEP-3 VL
EIVLTQSPATLSLSPGERATLSCTASSSVNSFYLHWYQQKPGLAPRLLIYSTSNLASGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCHQYHRSPYTFGQGTKLEIK 547 EGFR CDR- SYWMQ
H1 548 EGFR CDR- TIYPGDGDTTYTQKFQG H2 549 EGFR CDR- YDAPGYAMDY H3
550 EGFR CDR- RASQDINNYLA L1 551 EGFR CDR- YTSTLHP L2 552 EGFR CDR-
LQYDNLLYT L3 553 EGFR VH
QVQLVQSGAEVAKPGASVKLSCKASGYTFTSYWMQWVKQRPGQGLECIGTIYPGDGDTTYTQ
KFQGKATLTADKSSSTAYMQLSSLRSEDSAVYYCARYDAPGYAMDYWGQGTLVTVSS 554
EGFR VL
DIQMTQSPSSLSASVGDRVTITCRASQDINNYLAWYQHKPGKGPKLLIHYTSTLHPGIPSRFSGS
GSGRDYSFSISSLEPEDIATYYCLQYDNLLYTFGQGTKLEIK 555 EGFR CDR- RDFAWN
H1 556 EGFR CDR- YISYNGNTRYQPSLKS H2 557 EGFR CDR- ASRGFPY H3 558
EGFR CDR- HSSQDINSNIG L1 559 EGFR CDR- HGTNLDD L2 560 EGFR CDR-
VQYAQFPWT L3 561 EGFR VH
EVQLQESGPGLVKPSQTLSLTCTVSGYSISRDFAWNWIRQPPGKGLEWMGYISYNGNTRYQPS

LKSRITISRDTSKNQFFLKLNSVTAADTATYYCVTASRGFPYWGQGTLVTVSS 562 EGFR VL
DIQMTQSPSSMSVSVGDRVTITCHSSQDINSNIGWLQQKPGKSFKGLIYHGTNLDDGVPSRFSGS
GSGTDYTLTISSLQPEDFATYYCVQYAQFPWTFGGGTKLEIK 563 EGFR CDR- NYGVH
H1 564 EGFR CDR- VIWSGGNTDYNTPFTS H2 565 EGFR CDR- ALTYYDYEFAY H3 566
EGFR CDR- RASQSIGTNIH L1 567 EGFR CDR- YASESIS L2 568 EGFR CDR-
QQNNNWPTT L3 569 EGFR VH
QVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSGGNTDYNTPF
TSRLSINKDNSKSQVFFKMNSLQSNDTAIYYCARALTYYDYEFAYWGQGTLVTVSA 570
EGFR VL
DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSG
TDFTLSINSVESEDIADYYCQQNNNWPTTFGAGTKLELK 571 FRa CDR-H1 GYFMN 572
FRa CDR-H2 RIHPYDGDTFYNQKFQG 573 FRa CDR-H3 YDGSRAMDY 574 FRa CDR-
L1 KASQSVSFAGTSLMH 575 FRa CDR-L2 RASNLEA 576 FRa CDR-L3 QQSREYPYT
577 FRa VH
QVQLVQSGAEVVKPGASVKISCKASGYTFTGYFMNWVKQSPGQSLEWIGRIHPYDGDTFY
NQKFQGKATLTVDKSSNTAHMELLSLTSEDFAVYYCTRYDGSRAMDYWGQGTTVTVSS
578 FRa VL
DIVLTQSPLSLAVSLGQPAIISCKASQSVSFAGTSLMHWYHQKPGQQPRLLIYRASNLEAGVPD
RFSGSGSKTDFTLTISPVEAEDAATYYCQQSREYPYTFGGGTKLEIK 579 FRa CDR-H1
GYGLS 580 FRa CDR-H2 MISSGGSYTYYADSVKG 581 FRa CDR-H3 HGDDPAWFAY
582 FRa CDR-L1 SVSSSISSNNLH 583 FRa CDR-L2 GTSNLAS 584 FRa CDR-L3
QQWSSYPYMYT 585 FRa VH
EVQLVESGGGVVQPGRSLRLSCSASGFTFSGYGLSWVRQAPGKGLEWVAMISSGGSYTYY
ADSVKGRFAISRDNAKNTLFLQMDSLRPEDTGVYFCARHGDDPAWFAYWGQGTPVTVSS
586 FRa VL
DIQLTQSPSSLSASVGDRVTITCSVSSSISSNNLHWYQQKPGKAPKPWIYGTSNLASGVPSRFSG
SGSGTDYTFTISSLQPEDIATYYCQQWSSYPYMYTFGQGTKVEIK 587 MUC-1 CDR-
NYWMN H1 588 MUC-1 CDR- EIRLKSNNYTTHYAESVKG H2 589 MUC-1 CDR-
HYYFDY H3 590 MUC-1 CDR- RSSKSLLHSNGITYFF L1 591 MUC-1 CDR- QMSNLAS
L2 592 MUC-1 CDR- AQNLELPPT L3 593 MUC-1 VH
EVQLVESGGGLVQPGGSMRLSCVASGFPFSNYWMNWVRQAPGKGLEWVGEIRLKSNNYTTH
YAESVKGRFTISRDDSKNSLYLQMNSLKTEDTAVYYCTRHYYFDYWGQGTLVTVSS 594
MUC-1 VL
DIVMTQSPLSNPVTPGEPASISCRSSKSLLHSNGITYFFWYLQKPGQSPQLLIYQMSNLASGVPD
RFSGSGSGTDFTLRISRVEAEDVGVYYCAQNLELPPTFGQGTKVEIK 595 Mesothelin
SYWIG CDR-H1 596 Mesothelin IIDPGDSRTRYSPSFQG CDR-H2 597 Mesothelin
GQLYGGTYMDG CDR-H3 598 Mesothelin TGTSSDIGGYNSVS CDR-L1 599 Mesothelin
GVNNRPS CDR-L2 600 Mesothelin SSYDIESATPV CDR-L3 601 Mesothelin
QVELVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQAPGKGLEWMGIIDPGDSRTRYSPSF
VH QGQVTISADKSISTAYLQWSSLKASDTAMYYCARGQLYGGTYMDGWGQGTLVTVSS
602 Mesothelin
DIALTQPASVSGSPGQSITISCTGTSSDIGGYNSVSWYQQHPGKAPKLMIYGVNNRPSGV VL
SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYDIESATPVFGGGTKLTVL 603 ROR-1
CDR- AYNIH H1 604 ROR-1 CDR- SFDPYDGGSSYNQKFKD H2 605 ROR-1 CDR-
GWYYFDY H3 606 ROR-1 CDR- RASKSISKYLA L1 607 ROR-1 CDR- SGSTLQS L2 608
ROR-1 CDR- QQHDESPYT L3 609 ROR-1 VH
QVQLQESGPGLVKPSQTLSLTCTVSGYAFTAYNIHWVRQAPGQGLEWMGSFDPYDGGSSYNQ
KFKDRLTISKDTSKNQVVLTMTNMDPVDTATYYCARGWYYFDYWGHGTLVTVSS 610
ROR-1 VL

DIVMTQTPLSLPVTPGEPASISCRASKSISKYLAWYQQKPGQAPRLLIYSGSTLQSGIPPRFSGSG
YGTDFTLTINNIESEDAAYYFCQQHDESPYTFGEGTKVEIK 611 B7-H3 CDR- SFGMH H1
612 B7-H3 CDR- YISSDSSAIYYADTVKG H2 613 B7-H3 CDR- GRENIYYGSRLDY H3
614 B7-H3 CDR- KASQNVDTNVA L1 615 B7-H3 CDR- SASYRYS L2 616 B7-H3 CDR-
QQYNNYPFT L3 617 B7-H3 VH
DVQLVESGGGLVQPGGSRKLSCAASGFTFSSFGMHWVRQAPEKGLEWVAYISSDSSAIYY
ADTVKGRFTISRDNPKNTLFLQMTSLRSEDTAMYYCGRGRENIYYGSRLDYWGQGTTLTVSS
618 B7-H3 VL
DIAMTQSQKFMSTSVGDRVSVTCKASQNVDTNVAWYQQKPGQSPKALIYSASYRYSGVPD
RFTGSGSGTDFTLTINNVQSEDLAEYFCQQYNNYPFTFGSGTKLEIK 619 B7-H3 CDR-
SYGMS H1 620 B7-H3 CDR- TINSGGSNTYYPDSLKG H2 621 B7-H3 CDR- HDGGAMDY
H3 622 B7-H3 CDR- RASESIYSYLA L1 623 B7-H3 CDR- NTKTLPE L2 624 B7-H3
CDR- QHHYGTPPWT L3 625 B7-H3 VH
EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVATINSGGSNTYY
PDSLKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARHDGGAMDYWGQGTTVTVSS
626 B7-H3 VL
DIQMTQSPSSLSASVGDRVTITCRASESIYSYLAWYQQKPGKAPKLLVYNTKTLPEGVPSRFSGS
GSGTDFTLTISSLQPEDFATYYCQIIIIYGTPPWTFGQGTRLEIK 627 B7-H3 CDR- SFGMH
H1 628 B7-H3 CDR- YISSGSGTIYYADTVKG H2 629 B7-H3 CDR- HGYRYEGFDY H3
630 B7-H3 CDR- KASQNVDTNVA L1 631 B7-H3 CDR- SASYRYS L2 632 B7-H3 CDR-
QQYNNYPFT L3 633 B7-H3 VH
EVQLVESGGGLVQPGGSLRLSCAASGFTFSSFGMHWVRQAPGKGLEWVAYISSGSGTIY
YADTVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARHGYRYEGFDYWGQGTTVTVSS
634 B7-H3 VL
DIQMTQSPSFLSASVGDRVTITCKASQNVDTNVAWYQQKPGKAPKALIYSASYRYSGVPSRFS
GSGSGTDFTLTISSLQPEDFAEYFCQQYNNYPFTFGQGTKLEIK 635 B7-H3 CDR- NYVMH
H1 636 B7-H3 CDR- YINPYNDDVKYNEKFKG H2 637 B7-H3 CDR- WGYYGSPLYYFDY
H3 638 B7-H3 CDR- RASSRLIYMH L1 639 B7-H3 CDR- ATSNLAS L2 640 B7-H3 CDR-
QQWNSNPPT L3 641 B7-H3 VH
EVQLQQSGPELVKPGASVKMSCKASGYTFTNYVMHWVKQKPGQGLEWIGYINPYNDDVKYN
EKFKGKATQTSDKSSSTAYMELSSLTSEDSAVYYCARWGYYGSPLYYFDYWGQGTTLTVSS
642 B7-H3 VL
QIVLSQSPTILSASPGEKVTMTCRASSRLIYMHWYQQKPGSSPKPWIYATSNLASGVPAR
FSGSGSGTSYSLTISRVEAEDAATYYCQQWNSNPPTFGTGTKLELK 643 B7-H3 CDR-
NYVMH H1 644 B7-H3 CDR- YINPYNDDVKYNEKFKG H2 645 B7-H3 CDR-
WGYYGSPLYYFDY H3 646 B7-H3 CDR- RASSRLIYMH L1 647 B7-H3 CDR- ATSNLAS
L2 648 B7-H3 CDR- QQWNSNPPT L3 649 B7-H3 VH
QVQLVQSGAEVKKPGSSVKVSCKASGYTFTNYVMHWVRQAPGQGLEWMGYINPYNDDVKY
NE
KFKGRVTITADESTSTAYMELSSLRSEDTAVYYCARWGYYGSPLYYFDYWGQGTLVTVSS
650 B7-H3 VL
EIVLTQSPATLSLSPGERATLSCRASSRLIYMHWYQQKPGQAPRPLIYATSNLASGIPARFSGSGS
GTDFTLTISSLEPEDFAVYYCQQWNSNPPTFGQGTKVEIK 651 B7-H3 CDR- SYTIH H1 652
B7-H3 CDR- YINPNSRNTDYAQKFQG H2 653 B7-H3 CDR- YSGSTPYWYFDV H3 654
B7-H3 CDR- RASSSVSYMN L1 655 B7-H3 CDR- ATSNLAS L2 656 B7-H3 CDR-
QQWSSNPLT L3 657 B7-H3 VH
EVQLVQSGAEVKKPGSSVKVSCKASGYSFTSYTIHWVRQAPGQGLEWMGYINPNSRNTDYAQ
KFQGRVTLTADKSTSTAYMELSSLRSEDTAVYYCARYSGSTPYWYFDVWGQGTTVTVSS
658 B7-H3 VL
DIQLTQSPSFLSASVGDRVTITCRASSSVSYMNWYQQKPGKSPKPWIYATSNLASGVPSRFSVS

VSGTEHTLTISSLQPEDFATYYCQQWSSNPLTFGQGTKLEIK 659 B7-H3 CDR- SYWMH H1 660 B7-H3 CDR- LIHPDSGSTNYNEMFKN H2 661 B7-H3 CDR- GGRLYFDY H3 662 B7-H3 CDR- RSSQSLVHSNGDTYLR L1 663 B7-H3 CDR- KVSNRFS L2 664 B7-H3 CDR- SQSTHVPYT L3 665 B7-H3 VH
EVQLVQSGAEVKKPGSSVKVSCKASGYTFSSYWMHWVRQAPGQGLEWIGLIHPDSGSTNYNE
MFKNRATLTVDRSTSTAYVELSSLRSEDTAVYFCAGGGRLYFDYWGQGTTVTVSS 666 B7-H3 VL
DVVMTQSPLSLPVTPGEPASISCRSSQSLVHSNGDTYLRWYLQKPGQSPQLLIYKVSNRFSGVP
DRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPYTFGGGTKVEIK 667 B7-H3 CDR- SYWMH H1 668 B7-H3 CDR- LIHPESGSTNYNEMFKN H2 669 B7-H3 CDR- GGRLYFDY H3 670 B7-H3 CDR- RSSQSLVHSNQDTYLR L1 671 B7-H3 CDR- KVSNRFS L2 672 B7-H3 CDR- SQSTHVPYT L3 673 B7-H3 VH
EVQLVQSGAEVKKPGSSVKVSCKASGYTFSSYWMHWVRQAPGQGLEWIGLIHPESGSTNY
NEMFKNRATLTVDRSTSTAYMELSSLRSEDTAVYYCAGGGRLYFDYWGQGTTVTVSS 674 B7-H3 VL
DIVMTQSPLSLPVTPGEPASISCRSSQSLVHSNQDTYLRWYLQKPGQSPQLLIYKVSNRFSGVPD
RFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPYTFGGGTKVEIK 675 B7-H3 CDR- SGYSWH H1 676 B7-H3 CDR- YIHSSGSTNYNPSLKS H2 677 B7-H3 CDR- YDDYFEY H3 678 B7-H3 CDR- KASQNVGFNVAW L1 679 B7-H3 CDR- SASYRYS L2 680 B7-H3 CDR- QQYNWYPFT L3 681 B7-H3 VH
EVQLQESGPGLVKPSETLSLTCAVTGYSITSGYSWHWIRQFPGNGLEWMGYIHSSGSTNY
NPSLKSRISISRDTSKNQFFLKLSSVTAADTAVYYCAGYDDYFEYWGQGTTVTVSS 682 B7-H3 VL
DIQMTQSPSSLSASVGDRVTITCKASQNVGFNVAWYQQKPGKSPKALIYSASYRYSGV
PSRFSGSGSGTDFTLTISSLQPEDFAEYFCQQYNWYPFTFGQGTKLEIK 683 B7-H3 CDR- NYDIN H1 684 B7-H3 CDR- WIFPGDDSTQYNEKFKG H2 685 B7-H3 CDR- QTTGTWFAY H3 686 B7-H3 CDR- RASQSISDYLY L1 687 B7-H3 CDR- YASQSIS L2 688 B7-H3 CDR- QNGHSFPLT L3 689 B7-H3 VH
QVQLVQSGAEVVKPGASVKLSCKTSGYTFTNYDINWVRQRPGQGLEWIGWIFPGDDSTQY
NEKFKGKATLTTDTSTSTAYMELSSLRSEDTAVYFCARQTTGTWFAYWGQGTLVTVSS 690 B7-H3 VL
EIVMTQSPATLSVSPGERVTLSCRASQSISDYLYWYQQKSHESPRLLIKYASQSISGIPA
RFSGSGSGSEFTLTINSVEPEDVGVYYCQNGHSFPLTFGQGTKLELK 691 B7-H3 VH
QVQLQQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPILGIAN
YAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGGSGSYHMDVWGKGTTVTVSS 692 B7-H3 VL
EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIP
ARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPRITFGQGTRLEIK 693 B7-H3 CDR- IYNVH H1 694 B7-H3 CDR- TIFPGNGDTSYNQKFKD H2 695 B7-H3 CDR- WDDGNVGFAH H3 696 B7-H3 CDR- RASENINNYLT L1 697 B7-H3 CDR- HAKTLAE L2 698 B7-H3 CDR- QHHYGTPPT L3 699 B7-H3 VH
QVQLQQPGAELVKPGASVKMSCKASGYTFTIYNVHWIKQTPGQGLEWMGTIFPGNGDTSY
NQKFKDKATLTTDKSSKTAYMQLNSLTSEDSAVYYCARWDDGNVGFAHWGQGTLVTVSA 700 B7-H3 VL
DIQMTQSPASLSASVGETVTITCRASENINNYLTWFQQKQGKSPQLLVYHAKTLAEGVPS
RFSGSGSGTQFSLKINSLQPEDFGSYYCQHHYGTPPTFGGGTKLEIK 701 B7-H3 VH
EVQLVQSGAEVKKPGASVKVSCKASGYTFTIYNVHWVRQAPGQGLEWMGTIFPGNGDTS
YNQKFKDKVTMTTDTSTSTAYMELSSLRSEDTAVYYCARWDDGNVGFAHWGQGTLVTVSS 702 B7-H3 VL
DIQMTQSPSSLSASVGDRVTITCRASENINNYLTWFQQKQGKSPQLLIYHAKTLAEGVP

SRFSGSGSGTDFTLTISSLQPEDFATYYCQHHYGTPPTFGGGTKVEIK 703 B7-H3 VH
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NQKFKDRATLTTDKSTKTAYMELRSLRSDDTAVYYCARWDDGNVGFAHWGQGTLVTVSS
704 B7-H3 VL
DIQMTQSPSSLSASVGDRVTITCRASENINNYLTWFQQKPGKAPKLLVYHAKTLAEGVPS
RFSGSGSGTQFTLTISSLQPEDFATYYCQHHYGTPPTFGQGTKLEIK 705 HER3 H
QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYN
PSLKSRVTISVETSKNQFSLKLSSVTAADTAVYYCARDKWTWYFDLWGRGTLVTVSSAST
KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
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KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL
HNHYTQKSLSLSPGK 706 HER3 L
DIEMTQSPDSLAVSLGERATINCRSSQSVLYSSSNRNYLAWYQQNPGQPPKLLIYWASTRESGV
PDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPRTFGQGTKVEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADY
EKHKVYACEVTHQGLSSPVTKSFNRGEC 707 HER3 H
EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYVMAWVRQAPGKGLEWVSSISSSGGWTLY
ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTRGLKMATIFDYWGQGTLVTVSSA
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VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGK 708 HER3 L
QSALTQPASVSGSPGQSITISCTGTSSDVGSYNVVSWYQQHPGKAPKLIIYEVSQRPSGVSNRFS
GSKSGNTASLTISGLQTEDEADYYCCSYAGSSIFVIFGGGTKVTVLGQPKAAPSVTLFPPSSEEL
QANKATLVCLVSDFYPGAVTVAWKADGSPVKVGVETTKPSKQSNNKYAASSYLSLTPEQWKS
HRSYSCRVTHEGSTVEKTVAPAECS 709 HER3 H
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAINSQGKSTYYAD
SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARWGDEGFDIWGQGTLVTVSSASTKGPS
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LSLSPGK 710 HER3 L
DIQMTQSPSSLSASVGDRVTITCRASQGISNWLAWYQQKPGKAPKLLIYGASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQYSSFPTTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY
ACEVTHQGLSSPVTKSFNRGEC 711 HER3 H
QVQLVQSGAEVKKPGASVKVSCKASGYTFRSSYISWVRQAPGQGLEWMGWIYAGTGSPSYN
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YTQKSLSLSPG 712 HER3 L

DIVMTQSPDSLAVSLGERATINCKSSQSVLNSGNQKNYLTWYQQKPGQPPKLLIYWASTRESG
VPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQSDYSYPYTFGQGTKLEIKRTVAAPSVFIFPPSD
EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD
YEKHKVYACEVTHQGLSSPVTKSFNRGEC 713 PTK7 CDR- TSNMGVG H1 714 PTK7
CDR- IIIWWDDDKYYSPSLKS H2 715 PTK7 CDR- SNYGYAWFAY H3 716 PTK7 CDR-
KASQDIYPYLN L1 717 PTK7 CDR- RTNRLLD L2 718 PTK7 CDR- LQYDEFPLT L3 719
PTK7 VH
QITLKESGPTLVKPTQTLTLTCTFSGFSLSTSNMGVGWIRQPPGKALEWLAHIWWDDDKYYSPS
LKSRLTITKDTSKNQVVLTMTNMDPVDTATYYCVRSNYGYAWFAYWGQGTLVTVSS 720
PTK7 VL
DIQMTQSPSSLSASVGDRVTITCKASQDIYPYLNWFQQKPGKAPKTLIYRTNRLLDGVPS
RFSGSGSGTDFTFTISSLQPEDIATYYCLQYDEFPLTFGAGTKLEIK 721 PTK7 CDR-
DYAVII H1 722 PTK7 CDR- VISTYNDYTYNNQDFKG H2 723 PTK7 CDR-
GNSYFYALDY H3 724 PTK7 CDR- RASESVDSYGKSFMH L1 725 PTK7 CDR-
RASNLES L2 726 PTK7 CDR- QQSNEDPWT L3 727 PTK7 VH
QVQLVQSGPEVKKPGASVKVSCKASGYTFTDYAVHWVRQAPGKRLEWIGVISTYNDYTY
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728 PTK7 VL
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RYWMS H1 730 PTK7 CDR- DLNPDSSAINYVDSVKG H2 731 PTK7 CDR-
ITTLVPYTMDF H3 732 PTK7 CDR- ITNTDIDDDMN L1 733 PTK7 CDR- EGNGLRP L2
734 PTK7 CDR- LQSDNLPLT L3 735 PTK7 VH
EVQLVESGGGLVQPGGSLRLSCAASGFDFSRYWMSWVRQAPGKGLEWIGDLNPDSSAINY
VDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCTLITTLVPYTMDFWGQGTSVTVSS
736 PTK7 VL
ETTLTQSPAFMSATPGDKVNISCITNTDIDDDMNWYQQKPGEAAILLISEGNGLRPGIPPRFSGS
GYGTDFTLTINNIESEDAAYYFCLQSDNLPLTFGSGTKLEIK 737 hLIV22/LIV1 DYYMH
CDR-H1 738 hLIV22/LIV1 WIDPENGDTEYGPKFQG CDR-H2 739 hLIV22/LIV1
HNAHYGTWFAY CDR-H3 740 hLIV22/LIV1 RSSQSLLHSSGNTYLE CDR-L1 741
hLIV22/LIV1 KISTRFS CDR-L2 742 hLIV22/LIV1 FQGSHVPYT CDR-L3 743 hLIV22/LIV1
QVQLVQSGAEVKKPGASVKVSCKASGLTIEDYYMHWVRQAPGQGLEWMGWIDPENGDTEY
VH
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744 hLIV22/LIV1
DVVMTQSPLSLPVTLGQPASISCRSSQSLLHSSGNTYLEWYQQRPGQSPRPLIYKISTRFSGVPD
VL RFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPYTFGGGTKVEIK 745 hLIV22/LIV1
QVQLVQSGAEVKKPGASVKVSCKASGLTIEDYYMHWVRQAPGQGLEWMGWIDPENGDTEY
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HYTQKSLSLSPG 746 hLIV22/LIV1
DVVMTQSPLSLPVTLGQPASISCRSSQSLLHSSGNTYLEWYQQRPGQSPRPLIYKISTRFSGVPD
LC
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HKVYACEVTHQGLSSPVTKSFNRGEC 747 h15H3/avb6 GYFMN CDR-H1 748 h15H3/avb6 LINPYNGDSFYNQKFKG CDR-H2 749 h15H3/avb6 GLRRDFDY CDR-H3 750 h15H3/avb6 KSSQSLLDSDGKTYLN CDR-L1 751 h15H3/avb6 LVSELDS CDR-L2 752 h15H3/avb6 WQGTHFPRT CDR-L3 753 h15H3/avb6 QVQLVQSGAEVKKPGASVKVSCKASGYSFSGYFMNWVRQAPGQGLEWMGLINPYNGDSFY VH NQKFKGRVTMTRQTSTSTVYMELSSLRSEDTAVYYCVRGLRRDFDYWGQGTLVTVSS 754 h15H3/avb6 DVVMTQSPLSLPVTLGQPASISCKSSQSLLDSDGKTYLNWLFQRPGQSPRRLIYLVSELD VL SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRTFGGGTKLEIK 755 CD48 CDR- DFGMN H1 756 CD48 CDR- WINTFTGEPSYGNVFKG H2 757 CD48 CDR- RHGNGNVFDS H3 758 CD48 CDR- RASQSIGSNIH L1 759 CD48 CDR- YTSESIS L2 760 CD48 CDR- QQSNSWPLT L3 761 CD48 VH QVQLVQSGSELKKPGASVKVSCKASGYTFTDFGMNWVRQAPGQGLEWMGWINTFTGEPSYG NVFKGRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARRHGNGNVFDSWGQGTLVTVSS 762 CD48 VL EIVLTQSPDFQSVTPKEKVTITCRASQSIGSNIHWYQQKPDQSPKLLIKYTSESISGVPSRFSGSGS GTDFTLTINSLEAEDAATYYCQQSNSWPLTFGGGTKVEIKR 763 IGF-1R CDR- SYAIS H1 764 IGF-1R CDR- GIIPIFGTANYAQKFQG H2 765 IGF-1R CDR- APLRFLEWSTQDHYYYYYMDV H3 766 IGF-1R CDR- QGDSLRSYYAT L1 767 IGF-1R CDR- GENKRPS L2 768 IGF-1R CDR- KSRDGSGQHLV L3 769 IGF-1R VH EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANY AQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARAPLRFLEWSTQDHYYYYYMDVWG KGTTVTVSS 770 IGF-1R VL SSELTQDPAVSVALGQTVRITCQGDSLRSYYATWYQQKPGQAPILVIYGENKRPSGIPDR FSGSSSGNTASLTITGAQAEDEADYYCKSRDGSGQHLVFGGGTKLTVL 771 Claudin-18.2 SYWIN CDR-H1 772 Claudin-18.2 NIYPSDSYTNYNQKFKD CDR-H2 773 Claudin-18.2 SWRGNSFDY CDR-H3 774 Claudin-18.2 KSSQSLLNSGNQKNYLT CDR-L1 775 Claudin-18.2 WASTRES CDR-L2 776 Claudin-18.2 QNDYSYPFT CDR-L3 777 Claudin-18.2 QVQLQQPGAELVRPGASVKLSCKASGYTFTSYWINWVKQRPGQGLEWIGNIYPSDSYTN VH YNQKFKDKATLTVDKSSSTAYMQLSSPTSEDSAVYYCTRSWRGNSFDYWGQGTTLTVSS 778 Claudin-18.2 DIVMTQSPSSLTVTAGEKVTMSCKSSQSLLNSGNQKNYLTWYQQKPGQPPKLLIYWASTR VL ESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNDYSYPFTFGSGTKLEIK 779 Claudin-18.2 NYGMN CDR-H1 780 Claudin-18.2 WINTNTGEPTYAEEFKG CDR-H2 781 Claudin-18.2 LGFGNAMDY CDR-H3 782 Claudin-18.2 KSSQSLLNSGNQKNYLT CDR-L1 783 Claudin-18.2 WASTRES CDR-L2 784 Claudin-18.2 QNDYSYPLT CDR-L3 785 Claudin-18.2 QIQLVQSGPELKKPGETVKISCKASGYTFTNYGMNWVKQAPGKGLKWMGWINTNTGEPTY VH AEEFKGRFAFSLETSASTAYLQINNLKNEDTATYFCARLGFGNAMDYWGQGTSVTVSS 786 Claudin-18.2 DIVMTQSPSSLTVTAGEKVTMSCKSSQSLLNSGNQKNYLTWYQQKPGQPPKLLIYWASTR VL ESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNDYSYPLTFGAGTKLELK 787 Nectin-4 SYNMN CDR-H1 788 Nectin-4 YISSSSSTIYYADSVKG CDR-H2 789 Nectin-4 AYYYGMDV CDR-H3 790 Nectin-4 RASQGISGWLA CDR-L1 791 Nectin-4 AASTLQS CDR-L2 792 Nectin-4 QQANSFPPT CDR-L3 793 Nectin-4 VH EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYNMNWVRQAPGKGLEWVSYISSSSSTIYY ADSVKGRFTISRDNAKNSLSLQMNSLRDEDTAVYYCARAYYYGMDVWGQGTTVTVSS 794 Nectin-4 VL DIQMTQSPSSVSASVGDRVTITCRASQGISGWLAWYQQKPGKAPKFLIYAASTLQSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPPTFGGGTKVEIK 795 SLTRK6 SYGMH

CDR-H1 796 SLTRK6 VIWYDGSNQYYADSVKG CDR-H2 797 SLTRK6 GLTSGRYGMDV CDR-H3 798 SLTRK6 RSSQSLLLSHGFNYLD CDR-L1 799 SLTRK6 LGSSRAS CDR-L2 800 SLTRK6 MQPLQIPWT CDR-L3 801 SLTRK6 VH
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNQYY ADSVKGRFTISRDNSKNTLFLQMHSLRAEDTAVYYCARGLTSGRYGMDVWGQGTTVTVSS 802 SLTRK6 VL
DIVMTQSPLSLPVTPGEPASISCRSSQSLLLSHGFNYLDWYLQKPGQSPQLLIYLGSSRASGVPD RFSGSGSGTDFTLKISRVEAEDVGLYYCMQPLQIPWTFGQGTKVEIK 803 CD142 (TF) NYAMS CDR-H1 804 CD142 (TF) SISGSGDYTYYTDSVKG CDR-H2 805 CD142 (TF) SPWGYYLDS CDR-H3 806 CD142 (TF) RASQGISSRLA CDR-L1 807 CD142 (TF) AASSLQS CDR-L2 808 CD142 (TF) QQYNSYPYT CDR-L3 809 CD142 (TF)
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSSISGSGDYTY VH
YTDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSPWGYYLDSWGQGTLVTVSS 810 CD142 (TF)
DIQMTQSPPSLSASAGDRVTITCRASQGISSRLAWYQQKPEKAPKSLIYAASSLQSGVPS VL
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYPYTFGQGTKLEIK 811 h2G12/STn DHAIH CDR-H1 812 h2G12/STn YFSPGNDDIKYNEKFRG CDR-H2 813 h2G12/STn SLSTPY CDR-H3 814 h2G12/STn KSSQSLLNRGNHKNYLT CDR-L1 815 h2G12/STn WASTRES CDR-L2 816 h2G12/STn QNDYTYPYT CDR-L3 817 h2G12/STn
EVQLVQSGAEVKKPGASVKVSCKASGYTFTDHAIHWVRQAPGQGLEWMGYFSPGNDDIKY VH NEKFRGRVTMTADKSSSTAYMELRSLRSDDTAVYFCKRSLSTPYWGQGTLVTVSS 818 h2G12/STn
DIVMTQSPDSLAVSLGERATINCKSSQSLLNRGNHKNYLTWYQQKPGQPPKLLIYWAST VL
RESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYTYPYTFGQGTKVEIK 819 CD20 CDR- SYNMH H1 820 CD20 CDR- AIYPGNGDTSYNQKFKG H2 821 CD20 CDR- STYYGGDWYFNV H3 822 CD20 CDR- RASSSVSYIH L1 823 CD20 CDR- ATSNLAS L2 824 CD20 CDR- QQWTSNPPT L3 825 CD20 VH
QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSY NQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSA 826 CD20 VL
QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVR FSGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIK 827 HER2 CDR- DTYIH H1 828 HER2 CDR- RIYPTNGYTRYADSVKG H2 829 HER2 CDR- WGGDGFYAMDY H3 830 HER2 CDR- RASQDVNTAVA L1 831 HER2 CDR- SASFLYS L2 832 HER2 CDR- QQHYTTPPT L3 833 HER2 VH
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRY ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS 834 HER2 VL
DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK 835 CD79b CDR- SYWIE H1 836 CD79b CDR- EILPGGGDTNYNEIFKG H2 837 CD79b CDR- RVPIRLDY H3 838 CD79b CDR- KASQSVDYEGDSFLN L1 839 CD79b CDR- AASNLES L2 840 CD79b CDR- QQSNEDPLT L3 841 CD79b VH
EVQLVESGGGLVQPGGSLRLSCAASGYTFSSYWIEWVRQAPGKGLEWIGEILPGGGDTNYNEIF KGRATFSADTSKNTAYLQMNSLRAEDTAVYYCTRRVPIRLDYWGQGTLVTVSS 842 CD79b VL
DIQLTQSPSSLSASVGDRVTITCKASQSVDYEGDSFLNWYQQKPGKAPKLLIYAASNLES GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSNEDPLTFGQGTKVEIK 843 NaPi2B DFAMS CDR-H1 844 NaPi2B TIGRVAFHTYYPDSMKG CDR-H2 845 NaPi2B

HRGFDVGHFDF CDR-H3 846 NaPi2B RSSETLVHSSGNTYLE CDR-L1 847 NaPi2B RVSNRFS CDR-L2 848 NaPi2B FQGSFNPLT CDR-L3 849 NaPi2B VH EVQLVESGGGLVQPGGSLRLSCAASGFSFSDFAMSWVRQAPGKGLEWVATIGRVAFHTYY PDSMKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARHRGFDVGHFDFWGQGTLVTVSS 850 NaPi2B VL DIQMTQSPSSLSASVGDRVTITCRSSETLVHSSGNTYLEWYQQKPGKAPKLLIYRVSNRF SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCFQGSFNPLTFGQGTKVEIK 851 Muc16 CDR- NDYAWN H1 852 Muc16 CDR- YISYSGYTTYNPSLKS H2 853 Muc16 CDR- WTSGLDY H3 854 Muc16 CDR- KASDLIHNWLA L1 855 Muc16 CDR- GATSLET L2 856 Muc16 CDR- QQYWTTPFT L3 857 Muc16 VH EVQLVESGGGLVQPGGSLRLSCAASGYSITNDYAWNWVRQAPGKGLEWVGYISYSGYTTY NPSLKSRFTISRDTSKNTLYLQMNSLRAEDTAVYYCARWTSGLDYWGQGTLVTVSS 858 Muc16 VL DIQMTQSPSSLSASVGDRVTITCKASDLIHNWLAWYQQKPGKAPKLLIYGATSLETGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQQYWTTPFTFGQGTKVEIK 859 STEAP1 SDYAWN CDR-H1 860 STEAP1 YISNSGSTSYNPSLKS CDR-H2 861 STEAP1 ERNYDYDDYYYAMDY CDR-H3 862 STEAP1 KSSQSLLYRSNQKNYLA CDR-L1 863 STEAP1 WASTRES CDR-L2 864 STEAP1 QQYYNYPRT CDR-L3 865 STEAP1 VH EVQLVESGGGLVQPGGSLRLSCAVSGYSITSDYAWNWVRQAPGKGLEWVGYISNSGSTSYNPS LKSRFTISRDTSKNTLYLQMNSLRAEDTAVYYCARERNYDYDDYYYAMDYWGQGTLVTVSS 866 STEAPI VL DIQMTQSPSSLSASVGDRVTITCKSSQSLLYRSNQKNYLAWYQQKPGKAPKLLIYWASTRESG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYYNYPRTFGQGTKVEIK 867 BCMA CDR-NYWMH H1 868 BCMA CDR- ATYRGHSDTYYNQKFKG H2 869 BCMA CDR-GAIYDGYDVLDN H3 870 BCMA CDR- SASQDISNYLN L1 871 BCMA CDR- YTSNLHS L2 872 BCMA CDR- QQYRKLPWT L3 873 BCMA VH QVQLVQSGAEVKKPGSSVKVSCKASGGTFSNYWMHWVRQAPGQGLEWMGATYRGHSDTYY NQKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGAIYDGYDVLDNWGQGTLVTVSS 874 BCMA VL DIQMTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKLLIYYTSNLHSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQYRKLPWTFGQGTKLEIK 875 c-Met CDR- AYTMH H1 876 c-Met CDR- WIKPNNGLANYAQKFQG H2 877 c-Met CDR- SEITTEFDY H3 878 c-Met CDR- KSSESVDSYANSFLH L1 879 c-Met CDR- RASTRES L2 880 c-Met CDR-QQSKEDPLT L3 881 c-Met VH QVQLVQSGAEVKKPGASVKVSCKASGYIFTAYTMHWVRQAPGQGLEWMGWIKPNNGLAN YAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARSEITTEFDYWGQGTLVTVSS 882 c-Met VL DIVMTQSPDSLAVSLGERATINCKSSESVDSYANSFLHWYQQKPGQPPKLLIYRASTRE SGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQSKEDPLTFGGGTKVEIK 883 EGFR CDR- SDFAWN H1 884 EGFR CDR- YISYSGNTRYQPSLKS H2 885 EGFR CDR-AGRGFPY H3 886 EGFR CDR- HSSQDINSNIG L1 887 EGFR CDR- HGTNLDD L2 888 EGFR CDR- VQYAQFPWT L3 889 EGFR VH QVQLQESGPGLVKPSQTLSLTCTVSGYSISSDFAWNWIRQPPGKGLEWMGYISYSGNTRY QPSLKSRITISRDTSKNQFFLKLNSVTAADTATYYCVTAGRGFPYWGQGTLVTVSS 890 EGFR VL DIQMTQSPSSMSVSVGDRVTITCHSSQDINSNIGWLQQKPGKSFKGLIYHGTNLDDGVPS RFSGSGSGTDYTLTISSLQPEDFATYYCVQYAQFPWTFGGGTKLEIK 891 SLAMF7 DYYMA CDR-H1 892 SLAMF7 SINYDGSSTYYVDSVKG CDR-H2 893 SLAMF7 DRGYYFDY CDR-H3 894 SLAMF7 RSSQSLVHSNGNTYLH CDR-L1 895 SLAMF7 KVSNRFS CDR-L2 896 SLAMF7 SQSTHVPPFT CDR-L3 897 SLAMF7 VH

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYYMAWVRQAPGKGLEWVASINYDGSSTY
YVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDRGYYFDYWGQGTTVTVSS
898 SLAMF7 VL
DVVMTQTPLSLSVTPGQPASISCRSSQSLVHSNGNTYLHWYLQKPGQSPQLLIYKVSNRF
SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYFCSQSTHVPPFTFGGGTKVEIK 899 C4.4a
CDR- NAWMS H1 900 C4.4a CDR- YISSSGSTIYYADSVKG H2 901 C4.4a CDR-
EGLWAFDY H3 902 C4.4a CDR- TGSSSNIGAGYVVH L1 903 C4.4a CDR- DNNKRPS L2
904 C4.4a CDR- AAWDDRLNGPV L3 905 C4.4a VH
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVSYISSSGSTIYY
ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGLWAFDYWGQGTLVTVSS 906
C4.4a VL
ESVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYVVHWYQQLPGTAPKLLIYDNNKRPSGV
PDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDRLNGPVFGGGTKLTVL 907 GCC
CDR- GYYWS H1 908 GCC CDR- EINHRGNTNDNPSLKS H2 909 GCC CDR-
ERGYTYGNFDH H3 910 GCC CDR- RASQSVSRNLA L1 911 GCC CDR- GASTRAT L2
912 GCC CDR- QQYKTWPRT L3 913 GCC VH
QVQLQQWGAGLLKPSETLSLTCAVFGGSFSGYYWSWIRQPPGKGLEWIGEINHRGNTNDN
PSLKSRVTISVDTSKNQFALKLSSVTAADTAVYYCARERGYTYGNFDHWGQGTLVTVSS
914 GCC VL
EIVMTQSPATLSVSPGERATLSCRASQSVSRNLAWYQQKPGQAPRLLIYGASTRATGIP
ARFSGSGSGTEFTLTIGSLQSEDFAVYYCQQYKTWPRTFGQGTNVEIK 915 Ax1 CDR-H1
SYAMN 916 Ax1 CDR-H2 TTSGSGASTYYADSVKG 917 Ax1 CDR-H3 IWIAFDI 918
Ax1 CDR-L1 RASQSVSSSYLA 919 Ax1 CDR-L2 GASSRAT 920 Ax1 CDR-L3
QQYGSSPYT 921 Ax1 VH
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVSTTSGSGASTYY
ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIWIAFDIWGQGTMVTVSS 922
Ax1 VL
EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIP
DRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPYTFGQGTKLEIK 923 CR011/gpNM
SFNYYWS B CDR-H1 924 CR011/gpNM YIYYSGSTYSNPSLKS B CDR-H2 925
CR011/gpNM GYNWNYFDY B CDR-H3 926 CR011/gpNM RASQSVDNNLV B CDR-L1
927 CR011/gpNM GASTRAT B CDR-L2 928 CR011/gpNM QQYNNWPPWT B CDR-L3 929
CR011/gpNM
QVQLQESGPGLVKPSQTLSLTCTVSGGSISSFNYYWSWIRHHPGKGLEWIGYIYYSGSTY
B VH
SNPSLKSRVTISVDTSKNQFSLTLSSVTAADTAVYYCARGYNWNYFDYWGQGTLVTVSS
930 CR011/gpNM
EIVMTQSPATLSVSPGERATLSCRASQSVDNNLVWYQQKPGQAPRLLIYGASTRATGIPA
B VL RFSGSGSGTEFTLTISSLQSEDFAVYYCQQYNNWPPWTFGQGTKVEIK 931
CR011/gpNM
QVQLQESGPGLVKPSQTLSLTCTVSGGSISSFNYYWSWIRHHPGKGLEWIGYIYYSGSTYSNPSL
B HC
KSRVTISVDTSKNQFSLTLSSVTAADTAVYYCARGYNWNYFDYWGQGTLVTVSSASTKGPSV
FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP
SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGK 932 CR011/gpNM
EIVMTQSPATLSVSPGERATLSCRASQSVDNNLVWYQQKPGQAPRLLIYGASTRATGIPARFSG

B LC
SGSGTEFTLTISSLQSEDFAVYYCQQYNNWPPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSG
TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK
VYACEVTHQGLSSPVTKSFNRGEC 933 Prolactin TYWMH receptor CDR-H1 934 Prolactin
EIDPSDSYSNYNQKFKD receptor CDR-H2 935 Prolactin NGGLGPAWFSY receptor CDR-H3
936 Prolactin KASQYVGTAVA receptor CDR-L1 937 Prolactin SASNRYT receptor CDR-L2 938
Prolactin QQYSSYPWT receptor CDR-L3 939 Prolactin
EVQLVQSGAEVKKPGSSVKVSCKASGYTFTTYWMHWVRQAPGQGLEWIGEIDPSDSYSNY
receptor VH
NQKFKDRATLTVDKSTSTAYMELSSLRSEDTAVYYCARNGGLGPAWFSYWGQGTLVTVSS
940 Prolactin
DIQMTQSPSSVSASVGDRVTITCKASQYVGTAVAWYQQKPGKSPKLLIYSASNRYTGVPS
receptor VL RFSDSGSGTDFTLTISSLQPEDFATYFCQQYSSYPWTFGGGTKVEIK 941
FGFR2 CDR- SYAMS H1 942 FGFR2 CDR- AISGSGTSTYYADSVKG H2 943 FGFR2
CDR- VRYNWNHGDWFDP H3 944 FGFR2 CDR- SGSSSNIGNNYVS L1 945 FGFR2
CDR- ENYNRPA L2 946 FGFR2 CDR- SSWDDSLNYWV L3 947 FGFR2 VH
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGTSTYYADS
VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVRYNWNHGDWFDPWGQGTLVTVSS
948 FGFR2 VL
QSVLTQPPSASGTPGQRVTISCSGSSSNIGNNYVSWYQQLPGTAPKLLIYENYNRPAGVP
DRFSGSKSGTSASLAISGLRSEDEADYYCSSWDDSLNYWVFGGGTKLTVL 949 CDCP1
CDR- SYGMS H1 950 CDCP1 CDR- TISSGGSYKYYVDSVKG H2 951 CDCP1 CDR-
HPDYDGVWFAY H3 952 CDCP1 CDR- SVSSSVFYVH L1 953 CDCP1 CDR- DTSKLAS
L2 954 CDCP1 CDR- QQWNSNPPT L3 955 CDCP1 VH
EVQLVESGGGLVQPGGSLRLSCAASGFTFNSYGMSWVRQAPGKGLEWVATISSGGSYKYY
VDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARHPDYDGVWFAYWGQGTLVTVSS
956 CDCP1 VL
DIQMTQSPSSLSASVGDRVTITCSVSSSVFYVHWYQQKPGKAPKLLIYDTSKLASGVPSRFSGSG
SGTDFTFTISSLQPEDIATYYCQQWNSNPPTFGGGTKVEIK 957 CDCP1 CDR- SYGMS H1
958 CDCP1 CDR- TISSGGSYTYYPDSVKG H2 959 CDCP1 CDR- HPDYDGVWFAY H3
960 CDCP1 CDR- SVSSSVFYVH L1 961 CDCP1 CDR- DTSKLAS L2 962 CDCP1 CDR-
QQWNSNPPT L3 963 CDCP1 VH
EVQLVESGGDLVKPGGSLKLSCAASGFTFNSYGMSWVRQTPDKRLEWVATISSGGSYTYY
PDSVKGRFTISRDNAKNTLYLQMSSLKSEDTAMYYCARHPDYDGVWFAYWGQGTLVTVSA
964 CDCP1 VL
QIVLTQSPAIMSASPGEKVTMTCSVSSSVFYVHWYQQKSGTSPKRWIYDTSKLASGVPARF
SGSGSGTSYSLTISSMEAEDAATYYCQQWNSNPPTFGGGTKLEIK 965 CDCP1 CDR-
SYYMH H1 966 CDCP1 CDR- IINPSGGSTSYAQKFQG H2 967 CDCP1 CDR-
DGVLRYFDWLLDYYYYMDV H3 968 CDCP1 CDR- RASQSVGSYLA L1 969 CDCP1
CDR- DASNRAT L2 970 CDCP1 CDR- QQRANVFT L3 971 CDCP1 VH
EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSY
AQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDGVLRYFDWLLDYYYYMDVWGK
G TTVTVSS 972 CDCP1 VL
EIVLTQSPATLSLSPGERATLSCRASQSVGSYLAWYQQRPGQAPRLLIYDASNRATGIPA
RFSGSGSGTDFTLTISSLEPEDFAVYYCQQRANVFTFGQGTKVEIK 973 CDCP1 CDR-
SYYMH H1 974 CDCP1 CDR- IINPSGGSTSYAQKFQG H2 975 CDCP1 CDR-
DAELRHFDHLLDYHYYMDV H3 976 CDCP1 CDR- RASQSVGSYLA L1 977 CDCP1
CDR- DASNRAT L2 978 CDCP1 CDR- QQRAQEFT L3 979 CDCP1 VH
EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSYAQ
KFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDAELRHFDHLLDYHYYMDVWGQGTT

VTVSS 980 CDCP1 VL
EIVMTQSPATLSLSPGERATLSCRASQSVGSYLAWYQQKPGQAPRLLIYDASNRATGIPA
RFSGSGSGTDFTLTISSLQPEDFAVYYCQQRAQEFTFGQGTKVEIK 981 ASCT2 VH
QVQLVQSGSELKKPGAPVKVSCKASGYTFSTFGMSWVRQAPGQGLKWMGWIHTYAGVPIYG
DDFKGRFVFSLDTSVSTAYLQISSLKAEDTAVYFCARRSDNYRYFFDYWGQGTTVTVSS
982 ASCT2 VL
DIQMTQSPSSLSASLGDRVTITCRASQDIRNYLNWYQQKPGKAPKLLIYYTSRLHSGVPSRFSGS
GSGTDYTLTISSLQPEDFATYFCQQGHTLPPTFGQGTKLEIK 983 ASCT2 VH
QIQLVQSGPELKKPGAPVKISCKASGYTFTTFGMSWVKQAPGQGLKWMGWIHTYAGVPIYGD
DFKGRFVFSLDTSVSTAYLQISSVKAEDTATYFCARRSDNYRYFFDYWGQGTTLTVSS 984
ASCT2 VL
DIQMTQSPSSLSASLGDRVTITCRASQDIRNYLNWYQQKPGKAPKLLIYYTSRLHSGVPS
RFSGSGSGTDYTLTISSLQPEDFATYFCQQGHTLPPTFGQGTKLEIK 985 ASCT2 CDR-
NYYMA H1 986 ASCT2 CDR- SITKGGGNTYYRDSVKG H2 987 ASCT2 CDR-
QVTIAAVSTSYFDS H3 988 ASCT2 CDR- KTNQKVDYYGNSYVY L1 989 ASCT2 CDR-
LASNLAS L2 990 ASCT2 CDR- QQSRNLPYT L3 991 ASCT2 VH
EVQLVESGGGLVQSGRSIRLSCAASGFSFSNYYMAWVRQAPSKGLEWVASITKGGGNTYYRD
SVKGRFTFSRDNAKSTLYLQMDSLRSEDTATYYCARQVTIAAVSTSYFDSWGQGVMVTVSS
992 ASCT2 VL
DIVLTQSPALAVSLGQRATISCKTNQKVDYYGNSYVYWYQQKPGQQPKLLIYLASNLASGIPA
RFSGRGSGTDFTLTIDPVEADDTATYYCQQSRNLPYTFGAGTKLELK 993 CD123 CDR-
DYYMK H1 994 CD123 CDR- DIIPSNGATFYNQKFKG H2 995 CD123 CDR-
SHLLRASWFAY H3 996 CD123 CDR- KSSQSLLNSGNQKNYLT L1 997 CD123 CDR-
WASTRES L2 998 CD123 CDR- QNDYSYPYT L3 999 CD123 VH
QVQLVQSGAEVKKPGASVKMSCKASGYTFTDYYMKWVKQAPGQGLEWIGDIIPSNGATFYN
QKFKGKATLTVDRSISTAYMHLNRLRSDDTAVYYCTRSHLLRASWFAYWGQGTLVTVSS
1000 CD123 VL
DFVMTQSPDSLAVSLGERATINCKSSQSLLNSGNQKNYLTWYLQKPGQPPKLLIYWASTRESG
VPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYSYPYTFGQGTKLEIK 1001 GPC3
CDR- DYEMH H1 1002 GPC3 CDR- GIDPETGGTAYNQKFKG H2 1003 GPC3 CDR-
YYSFAY H3 1004 GPC3 CDR- RSSQSIVHSNANTYLQ L1 1005 GPC3 CDR- KVSNRFS L2
1006 GPC3 CDR- FQVSHVPYT L3 1007 GPC3 VH
EVQLVQSGAEVKKPGATVKISCKVSGYTFTDYEMHWVQQAPGKGLEWMGGIDPETGGTAYN
QKFKGRVTLTADKSTDTAYMELSSLRSEDTAVYYCGRYYSFAYWGQGTLVTVSS 1008
GPC3 VL
DVVMTQSPLSLPVTLGQPASISCRSSQSIVHSNANTYLQWFQQRPGQSPRLLIYKVSNRFSGVPD
RFSGSGSGTDFTLKISRVEAEDVGVYYCFQVSHVPYTFGQGTKLEIK 1009 TIGIT CDR-
SYAIS H1 1010 TIGIT CDR- SIIPIFGTANYAQKFQG H2 1011 TIGIT CDR-
GPSEVGAILGYVWFDP H3 1012 TIGIT CDR- RSSQSLLHSNGYNYLD L1 1013 TIGIT
CDR- LGSNRAS L2 1014 TIGIT CDR- MQARRIPIT L3 1015 TIGIT VH
QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGSIIPIFGTANYAQK
FQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGPSEVGAILGYVWFDPWGQGTLVTVSS
1016 TIGIT VL
DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPD
RFSGSGSGTDFTLKISRVEAEDVGVYYCMQARRIPITFGGGTKVEIK 1017 CD33 CDR-
NYDIN H1 1018 CD33 CDR- WIYPGDGSTKYNEKFKA H2 1019 CD33 CDR-
GYEDAMDY H3 1020 CD33 CDR- KASQDINSYLS L1 1021 CD33 CDR- RANRLVD L2
1022 CD33 CDR- LQYDEFPLT L3 1023 CD33 VH QVQLVQSGAE VKKPGASVKV
SCKASGYTFT NYDINWVRQA PGQGLEWIGW TYPGDGSTKY NEKFKAKATL
TADTSTSTAY MELRSLRSDD TAVYYCASGY EDAMDYWGQG TTVTVSS 1024

CD33 VL DIQMTQSPS SLSASVGDRVT INCKASQDINSYLSWFQQKPGKAPKTL IYRANRLVDGVPS RFSGSGSGQDYTLT ISSLQPEDFATYYCLQYDEFPLTFGGGTKVEIK 1025 BCMA CDR- DYYIH H1 1026 BCMA CDR- YINPNSGYTNYAQKFQG H2 1027 BCMA CDR- YMWERVTGFFDF H3 1028 BCMA CDR- LASEDISDDLA L1 1029 BCMA CDR- TTSSLQS L2 1030 BCMA CDR- QQTYKFPPT L3 1031 BCMA VH QVQLVQSGAEVKKPGASVKLSCKASGYTFTDYYIHWVRQAPGQGLEWIGYINPNSGYTNYAQ KFQGRATMTADKSINTAYVELSRLRSDDTAVYFCTRYMWERVTGFFDFWGQGTMVTVSS 1032 BCMA VL DIQMTQSPSSVSASVGDRVTITCLASEDISDDLAWYQQKPGKAPKVLVYTTSSLQSGVPSRFSG SGSGTDFTLTISSLQPEDFATYFCQQTYKFPPTFGGGTKVEIK 1033 <Q13433; MARKLSVILI LTFALSVTNP LHELKAAAFP QTTEKISPNW ESGINVDLAI STRQYHLQQL protein FYRYGENNSL SVEGFRKLLQ NIGIDKIKRI HIHHDHDHHS DHEHHSDHER HSDHEHHSEH EHHSDHDHHS HHNHAASGKN KRKALCPDHD SDSSGKDPRN SQGKGAHRPE HASGRRNVKD SVSASEVTST VYNTVSEGTH FLETIETPRP GKLFPKDVSS STPPSVTSKS RVSRLAGRKT NESVSEPRKG FMYSRNTNEN PQECFNASKL LTSHGMGIQV PLNATEFNYL CPAIINQIDA RSCLIHTSEK KAEIPPKTYS LQIAWVGGFI AISIISFLSL LGVILVPLMN RVFFKFLLSF LVALAVGTLS GDAFLHLLPH SHASHHHSHS HEEPAMEMKR GPLFSHLSSQ NIEESAYFDS TWKGLTALGG LYFMFLVEHV LTLIKQFKDK KKKNQKKPEN DDDVEIKKQL SKYESQLSTN EEKVDTDDRT EGYLRADSQE PSHFDSQQPA VLEEEEVMIA HAHPQEVYNE YVPRGCKNKC HSHFHDTLGQ SDDLIHHHHD YHHILHHHHH QNHHPHSHSQ RYSREELKDA GVATLAWMVI MGDGLHNFSD GLAIGAAFTE GLSSGLSTSV AVFCHELPHE LGDFAVLLKA GMTVKQAVLY NALSAMLAYL GMATGIFIGH YAENVSMWIF ALTAGLFMYV ALVDMVPEML HNDASDHGCS RWGYFFLQNA GMLLGFGIML LISIFEHKIV FRINF 1034 hLIV22 KGAHRPEH epitope

Compounds of Formula (II)

[0334] Some embodiments provide compounds of Formula (II):

##STR00067## [0335] or a pharmaceutically acceptable salt thereof, wherein: [0336] M is a succinimide or a hydrolyzed succinimide; [0337] R.sup.1 is hydrogen, hydroxyl, C.sub.1-6 alkoxy, —(C.sub.1-6 alkyl)C.sub.1-6alkoxy, —(CH.sub.2).sub.n—NR.sup.AR.sup.B, or PEG2 to PEG4; [0338] each R.sup.2 and R.sup.3 are independently —CO.sub.2H, —(C═O).sub.m—NR.sup.CR.sup.D, or —(CH.sub.2).sub.q—NR.sup.ER.sup.F; [0339] each R.sup.A, R.sup.B, R.sup.C, R.sup.D, R.sup.E, and R.sup.F are independently hydrogen or C.sub.1-3 alkyl; [0340] each subscript n is independently an integer from 0 to 6; [0341] each subscript m is independently 0 or 1; [0342] each subscript q is independently an integer from 0 to 6; [0343] X.sup.A is —CH.sub.2—, —O—, —S—, —NH—, or —N(CH.sub.3)—; [0344] X.sup.B is absent or a 2-16 membered heteroalkylene; [0345] X.sup.B, M, and L are each independently optionally substituted with a PEG Unit from PEG2 to PEG 72; and [0346] L is an optional linker as described herein.

[0347] In some embodiments, the compound of Formula (II) has the structure:

##STR00068##

or a pharmaceutically acceptable salt thereof, wherein: [0348] R.sup.1 is hydrogen, hydroxyl, C.sub.1-6 alkoxy, —(C.sub.1-6 alkyl)C.sub.1-6 alkoxy, —(CH.sub.2).sub.n—NR.sup.AR.sup.B, or PEG2 to PEG4; [0349] each R.sup.2 and R.sup.3 are independently —CO.sub.2H, —(C═O).sub.m—NR.sup.CR.sup.D, or —(CH.sub.2).sub.q—NR.sup.ER.sup.F; [0350] each R.sup.A, R.sup.B, R.sup.C, R.sup.D, R.sup.E, and R.sup.F are independently hydrogen or C.sub.1-3 alkyl; [0351] each subscript n is independently an integer from 0 to 6; [0352] each subscript m is independently 0 or 1; [0353] each subscript q is independently an integer from 0 to 6; [0354] X.sup.A is —CH.sub.2—, —O—, —S—, —NH—, or —N(CH.sub.3)—; [0355] X.sup.B is absent or 2-16 membered heteroalkylene; [0356] L is a linker having the formula (A).sub.a-(W).sub.w—(Y).sub.y

—, wherein: [0357] A is a C.sub.2-20 alkylene optionally substituted with 1-3 Rai; or a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R.sup.b1; [0358] each R.sup.a1 is independently selected from the group consisting of: C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, ═O, —NR.sup.d1R.sup.e1, —C(O)NR.sup.d1R.sup.e1, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl); [0359] each R.sup.h1 is independently selected from the group consisting of: C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, —NR.sup.d1R.sup.e1, —C(O)NR.sup.d1R.sup.e1, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl); [0360] each R.sup.d1 and R.sup.e1 are independently hydrogen or C.sub.1-3 alkyl; [0361] W is from 1-12 amino acids or has the structure:

##STR00069## [0362] wherein Su is a Sugar moiety; [0363] —O.sup.A— represents a glycosidic bond; [0364] each R.sup.9 is independently hydrogen, halogen, —CN, or —NO.sub.2; [0365] W.sub.1 is absent or —O—C(═O)—; [0366] custom-character represents covalent attachment to A or M; and * represents covalent attachment to Y, X.sup.A, or X.sup.B. [0367] Y is a self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety; [0368] subscript a is 0 or 1; [0369] subscript y is 0 or 1; [0370] subscript w is 0 or 1; [0371] M is

##STR00070## [0372] each AA is an independently selected amino acid, wherein (AA).sub.b is connected to the succinimide or hydrolyzed succinimide via a sulfur atom; [0373] each subscript b is independently an integer from 1 to 6; and [0374] X.sup.B and L are each independently optionally substituted with a PEG Unit from PEG2 to PEG 72.

[0375] As used herein, A, when present is covalently attached to M or M.sup.1, and Y, when present is attached to X.sup.B or to X.sup.A (when X.sup.B is absent).

[0376] In some embodiments, M is

##STR00071##

[0377] In some embodiments, M is

##STR00072##

In some aspects, M is

##STR00073##

In some aspects, M is

##STR00074##

[0378] In some embodiments, M is

##STR00075##

In some aspects, M is

##STR00076##

In some aspects, M is

##STR00077##

[0379] In some embodiments, M is

##STR00078##

In some aspects, M is

##STR00079##

In some aspects, M is

##STR00080##

[0380] In some embodiments, each AA is independently a natural amino acid; wherein (AA).sub.b is connected to the succinimide or hydrolyzed succinimide via a sulfur atom. In some embodiments, each AA is independently a natural amino acid; wherein (AA).sub.b is connected to the succinimide or hydrolyzed succinimide via a sulfur atom of a cysteine residue.

[0381] In some embodiments, each AA is independently a natural amino acid; wherein (AA).sub.b is connected to the succinimide or hydrolyzed succinimide via a nitrogen atom. In some embodiments, each AA is independently a natural amino acid; wherein (AA).sub.b is connected to the succinimide or hydrolyzed succinimide via the ϵ-nitrogen atom of a lysine residue.

[0382] In some embodiments, each subscript b is 1, 2, or 3. In some embodiments, each subscript b is 1. In some embodiments, each subscript b is 2. In some embodiments, each subscript b is 3. In some embodiments, each subscript b is 3, 4, 5, or 6. In some embodiments, each subscript b is 4. In some embodiments, each subscript b is 5. In some embodiments, each subscript b is 6.
[0383] In some embodiments, M is
##STR00081##
In some aspects, M is
##STR00082##
In some aspects, M is
##STR00083##
[0384] In some embodiments, M is
##STR00084##
In some aspects, M is
##STR00085##
In some aspects, M is
##STR00086##
[0385] In some embodiments, M is
##STR00087##
In some aspects, M is
##STR00088##
In some aspects, M is
##STR00089##
[0386] In some embodiments, R.sup.1 is methoxy and R.sup.2 and R.sup.3 are both —C(═O)NH.sub.2. In some embodiments, X.sup.A is —O— and X.sup.B is
##STR00090##
wherein custom-character represents covalent linkage to X.sup.A, and * represents covalent linkage to L, when present, or M. In some embodiments, R.sup.1 is methoxy; R.sup.2 and R.sup.3 are both —C(═O)NH.sub.2; X.sup.A is —O—; and X.sup.B is
##STR00091##
wherein custom-character represents covalent linkage to X.sup.A, and * represents covalent linkage to L, when present, or M. In some such embodiments, L is absent. In some embodiments, R.sup.1 is methoxy; R.sup.2 and R.sup.3 are both —C(═O)NH.sub.2; X.sup.A is —O—; X.sup.B is
##STR00092##
wherein custom-character represents covalent linkage to X.sup.A, and * represents covalent linkage to L; and subscript a and subscript y are both 0 (i.e., X.sup.B is covalently attached to W). In some embodiments, X.sup.A is —O—; X.sup.B is
##STR00093##
wherein custom-character represents covalent linkage to X.sup.A, and * represents covalent linkage to L. In some embodiments, R.sup.1 is methoxy; R.sup.2 and R.sup.3 are both —C(═O)NH.sub.2; X.sup.A is —O—; and X.sup.B is
##STR00094##
wherein custom-character represents covalent linkage to X.sup.A, and * represents covalent linkage to L; and subscript a and subscript w are both 0.
[0387] In some embodiments, R.sup.1 is methoxy; R.sup.2 and R.sup.3 are both —C(═O)NH.sub.2; X.sup.A is —O—; and X.sup.B is
##STR00095##
wherein custom-character represents covalent linkage to X.sup.A, and * represents covalent linkage to L; and subscript y and subscript w are both 0.
[0388] In some embodiments, R.sup.1 is methoxy; R.sup.2 and R.sup.3 are both —

C(═O)NH.sub.2; X.sup.A is —O—; and X.sup.B is
##STR00096##
wherein custom-character represents covalent linkage to X.sup.A, and * represents covalent linkage to L; and subscript y is 0.
[0389] In some embodiments, R.sup.1 is methoxy and R.sup.2 and R.sup.3 are both —C(═O)NH.sub.2. In some embodiments, X.sup.A is —CH.sub.2—; and X.sup.B is
##STR00097##
wherein custom-character represents covalent linkage to X.sup.A, and * represents covalent linkage to L, when present, or M. In some embodiments, R.sup.1 is methoxy; R.sup.2 and R.sup.3 are both —C(═O)NH.sub.2; X.sup.A is —CH.sub.2—; and X.sup.B is
##STR00098##
wherein custom-character represents covalent linkage to X.sup.A, and * represents covalent linkage to L, when present, or M. In some embodiments, R.sup.1 is methoxy; R.sup.2 and R.sup.3 are both —C(═O)NH.sub.2; X.sup.A is —CH.sub.2—; and X.sup.B is
##STR00099##
wherein custom-character represents covalent linkage to X.sup.A, and * represents covalent linkage to L; and subscript a and subscript y are both 0 (i.e., X.sup.B is covalently attached to W). In some embodiments, X.sup.A is —CH.sub.2—; and X.sup.B is
##STR00100##
wherein custom-character represents covalent linkage to X.sup.A, and * represents covalent linkage to L. In some embodiments, R.sup.1 is methoxy; R.sup.2 and R.sup.3 are both —C(═O)NH.sub.2; X.sup.A is —CH.sub.2—; and X.sup.B is
##STR00101##
wherein custom-character represents covalent linkage to X.sup.A, and * represents covalent linkage to L; and subscript a and subscript w are both 0 (i.e., X.sup.B is covalently bound to Y).
[0390] In some such embodiments, L is a linker having the formula -(A).sub.a-(W).sub.w—(Y).sub.y—.
[0391] In some embodiments: X.sup.B is absent and L is covalently attached to X.sup.A. In some embodiments: X.sup.B is absent and Y is covalently attached to X.sup.A. In some embodiments: X.sup.B is absent and Y is absent, and W is covalently attached to X.sup.A. In some embodiments: X.sup.B is absent, Y is absent, W is absent, and A is covalently attached to X.sup.A.
[0392] In some embodiments: X.sup.B is a 2-16 membered heteroalkylene and L is covalently attached to X.sup.B. In some embodiments: X.sup.B is a 2-16 membered heteroalkylene and Y is covalently attached to X.sup.B. In some embodiments: X.sup.B is a 2-16 membered heteroalkylene, Y is absent, and W is covalently attached to X.sup.B. In some embodiments: X.sup.B is a 2-16 membered heteroalkylene, Y is absent, W is absent, and A is covalently attached to X.sup.B.
[0393] In some embodiments, W.sub.1 is —OC(═O)— and subscript y is 1. In some embodiments, X.sup.A is —O— and X.sup.B and W are absent. In some embodiments, X.sup.A is NH or —O—, X.sup.B is absent, and W.sub.1 is —OC(═O). In some embodiments, X.sup.A is —N(CH.sub.3)—, X.sup.B is absent, and W.sub.1 is —OC(═O). In some embodiments, X.sup.A is —S—, X.sup.B is absent, and W.sub.1 is —OC(═O). In some embodiments, W.sub.1 is —OC(═O)— and X.sup.B is covalently attached to W via —O— or —NH—.
[0394] In some embodiments, A is covalently attached to M. In some embodiments, when subscript a is 0 and subscript w is 0, Y is covalently attached to M. In some embodiments, when subscripts a, y, and w, are each 0, X.sup.B is covalently attached to M.
[0395] In some embodiments, the compound of Formula (II) is selected from the group consisting of:
##STR00102## ##STR00103## ##STR00104## ##STR00105## ##STR00106## ##STR00107##
[0396] The structures shown above include all tautomeric forms. Thus, for example, the structure:

##STR00108##
is to be understood as encompassing the following tautomeric forms:
##STR00109## ##STR00110##
Compounds of Formula (II-A)
[0397] In some embodiments, the compound of Formula (II) has the structure of Formula (II-A):
##STR00111##
or a pharmaceutically acceptable salt thereof, wherein: [0398] L.sup.A is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, or —C(O)NR.sup.H(CH.sub.2).sub.1-6—; [0399] each R.sup.H is independently hydrogen or C.sub.1-3 alkyl;
[0400] Y is
##STR00112## [0401] # represents covalent attachment to NR.sup.HL.sup.A; [0402] ## represents covalent attachment to W or L.sup.B. [0403] L.sup.B is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, or —[NHC(O)(CH.sub.2).sub.1-4].sub.1-3—; and [0404] the remaining variables are as defined above in connection of Formula (II).
[0405] In some embodiments, R.sup.H is C.sub.1-3 alkyl. In some embodiments, R.sup.H is methyl. In some embodiments, R.sup.H is not hydrogen. In some embodiments, L.sup.A is —(CH.sub.2).sub.2-6—. In some embodiments, L.sup.A is —(CH.sub.2).sub.3—. In some embodiments, subscript y is 0. In some embodiments, subscript y is 1. In some embodiments, subscript w is 0. In some embodiments, subscript w is 1. In some embodiments, subscript y and subscript w are both 1. In some embodiments, subscript y and subscript w are both 0. When subscript y and subscript w are both 0, the compound of Formula (II) has the structure of Formula (II-B):
##STR00113##
or a pharmaceutically acceptable salt thereof, wherein: [0406] L.sup.A is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, or —C(O)NR.sup.H(CH.sub.2).sub.1-6—; [0407] each R.sup.H is independently hydrogen or C.sub.1-3 alkyl; [0408] L.sup.B is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, or —[NHC(O)(CH.sub.2).sub.1-4].sub.1-3-; and the remaining variables are as defined above in connection of Formula (II).
[0409] In some embodiments, W is a chain of 1-6 amino acids. In some embodiments, W is a chain of 1-4 amino acids. In some embodiments, W is a chain of 1-3 amino acids. In some embodiments, each amino acid of W is independently selected from the group consisting of alanine, valine, isoleucine, leucine, aspartic acid, glutamic acid, lysine, histidine, arginine, glycine, serine, threonine, phenylalanine, O-methylserine, O-methylaspartic acid, O-methylglutamic acid, N-methyllysine, O-methyltyrosine, O-methylhistidine, and O-methylthreonine.
[0410] In some embodiments, W is:
##STR00114##
wherein: [0411] custom-character represents covalent attachment to L.sup.B; and [0412] * represents covalent attachment to Y or NR.sup.H.
[0413] In some embodiments, L.sup.B is —C(O)(CH.sub.2).sub.2-6—. In some embodiments, L.sup.B is —C(O)(CH.sub.2).sub.2—. In some embodiments, L.sup.B is —C(O)(CH.sub.2).sub.3-. In some embodiments, L.sup.B is —C(O)(CH.sub.2).sub.4-. In some embodiments, L.sup.B is —C(O)(CH.sub.2).sub.5—. In some embodiments, L.sup.B is —C(O)(CH.sub.2).sub.6—. In some embodiments, L.sup.B is —[NHC(O)(CH.sub.2).sub.2].sub.2—. In some embodiments, M is
##STR00115##
In some embodiments, M is
##STR00116##
In some aspects, M is
##STR00117##
In some aspects, M is NH.sub.2
##STR00118##

[0414] In some embodiments, the compound of Formula (II-A) is selected from the group consisting of:
##STR00119## ##STR00120## ##STR00121## ##STR00122##
and pharmaceutically acceptable salts thereof.
Compounds of Formula (III)
[0415] Some embodiments provide compounds of Formula (III):
##STR00123##
or a pharmaceutically acceptable salt thereof, wherein: [0416] R.sup.1A is hydrogen, hydroxyl, C.sub.1-6 alkoxy, —(C.sub.1-6 alkyl)C.sub.1-6 alkoxy, —(CH.sub.2).sub.nn—NR.sup.AAR.sup.BB; [0417] each R.sup.2A and R.sup.3A are independently —CO.sub.2H, —(C═O).sub.mm—NR.sup.CCR.sup.DD, or —(CH.sub.2).sub.qq—NR.sup.EE1R.sup.FF1; [0418] each subscript nn is independently an integer from 0 to 6; [0419] each subscript mm is independently 0 or 1; [0420] each subscript qq is independently an integer from 0 to 6; [0421] Y.sup.1 is —CH.sub.2—, —O—, —S—, —NH—, or —N(CH.sub.3)—; [0422] X.sup.1 is a C.sub.2-C.sub.6 alkylene; [0423] Z.sup.1 is —NR.sup.EER.sup.FF, —C(═O)NR.sup.GGR.sup.HH, or —CO.sub.2H; [0424] each R.sup.AA, R.sup.BB, R.sup.CC, R.sup.DD, R.sup.EE1, and R.sup.FF1 are independently hydrogen or C.sub.1-3 alkyl; and [0425] each R.sup.EE, R.sup.FF, R.sup.GG, and R.sup.HH are independently hydrogen or C.sub.1-6 alkyl.
[0426] In some embodiments, R.sup.1A is hydrogen. In some embodiments, R.sup.1A is hydroxyl. In some embodiments, R.sup.1A is C.sub.1-6 alkoxy. In some embodiments, R.sup.1 is methoxy. In some embodiments, R.sup.1A is —(C.sub.1-6 alkyl)C.sub.1-6 alkoxy. In some embodiments, R.sup.1A is methoxyethyl.
[0427] In some embodiments, R.sup.1 is —(CH.sub.2).sub.nn—NR.sup.AAR.sup.BB. In some embodiments, R.sup.AA and R.sup.BB are both hydrogen. In some embodiments, R.sup.AA and R.sup.BB are independently C.sub.1-3 alkyl. In some embodiments, one of R.sup.AA and R.sup.BB is hydrogen and the other of R.sup.AA and R.sup.BB is C.sub.1-3 alkyl. In some embodiments, the C.sub.1-3 alkyl is methyl. In some embodiments, each subscript nn is 0. In some embodiments, each subscript nn is 1. In some embodiments, each subscript nn is 2. In some embodiments, each subscript nn is 3. In some embodiments, each subscript nn is 3, 4, 5, or 6. In some embodiments, each subscript nn is 4. In some embodiments, each subscript nn is 5. In some embodiments, each subscript nn is 6.
[0428] In some embodiments, each R.sup.2A and R.sup.3A are independently —CO.sub.2H, —(C═O).sub.m—NR.sup.CCR.sup.DD, or —(CH.sub.2).sub.qq—NR.sup.EE1R.sup.FF1; and R.sup.2A and R.sup.3A are the same. In some embodiments, each R.sup.2A and R.sup.3A are independently —CO.sub.2H, —(C═O).sub.mm—NR.sup.CCR.sup.DD, or —(CH.sub.2).sub.qq—NR.sup.EE1R.sup.FF1; and R.sup.2A and R.sup.3A are different.
[0429] In some embodiments, R.sup.2A is (C═O).sub.mmNR.sup.CCR.sup.DD. In some embodiments, R.sup.3A is —(C═O).sub.mm—NR.sup.CCR.sup.DD. In some embodiments, each R.sup.CC and each R.sup.DD is hydrogen. In some embodiments, each R.sup.CC and each R.sup.DD is independently C.sub.1-3 alkyl. In some embodiments, one of each R.sup.CC and R.sup.DD is hydrogen and the other of each R.sup.CC and R.sup.DD is C.sub.1-3 alkyl. In some embodiments, the C.sub.1-3 alkyl is methyl. In some embodiments, each subscript mm is 0. In some embodiments, each subscript mm is 1.
[0430] In some embodiments, R.sup.2A is —(CH.sub.2).sub.qq—NR.sup.EE1R.sup.FF1. In some embodiments, R.sup.3A is —(CH.sub.2).sub.qq—NR.sup.EE1R.sup.FF1. In some embodiments, each R.sup.EE1 and each R.sup.FF1 is hydrogen. In some embodiments, each R.sup.EE1 and each R.sup.FF1 is independently C.sub.1-3 alkyl. In some embodiments, one of each R.sup.EE1 and R.sup.FF1 is hydrogen and the other of each R.sup.EE1 and R.sup.FF1 is C.sub.1-3 alkyl. In some embodiments, the C.sub.1-3 alkyl is methyl. In some embodiments, each subscript q is 0. In some embodiments, each subscript q is an integer from 1 to 6. In some embodiments, each subscript qq is

1. In some embodiments, each subscript qq is 2. In some embodiments, each subscript qq is 3, 4, 5, or 6.
[0431] In some embodiments, R.sup.3A is —CO.sub.2H. In some embodiments, R.sup.2A is —CO.sub.2H.
[0432] In some embodiments, Y.sup.1 is —CH.sub.2—. In some embodiments, Y.sup.1 is —O—. In some embodiments, Y.sup.1 is —S—. In some embodiments, Y.sup.1 is —NH—. In some embodiments, Y.sup.1 is —N(CH.sub.3)—.
[0433] In some embodiments, X.sup.1 is a C.sub.2-C.sub.5 alkylene. In some embodiments, X.sup.1 is a C.sub.2-C.sub.4 alkylene. In some embodiments, X.sup.1 is ethylene or n-propylene. In some embodiments, X.sup.1 is ethylene. In some embodiments, X.sup.1 is n-propylene.
[0434] In some embodiments, Z.sup.1 is —NR.sup.E1R.sup.F1. In some embodiments, R.sup.EE and R.sup.FF are both hydrogen. In some embodiments, R.sup.EE and R.sup.FF are independently C.sub.1-6 alkyl. In some embodiments, one of R.sup.EE and R.sup.FF is hydrogen and the other of R.sup.EE and R.sup.FF is C.sub.1-6 alkyl. In some embodiments, the C.sub.1-6 alkyl is a C.sub.1-3 alkyl. In some embodiments, the C.sub.1-3 alkyl is methyl.
[0435] In some embodiments, Z.sup.1 is —C(═O)NR.sup.GGR.sup.HH. In some embodiments, R.sup.GG and R.sup.HH are both hydrogen. In some embodiments, R.sup.GG and R.sup.HH are independently C.sub.1-6 alkyl. In some embodiments, one of R.sup.GG and R.sup.HH is hydrogen and the other of R.sup.GG and R.sup.HH is C.sub.1-6 alkyl. In some embodiments, the C.sub.1-6 alkyl is a C.sub.1-3 alkyl. In some embodiments, the C.sub.1-3 alkyl is methyl. In some embodiments, Z.sup.1 is —CO.sub.2H. In some embodiments, Z.sup.1 is —NR.sup.EER.sup.FF In some embodiments, R.sup.EE is hydrogen and R.sup.FF is methyl.
[0436] In some embodiments, R.sup.1A is methoxy and R.sup.2A and R.sup.3A are both —C(═O)NH.sub.2. In some embodiments, Y.sup.1 is —O— and X.sup.1 is a C.sub.3 alkylene. In some embodiments, Y.sup.1 is —O— and X.sup.1 is n-propylene. In some embodiments, Y.sup.1 is —O—, X.sup.1 is n-propylene, and Z.sup.1 is —NH.sub.2. In some embodiments, Y.sup.1 is —O—, X.sup.1 is n-propylene, and Z.sup.1 is —NHCH.sub.3. In some embodiments, Y.sup.1 is —O— X.sup.1 is n-propylene, and Z.sup.1 is —N(CH.sub.3).sub.2.
[0437] In some embodiments, R.sup.1A is methoxy; R.sup.2A and R.sup.3A are both —C(═O)NH.sub.2; Y.sup.1 is —O—; X.sup.1 is n-propylene; and Z.sup.1 is —NH.sub.2. In some embodiments, R.sup.1A is methoxy; R.sup.2A and R.sup.3Aare both —C(═O)NH.sub.2; Y.sup.1 is —O—; X.sup.1 is n-propylene; and Z.sup.1 is —NHCH.sub.3. In some embodiments, R.sup.1A is methoxy; R.sup.2A and R.sup.3A are both —C(═O)NH.sub.2; Y.sup.1 is —O—; X.sup.1 is n-propylene; and Z.sup.1 is —N(CH.sub.3).sub.2.
[0438] In some embodiments, the compound of Formula (III) is
##STR00124##
Compounds of Formula (IV)
[0439] Some embodiments include a compound of Formula (IV):
##STR00125##
or a pharmaceutically acceptable salt thereof, wherein: [0440] R.sup.1C is hydrogen, hydroxyl, C.sub.1-6 alkoxy, —(C.sub.1-6 alkyl) C.sub.1-6 alkoxy, —(CH.sub.2).sub.n—NR.sup.AR.sup.B, or PEG2 to PEG4; [0441] R.sup.2C is —CO.sub.2R.sup.M, —(C═O)NR.sup.CR.sup.D, —S(O).sub.2NR.sup.CR.sup.D, —S(O).sub.2R.sup.M, —(CH.sub.2).sub.q—NR.sup.ER.sup.F, —(CH.sub.2).sub.q—OR.sup.M, —O(C═O)—NR.sup.ER.sup.F, or —NR.sup.M(C═O)—NR.sup.ER.sup.F, wherein R.sup.2C is attached at any on of positions labeled 1, 2, or 3; [0442] R.sup.3C is —CO.sub.2R.sup.M, —(C═O)NR.sup.CR.sup.D, —S(O).sub.2NR.sup.CR.sup.D, —S(O).sub.2R.sup.M, —(CH.sub.2).sub.q—NR.sup.ER.sup.F, —(CH.sub.2).sub.q—OR.sup.M, —O(C═O)—NR.sup.ER.sup.F, or —NR.sup.M(C═O)—NR.sup.ER.sup.F, wherein R.sup.3C is attached at any one of positions labeled 1′, 2′, or 3′; [0443] each R.sup.A, R.sup.B, R.sup.C, R.sup.D, R.sup.E, R.sup.F, and R.sup.M are independently hydrogen or C.sub.1-6 alkyl; [0444]

each subscript n is independently an integer from 0 to 6; [0445] each subscript q is independently an integer from 0 to 6; [0446] L.sup.E is —(C═O)— or —S(0).sub.2—; [0447] L.sup.C is —(CR.sup.IR.sup.J).sub.1-3— [0448] each R.sup.I and R.sup.J are independently hydrogen or C.sub.1-3 alkyl; [0449] subscript s is 0 or 1; [0450] each Cy.sup.1 is independently a 4-6 membered heterocycle, a 5-6 membered heteroaryl, or a C.sub.3-6 cycloalkyl, each optionally substituted with one or more R.sup.K; [0451] each R.sup.K is independently selected from the group consisting of: C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, ═O, —NR.sup.d2R.sup.e2, —C(O)NR.sup.d2R.sup.e2, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl); [0452] each R.sup.d2 and R.sup.e2 are independently hydrogen or C.sub.1-3 alkyl; [0453] L.sup.AA is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, —C(O)NR.sup.L(CH.sub.2).sub.1-6—, —(CH.sub.2).sub.1-6O—, —C(O)(CH.sub.2).sub.1-6O—, or —C(O)NR.sup.L(CH.sub.2).sub.1-6O—; [0454] R.sup.L is hydrogen or C.sub.1-3 alkyl; [0455] Cy.sup.2 is C.sub.3-6 cycloalkyl, 4-6 membered heterocycle, 5-6 membered heteroaryl, or phenyl, each optionally substituted with one or more R.sup.U; [0456] each R.sup.U is independently selected from the group consisting of —CO.sub.2R.sup.j1, —(C═O)NR.sup.d3R.sup.e3, —S(O).sub.2NR.sup.d3R.sup.e3, —(CH.sub.2).sub.g1—NR.sup.g1R.sup.h1, —(CH.sub.2).sub.q1—OR.sup.j1, and —(CH.sub.2).sup.q1—(OCH.sub.2CH.sub.2).sub.1-8OH; [0457] each R.sup.d3, R.sup.e3, R.sup.g1, R.sup.h1, and R.sup.j1 are independently hydrogen or C.sub.1-6 alkyl; [0458] subscript q1 is an integer from 0 to 6; [0459] subscripts t1 and t2 are independently 0 or 1, wherein at least one of t1 and t2 is 1; [0460] L.sup.D is —(CH.sub.2).sub.1-6—; [0461] subscript u is 0 or 1; [0462] Z is —N(R.sup.HH)— or —N.sup.+(C.sub.1-6 alkyl)(R.sup.HH)—; [0463] R.sup.HH is hydrogen, C.sub.1-6 alkyl, C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.1-3 alkoxy, —(CH.sub.2).sub.1-3 4-6 membered heterocycle, or —(CH.sub.2).sub.1-3 5-6 membered heteroaryl; [0464] Y is a self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety; [0465] subscript y is 0 or 1; [0466] W is a chain of 1-12 amino acids or has the structure:

##STR00126## [0467] wherein Su is a Sugar moiety; [0468] —O.sup.A— represents a glycosidic bond; [0469] each R.sup.9 is independently hydrogen, halogen, —CN, or —NO.sub.2; [0470] W.sup.1 is absent or —O—C(═O)—; [0471] custom-character represents covalent attachment to L.sup.BB; [0472] * represents covalent attachment to Y, L.sup.D, NR.sup.HH, or Cy.sup.2; [0473] subscript w is 0 or 1; [0474] L.sup.BB is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, or —[NHC(O)(CH.sub.2).sub.1-4]1-3-; and [0475] M is

##STR00127## [0476] each AA is an independently selected amino acid, wherein (AA).sub.b is connected to the succinimide or hydrolyzed succinimide via a sulfur atom; and [0477] each subscript b is independently an integer from 1 to 6.

[0478] In some embodiments, R.sup.1C is hydrogen. In some embodiments, R.sup.1C is hydroxyl. In some embodiments, R.sup.1C is C.sub.1-6 alkoxy. In some embodiments, R.sup.1C is methoxy. In some embodiments, R.sup.1C is —(C.sub.1-6 alkyl)C.sub.1-6 alkoxy. In some embodiments, R.sup.1C is methoxyethyl. In some embodiments, R.sup.1C is PEG2 to PEG4. In some embodiments, R.sup.1C is —(CH.sub.2).sub.n—NR.sup.AR.sup.B.

[0479] In some embodiments, R.sup.A and R.sup.B are both hydrogen. In some embodiments, R.sup.A and R.sup.B are independently C.sub.1-3 alkyl. In some embodiments, one of R.sup.A and R.sup.B is hydrogen and the other of R.sup.A and R.sup.B is C.sub.1-3 alkyl.

[0480] In some embodiments, each subscript n is 0. In some embodiments, each subscript n is 1. In some embodiments, each subscript n is 2. In some embodiments, each subscript n is 3, 4, 5, or 6.

[0481] In some embodiments, R.sup.2C and R.sup.3C are independently —CO.sub.2H, —(C═O).sub.m, —NR.sup.CR.sup.D, or —(CH.sub.2).sub.q—NR.sup.ER.sup.F; and R.sup.2C and R.sup.3C are the same. In some embodiments, R.sup.2C and R.sup.3C are independently —CO.sub.2H, —(C═O).sub.m—NR.sup.CR.sup.D, or —(CH.sub.2).sub.q—NR.sup.ER.sup.F; and R.sup.2C and R.sup.3C are different. In some embodiments, R.sup.2C is —(C═O).sub.m—

NR.sup.CR.sup.D. In some embodiments, R.sup.3C is —(C═O).sub.m—NR.sup.CR.sup.D. In some embodiments, R.sup.C and R.sup.D are both hydrogen. In some embodiments, R.sup.C and R.sup.D are each independently C.sub.1-3 alkyl. In some embodiments, one of R.sup.C and R.sup.D is hydrogen and the other of R.sup.C and R.sup.D is C.sub.1-3 alkyl. In some embodiments, each subscript m is 0. In some embodiments, each subscript m is 1.

[0482] In some embodiments, R.sup.2C is —(CH.sub.2).sub.q—NR.sup.ER.sup.F. In some embodiments, R.sup.3C is —(CH.sub.2).sub.q—NR.sup.ER.sup.F. In some embodiments, R.sup.E and R.sup.F are both hydrogen. In some embodiments, R.sup.E and R.sup.F are each independently C.sub.1-3 alkyl. In some embodiments, one of R.sup.E and R.sup.F is hydrogen and the other of R.sup.E and R.sup.F is C.sub.1-3 alkyl. In some embodiments, each subscript q is 0. In some embodiments, each subscript q is an integer from 1 to 6.

[0483] In some embodiments, R.sup.2C is —CO.sub.2R.sup.M. In some embodiments, R.sup.3C is —CO.sub.2R.sup.M. In some embodiments, R.sup.M is hydrogen. In some embodiments, R.sup.M is C.sub.1-3 alkyl.

[0484] In some embodiments, R.sup.2C is (CH.sub.2).sub.q—OR.sup.M.

[0485] In some embodiments, R.sup.3C is —(CH.sub.2).sub.q—OR.sup.M. In some embodiments, R.sup.M is hydrogen. In some embodiments, q is 0. In some embodiments, q is 1.

[0486] In some embodiments, R.sup.2C is —O(C═O)—NR.sup.ER.sup.F. In some embodiments, R.sup.3C is —O(C═O)—NR.sup.ER.sup.F. In some embodiments, R.sup.E and R.sup.F are both hydrogen. In some embodiments, R.sup.E and R.sup.F are each independently C.sub.1-3 alkyl. In some embodiments, R.sup.E and R.sup.F is hydrogen and the other of R.sup.E and R.sup.F is C.sub.1-3 alkyl.

[0487] In some embodiments, R.sup.2C is —NR.sup.M(C═O)—NR.sup.ER.sup.F. In some embodiments, R.sup.3C is —NR.sup.M(C═O)—NR.sup.ER.sup.F. In some embodiments, R.sup.E, R.sup.F, and R.sup.M are all hydrogen. In some embodiments, R.sup.E, R.sup.F, and R.sup.M are each independently C.sub.1-3 alkyl. In some embodiments, one of R.sup.E, R.sup.F, and R.sup.M is C.sub.1-3 alkyl and the rest of R.sup.E, R.sup.F, and R.sup.M is hydrogen.

[0488] In some embodiments, R.sup.2C is —S(O).sub.2NR.sup.CR.sup.D. In some embodiments, R.sup.3C is —S(O).sub.2NR.sup.CR.sup.D. In some embodiments, R.sup.c and R.sup.D are both hydrogen. In some embodiments, R.sup.c and R.sup.D are each independently C.sub.1-3 alkyl. In some embodiments, one of R.sup.C and R.sup.D is hydrogen and the other of R.sup.C and R.sup.D is C.sub.1-3 alkyl.

[0489] In some embodiments, R.sup.2C is —S(O).sub.2R.sup.M. In some embodiments, R.sup.3C is —S(O).sub.2R.sup.M. In some embodiments, R.sup.M is hydrogen. In some embodiments, R.sup.M is C.sub.1-3 alkyl.

[0490] In some embodiments, R.sup.2C is attached at position 1. In some embodiments, R.sup.2C is attached at position 2. In some embodiments, R.sup.2C is attached at position 3. In some embodiments, R.sup.3C is attached at position 1′. In some embodiments, R.sup.3C is attached at position 2′. In some embodiments, R.sup.3C is attached at position 3′.

[0491] In some embodiments, L.sup.E is —(C═O)—. In some embodiments, L.sup.E is —S(O).sub.2—.

[0492] In some embodiments, each R.sup.I and R.sup.J is hydrogen. In some embodiments, each R.sup.I and R.sup.J is C.sub.1-3 alkyl. In some embodiments, one of R.sup.I and R.sup.J is hydrogen and the other of R.sup.I and R.sup.J is C.sub.1-3 alkyl.

[0493] In some embodiments, L.sup.C is —(CR.sup.IR.sup.J)—.

[0494] In some embodiments, s is 0. In some embodiments, s is 1.

[0495] In some embodiments, each Cy.sup.1 is independently a 5-6 membered heteroaryl. In some embodiments, each Cy.sup.1 is pyrazole optionally substituted with one or more R.sup.K. In some embodiments, each Cy.sup.1 is independently selected from the group consisting of pyrazole, imidazole, furan, thiophene, thiazole, isothiazole, oxazole, isoxazole, pyrrole, pyridazine, pyridine,

pyrimidine, and pyrazine, each optionally substituted with one or more R.sup.K. In some embodiments, each Cy.sup.1 is independently selected from the group consisting of imidazole, furan, thiophene, thiazole, isothiazole, oxazole, isoxazole, pyrrole, pyridazine, pyridine, pyrimidine, and pyrazine, each optionally substituted with one or more R.sup.K. In some embodiments, each Cy.sup.1 is independently a C.sub.4-5 cycloalkyl optionally substituted with one or more R.sup.K. In some embodiments, each R.sup.K is independently selected from the group consisting of C.sub.1-3 alkyl, C.sub.1-3 haloalkyl, and halogen. In some embodiments, each R.sup.K is independently selected from the group consisting of methyl, ethyl, —CF.sub.3, and halogen.

[0496] In some embodiments, each Cy.sup.1 is the same. In some embodiments, each Cy.sup.1 is different.

[0497] In some embodiments, L.sup.AA is —(CH.sub.2).sub.1-6—. In some embodiments, L.sup.AA is —(CH.sub.2).sub.1-3—. In some embodiments, L.sup.AA is —(CH.sub.2).sub.1-6O —. In some embodiments, L.sup.AA is —(CH.sub.2).sub.1-3O—-.

[0498] In some embodiments, Cy.sup.2 is a 4-6 membered heterocycle. In some embodiments, Cy.sup.2 has the structure:

##STR00128##

wherein each of subscripts z1 and z2 is independently an integer from 1 to 3 and ** indicates attachment to L.sup.AA. In some embodiments, z1 and z2 are 1. In some embodiments, z1 and z2 are 2. In some embodiments, z1 is 1 and z2 is 2.

[0499] In some embodiments, Cy.sup.2has the structure:

##STR00129##

wherein [0500] Z.sup.1 is selected from the group consisting of —O—, —S—, —CR.sup.NR.sup.O—, and —NR.sup.P—; [0501] R.sup.N, R.sup.O, and R.sup.P are independently hydrogen or C.sub.1-6 alkyl; [0502] subscript z3 is an integer from 1 to 3; and [0503] ** indicates attachment to L.sup.AA.

[0504] In some embodiments, R.sup.N and R.sup.O are hydrogen. In some embodiments, R.sup.P is hydrogen. In some embodiments, R.sup.P is methyl.

[0505] In some embodiments, Cy.sup.2 is a 5-6 membered heteroaryl. In some embodiments, Cy.sup.2 is selected from the group consisting of:

##STR00130##

wherein [0506] Z.sup.2 is ═CR.sup.N— or =N; [0507] R.sup.N is hydrogen or C.sub.1-6 alkyl; and [0508] ** indicates attachment to L.sup.AA.

[0509] In some embodiments, Z.sup.2 is =CR.sup.N and R.sup.N is hydrogen. In some embodiments, Z.sup.2 is =N—.

[0510] In some embodiments, Cy.sup.2 is selected from the group consisting of:

##STR00131##

wherein Z.sup.3 is —O— or —S— and ** indicates attachment to L.sup.AA, L.sup.D, NR.sup.HH, Y, W, or L.sup.BB.

[0511] In some embodiments, ** indicates attachment to L.sup.AA. In some embodiments, ** indicates attachment to L.sup.D, NR.sup.HH, Y, W, or L.sup.BB.

[0512] In some embodiments, Cy.sup.2 is selected from the group consisting of:

##STR00132##

wherein ** indicates attachment to L.sup.AA.

[0513] In some embodiments, Cy.sup.2 is selected from the group consisting of:

##STR00133##

wherein [0514] each Z.sup.2 is independently ═CR.sup.N— or ═N—; and [0515] each R.sup.N is hydrogen or C.sub.1-6 alkyl.

[0516] In some embodiments, at least one Z.sup.2 is =N—. In some embodiments, one Z.sup.2 is ═N— and the remaining Z.sup.2 are ═CR.sup.N—. In some embodiments, two Z2 are ═N— and

the remaining Z.sup.2 are ═CR.sup.N—.
[0517] In some embodiments, R.sup.N is hydrogen.
[0518] In some embodiments, Cy.sup.2 is selected from the group consisting of:
##STR00134##
[0519] In some embodiments, Cy.sup.2 is cyclobutyl.
[0520] In some embodiments, each R.sup.d3, R.sup.e3, R.sup.g1, R.sup.h1, and R.sup.j1 are independently hydrogen or —CH.sub.3.
[0521] In some embodiments, each R.sup.U is independently selected from —CO.sub.2H, —(C═O)NH.sub.2, —S(O).sub.2NH.sub.2, —CH.sub.2NH.sub.2, and —CH.sub.2OH.
[0522] In some embodiments, t1 is 0 and t2 is 1. In some embodiments, t1 is 1 and t2 is 0. In some embodiments, t1 is 1 and t2 is 1.
[0523] In some embodiments, u is 1 and L.sup.D is —(CH.sub.2).sub.1-3. In some embodiments, u is 0.
[0524] In some embodiments, t2 is 1 and R.sup.HH is hydrogen. In some embodiments, t2 is 1 and R.sup.HH is C.sub.1-3 alkyl. In some embodiments, t2 is 1 and R.sup.HH is C.sub.3-4 cycloalkyl. In some embodiments, t2 is 1 and R.sup.HH is —(CH.sub.2) C.sub.3-4 cycloalkyl. In some embodiments, t2 is 1 and R.sup.HH is —(CH.sub.2) 4-5 membered heterocycle. In some embodiments, t2 is 1 and R.sup.HH is —(CH.sub.2) 5-membered heteroaryl.
[0525] In some embodiments, Z is —N(R.sup.HH)—. In other embodiments, Z is —N.sup.+(C.sub.1-6 alkyl)(R.sup.HH)—.
[0526] In some embodiments, Y is
##STR00135##
[0527] In some embodiments, Y is a cyclohexanecarboxyl, undecanoyl, caproyl, hexanoyl, butanoyl or propionyl group. In some embodiments, Y is PEG4 to PEG12. In some embodiments, y is 0. In some embodiments, y is 1.
[0528] In some embodiments, W is a chain of 1-12 amino acids. In some embodiments, W is a chain of 1-6 amino acids. In some embodiments, W is a chain of 1-3 amino acids.
[0529] In some embodiments, W is independently selected from the group consisting of alanine, valine, isoleucine, leucine, aspartic acid, glutamic acid, lysine, histidine, arginine, glycine, serine, threonine, phenylalanine, O-methylserine, O-methylaspartic acid, O-methylglutamic acid, N-methyllysine, O-methyltyrosine, O-methylhistidine, and O-methylthreonine. In some embodiments, each amino acid in W is independently selected from the group consisting of alanine, glycine, lysine, serine, aspartic acid, aspartate methyl ester, N,N-dimethyl-lysine, phenylalanine, citrulline, valine-alanine, valine-citrulline, phenylalanine-lysine or homoserine methyl ether.
[0530] In some embodiments, W has the structure:
##STR00136##
[0531] In some embodiments, W.sup.1 is —O—C(═O)—. In some embodiments, one R.sup.g is halogen, —CN, or —NO.sub.2, and the remaining R.sup.G are hydrogen. In some embodiments, each R.sup.g is hydrogen.
[0532] In some embodiments, w is 0. In some embodiments, w is 1.
[0533] In some embodiments, L.sup.BB is —(CH.sub.2).sub.1-3—. In some embodiments, L.sup.RR is —C(O)(CH.sub.2).sub.1-2—.
[0534] In some embodiments, L.sup.BB is —C(O)(CH.sub.2).sub.2—. In some embodiments, L.sup.BB is —[NHC(O)(CH.sub.2).sub.2]1-2-. In some embodiments, L.sup.BB is —[NHC(O)(CH.sub.2).sub.2].sub.2—.
[0535] In some embodiments, M is
##STR00137##
In some aspects, M is
##STR00138##
In some aspects, M is

##STR00139##
[0536] In some embodiments, M is
##STR00140##
In some aspects, M is
##STR00141##
In some aspects, M is
##STR00142##
[0537] In some embodiments, M is
##STR00143##
In some aspects, M is
##STR00144##
In some aspects, M is
##STR00145##
[0538] In some embodiments, each AA is independently a natural amino acid; wherein (AA)b is connected to the succinimide or hydrolyzed succinimide via a sulfur atom. In some embodiments, each AA is independently a natural amino acid; wherein (AA).sub.b is connected to the succinimide or hydrolyzed succinimide via a nitrogen atom. In some embodiments, each subscript b is 1. In some embodiments, each subscript b is 2. In some embodiments, each subscript b is 3, 4, 5, or 6.
[0539] In some embodiments, M is
##STR00146##
In some aspects, M is
##STR00147##
In some aspects, M is
##STR00148##
[0540] In some embodiments, M is
##STR00149##
In some aspects, M is
##STR00150##
In some aspects, M is
##STR00151##
[0541] In some embodiments, M is
##STR00152##
In some aspects, M is
##STR00153##
In some aspects, M is
##STR00154##
[0542] In some embodiments, M is
##STR00155##
[0543] Some embodiments of the compound of Formula (IV) include a compound selected from the group consisting of:
##STR00156## ##STR00157## ##STR00158## ##STR00159## ##STR00160## ##STR00161## ##STR00162## ##STR00163## ##STR00164## ##STR00165## ##STR00166## ##STR00167## ##STR00168## ##STR00169## ##STR00170## ##STR00171## ##STR00172## ##STR00173## ##STR00174## ##STR00175## ##STR00176## ##STR00177## ##STR00178## ##STR00179## ##STR00180## ##STR00181## ##STR00182## ##STR00183## ##STR00184## ##STR00185##
and pharmaceutically acceptable salts thereof.
Compounds of Formula (V)
[0544] Some embodiments include a compound of Formula (V):
##STR00186##

or a pharmaceutically acceptable salt thereof, wherein: [0545] R.sup.1C is hydrogen, hydroxyl, C.sub.1-6 alkoxy, —(C.sub.1-6 alkyl) C.sub.1-6 alkoxy, —(CH.sub.2).sub.n—NR.sup.AR.sup.B, or PEG2 to PEG4; [0546] R.sup.2C is —CO.sub.2R.sup.M, —(C═O)NR.sup.CR.sup.D, —S(O).sub.2NR.sup.CR.sup.D, —S(O).sub.2R.sup.M, —(CH.sub.2).sub.q—NR.sup.ER.sup.F, —(CH.sub.2).sub.q—OR.sup.M, —O(C═O)—NR.sup.ER.sup.F, or —NR.sup.M(C═O)—NR.sup.ER.sup.F, wherein R.sup.2C is attached at any one of positions labeled 1, 2, or 3; [0547] R.sup.3C is —CO.sub.2R.sup.M, —(C═O)NR.sup.CR.sup.D, —S(O).sub.2NR.sup.CR.sup.D, —S(O).sub.2R.sup.M, —(CH.sub.2).sub.q—NR.sup.ER.sup.F, —(CH.sub.2).sub.q—OR.sup.M, —O(C═O)—NR.sup.ER.sup.F, or —NR.sup.M(C═O)—NR.sup.ER.sup.F, wherein R.sup.3C is attached at any one of positions labeled 1′, 2′, or 3′; [0548] each R.sup.A, R.sup.B, R.sup.C, R.sup.D, R.sup.E, R.sup.F, and R.sup.M are independently hydrogen or C.sub.1-6 alkyl; [0549] each subscript n is independently an integer from 0 to 6; [0550] each subscript q is independently an integer from 0 to 6; [0551] L.sup.E is —(C═O)— or —S(O).sub.2—; [0552] L.sup.C is —(CR.sup.IR.sup.J).sub.1-3— [0553] each R.sup.I and R.sup.J are independently hydrogen or C.sub.1-3 alkyl; [0554] subscript s is 0 or 1; [0555] each Cy.sup.1 is independently a 4-6 membered heterocycle, a 5-6 membered heteroaryl, or a C.sub.3-6 cycloalkyl, each optionally substituted with one or more R.sup.K; [0556] each R.sup.K is independently selected from the group consisting of: C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, ═O, —NR.sup.DR.sup.e2, —C(O)NR.sup.DR.sup.e2, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl); [0557] each R.sup.d2 and R.sup.e2 are independently hydrogen or C.sub.1-3 alkyl; [0558] L.sup.AA is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, —C(O)NR.sup.L(CH.sub.2).sub.1-6—, —(CH.sub.2).sub.1-6O—, —C(O)(CH.sub.2).sub.1-6O—, or —C(O)NR.sup.L(CH.sub.2).sub.1-6O—; [0559] R.sup.L is hydrogen or C.sub.1-3 alkyl; [0560] Cy.sup.2 is C.sub.3-6 cycloalkyl, 4-6 membered heterocycle, 5-6 membered heteroaryl, or phenyl, each optionally substituted with one or more R.sup.U; [0561] each R.sup.U is independently selected from the group consisting of —CO.sub.2R.sup.j1, —(C═O)NR.sup.d3R.sup.e3, —S(O).sub.2NR.sup.d3R.sup.e3, —(CH.sub.2).sub.g1—NR.sup.g1R.sup.h1, —(CH.sub.2).sub.q1—OR.sup.j1, and —(CH.sub.2).sub.q1—(OCH.sub.2CH.sub.2).sub.1-8OH; [0562] each R.sup.d3, R.sup.e3, R.sup.g1, R.sup.h1, and R.sup.j1 are independently hydrogen or C.sub.1-6 alkyl; [0563] subscript q1 is an integer from 0 to 6; [0564] subscript t1 is 0 or 1; [0565] L.sup.D is —(CH.sub.2).sub.1-6—; [0566] subscript u is 0 or 1; [0567] when t1 is 0, ZZ is —NR.sup.QR.sup.R, —N.sup.+(C.sub.1-6 alkyl)R.sup.QR.sup.R, —C(═O)N.sup.SR.sup.T, —C(O)O(C.sub.1-6 alkyl), —CO.sub.2H, or an amino acid, or when t1 is 1, ZZ is hydrogen, —NR.sup.QR.sup.R, —N.sup.+(C.sub.1-6 alkyl)R.sup.QR.sup.R; —C(═O)N.sup.SR.sup.T, —C(O)O(C.sub.1-6 alkyl), —CO.sub.2H, or an amino acid; [0568] R.sup.Q is hydrogen, C.sub.1-6 alkyl, C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1—.sub.3C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.1-3 alkoxy, —(CH.sub.2).sub.1-3 4-6 membered heterocycle, or —(CH.sub.2).sub.1-3 5-6 membered heteroaryl, provided that [0569] if t1 is 0 and both Cy.sup.1 are

##STR00187##

then R.sup.Q is C.sub.2-6 alkyl, C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.1-3 alkoxy, —(CH.sub.2).sub.1-3 4-6 membered heterocycle, or —(CH.sub.2).sub.1-3 5-6 membered heteroaryl, and [0570] if t1 is 0 and at least one Cy.sup.1 is not

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then ZZ is —NR.sup.QR.sup.R, —N.sup.+(C.sub.1-6 alkyl)R.sup.QR.sup.R, or —C(═O)N.sup.SR.sup.T, and R.sup.Q is C.sub.1-6 alkyl, C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.1-3 alkoxy, —(CH.sub.2).sub.1-3 4-6 membered heterocycle, or —(CH.sub.2).sub.1-3 5-6 membered heteroaryl; and [0571] each R.sup.R, R.sup.S, and R.sup.T are independently hydrogen or C.sub.1-6 alkyl.

[0572] In some embodiments, R.sup.1C is hydrogen. In some embodiments, R.sup.1C is hydroxyl. In some embodiments, R.sup.1C is C.sub.1-6 alkoxy. In some embodiments, R.sup.1C is methoxy.

In some embodiments, R.sup.1C is —(C.sub.1-6 alkyl)C.sub.1-6 alkoxy. In some embodiments, R.sup.1C is methoxyethyl. In some embodiments, R.sup.1C is PEG2 to PEG4. In some embodiments, R.sup.1C is —(CH.sub.2).sub.n—NR.sup.AR.sup.B. In some embodiments, R.sup.A and R.sup.B are both hydrogen. In some embodiments, R.sup.A and R.sup.B are independently C.sub.1-3 alkyl. In some embodiments, one of R.sup.A and R.sup.B is hydrogen and the other of R.sup.A and R.sup.B is C.sub.1-3 alkyl. In some embodiments, each subscript n is 0. In some embodiments, each subscript n is 1. In some embodiments, each subscript n is 2. In some embodiments, each subscript n is 3, 4, 5, or 6.

[0573] In some embodiments, R.sup.2C and R.sup.3C are —CO.sub.2H, —(C═O).sub.m—NR.sup.CR.sup.D, or —(CH.sub.2).sub.q—NR.sup.ER.sup.F; and R.sup.2C and R.sup.3C are the same. In some embodiments, R.sup.2C and R.sup.3C are independently —CO.sub.2H, —(C═O).sub.m—NR.sup.CR.sup.D, or —(CH.sub.2).sub.q—NR.sup.ER.sup.F; and R.sup.2C and R.sup.3C are different.

[0574] In some embodiments, R.sup.2C is —(C═O).sub.m—NR.sup.CR.sup.D. In some embodiments, R.sup.3C is —(C═O).sub.m—NR.sup.CR.sup.D. In some embodiments, R.sup.C and R.sup.D are both hydrogen. In some embodiments, R.sup.C and R.sup.D are each independently C.sub.1-3 alkyl. In some embodiments, one of R.sup.C and R.sup.D is hydrogen and the other of R.sup.c and R.sup.D is C.sub.1-3 alkyl. In some embodiments, each subscript m is 0. In some embodiments, each subscript m is 1.

[0575] In some embodiments, R.sup.2C is —(CH.sub.2).sub.q—NR.sup.ER.sup.F. In some embodiments, R.sup.3C is —(CH.sub.2).sub.q—NR.sup.ER.sup.F. In some embodiments, R.sup.E and R.sup.F are both hydrogen. In some embodiments, R.sup.E and R.sup.F are each independently C.sub.1-3 alkyl. In some embodiments, one of R.sup.E and R.sup.F is hydrogen and the other of R.sup.E and R.sup.F is C.sub.1-3 alkyl.

[0576] In some embodiments, each subscript q is 0. In some embodiments, each subscript q is an integer from 1 to 6.

[0577] In some embodiments, R.sup.2C is —CO.sub.2R.sup.M. In some embodiments, R.sup.3C is —CO.sub.2R.sup.M.

[0578] In some embodiments, R.sup.M is hydrogen. In some embodiments, R.sup.M is C.sub.1-3 alkyl.

[0579] In some embodiments, R.sup.2C is —(CH.sub.2).sub.q—OR.sup.M. In some embodiments, R.sup.3C is —(CH.sub.2).sub.q—OR.sup.M.

[0580] In some embodiments, R.sup.M is hydrogen. In some embodiments, subscript q is 0. In some embodiments, subscript q is 1.

[0581] In some embodiments, R.sup.2C is —O(C═O)—NR.sup.ER.sup.F. In some embodiments, R.sup.3C is —O(C═O)—NR.sup.ER.sup.F. In some embodiments, R.sup.E and R.sup.F are both hydrogen. In some embodiments, R.sup.E and R.sup.F are each independently C.sub.1-3 alkyl. In some embodiments, one of R.sup.E and R.sup.F is hydrogen and the other of R.sup.E and R.sup.F is C.sub.1-3 alkyl.

[0582] In some embodiments, R.sup.2C is —NR.sup.M(C═O)—NR.sup.ER.sup.F. In some embodiments, R.sup.3C is —NR.sup.M(C═O)—NR.sup.ER.sup.F. In some embodiments, R.sup.E, R.sup.F, and R.sup.M are all hydrogen. In some embodiments, R.sup.E, R.sup.F, and R.sup.M are each independently C.sub.1-3 alkyl. In some embodiments, one of R.sup.E, R.sup.F, and R.sup.M is C.sub.1-3 alkyl and the rest of R.sup.E, R.sup.F, and R.sup.M is hydrogen.

[0583] In some embodiments, R.sup.2C is —S(O).sub.2NR.sup.CR.sup.D.

[0584] In some embodiments, R.sup.3C is —S(O).sub.2NR.sup.CR.sup.D. In some embodiments, R.sup.C and R.sup.Dare both hydrogen. In some embodiments, R.sup.c and R.sup.D are each independently C.sub.1-3 alkyl. In some embodiments, one of R.sup.C and R.sup.D is hydrogen and the other of R.sup.C and R.sup.D is C.sub.1-3 alkyl.

[0585] In some embodiments, R.sup.2C is —S(O).sub.2R.sup.M. In some embodiments, R.sup.3C

is —S(O).sub.2R.sup.M. In some embodiments, R.sup.M is hydrogen. In some embodiments, R.sup.M is C.sub.1-3 alkyl.
[0586] In some embodiments, R.sup.2C is attached at position 1. In some embodiments, R.sup.2C is attached at position 2. In some embodiments, R.sup.2C is attached at position 3. In some embodiments, R.sup.3C is attached at position 1′. In some embodiments, R.sup.3C is attached at position 2′. In some embodiments, R.sup.3C is attached at position 3′.
[0587] In some embodiments, L.sup.E is —(C═O)—. In some embodiments L.sup.E is —S(O).sub.2—.
[0588] In some embodiments, each R.sup.I and R.sup.J is hydrogen. In some embodiments, each R.sup.I and R.sup.J is C.sub.1-3 alkyl. In some embodiments, one of R.sup.I and R.sup.J is hydrogen and the other of R.sup.I and R.sup.J is C.sub.1-3 alkyl.
[0589] In some embodiments, L.sup.C is —(CR.sup.IR.sup.J)—.
[0590] In some embodiments, subscript s is 0. In some embodiments, subscript s is 1.
[0591] In some embodiments, each Cy.sup.1 is independently a 5-6 membered heteroaryl. In some embodiments, each Cy.sup.1 is pyrazole optionally substituted with one or more R.sup.K. In some embodiments, each Cy.sup.1 is independently selected from the group consisting of pyrazole, imidazole, furan, thiophene, thiazole, isothiazole, oxazole, isoxazole, pyrrole, pyridazine, pyridine, pyrimidine, and pyrazine, each optionally substituted with one or more R.sup.K. In some embodiments, each Cy.sup.1 is independently selected from the group consisting of imidazole, furan, thiophene, thiazole, isothiazole, oxazole, isoxazole, pyrrole, pyridazine, pyridine, pyrimidine, and pyrazine, each optionally substituted with one or more R.sup.K. In some embodiments, each Cy.sup.1 is independently a C.sub.4-5 cycloalkyl optionally substituted with one or more R.sup.K. In some embodiments, each R.sup.K is independently selected from the group consisting of C In some embodiments, each R.sup.K is independently selected from the group consisting of methyl, ethyl, —CF.sub.3, and halogen.
[0592] In some embodiments, each Cy.sup.1 is the same. In some embodiments, each Cy.sup.1 is different.
[0593] In some embodiments, L.sup.AA is —(CH.sub.2).sub.1-6—. In some embodiments, L.sup.AA is —(CH.sub.2).sub.1-3—. In some embodiments, L.sup.AA is —(CH.sub.2).sub.1-6O—. In some embodiments, L.sup.AA is —(CH.sub.2).sub.1-30—.
[0594] In some embodiments, Cy.sup.2 is a 4-6 membered heterocycle. In some embodiments, Cy.sup.2 has the structure:
##STR00189##
wherein each of subscripts z1 and z2 is independently an integer from 1 to 3 and ** indicates attachment to L.sup.AA.
[0595] In some embodiments, subscript z1 and subscript z2 are 1. In some embodiments, subscript z1 and subscript z2 are 2.
[0596] In some embodiments, subscript z1 is 1 and subscript z2 is 2.
[0597] In some embodiments, Cy.sup.2has the structure:
##STR00190##
wherein [0598] Z.sup.1 is selected from the group consisting of —O—, —S—, —CR.sup.NR.sup.O—, and —NR.sup.P—; [0599] R.sup.N, R.sup.O, and R.sup.P are independently hydrogen or C.sub.1-6 alkyl; [0600] subscript z3 is an integer from 1 to 3; and [0601] ** indicates attachment to L.sup.AA.
[0602] In some embodiments, R.sup.N and R.sup.O are hydrogen. In some embodiments, R.sup.P is hydrogen. In some embodiments, R.sup.P is methyl.
[0603] In some embodiments, Cy.sup.2 is a 5-6 membered heteroaryl.
[0604] In some embodiments, Cy.sup.2 is selected from the group consisting of:
##STR00191##
wherein [0605] Z.sup.2 is =CR.sup.N— or =N—; [0606] R.sup.N is hydrogen or C.sub.1-6 alkyl;

and [0607] ** indicates attachment to L.sup.AA.
[0608] In some embodiments, Z.sup.2 is =CR.sup.N— and R.sup.N is hydrogen. In some embodiments, Z.sup.2 is =N—.
[0609] In some embodiments, Cy.sup.2 is selected from the group consisting of:
##STR00192##
wherein Z.sup.3 is —O— or —S— and ** indicates attachment to L.sup.AA, L.sup.D, NR.sup.HH, Y, W, or L.sup.BB.
[0610] In some embodiments, ** indicates attachment to L.sup.AA. In some embodiments, ** indicates attachment to L.sup.D, NR.sup.HH, Y, W, or L.sup.BB.
[0611] In some embodiments, Cy.sup.2 is selected from the group consisting of:
##STR00193##
wherein ** indicates attachment to L.sup.AA.
[0612] In some embodiments, Cy.sup.2 is selected from the group consisting of:
##STR00194##
wherein [0613] each Z.sup.2 is independently ═CR.sup.N— or ═N—; and [0614] each R.sup.N is hydrogen or C.sub.1-6 alkyl.
[0615] In some embodiments, at least one Z.sup.2 is =N—. In some embodiments, one Z.sup.2 is ═N— and the remaining Z.sup.2 are ═CR.sup.N—. In some embodiments, two Z2 are —NR.sup.P— and the remaining Z.sup.2 are ═CR.sup.N—.
[0616] In some embodiments, R.sup.N is hydrogen.
[0617] In some embodiments, Cy.sup.2 is selected from the group consisting of:
##STR00195##
and
[0618] In some embodiments, Cy.sup.2 is cyclobutyl.
[0619] In some embodiments, R.sup.3, R.sup.e3, R.sup.g1, R.sup.h1, and R.sup.j1 are independently hydrogen or —CH.sub.3.
[0620] In some embodiments, ach RU is independently selected from —CO.sub.2H, —(C═O)NH.sub.2, —S(O).sub.2NH.sub.2, —CH.sub.2NH.sub.2, and —CH.sub.2OH.
[0621] In some embodiments, t1 is 0. In some embodiments, ti is 1.
[0622] In some embodiments, u is 1 and L.sup.D is —(CH.sub.2).sub.1-3. In some embodiments, u is 0.
[0623] In some embodiments, ZZ is —NR.sup.QR.sup.R. In some embodiments, R.sup.Q is C.sub.1-6 alkyl, In some embodiments, R.sup.Q is C.sub.3-6 cycloalkyl. In some embodiments, R.sup.Q is cyclopropyl. In some embodiments, R.sup.Q is —(CH.sub.2).sub.1-3C.sub.3-6 cycloalkyl. In some embodiments, R.sup.R is hydrogen.
[0624] In some embodiments, ZZ is —N*(C.sub.1-6 alkyl)R.sup.QR.sup.R.
[0625] In some embodiments, ZZ is —C(═O)N.sup.SR.sup.T.
[0626] In some embodiments, ZZ is —C(O)O(t-butyl).
[0627] In some embodiments, ZZ is —CO.sub.2H.
[0628] In some embodiments, ZZ is an amino acid selected from the group consisting of alanine, valine, isoleucine, leucine, aspartic acid, glutamic acid, lysine, histidine, arginine, glycine, serine, threonine, phenylalanine, O-methylserine, O-methylaspartic acid, O-methylglutamic acid, N-methyllysine, O-methyltyrosine, O-methylhistidine, and O-methylthreonine.
[0629] Some embodiments of Formula (V) include compounds selected from the group consisting of:
##STR00196## ##STR00197## ##STR00198## ##STR00199## ##STR00200## ##STR00201## ##STR00202## ##STR00203## ##STR00204## ##STR00205## ##STR00206##
and pharmaceutically acceptable salts thereof.
Linkers
[0630] As described herein, linkers (L) as defined in connection with Formulae (I), (II), and (II-A)

are optional groups that connect X.sup.A or X.sup.B, when present, with M or M.sup.1. For example, A, when present, is covalently attached to M or M.sup.1, and Y, when present, is attached to X.sup.B or to X.sup.A (when X.sup.B is absent). In some embodiments, the linker (L) has the formula -(A).sub.a-(W).sub.w—(Y).sub.y, wherein: [0631] A is a C.sub.2-20 alkylene optionally substituted with 1-3 Rai; or a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R.sup.b1; [0632] each R.sup.a1 is independently selected from the group consisting of: [0633] C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, ═O, —NR.sup.d1R.sup.e1, —C(O)NR.sup.d1R.sup.e1, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl); [0634] each R.sup.b1 is independently selected from the group consisting of: [0635] C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, ═O, —NR.sup.d1R.sup.e1, —C(O)NR.sup.d1R.sup.e1, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl); [0636] each R.sup.d1 and R.sup.e1 are independently hydrogen or C.sub.1-3 alkyl; [0637] a is 0 or 1; W is from 1-12 amino acids or has the structure: ##STR00207## [0638] wherein Su is a Sugar moiety; [0639] —O.sup.A— represents a glycosidic bond; [0640] each R.sup.9 is independently hydrogen, halogen, —CN, or —NO.sub.2; [0641] W.sub.1 is absent or O—C(═O); [0642] custom-character represents covalent attachment to A, when present, or M in compounds of Formula (II) and covalent attachment to A, M, or M.sup.1 in the ADCs and compounds described herein; [0643] * represents covalent attachment to Y, X.sup.A, or X.sup.B in compounds of Formula (II) and to Y, X.sup.A, or X.sup.B in the ADCs described herein; [0644] w is 0or 1; [0645] Y is a self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety; and [0646] y is 0 or 1.

[0647] In some embodiments, —O.sup.A— represents a glycosidic bond. In some embodiments, the glycosidic bond provides a β-glucuronidase or a β-mannosidase-cleavage site. In some embodiments, the β-glucuronidase-cleavage site is cleavable by human lysosomal β-glucuronidase. In some embodiments, the β-mannosidase-cleavage site is cleavable by human lysosomal β-mannosidase.

[0648] In some embodiments, a is 0. In some embodiments, a is 1. In some embodiments, w is 0. In some embodiments, w is 1. In some embodiments, y is 0. In some embodiments, y is 1. In some embodiments, a+y+w=1. In some embodiments, a+y+w=2. In some embodiments, a+y+w=3. In some embodiments, a+y+w=0 (i.e., the linker (L) is absent).

[0649] In some embodiments, A is a C.sub.2-20 alkylene optionally substituted with 1-3 R.sup.a1. In some embodiments, A is a C.sub.2-10 alkylene optionally substituted with 1-3 R.sup.a1. In some embodiments, A is a C.sub.4-10 alkylene optionally substituted with 1-3 R.sup.a1. In some embodiments, A is a C.sub.2-20 alkylene substituted with R.sup.a1. In some embodiments, A is a C.sub.2-10 alkylene substituted with R.sup.a1. In some embodiments, A is a C.sub.2-10 alkylene substituted with R.sup.a1.

[0650] In some embodiments, each R.sup.a1 is independently selected from the group consisting of: C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, ═O, —NR.sup.d1R.sup.e1, —C(O)NR.sup.d1R.sup.e1, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl). In some embodiments, each R.sup.a1 is C.sub.1-6 alkyl. In some embodiments, each R.sup.a1 is C.sub.1-6 haloalkyl. In some embodiments, each R.sup.a1 is C.sub.1-6 alkoxy. In some embodiments, each R.sup.a1 is C.sub.1-6 haloalkoxy. In some embodiments, each R.sup.a1 is halogen. In some embodiments, each R.sup.a1 is —OH. In some embodiments, each R.sup.a1 is ═O. In some embodiments, each R.sup.a1 is —NR.sup.d1R.sup.e1. In some embodiments, each R.sup.a1 is C(O)NR.sup.d1R.sup.e1°. In some embodiments, each R.sup.a1 is —C(O)(C.sub.1-C.sub.6 alkyl). In some embodiments, each R.sup.a1 is —C(O)O(C.sub.1-C.sub.6 alkyl). In some embodiments, one occurrence of R.sup.a1 is —NR.sup.d1R.sup.e1°. In some embodiments, A is a C.sub.2-20 alkylene substituted with 1 or 2 R.sup.a1, each of which is ═O.

[0651] In some embodiments, R.sup.d1 and R.sup.e1 are independently hydrogen or C.sub.1-3

alkyl. In some embodiments, one of R.sup.d1 and R.sup.e1 is hydrogen, and the other of R.sup.d1 and R.sup.e1 is C.sub.1-3 alkyl. In some embodiments, R.sup.d1 and R.sup.e1 are both hydrogen or C.sub.1-3 alkyl. In some embodiments, R.sup.d1 and R.sup.e1 are both C.sub.1-3 alkyl. In some embodiments, R.sup.d1 and R.sup.e1 are both methyl.

[0652] In some embodiments, A is a C.sub.2-20 alkylene. In some embodiments, A is a C.sub.2-10 alkylene. In some embodiments, A is a C.sub.2-10 alkylene. In some embodiments, A is a C.sub.2-6 alkylene. In some embodiments, A is a C.sub.4-10 alkylene.

[0653] In some embodiments, A is a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R.sup.b1. In some embodiments, A is a 2 to 20 membered heteroalkylene optionally substituted with 1-3 R.sup.b1. In some embodiments, A is a 2 to 12 membered heteroalkylene optionally substituted with 1-3 R.sup.b1. In some embodiments, A is a 4 to 12 membered heteroalkylene optionally substituted with 1-3 R.sup.b1. In some embodiments, A is a 4 to 8 membered heteroalkylene optionally substituted with 1-3 R.sup.b1. In some embodiments, A is a 2 to 40 membered heteroalkylene substituted with R.sup.b1. In some embodiments, A is a 2 to 20 membered heteroalkylene substituted with R.sup.b1. In some embodiments, A is a 2 to 12 membered heteroalkylene substituted with R.sup.b1. In some embodiments, A is a 4 to 12 membered heteroalkylene substituted with R.sup.b1. In some embodiments, A is a 4 to 8 membered heteroalkylene substituted with R.sup.b1.

[0654] In some embodiments, each R.sup.b1 is independently selected from the group consisting of: C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, —NR.sup.d1R.sup.e1, —C(O)NR.sup.d1R.sup.e1, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl). In some embodiments, each R.sup.b1 is C.sub.1-6 alkyl. In some embodiments, each R.sup.b1 is C.sub.1-6 haloalkyl. In some embodiments, each R.sup.b1 is C.sub.1-6 alkoxy. In some embodiments, each R.sup.b1 is C.sub.1-6 haloalkoxy. In some embodiments, each R.sup.b1 is halogen. In some embodiments, each R.sup.b1 is —OH. In some embodiments, each R.sup.b1 is —NR.sup.d1R.sup.e1. In some embodiments, each R.sup.b1 is C(O)NR.sup.d1R.sup.e1. In some embodiments, each R.sup.b1 is —C(O)(C.sub.1-6 alkyl). In some embodiments, each R.sup.b1 is —C(O)O(C.sub.1-6 alkyl). In some embodiments, one occurrence of R.sup.b1 is —NR.sup.d1R.sup.e1.

[0655] In some embodiments, R.sup.d1 and R.sup.e1 are independently hydrogen or C.sub.1-3 alkyl. In some embodiments, one of R.sup.d1 and R.sup.e1 is hydrogen, and the other of R.sup.d1 and R.sup.e1 is C.sub.1-3 alkyl. In some embodiments, R.sup.d1 and R.sup.e1 are both hydrogen or C.sub.1-3 alkyl. In some embodiments, R.sup.d1 and R.sup.e1 are both C.sub.1-3 alkyl. In some embodiments, R.sup.d1 and R.sup.e1 are both methyl.

[0656] In some embodiments, A is a 2 to 40 membered heteroalkylene. In some embodiments, A is a 2 to 20 membered heteroalkylene. In some embodiments, A is a 2 to 12 membered heteroalkylene. In some embodiments, A is a 4 to 12 membered heteroalkylene. In some embodiments, A is a 4 to 8 membered heteroalkylene. In some embodiments, A is selected from the group consisting of:

##STR00208##

wherein  custom-character represents covalent attachment to W or Y, and * represents covalent linkage to M.sup.1 or M (e.g., in compounds of Formula (I) or (II), respectively). In some embodiments, M is a succinimide. In some embodiments, M is a hydrolyzed succinimide. In some embodiments, M.sup.1 is a succinimide. In some embodiments, M.sup.1 is a hydrolyzed succinimide. It will be understood that a hydrolyzed succinimide may exist in two regioisomeric form(s). Those forms are exemplified below for hydrolysis of M, wherein the structures representing the regioisomers from that hydrolysis are formula M′ and M″; wherein the wavy lines adjacent to the bonds are as defined for A.

##STR00209##

[0657] In some embodiments, M′ is

##STR00210##
In some embodiments, M′ is
##STR00211##
In some embodiments, M″ is
##STR00212##
In some embodiments, M″ is
##STR00213##
[0658] In some embodiments, A is a PEG4 to PEG12. In some embodiments, A is a PEG4 to PEG8. Representative A groups include, but are not limited to:
##STR00214##
[0659] In some embodiments, w is 0. In some embodiments w is 1.
[0660] In some embodiments, W is a single amino acid. In some embodiments, W is a single natural amino acid. In some embodiments, W is a peptide including from 2-12 amino acids, wherein each amino acid is independently a natural or unnatural amino acid. In some embodiments, the natural or unnatural amino acid is a D or L isomer. In some embodiments, each amino acid is independently a natural amino acid. In some embodiments, each W is independently an alpha, beta, or gamma amino acid that is natural or unnatural. In some embodiments, W comprises a natural amino acid linked to an unnatural amino acid. In some embodiments, W comprises a natural or unnatural amino acid linked to a D-isomer of a natural or unnatural amino acid. In some embodiments, W is a dipeptide. In some embodiments, W is a tripeptide. In some embodiments, W is a tetrapeptide. In some embodiments, W is a pentapeptide. In some embodiments, W is a hexapeptide. In some embodiments, W is 7, 8, 9, 10, 11, or 12 amino acids. In some embodiments, each amino acid of W is independently selected from the group consisting of valine, alanine, β-alanine, glycine, lysine, leucine, phenylalanine, proline, aspartic acid, serine, glutamic acid, homoserine methyl ether, aspartate methyl ester, N,N-dimethyl lysine, arginine, valine-alanine, valine-citrulline, phenylalanine-lysine, and citrulline. In some embodiments, W is an aspartic acid. In some embodiments, W is a lysine. In some embodiments, W is a glycine. In some embodiments, W is an alanine. In some embodiments, W is aspartate methyl ester. In some embodiments, W is a N,N-dimethyl lysine. In some embodiments, W is a homoserine methyl ether. In some embodiments, W is a serine. In some embodiments, W is a valine-alanine.
[0661] In some embodiments, w is 1; W is from 1-12 amino acids; and the bond between W and the X.sup.B or between W and Y is enzymatically cleavable by a tumor-associated protease. In some embodiments, the tumor-associated protease is a cathepsin. In some embodiments, the tumor-associated protease is cathepsin B, C, or D.
[0662] In some embodiments, w is 1; and W has the structure of:
##STR00215## [0663] wherein Su is a Sugar moiety; [0664] —O.sup.A— represents a glycosidic bond; [0665] each R.sup.9 is independently hydrogen, halogen, —CN, or —NO.sub.2; [0666] W.sub.1 is absent or —O—C(═O)—; [0667] custom-character represents covalent attachment to A or M in compounds of Formula (II); and [0668] the * represents covalent attachment to Y, X.sup.A, or X.sup.B in compounds of Formula (II); [0669] In some embodiments, w is 1; and W has the structure of:
##STR00216## [0670] wherein Su is a Sugar moiety; [0671] —O.sup.A— represents a glycosidic bond; [0672] each R.sup.9 is independently hydrogen, halogen, —CN, or —NO.sub.2; [0673] W.sub.1 is absent or —O—C(═O)—; [0674] custom-character represents covalent attachment to A or M in the ADCs described herein; and [0675] the * represents covalent attachment to Y, X.sup.A, or X.sup.R in the ADCs described herein;
[0676] In some embodiments, —O.sup.A— represents a glycosidic bond. In some embodiments, the glycosidic bond provides a β-glucuronidase or a β-mannosidase-cleavage site. In some embodiments, the β-glucuronidase or a @-mannosidase-cleavage site is cleavable by human lysosomal β-glucuronidase or by human lysosomal β-mannosidase.

[0677] In some embodiments, W is
##STR00217##
In some embodiments, W is
##STR00218##
In some embodiments, W is
##STR00219##
[0678] In some embodiments, each R.sup.9 is hydrogen. In some embodiments, one R.sup.9 is hydrogen, and the remaining R.sup.9 are independently halo, —CN, or —NO.sub.2. In some embodiments, two R.sup.9 are hydrogen, and the remaining R.sup.9 is halo, —CN, or —NO.sub.2.
[0679] In some embodiments, one R.sup.9 is halogen, —CN, or —NO.sub.2, and the other R.sup.9 are hydrogen. In some embodiments, each R.sup.9 is hydrogen.
[0680] In some embodiments, O.sup.A—Su is charged neutral at physiological pH. In some embodiments, O.sup.A— Su is mannose. In some embodiments, O.sup.A— Su is
##STR00220##
In some embodiments, O.sup.A—Su comprises a carboxylate moiety. In some embodiments, O.sup.A—Su is glucuronic acid. In some embodiments, O.sup.A— Su is
##STR00221##
[0681] In some embodiments, W is
##STR00222##
In some embodiments, W is
##STR00223##
In some embodiments, W is
##STR00224##
In some embodiments, W is
##STR00225##
[0682] In some embodiments, a is 0.
[0683] In some embodiments, y is 0. In some embodiments y is 1.
[0684] In some embodiments, Y is a self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety. In some embodiments, Y is a self-immolative moiety or a non-self-immolative releasable moiety. In some embodiments, Y is a self-immolative moiety. In some embodiments, Y is a non-self-immolative moiety.
[0685] A non-self-immolative moiety is one which requires enzymatic cleavage, and in which part or all of the group remains bound to the Drug Unit after cleavage from the ADC, thereby forming free drug. Examples of a non-self-immolative moiety include, but are not limited to: -glycine-; and -glycine-glycine. When an ADC having Y is -glycine- or -glycine-glycine-undergoes enzymatic cleavage (for example, via a cancer-cell-associated protease or a lymphocyte-associated protease), the Drug Unit is cleaved from the ADC such that the free drug includes the glycine or glycine-glycine group from Y. In some embodiments, an independent hydrolysis reaction takes place within, or in proximity to, the target cell, further cleaving the glycine or glycine-glycine group from the free drug. In some embodiments, enzymatic cleavage of the non-self-immolative moiety, as described herein, does not result in any further hydrolysis step(s).
[0686] A self-immolative moiety refers to a bifunctional chemical moiety that is capable of covalently linking together two spaced chemical moieties into a normally stable tripartite molecule. The self-immolative group will spontaneously separate from the second chemical moiety if its bond to the first moiety is cleaved. For example, a self-immolative moiety includes a p-aminobenzyl alcohol (PAB) optionally substituted with one or more alkyl, alkoxy, halogen, cyano, or nitro groups. Other examples of self-immolative moieties include, but are not limited to, aromatic compounds that are electronically similar to the PAB group such as 2-aminoimidazol-5-methanol derivatives (see, e.g., Hay et al., 1999, *Bioorg. Med. Chem. Lett.* 9:2237), ortho or para-aminobenzylacetals, substituted and unsubstituted 4-aminobutyric acid amides (see, e.g., Rodrigues

et al., 1995, *Chemistry Biology* 2:223), appropriately substituted bicyclo[2.2.1] and bicyclo[2.2.2] ring systems (see, e.g., Storm et al., 1972, *J. Amer. Chem. Soc.* 94:5815), 2-aminophenylpropionic acid amides (see, e.g., Amsberry et al., 1990, *J. Org. Chem.* 55:5867), and elimination of amine-containing drugs that are substituted at the α-position of glycine (see, e.g., Kingsbury et al., 1984, *J. Med. Chem.* 27:1447).

[0687] In some embodiments, Y is a PAB group, optionally substituted with one or more alkyl, alkoxy, halogen, cyano, or nitro groups; a para-aminobenzyloxy-carbonyl (PABC) group optionally substituted with a sugar moiety; -glycine-; -glycine-glycine-; or a branched bis(hydroxymethyl)styrene (BHMS) unit, which is capable of incorporating (and releasing) multiple Drug Units.

[0688] In some embodiments, -(A).sub.a-(W).sub.W—(Y).sub.y comprises a non-self-immolative releasable linker, which provides release of the free drug once the ADC has been internalized into the target cell. In some embodiments, -(A).sub.a-(W).sub.w—(Y).sub.y comprises a releasable linker, which provides release of the free Drug with, or in the vicinity, of targeted cells. Releasable linkers possess a recognition site, such as a peptide cleavage site, sugar cleavage site, or disulfide cleavage side. In some embodiments, each releasable linker is a di-peptide. In some embodiments, each releasable linker is a disulfide. In some embodiments, each releasable linker is a hydrazone. In some embodiments, each releasable linker is independently Val-Cit-, -Phe-Lys-, or -Val-Ala-. In some embodiments, each releasable linker, when bound to a succinimide or hydrolyzed succinimide, is independently succinimido-caproyl (mc), succinimido-caproyl-valine-citrulline (sc-ve), succinimido-caproyl-valine-citrulline-paraaminobenzyloxycarbonyl (sc-vc-PABC), or SDPr-vc (where “S” refers to succinimido).

[0689] In some embodiments, -(A).sub.a-(W).sub.W—(Y).sub.y comprises a non-cleavable linker. Non-cleavable linkers are known in the art and, in some embodiments, are adapted for use with the ADCs described herein as the “Y” group. A non-cleavable linker is capable of linking a Drug Unit to an antibody in a generally stable and covalent manner and is substantially resistant to acid-induced cleavage, light-induced cleavage, peptidase- or esterase-induced cleavage, and disulfide bond cleavage. In some embodiments, the free drug is released from the ADCs containing non-cleavable linkers via alternative mechanisms, such as proteolytic antibody degradation. In some embodiments, the Drug Unit can exert a biological effect as a part of the ADC (i.e., while still conjugated to the antibody via a linker).

[0690] Reagents that form non-cleavable linker-maleimide and non-cleavable linker-succinimide compounds are known in the art and can adapted for use herein. Exemplary reagents comprise a maleimido or haloacetyl-based moiety, such as 6-maleimidocaproic acid N-hydroxy succinimide ester (MCC), N-succinimidyl 4-(maleimidomethyl)cyclohexanecarboxylate (SMCC), N-succinimidyl-4-(N-maleimidomethyl)-cyclohexane-1-carboxy-(6-amidocaproate) (LC-SMCC), maleimidoundecanoic acid N-succinimidyl ester (KMUA), γ-maleimidobutyric acid N-succinimidyl ester (GMBS), c-maleimidocaproic acid N-hydroxysuccinimide ester (EMCS), m-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), N—(α-maleimidoacetoxy)-succinimide ester [AMAS], succinimidyl-6-(β-maleimidopropionamido)hexanoate (SMPH), N-succinimidyl 4-(p-maleimidophenyl)-butyrate (SMPB), and N-(p-maleimidophenyl)isocyanate (PMPI), N-succinimidyl-4-(iodoacetyl)-aminobenzoate (STAB), N-succinimidyl iodoacetate (SIA), N-succinimidyl bromoacetate (SBA) and N-succinimidyl 3-(bromoacetamido)propionate (SBAP). Additional “A-M” and “A-M.sup.1” groups for use in the ADCs described herein are found, for example, in U.S. Pat. No. 8,142,784, incorporated herein by reference in its entirety.

[0691] In some embodiments, y is 1; and Y is

##STR00226##

wherein custom-character represents connection to W, A, or M in compounds of Formula (II); and the * represents connection to X.sup.A or X.sup.B, in compounds of Formula (II).

[0692] In some embodiments, y is 1; and Y is

##STR00227##
wherein custom-character represents connection to W, A, M or M.sup.1 in the ADCs described herein; and the * represents connection to X.sup.A or X.sup.B, in the ADCs described herein.
[0693] In some embodiments, -(A).sub.a-(W).sub.W—(Y).sub.y comprises a non-releasable linker, wherein the Drug is released after the ADC has been internalized into the target cell and degraded, liberating the Drug.
[0694] In some embodiments, the linker (L) is substituted with a polyethylene glycol moiety selected from the group consisting of PEG2 to PEG20. In some embodiments, L is substituted with a polyethylene glycol moiety selected from the group consisting of PEG2, PEG4, PEG6, PEG8, PEG10, PEG12, PEG16, and PEG20. In some embodiments, L is not substituted with a polyethylene glycol moiety selected from the group consisting of PEG2 to PEG20.
[0695] In some embodiments, polydisperse PEGs, monodisperse PEGs or discrete PEGs are used to make the ADCs and intermediates thereof. Polydisperse PEGs are a heterogeneous mixture of sizes and molecular weights whereas monodisperse PEGs are typically purified from heterogeneous mixtures and therefore provide a single chain length and molecular weight. Discrete PEGs are synthesized in step-wise fashion and not via a polymerization process. Discrete PEGs provide a single molecule with defined and specified chain length. The number of —CH.sub.2CH.sub.2O— subunits of a PEG Unit ranges, for example, from 8 to 24 or from 12 to 24, referred to as PEG8 to PEG24 and PEG12 to PEG24, respectively.
[0696] The PEG moieties provided herein, which are also referred to as PEG Units, comprise one or multiple polyethylene glycol chains. The polyethylene glycol chains are linked together, for example, in a linear, branched or star shaped configuration. Typically, at least one of the polyethylene glycol chains of a PEG Unit is derivatized at one end for covalent attachment to an appropriate site on a component of the ADC (e.g., L). Exemplary attachments to ADCs are by means of non-conditionally cleavable linkages or via conditionally cleavable linkages. Exemplary attachments are via amide linkage, ether linkages, ester linkages, hydrazone linkages, oxime linkages, disulfide linkages, peptide linkages or triazole linkages. In some embodiments, attachment to the Formula (I) ADC is by means of a non-conditionally cleavable linkage. In some embodiments, attachment to the ADC is not via an ester linkage, hydrazone linkage, oxime linkage, or disulfide linkage. In some embodiments, attachment to the ADC is not via a hydrazone linkage.
[0697] A conditionally cleavable linkage refers to a linkage that is not substantially sensitive to cleavage while circulating in plasma but is sensitive to cleavage in an intracellular or intratumoral environment. A non-conditionally cleavable linkage is one that is not substantially sensitive to cleavage in any biologically relevant environment in a subject that is administered the ADC. Chemical hydrolysis of a hydrazone, reduction of a disulfide bond, and enzymatic cleavage of a peptide bond or glycosidic bond of a Glucuronide Unit as described by WO 2007/011968 (which is incorporated by reference in its entirety) are examples of conditionally cleavable linkages.
[0698] In some embodiments, the PEG Unit is directly attached to the ADC (or an intermediate thereof) at L. In those embodiments, the other terminus (or termini) of the PEG Unit is free and untethered (i.e., not covalently attached), and in some embodiments, is a methoxy, carboxylic acid, alcohol or other suitable functional group. The methoxy, carboxylic acid, alcohol or other suitable functional group acts as a cap for the terminal polyethylene glycol subunit of the PEG Unit. By untethered, it is meant that the PEG Unit will not be covalently attached at that untethered site to a Drug Unit, to an antibody, or to a linking component to a Drug Unit and/or an antibody. Such an arrangement can allow a PEG Unit of sufficient length to assume a parallel orientation with respect to the drug in conjugated form, i.e., as a Drug Unit (D). For those embodiments in which the PEG Unit comprises more than one polyethylene glycol chain, the multiple polyethylene glycol chains are independently chosen, e.g., are the same or different chemical moieties (e.g., polyethylene glycol chains of different molecular weight or number of —CH.sub.2CH.sub.2O— subunits). A PEG Unit having multiple polyethylene glycol chains is attached to the ADC at a single attachment

site. The skilled artisan will understand that the PEG Unit, in addition to comprising repeating polyethylene glycol subunits, may also contain non-PEG material (e.g., to facilitate coupling of multiple polyethylene glycol chains to each other or to facilitate coupling to the ADC). Non-PEG material refers to the atoms in the PEG Unit that are not part of the repeating —CH.sub.2CH.sub.2O— subunits. In some embodiments provided herein, the PEG Unit comprises two monomeric polyethylene glycol chains attached to each other via non-PEG elements. In other embodiments provided herein, the PEG Unit comprises two linear polyethylene glycol chains attached to a central core that is attached to the ADC (i.e., the PEG Unit itself is branched).

[0699] There are a number of PEG attachment methods available to those skilled in the art: see, for example: Goodson, et al. (1990) *Bio/Technology* 8:343 (PEGylation of interleukin-2 at its glycosylation site after site-directed mutagenesis); EP 0 401 384 (coupling PEG to G-CSF); Malik, et al., (1992) *Exp. Hematol.* 20:1028-1035 (PEGylation of GM-CSF using tresyl chloride); ACT Pub. No. WO 90/12874 (PEGylation of erythropoietin containing a recombinantly introduced cysteine residue using a cysteine-specific mPEG derivative); U.S. Pat. No. 5,757,078 (PEGylation of EPO peptides); U.S. Pat. No. 5,672,662 (Poly(ethylene glycol) and related polymers monosubstituted with propionic or butanoic acids and functional derivatives thereof for biotechnical applications); U.S. Pat. No. 6,077,939 (PEGylation of an N-terminal α-carbon of a peptide); Veronese et al., (1985) *Appl. Biochem. Bioechnol* 11:141-142 (PEGylation of an N-terminal α-carbon of a peptide with PEG-nitrophenylcarbonate ("PEG-NPC") or PEG-trichlorophenylcarbonate); and Veronese (2001) *Biomaterials* 22:405-417 (Review article on peptide and protein PEGylation).

[0700] For example, in some embodiments, a PEG Unit is covalently bound to an amino acid residue via reactive groups of a polyethylene glycol-containing compound and the amino acid residue. Reactive groups of the amino acid residue include those that are reactive to an activated PEG molecule (e.g., a free amino or carboxyl group). For example, N-terminal amino acid residues and lysine (K) residues have a free amino group; and C-terminal amino acid residues have a free carboxyl group. Thiol groups (e.g., as found on cysteine residues) are also useful as a reactive group for forming a covalent attachment to a PEG. In addition, enzyme-assisted methods for introducing activated groups (e.g., hydrazide, aldehyde, and aromatic-amino groups) specifically at the C-terminus of a polypeptide have been described. See Schwarz, et al. (1990) *Methods Enzymol.* 184:160; Rose, et al. (1991) *Bioconjugate Chem.* 2:154; and Gaertner, et al. (1994) *J. Biol. Chem.* 269: 7224.

[0701] In some embodiments, a polyethylene glycol-containing compound forms a covalent attachment to an amino group using methoxylated PEG ("mPEG") having different reactive moieties. Non-limiting examples of such reactive moieties include succinimidyl succinate (SS), succinimidyl carbonate (SC), mPEG-imidate, para-nitrophenylcarbonate (NPC), succinimidyl propionate (SPA), and cyanuric chloride. Non-limiting examples of such mPEGs include mPEG-succinimidyl succinate (mPEG-SS), mPEG.sub.2-succinimidyl succinate (mPEG2-SS); mPEG-succinimidyl carbonate (mPEG-SC), mPEG.sub.2-succinimidyl carbonate (mPEG.sub.2-SC); mPEG-imidate, mPEG-para-nitrophenylcarbonate (mPEG-NPC), mPEG-imidate; mPEG2-para-nitrophenylcarbonate (mPEG2-NPC); mPEG-succinimidyl propionate (mPEG-SPA); mPEG2-succinimidyl propionate (mPEG-SPA); mPEG-N-hydroxy-succinimide (mPEG-NHS); mPEG.sub.2-N-hydroxy-succinimide (mPEG2-NHS); mPEG-cyanuric chloride; mPEG2-cyanuric chloride; mPEG.sub.2-Lysinol-NPC, and mPEG.sub.2-Lys-NHS.

[0702] Generally, at least one of the polyethylene glycol chains that make up the PEG is functionalized to provide covalent attachment to the ADC. Functionalization of the polyethylene glycol-containing compound that is the precursor to the PEG includes, for example, via an amine, thiol, NHS ester, maleimide, alkyne, azide, carbonyl, or other functional group. In some embodiments, the PEG further comprises non-PEG material (i.e., material not comprised of —CH.sub.2CH.sub.2O—) that provides coupling to the ADC or in constructing the polyethylene

glycol-containing compound or PEG facilitates coupling of two or more polyethylene glycol chains.

[0703] In some embodiments, the presence of the PEG Unit in an ADC is capable of having two potential impacts upon the pharmacokinetics of the resulting ADC. One impact is a decrease in clearance (and consequent increase in exposure) that arises from the reduction in non-specific interactions induced by the exposed hydrophobic elements of the Drug Unit. The second impact is a decrease in volume and rate of distribution that sometimes arises from the increase in the molecular weight of the ADC. Increasing the number of polyethylene glycol subunits increases the hydrodynamic radius of a conjugate, typically resulting in decreased diffusivity. In turn, decreased diffusivity typically diminishes the ability of the ADC to penetrate into a tumor. See Schmidt and Wittrup, *Mol Cancer Ther* 2009; 8:2861-2871. Because of these two competing pharmacokinetic effects, it can be desirable to use a PEG Unit that is sufficiently large to decrease the ADC clearance thus increasing plasma exposure, but not so large as to greatly diminish its diffusivity to an extent that it interferes with the ability of the ADC to reach the intended target cell population. See, e.g., Examples 1, 18, and 21 of US 2016/0310612, which is incorporated by reference herein (e.g., for methodology for selecting an optimal size of a PEG Unit for a particular Drug Unit, Linker, and/or drug-linker compound).

[0704] In one group of embodiments, the PEG Unit comprises one or more linear polyethylene glycol chains each having at 8 subunits, at least 9 subunits, at least 10 subunits, at least 11 subunits, at least 12 subunits, at least 13 subunits, at least 14 subunits, at least 15 subunits, at least 16 subunits, at least 17 subunits, at least 18 subunits, at least 19 subunits, at least 20 subunits, at least 21 subunits, at least 22 subunits, at least 23 subunits, or at least 24 subunits. In some embodiments, the PEG comprises a combined total of at least 8 subunits, at least 10 subunits, or at least 12 subunits. In some such embodiments, the PEG comprises no more than a combined total of about 72 subunits. In some such embodiments, the PEG comprises no more than a combined total of about 36 subunits. In some embodiments, the PEG comprises about 8 to about 24 subunits (referred to as PEG8 to PEG24).

[0705] In another group of embodiments, the PEG Unit comprises a combined total of from 8 to 72, 8 to 60, 8 to 48, 8 to 36 or 8 to 24 subunits, from 9 to 72, 9 to 60, 9 to 48, 9 to 36 or 9 to 24 subunits, from 10 to 72, 10 to 60, 10 to 48, 10 to 36 or 10 to 24 subunits, from 11 to 72, 11 to 60, 11 to 48, 11 to 36 or 11 to 24 subunits, from 12 to 72, 12 to 60, 12 to 48, 12 to 36 or 12 to 24 subunits, from 13 to 72, 13 to 60, 13 to 48, 13 to 36 or 13 to 24 subunits, from 14 to 72, 14 to 60, 14 to 48, 14 to 36 or 14 to 24 subunits, from 15 to 72, 15 to 60, 15 to 48, 15 to 36 or 15 to 24 subunits, from 16 to 72, 16 to 60, 16 to 48, 16 to 36 or 16 to 24 subunits, from 17 to 72, 17 to 60, 17 to 48, 17 to 36 or 17 to 24 subunits, from 18 to 72, 18 to 60, 18 to 48, 18 to 36 or 18 to 24 subunits, from 19 to 72, 19 to 60, 19 to 48, 19 to 36 or 19 to 24 subunits, from 20 to 72, 20 to 60, 20 to 48, 20 to 36 or 20 to 24 subunits, from 21 to 72, 21 to 60, 21 to 48, 21 to 36 or 21 to 24 subunits, from 22 to 72, 22 to 60, 22 to 48, 22 to 36 or 22 to 24 subunits, from 23 to 72, 23 to 60, 23 to 48, 23 to 36 or 23 to 24 subunits, or from 24 to 72, 24 to 60, 24 to 48, 24 to 36 or 24 subunits.

[0706] In some embodiments, illustrative linear PEGs used in any of the embodiments provided herein are as follows:

##STR00228## [0707] wherein the wavy line indicates the site of attachment to the ADC, and each subscript b is independently selected from the group consisting of 7 to 72, 8 to 72, 10 to 72, 12 to 72, 6 to 24, or 8 to 24. In some embodiments, each subscript b is about 8, about 12, or about 24.

[0708] As described herein, in some embodiments, the PEG Unit is selected such that it improves clearance of the resultant ADC but does not significantly impact the ability of the ADC to penetrate into the tumor.

[0709] In some embodiments, the PEG is from about 300 daltons to about 5 kilodaltons; from about 300 daltons to about 4 kilodaltons; from about 300 daltons to about 3 kilodaltons; from about 300 daltons to about 2 kilodaltons; from about 300 daltons to about 1 kilodalton; or any value in

between. In some embodiments, the PEG has at least 8, 10 or 12 subunits. In some embodiments, the PEG Unit is PEG8 to PEG72, for example, PEG8, PEG10, PEG12, PEG16, PEG20, PEG24, PEG28, PEG32, PEG36, PEG48, or PEG72.

[0710] In some embodiments, apart from the PEGylation of the ADC, there are no other PEG subunits present in the ADC (i.e., no PEG subunits are present as part of any of the other components of the conjugates and linkers provided herein, such as A and X.sup.B). In some embodiments, apart from the PEG, there are no more than 8, no more than 7, no more than 6, no more than 5, no more than 4, no more than 3, no more than 2 or no more than 1 other polyethylene glycol (—CH.sub.2CH.sub.2O—) subunits present in the ADC, or intermediate thereof (i.e., no more than 8, 7, 6, 5, 4, 3, 2, or 1 other polyethylene glycol subunits in other components of the ADCs (or intermediates thereof) provided herein).

[0711] It will be appreciated that when referring to polyethylene glycol subunits of a PEG Unit, and depending on context, the number of subunits can represent an average number, e.g., when referring to a population of ADCs or intermediates thereto and/or using polydisperse PEGs.

Methods of Use

[0712] In some embodiments, the ADCs or ADC compositions described herein, or pharmaceutically acceptable salts thereof, are used to deliver the conjugated drug to a target cell. Without being bound by theory, in some embodiments, an ADC associates with an antigen on the surface of a target cell. The Drug Unit can then be released as free drug to induce its biological effect (such as an immunostimulatory effect). The Drug Unit can also remain attached to the antibody, or a portion of the antibody and/or linker, and induce its biological effect.

[0713] Some embodiments provide a method of treating cancer in a subject in need thereof, comprising administering a therapeutically effective amount of an ADC or ADC composition described herein, or a pharmaceutically acceptable salt thereof, to the subject.

[0714] Some embodiments provide a method of treating cancer in a subject in need thereof, comprising administering a therapeutically effective amount of a composition comprising an ADC or ADC composition described herein, or a pharmaceutically acceptable salt thereof, to the subject.

[0715] Some embodiments provide a method of inducing an anti-tumor immune response in a subject in need thereof, comprising administering a therapeutically effective amount of a composition comprising an ADC or ADC composition described herein, or a pharmaceutically acceptable salt thereof, to the subject.

[0716] Some embodiments provide a method of inducing an anti-tumor immune response in a subject in need thereof, comprising administering a therapeutically effective amount of an ADC or ADC composition described herein, or a pharmaceutically acceptable salt thereof, to the subject.

[0717] Some embodiments provide a method of treating cancer in a subject in need thereof, comprising administering a therapeutically effective amount of an ADC or ADC composition as described herein, or a pharmaceutically acceptable salt thereof, to the subject in combination with another anticancer therapy (e.g., surgery and radiation therapy) and/or anticancer agent (e.g., an immunotherapy such as nivolumab or pembrolizumab). In some embodiments, the ADCs or ADC compositions described herein is administered before, during, or after administration of the anticancer therapy and/or anticancer agent to the subject. In some embodiments, the ADCs or ADC compositions described herein is administered to the subject following treatment with radiation and/or after surgery.

[0718] Some embodiments provide a method for delaying or preventing acquired resistance to an anticancer agent, comprising administering a therapeutically effective amount of an ADC as described herein, or a pharmaceutically acceptable salt thereof, to a patient at risk for developing or having acquired resistance to an anticancer agent. In some embodiments, the patient is administered a dose of the anticancer agent (e.g., at substantially the same time as a dose of an ADC or ADC composition as described herein, or a pharmaceutically acceptable salt thereof is administered to the patient).

[0719] Some embodiments provide a method of delaying and/or preventing development of cancer resistant to an anticancer agent in a subject, comprising administering to the subject a therapeutically effective amount of an ADC or ADC composition as described herein, or a pharmaceutically acceptable salt thereof, before, during, or after administration of a therapeutically effective amount of the anticancer agent.
[0720] The ADCs and or ADC compositions described herein are useful for inhibiting the multiplication of a cancer cell, causing apoptosis in a cancer cell, for increasing phagocytosis of a cancer cell, and/or for treating cancer in a subject in need thereof. In some embodiments, the ADCs or ADC compositions are used accordingly in a variety of settings for the treatment of cancers. In some embodiments, the ADCs or ADC compositions are used to deliver a drug to a cancer cell. Without being bound by theory, in some embodiments, the antibody of an ADC binds to or associates with a cancer-cell-associated antigen. In some embodiments, the antigen is attached to a cancer cell or an extracellular matrix protein associated with the cancer cell. In some embodiments, the drug is released in proximity to the cancer cell, thus recruiting/activating immune cells to attack the cancer cell. In some embodiments, the Drug Unit is cleaved from the ADC outside the cancer cell. In some embodiments, the Drug Unit remains attached to the antibody bound to the antigen.
[0721] In some embodiments, the antibody binds to the cancer cell. In some embodiments, the antibody binds to a cancer cell antigen which is on the surface of the cancer cell. In some embodiments, the antibody binds to a cancer cell antigen which is an extracellular matrix protein associated with the tumor cell or cancer cell. In some embodiments, the antibody of an ADC binds to or associates with a cancer-associated cell or an antigen on a cancer-associated cell. In some embodiments, the cancer-associated cell is a stromal cell in a tumor, for example, a cancer-associated fibroblast (CAF).
[0722] In some embodiments, the antibody of an ADC binds to or associates with an immune cell or an immune-cell-associated antigen. In some embodiments, the antigen is attached to an immune cell or is an extracellular matrix protein associated with the immune cell. In some embodiments, the drug is released in proximity to the immune cell, thus recruiting/activating the immune cell to attack a cancer cell. In some embodiments, the Drug Unit is cleaved from the ADC outside the immune cell. In some embodiments, the Drug Unit remains attached to the antibody bound to the antigen. In some embodiments, the immune cell is a lymphocyte, an antigen-presenting cell, a natural killer (NK) cell, a neutrophil, an eosinophil, a basophil, a mast cell, innate lymphoid cells or a combination of any of the foregoing. In some embodiments, the immune cell is selected from the group consisting of B cells, plasma cells, T cells, NKT cells, gamma delta T (76T) cells, monocytes, macrophages, dendritic cells, natural killer (NK) cells, neutrophils, eosinophils, basophils, mast cells, innate lymphoid cells and a combination of any of the foregoing.
[0723] The specificity of the antibody for a particular cancer cell can be important for determining those tumors or cancers that are most effectively treated. For example, ADCs that target a cancer cell antigen present on hematopoietic cancer cells in some embodiments treat hematologic malignancies. In some embodiments, ADCs target a cancer cell antigen present on abnormal cells of solid tumors for treating such solid tumors. In some embodiments an ADC are directed against abnormal cells of hematopoietic cancers such as, for example, lymphomas (Hodgkin Lymphoma and Non-Hodgkin Lymphomas) and leukemias.
[0724] Cancers, including, but not limited to, a tumor, metastasis, or other disease or disorder characterized by abnormal cells that are characterized by uncontrolled cell growth in some embodiments are treated or inhibited by administration of an ADC or ADC composition.
[0725] In some embodiments, the subject has previously undergone treatment for the cancer. In some embodiments, the prior treatment is surgery, radiation therapy, administration of one or more anticancer agents, or a combination of any of the foregoing.
[0726] In any of the methods described herein, the cancer is selected from the group consisting of: adenocarcinoma, adrenal gland cortical carcinoma, adrenal gland neuroblastoma, anus squamous

cell carcinoma, appendix adenocarcinoma, bladder urothelial carcinoma, bile duct adenocarcinoma, bladder carcinoma, bladder urothelial carcinoma, bone chordoma, bone marrow leukemia lymphocytic chronic, bone marrow leukemia non-lymphocytic acute myclocytic, bone marrow lymph proliferative disease, bone marrow multiple myeloma, bone sarcoma, brain astrocytoma, brain glioblastoma, brain medulloblastoma, brain meningioma, brain oligodendroglioma, breast adenoid cystic carcinoma, breast carcinoma, breast ductal carcinoma in situ, breast invasive ductal carcinoma, breast invasive lobular carcinoma, breast metaplastic carcinoma, cervix neuroendocrine carcinoma, cervix squamous cell carcinoma, colon adenocarcinoma, colon carcinoid tumor, duodenum adenocarcinoma, endometrioid tumor, esophagus adenocarcinoma, esophagus and stomach carcinoma, eye intraocular melanoma, eye intraocular squamous cell carcinoma, eye lacrimal duct carcinoma, fallopian tube serous carcinoma, gallbladder adenocarcinoma, gallbladder *glomus* tumor, gastroesophageal junction adenocarcinoma, head and neck adenoid cystic carcinoma, head and neck carcinoma, head and neck neuroblastoma, head and neck squamous cell carcinoma, kidney chromophore carcinoma, kidney medullary carcinoma, kidney renal cell carcinoma, kidney renal papillary carcinoma, kidney sarcomatoid carcinoma, kidney urothelial carcinoma, kidney carcinoma, leukemia lymphocytic, leukemia lymphocytic chronic, liver cholangiocarcinoma, liver hepatocellular carcinoma, liver carcinoma, lung adenocarcinoma, lung adenosquamous carcinoma, lung atypical carcinoid, lung carcinosarcoma, lung large cell neuroendocrine carcinoma, lung non-small cell lung carcinoma, lung sarcoma, lung sarcomatoid carcinoma, lung small cell carcinoma, lung small cell undifferentiated carcinoma, lung squamous cell carcinoma, upper aerodigestive tract squamous cell carcinoma, upper aerodigestive tract carcinoma, lymph node lymphoma diffuse large B cell, lymph node lymphoma follicular lymphoma, lymph node lymphoma mediastinal B-cell, lymph node lymphoma plasmablastic lung adenocarcinoma, lymphoma follicular lymphoma, lymphoma, non-Hodgkins, nasopharynx and paranasal sinuses undifferentiated carcinoma, ovary carcinoma, ovary carcinosarcoma, ovary clear cell carcinoma, ovary epithelial carcinoma, ovary granulosa cell tumor, ovary serous carcinoma, pancreas carcinoma, pancreas ductal adenocarcinoma, pancreas neuroendocrine carcinoma, peritoneum mesothelioma, peritoneum serous carcinoma, placenta choriocarcinoma, pleura mesothelioma, prostate acinar adenocarcinoma, prostate carcinoma, rectum adenocarcinoma, rectum squamous cell carcinoma, skin adnexal carcinoma, skin basal cell carcinoma, skin melanoma, skin Merkel cell carcinoma, skin squamous cell carcinoma, small intestine adenocarcinoma, small intestine gastrointestinal stromal tumors (GTSTs), large intestine/colon carcinoma, large intestine adenocarcinoma, soft tissue angiosarcoma, soft tissue Ewing sarcoma, soft tissue hemangioendothelioma, soft tissue inflammatory myofibroblastic tumor, soft tissue leiomyosarcoma, soft tissue liposarcoma, soft tissue neuroblastoma, soft tissue paraganglioma, soft tissue perivascular epitheliod cell tumor, soft tissue sarcoma, soft tissue synovial sarcoma, stomach adenocarcinoma, stomach adenocarcinoma diffuse-type, stomach adenocarcinoma intestinal type, stomach adenocarcinoma intestinal type, stomach leiomyosarcoma, thymus carcinoma, thymus thymoma lymphocytic, thyroid papillary carcinoma, unknown primary adenocarcinoma, unknown primary carcinoma, unknown primary malignant neoplasm, lymphoid neoplasm, unknown primary melanoma, unknown primary sarcomatoid carcinoma, unknown primary squamous cell carcinoma, unknown undifferentiated neuroendocrine carcinoma, unknown primary undifferentiated small cell carcinoma, uterus carcinosarcoma, uterus endometrial adenocarcinoma, uterus endometrial adenocarcinoma endometrioid, uterus endometrial adenocarcinoma papillary serous, and uterus leiomyosarcoma.

[0727] In some embodiments, the subject is concurrently administered one or more additional anticancer agents with the ADCs or ADC compositions described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the subject is concurrently receiving radiation therapy with the ADCs or ADC compositions described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the subject is administered one or more additional anticancer

agents after administration of the ADCs or ADC compositions described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the subject receives radiation therapy after administration of the ADCs or ADC compositions described herein, or a pharmaceutically acceptable salt thereof.

[0728] In some embodiments, the subject has discontinued a prior therapy, for example, due to unacceptable or unbearable side effects, wherein the prior therapy was too toxic, or wherein the subject developed resistance to the prior therapy.

[0729] Some embodiments provide a method for delaying or preventing a disease or disorder, comprising administering a therapeutically effective amount of an ADC or ADC composition as described herein, or a pharmaceutically acceptable salt thereof, and a vaccine against the disease or disorder, to a patient at risk for developing the disease or disorder. In some embodiments, the disease or disorder is cancer, as described herein. In some embodiments, the disease or disorder is a viral pathogen. In some embodiments, the vaccine is administered subcutaneously. In some embodiments, the vaccine is administered intramuscularly. In some embodiments, the ADC or ADC composition and the vaccine are administered via the same route (for example, the ADC and the vaccine are both administered subcutaneously). In some embodiments, the ADC or ADC composition, or a pharmaceutically acceptable salt thereof, and the vaccine are administered via different routes. In some embodiments, the vaccine and the ADC or ADC composition, or a pharmaceutically acceptable salt thereof, are provided in a single formulation. In some embodiments, the vaccine and the ADC or ADC composition, or a pharmaceutically acceptable salt thereof, are provided in separate formulations.

Compositions and Methods of Administration

[0730] Some embodiments provide a composition comprising a distribution of ADCs, as described herein (i.e., an ADC composition). In some embodiments, the composition comprises a distribution of ADCs, as described herein and at least one pharmaceutically acceptable carrier. In some embodiments, the route of administration is parenteral. Parenteral administration includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In some embodiments, the compositions are administered parenterally. In one of those embodiments, the ADCs are administered intravenously. Administration is typically through any convenient route, for example by infusion or bolus injection.

[0731] Compositions of an ADC are formulated so as to allow the ADC to be bioavailable upon administration of the composition to a subject. In some embodiments, compositions are in the form of one or more injectable dosage units.

[0732] In some embodiments, materials used in preparing the compositions are non-toxic in the amounts used. It will be evident to those of ordinary skill in the art that the optimal dosage of the active ingredient(s) in the composition will depend on a variety of factors. Relevant factors include, without limitation, the type of animal (e.g., human), the particular form of the compound, the manner of administration, and the composition employed.

[0733] In some embodiments, the ADC composition is a solid, for example, as a lyophilized powder, suitable for reconstitution into a liquid prior to administration. In some embodiments, the ADC composition is a liquid composition, such as a solution or a suspension. A liquid composition or suspension is useful for delivery by injection and a lyophilized solid is suitable for reconstitution as a liquid or suspension using a diluent suitable for injection. In a composition administered by injection, one or more of a surfactant, preservative, wetting agent, dispersing agent, suspending agent, buffer, stabilizer and isotonic agent is typically included.

[0734] In some embodiments, the liquid compositions, whether they are solutions, suspensions or other like form, can also include one or more of the following: sterile diluents such as water for injection, saline solution, physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or digylcerides which can serve as the solvent or suspending medium, polyethylene glycols, glycerin, cyclodextrin, propylene glycol or other solvents; antibacterial

agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as amino acids, acetates, citrates or phosphates; detergents, such as nonionic surfactants, polyols; and agents for the adjustment of tonicity such as sodium chloride or dextrose. A parenteral composition is typically enclosed in ampoule, a disposable syringe or a multiple-dose vial made of glass, plastic or other material. In some embodiments, the sterile diluent comprises physiological saline. In some embodiments, the sterile diluent is physiological saline. In some embodiments, the composition described herein are liquid injectable compositions that are sterile.

[0735] The amount of the ADC or ADC composition that is effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, which is usually determined by standard clinical techniques. In addition, in vitro or in vivo assays are sometimes employed to help identify optimal dosage ranges. The precise dose to be employed in the compositions will also depend on the route of parenteral administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each subject's circumstances.

[0736] In some embodiments, the compositions comprise an effective amount of an ADC such that a suitable dosage will be obtained. Typically, this amount is at least about 0.01% of the ADC by weight of the composition.

[0737] In some embodiments, the compositions dosage of an ADC or ADC composition administered to a subject is from about 0.01 mg/kg to about 100 mg/kg, from about 1 to about 100 mg of a per kg or from about 0.1 to about 25 mg/kg of the subject's body weight. In some embodiments, the dosage administered to a subject is about 0.01 mg/kg to about 15 mg/kg of the subject's body weight. In some embodiments, the dosage administered to a subject is about 0.1 mg/kg to about 15 mg/kg of the subject's body weight. In some embodiments, the dosage administered to a subject is about 0.1 mg/kg to about 20 mg/kg of the subject's body weight. In some embodiments, the dosage administered is about 0.1 mg/kg to about 5 mg/kg or about 0.1 mg/kg to about 10 mg/kg of the subject's body weight. In some embodiments, the dosage administered is about 1 mg/kg to about 15 mg/kg of the subject's body weight. In some embodiments, the dosage administered is about 1 mg/kg to about 10 mg/kg of the subject's body weight. In some embodiments, the dosage administered is about 0.1 to about 4 mg/kg, about 0.1 to about 3.2 mg/kg, or about 0.1 to about 2.7 mg/kg of the subject's body weight over a treatment cycle.

[0738] The term “carrier” refers to a diluent, adjuvant or excipient, with which a compound is administered. Such pharmaceutical carriers are liquids. Water is an exemplary carrier when the compounds are administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions are also useful as liquid carriers for injectable solutions. Suitable pharmaceutical carriers also include glycerol, propylene, glycol, or ethanol. The present compositions, if desired, will in some embodiments also contain minor amounts of wetting or emulsifying agents, and/or pH buffering agents.

[0739] In some embodiments, the ADCs or ADC compositions are formulated in accordance with routine procedures as a composition adapted for intravenous administration to animals, particularly human beings. Typically, the carriers or vehicles for intravenous administration are sterile isotonic aqueous buffer solutions. In some embodiments, the composition further comprises a local anesthetic, such as lignocaine, to ease pain at the site of the injection. In some embodiments, the ADC or ADC composition and the remainder of the formulation are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where an ADC or ADC composition is to be administered by infusion, it is sometimes dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the ADCs or ADC compositions are administered by injection, an

ampoule of sterile water for injection or saline is typically provided so that the ingredients can be mixed prior to administration.

[0740] The compositions are generally formulated as sterile, substantially isotonic and in full compliance with all Good Manufacturing Practice (GMP) regulations of the U.S. Food and Drug Administration.

Various Embodiments

[0741] Various embodiments disclosed herein include the following: [0742] 1. A compound of Formula (II):

##STR00229##

or a pharmaceutically acceptable salt thereof, wherein: [0743] R.sup.1 is hydrogen, hydroxyl, C.sub.1-6 alkoxy, —(C.sub.1-6 alkyl) C.sub.1-6 alkoxy, —(CH.sub.2).sub.n—NR.sup.AR.sup.B, or PEG2 to PEG4; [0744] each R.sup.2 and R.sup.3 are independently —CO.sub.2H, —(C═O).sub.m—NR.sup.CR.sup.D, or —(CH.sub.2).sub.q—NR.sup.ER.sup.F; [0745] each R.sup.A, R.sup.B, R.sup.C, R.sup.D, R.sup.E, and R.sup.F are independently hydrogen or C.sub.1-3 alkyl; [0746] each subscript n is independently an integer from 0 to 6; [0747] each subscript m is independently 0 or 1; [0748] each subscript q is independently an integer from 0 to 6; [0749] X.sup.A is —CH.sub.2—, —O—, —S—, —NH—, or —N(CH.sub.3)—; [0750] X.sup.B is absent or a 2-16 membered heteroalkylene; [0751] L is a linker having the formula -(A).sub.a-(W).sub.W—(Y).sub.y—, wherein: [0752] subscript a is 0 or 1; [0753] subscript y is 0 or 1; [0754] subscript w is 0 or 1; [0755] A is a C.sub.2-20 alkylene optionally substituted with 1-3 R.sup.a1; or a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R.sup.b1; [0756] each R.sup.a1 is independently selected from the group consisting of: C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, ═O, —NR.sup.d1R.sup.e1, —C(O)NR.sup.d1R.sup.e1, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl); [0757] each R.sup.b1 is independently selected from the group consisting of: C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, —NR.sup.d1R.sup.e1, —C(O)NR.sup.d1R.sup.e1, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl); [0758] each R.sup.d1 and R.sup.e1 are independently hydrogen or C.sub.1-3 alkyl; W is from 1-12 amino acids or has the structure:

##STR00230## [0759] wherein Su is a Sugar moiety; [0760] —O.sup.A— represents a glycosidic bond; [0761] each R.sup.9 is independently hydrogen, halogen, —CN, or —NO.sub.2; [0762] W.sup.1 is absent or —O—C(═O)—; custom-character represents covalent attachment to A or M; [0763] * represents covalent attachment to Y, X.sup.A, or X.sup.B; and [0764] Y is a self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety; [0765] M is

##STR00231## [0766] each AA is an independently selected amino acid, wherein (AA).sub.b is connected to the succinimide or hydrolyzed succinimide via a sulfur atom; [0767] each subscript b is independently an integer from 1 to 6; and [0768] X.sup.B and L are each independently optionally substituted with a PEG Unit from PEG2 to PEG 72. [0769] 2. The compound of Embodiment 1, wherein R.sup.1 is hydrogen. [0770] 3. The compound of Embodiment 1, wherein R.sup.1 is hydroxyl. [0771] 4. The compound of Embodiment 1, wherein R.sup.1 is C.sub.1-6 alkoxy. [0772] 5. The compound of Embodiment 1 or 4, wherein R.sup.1 is methoxy. [0773] 6. The compound of Embodiment 1, wherein R.sup.1 is —(C.sub.1-6 alkyl)C.sub.1-6 alkoxy. [0774] 7. The compound of Embodiment 1 or 6, wherein R.sup.1 is methoxyethyl. [0775] 8. The compound of Embodiment 1, wherein R.sup.1 is PEG2 to PEG4. [0776] 9. The compound of Embodiment 1, wherein R.sup.1 is —(CH.sub.2).sub.n—NR.sup.AR.sup.B. [0777] 10. The compound of Embodiment 1 or 9, wherein R.sup.A and R.sup.B are both hydrogen. [0778] 11. The compound of Embodiment 1 or 9, wherein R.sup.A and R.sup.B are independently C.sub.1-3 alkyl. [0779] 12. The compound of Embodiment 1 or 9, wherein one of R.sup.A and R.sup.B is hydrogen and the other of R.sup.A and R.sup.B is C.sub.1-3 alkyl. [0780] 13. The compound of any one of

Embodiments 1 or 9-12, wherein each subscript n is 0. [0781] 14. The compound of any one of Embodiments 1 or 9-12, wherein each subscript n is 1. [0782] 15. The compound of any one of Embodiments 1 or 9-12, wherein each subscript n is 2. [0783] 16. The compound of any one of Embodiments 1 or 9-12, wherein each subscript n is 3, 4, 5, or 6. [0784] 17. The compound of any one of Embodiments 1-16, wherein R.sup.2 and R.sup.3 are independently —CO.sub.2H, —(C═O).sub.m—NR.sup.CR.sup.D, or —(CH.sub.2).sub.q—NR.sup.ER.sup.F; and R.sup.2 and R.sup.3 are the same. [0785] 18. The compound of any one of Embodiments 1-16, wherein R.sup.2 and R.sup.3 are independently —C.sub.02H, —(C═O).sub.m—NR.sup.CR.sup.D, or —(CH.sub.2).sub.q—NR.sup.ER.sup.F; and R.sup.2 and R.sup.3 are different. [0786] 19. The compound of any one of Embodiments 1-18, wherein R.sup.2 is —(C═O).sub.m—NR.sup.CR.sup.D. [0787] 20. The compound of any one of Embodiments 1-18, wherein R.sup.3 is —(C═O).sub.m—NR.sup.CR.sup.D. [0788] 21. The compound of any one of Embodiments 1-20, wherein R.sup.C and R.sup.D are both hydrogen. [0789] 22. The compound of any one of Embodiments 1-20, wherein R.sup.C and R.sup.D are each independently C.sub.1-3 alkyl. [0790] 23. The compound of any one of Embodiments 1-20, wherein one of R.sup.C and R.sup.D is hydrogen and the other of R.sup.C and R.sup.D is C.sub.1-3 alkyl. [0791] 24. The compound of any one of Embodiments 1-20, wherein each subscript m is 0. [0792] 25. The compound of any one of Embodiments 1-20, wherein each subscript m is 1. [0793] 26. The compound of any one of Embodiments 1-18, wherein R.sup.2 is —(CH.sub.2).sub.q—NR.sup.ER.sup.F. [0794] 27. The compound of any one of Embodiments 1-18, wherein R.sup.3 is —(CH.sub.2).sub.q—NR.sup.ER.sup.F. [0795] 28. The compound of any one of Embodiments 1-18, 26, or 27, wherein R.sup.E and R.sup.F are both hydrogen. [0796] 29. The compound of any one of Embodiments 1-18, 26, or 27, wherein R.sup.E and R.sup.F are each independently C.sub.1-3 alkyl. [0797] 30. The compound of any one of Embodiments 1-18, 26, or 27, wherein one of R.sup.E and R.sup.F is hydrogen and the other of R.sup.E and R.sup.F is C.sub.1-3 alkyl. [0798] 31. The compound of any one of Embodiments 1-18, 26, or 27, wherein each subscript q is 0. [0799] 32. The compound of any one of Embodiments 1-18, 26, or 27, wherein each subscript q is an integer from 1 to 6. [0800] 33. The compound of any one of Embodiments 1-18, wherein R.sup.3 is —CO.sub.2H. [0801] 34. The compound of any one of Embodiments 1-18, wherein R.sup.2 is —CO.sub.2H. [0802] 35. The compound of any one of Embodiments 1-34, wherein X.sup.A is —CH.sub.2—. [0803] 36. The compound of any one of Embodiments 1-34, wherein X.sup.A is —O—. [0804] 37. The compound of any one of Embodiments 1-34, wherein X.sup.A is —S—. [0805] 38. The compound of any one of Embodiments 1-34, wherein X.sup.A is —NH—. [0806] 39. The compound of any one of Embodiments 1-38, wherein X.sup.B is a 2-16 membered heteroalkylene. [0807] 40. The compound of any one of Embodiments 1-39, wherein X.sup.B is a 2-12 membered heteroalkylene. [0808] 41. The compound of any one of Embodiments 1-40, wherein X.sup.B is a 2-8 membered heteroalkylene. [0809] 42. The compound of any one of Embodiments 39-41, wherein the heteroalkylene is branched, having 1-4 methyl groups. [0810] 43. The compound of any one of Embodiments 39-42, wherein the heteroalkylene is branched, having 1 or 2 methyl groups. [0811] 44. The compound of any one of Embodiments 39-43, wherein the heteroalkylene is substituted with 1-3 fluoro groups. [0812] 45. The compound of any one of Embodiments 1-44, wherein X.sup.B comprises one or two nitrogen atoms. [0813] 46. The compound of any one of Embodiments 1-45, wherein X.sup.B comprises one or two oxo groups. [0814] 47. The compound of any one of Embodiments 1-46, wherein X.sup.B Comprises one nitrogen atom and one oxo group. [0815] 48. The compound of any one of Embodiments 1-47, wherein X.sup.B comprises two nitrogen atoms and one oxo group.

[0816] 49. The compound of any one of Embodiments 1-41 or 45-47, wherein X.sup.B is ##STR00232##

wherein custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L or M. [0817] 50. The compound of any one of Embodiments 1-41 or 45-47,

wherein X.sup.B
##STR00233##
wherein custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L or M. [0818] 51. The compound of any one of Embodiments 1-41 or 45-47, wherein X.sup.B is
##STR00234##
wherein custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L or M. [0819] 52. The compound of any one of Embodiments 1-41 or 45-47, wherein X.sup.B is
##STR00235##
wherein custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L or M. [0820] 53. The compound of any one of Embodiments 1-43 or 48, wherein X.sup.B is
##STR00236##
wherein custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L. [0821] 54. The compound of any one of Embodiments 1-43 or 45, wherein X.sup.B is
##STR00237##
wherein custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L. [0822] 55. The compound of any one of Embodiments 1-38, wherein X.sup.B is absent. [0823] 56. The compound of any one of Embodiments 1-55, wherein subscript a is 1. [0824] 57. The compound of any one of Embodiments 1-56, wherein subscript y is 1. [0825] 58. The compound of any one of Embodiments 1-57, wherein subscript w is 1. [0826] 59. The compound of any one of Embodiments 1-55, wherein the sum of subscript a, subscript y, and subscript w is 1. [0827] 60. The compound of any one of Embodiments 1-55, wherein the sum of subscript a, subscript y, and subscript w is 2. [0828] 61. The compound of any one of Embodiments 1-58, wherein the sum of subscript a, subscript y, and subscript w is 3. [0829] 62. The compound of any one of Embodiments 1-61, wherein Y is a self-immolative moiety. [0830] 63. The compound of any one of Embodiments 1-61, wherein Y is
##STR00238## [0831] 64. The compound of any one of Embodiments 1-54 or 56-61, wherein Y is a non-cleavable moiety and a is 0. [0832] 65. The compound of any one of Embodiments 1-54, 56-61, or 64, wherein Y is a cyclohexanecarboxyl, undecanoyl, caproyl, hexanoyl, butanoyl or propionyl group. [0833] 66. The compound of any one of Embodiments 1-54, 56-61, or 64, wherein Y is PEG4 to PEG12. [0834] 67. The compound of any one of Embodiments 1-66, wherein W is from 1-12 amino acids. [0835] 68. The compound of any one of Embodiments 1-67, wherein W is from 1-6 amino acids. [0836] 69. The compound of any one of Embodiments 1-68, wherein each amino acid in W is independently selected from the group consisting of alanine, glycine, lysine, serine, aspartic acid, aspartate methyl ester, N,N-dimethyl-lysine, phenylalanine, citrulline, valine-alanine, valine-citrulline, phenylalanine-lysine or homoserine methyl ether. [0837] 70. The compound of any one of Embodiments 1-66, wherein W has the structure:
##STR00239## [0838] wherein Su is a Sugar moiety; [0839] —O.sup.A— represents a glycosidic bond; [0840] each R.sup.9 is independently hydrogen, halogen, —CN, or —NO.sub.2; [0841] W.sup.1 is absent or O—C(═O); [0842] custom-character represents covalent attachment to A or M; and [0843] * represents covalent attachment to Y, X.sup.A, or X.sup.B. [0844] 71. The compound of any one of Embodiments 1-66 or 70, wherein W.sup.1 is —O—C(═O)—. [0845] 72. The compound of any one of Embodiments 1-66 or 70-71, wherein one R.sup.9 is halogen, —CN, or —NO.sub.2, and the remaining R.sup.9 are hydrogen. [0846] 73. The compound of any one of Embodiments 1-66 or 70-71, wherein each R.sup.9 is hydrogen. [0847] 74. The compound of any one of Embodiments 1-73, wherein A is C.sub.2-20 alkylene optionally substituted with 1-3 R.sup.a1 [0848] 75. The compound of any one of Embodiments 1-74, wherein A is C.sub.4-10

alkylene optionally substituted with 1-3 R.sup.a1. [0849] 76. The compound of any one of Embodiments 1-75, wherein A is C.sub.2-20 alkylene substituted with R.sup.a1. [0850] 77. The compound of any one of Embodiments 1-76, wherein A is C.sub.4-1o alkylene substituted with R.sup.a1. [0851] 78. The compound of any one of Embodiments 1-75, wherein A is C.sub.2-20 alkylene. [0852] 79. The compound of any one of Embodiments 1-75, wherein A is C.sub.4-10 alkylene. [0853] 80. The compound of any one of Embodiments 1-73, wherein A is a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R.sup.b1. [0854] 81. The compound of any one of Embodiments 1-72, wherein A is a 4 to 12 membered heteroalkylene optionally substituted with 1-3 R.sup.b1. [0855] 82. The compound of any one of Embodiments 1-73 or 80, wherein A is a 2 to 40 membered heteroalkylene optionally substituted with one R.sup.b1. [0856] 83. The compound of any one of Embodiments 1-73 or 80, wherein A is a 4 to 12 membered heteroalkylene optionally substituted with one R.sup.b1. [0857] 84. The compound of any one of Embodiments 1-73 or 80, wherein A is a 2 to 40 membered heteroalkylene. [0858] 85. The compound of any one of Embodiments 1-73 or 80, wherein A is a 4 to 12 membered heteroalkylene. [0859] 86. The compound of any one of Embodiments 1-73 or 84-85, wherein A is
##STR00240##
wherein custom-character represents covalent attachment to W, and * represents covalent linkage to M. [0860] 87. The compound of any one of Embodiments 1-54 or 61-73, wherein subscript a is 0. [0861] 88. The compound of any one of Embodiments 1-54 or 67-79, wherein subscript y is 0. [0862] 89. The compound of any one of Embodiments 1-54, 58-66, or 79-80, wherein subscript w is 0. [0863] 90. The compound of any one of Embodiments 1-54, wherein the sum of subscript a, subscript y, and subscript w is 0.
##STR00241## [0864] 91. The compound of any one of Embodiments 1-90, wherein M is
##STR00242## [0865] 92. The compound of any one of Embodiments 1-90, wherein M is
##STR00243## [0866] 93. The compound of any one of Embodiments 1-90, wherein M is b 94. The compound of any one of Embodiments 1-93, wherein each AA is independently a natural amino acid; wherein (AA).sub.b is connected to the succinimide or hydrolyzed succinimide via a sulfur atom. [0867] 95. The compound of any one of Embodiments 1-93, wherein each AA is independently a natural amino acid; wherein (AA).sub.b is connected to the succinimide or hydrolyzed succinimide via a nitrogen atom. [0868] 96. The compound of any one of Embodiments 1-95, wherein each subscript b is 1. [0869] 97. The compound of any one of Embodiments 1-95, wherein each subscript b is 2. [0870] 98. The compound of any one of Embodiments 1-95, wherein each subscript b is 3, 4, 5, or 6. [0871] 99. The compound of any one of Embodiments 1-91, 94, or 96, wherein M is
##STR00244##
[0872] 100. The compound of any one of Embodiments 1-90, 92, or 96, wherein M is
##STR00245## [0873] 101. The compound of any one of Embodiments 1-90, 93, or 96, wherein M is
##STR00246## [0874] 102. The compound of any one of Embodiments 1-90, wherein M is
##STR00247## [0875] 103. The compound of any one of Embodiments 1-102, wherein one of X.sup.B and L are substituted with an independently selected PEG Unit from PEG2 to PEG 72. [0876] 104. The compound of any one of Embodiments 1-102, wherein X.sup.B and L are unsubstituted. [0877] 105. The compound of Embodiment 1, selected from the group consisting of:
##STR00248## ##STR00249## ##STR00250## ##STR00251## ##STR00252## ##STR00253##
[0878] and pharmaceutically acceptable salts thereof. [0879] 106. The compound of Embodiment 1, having the structure of Formula (II-A):
##STR00254##
or a pharmaceutically acceptable salt thereof, wherein: [0880] L.sup.A is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, or —C(O)NR.sup.H(CH.sub.2).sub.1-6—; [0881] each R.sup.H is independently hydrogen or C.sub.1-3 alkyl; [0882] Y is

##STR00255## [0883] # represents covalent attachment to —NR.sup.HL.sup.A; [0884] ## represents covalent attachment to W or L.sup.B; and [0885] L.sup.B is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, or —[NHC(O)(CH.sub.2).sub.1-4]1-3-. [0886] 107. The compound of Embodiment 106, wherein R.sup.H is methyl. [0887] 108. The compound of Embodiment 106 or 107, wherein L.sup.A is —(CH.sub.2).sub.2-6—. [0888] 109. The compound of Embodiment 106 or 107, wherein L.sup.A is (CH.sub.2).sub.3—. [0889] 110. The compound of any one of Embodiments 106-109, wherein y is 0. [0890] 111. The compound of any one of Embodiments 106-109, wherein y is 1. [0891] 112. The compound of any one of Embodiments 106-111, wherein W is a chain of 1-3 amino acids. [0892] 113. The compound of Embodiment 112, wherein each amino acid of W is independently selected from the group consisting of alanine, valine, isoleucine, leucine, aspartic acid, glutamic acid, lysine, histidine, arginine, glycine, serine, threonine, phenylalanine, O-methylserine, O-methylaspartic acid, O-methylglutamic acid, N-methyllysine, O-methyltyrosine, O-methylhistidine, and O-methylthreonine. [0893] 114. The compound of any one of Embodiments 106-111, wherein W is:

##STR00256##

wherein: [0894] custom-character represents covalent attachment to L.sup.B; and [0895] * represents covalent attachment to Y or NR.sup.H. [0896] 115. The compound of any one of Embodiments 106-114, wherein L.sup.B is —C(O)(CH.sub.2).sub.2— [0897] 116. The compound of any one of Embodiments 106-114, wherein L.sup.B is —[NHC(O)(CH.sub.2).sub.2].sub.2—. [0898] 117. The compound of Embodiment 106, selected from the group consisting of:

##STR00257## ##STR00258## ##STR00259## ##STR00260## ##STR00261## ##STR00262## ##STR00263## ##STR00264##

and pharmaceutically acceptable salts thereof. [0899] 118. An antibody-drug conjugate (ADC) having the formula:

Ab-(S*-M.sup.1-(D)).sub.p

wherein: [0900] Ab is an antibody; [0901] each S* is a sulfur atom from a cysteine residue of the antibody; [0902] M.sup.1 is a succinimide or a hydrolyzed succinimide; [0903] subscript p is an integer from 2 to 8; and [0904] each (D) is a Drug-Linker Unit of Formula (I):

##STR00265## [0905] wherein: [0906] custom-character represents covalent attachment of L to M.sup.1; [0907] R.sup.1 is hydrogen, hydroxyl, C.sub.1-6 alkoxy, —(C.sub.1-6 alkyl)C.sub.1-6 alkoxy, —(CH.sub.2).sub.n—NR.sup.AR.sup.B, or PEG2 to PEG4; [0908] R.sup.2 and R.sup.3 are independently —CO.sub.2H, —(C═O).sub.m—NR.sup.CR.sup.D, or —(CH.sub.2).sub.q—NR.sup.ER.sup.F; [0909] each R.sup.A, R.sup.B, R.sup.C, R.sup.D, R.sup.E, and R.sup.F are independently hydrogen or C.sub.1-3 alkyl; [0910] each subscript n is independently an integer from 0 to 6; [0911] each subscript m is independently 0 or 1; [0912] each subscript q is an integer from 0 to 6; [0913] X.sup.A is —CH.sub.2—, —O—, —S—, —NH—, or —N(CH.sub.3)—; [0914] X.sup.R is absent or a 2-16 membered heteroalkylene; [0915] L has the formula -(A).sub.a-(W).sub.W—(Y).sub.y—, wherein: [0916] subscript a is 0 or 1; [0917] subscript y is 0 or 1; [0918] subscript w is 0 or 1; [0919] A is a C.sub.2-20 alkylene optionally substituted with 1-3 R.sup.a1; or a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R.sup.b1; [0920] each R.sup.a1 is independently selected from the group consisting of: C.sub.1 6 alkyl, C.sub.1 6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, ═O, —NR.sup.d1R.sup.e1, —C(O)NR.sup.a1R.sup.e1, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl); [0921] each R.sup.b1 is independently selected from the group consisting of: C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, —NR.sup.d1R.sup.e1, —C(O)NR.sup.d1R.sup.e1, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl); [0922] each R.sup.d1 and R.sup.e1 are independently hydrogen or C.sub.1-3 alkyl; [0923] W is from 1-12 amino acids or has the structure:

##STR00266## [0924] wherein Su is a Sugar moiety; [0925] —O.sup.A— represents a glycosidic

bond; [0926] each R.sup.9 is independently hydrogen, halogen, —CN, or —NO.sub.2; [0927] W.sup.1 is absent or —O—C(═O)—; [0928]  represents covalent attachment to A or M.sup.1; [0929] * represents covalent attachment to Y, X.sup.1, or X.sup.A. [0930] Y is self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety; and [0931] X.sup.B and L are each independently optionally substituted with a PEG Unit from PEG2 to PEG 72. [0932] 119. The ADC of Embodiment 118, wherein R.sup.1 is hydrogen. [0933] 120. The ADC of Embodiment 118, wherein R.sup.1 is hydroxyl. [0934] 121. The ADC of Embodiment 118, wherein R.sup.1 is C.sub.1-6 alkoxy. [0935] 122. The ADC of Embodiment 118 or 121, wherein R.sup.1 is methoxy. [0936] 123. The ADC of Embodiment 118, wherein R.sup.1 is —(C.sub.1-6 alkyl)C.sub.1-6 alkoxy. [0937] 124. The ADC of Embodiment 118 or 123, wherein R.sup.1 is methoxyethyl. [0938] 125. The ADC of Embodiment 118, wherein R.sup.1 is PEG2 to PEG4. [0939] 126. The ADC of Embodiment 118, wherein R.sup.1 is —(CH.sub.2).sub.n—NR.sup.AR.sup.B. [0940] 127. The ADC of Embodiment 118 or 126, wherein R.sup.A and R.sup.B are both hydrogen. [0941] 128. The ADC of Embodiment 118 or 126, wherein R.sup.A and R.sup.B are independently C.sub.1-3 alkyl. [0942] 129. The ADC of Embodiment 118 or 126, wherein one of R.sup.A and R.sup.B is hydrogen and the other of R.sup.A and R.sup.B is C.sub.1-3 alkyl. [0943] 130. The ADC of any one of Embodiments 118 or 126-129, wherein each subscript n is 0. [0944] 131. The ADC of any one of Embodiments 118 or 126-129, wherein each subscript n is 1. [0945] 132. The ADC of any one of Embodiments 118 or 126-129, wherein each subscript n is 2. [0946] 133. The ADC of any one of Embodiments 118 or 126-129, wherein each subscript n is 3,4, 5, or 6. [0947] 134. The ADC of any one of Embodiments 118-133, wherein R.sup.2 and R.sup.3 are independently —CO.sub.2H or —(C═O).sub.m—NR.sup.CR.sup.D, or —(CH.sub.2).sub.q—NR.sup.ER.sup.F; and R.sup.2 and R.sup.3 are the same. [0948] 135. The ADC of any one of Embodiments 118-133, wherein R.sup.2 and R.sup.3 are independently —CO.sub.2H or —(C═O).sub.m—NR.sup.CR.sup.D, or —(CH.sub.2).sub.q—NR.sup.ER.sup.F; and R.sup.2 and R.sup.3 are different. [0949] 136. The ADC of any one of Embodiments 118-135, wherein R.sup.2 is —(C═O).sub.m—NR.sup.CR.sup.D. [0950] 137. The ADC of any one of Embodiments 118-135, wherein R.sup.3 is —(C═O).sub.m—NR.sup.CR.sup.D. [0951] 138. The ADC of any one of Embodiments 118-137, wherein R.sup.C and R.sup.D are both hydrogen. [0952] 139. The ADC of any one of Embodiments 118-137, wherein R.sup.C and R.sup.D are each independently C.sub.1-3 alkyl. [0953] 140. The ADC of any one of Embodiments 118-137, wherein one of R.sup.C and R.sup.D is hydrogen and the other of R.sup.C and R.sup.D is C.sub.1-3 alkyl. [0954] 141. The ADC of any one of Embodiments 118-140, wherein each subscript m is 0. [0955] 142. The ADC of any one of Embodiments 118-140, wherein each subscript m is 1. [0956] 143. The ADC of any one of Embodiments 118-135, wherein R.sup.2 is —(CH.sub.2).sub.q—NR.sup.ER.sup.F. [0957] 144. The ADC of any one of Embodiments 118-135, wherein R.sup.3 is —(CH.sub.2).sub.q—NR.sup.ER.sup.F. [0958] 145. The ADC of any one of Embodiments 118-135, 143, or 144, wherein R.sup.E and R.sup.F are both hydrogen. [0959] 146. The ADC of any one of Embodiments 118-135, 143, or 144, wherein R.sup.E and R.sup.F are each independently C.sub.1-3 alkyl. [0960] 147. The ADC of any one of Embodiments 118-135, 143, or 144, wherein one of R.sup.E and R.sup.F is hydrogen and the other of R.sup.E and R.sup.F is C.sub.1-3 alkyl. [0961] 148. The ADC of any one of Embodiments 118-135, 143, or 144, wherein each subscript q is 0. [0962] 149. The ADC of any one of Embodiments 118-135, 143, or 144, wherein each subscript q is an integer from 1 to 6. [0963] 150. The ADC of any one of Embodiments 118-135, wherein R.sup.3 is —CO.sub.2H. [0964] 151. The ADC of any one of Embodiments 118-135, wherein R.sup.2 is —CO.sub.2H. [0965] 152. The ADC of any one of Embodiments 118-151, wherein X.sup.A is —CH.sub.2—. [0966] 153. The ADC of any one of Embodiments 118-151, wherein X.sup.A is —O—. [0967] 154. The ADC of any one of Embodiments 118-151, wherein X.sup.A is —S—155. The ADC of any one of Embodiments 118-151, wherein X.sup.A is —NH—. [0968] 156. The ADC of any one of Embodiments 118-155, wherein X.sup.B is a 2-16 membered heteroalkylene. [0969] 157. The

ADC of any one of Embodiments 118-155, wherein X.sup.B is a 2-12 membered heteroalkylene. [0970] 158. The ADC of any one of Embodiments 118-157, wherein X.sup.B is a 2-8 membered heteroalkylene. [0971] 159. The ADC of any one of Embodiments 118-158, wherein the heteroalkylene is branched, having 1-4 methyl groups. [0972] 160. The ADC of any one of Embodiments 118-159, wherein the heteroalkylene is branched, having 1 or 2 methyl groups. [0973] 161. The ADC of any one of Embodiments 118-160, wherein the heteroalkylene is substituted with 1-3 fluoro groups. [0974] 162. The ADC of any one of Embodiments 118-161, wherein X.sup.B comprises one or two nitrogen atoms. [0975] 163. The ADC of any one of Embodiments 118-162, wherein X.sup.B comprises one or two oxo groups. [0976] 164. The ADC of any one of Embodiments 118-163, wherein X.sup.B comprises one nitrogen atom and one oxo group. [0977] 165. The ADC of any one of Embodiments 118-163, wherein X.sup.B comprises two nitrogen atoms and one oxo groups. [0978] 166. The ADC of any one of Embodiments 118-158 or 162-164, wherein X.sup.B is

##STR00267##

wherein  custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L or M.sup.1. [0979] 167. The ADC of any one of Embodiments 118-158 or 162-164, wherein X.sup.B is

##STR00268##

wherein  custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L or M.sup.1. [0980] 168. The ADC of any one of Embodiments 118-158 or 162-163, wherein X.sup.B is

##STR00269##

wherein  custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L or M.sup.1. [0981] 169. The ADC of any one of Embodiments 118-158 or 162-164, wherein X.sup.B is

##STR00270##

wherein  custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L or M.sup.1. [0982] 170. The ADC of any one of Embodiments 118-158 or 162-165, wherein X.sup.B is

##STR00271##

wherein  custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L. [0983] 171. The ADC of any one of Embodiments 118-158 or 162-165, wherein X.sup.B is

##STR00272##

wherein  custom-character represents covalent attachment to X.sup.A, and * represents covalent attachment to L. [0984] 172. The ADC of any one of Embodiments 118-158, wherein X.sup.B is absent. [0985] 173. The ADC of any one of Embodiments 118-171, wherein subscript a is 1. [0986] 174. The ADC of any one of Embodiments 118 to 171 or 173, wherein subscript y is 1. [0987] 175. The ADC of any one of Embodiments 118-173, wherein subscript w is 1. [0988] 176. The ADC of any one of Embodiments 118-171, wherein the sum of subscript a, subscript y, and subscript w is 1. [0989] 177. The ADC of any one of Embodiments 118-171, wherein the sum of subscript a, subscript y, and subscript w is 2. [0990] 178. The ADC of any one of Embodiments 118-171, wherein the sum of subscript a, subscript y, and subscript w is 3. [0991] 179. The ADC of any one of Embodiments 118-178, wherein Y is a self-immolative moiety. [0992] 180. The ADC of any one of Embodiments 118-178, wherein Y is

##STR00273## [0993] 181. The ADC of any one of Embodiments 118-172, wherein Y is a non-cleavable moiety and a is 0. [0994] 182. The ADC of any one of Embodiments 118-178 or 181, wherein Y is MCC or SMCC. [0995] 183. The ADC of any one of Embodiments 118-178 or 181, wherein Y is PEG4 to PEG12. [0996] 184. The ADC of any one of Embodiments 118-183, wherein W is from 1-12 amino acids. [0997] 185. The ADC of any one of Embodiments 118-184, wherein

W is from 1-6 amino acids. [0998] 186. The ADC of any one of Embodiments 118-185, wherein each amino acid in W is selected from the group consisting of alanine, glycine, lysine, serine, aspartic acid, aspartate methyl ester, N,N-dimethyl-lysine, phenylalanine, citrulline, valine-alanine, valine-citrulline, phenylalanine-lysine or homoserine methyl ether. [0999] 187. The ADC of any one of Embodiments 118-183, wherein W has the structure:
##STR00274## [1000] wherein Su is a Sugar moiety; [1001] —O.sup.A— represents a glycosidic bond; [1002] each R.sup.9 is independently hydrogen, halogen, —CN, or —NO.sub.2; [1003] W.sup.1 is absent or —O—C(═O)—; [1004] custom-character represents covalent attachment to A or M.sup.1; and [1005] * represents covalent attachment to Y, X.sup.B, or X.sup.A. [1006] 188. The ADC of any one of Embodiments 118-187, wherein W.sup.1 is —O—C(═O)—. [1007] 189. The ADC of any one of Embodiments 118-187, wherein W.sup.1 is absent. [1008] 190. The ADC of any one of Embodiments 118-188, wherein one R.sup.9 is halogen, —CN, or —NO.sub.2, and the remaining R.sup.G are hydrogen. [1009] 191. The ADC of any one of Embodiments 118-188, wherein each R.sup.9 is hydrogen. [1010] 192. The ADC of any one of Embodiments 118-191, wherein A is C.sub.2-20 alkylene optionally substituted with 1-3 R.sup.a1 [1011] 193. The ADC of any one of Embodiments 118-192, wherein A is C.sub.4-10 alkylene optionally substituted with 1-3 R.sup.a1 [1012] 194. The ADC of any one of Embodiments 118-191, wherein A is C.sub.2-20 alkylene substituted with R.sup.a1. [1013] 195. The ADC of any one of Embodiments 118-192, wherein A is C.sub.4-10 alkylene substituted with R.sup.a1. [1014] 196. The ADC of any one of Embodiments 118-191, wherein A is C.sub.2-20 alkylene. [1015] 197. The ADC of any one of Embodiments 118-192, wherein A is C.sub.4-10 alkylene. [1016] 198. The ADC of any one of Embodiments 118-191, wherein A is a 2 to 40 membered heteroalkylene optionally substituted with 1-3 R.sup.b1. [1017] 199. The ADC of any one of Embodiments 118-191, wherein A is a 4 to 12 membered heteroalkylene optionally substituted with 1-3 R.sup.b1. [1018] 200. The ADC of any one of Embodiments 118-191 or 199, wherein A is a 2 to 40 membered heteroalkylene optionally substituted with one R.sup.b1. [1019] 201. The ADC of any one of Embodiments 118-191 or 199, wherein A is a 4 to 12 membered heteroalkylene optionally substituted with one R.sup.b1. [1020] 202. The ADC of any one of Embodiments 118-191 or 199, wherein A is a 2 to 40 membered heteroalkylene. [1021] 203. The ADC of any one of Embodiments 118-191 or 199, wherein A is a 4 to 12 membered heteroalkylene. [1022] 204. The ADC of any one of Embodiments 118-191 or 202-203, wherein A is
##STR00275## [1023] 205. The ADC of any one of Embodiments 118-145, wherein subscript a is 0. [1024] 206. The ADC of any one of Embodiments 118-145, wherein in subscript y is 0. [1025] 207. The ADC of any one of Embodiments 118-145, wherein subscript w is 0. [1026] 208. The ADC of any one of Embodiments 118-145 or 205-207, wherein the sum of subscript a, subscript y, and subscript w is 0. [1027] 209. The ADC of any one of Embodiments 118-208, wherein the linker is a cleavable linker. [1028] 210. The ADC of any one of Embodiments 118-209, wherein the linker is cleavable by one or more of cathepsin B, C, or D; β-glucuronidase; and β-mannosidase. [1029] 211. The ADC of Embodiments 118-208, wherein the linker is a non-cleavable linker. [1030] 212. The ADC of any one of Embodiments 118-211, wherein the antibody is a humanized antibody. [1031] 213. The ADC of any one of Embodiments 118-212, wherein the antibody is a monoclonal antibody. [1032] 214. The ADC of any one of Embodiments 118-187, wherein the antibody is fucosylated. [1033] 215. The ADC of any one of Embodiments 118-187, wherein the antibody is afucosylated. [1034] 216. A compound having the structure of Formula (IV):
##STR00276##
or a pharmaceutically acceptable salt thereof, wherein: [1035] R.sup.1C is hydrogen, hydroxyl, C.sub.1-6 alkoxy, —(C.sub.1-6 alkyl) C.sub.1-6 alkoxy, —(CH.sub.2).sub.n—NR.sup.AR.sup.B, or PEG2 to PEG4; [1036] R.sup.2C is —CO.sub.2R.sup.M, —(C═O)NR.sup.CR.sup.D, —S(O).sub.2NR.sup.CR.sup.D, —S(O).sub.2R.sup.M, —(CH.sub.2).sub.q—NR.sup.ER.sup.F, —(CH.sub.2).sub.q—OR.sup.M, —O(C═O)—NR.sup.ER.sup.F, or —NR.sup.M(C═O)—

NR.sup.ER.sup.N, wherein R.sup.2C is attached at any one of positions labeled 1, 2, or 3; [1037] R.sup.3C is —CO.sub.2R.sup.M, —(C═O)NR.sup.CR.sup.D, —S(O).sub.2NR.sup.CR.sup.D, —S(O).sub.2R.sup.M, —(CH.sub.2).sub.q—NR.sup.ER.sup.F, —(CH.sub.2).sub.q—OR.sup.M, —O(C═O)—NR.sup.ER.sup.F, or —NR.sup.M(C═O)—NR.sup.ER.sup.F, wherein R.sup.3C is attached at any one of positions labeled 1′, 2′, or 3′; [1038] each R.sup.A, R.sup.B, R.sup.c, R.sup.D, R.sup.E, R.sup.F, and R.sup.M are independently hydrogen or C.sub.1-6 alkyl; [1039] each subscript n is independently an integer from 0 to 6; [1040] each subscript q is independently an integer from 0 to 6; [1041] L.sup.E is —(C═O)— or —S(O).sub.2—; [1042] L.sup.C is —(CR.sup.IR.sup.J).sub.1-3— [1043] each R.sup.I and R.sup.J are independently hydrogen or C.sub.1-3 alkyl; [1044] subscript s is 0 or 1; [1045] each Cy.sup.1 is independently a 4-6 membered heterocycle, a 5-6 membered heteroaryl, or a C.sub.3-6 cycloalkyl, each optionally substituted with one or more R.sup.K; [1046] each R.sup.K is independently selected from the group consisting of: C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, ═O, —NR.sup.DR.sup.e2, —C(O)NR.sup.d2R.sup.e2, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl); [1047] each R.sup.d2 and R.sup.e2 are independently hydrogen or C.sub.1-3 alkyl; [1048] L.sup.AA is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, —C(O)NR.sup.L(CH.sub.2).sub.1-6—, —(CH.sub.2).sub.1-6O—, —C(O)(CH.sub.2).sub.1-6O—, or —C(O)NR.sup.L(CH.sub.2).sub.1-6O—; [1049] R.sup.L is hydrogen or C.sub.1-3 alkyl; [1050] Cy.sup.2 is C.sub.3-6 cycloalkyl, 4-6 membered heterocycle, 5-6 membered heteroaryl, or phenyl, each optionally substituted with one or more RU; [1051] each R.sup.U is independently selected from the group consisting of —CO.sub.2R.sup.j1, —(C═O)NR.sup.d3R.sup.e3, —S(O).sub.2NR.sup.d3R.sup.e3, —(CH.sub.2).sub.q1—NR.sup.g1R.sup.h1, —(CH.sub.2).sub.q1—OR.sup.j1, and —(CH.sub.2).sub.1i-(OCH.sub.2CH.sub.2).sub.1-8OH; [1052] each R.sup.d3, R.sup.e3, R.sup.g1, R.sup.h1, and R.sup.j1 are independently hydrogen or C.sub.1-6 alkyl; [1053] subscript q1 is an integer from 0 to 6; [1054] subscripts t1 and t2 are independently 0 or 1, wherein at least one of t1 and t2 is 1; [1055] L.sup.D is —(CH.sub.2).sub.1-6—; [1056] subscript u is 0 or 1; [1057] Z is —N(R.sup.HH)— or —N.sup.+(C.sub.1-6 alkyl)(R.sup.HH)—; [1058] R.sup.HH is hydrogen, C.sub.1-6 alkyl, C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.1-3 alkoxy, —(CH.sub.2).sub.1-3 4-6 membered heterocycle, or —(CH.sub.2).sub.1-3 5-6 membered heteroaryl; [1059] Y is a self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety; [1060] subscript y is 0 or 1; [1061] W is a chain of 1-12 amino acids or has the structure:

##STR00277## [1062] wherein Su is a Sugar moiety; [1063] —O.sup.A— represents a glycosidic bond; [1064] each R.sup.9 is independently hydrogen, halogen, —CN, or —NO.sub.2; [1065] W.sup.1 is absent or —O—C(═O)—; [1066] custom-character represents covalent attachment to L.sup.BB; [1067] * represents covalent attachment to Y, L.sup.D, NR.sup.HH, or Cy.sup.2; [1068] subscript w is 0 or 1; [1069] L.sup.BB is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, or —[NHC(O)(CH.sub.2).sub.1-4].sub.1-3—; and [1070] M is

##STR00278## [1071] each AA is an independently selected amino acid, wherein (AA).sub.b is connected to the succinimide or hydrolyzed succinimide via a sulfur atom; and [1072] each subscript b is independently an integer from 1 to 6. [1073] 217. The compound of Embodiment 216, wherein R.sup.1C is hydrogen. [1074] 218. The compound of Embodiment 216, wherein R.sup.1C is hydroxyl. [1075] 219. The compound of Embodiment 216, wherein R.sup.1C is C.sub.1-6 alkoxy. [1076] 220. The compound of Embodiment 216, wherein R.sup.1C is methoxy. [1077] 221. The compound of Embodiment 216, wherein R.sup.1C is —(C.sub.1-6 alkyl)C.sub.1-6 alkoxy. [1078] 222. The compound of Embodiment 216, wherein R.sup.1C is methoxyethyl. [1079] 223. The compound of Embodiment 216, wherein R.sup.1C is PEG2 to PEG4. [1080] 224. The compound of Embodiment 216, wherein R.sup.1C is —(CH.sub.2).sub.n—NR.sup.AR.sup.B. [1081] 225. The compound of any one of Embodiments 216-224, wherein R.sup.A and R.sup.B are both hydrogen. [1082] 226. The compound of any one of Embodiments 216-224, wherein R.sup.A

and R.sup.B are independently C.sub.1-3 alkyl. [1083] 227. The compound of any one of Embodiments 216-224, wherein one of R.sup.A and R.sup.B is hydrogen and the other of R.sup.A and R.sup.B is C.sub.1-3 alkyl. [1084] 228. The compound of any one of Embodiments 216-227, wherein each subscript n is 0. [1085] 229. The compound of any one of Embodiments 216-227, wherein each subscript n is 1. [1086] 230. The compound of any one of Embodiments 216-227, wherein each subscript n is 2. [1087] 231. The compound of any one of Embodiments 216-227, wherein each subscript n is 3, 4, 5, or 6. [1088] 232. The compound of any one of Embodiments 216-231, wherein R.sup.2C and R.sup.3C are independently —CO.sub.2H, —(C═O).sub.m—NR.sup.CR.sup.D, or —(CH.sub.2).sub.q—NR.sup.ER.sup.F; and R.sup.2C and R.sup.3C are the same. [1089] 233. The compound of any one of Embodiments 216-231, wherein R.sup.2C and R.sup.3C are independently —CO.sub.2H, —(C═O).sub.m—NR.sup.CR.sup.D, or —(CH.sub.2).sub.q—NR.sup.ER.sup.F; and R.sup.2C and R.sup.3C are different. [1090] 234. The compound of any one of Embodiments 216-231, wherein R.sup.2C is —(C═O).sub.m—NR.sup.CR.sup.D. [1091] 235. The compound of any one of Embodiments 216-231, wherein R.sup.3C is —(C═O).sub.m—NR.sup.CR.sup.D. [1092] 236. The compound of any one of Embodiments 216-235, wherein R.sup.C and R.sup.D are both hydrogen. [1093] 237. The compound of any one of Embodiments 216-235, wherein R.sup.C and R.sup.D are each independently C.sub.1-3 alkyl. [1094] 238. The compound of any one of Embodiments 216-235, wherein one of R.sup.C and R.sup.D is hydrogen and the other of R.sup.C and R.sup.D is C.sub.1-3 alkyl. [1095] 239. The compound of any one of Embodiments 216-238, wherein each subscript m is 0. [1096] 240. The compound of any one of Embodiments 216-238, wherein each subscript m is 1. [1097] 241. The compound of any one of Embodiments 216-240, wherein R.sup.2C is —(CH.sub.2).sub.q—NR.sup.ER.sup.F. [1098] 242. The compound of any one of Embodiments 216-241, wherein R.sup.3C is —(CH.sub.2).sub.q—NR.sup.ER.sup.F. [1099] 243. The compound of any one of Embodiments 216-242, wherein R.sup.E and R.sup.F are both hydrogen. [1100] 244. The compound of any one of Embodiments 216-242, wherein R.sup.E and R.sup.F are each independently C.sub.1-3 alkyl. [1101] 245. The compound of any one of Embodiments 216-242, wherein one of R.sup.E and R.sup.F is hydrogen and the other of R.sup.E and R.sup.F is C.sub.1-3 alkyl. [1102] 246. The compound of any one of Embodiments 216-245, wherein each subscript q is 0. [1103] 247. The compound of any one of Embodiments 216-245, wherein each subscript q is an integer from 1 to 6. [1104] 248. The compound of any one of Embodiments 216-247, wherein R.sup.2C is —CO.sub.2R.sup.M. [1105] 249. The compound of any one of Embodiments 216-248, wherein R.sup.3C is —CO.sub.2R.sup.M. [1106] 250. The compound of Embodiment 248 or 249, wherein R.sup.M is hydrogen. [1107] 251. The compound of Embodiment 248 or 249, wherein R.sup.M is C.sub.1-3 alkyl. [1108] 252. The compound of any one of Embodiments 216-247, wherein R.sup.2C is —(CH.sub.2).sub.q-OR.sup.M. [1109] 253. The compound of any one of Embodiments 216-247 and 252, wherein R.sup.3C is —(CH.sub.2).sub.q-OR.sup.M. [1110] 254. The compound of Embodiment 252 or 253, wherein R.sup.M is hydrogen. [1111] 255. The compound of any one of Embodiments 252-254, wherein q is 0. [1112] 256. The compound of any one of Embodiments 252-254, wherein q is 1. [1113] 257. The compound of any one of Embodiments 216-247, wherein R.sup.2C is —O(C═O)—NR.sup.ER.sup.F. [1114] 258. The compound of any one of Embodiments 216-247 and 257, wherein R.sup.3C is —O(C═O)—NR.sup.ER.sup.F. [1115] 259. The compound of any one of Embodiments 216-258, wherein R.sup.E and R.sup.F are both hydrogen. [1116] 260. The compound of any one of Embodiments 216-258, wherein R.sup.E and R.sup.F are each independently C.sub.1-3 alkyl. [1117] 261. The compound of any one of Embodiments 216-258, wherein one of R.sup.E and R.sup.F is hydrogen and the other of R.sup.E and R.sup.F is C.sub.1-3 alkyl. [1118] 262. The compound of any one of Embodiments 216-247, wherein R.sup.2C is —NR.sup.M(C═O)—NR.sup.ER.sup.F. [1119] 263. The compound of any one of Embodiments 216-247 and 262, wherein R.sup.3C is —NR.sup.M(C═O)—NR.sup.ER.sup.F. [1120] 264. The compound of Embodiment 262 or 263,

wherein R.sup.E, R.sup.F, and R.sup.M are all hydrogen. [1121] 265. The compound of Embodiment 262 or 263, wherein R.sup.E, R.sup.F, and R.sup.M are each independently C.sub.1-3 alkyl. [1122] 266. The compound of Embodiment 262 or 263, wherein one of R.sup.E, R.sup.F, and R.sup.M is C.sub.1-3 alkyl and the rest of R.sup.E, R.sup.F, and R.sup.M is hydrogen. [1123] 267. The compound of any one of Embodiments 216-247, wherein R.sup.2C is —S(O).sub.2NR.sup.cR.sup.D. [1124] 268. The compound of any one of Embodiments 216-247 and 267, wherein R.sup.3C is —S(O).sub.2NR.sup.CR.sup.D. [1125] 269. The compound of Embodiment 267 or 268, wherein R.sup.C and R.sup.D are both hydrogen. [1126] 270. The compound of Embodiment 267 or 268, wherein R.sup.C and R.sup.D are each independently C.sub.1-3 alkyl. [1127] 271. The compound of Embodiment 267 or 268, wherein one of R.sup.C and R.sup.D is hydrogen and the other of R.sup.C and R.sup.D is C.sub.1-3 alkyl. [1128] 272. The compound of any one of Embodiments 216-247, wherein R.sup.2C is —S(O).sub.2R.sup.M. [1129] 273. The compound of any one of Embodiments 216-247 and 272, wherein R.sup.3C is —S(O).sub.2R.sup.M. [1130] 274. The compound of Embodiment 272 or 273, wherein R.sup.M is hydrogen. [1131] 275. The compound of Embodiment 272 or 273, wherein R.sup.M is C.sub.1-3 alkyl. [1132] 276. The compound of any one of Embodiments 216-275, wherein R.sup.2C is attached at position 1. [1133] 277. The compound of any one of Embodiments 216-275, wherein R.sup.2C is attached at position 2. [1134] 278. The compound of any one of Embodiments 216-275, wherein R.sup.2C is attached at position 3. [1135] 279. The compound of any one of Embodiments 216-275, wherein R.sup.3C is attached at position 1′. [1136] 280. The compound of any one of Embodiments 216-275, wherein R.sup.3C is attached at position 2′. [1137] 281. The compound of any one of Embodiments 216-275, wherein R.sup.3C is attached at position 3′. [1138] 282. The compound of any one of Embodiments 216-281, wherein L.sup.E is —(C═O)—. [1139] 283. The compound of any one of Embodiments 216-281, wherein L.sup.E is —S(O).sub.2—. [1140] 284. The compound of any one of Embodiments 216-283, wherein each R.sup.I and R.sup.J is hydrogen. [1141] 285. The compound of any one of Embodiments 216-283, wherein each R.sup.I and R.sup.J is C.sub.1-3 alkyl. [1142] 286. The compound of any one of Embodiments 216-283, wherein one of R.sup.I and R.sup.J is hydrogen and the other of R.sup.I and R.sup.J is C.sub.1-3 alkyl. [1143] 287. The compound of any one of Embodiments 216-286, wherein L.sup.C is —(CR.sup.IR.sup.J)—. [1144] 288. The compound of any one of Embodiments 216-287, wherein s is 0. [1145] 289. The compound of any one of Embodiments 216-287, wherein s is 1. [1146] 290. The compound of any one of Embodiments 216-289, wherein each Cy.sup.1 is independently a 5-6 membered heteroaryl. [1147] 291. The compound of any one of Embodiments 216-289, wherein each Cy.sup.1 is pyrazole optionally substituted with one or more R.sup.K. [1148] 292. The compound of any one of Embodiments 216-289, wherein each Cy.sup.1 is independently selected from the group consisting of pyrazole, imidazole, furan, thiophene, thiazole, isothiazole, oxazole, isoxazole, pyrrole, pyridazine, pyridine, pyrimidine, and pyrazine, each optionally substituted with one or more R.sup.K. [1149] 293. The compound of any one of Embodiments 216-289, wherein each Cy.sup.1 is independently selected from the group consisting of imidazole, furan, thiophene, thiazole, isothiazole, oxazole, isoxazole, pyrrole, pyridazine, pyridine, pyrimidine, and pyrazine, each optionally substituted with one or more R.sup.K. [1150] 294. The compound of any one of Embodiments 216-289, wherein each Cy.sup.1 is independently a C.sub.4-5 cycloalkyl optionally substituted with one or more R.sup.K. [1151] 295. The compound of any one of Embodiments 216-294, wherein each R.sup.K is independently selected from the group consisting of C.sub.1-3 alkyl, C.sub.1-3 haloalkyl, and halogen. [1152] 296. The compound of Embodiment 295, wherein each R.sup.K is independently selected from the group consisting of methyl, ethyl, —CF.sub.3, and halogen. [1153] 297. The compound of any one of Embodiments 216-296, wherein each Cy.sup.1 is the same. [1154] 298. The compound of any one of Embodiments 216-296, wherein each Cy.sup.1 is different. [1155] 299. The compound of any one of Embodiments 216-298, wherein L.sup.AA is —(CH.sub.2).sub.1-6—. [1156] 300. The

compound of any one of Embodiments 216-298, wherein L.sup.AA is —(CH.sub.2).sub.1-3—. [1157] 301. The compound of any one of Embodiments 216-298, wherein L.sup.AA is —(CH.sub.2).sub.1-6O—. [1158] 302. The compound of any one of Embodiments 216-298, wherein L.sup.AA is —(CH.sub.2).sub.1-3O—. [1159] 303. The compound of any one of Embodiments 216-302, wherein Cy.sup.2 is a 4-6 membered heterocycle. [1160] 304. The compound of any one of Embodiments 216-302, wherein Cy.sup.2 has the structure:

##STR00279##

wherein each of subscripts z1 and z2 is independently an integer from 1 to 3 and ** indicates attachment to L.sup.AA. [1161] 305. The compound of Embodiment 304, wherein z1 and z2 are 1. [1162] 306. The compound of Embodiment 304, wherein z1 and z2 are 2. [1163] 307. The compound of Embodiment 304, wherein z1 is 1 and z2 is 2. [1164] 308. The compound of any one of Embodiments 216-302, wherein Cy.sup.2 has the structure:

##STR00280##

wherein [1165] Z.sup.1 is selected from the group consisting of —O—, —S—, —CR.sup.NR.sup.O—, and —NR.sup.P—; R.sup.N, R.sup.O, and R.sup.P are independently hydrogen or C.sub.1-6 alkyl; [1166] subscript z3 is an integer from 1 to 3; and [1167] ** indicates attachment to L.sup.AA. [1168] 309. The compound of Embodiment 308, wherein R.sup.N and R.sup.O are hydrogen. [1169] 310. The compound of Embodiment 308, wherein R.sup.P is hydrogen. [1170] 311. The compound of Embodiment 308, wherein R.sup.P is methyl. [1171] 312. The compound of any one of Embodiments 216-302, wherein Cy.sup.2 is a 5-6 membered heteroaryl. [1172] 313. The compound of any one of Embodiments 216-302, wherein Cy.sup.2 is selected from the group consisting of:

##STR00281##

wherein [1173] Z.sup.2 is ═CR.sup.N— or ═N—; [1174] R.sup.N is hydrogen or C.sub.1-6 alkyl; and [1175] ** indicates attachment to L.sup.AA. [1176] 314. The compound of Embodiment 313, wherein Z.sup.2 is ═CR.sup.N—. [1177] 315. The compound of Embodiment 314, wherein R.sup.N is hydrogen. [1178] 316. The compound of Embodiment 313, wherein Z.sup.2 is ═N—. [1179] 317. The compound of any one of Embodiments 216-302, wherein Cy.sup.2 is selected from the group consisting of:

##STR00282##

wherein Z.sup.3 is —O— or —S— and ** indicates attachment to L.sup.AA, L.sup.D, NR.sup.HH, Y, W, or L.sup.BB. [1180] 318. The compound of Embodiment 317, wherein ** indicates attachment to L.sup.AA. [1181] 319. The compound of Embodiment 317, wherein ** indicates attachment to L.sup.D, NR.sup.HH, Y, W, or L.sup.BB. [1182] 320. The compound of any one of Embodiments 216-302, wherein Cy.sup.2 is selected from the group consisting of:

##STR00283##

wherein ** indicates attachment to L.sup.AA. [1183] 321. The compound of any one of Embodiments 216-302, wherein Cy.sup.2 is selected from the group consisting of:

##STR00284##

wherein [1184] each Z.sup.2 is independently ═CR.sup.N— or ═N—; and [1185] each R.sup.N is hydrogen or C.sub.1-6 alkyl. [1186] 322. The compound of Embodiment 321, wherein at least one Z.sup.2 is ═N—. [1187] 323. The compound of Embodiment 321, wherein one Z.sup.2 is ═N— and the remaining Z.sup.2 are ═CR.sup.N—. [1188] 324. The compound of Embodiment 321, wherein two Z.sup.2 are —═N— and the remaining Z.sup.2 are ═CR.sup.N—. [1189] 325. The compound of any one of Embodiments 321, 323, and 324, wherein R.sup.N is hydrogen. [1190] 326. The compound of any one of Embodiments 216-302, wherein Cy.sup.2 is

##STR00285## [1191] 327. The compound of any one of Embodiments 216-302, wherein Cy.sup.2 is

##STR00286## [1192] 328. The compound of any one of Embodiments 216-302, wherein Cy.sup.2 is

##STR00287## [1193] 329. The compound of any one of Embodiments 216-302, wherein Cy.sup.2 is cyclobutyl. [1194] 330. The compound of any one of Embodiments 216-329, wherein each R.sup.d3, R.sup.e3, R.sup.g1, R.sup.h1, and R.sup.j1 are independently hydrogen or —CH.sub.3. [1195] 331. The compound of any one of Embodiments 216-330, wherein each Ru is independently selected from —CO.sub.2H, —(C═O)NH.sub.2, —S(O).sub.2NH.sub.2, —CH.sub.2NH.sub.2, and —CH.sub.2OH. [1196] 332. The compound of any one of Embodiments 216-331, wherein t1 is 0 and t2 is 1. [1197] 333. The compound of any one of Embodiments 216-331, wherein t1 is 1 and t2 is 0. [1198] 334. The compound of any one of Embodiments 216-331, wherein t1 is 1 and t2 is 1. [1199] 335. The compound of any one of Embodiments 216-334, wherein u is 1 and L.sup.D is —(CH.sub.2).sub.1-3—. [1200] 336. The compound of any one of Embodiments 216-334, wherein u is 0. [1201] 337. The compound of any one of Embodiments 216-331, wherein t2 is 1 and R.sup.HH is hydrogen. [1202] 338. The compound of any one of Embodiments 216-331, wherein t2 is 1 and R.sup.HH is C.sub.1-3 alkyl. [1203] 339. The compound of any one of Embodiments 216-331, wherein t2 is 1 and R.sup.HH is C.sub.3-4 cycloalkyl. [1204] 340. The compound of any one of Embodiments 216-331, wherein t2 is 1 and R.sup.HH is —(CH.sub.2) C.sub.3-4 cycloalkyl. [1205] 341. The compound of any one of Embodiments 216-331, wherein t2 is 1 and R.sup.HH is —(CH.sub.2) 4-5 membered heterocycle. [1206] 342. The compound of any one of Embodiments 216-331, wherein t2 is 1 and R.sup.HH is —(CH.sub.2) 5-membered heteroaryl. [1207] 343. The compound of any one of Embodiments 216-331 and 333-342, wherein Z is —N(R.sup.HH)—. [1208] 344. The compound of any one of Embodiments 216-343, wherein Y is
##STR00288## [1209] 345. The compound of any one of Embodiments 216-343, wherein Y is a cyclohexanecarboxyl, undecanoyl, caproyl, hexanoyl, butanoyl or propionyl group. [1210] 346. The compound of any one of Embodiments 216-343, wherein Y is PEG4 to PEG12. [1211] 347. The compound of any one of Embodiments 216-343, wherein y is 0. [1212] 348. The compound of any one of Embodiments 216-346, wherein y is 1. [1213] 349. The compound of any one of Embodiments 216-348, wherein W is a chain of 1-12 amino acids. [1214] 350. The compound of any one of Embodiments 216-348, wherein W is a chain of 1-6 amino acids. [1215] 351. The compound of any one of Embodiments 216-348, wherein W is a chain of 1-3 amino acids. [1216] 352. The compound of Embodiment 216-351, wherein each amino acid of W is independently selected from the group consisting of alanine, valine, isoleucine, leucine, aspartic acid, glutamic acid, lysine, histidine, arginine, glycine, serine, threonine, phenylalanine, O-methylserine, O-methylaspartic acid, O-methylglutamic acid, N-methyllysine, O-methyltyrosine, O-methylhistidine, and O-methylthreonine. [1217] 353. The compound of any one of Embodiments 216-351, wherein each amino acid in W is independently selected from the group consisting of alanine, glycine, lysine, serine, aspartic acid, aspartate methyl ester, N,N-dimethyl-lysine, phenylalanine, citrulline, valine-alanine, valine-citrulline, phenylalanine-lysine or homoserine methyl ether. [1218] 354. The compound of any one of Embodiments 216-348, wherein W has the structure:
##STR00289## [1219] 355. The compound of Embodiment 354, wherein W.sup.1 is —O—C(═O)—. [1220] 356. The compound of Embodiment 354 or 355, wherein one R.sup.9 is halogen, —CN, or —NO.sub.2, and the remaining R.sup.G are hydrogen. [1221] 357. The compound of Embodiment 354 or 355, wherein each R.sup.9 is hydrogen. [1222] 358. The compound of any one of Embodiments 216-348, wherein w is 0. [1223] 359. The compound of any one of Embodiments 216-348, wherein w is 1. [1224] 360. The compound of any one of Embodiments 216-359, wherein L.sup.11 is —(CH.sub.2).sub.1-3—. [1225] 361. The compound of any one of Embodiments 216-359, wherein L.sup.BB is C(O)(CH.sub.2).sub.1-2—. [1226] 362. The compound of Embodiment 361, wherein L.sup.BB is —C(O)(CH.sub.2).sub.2—. [1227] 363. The compound of any one of Embodiments 216-359, wherein L.sup.BB is —[NHC(O)(CH.sub.2).sub.2].sub.1-2—. [1228] 364. The compound of Embodiment 363, wherein L.sup.BB is [NHC(O)(CH.sub.2).sub.2].sub.2. [1229] 365. The compound of any one of Embodiments 216-364, wherein M is
##STR00290## [1230] 366. The compound of any one of Embodiments 216-364, wherein M is

##STR00291## [1231] 367. The compound of any one of Embodiments 216-364, wherein M is
##STR00292## [1232] 368. The compound of any one of Embodiments 216-367, wherein each AA is independently a natural amino acid; wherein (AA).sub.b is connected to the succinimide or hydrolyzed succinimide via a sulfur atom. [1233] 369. The compound of any one of Embodiments 216-367, wherein each AA is independently a natural amino acid; wherein (AA).sub.b is connected to the succinimide or hydrolyzed succinimide via a nitrogen atom. [1234] 370. The compound of any one of Embodiments 216-369, wherein each subscript b is 1. [1235] 371. The compound of any one of Embodiments 216-369, wherein each subscript b is 2. [1236] 372. The compound of any one of Embodiments 216-369, wherein each subscript b is 3, 4, 5, or 6. [1237] 373. The compound of any one of Embodiments 216-365, wherein M is
##STR00293## [1238] 374. The compound of any one of Embodiments 216-364, wherein M is
##STR00294## [1239] 375. The compound of any one of Embodiments 216-364, wherein M is
##STR00295## [1240] 376. The compound of any one of Embodiments 216-364, wherein M is
##STR00296## [1241] 377. The compound of Embodiment 216, selected from the group consisting of:
##STR00297## ##STR00298## ##STR00299## ##STR00300## ##STR00301## ##STR00302## ##STR00303## ##STR00304## ##STR00305## ##STR00306## ##STR00307## ##STR00308## ##STR00309## ##STR00310## ##STR00311## ##STR00312## ##STR00313## ##STR00314## ##STR00315## ##STR00316## ##STR00317## ##STR00318## ##STR00319## ##STR00320##
##STR00321## ##STR00322## ##STR00323## ##STR00324## ##STR00325## ##STR00326##
and pharmaceutically acceptable salts thereof. [1242] 378. A compound having the structure of Formula (V):
##STR00327##
or a pharmaceutically acceptable salt thereof, wherein: [1243] R.sup.1C is hydrogen, hydroxyl, C.sub.1-6 alkoxy, —(C.sub.1-6 alkyl) C.sub.1-6 alkoxy, —(CH.sub.2).sub.n—NR.sup.AR.sup.B, or PEG2 to PEG4; [1244] R.sup.2C is —CO.sub.2R.sup.M, —(C═O)NR.sup.CR.sup.D, —S(O).sub.2NR.sup.CR.sup.D, —S(O).sub.2R.sup.M, —(CH.sub.2).sub.q—NR.sup.ER.sup.F, —(CH.sub.2).sub.q—OR.sup.M, —O(C═O)—NR.sup.ER.sup.F, or —NR.sup.M(C═O)—NR.sup.ER.sup.N, wherein R.sup.2C is attached at any one of positions labeled 1, 2, or 3; [1245] R.sup.3C is —CO.sub.2R.sup.M, —(C═O)NR.sup.CR.sup.D, —S(O).sub.2NR.sup.CR.sup.D, —S(O).sub.2R.sup.M, —(CH.sub.2).sub.q—NR.sup.ER.sup.F, —(CH.sub.2).sub.q—OR.sup.M, —O(C═O)—NR.sup.ER.sup.F, or —NR.sup.M(C═O)—NR.sup.ER.sup.F, wherein R.sup.3C is attached at any one of positions labeled 1′, 2′, or 3′; [1246] each R.sup.A, R.sup.B, R.sup.c, R.sup.D, R.sup.E, R.sup.F, and R.sup.M are independently hydrogen or C.sub.1-6 alkyl; [1247] each subscript n is independently an integer from 0 to 6; [1248] each subscript q is independently an integer from 0 to 6; [1249] L.sup.E is —(C═O)— or —S(O).sub.2—; [1250] L.sup.C is —(CR.sup.IR.sup.J).sub.1-3— [1251] each R.sup.I and R.sup.J are independently hydrogen or C.sub.1-3 alkyl; [1252] subscript s is 0 or 1; [1253] each Cy.sup.1 is independently a 4-6 membered heterocycle, a 5-6 membered heteroaryl, or a C.sub.3-6 cycloalkyl, each optionally substituted with one or more R.sup.K; [1254] each R.sup.K is independently selected from the group consisting of: C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, ═O, —NR.sup.d2R.sup.e2, —C(O)NR.sup.d2R.sup.e2, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl); [1255] each R.sup.d2 and R.sup.e2 are independently hydrogen or C.sub.1-3 alkyl; [1256] L.sup.AA is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, —C(O)NR.sup.L(CH.sub.2).sub.1-6—, —(CH.sub.2).sub.1-6O—, —C(O)(CH.sub.2).sub.1-6O—, or —C(O)NR.sup.L(CH.sub.2).sub.1-6O—; [1257] R.sup.L is hydrogen or C.sub.1-3 alkyl; [1258] Cy.sup.2 is C.sub.3-6 cycloalkyl, 4-6 membered heterocycle, 5-6 membered heteroaryl, or phenyl, each optionally substituted with one or more RU; [1259] each R.sup.U is independently selected from the group consisting of —CO.sub.2R.sup.j1, —(C═O)NR.sup.d3R.sup.e3, —

S(O).sub.2NR.sup.d3R.sup.e3, —(CH.sub.2).sub.q1—NR.sup.g1R.sup.h1, —(CH.sub.2).sub.q1—OR.sup.j1, and —(CH.sub.2).sub.q1—(OCH.sub.2CH.sub.2).sub.1-8OH; [1260] each R.sup.d3, R.sup.e3, R.sup.9, R.sup.h1, and R.sup.j1 are independently hydrogen or C.sub.1-6 alkyl; [1261] subscript q1 is an integer from 0 to 6; [1262] subscript t1 is 0 or 1; [1263] L.sup.D is —(CH.sub.2).sub.1-6—; [1264] subscript u is 0 or 1; [1265] when t1 is 0, ZZ is —NR.sup.QR.sup.R, —N.sup.+(C.sub.1-6 alkyl)R.sup.QR.sup.R, —C(═O)N.sup.SR.sup.T, —C(O)O(C.sub.1-6 alkyl), —CO.sub.2H, or an amino acid, or when t1 is 1, ZZ is hydrogen, —NR.sup.QR.sup.R, —N.sup.+(C.sub.1-6 alkyl)R.sup.QR.sup.R; —C(═O)N.sup.SR.sup.T, —C(O)O(C.sub.1-6 alkyl), —CO.sub.2H, or an amino acid; [1266] R.sup.Q is hydrogen, C.sub.1-6 alkyl, C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.1-3 alkoxy, —(CH.sub.2).sub.1-3 4-6 membered heterocycle, or —(CH.sub.2).sub.1-3 5-6 membered heteroaryl, provided that [1267] if t1 is 0 and both Cy.sup.1 are

##STR00328##

then R.sup.Q is C.sub.2-6 alkyl, C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.1-3 alkoxy, —(CH.sub.2).sub.1-3 4-6 membered heterocycle, or —(CH.sub.2).sub.1-3 5-6 membered heteroaryl, and [1268] if t1 is 0 and at least one Cy.sup.1 is not

##STR00329##

then ZZ is —NR.sup.QR.sup.R,—N+(C.sub.1-6 alkyl)R.sup.QR.sup.R, or —C(═O)N.sup.SR.sup.T, and R.sup.Q is C.sub.1-6 alkyl, C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.3-6cycloalkyl, —(CH.sub.2).sub.1-3C.sub.1-3 alkoxy, —(CH.sub.2).sub.1-3 4-6 membered heterocycle, or —(CH.sub.2).sub.1-3 5-6 membered heteroaryl; and [1269] each R.sup.R, R.sup.S, and R.sup.T are independently hydrogen or C.sub.1-6 alkyl. [1270] 379. The compound of Embodiment 378, wherein R.sup.1C is hydrogen. [1271] 380. The compound of Embodiment 378, wherein R.sup.1C is hydroxyl. [1272] 381. The compound of Embodiment 378, wherein R.sup.1C is C.sub.1-6 alkoxy. [1273] 382. The compound of Embodiment 378, wherein R.sup.1C is methoxy. [1274] 383. The compound of Embodiment 378, wherein R.sup.1C is —(C.sub.1-6 alkyl)C.sub.1-6 alkoxy. [1275] 384. The compound of Embodiment 378, wherein R.sup.1C is methoxyethyl. [1276] 385. The compound of Embodiment 378, wherein R.sup.1C is PEG2 to PEG4. [1277] 386. The compound of Embodiment 378, wherein R.sup.1C is —(CH.sub.2).sub.n—NR.sup.AR.sup.B. [1278] 387. The compound of any one of Embodiments 378-386, wherein R.sup.A and R.sup.B are both hydrogen. [1279] 388. The compound of any one of Embodiments 378-386, wherein R.sup.A and R.sup.B are independently C.sub.1-3 alkyl. [1280] 389. The compound of any one of Embodiments 378-386, wherein one of R.sup.A and R.sup.B is hydrogen and the other of R.sup.A and R.sup.B is C.sub.1-3 alkyl. [1281] 390. The compound of any one of Embodiments 378-389, wherein each subscript n is 0. [1282] 391. The compound of any one of Embodiments 378-389, wherein each subscript n is 1. [1283] 392. The compound of any one of Embodiments 378-389, wherein each subscript n is 2. [1284] 393. The compound of any one of Embodiments 378-389, wherein each subscript n is 3, 4, 5, or 6. [1285] 394. The compound of any one of Embodiments 378-393, wherein R.sup.2C and R.sup.3C are independently —CO.sub.2H, —(C═O).sub.m—NR.sup.CR.sup.D, or —(CH.sub.2).sub.q—NR.sup.ER.sup.F; and R.sup.2C and R.sup.3C are the same. [1286] 395. The compound of any one of Embodiments 378-393, wherein R.sup.2C and R.sup.3C are independently —C.sub.02H, —(C═O).sub.m—NR.sup.CR.sup.D, or —(CH.sub.2).sub.q—NR.sup.ER.sup.F; and R.sup.2C and R.sup.3C are different. [1287] 396. The compound of any one of Embodiments 378-393, wherein R.sup.2C is —(C═O).sub.m—NR.sup.CR.sup.D. [1288] 397. The compound of any one of Embodiments 378-396, wherein R.sup.3C is —(C═O).sub.m—NR.sup.CR.sup.D. [1289] 398. The compound of any one of Embodiments 378-397, wherein R.sup.C and R.sup.D are both hydrogen. [1290] 399. The compound of any one of Embodiments 378-397, wherein R.sup.C and R.sup.D are each independently C.sub.1-3 alkyl. [1291] 400. The compound of any one of Embodiments 378-397, wherein one of R.sup.C and R.sup.D is hydrogen and the other of R.sup.C and R.sup.D is C.sub.1-

3 alkyl. [1292] 401. The compound of Embodiment 396 or 397, wherein each subscript m is 0. [1293] 402. The compound of Embodiment 396 or 397, wherein each subscript m is 1. [1294] 403. The compound of any one of Embodiments 378-393, wherein R.sup.2C is —(CH.sub.2).sub.q—NR.sup.ER.sup.F. [1295] 404. The compound of any one of Embodiments 378-393 and 403, wherein R.sup.3C is —(CH.sub.2).sub.q—NR.sup.ER.sup.F. [1296] 405. The compound of any one of Embodiments 378-404, wherein R.sup.E and R.sup.F are both hydrogen. [1297] 406. The compound of any one of Embodiments 378-404, wherein R.sup.E and R.sup.F are each independently C.sub.1-3 alkyl. [1298] 407. The compound of any one of Embodiments 378-404, wherein one of R.sup.E and R.sup.F is hydrogen and the other of R.sup.E and R.sup.F is C.sub.1-3 alkyl. [1299] 408. The compound of any one of Embodiments 378-407, wherein each subscript q is 0. [1300] 409. The compound of any one of Embodiments 378-407, wherein each subscript q is an integer from 1 to 6. [1301] 410. The compound of any one of Embodiments 378-393, wherein R.sup.2C is —CO.sub.2R.sup.M. [1302] 411. The compound of any one of Embodiments 378-393 and 410, wherein R.sup.3C is —CO.sub.2R.sup.M. [1303] 412. The compound of Embodiment 410 or 411, wherein R.sup.M is hydrogen. [1304] 413. The compound of Embodiment 410 or 411, wherein R.sup.M is C.sub.1-3 alkyl. [1305] 414. The compound of any one of Embodiments 378-393, wherein R.sup.2C is —(CH.sub.2).sub.q—OR.sup.M. [1306] 415. The compound of any one of Embodiments 378-393 and 414, wherein R.sup.3C is —(CH.sub.2).sub.q—OR.sup.M. [1307] 416. The compound of Embodiment 414 or 415, wherein R.sup.M is hydrogen. [1308] 417. The compound of any one of Embodiments 414-415, wherein q is 0. [1309] 418. The compound of any one of Embodiments 414-415, wherein q is 1. [1310] 419. The compound of any one of Embodiments 378-393, wherein R.sup.2C is —O(C═O)—NR.sup.ER.sup.F. [1311] 420. The compound of any one of Embodiments 378-393 and 419, wherein R.sup.3C is —O(C═O)—NR.sup.ER.sup.F. [1312] 421. The compound of Embodiment 419 or 420, wherein R.sup.E and R.sup.F are both hydrogen. [1313] 422. The compound of Embodiment 419 or 420, wherein R.sup.E and R.sup.F are each independently C.sub.1-3 alkyl. [1314] 423. The compound of Embodiment 419 or 420, wherein one of R.sup.E and R.sup.F is hydrogen and the other of R.sup.E and R.sup.F is C.sub.1-3 alkyl. [1315] 424. The compound of any one of Embodiments 378-393, wherein R.sup.2C is —NR.sup.M(C═O)—NR.sup.ER.sup.F. [1316] 425. The compound of any one of Embodiments 378-393 and 424, wherein R.sup.3C is —NR.sup.M(C═O)—NR.sup.ER.sup.F. [1317] 426. The compound of Embodiment 424 or 425, wherein R.sup.E, R.sup.F, and R.sup.M are all hydrogen. [1318] 427. The compound of Embodiment 424 or 425, wherein R.sup.E, R.sup.F, and R.sup.M are each independently C.sub.1-3 alkyl. [1319] 428. The compound of Embodiment 424 or 425, wherein one of R.sup.E, R.sup.F, and R.sup.M is C.sub.1-3 alkyl and the rest of R.sup.E, R.sup.F, and R.sup.m is hydrogen. [1320] 429. The compound of any one of Embodiments 378-393, wherein R.sup.2C is —S(O).sub.2NR.sup.cR.sup.D. [1321] 430. The compound of any one of Embodiments 378-393 and 429, wherein R.sup.3C is —S(O).sub.2NR.sup.CR.sup.D. [1322] 431. The compound of Embodiment 429 or 430, wherein R.sup.C and R.sup.D are both hydrogen. [1323] 432. The compound of Embodiment 429 or 430, wherein R.sup.C and R.sup.D are each independently C.sub.1-3 alkyl. [1324] 433. The compound of Embodiment 429 or 430, wherein one of R.sup.C and R.sup.D is hydrogen and the other of R.sup.C and R.sup.D is C.sub.1-3 alkyl. [1325] 434. The compound of any one of Embodiments 378-393, wherein R.sup.2C is —S(O).sub.2R.sup.M. [1326] 435. The compound of any one of Embodiments 378-393 and 434, wherein R.sup.3C is —S(O).sub.2R.sup.M. [1327] 436. The compound of Embodiment 434 or 435, wherein R.sup.M is hydrogen. [1328] 437. The compound of Embodiment 434 or 435, wherein R.sup.M is C.sub.1-3 alkyl. [1329] 438. The compound of any one of Embodiments 378-437, wherein R.sup.2C is attached at position 1. [1330] 439. The compound of any one of Embodiments 378-437, wherein R.sup.2C is attached at position 2. [1331] 440. The compound of any one of Embodiments 378-437, wherein R.sup.2C is attached at position 3. [1332] 441. The compound of any one of Embodiments 378-437, wherein R.sup.3C is attached

at position 1′. [1333] 442. The compound of any one of Embodiments 378-437, wherein R.sup.3C is attached at position 2′. [1334] 443. The compound of any one of Embodiments 378-437, wherein R.sup.3C is attached at position 3′. [1335] 444. The compound of any one of Embodiments 378-443, wherein L.sup.E is —(C═O)—. [1336] 445. The compound of any one of Embodiments 378-443, wherein L.sup.E is —S(O).sub.2—. [1337] 446. The compound of any one of Embodiments 378-445, wherein each R.sup.I and R.sup.J is hydrogen. [1338] 447. The compound of any one of Embodiments 378-445, wherein each R.sup.I and R.sup.J is C.sub.1-3 alkyl. [1339] 448. The compound of any one of Embodiments 378-445, wherein one of R.sup.I and R.sup.J is hydrogen and the other of R.sup.I and R.sup.J is C.sub.1-3 alkyl. [1340] 449. The compound of any one of Embodiments 378-448, wherein L.sup.C is —(CR.sup.IR.sup.J)—. [1341] 450. The compound of any one of Embodiments 378-449, wherein s is 0. [1342] 451. The compound of any one of Embodiments 378-449, wherein s is 1. [1343] 452. The compound of any one of Embodiments 378-451, wherein each Cy.sup.1 is independently a 5-6 membered heteroaryl. [1344] 453. The compound of any one of Embodiments 378-451, wherein each Cy.sup.i is pyrazole optionally substituted with one or more R.sup.K. [1345] 454. The compound of any one of Embodiments 378-451, wherein each Cy.sup.1 is independently selected from the group consisting of pyrazole, imidazole, furan, thiophene, thiazole, isothiazole, oxazole, isoxazole, pyrrole, pyridazine, pyridine, pyrimidine, and pyrazine, each optionally substituted with one or more R.sup.K. [1346] 455. The compound of any one of Embodiments 378-451, wherein each Cy.sup.i is independently selected from the group consisting of imidazole, furan, thiophene, thiazole, isothiazole, oxazole, isoxazole, pyrrole, pyridazine, pyridine, pyrimidine, and pyrazine, each optionally substituted with one or more R.sup.K. [1347] 456. The compound of any one of Embodiments 378-451, wherein each Cy.sup.1 is independently a C.sub.4-5 cycloalkyl optionally substituted with one or more R.sup.K. [1348] 457. The compound of any one of Embodiments 378-456, wherein each R.sup.K is independently selected from the group consisting of C.sub.1-3 alkyl, C.sub.1-3 haloalkyl, and halogen. [1349] 458. The compound of Embodiment 457, wherein each R.sup.K is independently selected from the group consisting of methyl, ethyl, —CF.sub.3, and halogen. [1350] 459. The compound of any one of Embodiments 378-451, wherein each Cy.sup.1 is the same. [1351] 460. The compound of any one of Embodiments 378-451, wherein each Cy.sup.1 is different. [1352] 461. The compound of any one of Embodiments 378-460, wherein L.sup.AA is —(CH.sub.2).sub.1-6—. [1353] 462. The compound of any one of Embodiments 378-460, wherein L.sup.AA is —(CH.sub.2).sub.1-3—. [1354] 463. The compound of any one of Embodiments 378-460, wherein L.sup.AA is —(CH.sub.2).sub.1-6O—. [1355] 464. The compound of any one of Embodiments 378-460, wherein L.sup.AA is —(CH.sub.2).sub.1-3O—. [1356] 465. The compound of any one of Embodiments 378-464, wherein Cy.sup.2 is a 4-6 membered heterocycle. [1357] 466. The compound of any one of Embodiments 378-464, wherein Cy.sup.2 has the structure:

##STR00330##

wherein each of subscripts z1 and z2 is independently an integer from 1 to 3 and ** indicates attachment to L.sup.AA [1358] 467. The compound of Embodiment 466, wherein z1 and z2 are 1. [1359] 468. The compound of Embodiment 466, wherein z1 and z2 are 2. [1360] 469. The compound of Embodiment 466, wherein z1 is 1 and z2 is 2. [1361] 470. The compound of any one of Embodiments 378-464, wherein Cy.sup.2 has the structure:

##STR00331##

wherein [1362] Z.sup.1 is selected from the group consisting of —O—, —S—, —CR.sup.NR.sup.O—, and —NR.sup.P—; [1363] R.sup.N, R.sup.O, and R.sup.P are independently hydrogen or C.sub.1-6 alkyl; subscript z3 is an integer from 1 to 3; and [1364] ** indicates attachment to L.sup.AA [1365] 471. The compound of Embodiment 470, wherein R.sup.N and R.sup.O are hydrogen. [1366] 472. The compound of Embodiment 470, wherein R.sup.P is hydrogen. [1367] 473. The compound of Embodiment 470, wherein R.sup.P is methyl. [1368] 474.

The compound of any one of Embodiments 378-464, wherein Cy.sup.2 is a 5-6 membered heteroaryl. [1369] 475. The compound of any one of Embodiments 378-464, wherein Cy.sup.2 is selected from the group consisting of:
##STR00332##
wherein [1370] Z.sup.2 is ═CR.sup.N— or ═N—; [1371] R.sup.N is hydrogen or C.sub.1-6 alkyl; and [1372] ** indicates attachment to L.sup.AA. [1373] 476. The compound of Embodiment 475, wherein Z.sup.2 is ═CR.sup.N—. [1374] 477. The compound of Embodiment 476, wherein R.sup.N is hydrogen. [1375] 478. The compound of Embodiment 475, wherein Z.sup.2 is ═N—. [1376] 479. The compound of any one of Embodiments 378-464, wherein Cy.sup.2 is selected from the group consisting of:
##STR00333##
wherein Z.sup.3 is —O— or —S— and ** indicates attachment to L.sup.AA, L.sup.D, NR.sup.HH, Y, W, or L.sup.BB. [1377] 480. The compound of Embodiment 479, wherein ** indicates attachment to L.sup.AA [1378] 481. The compound of Embodiment 479, wherein ** indicates attachment to L.sup.D, NR.sup.HH, Y, W, or L.sup.BB. [1379] 482. The compound of any one of Embodiments 378-464, wherein Cy.sup.2 is selected from the group consisting of:
##STR00334##
wherein ** indicates attachment to L.sup.AA. [1380] 483. The compound of any one of Embodiments 378-464, wherein Cy.sup.2 is selected from the group consisting of:
##STR00335##
wherein [1381] each Z.sup.2 is independently ═CR.sup.N— or ═N—; and [1382] each R.sup.N is independently hydrogen or C.sub.1-6 alkyl. [1383] 484. The compound of Embodiment 483, wherein at least one Z.sup.2 is ═N—. [1384] 485. The compound of Embodiment 483, wherein one Z.sup.2 is ═N— and the remaining Z.sup.2 are ═CR.sup.N—. [1385] 486. The compound of Embodiment 483, wherein two Z.sup.2 are ═N— and the remaining Z.sup.2 are ═CR.sup.N—. [1386] 487. The compound of any one of Embodiments 483, 485, and 486, wherein R.sup.N and R.sup.O are hydrogen. [1387] 488. The compound of any one of Embodiments 378-464, wherein Cy.sup.2 is
##STR00336## [1388] 489. The compound of any one of Embodiments 378-464, wherein Cy.sup.2 is
##STR00337## [1389] 490. The compound of any one of Embodiments 378-464, wherein Cy.sup.2 is
##STR00338## [1390] 491. The compound of any one of Embodiments 378-464, wherein Cy.sup.2 is cyclobutyl. [1391] 492. The compound of any one of Embodiments 378-491, wherein each R.sup.d3, R.sup.e3, R.sup.9, R.sup.h1, and R.sup.j1 are independently hydrogen or —CH.sub.3. [1392] 493. The compound of any one of Embodiments 378-492, wherein each Ru is independently selected from —CO.sub.2H, —(C═O)NH.sub.2, —S(O).sub.2NH.sub.2, —CH.sub.2NH.sub.2, and —CH.sub.2OH. [1393] 494. The compound of any one of Embodiments 378-493, wherein t1 is 0. [1394] 495. The compound of any one of Embodiments 378-493, wherein t1 is 1. [1395] 496. The compound of any one of Embodiments 378-495, wherein u is 1 and L.sup.D is —(CH.sub.2).sub.1-3. [1396] 497. The compound of any one of Embodiments 378-495, wherein u is 0. [1397] 498. The compound of any one of Embodiments 378-497, wherein ZZ is —NR.sup.QR.sup.R. [1398] 499. The compound of Embodiment 498, wherein R.sup.Q is C.sub.1-6 alkyl, [1399] 500. The compound of Embodiment 498, wherein R.sup.Q is C.sub.3-6 cycloalkyl. [1400] 501. The compound of Embodiment 500, wherein R.sup.Q is cyclopropyl. [1401] 502. The compound of Embodiment 498, wherein R.sup.Q is —(CH.sub.2).sub.1-3C.sub.3-6 cycloalkyl. [1402] 503. The compound of any one of Embodiments 498-501, wherein R.sup.R is hydrogen. [1403] 504. The compound of any one of Embodiments 378-497, wherein ZZ is —C(═O)N.sup.SR.sup.T. [1404] 505. The compound of any one of Embodiments 378-497, wherein ZZ is —C(O)O(t-butyl). [1405] 506. The compound of any one of Embodiments 378-497, wherein

ZZ is —CO.sub.2H. [1406] 507. The compound of any one of Embodiments 378-497, wherein ZZ is an amino acid selected from the group consisting of alanine, valine, isoleucine, leucine, aspartic acid, glutamic acid, lysine, histidine, arginine, glycine, serine, threonine, phenylalanine, O-methylserine, O-methylaspartic acid, O-methylglutamic acid, N-methyllysine, O-methyltyrosine, O-methylhistidine, and O-methylthreonine. [1407] 508. The compound of Embodiment 378, selected from the group consisting of:
##STR00339## ##STR00340## ##STR00341## ##STR00342## ##STR00343## ##STR00344## ##STR00345## ##STR00346## ##STR00347## ##STR00348## ##STR00349## ##STR00350## and pharmaceutically acceptable salts thereof. [1408] 509. An antibody-drug conjugate (ADC) having the formula:

Ab-(S*-(D′)).sub.p
wherein: [1409] Ab is an antibody; [1410] each S* is a sulfur atom from a cysteine residue of the antibody; [1411] D′ is a Drug-Linker Unit that is a radical of the compound of Formula (IV) according to any one of Embodiments 216-377; and [1412] subscript p is an integer from 2 to 8. [1413] 510. The ADC of Embodiment 509, wherein the radical of the compound of Formula (IV) comprises a radical in substituent M. [1414] 511. The ADC of Embodiment 510, wherein D′ has the structure:
##STR00351##
where *** indicates attachment to S*. [1415] 512. The ADC of any one of Embodiments 509 to 511, wherein the antibody is a humanized antibody. [1416] 513. The ADC of Embodiment 509 or 511, wherein the antibody is a monoclonal antibody. [1417] 514. The ADC of Embodiment 509 or 511, wherein the antibody is fucosylated. [1418] 515. The ADC of Embodiment 509 or 511, wherein the antibody is afucosylated. [1419] 516. A composition comprising a distribution of the ADCs of any one of Embodiments 118-215 and 509-515. [1420] 517. The composition of Embodiment 516, further comprising and at least one pharmaceutically acceptable carrier. [1421] 518. A method of treating cancer in a subject in need thereof, comprising administering a therapeutically effective amount of the composition of Embodiment 516 or 517, to the subject. [1422] 519. A method of treating cancer in a subject in need thereof, comprising administering a therapeutically effective amount of the ADC of any one of Embodiments 118-215 and 509-515, to the subject. [1423] 520. A method of inducing an anti-tumor immune response in a subject in need thereof, comprising administering a therapeutically effective amount of the composition of Embodiment 516 or 517, to the subject. [1424] 521. A method of inducing an anti-tumor immune response in a subject in need thereof, comprising administering a therapeutically effective amount of the ADC of any one of Embodiments 118-215 and 509-515, to the subject. [1425] 522. A compound of Formula (III):
##STR00352##
or a pharmaceutically acceptable salt thereof, wherein: [1426] R.sup.1A is hydrogen, hydroxyl, C.sub.1-6 alkoxy, —(C.sub.1-6 alkyl)C.sub.1-6 alkoxy, —(CH.sub.2).sub.nn—NR.sup.AAR.sup.BB; [1427] R.sup.2A and R.sup.3A are independently —CO.sub.2H, —(C═O).sub.m—NR.sup.CCR.sup.DD, or —(CH.sub.2).sub.q—NR.sup.EE1R.sup.FF1; [1428] each subscript nn is independently an integer from 0 to 6; [1429] each subscript mm is independently 0 or 1; [1430] each subscript qq is an integer from 0 to 6; [1431] Y.sup.1 is —CH.sub.2—, —O—, —S—, —NH—, or —N(CH.sub.3)—; [1432] X.sup.1 is a C.sub.2-6 alkylene; [1433] Z.sup.1 is —NR.sup.EER.sup.FF, —C(═O)NR.sup.GGR.sup.HH, or —CO.sub.2H; [1434] each R.sup.AA, R.sup.BB, R.sup.CC, and R.sup.DD, R.sup.EE1, and R.sup.FF1 are independently hydrogen or C.sub.1-3 alkyl; and [1435] each R.sup.EE, R.sup.FF, R.sup.GG, and R.sup.HH are independently hydrogen or C.sub.1-6 alkyl. [1436] 523. The compound of Embodiment 522, wherein R.sup.1A is hydrogen. [1437] 524. The compound of Embodiment 522, wherein R.sup.1A is hydroxyl. [1438] 525. The compound of Embodiment 522, wherein R.sup.1A is C.sub.1-6 alkoxy. [1439] 526. The

compound of Embodiment 522 or 525, wherein R.sup.1 is methoxy. [1440] 527. The compound of Embodiment 522, wherein R.sup.1A is —(C.sub.1-6 alkyl)C.sub.1-6 alkoxy [1441] 528. The compound of Embodiment 522 or 527, wherein R.sup.1A is methoxyethyl. [1442] 529. The compound of Embodiment 522, wherein R.sup.1 is —(CH.sub.2).sub.nn—NR.sup.AAR.sup.BB. [1443] 530. The compound of Embodiment 522 or 529, wherein R.sup.AA and R.sup.BB are both hydrogen. [1444] 531. The compound of Embodiment 522 or 529, wherein R.sup.AA and R.sup.BB are independently C.sub.1-3 alkyl. [1445] 532. The compound of Embodiment 522 or 529, wherein one of R.sup.AA and R.sup.BB is hydrogen and the other of R.sup.AA and R.sup.BB is C.sub.1-3 alkyl. [1446] 533. The compound of any one of Embodiments 522 or 529-532, wherein each subscript nn is 0. [1447] 534. The compound of any one of Embodiments 522 or 529-532, wherein each subscript nn is 1. [1448] 535. The compound of any one of Embodiments 522 or 529-532, wherein each subscript nn is 2. [1449] 536. The compound of any one of Embodiments 522 or 529-532, wherein each subscript nn is 3, 4, 5, or 6. [1450] 537. The compound of any one of Embodiments 522-536, wherein R.sup.2A and R.sup.3A are independently —CO.sub.2H, —(C═O).sub.mm—NR.sup.CCR.sup.DD, or —(CH.sub.2).sub.q—NR.sup.EE1R.sup.FF1; and R.sup.2A and R.sup.3A are the same. [1451] 538. The compound of any one of Embodiments 522-536, wherein R.sup.2A and R.sup.3A are independently —CO.sub.2H, —(C═O).sub.mm—NR.sup.CCR.sup.DD, or —(CH.sub.2).sub.q—NR.sup.EE1R.sup.FF1; and R.sup.2A and R.sup.3A are different. [1452] 539. The compound of any one of Embodiments 522-538, wherein R.sup.2A is —(C═O).sub.mm—NR.sup.CCR.sup.DD. [1453] 540. The compound of any one of Embodiments 522-538, wherein R.sup.3A is —(C═O).sub.mm—NR.sup.CCR.sup.DD. [1454] 541. The compound of any one of Embodiments 522-537 or 539-540, wherein each R.sup.CC and each R.sup.DD is hydrogen. [1455] 542. The compound of any one of Embodiments 522-537 or 539-540, wherein each R.sup.CC and each R.sup.DD is independently C.sub.1-3 alkyl. [1456] 543. The compound of any one of Embodiments 522-536 or 538-540, wherein one of each R.sup.CC and R.sup.DD is hydrogen and the other of each R.sup.CC and R.sup.DD is C.sub.1-3 alkyl. [1457] 544. The compound of any one of Embodiments 522-543, wherein each subscript mm is 0. [1458] 545. The compound of any one of Embodiments 522-543, wherein each subscript mm is 1. [1459] 546. The compound of any one of Embodiments 522-538, wherein R.sup.2A is —(CH.sub.2).sub.q—NR.sup.EE1R.sup.FF1. [1460] 547. The compound of any one of Embodiments 522-538, wherein R.sup.3A is —(CH.sub.2).sub.q—NR.sup.EE1R.sup.FF1. [1461] 548. The compound of any one of Embodiments 522-538 or 546-547, wherein each R.sup.EE1 and each R.sup.FF1 is hydrogen. [1462] 549. The compound of any one of Embodiments 522-538 or 546-547, wherein each R.sup.EE1 and each R.sup.FF1 is independently C.sub.1-3 alkyl. [1463] 550. The compound of any one of Embodiments 522-538 or 546-547, wherein one of each R.sup.EE1 and each R.sup.FF1 is hydrogen and the other of each R.sup.EE1 and each R.sup.FF1 is C.sub.1-3 alkyl. [1464] 551. The compound of any one of Embodiments 522-538 or 546-547, wherein each subscript qq is 0. [1465] 552. The compound of any one of Embodiments 522-538 or 546-550, wherein each subscript qq is an integer from 1 to 6. [1466] 553. The compound of any one of Embodiments 522-538, wherein R.sup.3A is —CO.sub.2H. [1467] 554. The compound of any one of Embodiments 522-538, wherein R.sup.2A is —CO.sub.2H. [1468] 555. The compound of any one of Embodiments 522-554, wherein Y.sup.1 is —CH.sub.2—. [1469] 556. The compound of any one of Embodiments 522-554, wherein Y.sup.1 is —O—. [1470] 557. The compound of any one of Embodiments 522-554, wherein Y.sup.1 is —S—. [1471] 558. The compound of any one of Embodiments 522-554, wherein Y.sup.i is —NH—. [1472] 559. The compound of any one of Embodiments 522-558, wherein X.sup.1 is a C.sub.2-5 alkylene. [1473] 560. The compound of any one of Embodiments 522-559, wherein X.sup.1 is a C.sub.2-4 alkylene. [1474] 561. The compound of any one of Embodiments 522-560, wherein X.sup.1 is ethylene or n-propylene. [1475] 562. The compound of any one of Embodiments 522-561, wherein Z.sup.1 is —NR.sup.E1R.sup.F1. [1476] 563. The compound of any one of Embodiments 522-562, wherein R.sup.EE and R.sup.FF are both

hydrogen. [1477] 564. The compound of any one of Embodiments 522-562, wherein R.sup.EE and R.sup.FF are independently C.sub.1-6 alkyl. [1478] 565. The compound of any one of Embodiments 522-562, wherein one of R.sup.EE and R.sup.FF is hydrogen and the other of R.sup.EE and R.sup.FF is C.sub.1-6 alkyl. [1479] 566. The compound of Embodiment 564 or 565, wherein the C.sub.1-6 alkyl is a C.sub.1-3 alkyl. [1480] 567. The compound of Embodiment 566, wherein the C.sub.1-3 alkyl is methyl. [1481] 568. The compound of any one of Embodiments 522-561, wherein Z.sup.1 is —C(═O)NR.sup.GGR.sup.HH. [1482] 569. The compound of any one of Embodiments 522-561 or 568, wherein R.sup.GG and R.sup.HH are both hydrogen. [1483] 570. The compound of any one of Embodiments 522-561 or 568, wherein R.sup.GG and R.sup.HH are independently C.sub.1-6 alkyl. [1484] 571. The compound of any one of Embodiments 522-561 or 568, wherein one of R.sup.GG and R.sup.HH is hydrogen and the other of R.sup.GG and R.sup.HH is C.sub.1-6 alkyl. [1485] 572. The compound of Embodiment 570 or 571, wherein the C.sub.1-6 alkyl is a C.sub.1-3 alkyl. [1486] 573. The compound of Embodiment 569, wherein the C.sub.1-3 alkyl is methyl. [1487] 574. The compound of any one of Embodiments 522-561, wherein Z.sup.1 is —CO.sub.2H. [1488] 575. The compound of Embodiment 522, wherein R.sup.1A is methoxy and R.sup.2A and R.sup.3A are both —C(═O)NH.sub.2. [1489] 576. The compound of Embodiment 522 or 575, wherein Y.sup.l is —O— and X.sup.1 is a C.sub.3 alkylene. [1490] 577. The compound of any one of Embodiments 522 or 575-576, wherein X.sup.1 is n-propylene. [1491] 578. The compound of any one of Embodiments 522 or 575-577, wherein Z.sup.1 is —NR.sup.EER.sup.FF. [1492] 579. The compound of any one of Embodiments 522 or 575-578, wherein R.sup.EE is hydrogen and R.sup.FF is methyl.

EXAMPLES

General Methods:

[1493] All commercially available anhydrous solvents were used without further purification. All commercially available reagents were used without further purification unless otherwise noted. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 aluminum sheets or glass plates (EMD Chemicals, Gibbstown, NJ). Flash column chromatography was performed on a Biotage Isolera One™ flash purification system 20 or Biotage Selekt™ flash purification system (Charlotte, NC). UPLC-MS analysis was performed on one of four systems. UPLC-MS system 1: Waters single quad detector mass spectrometer interfaced to a Waters Acquity UPLC system equipped with a Waters Acquity UPLC BEH C18 2.1×50 mm, 1.7 μm, reversed-phase column. UPLC-MS system 2: Waters Xevo G2 TOF mass spectrometer interfaced to a Waters Acquity H-class Ultra Performance LC equipped with a C8 Phenomenex Synergi 2.0×150 mm, 4 μm, 80 Å reversed-phase column with a Waters 2996 Photodiode Array Detector. UPLC-MS system 3 (C18): Shimadzu LC-20 AD & MS 2020 interfaced with a diode array detector (DAD) and positive ESI mass spectrometer equipped with either a Luna-C18 2.0×30 mm, 3 μm particle size reversed-phase column maintained at 40° C. or a Kinetex-C18 2.1×30 mm, 5 μm reversed-phase column maintained at 40° C. UPLC-MS system 4 (C18): Agilent 1200 series LC system interfaced a diode array detector (DAD) and Agilent 6110B positive ESI quadrapole mass spectrometer equipped with a Kinetex-C18 2.1×50 mm, 5 m reversed-phase column maintained at 40° C.

[1494] Compounds were eluted using one of Methods A-E, as described herein.

[1495] Method A—a linear gradient of 5-95% acetonitrile in water (1 mL/min) over 1.0 min, followed by isocratic flow of 95% acetonitrile to 1.80 min (1.0 mL/min) and column equilibration back to 5% acetonitrile to 2.20 min (1.2 mL/min). The water contained 0.037% TFA (v/v) and the acetonitrile contained 0.018% TFA (v/v). The column used was a Phenomenex Luna C18 2.0×30 mm, 3 m reversed-phase column.

[1496] Method B—a linear gradient of 5-95% acetonitrile in water (1 mL/min) over 1.0 min, followed by isocratic flow of 95% acetonitrile to 1.80 min (1.0 mL/min) and column equilibration back to 5% acetonitrile to 2.20 min (1.2 mL/min). The water contained 0.05% TFA (v/v) and the

acetonitrile contained 0.05% TFA (v/v). The column used was a Phenomenex Kinetex C18 2.1×300 mm, 5 m reversed-phase column.
[1497] Method C—isocratic flow of 5% acetonitrile in water for 0.4 min, followed by a linear gradient of 5-95% acetonitrile in water to 3.0 min, followed by isocratic flow for 95% acetonitrile to 4.0 min and column equilibration back to 5% acetonitrile to 4.5 min. The flow rate was 1.0 mL/min and the water contained 0.05% TFA (v/v) and the acetonitrile contained 0.05% TFA (v/v). The column used was a Phenomenex Kinetex C18 2.1×30 mm, 5 m reversed-phase column.
[1498] Method D—a linear gradient of 3-60% acetonitrile over 1.7 min, then 60-95% acetonitrile to 2.0 min, followed by isocratic flow of 95% acetonitrile to 2.5 min followed by column equilibration back to 3% acetonitrile. The flow rate was 0.6 mL/min and the water contained 0.1% (v/v) formic acid and the acetonitrile contained 0.1% (v/v) formic acid. The column used was either a Waters Acquity UPLC BEH C18 2.1×50 mm, 1.7 μm, reversed-phase column or a C8 Phenomenex Synergi 2.0×150 mm, 4 μm, reversed-phase column.
[1499] Method E—a linear gradient of 3-95% acetonitrile over 1.5 min, followed by isocratic elution of 95% acetonitrile to 2.4 min, followed by equilibration back to 3% acetonitrile. The flow rate was 0.6 mL/min and the water contained 0.1% (v/v) formic acid and the acetonitrile contained 0.1% (v/v) formic acid. The column used was either a Waters Acquity UPLC BEH C18 2.1×50 mm, 1.7 μm, reversed-phase column or a C8 Phenomenex Synergi 2.0×150 mm, 4 m, reversed-phase column.
[1500] Unless otherwise specified, preparatory HPLC (PrepHPLC) was performed on one of two instruments using the procedures listed herein: (Method F) a Shimadzu LC-8a preparative HPLC with a Phenomenex Luna C-18 250×50 mm, 10 m using water/acetonitrile mobile phase with 0.09% (v/v) TFA at a flow rate of 80 mL/min or on a Teledyne ISCO ACCQPrep HP150 equipped with one of three Phenomemex preparatory HPLC columns: (i) (Method G) 10×250 mm Synergi C12, 4 μm, Max-RP 80 Å LC Column, (ii) (Method H) 21.2×250 mm Synergi C12, 4 μm, Max-RP 80 Å LC Column or (iii) (Method I) 30×250 mm Synergi C12, 4 μm, Max-RP 80 Å LC Column using acetonitrile/water mobile phases containing either 0.05% (v/v) trifluoroacetic acid or 0.1% (v/v) formic acid as additives.
[1501] NMR spectra were recorded on one of three instruments: Bruker Avance III HD (400 MHz), Varian 400-MR (400 MHz) or Bruker Avance NEO (400 MHz).
Example 1
Synthetic Procedures for Sting Agonists and Linkers
Synthesis of (E)-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-hydroxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazole-5-carboxamide (Compound 1)
##STR00353## ##STR00354##
Synthesis of 4-chloro-3-methoxy-5-nitrobenzamide (Compound 2a)
##STR00355##
[1502] Compound 1a (methyl 4-chloro-3-methoxy-5-nitrobenzoate, 18 g, 73 mmol, 1 equiv.) was added into aqueous NH.sub.4OH solution (300 mL, 28% NH.sub.3 in H.sub.2O) at 25° C. The reaction mixture was stirred at 40° C. for 16 hrs, during which time a precipitate was formed. The precipitate was collected by filtration, washed with water and dried in vacuo to give 2a (13 grams, 56 mmols, 77% yield) as a yellow solid. This product was used in subsequent steps without further purification. UPLC-MS (Method A, ESI+): m/z (M+H).sup.+ 231.0 (theoretical); 231.2 (observed). HPLC retention time: 0.93 min. .sup.1H NMR (DMSO-d.sub.6, 400 MHz): δ=8.29 (br s, 1H), 8.05 (d, J=2.0 Hz, 1H), 7.88 (d, J=1.6 Hz, 1H), 7.79 (br s, 1H), 4.02 (s, 3H).
Synthesis of tert-butyl (E)-(4-((4-carbamoyl-2-methoxy-6-nitrophenyl)amino)but-2-en-1-yl)carbamate (Compound 4a)
##STR00356##
[1503] To a solution of 2a (10 g, 43.4 mmol, 1 equiv.) in ethanol (EtOH, 200 mL) was added 3a

(tert-butyl (E)-(4-aminobut-2-en-1-yl)carbamate, 9.69 g, 52.0 mmol, 1.2 equiv.) and N,N-diisopropylethylamine (DIPEA, 16.8 g, 130 mmol, 3 equiv.) at 25° C. The reaction mixture was stirred at 80° C. for 64 hours which point the precipitate was collected by filtration, washed with ethanol, and dried under high vacuum to give 4a (8 grams, 21 mmols, 48% yield) as a red solid. This product was used in subsequent steps without further purification. 1H NMR (DMSO-d.sub.6, 400 MHz): δ=8.18 (s, 1H), 8.01 (br s, 11H), 7.74 (br t, J=5.6 Hz, 1H), 7.55 (s, 1H), 7.31 (br s, 1H), 6.92 (br s, 1H), 5.53 (br s, 2H), 4.08 (br s, 2H), 3.87 (s, 311), 3.47 (br s, 2H), 1.35 (s, 911).

Synthesis of Compound 5a

##STR00357##

[1504] Compound 4a (8 g, 21.0 mmol, 1 equiv.) was added into a 4M solution of HCl in ethyl acetate (200 mL, 800 mmol HCl) at 25° C. The reaction mixture was stirred at 25° C. for 1 h. The precipitate was collected by filtration, washed with EtOAc and dried under high vacuum to give 5a as HCl salt (7.2 g, quantitative yield) as a red solid. This product was used in subsequent steps without further purification. .sup.1H NMR (DMSO-d.sub.6, 400 MHz): 3=8.21 (d, J=1.6 Hz, 11H), 8.02 (br s, 4H), 7.59 (d, J=2.0 Hz, 1H), 7.34 (br s, 1H), 5.87 (td, J=5.6, 15.6 Hz, 1H), 5.67-5.56 (m, 1H), 4.17 (br d, J=5.6 Hz, 2H), 3.89 (s, 3H), 3.39 (br t, J=5.6 Hz, 2H).

Synthesis of Compound 2b

##STR00358##

[1505] To a solution of compound 2a (4-chloro-3-methoxy-5-nitrobenzamide, 16 g, 69.4 mmol, 1 equiv.) in dichloromethane (DCM, 500 mL) was added a solution of boron tribromide (BBr.sub.3, 1 M in DCM, 275 mL, 4 equiv.) dropwise at 20° C. under nitrogen. The reaction mixture was stirred at 20° C. for 16 h, upon which LC-MS analysis (Method B) showed the reaction was complete. The reaction mixture was poured into ice water (2 L) and stirred vigorously for 20 min. The resulting suspension was filtered and the filtrate was extracted with ethyl acetate (2×300 mL), dried over anhydrous Na.sub.2SO.sub.4, filtered and concentrated in vacuo to give a crude product. The crude product (9 g) was dissolved in DMF (30 mL) and purified by reversed-phase flash chromatography on a Biotage Isolera One (330 gram Agela C18 column (20-35 μm particle size), utilizing water/acetonitrile with 0.09% (v/v) TFA eluting with a gradient of 20-40% acetonitrile over 20 min followed by 40-45% acetonitrile at 35 min to give 2b (6 grams, 27.7 mmols, 40% yield) as an off-white solid. LCMS (Method B, ESI+): m/z [M+H].sup.+ 217.0 (theoretical); 217.2 (observed). HPLC retention time: 0.84 min.

Synthesis of Compound 3b

##STR00359##

[1506] To a solution of 2b (4.5 g, 20.8 mmol, 1 equiv.) in dimethylformamide (DMF, 20 mL) was added 1-(chloromethyl)-4-methoxybenzene (PMBCl, 3.42 g, 21.8 mmol, 1.05 equiv.) and cesium carbonate (Cs.sub.2CO.sub.3, 7.45 g, 22.9 mmol, 1.1 equiv.), the reaction mixture was stirred at 25° C. for 12 h, upon which LC-MS analysis (Method B) showed the reaction was complete. The reaction mixture was poured into ice water, and the precipitate was filtered and dried to give 3b (6.4 grams, 19.0 mmols, 91% yield)) as a light yellow solid. This product was used in subsequent steps without further purification. LC-MS (Method B, EST+): m/z [M+H].sup.+: 337.1 (theoretical); 337.2 (observed). HPLC Retention Time: 1.11 min.

Synthesis of Compound 5

##STR00360##

[1507] A solution of 5a (762 mg, 2.16 mmol, 1.2 equiv.) in n-butanol (10 mL) was added to a vial, followed by the addition of DIPEA (1.11 g, 8.62 mmol, 4.8 equiv.) and sodium bicarbonate (457 mg, 4.31 mmol, 2 equiv.). The vial was scaled and the reaction mixture was stirred at 20° C. for 10 min. This was followed by the addition of 3b (600 mg, 1.78 mmol, 2.4 equiv.), and the reaction mixture was stirred at 115° C. for 20 hours upon which time UPLC-MS analysis (Method B) showed the reaction was complete. Four additional vials were set up as described above. All five reaction mixtures were combined at the end of the reaction. The resulting combined reaction

mixture was cooled to 20° C. and diluted with MeCN (180 mL). The solid material in the reaction mixture was filtered and rinsed with MeCN (80 mL) to give a dark red solid. The solid was then washed with water and dried under high vacuum to give 5 (2.7 grams, 4.65 mmols, 52% yield) as a brick-red solid. This product was used in subsequent steps without further purification. 1H NMR (400 MHz, DMSO-d.sub.6): δ=8.17 (dd, J=1.9, 7.8 Hz, 2H), 8.08-7.96 (m, 2H), 7.77-7.63 (m, 3H), 7.51 (d, J=1.8 Hz, 1H), 7.37 (d, J=8.6 Hz, 2H), 7.33 (br s, 2H), 6.92 (d, J=8.6 Hz, 2H), 5.57-5.42 (m, 211), 5.04 (s, 211), 4.01 (q, J=5.8 Hz, 411), 3.79 (s, 3H), 3.74 (s, 3H).

Synthesis of Compound 6

##STR00361##

[1508] To a solution of 5 (2 g, 3.45 mmol, 1 equiv.) in a 1:1 (v/v) mixture of methanol and water (160 mL) was added Na.sub.2CO.sub.3 (10.95 g, 103 mmol, 30 equiv.) and sodium dithionite (Na.sub.2S2O.sub.4, 8.40 g, 48.2 mmol, 14 equiv.). The resulting red reaction mixture was stirred at 25° C. for 12 h, upon which the red mixture turned into a pale yellow color, and UPLC-MS analysis (Method B) showed the reaction was complete. The reaction mixture was filtered, and the filtrate was concentrated and diluted with water. The mixture was extracted with EtOAc and the organic layer was concentrated to give 6 (1.0 grams, 1.81 mmols, 52% yield) as an off-white solid. This product was used in subsequent steps without further purification. 1H NMR (400 MHz, DMSO-d.sub.6): δ=7.61 (br s, 2H), 7.37 (d, J=8.6 Hz, 2H), 6.97 (br s, 2H), 6.94 (s, 1H), 6.93-6.90 (m, 2H), 6.86 (s, 2H), 6.77 (d, J=1.8 Hz, 1H), 5.71-5.53 (m, 2H), 4.98 (s, 2H), 4.65 (br d, J=12.6 Hz, 4H), 3.74 (s, 3H), 3.71 (s, 3H), 3.49 (br s, 4H).

Synthesis of Compound 7

##STR00362##

[1509] To a solution of 6 (1.4 g, 2.69 mmol, 1 equiv.) in methanol (20 mL) was added cyanogen bromide (BrCN, 1.71 g, 16.1 mmol, 6 equiv.). The reaction mixture was stirred at 25° C. for 2 h, during which time a precipitate was observed. LC-MS analysis (Method C) showed the reaction was complete. The solid was collected by filtration, washed with ethanol and petroleum ether to give 7 (1.2 g, 1.64 mmols, 61% yield) as a light yellow solid. This product was used in subsequent steps without further purification. LC-MS (Method C, ESI+): m/z [M+H]+ 571.2 (theoretical); 571 (observed). HPLC retention time: 1.634 min. .sup.1H NMR (400 MHz, DMSO-d.sub.6): δ=12.94 (br s, 2H), 8.63 (br d, J=12.8 Hz, 4H), 8.08 (br s, 2H), 7.62-7.52 (m, 3H), 7.47 (br s, 2H), 7.38 (s, 1H), 7.24 (d, J=8.6 Hz, 2H), 6.84 (d, J=8.6 Hz, 2H), 5.81-5.69 (m, 1H), 5.57 (td, J=5.4, 15.5 Hz, 1H), 5.07 (s, 2H), 4.80 (br t, J=6.6 Hz, 4H), 3.74 (s, 3H), 3.69 (s, 3H).

Synthesis of Compound 9

##STR00363##

[1510] To a solution of compound 8 (1-ethyl-3-methyl-1H-pyrazole-5-carboxylic acid, 331 mg, 2.15 mmol, 2.1 equiv.) in dimethylformamide (DMF, 3 mL) was added 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 973 mg, 2.56 mmol, 2.5 equiv.) and the reaction mixture was stirred at 60° C. for 10 min. A solution of DIPEA (596 mg, 4.61 mmol, 4.5 equiv.) and 7 (750 mg, 1.02 mmol, 1 equiv.) in DMF (1 mL) was then added to the reaction mixture, which was stirred at 60° C. for 2 h, upon which LC-MS analysis (Method B,) showed the reaction was complete. The reaction mixture was poured into ice water, the solid was collected by filtration and dried to give a crude product. The crude product was used in the next step without further purification. LC-MS (Method B, ESI+): m/z [M+H].sup.+ 843.4 (theoretical); 843.4 (observed). HPLC Retention Time: 1.062 min.

Synthesis of Compound 1

##STR00364##

[1511] Compound 9 (700 mg, 0.83 mmol) was added to a glass vial containing trifluoroacetic acid (TFA, 3 mL), and the resulting mixture was stirred at 25° C. for 2 h, upon which LC-MS analysis showed the reaction was complete. The TFA was removed in vacuo and the residue was dissolved in DMSO and acetonitrile and purified by preparatory HPLC (Method F,) to give 1 (40 mg, 0.055

mmols, 7% yield over 2 steps) as an off-white solid. LCMS (Method B, ESI+): m/z [M+H]+ 723.3 (theoretical); 723.1 (observed): [M+H].sup.+, HPLC retention time: 2.04 min. .sup.1H NMR (400 MHz, DMSO-d.sub.6): δ=13.00-12.51 (m, 2H), 10.41 (s, 1H), 7.96 (br s, 1H), 7.81 (br s, 1H), 7.63 (s, 1H), 7.43 (s, 1H), 7.37-7.28 (m, 2H), 7.22 (br s, 1H), 7.14-7.07 (m, 1H), 6.51 (br d, J=11.0 Hz, 2H), 5.97-5.75 (m, 2H), 4.91 (br dd, J=3.5, 16.3 Hz, 4H), 4.51 (br d, J=3.3 Hz, 4H), 3.77 (s, 3H), 2.10 (d, J=6.0 Hz, 6H), 1.25 (dt, J=3.6, 6.9 Hz, 6H).

Synthesis of (2S,3S,4S,5R,6S)-6-(4-((((2-((((5-carbamoyl-1-((E)-4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazol-7-yl)oxy)carbonyl)(methyl)amino)ethyl)(methyl)carbamoyl)oxy)methyl)-3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid (Compound 11)

Synthesis of Compound 10b

##STR00365##

[1512] Compound 10a was prepared as previously reported (*ACS Med. Chem. Lett.* 2010, 1, 6, 277-280).

[1513] An oven-dried 4 mL glass vial was charged with 10a (150 mg, 0.20 mmol, 1 equiv.) and pentafluorophenyl carbonate (88 mg, 0.22 mmol, 1.1 equiv.), DMF (1 mL) and DIPEA (0.15 mL, 0.86 mmol, 4.3 equiv.). The reaction mixture was stirred at room temperature for 30 minutes upon which a light pink homogenous solution was observed. Tert-butyl methyl(2-(methylamino)ethyl)carbamate (50 uL, 0.27 mmol, 1.3 equiv.) was added to the solution, which resulted in the reaction mixture turning to a light yellow color. The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with water (50 mL), transferred to a separatory funnel and extracted with EtOAc (3×50 mL). The organic layers were collected and combined, washed with 1M HCl, dried with MgSO.sub.4, filtered and the solvent removed in vacuo. The resulting solid was purified by flash column chromatography (25 g SiO.sub.2 column, eluting with 0-25% MeOH in DCM) to yield 10b as a light yellow solid (70.4 mg, 0.073 mmol, 36% yield). UPLC-MS (Method E, EST+) m/z [(M-Boc)+2H].sup.+: 863.33 (theoretical); 863.14 (observed). HPLC retention time: 1.54 min.

Synthesis of Compound 10c

##STR00366##

[1514] Compound 10b (70.4 mg, 0.073 mmol, 1 equiv.) was transferred as a solution in MeOH to an oven-dried 4 mL glass vial equipped with a magnetic stir bar. The MeOH was removed under vacuum and the vial back-filled with argon. To the vial, under Ar, was added MeOH (0.5 mL) and the resulting solution was cooled to 0° C. and sodium methoxide (0.5 M solution in MeOH, 150 μL, 0.075 mmol, 1 equiv.) was added. The reaction was monitored by LC-MS (Method D) and upon complete removal of all three acetate groups, lithium hydroxide (1M in water, 0.225 mL, 0.225 mmol, 3 equiv.) was added and the reaction mixture was stirred at room temperature for 30 min. DMSO (0.5 mL) and glacial acetic acid (50 uL) were added to the reaction mixture, yielding a homogenous solution. The crude product was purified by preparatory HPLC (Method H, 5-40% MeCN in water with 0.05% TFA as mobile phase additive) to give 10c as a white solid (16.8 mg, 0.028 mmol, 38% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+ 601.26 (theoretical); 601.15 (observed). HPLC retention time: 1.09 min.

Synthesis of Compound 10d

##STR00367##

[1515] Compound 10c (16.8 mg, 0.028 mmol, 1 equiv.) was added to an oven-dried 4 mL glass vial equipped with a magnetic stir bar as a solution in McOH. The McOH was removed under vacuum and the vial filled with argon. To the vial was added 3-(maleimido)propionic acid N-hydroxysuccinimide ester (MP-OSu, 16 mg, 0.06 mmol, 2 equiv.) followed by DMF (0.5 mL) and DIPEA (50 uL, 0.28 mmol, 10 equiv.). After 15 minutes, DMSO (0.5 mL) and glacial acetic acid

(100 uL) were added and the crude product purified by preparatory HPLC (Method H, 10-60% MeCN in water with 0.05% TFA as mobile phase additive) to give 10d as a white solid (15 mg, 0.020 mmol, 71% yield). UPLC-MS (Method A, ESI+): m/z [M+H].sup.+: 752.29 (theoretical); 752.26 (observed). HPLC retention time: 1.27 min.

Synthesis of Compound 10

##STR00368##

[1516] Compound 10d (15 mg, 0.020 mmols, 1 equiv.) was dissolved in 20% (v/v) TFA in DCM (1 mL) and transferred to a 4 mL glass vial equipped with a magnetic stir bar. The vial was left uncapped and the reaction progress was monitored by LC-MS. After 2 h, the solvent was removed in vacuo to give 10 as a white solid (13 mg, 0.02 mmol, quantitative yield) which was used in subsequent steps without any further purification. UPLC-MS (Method D, ESI+): m/z [M+H]+: 652.24 (theoretical); 652.45 (observed). HPLC retention time: 0.69 min.

Synthesis of Compound 11

##STR00369## ##STR00370##

[1517] To an oven-dried 4 mL glass vial was added Compound 1 (9.5 mg, 0.010 mmol, 1 equiv.) followed by DMF (0.5 mL), p-nitrophenyl carbonate (9.0 mg, 0.030 mmol, 3 equiv.) and DIPEA (20 uL, 0.115 mmol, 11.5 equiv.). The reaction mixture was stirred at room temperature for 1 hour at which point full conversion to 11a was confirmed by UPLC-MS analysis (Method D). Compound 10 (20 mg, 0.031 mmol, 3.1 equiv.) was added in a single portion to the reaction mixture which was stirred at room temperature for 2 h. Glacial acetic acid (20 uL) was added and the crude product purified by preparatory HPLC (Method H, 0-45% MeCN in water with 0.05% TFA as mobile phase additive). The fractions containing 11 were combined and the solvent was removed via lyophilization to give 11 (6.31 mg, 0.0039 mmol, 39% yield). Compound 1 was also recovered (2.81 mg, 0.0030 mmol, 30% recovery) as a white fluffy solid. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+: 1400.52 (theoretical); 1400.25 (observed) & [M+2H].sup.2+=701.43 (observed). HPLC retention time: 1.28 min.

Synthesis of (E)-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-7-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-methylpropanamido)propoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazole-5-carboxamide (Compound 12)

##STR00371##

[1518] Compound 12a was prepared as previously reported (WO2017/175147, example 40, page 292).

[1519] To a solution of 12a (28.7 mg, 0.032 mmol, 1.0 equiv.) in DMA (635 μL) was added MP-OSu (15.9 mg, 0.0596 mmol, 1.9 equiv.), and DIPEA (35 μL, 0.199 mmol, 6.2 equiv.). The reaction mixture was stirred for 1 h at room temperature. Upon completion, the solution was concentrated under reduced pressure and the crude product was purified by preparatory HPLC (Method G, 20-50-95% MeCN in water with 0.1% formic acid as mobile phase additive) to yield 12 (46% yield, 17.8 mg, 0.0152 mmol). UPLC-MS (Method D, ESI+): m/z [M+H]+ 945.40 (theoretical); 945.72 (observed). HPLC retention time: 1.79 min.

Synthesis of (2S,3S,4S,5R,6S)-6-(4-((((3-((5-carbamoyl-1-((E)-4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazol-7-yl)oxy)propyl)(methyl)carbamoyl)oxy)methyl)-3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid (Compound 13)

Synthesis of Compounds 13a and 13b

##STR00372##

[1520] Compound 10a (13 mg, 0.017 mmol) was dissolved in DMA (87 μL). To this solution was added pentafluorophenyl carbonate (13.7 mg, 0.035 mmol), and DIPEA (14 μL, 0.078 mmol). The

mixture was stirred for 30 min at room temperature. Upon full conversion to intermediate 13a, this solution was transferred to a second vial containing 12a (10.6 mg, 0.012 mmol). The reaction mixture was stirred for 18 h at room temperature. The reaction was then diluted with water and extracted three times with EtOAc (20 mL×3). The combined organic layers were then washed with 1M HCl. The organic layers were combined, dried with MgSO.sub.4, filtered, and concentrated in vacuo. The product was purified by preparatory HPLC (Method H, 5-50-95% MeCN in water using 0.05% TFA as mobile phase additive) to yield compound 13b as a trifluoroacetate salt (10.0 mg, 0.0056 mmol, 48% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+1568.60 (theoretical); 1568.95 (observed). HPLC retention time: 1.70 min.

Synthesis of Compound 13c

##STR00373##

[1521] To a dry, well purged glass vial was added compound 13b (10.0 mg, 0.0056 mmol) in anhydrous methanol (40 μL). The solution was cooled in an ice bath, and NaOMe (0.5 M in MeOH, 11.13 μL) was added. After about 1 h, 1 M aqueous LiOH (17 μL, 0.017 mmols, 3 equiv.) solution was added. Significant white precipitate formed upon the addition of the LiOH solution. After 1 hr, glacial acetic acid (12 μL) was added, and the solvents were removed in vacuo. The crude product was purified by preparatory HPLC (Method G, 20-60-95% MeCN in water, with 0.05% TFA as mobile phase additive) to yield compound 13c as trifluoroacetate salt (4.13 mg, 0.0029 mmol, 52% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1206.49 (theoretical); 1206.50 (observed). HPLC retention time: 1.45 min.

Synthesis of Compound 13

##STR00374##

[1522] Compound 13c (4.13 mg, 0.00342 mmol, 1.0 equiv.) was dissolved in DMA (68 L) in a glass vial under argon. MP-OSu (1.82 mg, 0.00685 mmol, 2 equiv.) and DIPEA (3.0 μL, 0.0171 mmol, 5 equiv.) were added and the reaction mixture was stirred for 1 h at RT. Glacial acetic acid (3.0 μL) was added, and the crude product purified by preparatory HPLC (Method G, 10-60-95% MeCN in water using 0.1% formic acid as mobile phase additive) to yield 13 as trifluoroacetate salt (5.43 mg, 0.0034 mmol, 93% yield). UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=1357.52 (theoretical); 1357.82 (observed). HPLC retention time: 1.54 min.

Synthesis of 4-((S)-2-((S)-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-methylbutanamido)propanamido)benzyl (3-((5-carbamoyl-1-((E)-4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazol-7-yl)oxy)propyl) (methyl)carbamate (Compound 14)

##STR00375##

[1523] To a dry glass vial charged with compound 12a (2.6 mg, 0.0033 mmol) was added DMA (66 μL) followed by MP-Val-Ala-PAB-Opfp (14a, 3.2 mg, 0.049 mmol, 15 equiv.) and DIPEA (2.8 μL, 0.016 mmol, 4.9 equiv.). The reaction mixture was stirred for 30 minutes at RT and then glacial acetic acid (2.85 μL) was added, and the crude product purified by preparatory HPLC (Method G, 30-60-95% MeCN in water, with 0.1% formic acid as mobile phase additive), to yield compound 14 as trifluoroacetate salt (4.0 mg, 0.0027 mmol, 82% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1264.56 (theoretical); 1264.85 (observed). HPLC retention time: 1.75 min.

Synthesis of (E)-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-hydroxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-7-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-methylpropanamido)propoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazole-5-carboxamide (Compound 15)

Synthesis of Compound 15b

##STR00376##

[1524] Compound 15a was prepared as previously reported (WO2017/175147, page 292)

[1525] To a dry glass vial containing compound 15a (31.4 mg, 0.0280 mmol) in DCM (280 μL)

was added boron tribromide (BBr.sub.3, 1M in DCM, 168 μL, 0.168 mmol, 6 equiv.) dropwise. The reaction mixture was stirred at 40° C. for 18 h. The reaction mixture was cooled to RT and cold water (170 μL) was slowly added. The resulting mixture was concentrated in vacuo and purified by preparatory HPLC (20-50-95%, 0.1% formic acid in acetonitrile, Method G). Fractions containing the desired product were combined and solvent removed via lyophilization to yield compound 15b as the formate salt (17% yield, 4.36 mg, 0.0047 mmol). UPLC-MS (Method D, ESI+): m/z [M+H]=780.36 (theoretical); 780.38 (observed). HPLC retention time: 1.33 min.

Synthesis of Compound 15

##STR00377##

[1526] To a dry 4 mL vial containing 2,5-dioxopyrrolidin-1-yl 3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoate (MP-OSu, 1.7 mg, 0.0063 mmol) was added compound 15b (3.9 mg, 0.0042 mmol) as a solution in DMA (423 μL). To the mixture was added DIPEA (3.7 μL, 0.0211 mmol, 5 equiv.) and the reaction mixture was stirred for 30 min at RT, after which glacial acetic acid (3.68 μL) was added, and the product was purified via preparatory HPLC (10-40-95%, 0.05% TFA in acetonitrile, Method G). Fractions containing the desired product were combined and solvents removed via lyophilization to yield compound 15 as trifluoroacetate salt (20% yield, 1.0 mg, 0.0009 mmol). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=931.39 (theoretical); 931.41 (observed). HPLC retention time: 1.62 min.

Synthesis of S-(1-(3-((3-((5-carbamoyl-1-(E)-4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazol-7-yl)oxy)propyl) (methyl)amino)-3-oxopropyl)-2,5-dioxopyrrolidin-3-yl)-L-cysteine (Compound 16)

##STR00378##

[1527] Compound 12 (1.5 mg, 0.0015 mmol, 1 equiv.) was dissolved in DMSO (50 μL). L-cysteine (1 M, 2.2 μL, 0.0022 mmols, 1.5 equiv.) was added as a solution in water. The reaction mixture was stirred at 30° C. for 30 min, and subsequently purified directly via preparatory HPLC (30-70-95%, 0.05% TFA in acetonitrile, Method G). Fractions containing the desired product were combined and frozen. The solvents were removed via lyophilization to yield compound 16 as the trifluoroacetate salt (49% yield, 1.03 mg, 0.0007 mmol). UPLC-MS (Method E, ESI+): m/z [M+H].sup.+1066.42 (theoretical); 1066.44 (observed). HPLC retention time: 1.65 min.

Synthesis of (S,E)-4-((3-((5-carbamoyl-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazol-7-yl)oxy)propyl)(methyl)amino)-3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-4-oxobutanoic acid (Compound

##STR00379## ##STR00380##

Synthesis of Compound 17a

[1528] An oven dried 4 mL vial equipped with a stir bar was charged with compound 12a (10 mg, 0.011 mmol, 1.0 equiv.), Fmoc-aspartate 4-tert-butyl ester (9.1 mg, 0.022 mmol, 2.0 equiv.) and HATU (8.4 mg, 0.022 mmol, 2.0 equiv.), followed by DMF (0.5 mL) and DIPEA (9.6 uL, 0.055 mmol, 5.0 equiv.). The reaction mixture was stirred at room temperature overnight and full conversion to the amide was observed. Solvent was removed in vacuo, and the resulting crude oil was dissolved in DCM and the desired product isolated by flash chromatography (10 g SiO.sub.2, 0-40% MeOH in DCM) to give 17a (12 mg, 0.0104 mmol, 94% yield) as a light brown solid. The isolated material still contained some impurities, but was used in subsequent steps without further purification. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1187.54 (theoretical); 1187.53 (observed). HPLC retention time: 2.40 min.

Synthesis of Compound 17b

[1529] An oven dried 4 mL vial equipped with a stir bar was charged with 17a (12 mg, 0.0104 mmol, 1.0 equiv.) and 20% piperidine in DMF (1 mL). The reaction mixture was stirred for 1 hour, solvent removed in vacuo and product purified by prepHPLC (Method G, 5-95% acetonitrile in

water) to yield 17b (9.3 mg, 0.0096 mmol, 93% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=965.47 (theoretical); 965.48 (observed). HPLC retention time: 1.68 min.

Synthesis of Compound 17c

[1530] A stock solution of MP-OSu and DIPEA was prepared by dissolving 7.7 mg of MP-OSu and 10 μL of DIPEA in 1.0 mL of DMF. An oven dried 4 mL vial equipped with a stir bar was charged with 17b (9.3 mg, 0.0096 mmol, 1.0 equiv.) and 0.5 mL of the stock solution containing MP-OSu (3.8 mg, 0.014 mmol, 1.5 equiv.) and DIPEA (0.029 mmol, 3 equiv.) was added to the vial. The reaction mixture was stirred at room temperature for 2 hours and solvent removed in vacuo to yield crude 17c, which was used in the next step without any further purification. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1116.50 (theoretical); 1116.80 (observed). HPLC retention time: 1.51 min.

Synthesis of Compound 17

[1531] A 4 mL vial was charged with compound 17c (10.7 mg, 0.0096 mmol, 1 equiv.) dissolved in 20% (v/v) TFA in DCM (1 mL) and the reaction mixture was stirred at room temperature for 3 hours. Solvent was subsequently removed in vacuo, and the crude product was dissolved in DMSO (0.75 mL) and purified by prepHPLC (Method G, 5-50% MeCN in water) to give Compound 17 (5.4 mg, 0.0051 mmol, 53% yield) as a white solid. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1060.44 (theoretical); 1061.12 (observed). HPLC retention time: 1.28 min.

Synthesis of (S,E)-7-(3-(6-amino-2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-N-methylhexanamido)propoxy)-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazole-5-carboxamide (Compound 18) ##STR00381## ##STR00382##

Synthesis of Compound 18a

[1532] An oven dried 4 mL vial equipped with a stir bar was charged with HATU (7.8 mg, 0.021 mmol, 2.0 equiv.) and Fmoc-lysine N-epsilon-Boc (9.6 mg, 0.021 mmol, 2.0 equiv.); to which was added a solution of compound 12a (9.3 mg, 0.0103 mmol, 1.0 equiv.) and DIPEA (9 uL, 0.051 mmol, 5 equiv.) in DMF (0.5 mL). The vial was capped and scaled with parafilm and the mixture was stirred at RT overnight. Full conversion was observed by UPLC-MS (Method D). Solvent was removed in vacuo and product was purified by flash chromatography (10 g SiO.sub.2, 0-40% MeOH in DCM) to give 18a (12 mg, 0.0097 mmol, 95%) as a tan solid. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1244.60 (theoretical); 1244.61 (observed). HPLC retention time: 2.40 min.

Synthesis of Compound 18b

[1533] An oven-dried 4 mL vial equipped with a stir bar was charged with 18a (12 mg, 0.0096 mmol) and 20% (v/v) piperidine in DMF (1 mL) was added to the reaction. The reaction mixture was stirred until full conversion was observed by UPLC-MS (Method D), which took approximately 1 hour. Solvent was removed in vacuo and product was purified by preparatory HPLC (Method G, 5-95% MeCN in water with 0.1% (v/v) formic acid). The HPLC solvents were removed in vacuo to give 18b (4.2 mg, 0.0041 mmol, 36%) as an off-white solid. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1022.53 (theoretical); 1022.80 (observed). HPLC retention time: 1.30 min.

Synthesis of Compound 18c

[1534] An oven-dried 4 mL vial equipped with a stir bar was charged with 18b (4.2 mg, 0.0034 mmol, 1 equiv.), followed by MP-OSu (1.8 mg, 0.0068 mmol, 2.0 equiv.), DIPEA (5.9 μL, 0.034 mmol, 10 equiv.) and DMF (0.8 mL). The reaction mixture was stirred at room temperature for 3 hours at which point UPLC-MS (Method D) analysis showed full conversion. Solvent was removed in vacuo to yield the crude product 18c, which was used in the next step without purification. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1173.56 (theoretical); 1173.94 (observed). HPLC retention time: 1.54 min.

Synthesis of Compound 18

[1535] An oven-dried 4 mL vial containing a stir bar was charged with crude 18c from the previous step (0.0034 mmol,) and 20% (v/v) TFA in DCM (1 mL) was added. The reaction mixture was stirred for one hour and the product was subsequently purified by preparatory HPLC (Method G, 5-50% MeCN in water with 0.1% (v/v) formic acid). The HPLC solvents were removed in vacuo to give 18c (4.2 mg, 0.0035 mmol, 56% yield over 2 steps) as a white solid. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1073.51 (theoretical); 1073.73 (observed). HPLC retention time: 1.15 min.

##STR00383## ##STR00384##

General Methods for HATU Coupling, Fmoc Deprotection, and MP Coupling

[1536] HATU coupling (Method 1): An oven-dried 4 mL vial equipped with a stir bar was charged with compound 12a (1.0 equiv.), HATU (2.0 equiv.), DIPEA (5 equiv.) and DMF (20 mM in 12a) and the reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo and product purified via chromatography.

[1537] Fmoc deprotection (Method 2): An oven-dried 4 mL vial equipped with a stir bar was charged with the HATU coupled product from above, which was dissolved in 20% (v/v) piperidine in DMF (1 mL). The reaction mixture was stirred at room temperature for 1 hour, solvent removed in vacuo, and product purified via chromatography.

[1538] MP coupling (Method 3): An oven-dried 4 mL vial equipped with a stir bar was charged with the product from the previous reaction, to which was added MP-OSu (2 equiv.) and DIPEA (10 equiv.) and DMF (10 mM in Fmoc-deprotected amine starting material). The reaction mixture was stirred at room temperature for 3 hours, solvent removed in vacuo and product purified by preparatory HPLC.

[1539] Compound 19a was prepared according to General Method 1 (8.0 mg, 0.0075 mol, 85% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1073.47 (theoretical); 1074.03 (observed). HPLC retention time: 1.76 min.

[1540] Compound 19b was prepared according to General Method 2 (6.1 mg, 0.0072 mol, 95% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=851.41 (theoretical); 851.69 (observed). HPLC retention time: 1.15 min.

[1541] Compound 19 was prepared according to General Method 3 (4.3 mg, 0.0043 mol, 60% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1002.43 (theoretical); 1002.72 (observed). HPLC retention time: 1.31 min.

[1542] Compound 20a was prepared according to General Method 1 (8.7 mg, 0.0080 mol, 91% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1087.49 (theoretical); 1087.90 (observed). HPLC retention time: 1.75 min.

[1543] Compound 20b was prepared according to General Method 2 (5.6 mg, 0.0065 mol, 81% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=865.42 (theoretical); 865.66 (observed). HPLC retention time: 1.12 min.

[1544] Compound 20 was prepared according to General Method 3 (3.4 mg, 0.0034 mol, 52% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1016.45 (theoretical); 1017.08 (observed). HPLC retention time: 1.33 min.

[1545] Compound 21a was prepared according to General Method 1 (14 mg, 0.0119, mmol). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1145.50 (theoretical); 1145.42 (observed). HPLC retention time: 1.74 min.

[1546] Compound 21b was prepared according to General Method 2 (7.2 mg, 0.0078 mol, 76% yield over 2 steps). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=923.43 (theoretical); 923.67 (observed). HPLC retention time: 1.13 min.

[1547] Compound 21 was prepared according to General Method 3 (1.5 mg, 0.0014 mols, 22% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1074.45 (theoretical); 1074.90 (observed). HPLC retention time: 1.36 min.

[1548] Compound 22a was prepared according to General Method 1 (7.6 mg, 0.0065 mols, 63% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1172.58 (theoretical); 1172.59 (observed). HPLC retention time: 1.84 min.
[1549] Compound 22b was prepared according to General Method 2 (6.1 mg, 0.0064 mmols, 57% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=950.51 (theoretical); 950.83 (observed). HPLC retention time: 0.99 min.
[1550] Compound 22 was prepared according to General Method 1 (2.6 mg, 0.0023 mols, 37% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1101.54 (theoretical); 1101.96 (observed). HPLC retention time: 1.18 min.
[1551] Compound 23a was prepared according to General Method 1 (12 mg, 0.0105 mmol). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1117.50 (theoretical); 1117.77 (observed). HPLC retention time: 1.75 min.
[1552] Compound 23b was prepared according to General Method 2 (7.2 mg, 0.00804 mmol, 91% over 2 steps). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=895.43 (theoretical); 895.73 (observed). HPLC retention time: 1.12 min.
[1553] Compound 23 was prepared according to General Method 3 (8.4 mg, 0.0047, 58% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1046.46 (theoretical); 1047.06 (observed). HPLC retention time: 1.36 min.
Synthesis of (S,E)-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-7-(3-(2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3-hydroxy-N-methylpropanamido)propoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazole-5-carboxamide (Compound 0 NH.SUB.2 .0 ##STR00385## ##STR00386##
Synthesis of Compound 24a
[1554] An oven dried 4 mL vial equipped with a stir bar was charged with HATU (6.7 mg, 0.018 mmol, 2.0 equiv.) and 2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-methoxy-propanoic acid (6.0 mg, 0.018 mmol, 2.0 equiv.), and a solution of compound 12a (8 mg, 0.0088 mmols, 1.0 equiv.) and DIPEA (8 uL, 0.044 mmols, 5 equiv.) in DMF (0.5 mL) was added to the vial. The vial was capped and sealed with parafilm and the reaction mixture was stirred at room temperature overnight, upon which full conversion was observed by UPLC-MS (Method D). Solvent was removed in vacuo and product purified by flash chromatography (10 g SiO.sub.2, 0-40% MeOH in DCM) to give 24a (15 mg), which was used in the next reaction without further purification. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1345.59 (theoretical); 1346.12 (observed). HPLC retention time: 2.23 min.
Synthesis of Compound 24b
[1555] An oven-dried 4 mL vial equipped with a stir bar was charged with 24a (15 mg, 0.011 mmol) and 20% (v/v) piperidine in DMF (1 mL) was added to it. The reaction mixture was stirred until full conversion was observed by UPLC-MS (Method D), which took approximately 1 hour. Solvent was removed in vacuo and the crude product was purified by preparatory HPLC (Method G, 5-95% MeCN in water with 0.1% (v/v) formic acid); the HPLC solvents were removed in vacuo to give 24b (8.4 mg, 0.0075 mmol, 94% over 2 steps) as an off-white solid. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1123.53 (theoretical); 1123.98 (observed). HPLC retention time: 1.47 min.
Synthesis of Compound 24c
[1556] An oven-dried 4 mL vial equipped with a stir bar was charged with 24b (8.4 mg, 0.0075 mmol, 1 equiv.), followed by MP-OSu (3.0 mg, 0.011 mmol, 1.5 equiv.), DIPEA (3.9 μL, 0.022 mmol, 3 equiv.) and DMF (0.5 mL). The reaction mixture was stirred at room temperature for 3 hours at which point UPLC-MS (Method D) analysis showed full conversion. Solvent was removed in vacuo and the resulting crude product was used in the next step without purification. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1274.55 (theoretical); 1275.21 (observed). HPLC

retention time: 1.89 min.
Synthesis of Compound 24
[1557] An oven-dried 4 mL vial containing a stir bar was charged with crude 24c (0.0075 mmol,) and 20% (v/v) TFA in DCM (1 mL) was added to the vial. The reaction mixture was stirred for 20 minutes, and solvent removed in vacuo. The resulting crude product was dissolved in DMSO (0.5 mL) and purified by preparatory HPLC (Method G, 5-50% MeCN in water with 0.1% (v/v) formic acid) and solvent removed in vacuo to give 24 (4.0 mg, 0.0031 mmol, 42% yield over 2 steps) as a white solid. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=1032.44 (theoretical); 1033.09 (observed). HPLC retention time: 1.28 min.
Synthesis of (E)-7-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-methylpropanamido)propoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1-(4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-5-sulfamoyl-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazole-5-carboxamide (Compound 25)
##STR00387## ##STR00388## ##STR00389##
Synthesis of 25a
[1558] A 5 mL oven-dried microwave vial with stir bar was charged with 4-chloro-3-nitro-benzenesulfonamide (250 mg, 1.06 mmol, 1 equiv.), tert-butyl N—[(E)-4-aminobut-2-enyl]carbamate hydrochloride (353 mg, 1.6 mmol, 1.5 equiv.) and sodium carbonate (336 mg, 3.2 mmol, 3 equiv.). To the vial was added 1-butanol (3 mL) followed by DIPEA (1.1 mL, 6.34 mmol, 6 equiv.) and additional 1-butanol to bring the total volume of the reaction up to 5 mL. The vial was sealed and heated to 140° C. in the microwave reactor for 120 minutes.
[1559] The crude product was poured into brine (100 mL) and extracted with EtOAc (3×200 mL), organics combined, washed with brine (2×100 mL), dried with MgSO.sub.4, filtered and solvent removed in vacuo to give a bright red oil. This material was purified by flash chromatography (dry loaded on celite, 25 g Sfar, HC Duo, SiO2 column, 0-40% MeOH in DCM) to give 25a (295 mg, 0.763 mmol, 72% yield) as a bright yellow solid. UPLC-MS (Method D, ESI+): m/z [M+H−Boc].sup.+=287.1 (theoretical); 287.4 (observed). HPLC retention time: 1.53 min.
Synthesis of 25b
[1560] A 20 mL vial was charged with 25a (295 mg, 0.763 mmol, 1 equiv.) which was dissolved in methanol (7.5 mL) and 4M HCl in 1,4-dioxane (40 eq, 7.5 mL, 30.0 mmol). The solution was stirred at 40° C. for 30 minutes and solvent removed in vacuo to give 25b as the 2×HCl salt (274 mg, 0.764 mmol, quantitative yield) as a bright red solid. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=287.1 (theoretical); 287.6 (observed). HPLC retention time: 0.52 min.
Synthesis of 25c
[1561] An oven dried 5 mL microwave vial with stir bar was charged with 25b (135 mg, 0.376 mmol, 1 equiv.), tert-butyl N-[3-(5-carbamoyl-2-chloro-3-nitro-phenoxy)propyl]carbamate (211 mg, 0.564 mmol, 1.5 equiv., prepared as described below) and sodium carbonate (119 mg, 1.13 mmol, 3 equiv.) which was followed by addition of n-butanol (3.75 mL) and DIPEA (0.39 mL, 2.25 mmol, 6 equiv.). The vial was sealed and heated to 140° C. for 3 hours in a microwave reactor to give a bright red heterogenous mixture. This solution was filtered over celite washing with 1:1 DCM:MeOH (100 mL), solvent removed in vacuo and crude product was loaded onto celite and purified by flash chromatography (25 g SiO2 column, 0-40% MeOH in DCM) to give 25c (245 mg, 0.384 mmol) as a mixture of product and starting material (3:2). Product mixture was used in the next step without any further purification. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=638.2 (theoretical); 638.5 (observed). HPLC retention time: 1.75 min.
Synthesis of 25d
[1562] A20 mL vial with stirbar was charged with 25c (245 mg, 0.384 mmol, 1 equiv.) and sodium bicarbonate (580 mg, 6.90 mmol, 18 equiv.) and methanol (4 mL) was added. To the vial was then added sodium hydrosulfite (1.20 g, 6.90 mmol, 18 equiv. in 4 mL water) and the vial was heated to 50° C. for 60 minutes. The reaction was cooled to room temperature, filtered over celite washing

with MeOH (50 mL) and DCM (50 mL) and the crude product loaded onto celite. The product was purified by flash chromatography (25 g Sfar HC Duo, SiO2 column, 0-40% 10:1 McOH:NH.sub.4OH in DCM) to give 25d (89 mg, 0.154 mmol, 41% yield over 2 steps) as a mixture of inseparable rotational conformers. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=578.3 (theoretical); 578.5 (observed). HPLC retention time: 0.98 & 1.18 min.

Synthesis of 25e

[1563] Two identical reactions were setup side by side. An oven dried 4 mL vial with stir bar was charged with 25d (45 mg, 0.156 mmol, 1 equiv.), dissolved in methanol (1 mL) and cyanogen bromide (200 uL, 1.20 mmol, 8 equiv.) was added. Reaction was stirred overnight, and solvent removed in vacuo and two reactions combined to give 25e as the 2×HBr salt (120 mg, 0.15 mmol, 97% yield) as a light gray solid. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=628.3 (theoretical); 628.4 (observed). HPLC retention time: 0.79 min.

Synthesis of 25f

[1564] An oven dried 4 mL vial with stir bar was charged with 25e (120 mg, 0.152 mmol, 1 equiv.), 2-ethyl-5-methyl-pyrazole-3-carboxylic acid (94 mg, 0.61 mmol, 4.0 equiv.) and HATU (231 mg, 0.61 mmol, 4 equiv.). The solids were dissolved in DMF (1 mL) and DIPEA (0.22 mL, 1.2 mmol, 8 equiv.) was added. The reaction was stirred at room temperature overnight, acetic acid was added (100 uL) and product purified by prepHPLC (Method T, 5-95% MeCN in water with 0.05% TFA) and solvent removed in vacuo to give 25f (107 mg, 0.12 mmol, 78% yield) as an off-white solid. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=900.4 (theoretical); 900.6 (observed). HPLC retention time: 1.69 min.

Synthesis of 252

[1565] Compound 25f (107 mg, 0.12 mmol, 1 equiv.) was added to a 20 mL vial with stir bar and dissolved in 20% TFA in DCM (5 mL). Reaction was stirred at room temperature for 20 minutes and then solvent removed in vacuo to give 25 g as the 3×TFA salt and an off-white solid (70 mg, 0.0615 mmol, 52% yield). A sample of analytical purity was obtained by prepHPLC purification (Method G, 5-95% MeCN in water with 0.05% TFA). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=800.3 (theoretical); 800.6 (observed). HPLC retention time: 1.12 min.

Synthesis of 25

[1566] An oven dried 4 mL vial with stir bar was charged with 25g (12 mg, 0.011 mmol, 1 equiv.) which was dissolved in DMF (1 mL) and then both DIPEA (15 uL, 0.087 mmol, 8 equiv.) and MP-OSu (4.3 mg, 0.0163 mmol, 1.5 equiv.) were added to the reaction. The solution was stirred at room temperature for 30 minutes, quenched with 20% TFA in DCM (100 uL) and purified by prepHPLC (Method G, 5-95% MeCN in water with 0.05% TFA) to 25 as the 2×TFA salt (5.7 mg, 0.0048 mmol, 45% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=951.4 (theoretical); 951.2 (observed). HPLC retention time: 2.18 min.

Synthesis of (E)-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-7-(2-(1-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl)azetidin-3-yl)ethoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazole-5-carboxamide (Compound 26)

##STR00390## ##STR00391## ##STR00392##

Synthesis of 26a

[1567] An oven dried 8 mL vial with stir bar was charged with 2b (100 mg, 0.462 mmol, 1 equiv.) and potassium carbonate (191 mg, 1.39 mmol, 3 equiv.) followed by addition of tert-butyl 3-(2-bromoethyl)azetidine-1-carboxylate (152 mg, 0.577 mmol, 1.25 equiv.). The starting materials were dissolved in DMF (3 mL), vial sealed with parafilm and stirred at 70° C. for 24 hours. The crude material was poured into a separatory funnel containing saturated ammonium chloride (100 mL) and EtOAc (100 mL each), shaken, layers separated, and aqueous layer extracted with EtOAc (2×100 mL). The combined organic fractions were washed with brine (2×50 mL), dried with MgSO.sub.4, filtered and solvent removed in vacuo to give crude product as a light-yellow solid.

The crude product was purified by flash chromatography (25 g Sfar HC Duo SiO.sub.2 column, 0-20% MeOH in DCM) to give 26a as a yellow solid (86 mg, 0.215 mmol, 47% yield). UPLC-MS (Method D, EST+): m/z [M+H].sup.+=400.1 (theoretical); 400.5 (observed). HPLC retention time: 1.79 min.

Synthesis of 26b

[1568] An oven-dried 2 mL microwave vial was charged with 25a (35 mg, 0.0875 mmol, 1 equiv.), 5a (62 mg, 0.175 mmol, 2 equiv.) and sodium carbonate (28 mg, 0.263 mmol, 3 equiv.) and to this vial was added n-butanol (1 mL) and DIPEA (0.1 mL, 0.5 mmol, 6 equiv.). The vial was sealed and heated to 140° C. for 3 hours in a microwave reactor. The reaction was then filtered over celite washing with 1:1 MeOH:DCM (100 mL), solvent removed in vacuo and crude material loaded onto celite. The product was purified by flash chromatography (25 g Sfar HC Duo SiO.sub.2 column, 0-20% MeOH in DCM) to give 25b as a bright red solid (38 mg, 0.0592 mmol, 68% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=644.3 (theoretical); 644.6 (observed). HPLC retention time: 1.72 min.

Synthesis of 26c

[1569] An oven-dried 4 mL vial was charged with 25b (38 mg, 0.0592 mmol, 1 equiv.) which was dissolved in methanol (1 mL) and sodium bicarbonate (90 mg, 1.1 mmol, 18 equiv.) was added followed by sodium hydrosulfite (186 mg, 1.07 mmol, 18 equiv.) as a solution in water (1 mL). The reaction was heated to 50° C. for 1 hour and filtered over celite washing with 1:1 DCM:McOH (50 mL). The crude product was loaded onto celite and purified by flash chromatography (25 g Sfar HC Duo, SiO.sub.2 column, 0-40% 10:1 MeOH:NH.sub.4OH in DCM) to give 25c (10 mg, 0.017 mmol, 29% yield) as a light yellow solid. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=584.3 (theoretical); 584.6 (observed). HPLC retention time: 1.18 min.

Synthesis of 26d

[1570] An oven dried 4 mL vial with stir bar was charged with 25c (10 mg, 0.017 mmol, 10 equiv.) which was dissolved in methanol (0.5 mL) and cyanogen bromide (0.050 mL, 0.150 mmol, 3M in DCM, 8.7 equiv.) was added. The reaction was stirred for 18 hours and solvent removed in vacuo to give the 25d as a light grey solid and the 2×HBr salt (13 mg, 0.0165 mmol, 95% yield) which was used without any further purification. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=634.3 (theoretical); 634.6 (observed). HPLC retention time: 0.98 min.

Synthesis of 26e

[1571] An oven dried 4 mL vial with stir bar was charged with 25d (13 mg, 0.0165 mmol, 1 equiv.), HATU (25 mg, 0.066 mmol, 4 equiv.) and 2-ethyl-5-methyl-pyrazole-3-carboxylic acid (10 mg, 0.066 mmol, 4 equiv.) which were dissolved in DMF (0.5 mL) and then DIPEA (0.050 mL, 0.20 mmol, 17 equiv.) was added. The reaction was stirred at room temperature for 24 hours. The reaction was quenched with acetic acid (100 uL) and product purified by via prepHPLC (Method H, 5-95% MeCN in water with 0.05% TFA) to give 25e as the 2×TFA salt (14 mg, 0.016 mmol, 95% yield) as a light tan solid. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=906.4 (theoretical); 906.3 (observed). HPLC retention time: 2.44 min.

Synthesis of 26f

[1572] An oven dried 4 mL vial with stir bar was charged with 25e (14 mg, 0.016 mmol, 1 equiv.) which was dissolved in 20% TFA in DCM (1 mL) and stirred at room temperature for 15 minutes. Solvent was removed in vacuo to give 25f as the 3×TFA salt (15 mg, 0.013 mmol, 82% yield) as a white solid and the product used without any further purification. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=806.4 (theoretical); 806.6 (observed). HPLC retention time: 1.25 min.

Synthesis of 26

[1573] An oven dried 4 mL vial with stir bar was charged with 25f (5.7 mg, 0.0050 mmol, 1 equiv.) in DMSO (0.5 mL) and MP-OSu (2.0 mg, 0.00750 mmol, 1.5 equiv.) and DIPEA (5 uL, 0.030 mmol, 6 equiv.) was added. The reaction was stirred at room temperature for 1 hour. The reaction was quenched added 20% TFA in DCM (100 uL) and product purified by prepHPLC (Method G, 5-

95% MeCN in water with 0.05% TFA) to give 25 as the 2×TFA salt (3.8 mg, 0.00321 mmol, 64% yield) as a white solid. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=957.4 (theoretical); 957.3 (observed). HPLC retention time: 2.19 min.

Synthesis of (E)-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-7-(3-((1-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl)azetidin-3-yl)oxy)propoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazole-5-carboxamide (Compound 27)

##STR00393## ##STR00394## ##STR00395##

Synthesis of 27a

[1574] An oven dried 8 mL vial with stir bar was charged with 2b as the TFA salt (150 mg, 0.454 mmol, 1 equiv.), tert-butyl 3-(3-bromopropoxy)azetidine-1-carboxylate (133 mg, 0.454 mmol, 1 equiv.) and potassium carbonate (141 mg, 1.02 mmol, 2.3 equiv.) which were dissolved in DMF (4.5 mL) and heated to 55° C. for 24 hours. The reaction was poured into a separatory funnel containing sat. NaHCO.sub.3 (100 mL) and EtOAc (100 mL), shaken, layers separated, and aqueous layer extracted with EtOAc (3×50 mL). The organic fractions were combined and further washed with sat. NaHCO.sub.3 (3×50 mL) and brine (2×50 mL). They were then dried with MgSO.sub.4, filtered and solvent removed in vacuo to 27a (194 mg, 0.353 mmol, 78% yield) as a light yellow solid in a 4:1 ratio of starting material to product and used without further purification. MS (Method D, ESI+): m/z [M+H].sup.+=430.1 (theoretical); 430.6 (observed). HPLC retention time: 1.82 min.

Synthesis of 27b

[1575] An oven-dried 5 mL microwave vial was charged with Sodium carbonate (144 mg, 1.36 mmol, 3.00 eq), 5a as the 2×HCL salt (240 mg, 0.678 mmol, 1.50 eq) and 27a (194 mg, 0.452 mmol, 1 equiv.) and then 1-butanol (4 mL) and DIPEA (0.5 mL, 2.7 mmol, 6 equiv.) were added. The vial was sealed and heated to 140° C. for 3 hours in a microwave reactor. The reaction was cooled to room temperature and solution was filtered over celite washing with 1:1 MeOH:DCM (100 mL). The crude product was loaded onto celite and purified by flash chromatography (25 g Sfar HC Duo, SiO.sub.2 column, 0-20% MeOH in DCM) to give 27b (95 mg, 0.141 mmol, 31% yield) as a bright red solid. MS (Method D, ESI+): m/z [M+H].sup.+=674.3 (theoretical); 674.6 (observed). HPLC retention time: 1.73 min.

Synthesis of 27c

[1576] A 20 mL vial was charged 27b (95 mg, 0.141 mmol, 1 equiv.) and sodium bicarbonate (442 mg, 5.3 mmol, 37 equiv.) and starting material dissolved in methanol (4 mL). To the vial was added sodium hydrosulfite (442 mg, 2.54 mmol, 18 equiv.) as solution in water (4 mL) and reaction was heated, open to the atmosphere, to 50° C. for 1 hour. The solution went from bright red to light yellow over the course of an hour. The reaction was filtered, filter cake washed with 1:1 MeOH:DCM (3×50 mL), solvent removed in vacuo, crude product redissolved in 1:1 MeOH:DCM (100 mL) and filtered over celite. The crude product was loaded onto celite and purified by flash chromatography (25 g Sfar HC Duo, SiO.sub.2 column, 0-40% 10:1 MeOH:NH.sub.4OH in DCM) to give 27c (42 mg, 0.0689 mmol, 49% yield) as an off-white solid. UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=614.3 (theoretical); 614.5 (observed). HPLC retention time: 0.78 min.

Synthesis of 27d

[1577] An oven-dried 4 mL vial was charged with 27c (42 mg, 0.0689 mmol, 1 equiv.) which was dissolved in methanol (1.3 mL) and then cyanogen bromide (3M in DCM, 0.14 mL, 0.414 mmol, 6 equiv.) was added. The vial was stirred at room temperature for 24 hours and solvent removed in vacuo to give 27d as the 2×HBr salt (57 mg, 0.0694 mmol, quantitative yield) as an off-white solid. MS (Method D, ESI+): m/z [M+H].sup.+=664.3 (theoretical); 664.7 (observed). HPLC retention time: 0.95 min.

Synthesis of 27e

[1578] An oven dried 4 mL vial with stir bar was charged with 27d (57 mg, 0.0694 mmol, 1 equiv.),

2-ethyl-5-methyl-pyrazole-3-carboxylic acid (43 mg, 0.278 mmol, 4 equiv.) and HATU (106 mg, 0.278 mmol, 4 equiv.) which were dissolved in DMF (1 mL) and then DIPEA (0.097 mL, 0.555 mmol, 8 equiv.) was added. The reaction was stirred at room temperature for 24 hours, quenched with 20% TFA in MeCN (200 uL) and product purified by prepHPLC (Method 1, 5-95% MeCN in water with 0.05% TFA), solvent removed via lyophilization to give 27e as the 2×TFA salt (35 mg, 0.0302 mmol, 43% yield) as a tan solid. A sample of analytical purity was prepared via a second prepHPLC purification (Method G, 5-60% MeCN in water with 0.05% TFA). MS (Method D, ESI+): m/z [M+H].sup.+=936.4 (theoretical); 936.3 (observed). HPLC retention time: 2.37 min.

Synthesis of 27f

[1579] A 20 mL vial was charged with 27e (31 mg, 0.0266 mmol. 1 equiv.) which was dissolved in 20% TFA in DCM (2 mL) and stirred at room temperature for 15 minutes. Solvent was removed in vacuo and crude product purified by prepHPLC (Method H, 5-95% MeCN in water with 0.05% TFA) to give 27f as the 3×TFA salt (7.2 mg, 0.0061 mmol, 23% yield) as a white solid. MS (Method D, ESI+): m/z [M+H].sup.+=836.4 (theoretical); 836.3 (observed). HPLC retention time: 2.02 min.

Synthesis of 27

[1580] An oven-dried 4 mL vial was charged with 27f (10 mM in DMSO, 0.50 mL, 0.0050 mmol, 1 equiv.) and then MP-OSu (2.0 mg, 0.0075 mmol, 1.5 equiv.) and DIPEA (20 uL, 0.12 mmol, 23 equiv.) was added. The reaction was stirred at room temperature for 90 minutes, quenched with 20% TFA in MeCN (100 uL) and crude product was purified by prepHPLC (Method G, 5-95% McCN in water with 0.05% TFA) to 27 as the 3×TFA salt (3.6 mg, 0.0029 mmol, 58% yield) as a white solid. MS (Method D, ESI+): m/z [M+H].sup.+=987.4 (theoretical); 987.2 (observed). HPLC retention time: 2.23 min.

Synthesis of S-(1-(3-((3-((5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1-((E)-4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-5-sulfamoyl-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazol-7-yl)oxy)propyl)(methyl)amino)-3-oxopropyl)-2,5-dioxopyrrolidin-3-yl)-L-cysteine (Compound 28)

##STR00396##

[1581] A 1.7 mL eppendorf tube was charged with 25 (10 mM in DMSO, 100 μL, 0.00100 mmol, 1 equiv.) and L-cysteine (15 mM in 4:1 DMSO:water, 150 μL, 0.00300 mmol, 3 equiv.) was added. The reaction was heated to 37° C. for 90 minutes and the crude product was then purified by prepHPLC (Method G, 5-95% MeCN in water with 0.05% TFA) to give 28 as the 2×TFA salt (1.1 mg, 0.000861 mmol, 86% yield) as a white solid. MS (Method D, ESI+): m/z [M+H].sup.+=1072.4 (theoretical); 1072.2 (observed). HPLC retention time: 1.98 min.

Synthesis of S-(1-(3-(3-(2-((5-carbamoyl-1-((E)-4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazol-7-yl)oxy)ethyl)azetidin-1-yl)-3-oxopropyl)-2,5-dioxopyrrolidin-3-yl)-L-cysteine (Compound 29)

##STR00397##

[1582] A 1.7 mL eppendorf tube was charged with 26 (10 mM in DMSO, 100 μL, 0.00100 mmol, 1 equiv.) and L-cysteine (15 mM in 4:1 DMSO:water, 150 μL, 0.00300 mmol, 3 equiv.) was added. The reaction was heated to 37° C. for 2 hours and the crude product was then purified by prepHPLC (Method G, 5-95% MeCN in water with 0.05% TFA) to give 29 as the 2×TFA salt (0.91 mg, 0.000697 mmol, 70% yield) as a white solid. MS (Method D, ESI+): m/z [M+H].sup.+=1078.4 (theoretical); 1078.3 (observed). HPLC retention time: 2.03 min.

S-(1-(3-(3-(3-((5-carbamoyl-1-((E)-4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazol-7-yl)oxy)propoxy)azetidin-1-yl)-3-oxopropyl)-2,5-dioxopyrrolidin-3-yl)-L-cysteine (Compound 30)

##STR00398##

[1583] A 1.7 mL eppendorf tube was charged with 27 (10 mM in DMSO, 100 μL, 0.00100 mmol, 1 equiv.) and L-cysteine (100 mM in DMSO, 30 μL, 0.00300 mmol, 3 equiv.) and the solution incubated at 37° C. for 30 minutes. The crude product was purified by prepHPLC (Method G, 5-95% MeCN in water with 0.05%) to give 30 as the 2×TFA salt (1.2 mg, 0.000913 mmol, 61% yield) as a white solid. MS (Method D, ESI+): m/z [M+H].sup.+=1108.4 (theoretical); 1108.5 (observed). HPLC retention time: 2.08 min.

Library Synthesis of Amide Analogs. Scheme and General Methods. Compounds 31-60.

##STR00399##

[1584] HATU Couplings (General Method 4A) To a solution of carboxylic acid (4 equiv.) in DMA (400 μL) was added HATU (6.2 mg, 0.016 mmol, 4 equiv.) and DIPEA (4.3 μL, 0.025 mmol, 6 equiv.). The mixture was stirred at room temperature for 30 minutes and then compound 7 (3 mg, 0.0041 mmol, 1 equiv.) was added to the mixture, and was heated to 70° C. for 18 hr. At which point, acetic acid (4.3 μL) was added, and resulting products were purified by prepHPLC (20-50-95% MeCN in water with 0.1% FA). All molecules were characterized using LC-MS Method D with ESI+ ionization.

[1585] COMU Couplings (General Method 4B) To a solution of carboxylic acid (4 equiv.) in DMA (400 L) was added COMU (7 mg, 0.016 mmol, 4 equiv.) and DIPEA (4.3 μL, 0.025 mmol, 6 equiv.). The mixture was stirred at room temperature for 30 min and then compound 7 (3 mg, 0.0041 mmol, 1 equiv.) was added to the mixture, and the solution was heated to 40° C. for 18 hr. At which point, acetic acid was added (4.3 μL), and the resulting products were purified by prepHPLC (20-50-95% MeCN in water with 0.1% FA).

##STR00400##

[1586] PMB deprotection (General Method 5) The resulting amide from the previous step was dissolved in 50% TFA in MeCN (0.01 M) and stirred at 30° C. for 30 min. Upon completion, the mixture was concentrated, and the product purified by prep-HPLC (20-50-95% water/acetonitrile 0.1% TFA).

[1587] Examples below were prepared using the general methods specified above.

TABLE-US-00002 Yield (over PMB LC-MS Phenol LC-MS Cmpd. Structure Method 2 steps) data data 31 [00401]embedded image HATU - Method 4a 45% 1.74 mg 0.00183 mmol RT: 1.49 Theoretical: 843.4 Observed: 843.5 RT: 1.25 Theoretical: 723.3 Observed: 723.5 32 [00402] embedded image HATU - Method 4a 58% 2.25 mg 0.00237 mmol RT: 1.67 Theoretical: 843.4 Observed: 843.5 RT: 1.42 Theoretical: 723.3 Observed: 723.5 33 [00403]embedded image HATU - Method 4a 56% 2.00 mg 0.00231 mmol RT: 1.78 Theoretical: 759.2 Observed: 759.4 RT: 1.60 Theoretical: 639.2 Observed: 639.3 34 [00404]embedded image HATU - Method 4a 61% 2.24 mg 0.00251 mmol RT: 1.92 Theoretical: 787.3 Observed: 787.4 RT: 1.74 Theoretical: 667.2 Observed: 667.4 35 [00405]embedded image HATU - Method 4a 59% 2.19 mg 0.00244 mmol RT: 2.00 Theoretical: 791.2 Observed: 791.3 RT: 1.85 Theoretical: 671.1 Observed: 671.3 36 [00406]embedded image HATU - Method 4a 40% 1.52 mg 0.00164 mmol RT: 2.14 Theoretical: 819.2 Observed: 819.4 RT: 2.01 Theoretical: 699.2 Observed: 699.3 37 [00407]embedded image COMU - Method 4b 35% 1.32 mg 0.00143 mmol RT: 2.02 Theoretical: 815.3 Observed: 815.5 RT: 1.63 Theoretical: 695.3 Observed: 695.4 38 [00408]embedded image COMU - Method 4b 39% 1.47 mg 0.00158 mmol RT: 2.02 Theoretical: 821.2 Observed: 821.4 RT: 1.63 Theoretical: 701.2 Observed: 701.3 39 [00409]embedded image COMU - Method 4b 57% 2.08 mg 0.00232 mmol RT: 1.86 Theoretical: 789.3 Observed: 789.5 RT: 1.65 Theoretical: 669.2 Observed: 669.4 40 [00410]embedded image COMU - Method 4b 36% 1.37 mg 0.00148 mmol RT: 2.00 Theoretical: 821.2 Observed: 821.4 RT: 1.61 Theoretical: 701.2 Observed: 701.3 41 [00411]embedded image HATU - Method 4a 66% 2.50 mg 0.00272 mmol RT: 2.24 Theoretical: 813.3 Observed: 813.5 RT: 1.84 Theoretical: 693.3 Observed: 693.5 42 [00412]embedded image COMU - Method 4b 45% 1.64 mg 0.00184 mmol RT: 1.59 Theoretical: 783.3 Observed: 783.4 RT: 1.31 Theoretical: 663.2 Observed: 663.4 43 [00413]embedded image COMU - Method 4b 29% 1.07 mg 0.00120 mmol

RT: 1.63 Theoretical: 783.3 Observed: 783.4 RT: 1.36 Theoretical: 663.2 Observed: 663.4 44 [00414]embedded image COMU - Method 4b 55% 2.00 mg 0.00225 mmol RT: 1.47 Theoretical: 783.3 Observed: 783.4 RT: 1.19 Theoretical: 663.2 Observed: 663.4 45 [00415]embedded image COMU - Method 4b 37% 1.36 mg 0.00153 mg RT: 1.61 Theoretical: 783.3 Observed: 783.4 RT: 1.34 Theoretical: 663.2 Observed: 663.4 46 [00416]embedded image COMU - Method 4b 63% 2.30 mg 0.00258 mmol RT: 1.62 Theoretical: 783.3 Observed: 783.4 RT: 1.34 Theoretical: 663.2 Observed: 663.4 47 [00417]embedded image COMU - Method 4b 46% 1.67 mg 0.00187 mmol RT: 1.74 Theoretical: 787.3 Observed: 787.5 RT: 1.46 Theoretical: 667.2 Observed: 667.4 48 [00418]embedded image COMU - Method 4b 60% 2.35 mg 0.00247 mmol RT: 1.79 Theoretical: 843.4 Observed: 843.5 RT: 1.52 Theoretical: 723.3 Observed: 723.5 49 [00419]embedded image COMU - Method 4b 60% 2.42 mg 0.00244 mmol RT: 2.18 Theoretical: 883.3 Observed: 883.5 RT: 1.90 Theoretical: 763.2 Observed: 763.4 50 [00420]embedded image COMU - Method 4b 55% 2.17 mg 0.00225 mmol RT: 2.17 Theoretical: 855.2 Observed: 855.4 RT: 1.59 Theoretical: 735.2 Observed: 735.3 51 [00421]embedded image COMU - Method 4b 71% 2.76 mg 0.00289 mmol RT: 1.89 Theoretical: 847.3 Observed: 847.5 RT: 1.31 Theoretical: 727.3 Observed: 727.6 52 [00422]embedded image COMU - Method 4b 51% 2.23 mg 0.00211 mmol RT: 2.50 Theoretical: 951.3 Observed: 951.6 RT: 1.99 Theoretical: 831.3 Observed: 831.6 53 [00423]embedded image COMU - Method 4b 51% 2.00 mg 0.00210 mmol RT: 2.01 Theoretical: 843.4 Observed: 843.5 RT: 1.44 Theoretical: 723.3 Observed: 723.6 54 [00424]embedded image COMU - Method 4b 52% 1.97 mg 0.00214 mmol RT: 1.86 Theoretical: 815.3 Observed: 615.5 RT: 1.28 Theoretical: 695.3 Observed: 695.5 55 [00425]embedded image HATU - Method 4a 56% 2.04 mg 0.00228 mmol RT: 1.88 Theoretical: 1027.4 Observed: 1028.0 RT: 1.35 Theoretical: 667.2 Observed: 667.8 56 [00426]embedded image COMU - Method 4b 63% 2.24 mg 0.00257 mmol RT: 1.78 Theoretical: 763.4 Observed: 763.5 RT: 1.11 Theoretical: 643.3 Observed: 643.9 57 [00427]embedded image HATU - Method 4a 60% 2.08 mg 0.00247 mmol RT: 1.31 Theoretical: 735.3 Observed: 735.7 RT: 0.99 Theoretical: 615.3 Observed: 615.6 58 [00428]embedded image HATU - Method 4a 55% 2.02 mg 0.00225 mmol RT: 1.88 Theoretical: 789.3 Observed: 789.4 RT: 1.60 Theoretical: 669.2 Observed: 669.3 59 [00429]embedded image HATU - Method 4a 56% 2.00 mg 0.00230 mmol RT: 1.81 Theoretical: 761.2 Observed: 761.4 RT: 1.56 Theoretical: 641.2 Observed: 641.3 60 [00430]embedded image HATU - Method 4a 48% 1.82 mg 0.00196 mmol RT: 1.98 Theoretical: 821.2 Observed: 821.4 RT: 1.68 Theoretical: 701.2 Observed: 701.4

Synthesis of methyl 4-chloro-3-((4-methoxybenzyl)oxy)-5-nitrobenzoate (Compound 61) ##STR00431##

Synthesis of 61a

[1588] To a solution of methyl 4-chloro-3-methoxy-5-nitrobenzoate (15 g, 61 mmol, 1 equiv.) in DC (60 mL) at 0° C. under nitrogen was added BBr.sub.3 (1 M in DCM, 153 mL, 153 mmols, 2.5 equiv.) dropwise over 20 min. The reaction mixture was stirred at 0° C. for 30 min and then allowed to warm to 25° C. and stirred for a further 12 h. The reaction mixture was cooled to 0° C., quenched with methanol, and concentrated in vacuo to give 61a (12.3 g, 56.5 mmols, 93% yield) as dark brown oil. LC-MS (Method C, ESI+): m/z [M+H].sup.+=218.0 (theoretical); 217.9 (observed). HPLC retention time: 0.21 min.

Synthesis of 61b

[1589] To a solution of 61a (26.6 g, 122 mmol, 1 equiv.) in methanol (800 mL), was added concentrated H.sub.2SO.sub.4 (600 mg, 6.11 mmol, 0.05 equiv.), the mixture was stirred at 60° C. for 12 h. LCMS analysis (Method C) showed the reaction was completed. The mixture was cooled to room temperature and concentrated in vacuo. The crude residue was diluted with water (50 mL) and saturated NaHCO.sub.3 (50 mL) was carefully added to achieve a pH>7. The resultant solid was collected by filtration, washed with water (25 mL) and dried under vacuum to give 61b (25 g, 88% yield) as a brown solid. LC-MS (Method C, EST+): m/z [M+H].sup.+=232.0 (theoretical); 231.9 (observed). HPLC retention time: 0.92 min.

Synthesis of 61

[1590] To a solution of 61b (18 g, 78 mmol, 1 equiv.) in DMF (200 mL) was added Cs.sub.2CO.sub.3 (27.9 g, 86 mmol, 1.1 equiv.) and 1-(chloromethyl)-4-methoxybenzene (12.8 g, 82 mmol, 1.05 equiv.) and the mixture was stirred at 25° C. for 16 h. LCMS analysis (Method C) showed the reaction was completed. The reaction was poured into water, filtered and dried under high vacuum to give 61 (22.3 g, 82% yield) as a light-yellow solid. .sup.1H NMR (400 MHz, DMSO-d.sub.6): δ=8.11 (d, J=1.4 Hz, 1H), 7.97 (d, J=1.4 Hz, 1H), 7.43 (d, J=8.5 Hz, 2H), 6.99 (d, J=8.5 Hz, 2H), 5.33 (s, 2H), 3.92 (s, 3H), 3.77 (s, 3H).

Synthesis of methyl (E)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1-(4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-hydroxy-5-(methoxycarbonyl)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxylate (Compound 62)

##STR00432## ##STR00433##

Synthesis of 62a

[1591] To a solution of tert-butyl (E)-(4-aminobut-2-en-1-yl)carbamate (12.5 g, 67.2 mmol, 1.1 equiv.) in DMSO (150 mL) was added methyl 4-chloro-3-methoxy-5-nitrobenzoate (15 g, 61.1 mmol, 1 equiv.) and DIPEA (39.5 g, 305 mmol, 5 equiv.) the mixture was stirred at 100° C. for 12 h. The mixture was poured into water, extracted with EtOAc and concentrated in vacuo to give 62a (16.4 g, 41.4 mmols, 68% yield) as a dark red solid. LC-MS (Method C, ESI+): m/z [M-tBu]+=340.1 (theoretical); 340.1 (observed). HPLC retention time: 1.08 min.

Synthesis of 62b

[1592] 62a (21 g, 53.1 mmol, 1 equiv.) was added to a solution of HCl in ethyl acetate (4 M, 350 mL, 1400 mmols, 26 equiv.) and the mixture was stirred at 25° C. for 2 h. The mixture was concentrated in vacuo and crude solid washed with EtOAc to give 62b as the HCl salt (14.5 g, 43.7 mmols, 82% yield) as a dark red solid. .sup.1H NMR (400 MHz, DMSO-d.sub.6): δ=8.19 (d, J=1.8 Hz, 1H), 8.12 (br s, 1H), 8.01 (br s, 3H), 7.46 (d, J=1.6 Hz, 1H), 5.87 (td, J=5.8, 15.5 Hz, 1H), 5.71-5.55 (m, 1H), 4.21 (br s, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.42-3.35 (m, 2H).

Synthesis of 62c

[1593] To a solution of 61 (4.5 g, 12.8 mmol) in DMSO (70 mL) was added 62b (4.67 g, 14.1 mmol, HCl salt) and DIPEA (8.3 g, 64 mmol, 5 equiv.) and the reaction was stirred at 80° C. for 10 h. The mixture was poured into ice water, extracted with EtOAc and concentrated in vacuo. The residue was recrystallized (ethyl acetate, 20V, reflux) to give 62c (6.4 g, 10.5 mmols, 82% yield) as a dark red solid. MS (Method C, ESI+): m/z [M+H].sup.+=611.2 (theoretical); 611.2 (observed). HPLC retention time: 1.34 min. .sup.1H NMR (400 MHz, DMSO-d.sub.6): δ=8.06 (dd, J=1.5, 9.5 Hz, 2H), 7.96 (br d, J=2.9 Hz, 2H), 7.44 (s, 1H), 7.36 (d, J=8.5 Hz, 2H), 7.30 (s, 1H), 6.94 (d, J=8.5 Hz, 2H), 5.53-5.29 (m, 2H), 5.00 (s, 2H), 4.03 (br t, J=5.4 Hz, 4H), 3.84 (s, 6H), 3.76 (d, J=3.5 Hz, 6H).

Synthesis of 62d

[1594] To a solution of 62c (6.0 g, 9.83 mmol, 1 equiv.) in MeOH (300 mL) was added NH.sub.4OH (60 mL, 28% NH.sub.3 in H.sub.2O) and Na.sub.2S204 (20.5 g, 118 mmol, 12 equiv.). The mixture was stirred at 25° C. for 16 h and went from bright red to a light yellow/nearly colorless heterogenous mixture. The mixture was filtered, concentrated to remove MeOH and the remaining aqueous solution was extracted with EtOAc. The organic phases were combined, dried with Na.sub.2SO.sub.4 and concentrated in vacuo to give 62d (4.0 g, 7.25 mmols, 74% yield) as an off white solid. MS (Method B, ESI+): m/z [M+H].sup.+=551.25 (theoretical); 551.2 (observed). HPLC retention time: 1.29 min.

Synthesis of 62e

[1595] To a solution of 62d (4.0 g, 7.25 mmol, 1 equiv.) in MeOH (200 mL) was added BrCN (4.62 g, 43.6 mmol, 6 equiv.). The mixture was stirred at 25° C. for 2 h at which point LC-MS analysis (Method C) showed full conversion. The reaction mixture was concentrated in vacuo and the crude product washed with ethanol and petroleum ether to give 62e as the 2×HBr salt (2.6 g, 3.53 mmols

49% yield) as an off white solid. MS (Method C, ESI+): m/z [M+H].sup.+=601.2 (theoretical); 601.3 (observed). HPLC retention time: 2.73 min. .sup.1H NMR (400 MHz, DMSO-d.sub.6): δ=12.87 (br s, 1H), 8.72 (br d, J=17.0 Hz, 4H), 7.59 (s, 2H), 7.42 (s, 1H), 7.26-7.16 (m, 3H), 6.82 (d, J=8.6 Hz, 2H), 5.70 (br d, J=15.7 Hz, 1H), 5.57-5.48 (m, 1H), 5.00 (s, 2H), 4.83-4.73 (m, 4H), 3.88 (s, 6H), 3.71 (s, 3H), 3.65 (s, 3H).

Synthesis of 62f

[1596] To a solution of 1-ethyl-3-methyl-1H-pyrazole-5-carboxylic acid (3.15 g, 20.5 mmol, 2.6 equiv.) in DMF (30 mL) was added HATU (8.38 g, 22.0 mmol, 2.8 equiv.) and the solution was stirred at 60° C. for 10 min. A second solution containing DIPEA (5.09 g, 39 mmol, 5 equiv.) and 62e (6.0 g, 7.87 mmol, 1 equiv. 2×HBr salt) in DMF, 30 mL) was prepared and added to the activated acid. The reaction was then stirred at 60° C. for 2 h. The solution was poured into water, filtered and triturated with acetonitrile to give 62f (2.54 g, 2.91 mmols, 37% yield) as an off-white solid. MS (Method C, ESI+): m/z [M+H].sup.+=873.4 (theoretical); 873.4 (observed). HPLC retention time: 3.44 min. .sup.1H NMR (400 MHz, DMSO-d.sub.6) 5=12.88 (br s, 2H), 7.74 (br s, 2H), 7.22 (br s, 1H), 7.16-6.97 (m, 3H), 6.66 (br d, J=7.9 Hz, 2H), 6.57-6.36 (m, 2H), 5.87-5.37 (m, 2H), 4.78 (br s, 6H), 4.51 (br dd, J=7.0, 17.3 Hz, 4H), 3.85 (s, 6H), 3.59 (s, 3H), 3.52 (br s, 3H), 2.10 (br d, J=11.1 Hz, 6H), 1.26 (td, J=6.8, 18.8 Hz, 6H).

Synthesis of 62

[1597] An oven-dried 4 mL vial with stir bar was charged with 62f (9 mg, 0.010 mmols, 1 equiv.) which was dissolved in 1:1 MeCN:TFA (1 mL) and stirred for 1 hour at room temperature. Solvent was removed in vacuo and product dried on high-vac overnight to give 62 (7.5 mg, 0.0099 mmols, quant. yield) as a tan solid. MS (Method D, ESI+): m/z [M+H].sup.+=753.3 (theoretical); 753.7 (observed). HPLC retention time: 1.99 min.

Synthesis of (E)-1-(4-(5-carboxy-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-hydroxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazole-5-carboxylic acid (Compound 63)

##STR00434##

Synthesis of 63a

[1598] Compound 62f (100 mg, 0.115 mmols, 1 equiv.) was dissolved in acetonitrile (1 mL), 1M LiOH (1 mL, 1 mmol, 9 equiv.) was added and the solution was heated to 80° C. for 1 hour. The vial was cooled, solvent removed in vacuo and product purified by prepHPLC (Method I, 5-95% MeCN in water with 0.1% TFA) to give 63a (78 mg, 0.092 mmols, 97% yield) as a white solid. MS (Method D, ESI+): m/z [M+H].sup.+=845.3 (theoretical); 845.8 (observed). HPLC retention time: 1.95 min.

Synthesis of 63

[1599] Compound 63 was prepared as previously described (see “Synthesis of 62”). MS (Method D, ESI+): m/z [M+H].sup.+=725.3 (theoretical); 725.4 (observed). HPLC retention time: 1.83 min.

Synthesis of (E)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1-(4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-hydroxy-5-(methoxycarbonyl)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxylic acid (Compound 64) and (E)-2-41-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1-(4-42-41-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-5-(methoxycarbonyl)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-7-hydroxy-1H-benzo[d]imidazole-5-carboxylic acid Compound 65)

##STR00435## ##STR00436##

Synthesis of 64a and 65a

[1600] An inseparable 1:1 mixture of compounds 64a and 65a was prepared as previously described (see “Synthesis of 65a”) substituting sodium hydroxide for lithium hydroxide and quenching the reaction at 50% conversion followed by purification via prepHPLC (Method H with 0.1% FA). MS (Method D, ESI+): m/z [M+H].sup.+=859.4 (theoretical); 859.5 (observed). HPLC retention time: 2.46 min.

Synthesis of 64 and 65

[1601] An inseparable 1:1 mixture of compounds 64a and 65a was prepared as previously described (see “Synthesis of 65a”). MS (Method D, ESI+): m/z [M+H].sup.+=739.4 (theoretical); 739.4 (observed). HPLC retention time: 1.99 and 2.04 min.

Synthesis of methyl (E)-7-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-methylpropanamido)propoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1-(4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-5-(methoxycarbonyl)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazole-5-carboxylate (Compound 66)

##STR00437## ##STR00438##

Synthesis of 66a

[1602] Compound 62 (397 mg, 0.527 mmol, 1 equiv.), tert-butyl (3-bromopropyl) (methyl)carbamate (146 mg, 0.580 mmol, 1.1 equiv.) and potassium carbonate (218 mg, 1.58 mmol, 3 equiv.) were dissolved in DMF (5.3 mL) in a 20 mL vial. The reaction was stirred at 55° C. for 18 hours and then the mixture was filtered washing with methanol and the filtrate concentrated in vacuo. To the crude solid was added cold water and the precipitate isolated via filtration to give 66a (232 mg, 0.251 mmol, 48% yield). MS (Method E, ESI+): m/z [M+H].sup.+=924.4 (theoretical); 924.9 (observed). HPLC retention time: 2.42 min.

Synthesis of 66b

[1603] Compound 66a (232 mg, 0.251 mmol, 1 equiv.) was dissolved in methanol (2.5 mL) and 4M HCl in dioxane was added (0.5 mL, 2.01 mmol, 8 equiv.). The reaction stirred at 30° C. for 90 minutes. The solvent was in vacuo and the crude product purified by prepHPLC (Method I with 0.05% TFA) to afford 66b (206 mg, 0.24 mmol, 96% yield). MS (Method E, ESI+): m/z [M+H].sup.+=824.4 (theoretical); 824.9 (observed). HPLC retention time: 1.56 min.

Synthesis of 66

[1604] Compound 66 (25 mg, 0.0291 mmol, 1 equiv.) and MP-OSu (11.6 mg, 0.0436 mmol, 1.5 equiv.) were dissolved in DMA (0.58 mL) and DIPEA (20 μL, 0.116 mmol) was added. The reaction was stirred at room temperature for 1 hour. The mixture was directly purified by prepHPLC (Method H, with 0.05% TFA) to afford 66 as a white solid (10.88 mg, 0.0112 mmol, 38% yield). MS (Method D, ESI+): m/z [M+H].sup.+=975.4 (theoretical); 975.4 (observed). HPLC retention time: 2.24 min.

Synthesis of (2S,3S,4S,5R,6S)-6-(3-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)-4-((((3-((2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1-((E)-4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-5-(methoxycarbonyl)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-5-(methoxycarbonyl)-1H-benzo[d]imidazol-7-yl)oxy)propyl)(methyl)carbamoyl)oxy)methyl)phenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid (Compound 67)

##STR00439## ##STR00440##

Synthesis of 67a

[1605] Compound 13a (65 mg, 0.0868 mmol, 1.4 equiv.) and bis(pentafluorophenyl) carbonate (120 mg, 0.304 mmol, 5 equiv.) were dissolved in DMA (0.43 mL) and DIPEA (70 μL, 0.404 mmol, 6.7 equiv.) was added. The reaction was stirred for 30 minutes and then 66b (52 mg, 0.0607 mmol, 1 equiv.) was added. The reaction was stirred at room temperature for 18 hours. The solution was diluted with H.sub.2O and extracted with EtOAc (3×), and the combined organics were washed with 1M HCl (3×), dried with MgSO.sub.4, filtered and solvent removed in vacuo to give a crude solid. This material was dissolved in DMSO and purified by prepHPLC (Method H, with 0.05% TFA) to give 67a as a white solid (33.1 mg, 0.0207 mmol, 34% yield). LCMS (Method D, ESI+) m/z [M+H]+ 1598.6 (theoretical), 1598.6 (observed). LCMS retention time 2.65 min.

[1606] MS (Method D, ESI+): m/z [M+H].sup.+=1598.6 (theoretical); 1598.6 (observed). HPLC retention time: 2.65 min.

Synthesis of 67b

[1607] Compound 67a (33.1 mg, 0.0207 mmol) was dissolved in dry methanol (0.21 mL), cooled in an ice bath, and 0.5M NaOMe in MeOH (41.5 μL, 0.0414 mmol, 2 equiv.) was added. The reaction was monitored by LCMS (Method D) and upon full acetate deprotection, 1M LiOH (62 μL, 0.0621 mmol, 3 equiv.) was added. The reaction stirred at room temperature for 1h monitoring by LCMS (Method E). Upon full conversion, acetic acid (62 L) was added, solvent removed in vacuo and crude product purified via prepHPLC (Method H, with 0.05% TFA) to give 67b as a white solid (10.1 mg, 0.0075 mmol, 36% yield). LCMS (Method D, ESI+) m/z [M+H]+ 1236.5 (theoretical), 1236.5 (observed). LCMS retention time 2.31 min.
[1608] MS (Method D, ESI+): m/z [M+H].sup.+=1236.5 (theoretical); 1236.5 (observed). HPLC retention time: 2.31 min.
Synthesis of 67
[1609] Compound 67b (10.1 mg, 0.0075 mmol, 1 equiv.) and MP-OSu (3.0 mg, 0.0112 mmol, 1.5 equiv.) were dissolved in DMA (150 μL), DIPEA (4 μL, 0.0224 mmol) was added. The reaction was stirred for 30 min at room temperature at which point acetic acid (4 μL) was added, and the mixture was purified via prepHPLC (Method G, with 0.05% TFA) to obtain 67 as a white solid (3.3 mg, 0.0024 mmol, 32% yield). LCMS (Method E, ESI+) m/z [M+H]+ 1387.5 (theoretical), 1387.5 (observed). LCMS retention time 1.92 min.
[1610] MS (Method E, ESI+): m/z [M+H].sup.+=1387.5 (theoretical); 1387.5 (observed). HPLC retention time: 1.92 min.
Synthesis of (E)-1-(4-(5-carboxy-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-7-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-methylpropanamido)propoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazole-5-carboxylic acid (Compound 68)
##STR00441##
Synthesis of 68a
[1611] Compound 66b (30 mg, 0.032 mmol) was dissolved in methanol (0.32 mL) and 1M LiOH (0.256 mL, 0.256 mmols, 8 equiv.) was added. The mixture was stirred at 80° C. for 1h. The mixture was concentrated in vacuo and purified via prepHPLC (Method H with 0.05% TFA) to afford 68a as a white solid (17.4 mg, 0.0191 mmol, 60% yield). MS (Method D, ESI+): m/z [M+H].sup.+=796.4 (theoretical); 796.4 (observed). HPLC retention time: 1.83 min.
Synthesis of 68
[1612] Compound 68a (16.7 mg, 0.0183 mmol, 1 equiv.) and MP-OSu (7.3 mg, 0.0275 mmol, 1.5 equiv.) were dissolved in DMA (0.37 mL) and DIPEA (10 μL, 0.0574 mmol, 2 equiv.) was added. The reaction was stirred at room temperature for 1 hour, AcOH (10 μL) was added and the crude product was purified via prepHPLC (Method H with 0.05% TFA) to afford 68 as a white solid (7.6 mg, 0.0080 mmol, 44% yield). MS (Method D, ESI+): m/z [M+H].sup.+=974.4 (theoretical); 974.4 (observed). HPLC retention time: 2.42 min.
Synthesis of 1-((E)-4-(5-carboxy-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-7-(3-((((4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-2-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamidobenzyl)oxy)carbonyl) (methyl)amino)propoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazole-5-carboxylic acid (Compound 69)
##STR00442## ##STR00443##
Synthesis of 69a
[1613] Compound 69a was prepared as previously described (see “Synthesis of 67a”). MS (Method E, ESI+): m/z [M+H].sup.+=1570.6 (theoretical); 1570.4 (observed). HPLC retention time: 1.95 min.
Synthesis of 69b
[1614] Compound 69b was prepared as previously described (see “Synthesis of 67b”). MS (Method E, ESI+): m/z [M+H].sup.+=1208.5 (theoretical); 1208.3 (observed). HPLC retention

time: 1.48 min.
Synthesis of 69
[1615] Compound 69 was prepared as previously described (see “Synthesis of 67”). MS (Method E, ESI+): m/z [M+H].sup.+=1359.5 (theoretical); 1359.4 (observed). HPLC retention time: 1.68 min.
Synthesis of (E)-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-(3-morpholinopropoxy)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazole-5-carboxamide (Compound 701
##STR00444##
Synthesis of 70
[1616] To a solution of compound A (6 mg, 0.00706 mmol) in dry DCM (0.10 mL) was added BBr.sub.3 (0.04 mL, 1M in DCM) dropwise. The slurry that formed was stirred overnight at 30° C. under argon. The reaction was monitored by UPLC-MS. Upon completion, cold water (0.10 mL) was added and the mixture was stirred vigorously. After 30 min., the solvent was evaporated, and the product purified by prepHPLC (Method G) using formic acid as the additive. Pure fractions were collected, frozen, and lyophilized to afford compound 70 (5.14 mg, 0.00528 mmol, 75% yield) as a white solid. UPLC-MS (Method D, EST+): m/z [M+H].sup.+=836.9 (theoretical), 836.6 (observed). HPLC retention time: 1.34 min.
[1617] The cysteine adducts of compounds 17-24 were prepared using the following method.
[1618] General Method 6. A 10 mM solution of maleimide was incubated with 1 equiv. of L-cysteine (100 mM in water) at 37° C. for 1 hour and the product used without any further purification.
TABLE-US-00003 Compound Structure LC-MS data 71 [00445]  embedded image RT: 1.17 Theoretical: 1181.5 Observed: 1182.1 72 [00446]  embedded image RT: 1.21 Theoretical: 1195.5 Observed: 1195.7 73 [00447]  embedded image RT: 1.17 Theoretical: 1123.5 Observed: 1124.0 74 [00448]  embedded image RT: 1.19 Theoretical: 1137.5 Observed: 1137.9 75 [00449]  embedded image RT: 1.16 Theoretical: 1153.5 Observed: 1153.8 76 [00450]embedded image RT: 1.19 Theoretical: 1167.5 Observed: 1168.0
Synthesis of tert-butyl (3-(5-carbamoyl-2-chloro-3-nitrophenoxy)propyl)(methyl)carbamate (Compound 77)
##STR00451##
[1619] A flame-dried 100 mL RB with stir bar was charged with a solution of 2b (1.0 g, 4.62 mmol, 1 equiv.) in DMF (10 mL), potassium carbonate (830 mg, 6.00 mmol, 1.3 equiv.) and a solution of tert-butyl N-(3-bromopropyl)-N-methyl-carbamate (1.20 eq, 1.40 g, 5.54 mmol, 1.20 equiv.) in DMF (5 mL). Additional DMF was added to bring the total volume to 45 mL and the reaction was heated to 70° C. for 24 hours. The reaction was cooled to room temperature and filtered over celite washing with DMF (3×10 mL). This solution was poured into ice water (900 mL), stirred for 90 minutes and crude product isolated via filtration. Finally, the filtrate was washed with cold water (300 mL) and dried in vacuo overnight to give 77 (1.23 g, 3.16 mmol, 68% yield).
Synthesis of tert-butyl (E)-(3-((2-amino-5-carbamoyl-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazol-7-yl)oxy)propyl)(methyl)carbamate (Compound 78)
##STR00452## ##STR00453##
Synthesis of 78a
[1620] A 500 mL round bottom flask with stir bar was charged with 4a (3.0 g, 7.9 mmol, 1 equiv.) and sodium bicarbonate (12.5 g, 148 mmol, 19 equiv.) and ethanol (105 mL) was added to give a heterogenous solution. This solution was cooled in an ice-bath and a solution of sodium hydrosulfite (25.8 g, 148 mmol, 19 equiv.) in 105 mL water was added dropwise at such a rate to keep the internal temperature below 10° C. The mixture was heated open to the atmosphere to 45° C. for 1 hour and cooled to room temperature. The mixture was filtered over celite, washing with

EtOH (100 mL) and solvent removed in vacuo. The crude material was redissolved in 1:1 DCM:MeOH (200 mL), filtered over celite and solvent removed in vacuo. This procedure was repeated once more and then the crude product was loaded onto celite and purified by flash chromatography (50 g Sfar HC Duo, SiO2 column, 0-40% 10:1 NH.sub.4OH:MeOH in DCM) to give 78a (1.45 g, 4.13 mmol, 52% yield). MS (Method D, EST+): m/z [M+H].sup.+=351.2 (theoretical); 351.1 (observed). HPLC retention time: 1.53 min.

Synthesis of 78b

[1621] An oven-dried 200 mL round bottom flask was charged with 78a (1.95 g, 5.58 mmol, 1 equiv.) which was dissolved in methanol (45 mL) and cyanogen bromide (3M in DCM, 5.6 mL, 16.7 mmol, 3 equiv.) was added to give a yellow homogenous solution. The reaction was stirred at room temperature for 48 hours and solvent removed in vacuo to give 78b as the HBr salt (2.48 g, 5.44 mmol, 98% yield). MS (Method D, ESI+): m/z [M+H]J=376.2 (theoretical); 376.1 (observed). HPLC retention time: 0.71 min.

Synthesis of 78c

[1622] A flame dried 40 mL vial with stir bar was charged with 78b HBr (867 mg, 1.90 mmol, 1 equiv.), 2-ethyl-5-methyl-pyrazole-3-carboxylic acid (879 mg, 5.70 mmol, 3 equiv.), and HATU (2.17 g, 5.70 mmol, 3 equiv.). The solids were dissolved in DMF (15 mL) and then DIPEA (2.0 mL, 11.4 mmol, 6 equiv.) was added. The vial was sealed and stirred at room temperature for 48 hours. The solution was poured into ice-cold water (450 mL) with NH4OH (28% NH.sub.3 in water, 10 mL) and allowed to precipitate at 4° C. overnight. The white precipitate was isolated via filtration and dried in vacuo overnight to give 78c (658 mg, 1.29 mmol, 68% yield). MS (Method D, ESI+): m/z [M+H].sup.+=512.3 (theoretical); 512.2 (observed). HPLC retention time: 2.35 min.

Synthesis of 78d

[1623] An oven dried 8 mL, vial with stir bar was charged with 78c (800 mg, 1.56 mmol, 3 equiv.) which was stirred in 3M HCl in MeOH (5.2 mL, 15.6 mmol HCl, 10 equiv.) for 1 hour. The solvent removed in vacuo to give 78d as the 2×HCl salt (700 mg, 1.56 mmol, quantitative yield). MS (Method D, ESI+): m/z [M+H].sup.+=412.2 (theoretical); 412.5 (observed). HPLC retention time: 0.73 min.

Synthesis of 78e

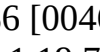
[1624] An oven-dried 20 mL microwave vial was charged with 78e (700 mg, 1.56 mmol, 1 equiv.), 77 (909 mg, 2.34 mmol, 1.5 equiv.) and sodium carbonate (497 mg, 4.69 mmol, 3 equiv.) and to the mixture was added 1-butanol (15 mL) and DIPEA (1.6 mL, 9.38 mmol, 6 equiv.). The vial was scaled and heated in a microwave reactor at 140° C. for 3 hours to give a bright red heterogenous mixture. This mixture was poured into DCM (100 mL) and filtered over celite washing with DCM (50 mL) and MeOH (50 mL). The crude product was loaded onto celite and purified via flash chromatography (50 g Sfar HC Duo, SiO2 column, 0-20% MeOH in DCM) to give 78e (569 mg, 0.746 mmol, 48% yield) as a bright red solid. MS (Method D, ESI+): m/z [M+H].sup.+763.4 (theoretical); 763.4 (observed). HPLC retention time: 2.17 min.

Synthesis of 78f

[1625] To a mixture of 78e (569 mg, 0.746 mmol, 1 equiv.) in methanol (8 mL) and NH.sub.4OH (2.0 mL, 28% NH.sub.3 in water) was added a solution of sodium hydrosulfite (2.34 g, 13.4 mmol, 18 equiv.) in water (8 mL). This solution was heated at 50° C. for 1 hour. The reaction was poured into a separatory funnel containing water (250 mL) and EtOAc (250 mL). The mixture was shaken, layers separated and the aqueous layer was further extracted with EtOAc (3×100 mL). The organics were combined, washed with brine (2×100 mL), dried with MgSO.sub.4, filtered and solvent removed in vacuo to give 78f (400 mg, 0.546 mmol, 73% yield) as a tan solid. MS (Method D, ESI+): m/z [M+H].sup.+=733.4 (theoretical); 733.6 (observed). HPLC retention time: 1.39 min.

Synthesis of 78

[1626] To a solution of 78f (1.00 eq, 400 mg, 0.546 mmol) in methanol (5.5 mL) was added cyanogen bromide (3M in DCM, 0.55 mL, 1.65 mmol, 3 equiv.) and the mixture was stirred at

room temperature for 24 hours. The solvent was removed in vacuo to give 78 as the HBr salt (456 mg, 0.544 mmol, quantitative yield). MS (Method D, ESI+): m/z [M+H].sup.+=758.4 (theoretical); 758.6 (observed). HPLC retention time: 1.19 min.
Library Synthesis of Amide Analogs, Group #2. Scheme and General Methods. Compounds 71-95.
##STR00454##
[1627] COMU Couplings (General Method 7A): A 2 mL microwave vial was charged with a solution of compound 78 (20 mg, 0.0238 mmol, 1 equiv.) in DMA (0.50 mL). The respective carboxylic acid (2 equiv.), COMU (20.4 mg, 0.0477 mmol, 2 equiv.) and DIPEA (20.8 μL, 0.119 mmol, 5 equiv.) were added. The vial was sealed and heated to 80° C. in a microwave reactor for 1h. The reaction was monitored via UPLC-MS (Method E, ESI+). Upon completion, acetic acid (20 μL) was added and the resulting product was purified by prepHPLC (Method H) using 0.05% TFA as the additive. Pure fractions were collected, frozen, and lyophilized to afford product as a white solid.
[1628] HATU Couplings (General Method 7B): A 2 mL microwave vial was charged with a solution of compound 78 (20 mg, 0.0238 mmol, 1 equiv.) in DMA (0.50 mL). The respective carboxylic acid (4 equiv.), HATU (36.3 mg, 0.0954 mmol, 2 equiv.) and DIPEA (20.8 μL, 0.119 mmol, 5 equiv.) were added. The vial was sealed and heated to 80° C. a microwave reactor for 1h. The reaction was monitored via UPLC-MS (Method E, ESI+). Upon completion, acetic acid (20 L) was added and the resulting product was purified by prepHPLC (Method H) using 0.05% TFA as the additive. Pure fractions were collected, frozen, and lyophilized to afford product as a white solid.
##STR00455##
[1629] Boc Deprotection (General Method 8): The resulting product general method 7A or 7B was dissolved in MeOH (0.01 M), to which 4M HCl in dioxane (8 equiv.) was added. The solution stirred at room temperature for 30 min. The reaction was monitored via UPLC-MS (Method E, ESI+). Upon completion, the solution was concentrated, redissolved in DMSO, and purified via prepHPLC (Method G or H) using TFA as the additive. Pure fractions were collected, frozen, and lyophilized to afford product as a white solid.
TABLE-US-00004 Yield Boc LC- Amine LC- (over 2 Cmpd. Structure Method MS data MS data steps) 79 [00456]  embedded image 7A RT: 1.57 Theoretical: 864.4 Observed: 864.7 Theoretical: RT: 1.32 764.3 Observed: 764.4 17% 4.5 mg 0.00406 mmol 80 [00457]  embedded image 7A RT: 2.18 Theoretical: 864.4 Observed: 864.4 Theoretical: RT: 1.24 764.3 Observed: 764.4 19% 5.0 mg 0.00455 mmol 81 [00458]  embedded image 7A RT: 1.79 Theoretical: 867.4 Observed: 867.7 Theoretical: RT: 1.55 767.3 Observed: 767.3 18% 4.8 mg 0.00436 mmol 82 [00459]
 embedded image 7A RT: 1.83 Theoretical: 867.4 Observed: 967.4 Theoretical: RT: 1.37 767.3 Observed: 767.3 9% 2.4 mg 0.00216 mmol 83 [00460]  embedded image 7B RT: 1.85 Theoretical: 883.4 Observed: 883.4 Theoretical: RT: 1.35 783.3 Observed: 783.3 10% 2.8 mg 0.00247 mmol 84 [00461]  embedded image 7A RT: 1.69 Theoretical: 864.4 Observed: 864.4 Theoretical: RT: 1.18 764.3 Observed: 764.4 5% 1.2 mg 0.00110 mmol 85 [00462]  embedded image 7B RT: 1.75 Theoretical: 894.4 Observed: 894.5 Theoretical: RT: 1.31 794.4 Observed: 794.4 3% 0.88 mg 0.00077 mmol 86 [00463]  embedded image 7B RT: 1.59 Theoretical: 894.4 Observed: 894.5 Theoretical: RT: 1.19 794.4 Observed: 794.4 11% 3.1 mg 0.00270 mmol 87 [00464]
 embedded image 7B RT: 1.70 Theoretical: 894.4 Observed: 894.5 Theoretical: RT: 1.38 794.4 Observed: 794.4 13% 3.5 mg 0.00307 mmol 88 [00465]  embedded image 7B RT: 1.63 Theoretical: 880.4 Observed: 880.5 Theoretical: RT: 1.28 780.4 Observed: 780.4 16% 4.4 mg 0.00391 mmol 89 [00466]  embedded image 7B RT: 1.77 Theoretical: 894.4 Observed: 894.5 Theoretical: RT: 1.46 794.4 Observed: 794.4 9% 2.4 mg 0.00211 mmol 90 [00467]
 embedded image 7B RT: 1.70 Theoretical: 883.4 Observed: 883.4 Theoretical: RT: 1.30 783.3 Observed: 783.4 17% 4.7 mg 0.00416 mmol 91 [00468]  embedded image 7B RT: 1.65 Theoretical: 880.4 Observed: 880.5 Theoretical: RT: 1.32 780.4 Observed: 780.4 6% 1.7 mg

0.00153 mmol 92 [00469]embedded image 7B RT: 1.83 Theoretical: 948.4 Observed: 948.5 Theoretical: RT: 1.49 848.4 Observed: 848.4 10% 2.7 mg 0.00229 mmol 93 [00470]
embedded image 7B RT: 1.74 Theoretical: 880.4 Observed: 880.5 Theoretical: RT: 1.37 780.4 Observed: 780.4 22% 5.9 mg 0.00529 mmol 94 [00471]embedded image 7B RT: 1.88 Theoretical: 911.4 Observed: 911.5 Theoretical: RT: 1.38 811.3 Observed: 811.4 30% 8.1 mg 0.00703 mmol 95 [00472]embedded image 7B RT: 1.86 Theoretical: 895.4 Observed: 895.5 Theoretical: RT: 1.41 795.4 Observed: 795.4 8% 2.1 mg 0.0018 mmol
##STR00473##
[1630] Maleimide Couplings (General Method 9): The resulting amine from the previous reaction (compounds 79-95) was dissolved in DMSO (0.01M), to which was added MP-OSu (2 equiv.) and DIPEA (5 equiv.). The mixture was stirred at 30° C. overnight, and monitored by UPLC-MS (Method E, ESI+). Upon completion, the resulting product was purified via prepHPLC (Method G) using 0.05% TEA as the additive.
TABLE-US-00005 LC-MS data Cmpd. Structure [M + H].sup.+ Yield 96 [00474]
embedded image RT: 1.38 Theoretical: 915.4 Observed: 915.4 68% 3.14 mg 0.0027 mmol 97 [00475]embedded image RT: 1.65 Theoretical: 918.4 Observed: 918.4 62% 3.11 mg 0.0027 mmol 98 [00476]embedded image RT: 1.42 Theoretical: 915.4 Observed: 915.4 84% 4.38 mg 0.0038 mmol 99 [00477]embedded image RT: 1.47 Theoretical: 934.3 Observed: 934.4 31% 0.89 mg 0.0008 mmol 100 [00478]embedded image RT: 1.50 Theoretical: 918.4 Observed: 918.4 53% 1.3 mg 0.0011 mmol 101 [00479]embedded image RT: 1.35 Theoretical: 915.4 Observed: 915.4 86% 5.88 mg 0.0051 mmol 102 [00480]embedded image RT: 1.45 Theoretical: 945.4 Observed: 945.4 40% 0.36 mg 0.0003 mmol 103 [00481]embedded image RT: 1.37 Theoretical: 945.4 Observed: 945.4 41% 1.29 mg 0.0011 mmol 104 [00482]embedded image RT: 1.67 Theoretical: 945.4 Observed: 945.5 52% 1.87 mg 0.0016 mmol 105 [00483]embedded image RT: 1.48 Theoretical: 931.4 Observed: 931.4 88% 4.00 mg 0.0035 mmol 106 [00484]embedded image RT: 1.61 Theoretical: 945.4 Observed: 945.4 31% 0.76 mg 0.0006 mmol 107 [00485]
embedded image RT: 1.45 Theoretical: 934.3 Observed: 934.4 51% 2.46 mg 0.0021 mmol 108 [00486]embedded image RT: 1.49 Theoretical: 931.4 Observed: 931.4 53% 0.94 mg 0.0008 mmol 109 [00487]embedded image RT: 1.83 Theoretical: 999.4 Observed: 999.4 51% 1.43 mg 0.0012 mmol 110 [00488]embedded image RT: 1.50 Theoretical: 931.4 Observed: 931.4 63% 3.86 mg 0.0033 mmol 111 [00489]embedded image RT: 1.50 Theoretical: 962.4 Observed: 962.4 40% 3.39 mg 0.0028 mmol 112 [00490]embedded image RT: 1.59 Theoretical: 946.4 Observed: 946.4 31% 0.67 mg 0.0006 mmol
Synthesis of methyl (E)-1-(4-(5-carbamoyl-7-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-methylpropanamido)propoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazole-5-carboxylate (Compound 113)
##STR00491## ##STR00492## ##STR00493##
Synthesis of methyl (E)-3-amino-4-((4-((tert-butoxycarbonyl)amino)but-2-en-1-yl)amino)-5-methoxybenzoate (Compound 113a)
##STR00494##
[1631] Compound 62a (500 mg, 1.26 mmol, 1 equiv.) was dissolved in MeOH (20 mL) and NH.sub.4OH (6 mL). Na.sub.2S.sub.2O.sub.4 (1.10 g, 6.32 mmol, 5 equiv.) in H2O (5 mL) was slowly added and the mixture stirred at room temperature for 30 min. The reaction was monitored by UPLC-MS (Method E, ESI+). Upon completion, the mixture was filtered and concentrated. The resulting product was redissolved in EtOAc and washed with H.sub.2O (×3). The organics were collected, dried with MgSO.sub.4, filtered, and concentrated to afford compound 113a (343 mg, 0.938 mmol, 74% yield) as a yellow solid. The resulting product was used without further purification. UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=366.2 (theoretical), 366.2 (observed). HPLC retention time: 1.54 min.

Synthesis of methyl (E)-2-amino-1-(4-((tert-butoxycarbonyl)amino)but-2-en-1-yl)-7-methoxy-1H-benzo[d]imidazole-5-carboxylate hydrobromide (Compound 113b)
##STR00495##
[1632] Compound 113a (343 mg, 0.938 mmol, 1 equiv.) was dissolved in MeOH (9.3 mL) to which CNBr (3 M in MeCN, 0.374 mL, 1.2 equiv.) was added. The reaction stirred for 18 h at room temperature, and monitored by UPLC-MS (Method E, ESI+). Upon completion, the solution was concentrated to afford compound 113b (402 mg, 0.853 mmol, 91% yield), which was used without further purification. UPLC-MS (Method E, EST+): m/z [M+H].sup.+=391.2 (theoretical), 391.1 (observed). HPLC retention time: 1.51 min.
Synthesis of methyl (E)-1-(4-((tert-butoxycarbonyl)amino)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazole-5-carboxylate (Compound 113c)
##STR00496##
[1633] Compound 113b (402 mg, 0.853 mmol, 1 equiv.), 1-ethyl-3-methyl-1H-pyrazole-5-carboxylic acid (394 mg, 2.56 mmol, 3 equiv.) and HATU (973 mg, 2.56 mmol, 3 equiv.) were dissolved in DMA (1.7 mL) in a 5 mL microwave vial. DIPEA (0.74 mL, 4.26 mmol, 5 equiv.) was added, and the reaction was heated to 80° C. in a microwave reactor for 1 h. The reaction was monitored via UPLC-MS (Method E, ESI+). Upon completion, the reaction mixture was slowly added to ice-cold water (300 mL) to precipitate compound 113c (295 mg, 0.560 mmol, 66% yield), which was used without further purification. UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=527.3 (theoretical), 527.1 (observed). HPLC retention time: 2.30 min.
Synthesis of methyl (E)-1-(4-aminobut-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazole-5-carboxylate (Compound 113d)
##STR00497##
[1634] Compound 113c (319 mg, 0.606 mmol, 1 equiv.) was dissolved in MeOH (1 mL), to which HCl in dioxane (4 M, 1.2 mL, 4.85 mmol, 8 equiv.) was added. The reaction was stirred at room temperature for 30 min. and was monitored by UPLC-MS (Method E, ESI+). Upon completion, the solution was concentrated and compound 113d (280 mg, 0.605 mmol, quantitative yield) was used without further purification. UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=427.2 (theoretical), 427.2 (observed). HPLC retention time: 1.54 min.
Synthesis of methyl (E)-1-(4-((2-(3-((tert-butoxycarbonyl)(methyl)amino)propoxy)-4-carbamoyl-6-nitrophenyl)amino)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazole-5-carboxylate (Compound 113e)
##STR00498##
[1635] Compound 113d (280 mg, 0.605 mmol, 1 equiv.) and compound 77 (305 mg, 0.787 mmol, 1.3 equiv.) were dissolved in DMSO (3.0 mL) to which DIPEA (0.316 mL, 1.82 mmol, 3 equiv.) was added. The reaction stirred at 80° C. for 18 h and monitored via UPLC-MS (Method E, ESI+). Upon completion, AcOH (0.30 mL) was added, and the product was purified by prepHPLC (Method T) using 0.05% TFA as the additive. Pure fractions were collected, frozen, and lyophilized to afford compound 113e (58.6 mg, 0.0753 mmol, 12% yield) as an orange solid. UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=778.3 (theoretical), 778.4 (observed). HPLC retention time: 1.88 min.
Synthesis of methyl (E)-1-(4-((2-amino-6-(3-((tert-butoxycarbonyl)(methyl)amino)propoxy)-4-carbamoylphenyl)amino)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazole-5-carboxylate (Compound 113f)
##STR00499##
[1636] Compound 113e (58.6 mg, 0.0753 mmol, 1 equiv.) was dissolved in a 1:1 mixture of AcOH/DCM (0.75 mL) and cooled to 0° C. Zn (49.2 mg, 0.753 mmol, 10 equiv.) was added and the mixture was allowed to warm to room temperature while stirring for 30 min. The reaction was monitored via UPLC-MS (Method E, ESI+). Upon completion, the solution was concentrated and redissolved in DCM to be purified by flash chromatography (25 g SiO2 column, 0-40%

MeOH:NH.sub.4OH (10:1) in DCM) to afford compound 113f (28.3 mg, 0.378 mmol, 50% yield). UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=748.4 (theoretical), 748.4 (observed). HPLC retention time: 1.84 min.

Synthesis of methyl (E)-1-(4-(2-amino-7-(3-((tert-butoxycarbonyl)(methyl)amino)propoxy)-5-carbamoyl-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazole-5-carboxylate (Compound 113g)

##STR00500##

[1637] Compound 113f (28.3 mg, 0.378 mmol, 1 equiv.) was dissolved in MeOH (0.38 mL) to which CNBr (3 M in MeCN, 15 μL, 0.0454 mmol, 1.2 equiv.) was added. The reaction stirred at room temperature for 18 h and was monitored via UPLC-MS (Method E, ESI+). Upon completion, the solution was concentrated to afford product 113g (30.7 mg, 0.360 mmol, quantitative yield), which was used without further purification. UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=773.4 (theoretical), 773.4 (observed). HPLC retention time: 1.53 min.

Synthesis of methyl (E)-1-(4-(7-(3-((tert-butoxycarbonyl)(methyl)amino)propoxy)-5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazole-5-carboxylate (Compound H)

##STR00501##

[1638] Compound 113g (30.7 mg, 0.0360 mmol, 1 equiv.), 1-ethyl-3-methyl-1H-pyrazole-5-carboxylic acid (22.1 mg, 0.144 mmol, 4 equiv.), and HATU (54.6 mg, 0.144 mmol, 4 equiv.) were dissolved in DMA (0.50 mL) in a 2 mL microwave vial. DIPEA (0.025 mL, 0.144 mmol, 4 equiv.) was added, and the reaction was heated in a microwave reactor at 80° C. for 1 h. The reaction was monitored via UPLC-MS (Method E, ESI+). Upon completion, the product was purified by prepHPLC (Method H) using 0.05% TFA as the additive. Pure fractions were collected, frozen, and lyophilized to afford compound 113h (6.52 mg, 0.0064 mmol, 18% yield) as a white solid. UPLC-MS (Method E, ESI+): m/z [M+H]=909.4 (theoretical), 909.5 (observed). HPLC retention time: 1.90 min.

Synthesis of methyl (E)-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-(3-(methylamino)propoxy)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazole-5-carboxylate (Compound 113i)

##STR00502##

[1639] Compound 113h (3.02 mg, 0.0030 mmol, 1 equiv.) was dissolved in MeOH (0.30 mL) to which HCl in dioxane (4 M, 6.00 μL, 0.0236 mmol, 8 equiv.) was added. The reaction stirred for 30 min at room temperature and monitored via UPLC-MS (Method E, ESI+). Upon completion, the product was purified via prepHPLC (Method G) using 0.05% TFA as the additive. Pure fractions were collected, frozen, and lyophilized to afford compound 113i (1.35 mg, 0.0013 mmol, 44% yield) as a white solid. UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=809.4 (theoretical), 809.4 (observed). HPLC retention time: 1.57 min.

##STR00503##

[1640] Compound 113i (7.53 mg, 0.0085 mmol, 1 equiv.) and MP-OSu (4.55 mg, 0.0171 mmol, 2 equiv.) were dissolved in DMA (0.854 mL), and DIPEA (42.7 μL, 0.0074 mmol, 5 equiv.) was added. The reaction stirred at room temperature for 18 h and monitored by UPLC-MS (Method E, ESI+). Upon completion, AcOH (42 μL) was added, and the product was purified via prepHPLC (Method G) using 0.05% TFA as the additive. Pure fractions were collected, frozen, and lyophilized to afford compound 113 (4.43 mg, 0.0041 mmol, 48% yield) as a white solid. UPLC-MS (Method E, ESI+): m/z [M+]H.sup.+=960.4 (theoretical), 960.5 (observed). HPLC retention time: 1.79 min.

Linker Library Synthesis (Compounds 114-124).

##STR00504##

[1641] Amide coupling (General Method 10): A mixture of Compound 12a (1 equiv.), HATU (2 equiv.), DIPEA (5 equiv.), the appropriate L-amino acid (2 equiv.) was prepared in DMF (0.02 M in

12a) and stirred at room temperature overnight. The solvent was removed in vacuo, and resulting product used in the next step without further purification.
[1642] Fmoc deprotection (General Method 11): The resulting Fmoc-protected amine was dissolved in 20% piperidine in DMF (1 mL) and stirred at room temperature for 15 minutes. The solvent was removed in vacuo and the product purified via prep HPLC (Method H, 5-95% in McCN in H.sub.2O in 0.05% TFA).
TABLE-US-00006 Compound UPLC-MS [M + H].sup.+ Yield [00505]  embedded image RT: 1.83 min Theoretical: 907.5 Observed: 907.5 18.6 mg (58%) [00506]  embedded image RT: 1.77 Theoretical: 907.5 Observed: 907.5 24.9 mg (78%) [00507]embedded image RT: 1.76 Theoretical: 941.5 Observed: 941.5 13.5 mg (28%) [00508]  embedded image RT: 2.05 Theoretical: 937.4 Observed: 937.5 9.8 mg (35%) [00509]  embedded image RT: 1.93 Theoretical: 971.5 Observed: 971.5 18.6 mg (64%) [00510]  embedded image RT: 1.93 Theoretical: 945.5 Observed: 945.5 19.4 (64%) [00511]  embedded image RT: 2.05 Theoretical: 909.4 Observed: 909.5 24.5 mg (76.4%)
##STR00512##
[1643] Synthesis of maleimide containing drug-linkers (compounds 121-125) was performed according to General Method 9.
TABLE-US-00007 UPLC-MS Compound [M + H].sup.+ Yield [00513]  embedded image RT: 2.16 Theoretical: 1058.5 Observed: 1058.5 1.5 mg (42%) [00514]  embedded image RT: 2.00 Theoretical: 1092.5 Observed: 1092.5 0.5 mg (21%) [00515]  embedded image RT: 2.21 Theoretical: 1088.5 Observed: 1088.5 1.1 mg (32%) [00516]  embedded image RT: 1.81 Theoretical: 1122.5 Observed: 1122.6 1.1 mg (32%) [00517]  embedded image RT: 1.79 Theoretical: 1060.5 Observed: 1060.5 0.3 mg (8.6%)
(E)-1-(4-(5-carbamoyl-7-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-methylpropanamido)propoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazole-5-carboxylic acid (Compound 126)
##STR00518##
Synthesis of Compound 126a
[1644] Compound 113h (25.44 mg, 0.0249 mmol, 1 equiv.) was dissolved in MeOH (166 μL). An aqueous solution of 1M LiOH (200 μL, 8 equiv.) was added and the reaction was stirred at 80° C. for 2h. Upon completion, the solution was concentrated under reduced pressure and purified by prepHPLC (Method H) using 0.05% TFA as the additive. Pure fractions were collected, frozen, and lyophilized to afford compound 126a (7.1 mg, 0.0071 mmol, 28% yield) as a white solid. UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=895.4 (theoretical), 895.6 (observed). HPLC retention time: 1.97 min.
Synthesis of compound 126b
[1645] Compound 126b was prepared following the same procedure used to prepare compound 113i. UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=795.4 (theoretical), 795.6 (observed). HPLC retention time: 1.40 min.
Synthesis of compound 126
[1646] Compound 126 was prepared following the same procedure used to prepare compound 113. UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=946.4 (theoretical), 946.6 (observed). HPLC retention time: 1.68 min.
Synthesis of tert-butyl (E)-(3-((5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1-(4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-5-(N-methylsulfamoyl)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazol-7-yl)oxy)propyl)(methyl)carbamate (Compound 127)
##STR00519##
[1647] Compound 127 was prepared following the same procedures as compound 25f substituting

4-chloro-N-methyl-3-nitrobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide. UPLC-MS (Method E, EST+): m/z [M+H].sup.+=914.4 (theoretical), 914.6 (observed). HPLC retention time: 1.80 min.

Synthesis of (E)-7-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-methylpropanamido)propoxy)-2-(1-ethyl-3-methyl-H-pyrazole-5-carboxamido)-1-(4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-5-(N-methylsulfamoyl)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazole-5-carboxamide (Compound 128)

##STR00520##

Synthesis of 128a

[1648] Compound 128a was prepared following the same procedure used to prepare compound 66b. UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=814.4 (theoretical), 814.5 (observed). HPLC retention time: 1.53 min.

Synthesis of 128

[1649] Compound 128 was prepared following the same procedure used to prepare compound 12. UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=965.4 (theoretical), 965.6 (observed). HPLC retention time: 1.60 min.

Synthesis of S-(1-(3-((3-((5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1-((E)-4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-5-(methoxycarbonyl)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazol-7-yl)oxy)propyl) (methyl)amino)-3-oxopropyl)-2,5-dioxopyrrolidin-3-yl)-L-cysteine (Compound 129)

##STR00521##

[1650] Compound 129 was prepared following General Method 6. UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=1081.4 (theoretical), 1081.6 (observed). HPLC retention time: 1.88 min.

Synthesis of 1-((E)-4-(7-(3-(3-(3-(((R)-2-amino-2-carboxyethyl)thio)-2,5-dioxopyrrolidin-1-yl)-N-methylpropanamido)propoxy)-5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazole-5-carboxylic acid (Compound 130)

##STR00522##

[1651] Compound 130 was prepared following General Method 6. UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=1067.4 (theoretical), 1067.6 (observed). HPLC retention time: 1.49 min.

Synthesis of (E)-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-7-(3-(6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-methylhexanamido)propoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazole-5-carboxamide (Compound 131)

##STR00523##

[1652] Compound 131 was prepared following the same procedure as compound 12 substituting 2,5-dioxopyrrolidin-1-yl 6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoate for 2,5-dioxopyrrolidin-1-yl 3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoate. UPLC-MS (Method E, EST+): m/z [M+H].sup.+=987.5 (theoretical), 987.7 (observed). HPLC retention time: 1.85 min.

Synthesis of S-(1-(6-((3-((5-carbamoyl-1-(E)-4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazol-7-yl)oxy)propyl)(methyl)amino)-6-oxohexyl)-2,5-dioxopyrrolidin-3-yl)-L-cysteine (Compound 132)

##STR00524##

[1653] Compound 132 was prepared following General Method 6. UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=1108.5 (theoretical), 1108.7 (observed). HPLC retention time: 1.42 min.

Synthesis of (E)-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-7-(3-(N-cyclopropyl-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazole-5-carboxamide (Compound 133)

##STR00525## ##STR00526##
Synthesis of 133a
[1654] An oven-dried 4 mL vial was charged with 1 (10 mg, 0.0105 mmol, 1 equiv), potassium carbonate (7.3 mg, 0.0526 mmol, 5 equiv.), and tert-butyl N-(3-bromopropyl)-N-cyclopropyl-carbamate (0.49 mL of a 9 mg/mL solution in DMF, 0.0158 mmol, 1.50 equiv.) and starting materials were dissolved in DMF (0.50 mL). The reaction was stirred overnight at 55° C. and purified by preparatory HPLC (Method B), after which it was frozen and lyophilized to afford compound 133a (8.8 mg, 0.0077 mmol, 73% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=920.45 (theoretical), 920.64 (observed). HPLC retention time: 2.32 min.
Synthesis of 133b
[1655] An oven-dried 4 mL vial was charged with 133a (8.8 mg, 0.0077 mmol) and 20% TFA in DCM (100 μL). The reaction was stirred for 30 minutes at room temperature and purified by preparatory HPLC (Method B), after which it was frozen and lyophilized to afford compound 133b (5.0 mg, 0.0043 mmol, 56% yield). UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=820.40 (theoretical), 820.49 (observed). HPLC retention time: 1.29 min.
Synthesis of 133
[1656] An oven-dried 8 mL vial was charged with 133b (3.3 mg, 0.0085 mmols, 1 equiv.) which was dissolved in DMSO (1 mL) and a solution of 2,5-dioxopyrrolidin-1-yl 3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoate in DMSO (10 mM in DMSO, 0.43 mL, 0.0043 mmol, 1.5 equiv.) and DIPEA (1.5 μL, 0.00851 mmol, 3 equiv.). The reaction was heated to 30° C. overnight, quenched with acetic acid and purified by preparatory HPLC (Method B), after which the compound was frozen and lyophilized to afford 133 (1.9 mg, 0.00158 mmol, 56% yield).
[1657] UPLC-MS (Method D, ESI+): m/z [M+H].sup.+=971.43 (theoretical), 971.48 (observed). HPLC retention time: 1.99 min.
Synthesis of 3-((5-carbamoyl-1-((E)-4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazol-7-yl)oxy)-N-(4-(((2S,3R,4S,5S,6S)-6-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)-2-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)propanamido)benzyl)-N,N-dimethylpropan-1-aminium 2,2,2-trifluoroacetate (Compound 134)
##STR00527## ##STR00528##
Synthesis of 134a
[1658] An oven-dried 8 mL vial was charged with (E)-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-7-(3-(dimethylamino)propoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazole-5-carboxamide (20 mg, 0.0248 mmol, 1 equiv., prepared as previously described WO2017/175147, example 39, page 291) and (2S,3R,4S,5S,6S)-2-(3-(3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-4-(bromomethyl)phenoxy)-6-(methoxycarbonyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (60.3 mg, 0.0743 mmol, 3 equiv, prepared as previously described, *Mol Cancer Ther* 2016 15(5), 938-945) and azeotroped with anhydrous acetonitrile. To the vial was added 2-butanone (2.5 mL) and the solution was heated to 100° C. overnight. The compound was directly purified by preparatory HPLC (Method B), frozen and lyophilized to afford 134a (11.3 mg, 0.0070 mmol, 28% yield). UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=1538.64 (theoretical), 1538.83 (observed). HPLC retention time: 2.55 min
Synthesis of 134b
[1659] An oven-dried 4 mL vial was charged with 134a (4.5 mg, 0.0094 mmol, 1 equiv.) and dissolved in anhydrous MeOH (0.5 mL). The vial was cooled in an acetonitrile/dry-ice bath at −40° C. and 0.5 M NaOMe (19 μL, 0.0094 mmol, 1 equiv) was added. The reaction was stirred for 1 hour before it was warmed to room temperature and LiOH (1 M in H.sub.2O, 31 μL, 0.031 mmols, 3 equiv.) was added. The reaction was stirred at room temperature for 1 hour and then directly

purified by preparatory HPLC (Method B) then frozen and lyophilized to afford 134b (5.8 mg, 0.0049 mmol, 48% yield). UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=1176.52 (theoretical), 1176.76 (observed). HPLC retention time: 1.29 min

Synthesis of 134

[1660] 134b (5.8 mg, 0.0038 mmols, 1 equiv.) was added to an oven-dried 4 mL vial and dissolved in DMSO (1 mL) and then MP-OSu (10 mM in DMSO, 0.57 mL, 0.0057 mL, 1.5 equiv.) and DIPEA (2 μL, 0.0115 mmol, 3 equiv.) were added. The solution was stirred for 30 min, quenched with acetic acid and purified by preparatory HPLC (Method B), then frozen and lyophilized to afford 134 (3.6 mg, 0.0023 mmol, 61% yield). UPLC-MS (Method E, ESI+): m/z [M+H].sup.+=1327.55 (theoretical), 1327.77 (observed). HPLC retention time: 1.38 min.

Synthesis of (E)-7-(2-(azetidin-3-yl)ethoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1-(4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-5-sulfamoyl-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazole-5-carboxamide (Compound 135)

##STR00529## ##STR00530## ##STR00531##

Synthesis of 135a

[1661] To a solution of 25a (1.61 g, 4.18 mmol, 1 equiv.) in MeOH (63 mL) and aq. NH.sub.4OH (21 mL) was added aq. Na.sub.2S.sub.2O.sub.4 (1 M, 21 mL, 21 mmol, 5 equiv.). The mixture was stirred for 1 hour at 30° C., and the reaction was monitored by UPLC-MS (Method E, ESI+). Upon completion, the solution was filtered over celite and washed with MeOH. The filtrate was concentrated and the product was purified by flash chromatography (dry loaded on celite, Sfar HC Duo SiO.sub.2 column, 10:1 MeOH:NH.sub.4OH gradient in DCM) to yield 135a (774 mg, 2.17 mmol, 52% yield). LC-MS (Method E, ESI+): m/z [M+H].sup.+=357.2 (theoretical), 357.3 (observed). HPLC retention time: 1.44 min.

Synthesis of 135b

[1662] To a solution of compound 135a (774 mg, 2.17 mmol, 1 equiv.) in MeOH (4 mL) was added cyanogen bromide in MeCN (3 M, 1.5 mL, 4.35 mmol, 2 equiv.). The solution stirred for 18 hours at 30° C. and was monitored via UPLC-MS (Method E, ESI+). Upon completion, solvent was removed in vacuo to yield 135b (1.0 g, 2.25 mmol, quantitative yield). LC-MS (Method E, ESI+): m/z [M+H].sup.+=382.2 (theoretical), 382.2 (observed). HPLC retention time: 1.12 min.

Synthesis of 135c

[1663] A microwave vial was charged with a solution of 135b (1.0 g, 2.25 mmol, 1 equiv.) in DMA (11 mL), to which was added compound 8 (1.0 g, 6.74 mmol, 3 equiv.), HATU (2.6 g, 6.74 mmol, 3 equiv.) and DIPEA (1.2 mL, 6.74 mmol, 3 equiv.). This mixture was heated to 80° C. for 1 hour in a microwave reactor. Upon completion, 135c was isolated by precipitation with cold water (1.0 g, 1.93 mmol, 86% yield). LC-MS (Method E, ESI+): m/z [M+H].sup.+=518.2 (theoretical), 518.3 (observed). HPLC retention time: 1.60 min.

Synthesis of 135d

[1664] To a solution of 135c (1.0 g, 1.93 mmol, 1 equiv.) in MeOH (3.3 mL) was added HCl in dioxane (4 M, 5.3 mL, 21 mmol, 8 equiv.). The mixture stirred for 1 hour at 30° C. Upon completion, solvent was removed in vacuo and 135d (1.2 g, 2.65 mmol, quantitative yield) was used without further purification. LC-MS (Method E, ESI+): m/z [M+H].sup.+=418.2 (theoretical), 418.2 (observed). HPLC retention time: 1.09 min.

Synthesis of 135e

[1665] Compounds 135d (200 mg, 0.408 mmol, 1 equiv.) and 26a (245 mg, 0.612 mmol, 1.5 equiv.) were dissolved in n-butanol (2.0 mL) in a 5 mL microwave vial to which Na.sub.2CO.sub.3 (130 mg, 1.22 mmol, 3 equiv.) and DIPEA (0.36 mL, 2.04 mmol, 5 equiv.) were added. The reaction was heated via microwave reactor at 140° C. for 3 hours. The resulting product was filtered and washed with MeOH and DCM. The filtrate was concentrated and purified via flash chromatography (dry loaded on celite, Sfar HC Duo SiO.sub.2 column, 10:1 MeOH:NH.sub.4OH gradient in DCM) to yield 135e (51 mg, 0.0651 mmol, 16% yield). LC-MS (Method E, ESI+): m/z

[M+H].sup.+=781.3 (theoretical), 781.4 (observed). HPLC retention time: 1.72 min.
Synthesis of 135f
[1666] Compound 135f (30 mg, 0.0402 mmol, 62% yield) was prepared using the same procedure as 135a, using 135e (51 mg, 0.0651 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=751.3 (theoretical), 751.4 (observed). HPLC retention time: 1.46 min.
Synthesis of 1352
[1667] Compound 135g (34 mg, 00394 mmol, quantitative yield) was prepared using the same procedure as 135b, using 135f (30 mg, 0.0402 mmol, 1 equiv.) as the starting material. LC-MS (Method E, EST+): m/z [M+H].sup.+=776.3 (theoretical), 776.4 (observed). HPLC retention time: 1.54 min.
Synthesis of 135h
[1668] Compound 135h was prepared using the same procedure as 135c, using 135g (17 mg, 0.0197 mmol, 1 equiv.) as the starting material. Upon completion, the product was purified by preparatory HPLC (Method H). Pure fractions were collected, frozen and lyophilized to afford 135h (2.34 mg, 0.0021 mmol, 10% yield) as a white powder. LC-MS (Method E, ESI+): m/z [M+H].sup.+912.4 (theoretical), 912.5 (observed). HPLC retention time: 1.65 min.
Synthesis of 135
[1669] Compound 135h (2.34 mg, 0.0021 mmol, 1 equiv.) was dissolved in MeOH (0.21 mL) and HCl in dioxane (4 M, 4.1 μL, 0.0164 mmol, 8 equiv.) was added. The solution was heated to 40° C. for 1 hour. Then solvent was removed in vacuo and 135 (1.86 mg, 0.0020 mmol, quantitative yield) was used without further purification. LC-MS (Method E, ESI+): m/z [M+H].sup.+=812.3 (theoretical), 812.4 (observed). HPLC retention time: 1.26 min.
Synthesis of (E)-7-(2-(azetidin-3-yl)ethoxy)-2-(1,3-dimethyl-1H-pyrazole-5-carboxamido)-1-(4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-5-sulfamoyl-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazole-5-carboxamide (Compound 136)
##STR00532##
Synthesis of 136a
[1670] Compound 136a (3.15 mg, 0.0028 mmol, 14% yield) was prepared using the same procedure as 135h, using 135g (17 mg, 0.0197 mmol, 1 equiv.) and 1, 3-dimethyl-1H-pyrazole-5-carboxylic acid as the starting materials. LC-MS (Method E, ESI+): m/z [M+H].sup.+=898.4 (theoretical), 898.5 (observed). HPLC retention time: 1.62 min.
Synthesis of 136
[1671] Compound 136 (2.09 mg, 0.0023 mmol, 82% yield) was prepared using the same procedure as 135, using 136a (3.15 mg, 0.0028 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=798.3 (theoretical), 798.4 (observed). HPLC retention time: 1.24 min.
Synthesis of (E)-7-(3-(azetidin-3-yloxy)propoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1-(4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-5-sulfamoyl-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazole-5-carboxamide (Compound 137)
##STR00533## ##STR00534##
Synthesis of 137a
[1672] Compound 137a (72 mg, 0.0893 mmol, 22% yield) was prepared using the same procedure as 135e, using 135d (200 mg, 0.408 mmol, 1 equiv.) and 27a (263 mg, 0.612 mmol, 1.5 equiv.) as the starting materials. LC-MS (Method E, ESI+): m/z [M+H].sup.+=811.3 (theoretical), 811.4 (observed). HPLC retention time: 1.72 min.
Synthesis of 137b
[1673] Compound 137b (30 mg, 0.0386 mmol, 43% yield) was prepared using the same method as 135a, using 137a (72 mg, 0.0893 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=781.3 (theoretical), 781.4 (observed). HPLC retention time: 1.46 min.
Synthesis of 137c
[1674] Compound 137c (34 mg, 0.0387 mmol, quantitative yield) was prepared using the same

procedure as 135b, using 137b (30 mg, 0.03896 mmol, 1 equiv.) as the starting material. LC-MS (Method E, EST+): m/z [M+H].sup.+=806.3 (theoretical), 806.4 (observed). HPLC retention time: 1.53 min.

Synthesis of 137d

[1675] Compound 137d (4.21 mg, 0.0036 mmol, 19% yield) was prepared using the same procedure as 135h, using 137c (17 mg, 0.0194 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=942.4 (theoretical), 942.5 (observed). HPLC retention time: 1.65 min.

Synthesis of Compound 137

[1676] Compound 137 (3.35 mg, 0.0035 mmol, quantitative yield), was prepared using the same procedure as 135, using 137d (4.21 mg, 0.0036 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=842.3 (theoretical), 842.4 (observed). HPLC retention time: 1.29 min.

Synthesis of (E)-7-(3-(azetidin-3-yloxy)propoxy)-2-(1,3-dimethyl-1H-pyrazole-5-carboxamido)-1-(4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-5-sulfamoyl-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazole-5-carboxamide (Compound 138)

##STR00535##

Synthesis of 138a

[1677] Compound 138a (3.00 mg, 0.0026 mmol, 13% yield) was prepared using the same procedure as 135h, using 137c (17 mg, 0.0197 mmol, 1 equiv.) and 1, 3-dimethyl-1H-pyrazole-5-carboxylic acid as the starting materials. LC-MS (Method E, EST+): m/z [M+H].sup.+=928.4 (theoretical), 928.5 (observed). HPLC retention time: 1.62 min.

Synthesis of 138

[1678] Compound 138 (2.35 mg, 0.0025 mmol, quantitative yield), was prepared using the same procedure as 135, using 138a (3.00 mg, 0.0026 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=828.3 (theoretical), 828.4 (observed). HPLC retention time: 1.26 min.

Synthesis of (E)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1-(4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-5-sulfamoyl-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-7-(3-(methylamino)propoxy)-1H-benzo[d]imidazole-5-carboxamide (Compound 139)

##STR00536## ##STR00537##

Synthesis of 139a

[1679] Compound 139a (125 mg, 0.162 mmol, 29% yield) was prepared using the same procedure as 135e, using 135d (250 mg, 0.551 mmol, 1 equiv.) and 77 (320 mg, 0.826 mmol, 1.5 equiv.) as the starting materials. LC-MS (Method E, ESI+): m/z [M+H].sup.+=769.3 (theoretical), 769.4 (observed). HPLC retention time: 1.67 min.

Synthesis of 139b

[1680] Compound 139b (51 mg, 0.0686 mmol, 42% yield) was prepared using the same procedure as 135a, using 139a (125 mg, 0.162 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=739.3 (theoretical), 739.4 (observed). HPLC retention time: 1.45 min.

Synthesis of 139c

[1681] Compound 139c (57 mg, 0.0670 mmol, quantitative yield) was prepared using the same procedure as 135b, using 139b (51 mg, 0.0686 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=764.3 (theoretical), 764.4 (observed). HPLC retention time: 1.31 min.

Synthesis of 139d

[1682] Compound 139d (34 mg, 0.0303 mmol, 45% yield) was prepared following the same procedure as 135h using 139c (57 mg, 0.0670 mmol, 1 equiv.) and 1, 3-dimethyl-1H-pyrazole-5-carboxylic acid as the starting materials. LC-MS (Method E, EST+): m/z [M+H].sup.+=886.4 (theoretical), 886.5 (observed). HPLC retention time: 1.61 min.

Synthesis of 139

[1683] Compound 139 (27 mg, 0.0291, quantitative yield) was prepared using the same procedure as 135, using 139d (34 mg, 0.0303 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=786.3 (theoretical), 786.4 (observed). HPLC retention time: 1.23 min.

Synthesis of (E)-7-(2-(azetidin-3-yl)ethoxy)-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1,3-dimethyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazole-5-carboxamide (Compound 140)

##STR00538## ##STR00539##

Synthesis of 140a

[1684] Compound 140a (380 mg, 0.490 mmol, 78% yield) was prepared using the same procedure as 135e, using 26a (250 mg, 0.625 mmol, 1 equiv.) and 78d (420 mg, 0.938 mmol, 1.5 equiv.) as the starting materials. The product was precipitated in cold water and used without further purification. LC-MS (Method E, ESI+): m/z [M+H].sup.+=775.3 (theoretical), 775.4 (observed). HPLC retention time: 1.66 min.

Synthesis of 140b

[1685] Compound 140b (193 mg, 0.260 mmol, 53% yield) was prepared using the same procedure as 135a, using 140a (380 mg, 0.490 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=745.4 (theoretical), 745.5 (observed). HPLC retention time: 1.44 min.

Synthesis of 140c

[1686] Compound 140c (212 mg, 0.249 mmol, quantitative yield) was prepared using the same procedure as 135b, using 140b (193 mg, 0.260 mmol, 1 equiv.) as the starting material. LC-MS (Method E, EST+): m/z [M+H].sup.+=770.4 (theoretical), 770.5 (observed). HPLC retention time: 1.60 min.

Synthesis of 140d

[1687] Compound 140d (38 mg, 0.0339 mmol, 27% yield) was prepared using the same procedure as 135h, using 140c (106 mg, 0.124 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=892.4 (theoretical), 892.5 (observed). HPLC retention time: 1.59 min.

Synthesis of 140

[1688] Compound 140 (30 mg, 0.0334 mmol, quantitative yield) was prepared using the same procedure as 135, using 140d (38 mg, 0.0339 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=792.4 (theoretical), 792.5 (observed). HPLC retention time: 1.28 min.

Synthesis of (E)-N-(7-(2-(azetidin-3-yl)ethoxy)-5-carbamoyl-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazol-2-yl)-4-ethyl-2-methyloxazole-5-carboxamide (Compound 141)

##STR00540##

Synthesis of 141a

[1689] Compound 141a (27 mg, 0.0237 mmol, 19% yield) was prepared using the same procedure as 135h, using 140c (106 mg, 0.124 mmol, 1 equiv.) and 4-ethyl-2-methyl-oxazole-5-carboxylic acid as the starting materials. LC-MS (Method E, ESI+): m/z [M+H]+=907.4 (theoretical), 907.5 (observed). HPLC retention time: 1.57 min.

Synthesis of 141

[1690] Compound 141 (21 mg, 0.0230 mmol, quantitative yield), was prepared using the same procedure as 135, using 141a (27 mg, 0.0237 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=807.4 (theoretical), 807.5 (observed). HPLC retention time: 1.26 min.

Synthesis of (E)-7-(3-(azetidin-3-yloxy)propoxy)-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1,3-dimethyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazole-5-carboxamide (Compound 142)

##STR00541##

Synthesis of 142a

[1691] Compound 142a was prepared using the same procedure as 135e, using 27a (250 mg, 0.582 mmol, 1 equiv.) and 78d (391 mg, 0.872 mmol, 1.5 equiv.) as the starting materials. The product was precipitated with cold water and used without further purification. LC-MS (Method E, ESI+): m/z [M+H].sup.+=805.4 (theoretical), 805.4 (observed). HPLC retention time: 1.66 min.

Synthesis of 142b

[1692] Compound 142b (193 mg, 0.250 mmol, 37% yield over 2 steps) was prepared using the same procedure as 135a, using 142a (548 mg, 0.681 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=775.4 (theoretical), 775.5 (observed). HPLC retention time: 1.50 min.

Synthesis of 142c

[1693] Compound 142c (164 mg, 0.186 mmol, 75% yield) was prepared using the same procedure as 135b, using 142b (193 mg, 0.260 mmol, 1 equiv.) as the starting material. LC-MS (Method E, EST+): m/z [M+H].sup.+=800.4 (theoretical), 800.5 (observed). HPLC retention time: 1.33 min.

Synthesis of 142d

[1694] Compound 142d (40 mg, 0.0345 mmol, 37% yield) was prepared using the same procedure as 135h, using 142c (48 mg, 0.373 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=922.4 (theoretical), 922.5 (observed). HPLC retention time: 1.58 min.

Synthesis of 142

[1695] Compound 142 (32 mg, 0.0323 mmol, quantitative yield) was prepared using the same procedure as 135, using 142d (40 mg, 0.0345 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=822.4 (theoretical), 822.5 (observed). HPLC retention time: 1.29 min.

Synthesis of (E)-N-(7-(3-(azetidin-3-yloxy)propoxy)-5-carbamoyl-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazol-2-yl)-4-ethyl-2-methyloxazole-5-carboxamide (Compound 143)

##STR00542##

Synthesis of 143a

[1696] Compound 143a (31 mg, 0.0263 mmol, 28% yield) was prepared using the same procedure as 135h, using 142c (82 mg, 0.0.0931 mmol, 1 equiv.) and 4-ethyl-2-methyl-oxazole-5-carboxylic acid as the starting materials. LC-MS (Method E, ESI+): m/z [M+H].sup.+=937.4 (theoretical), 937.5 (observed). HPLC retention time: 1.56 min.

Synthesis of 143

[1697] Compound 143 (25 mg, 0.0261 mmol, quantitative yield), was prepared using the same procedure as 135, using 141a (31 mg, 0.0263 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=837.4 (theoretical), 837.5 (observed). HPLC retention time: 1.29 min.

Synthesis of (E)-7-(2-(1-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl)azetidin-3-yl)ethoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1-(4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-5-sulfamoyl-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazole-5-carboxamide (Compound 144)

##STR00543##

[1698] The ×2 TFA salt of compound 144 (0.59 mg, 0.0005 mmol, 24% yield) was prepared according to general method 9, using compound 135 (1.86 mg, 0.0020 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=963.4 (theoretical), 963.5 (observed). HPLC retention time: 1.44 min.

Synthesis of (E)-2-(1,3-dimethyl-1H-pyrazole-5-carboxamido)-7-(2-(1-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl)azetidin-3-yl)ethoxy)-1-(4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-5-sulfamoyl-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazole-5-carboxamide (Compound 145)

##STR00544##
[1699] The ×2 TFA salt of compound 145 (0.31 mg, 0.0003 mmol, 12% yield) was prepared according to general method 9, using compound 136 (2.09 mg, 0.0023 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=949.3 (theoretical), 949.5 (observed). HPLC retention time: 1.40 min.
Synthesis of (E)-7-(3-((1-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl)azetidin-3-yl)oxy)propoxy)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-1-(4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-5-sulfamoyl-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazole-5-carboxamide (Compound 146)
##STR00545##
[1700] The ×2 TFA salt of compound 146 (0.92 mg, 0.0008 mmol, 21% yield) was prepared according to general method 9, using compound 137 (3.35 mg, 0.0035 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=993.4 (theoretical), 993.5 (observed). HPLC retention time: 1.43 min.
Synthesis of (E)-2-(1,3-dimethyl-1H-pyrazole-5-carboxamido)-7-(3-((1-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl)azetidin-3-yl)oxy)propoxy)-1-(4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-5-sulfamoyl-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazole-5-carboxamide (Compound 147)
##STR00546##
[1701] The ×2 TFA salt of compound 147 (0.36 mg, 0.0003 mmol, 12% yield) was prepared according to general method 9, using compound 136 (2.83 mg, 0.0024 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=979.4 (theoretical), 979.5 (observed). HPLC retention time: 1.41 min.
Synthesis of (E)-2-(1,3-dimethyl-1H-pyrazole-5-carboxamido)-7-(3-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-methylpropanamido)propoxy)-1-(4-(2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-5-sulfamoyl-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-1H-benzo[d]imidazole-5-carboxamide (Compound 148)
##STR00547##
[1702] The ×2 TFA salt of compound 148 (15 mg, 0.0129 mmol, 44% yield) was prepared according to general method 9, using compound 139 as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=937.3 (theoretical), 937.4 (observed). HPLC retention time: 1.42 min.
Synthesis of (E)-1-(4-(5-carbamoyl-2-(1,3-dimethyl-1H-pyrazole-5-carboxamido)-7-(2-(1-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl)azetidin-3-yl)ethoxy)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazole-5-carboxamide (Compound 149)
##STR00548##
[1703] The ×2 TFA salt of compound 149 (16 mg, 0.0136 mmol, 41% yield) was prepared according to general method 9, using compound 140 (30 mg, 0.0334 mmol, 1 equiv). as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=943.4 (theoretical), 943.5 (observed). HPLC retention time: 1.41 min.
Synthesis of (E)-N-(5-carbamoyl-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-7-(2-(1-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl)azetidin-3-yl)ethoxy)-1H-benzo[d]imidazol-2-yl)-4-ethyl-2-methyloxazole-5-carboxamide (Compound 150)
##STR00549##
[1704] The ×2 TFA salt of compound 150 (15 mg, 0.0123 mmol, 53% yield) was prepared according to general method 9, using compound 141 (21 mg, 0.0230 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=943.4 (theoretical), 943.5 (observed). HPLC retention time: 1.41 min.
Synthesis of (E)-1-(4-(5-carbamoyl-2-(1,3-dimethyl-1H-pyrazole-5-carboxamido)-7-(3-((1-(3-(2,5-

dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl)azetidin-3-yl)oxy)propoxy)-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazole-5-carboxamide (Compound 151)
##STR00550##
[1705] The ×2 TFA salt of compound 151 (22 mg, 0.0182 mmol, 56% yield) was prepared according to general method 9, using compound 142 (30 mg, 0.0323 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=973.4 (theoretical), 973.5 (observed). HPLC retention time: 1.42 min.
Synthesis of (E)-N-(5-carbamoyl-1-(4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-7-(3-((1-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanoyl)azetidin-3-yl)oxy)propoxy)-1H-benzo[d]imidazol-2-yl)-4-ethyl-2-methyloxazole-5-carboxamide (Compound 152)
##STR00551##
[1706] The ×2 TFA salt of compound 152 (20 mg, 0.0168 mmol, 43% yield) was prepared according to general method 9, using compound 143 (37 mg, 0.0388 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=988.4 (theoretical), 988.5 (observed). HPLC retention time: 1.40 min.
Synthesis of S-(1-(3-(3-(2-((5-carbamoyl-1-((E)-4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1,3-dimethyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazol-7-yl)oxy)ethyl)azetidin-1-yl)-3-oxopropyl)-2,5-dioxopyrrolidin-3-yl)-L-cysteine (Compound 153)
##STR00552##
[1707] To a solution of compound 149 (10 mM in DMSO, 0.42 mL, 0.0042 mmol, 1 equiv.) was added 1-cysteine (0.1 M H.sub.2O, 63 μL, 0.063 mmol, 1.5 equiv.). The reaction stirred at 30° C. for 1 h and was monitored by UPLC-MS. Upon completion, the reaction mixture was purified directly by preparatory HPLC (method G). Pure fractions were collected, frozen, and lyophilized to yield compound 153 (2.17 mg, 0.0015 mmol, 36% yield). LC-MS (Method E, ESI+): m/z [M+H].sup.+=1079.4 (theoretical), 1079.5 (observed). HPLC retention time: 1.28 min.
Synthesis of S-(1-(3-(3-(2-((5-carbamoyl-1-((E)-4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(4-ethyl-2-methyloxazole-5-carboxamido)-1H-benzo[d]imidazol-7-yl)oxy)ethyl)azetidin-1-yl)-3-oxopropyl)-2,5-dioxopyrrolidin-3-yl)-L-cysteine (Compound 154)
##STR00553##
[1708] Compound 150 (2.35 mg, 0.0017 mmol, 39% yield) was prepared using the same procedure as compound 153, using compound 145 (10 mM in DMSO, 0.43 mL, 0.0043 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=1064.4 (theoretical), 1064.5 (observed). HPLC retention time: 1.29 min.
Synthesis of S-(1-(3-(3-(3-((5-carbamoyl-1-((E)-4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(1,3-dimethyl-1H-pyrazole-5-carboxamido)-1H-benzo[d]imidazol-7-yl)oxy)propoxy)azetidin-1-yl)-3-oxopropyl)-2,5-dioxopyrrolidin-3-yl)-L-cysteine (Compound 155)
##STR00554##
[1709] Compound 155 (2.34 mg, 0.0016 mmol, 39% yield) was prepared using the same procedure as compound 153, using compound 151 (10 mM in DMSO, 0.41 mL, 0.0041 mmol, 1 equiv.) as the starting material. LC-MS (Method E, ESI+): m/z [M+H].sup.+=1109.4 (theoretical), 1109.5 (observed). HPLC retention time: 1.30 min.
Synthesis of S-(1-(3-(3-(3-((5-carbamoyl-1-((E)-4-(5-carbamoyl-2-(1-ethyl-3-methyl-1H-pyrazole-5-carboxamido)-7-methoxy-1H-benzo[d]imidazol-1-yl)but-2-en-1-yl)-2-(4-ethyl-2-methyloxazole-5-carboxamido)-1H-benzo[d]imidazol-7-yl)oxy)propoxy)azetidin-1-yl)-3-oxopropyl)-2,5-dioxopyrrolidin-3-yl)-L-cysteine (Compound 156)

##STR00555##
[1710] Compound 156 (2.31 mg, 0.0016 mmol, 39% yield) was prepared using the same procedure as compound 153, using compound 152 (10 in mM DMSO, 0.42 mL, 0.0042 mmol, 1 equiv.) as the starting material. LC-MS (Method E, EST+): m/z [M+H].sup.+=1094.4 (theoretical), 1094.5 (observed). HPLC retention time: 1.32 min.

General Procedures for the Preparation of ADCs:

[1711] ADCs were prepared as described previously (*Methods Enzymol.* 2012, 502, 123-138). Briefly, DAR (drug-to-antibody ratio) conjugates were prepared by partial reduction of the antibody inter-chain disulfide bonds using a sub-stoichiometric amount of tris(2-carboxyethyl)phosphine (TCEP). TCEP was added at approximately 2.2 molar equivalents relative to the antibody (TCEP:antibody) to a pre-warmed (37° C.) antibody stock solution in phosphate buffered saline, (PBS, Gibco, PN 10010023) and 1 M EDTA. The reduction reaction mixture was incubated at 37° C. for approximately 60 minutes. Conjugation of the partially-reduced antibody with maleimide drug-linker was carried out at room temperature by diluting the antibody with propylene glycol to improve drug solubility and adding 1.2 molar equivalents of the drug-linker per reduced cysteine. The propylene glycol was added to achieve a final co-solvent concentration of 40% (including addition of DMSO drug stock); half of the propylene glycol was added to the antibody and half to the drug stock before mixing to start the conjugation reaction. The conjugation reaction was allowed to proceed for 30 minutes at room temperature or until all available antibody cysteine thiols had been alkylated by drug-linker as indicated by reversed-phase HPLC (Method G). Removal of excess drug-linker was achieved by incubating the reaction mixture with 100% molar excess QuadraSil® MP resin (Millipore Sigma, PN 679526) for 30 minutes at room temperature. Buffer exchange into formulation buffer (PBS, Gibco, PN 10010023) was achieved by gel filtration chromatography using a prepacked PD-10 column (GE Life Sciences, PN 17043501) according to manufacturer's instructions. Further removal of residual drug-linker was achieved by repeated diafiltration (5-10 times) of the reaction mixture containing the ADCs in formulation buffer using a 30 kilodalton molecular weight cutoff centrifugal filter (Millipore Sigma, PN Z717185), until there was no detectable free drug-linker remaining, as indicated by HPLC analysis (Method K).

General Procedures for the Characterization of ADCs:

[1712] ADCs were characterized using the following methods:

[1713] Method I: Size-exclusion chromatography (SEC) was performed with a Waters ACQUITY UPLC system and an Acquity UPLC Protein BEH SEC Column, (200 Å, 1.7 m, 4.6×150 mm, PN: 186005225). The mobile phase used was 7.5% isopropanol in 92.5% aqueous (25 mM sodium phosphate, 350 mM NaCl, pH 6.8), v/v. Elution was performed isocratically at a flow rate of 0.4 mL/min at ambient temperature.

[1714] Method J: Reversed-phase chromatography (RP-HPLC) was performed on a Waters 2695 HPLC system and an Agilent PLRP-S column (1000 Å, 8 μm 50×2.1 mm, PN: PL1912-1802). ADCs were treated with 10 mM DTT to reduce disulfide bonds prior to analysis. Sample elution was done using Mobile Phase A (0.05% (v/v) TFA in water) and Mobile Phase B (0.01% (v/v) TFA in MeCN) with a gradient of 25-44% B over 12.5 minutes at 80° C. The drug-to-antibody ratio (DAR) was calculated based on the integrated peak area measured at UV 280 nm.

Calculations of Molar Ratios

[1715] The average drug loading per antibody light-chain (MR.sub.DLC) or antibody heavy-chain (MR.sub.DHC) was calculated using the equations below:

[00001] $MR_{DLC} = \frac{\text{.Math. (LC\%area}_n \times \text{MR}_n)}{100}$ [1716] where MR.sub.DLC═average drug-to-light chain ratio [1717] LC % area.sub.n=% area of the nth loaded light chain species [1718] % areas based on light chain peaks only [1719] MR.sub.n=drug-to-antibody ratio of the nth loaded species [1720] AND

[00002] $MR_{\text{DHC}} = \frac{\text{.Math. (HC\%area}_n \times \text{MR}_n)}{100}$

where MR.sub.DHC═average drug-to-heavy chain ratio [1721] HC % area.sub.n=% area of the nth loaded heavy chain species [1722] % areas based on heavy chain peaks only [1723] MR.sub.n=drug-to-antibody ratio of the nth loaded species
[1724] The average drug loading per antibody (MR.sub.D) was calculated using the equation below:
[00003]$MR_D = 2 \times (\mathrm{MR}_{DLC} + MR_{DHC})$ [1725] where MR.sub.D=average drug-to-antibody ratio
[1726] MR.sub.DLC═average drug-to-light chain ratio [1727] MR.sub.DHC═average drug-to-heavy chain ratio
[1728] Method K: Residual unconjugated drug linker was measured on a Waters ACQUITY UPLC system using an ACQUITY UPLC BEH C18 Column (130 Å, 1.7 μm, 2.1 mm×50 mm, PN: 186002350). ADC samples were treated with 2×volumes of ice-cold MeOH to induce precipitation and pelleted by centrifugation. The supernatant, containing any residual, unconjugated drug-linker, was injected onto the system. Sample elution was done using Mobile Phase A (0.05% (v/v) TFA in Water) and Mobile Phase B (0.01% TFA (v/v) in MeCN) with a gradient of 1-95% B over 2 minutes at 50° C. Detection was performed at 215 nm and quantitation of the residual drug-linker compound was achieved using an external standard of the corresponding linker.
Example 2
In Vitro Potency Evaluation of Sting Agonists and Corresponding ADCS
Experimental Procedures of In Vitro Biological Assays
THP1-Dual™ Cell Reporter Assay
[1729] Potency of compounds and ADCs was evaluated using the THP1-Dual™ cells (Invivogen PN: thpd-nfis [also referred to as THP1 dual reporter cells]), which contain an IRF-Lucia luciferase reporter. Cells were cultured in RPMI-1640 (Gibco) with 10% heat-inactivated fetal bovine serum, Pen-Strep (100 U/mL-100 g/mL, Gibco), HEPES (10 mM, Gibco)), sodium pyruvate (1 mM, Gibco), MEM non-essential amino acids (1×, Gibco), GlutaMAX (1×, Gibco), and beta-mercaptoethanol (55 μM, Gibco). Cells were plated in a 96-well flat bottom tissue culture-treated clear polystyrene plate (Corning Costar #3596) at ˜100,000 cells per well in 200 μL with the indicated concentration of the compound or ADC. The supernatant was harvested at 24 hours (compounds) or 48 hours (ADC) post plating for the reporter assay, or as indicated. To measure Lucia reporter signal, 10 L of the supernatant was combined with 40 L of QUANTI-Luc™ Luminescence assay reagent (Invivogen PN: rep-qlc1) in a 96-well clear flat bottom tissue culture-treated black polystyrene plate (Corning Costar #3603) and read on a Perkin Elmer Envision plate reader.
Bone Marrow-Derived Macrophage Assay
[1730] Potency of the compounds described herein was evaluated using mouse bone-marrow derived macrophages cultured from wild type (C57BL/6J, the Jackson Laboratory #000664) or STING-deficient (C57BL/6J-Sting1.sup.gt/J, the Jackson Laboratory #017537) mice. Briefly, mouse bone marrow cells were cultured for 7-10 days in RPMI-1640 (Gibco) with 10% heat-inactivated fetal bovine serum, Pen-Strep (100 U/mL-100 g/mL, Gibco), HEPES (10 mM, Gibco), sodium pyruvate (1 mM, Gibco), GlutaMAX (1×, Gibco), beta-mercaptoethanol (55 M, Gibco) and 20-40 ng/mL murine M-CSF (Peprotech, #315-02). Cells were plated in a 96-well flat bottom tissue culture-treated clear polystyrene plate (Corning Costar #3596) at ˜100,000 cells per well in 200 μL with the indicated concentration of the compound. The supernatant was harvested at 24 hours and cytokines were measured using a Milliplex MAP mouse cytokine/chemokine magnetic bead panel assay kit (MCYTOMAG-70k custom 11-plex kit: MCP1, MIP1α, MIP1β, TNFα, IFNγ, IL-10, IL-12p70, IL-1β, IL-6, IP10, RANTES) and analyzed using a Luminex™ MAGPIX™ Instrument System.
Bystander Activity Assay
[1731] Bystander activity of ADCs was evaluated using Renca cancer cells and THP1-Dual™ cells (InvivoGen) which contain an IRF-Lucia luciferase reporter. Cells were cultured in RPMI-1640

(Gibco) with 10% heat-inactivated fetal bovine serum, Pen-Strep (100 U/ml-100 µg/ml, Gibco), HEPES (10 mM, Gibco), sodium pyruvate (1 mM, Gibco), MEM non-essential amino acids (1×, Gibco), GlutaMAX (1×, Gibco), and beta-mercaptoethanol (55 µM, Gibco). Renca cells were plated in a 96-well flat bottom tissue culture-treated clear polystyrene plate (Corning Costar #3596) at 50,000 cells per well in 100 µL. On the day following the initial plating, 50,000 THP1-Dual™ cells were added to each well with the indicated concentration of ADC in a total volume of 200 µL. Supernatant was harvested at 48 hours post addition of the THP1-Dual™ cells. To measure Lucia reporter signal, 10 µL of supernatant was combined with 40 µL of QUANTI-Luc™ Luminescence assay reagent (Invivogen PN: rep-qlc1) in a 96-well clear flat bottom tissue culture-treated black polystyrene plate (Corning Costar PN: 3603) and read on a Perkin Elmer Envision plate reader. In some experiments, HEK 293T cells engineered to express a murine protein typically expressed by immune cells (target antigen C an immune cell antigen) were plated as above instead of Renca tumor cells.

Cancer Cell Direct Cytotoxicity Assay

[1732] Cancer cells were counted and plated in 40 µL complete growth media in 384-well, white-walled tissue culture treated plates (Corning). Cell plates were incubated at 37° C. and with 5% CO.sub.2 overnight to allow the cells to equilibrate. Stock solutions containing ADCs or free drugs were serially diluted in RPMI-1640+20% fetal bovine serum (FBS). 10 µL of each concentration were then added to each cell plate in duplicate. Cells were then incubated at 37° C. and with 5% CO.sub.2 for 96 hours, upon which, the cell plates were removed from the incubator and allowed to cool to room temperature for 30 minutes prior to analysis. CellTiter-Glo® luminescent assay reagent (Promega Corporation, Madison, WI) was prepared according to Promega's protocol. 10 µL of CellTiter-Glo® were added to assay plates using a Formulatrix Tempest liquid handler (Formulatrix) and the plates were protected from light for 30 minutes at room temperature. The luminescence of the samples was measured using an EnVision Multimode plate reader (Perkin Elmer, Waltham, MA). Raw data were analyzed in Graphpad Prism (San Diego, CA) using a nonlinear, 4-parameter curve fit model [Y=Bottom+(Top-Bottom)/(1+10{circumflex over ( )}((Log EC50−X)*HillSlope))]. Results are reported as X50 values, which are defined as the concentration of ADC or free drug required to reduce cell viability to 50%.

SU-DHL-1 Assay

[1733] Potency of ADCs was evaluated using the SU-DHL-1 lymphoma cells. Cells were cultured in RPMI-1640 (Gibco) with 10% heat-inactivated fetal bovine serum, Pen-Strep (100 U/mL-100 g/mL, Gibco), HEPES (10 mM, Gibco)), sodium pyruvate (1 mM, Gibco), MEM non-essential amino acids (1×, Gibco), GlutaMAX (1×, Gibco), and beta-mercaptoethanol (55 M, Gibco). Cells were plated in a 96-well flat bottom tissue culture-treated clear polystyrene plate (Corning Costar #3596) at ˜100,000 cells per well in 200 L with the indicated concentration of ADC. After 48 hours, the 50 µL supernatant was harvested and cytokine production was evaluated using a MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead panel (HCYTOMAG-60K custom 8-plex kit: IL-6, IL-8, MCP1, TNFα, GRO, IP-10, MIP1α, and MIP1β). Cell viability was evaluated by adding 100 µL CellTiter-Glo® luminescent assay reagent (Promega Corporation, Madison, WI) to remaining 150 µL of cells in the plate and transferring the mixture to a 96-well black-walled plate (Corning Costar #3603). Plates were protected from light for 30 minutes at room temperature, and the luminescence of the samples was measured using an EnVision Multimode plate reader (Perkin Elmer, Waltham, MA).

Tumor/PBMC Co-Culture Assay

[1734] Tumor cells were transfected with Incucyte® Cytolight red lentivirus per manufacturer's instructions and stable polyclonal cell populations expressing mKate2 (red fluorescent protein, RFP) were generated under puromycin selection. Live-cell killing assays were performed by seeding RFP+ tumor cells (MDA-MB-468, HCT 15, HT-1080) in 96-well flat bottom plates (Corning #3603) at a variety of densities (1×10.sup.4 or 2.5×10.sup.3) and grown overnight. The

following day, PBMCs isolated from healthy donors were added at 10:1 or 40:1 E:T ratios and cultures were treated with the indicated small molecule drugs or ADCs. Automated cell imaging was performed at 10-fold magnification using an IncuCyte S3 live-cell analysis system (Sartorius). Images were acquired in approximately 2-to-3-hour intervals with four fields of view per well for 3-4 days. Data were analyzed using the IncuCyte® analysis software. Area (μm.sup.2) and red mean intensity (RCU) filter thresholds were enforced to remove debris and red fluorescent anomalies. Tumor cell killing was quantified by calculating the confluence of red fluorescent tumor cells (normalized to t=0) at 72- or 96-hours. Molar concentrations of unconjugated compound 16, compound 12 mAb conjugate, or unconjugated mAb (adjusted to equivalent payload concentration) were plotted.

[1735] To determine STING pathway activation and quantify T cell numbers, identical tumor-immune cell (MDA-MB-468 tumor cells and PBMCs) cocultures were established in tandem. At 48-hours post treatment, supernatants were harvested and CXCL10/IP-10 production was evaluated by ELISA (ThermoFisher, #CHC2363). Optical density (450 nm) was measured using a SpectraMax M3 (Molecular Devices) microplate reader. Following supernatant harvest, cells were dissociated (TrypLE Express, Gibco) and dead cells were stained with LIVE/DEAD Fixable Near-JR Dead Cell Stain Kit (ThermoFisher, L34994) per manufacturer's instructions. After the viability stain, Fc-gamma receptors were blocked using human TruStain FcX (Biolegend, 422302). Cells were washed 1× with cell staining buffer (BD, 554657) and subsequently stained (30 min, at 4° C.) with antibodies for detection of surface antigens. The following antibodies were used: CD8 V450 (clone RPA-T8, BD), CD14 BV650 (clone M5E2, Biolegend), CD19 SB702 (clone HIB19, ThermoFisher), CD4 FITC (clone OKT4, Tonbo), CD56 PerCP-eF710 (clone TULY56, ThermoFisher), CD69 PE-Cy7 (clone FN50, Biolegend), CD86 APC (clone IT2.2, ThermoFisher), and HLA-DR A700 (clone LN3, ThermoFisher). Following the final wash, cell pellets were resuspended in 200 μL staining buffer and analyzed on an NXT Attune flow cytometer (ThermoFisher). Flow cytometry data were analyzed using FlowJo software and CD8+ T cells were quantified by counting the total number of CD8+ cell events within the RFP —/live/CD19−/CD14−/CD56− gate.

[1736] MDA-MB-468 and HCT15 tumor cells were cultured in RPMI-1640 (Gibco) with 10% heat-inactivated fetal bovine serum, Pen-Strep (100 U/mL-100 mg/mL, Gibco), HEPES (10 mM, Gibco)), sodium pyruvate (1 mM, Gibco), MEM non-essential amino acids (1×, Gibco), GlutaMAX (1×, Gibco), and beta-mercaptoethanol (55 μM, Gibco). HT-1080 cells were cultured in DMEM (Gibco) with 10% heat-inactivated fetal bovine serum, Pen-Strep (100 U/mL-100 mg/mL, Gibco), HEPES (10 mM, Gibco)), sodium pyruvate (1 mM, Gibco), MEM non-essential amino acids (1×, Gibco), GlutaMAX (1×, Gibco), and beta-mercaptoethanol (55 μM, Gibco).

Results from In Vitro Biological Assays

[1737] STING agonist compounds were assessed for their ability to activate THP1-Dual™ reporter cells, a human monocytic cell line in which type I interferon (IRF) signaling can be monitored via a secreted luciferase reporter protein (Lucia). THP1-Dual™ cells were treated with increasing concentrations of the agonists for 24 h, then supernatants were harvested and the Lucia reporter signal was quantified using QUANTI-Luc™ Luminescence assay reagent. Compound A and compound 1 were significantly more potent than (2′, 3′)-Rp,Rpc-diAMPS disodium (Compound B) and activated the Lucia reporter with EC50 values of 3 and 5 nM respectively. Compound 12a was less potent than compound 1 and compound A (FIG. **1**, EC.sub.50 value of 21 nM). Both compound 1 and 12a induced cytokine production when used to stimulate wild type (WT), but not STING-deficient, murine bone marrow-derived macrophages, indicating the activity of these compounds is STING-dependent (FIG. **2**).

[1738] The STING agonist compounds were conjugated to both targeted and non-binding antibodies and the resulting ADCs were assessed for their ability to activate THP1-Dual™ reporter cells. Compound 1 was conjugated using a cleavable glucuronide-based linker (11). Compound 12a

was conjugated using a non-cleavable, cleavable peptide-based, and cleavable glucuronide-based linker (Compounds 12, 14 and 13, respectively). THP1-Dual™ cells were treated with increasing concentrations of ADCs with a non-binding or targeted mAb conjugated to a compound for 48h, then supernatants were harvested, and the Lucia reporter signal was quantified using QUANTI-Luc™ Luminescence assay reagent. Although compound 12a was less potent than compound 1 as a free drug (FIG. **1**), compound 12a was more potent when conjugated to a targeted mAb via a cleavable glucuronide linker (13) than the similar compound 1 conjugate (11). Furthermore, compound 12a was more potent when conjugated to a targeted mAb via a non-cleavable linker (12) than either cleavable linker 13 or 14 (FIG. **3**), demonstrating that conjugation of STING agonist small molecules to an antibody can increase their potency.

[1739] Compound 12 and the cysteine adduct (compound 16) that is released upon cleavage of the mAb conjugate in the endo-lysosome were assessed for their ability to activate THP1-Dual™ reporter cells. THP1-Dual™ cells were treated with increasing concentrations of the compounds for 24 h, then supernatants were harvested and the Lucia reporter signal was quantified using QUANTI-Luc™ Luminescence assay reagent. Both compound 12 and compound 16 were active with EC50 values (37 nM and 34 nM, respectively) similar to the parent free drug 12a (21 nM, FIG. **4** and FIG. **1**).

[1740] Compound 15b was also evaluated, both as a free drug and when conjugated to a targeted antibody using a non-cleavable linker (15). THP1-Dual™ cells were treated with increasing concentrations of free drug or ADCs with a non-binding or targeted mAb conjugated to a compound for 48h; then supernatants were harvested, and the Lucia reporter signal was quantified using QUANTI-Luc™ Luminescence assay reagent. Compound 15b was more potent than 12a, while the potency of the ADC of 15 was similar to that of the ADC of 12 when linked to the same targeted mAb (FIG. **5**).

[1741] Compound 12a was conjugated to both targeted and non-binding antibodies using a variety of non-cleavable linkers (12, 17, 19-24) and the resulting ADCs were assessed for their ability to activate THP1-Dual™ reporter cells. All conjugates with the targeted mAb were active with EC50 values ranging from −1.7-7.3 ng/mL (Table 1). We also evaluated the ability of these linkers to directly kill cancer cells when conjugated to targeted mAbs binding tumor antigen A or antigen B (CD30). All conjugates were active in a subset of cancer cell lines (regardless of target antigen expression), indicating target-independent killing of some cancer cells; compounds 1, 12a, and 16 also demonstrated direct cytotoxic activity on a subset of cancer cell lines (Table 2; targeted mAb A conjugates comprise a mAb targeting the tumor antigen A conjugated to various drug linker compounds; targeted mAb B conjugates comprise the cAC10 mAb targeting CD30 conjugated to various drug linkers).

TABLE-US-00008 TABLE 1 Activity of target STING agonist ADCs in THP1-Dual ™ reporter cells. Compound EC.sub.50 (ng/mL)** 12 4.2 17 2.2 19 7.3 20 1.7 21 4.2 22 4.7 23 2.4 24 2.1 25 307 26 14.4 27 10.4 66 >10,000 67 >10,000 68 >10,000 69 >10,000 96 >10,000 97 * 98 >10,000 99 * 100 * 101 >10,000 102 >10,000 103 >10,000 104 >10,000 105 52.5 106 >10,000 107 >10,000 108 63.5 109 >10,000 110 >10,000 111 13.2 112 2 121 3.0 122 5.6 123 1.6 124 9.1 125 1.4 126 >10,000 128 >10,000 131 3.6 133 12.2 134 10.3 144 >10,000 145 >10,000 146 >10,000 147 >10,000 148 >10,000 149 >10,000 150 7.9 151 >10,000 152 6.5 *ADCs with >10% aggregate were not evaluated **For some compounds, EC50 values comprise the average value from multiple experiments

TABLE-US-00009 TABLE 2 Direct cytotoxicity data of various ADCs and compounds onhuman cancer cell lines. Target A expression + + + + + + + + + + + Target B expression − − − + + + + − − − − − SU- 786-O A2058 BxPC3 DEL DELBVR Karpas299 L540cy Ls174T MDAMB231 MOLM-13 DHL-4 ADC X50 (ng/mL) Targeted mAb A 12 (8 load) >1K >1K >1K 0.01 0.04 1 1 >1K >1K 1 >1K Targeted mAb A 12 (4 load) >1K >1K >1K 0.012 0.03 3 2 >1K >1K 12 >1K Targeted mAb B 12 (8 load) >1K >1K >1K <0.004 0.004 1 1 >1K >1K 2 >1K Targeted mAb B 12 (4 load) >1K

>1K >1K 0.01 0.1 2 1 >1K >1K 7 >1K Targeted mAb A 17 (8 load) >1K >1K >1K <0.004 0.004 1 1 >1K >1K 2 >1K Targeted mAb A 17 (4 load) >1K >1K >1K 0.1 0.03 5 2 >1K >1K 26 >1K Targeted mAb B 17 (8 load) >1K >1K >1K <0.004 <0.004 1 0.2 >1K >1K 2 >1K Targeted mAb B 17 (4 load) >1K >1K >1K 0.004 0.01 1 1 >1K >1K 25 >1K Targeted mAb A 21 (8 load) >1K >1K >1K 0.01 0.03 4 1 >1K >1K 2 >1K Targeted mAb A 21 (4 load) >1K >1K >1K 0.1 0.2 7 2 >1K >1K 20 >1K Targeted mAb B 21 (8 load) >1K >1K >1K <0.004 0.01 1 0.4 >1K >1K 2 >1K Targeted mAb A 22 (6 load) >1K >1K >1K 0.02 0.1 2 1 >1K >1K 2 >1K Targeted mAb A 22 (2 load) >1K >1K >1K 0.03 0.2 29 4 >1K >1K 29 >1K Targeted mAb B 22 (6 load) >1K >1K >1K 0.01 0.1 1 1 >1K >1K 3 >1K Targeted mAb A 19 (8 load) >1K >1K >1K <0.004 0.02 1 1 >1K >1K 1 >1K Targeted mAb A 19 (4 load) >1K >1K >1K 0.01 0.1 3 5 >1K >1K 13 >1K Targeted mAb B 19 (8 load) >1K >1K >1K <0.004 0.01 0.3 0.3 >1K >1K 0.4 >1K Targeted mAb B 19 (4 load) >1K >1K >1K <0.004 0.02 0.5 1 >1K >1K 1 >1K Targeted mAb A 20 (8 load) >1K >1K >1K 0.01 0.02 0.2 0.3 >1K >1K 1 >1K Targeted mAb A 20 (4 load) >1K >1K >1K 0.01 0.02 1 1 >1K >1K 10 >1K Targeted mAb B 20 (8 load) >1K >1K >1K <0.004 <0.004 0.1 0.1 >1K >1K 0.2 >1K Targeted mAb B 20 (4 load) >1K >1K >1K <0.004 0.02 0.1 0.5 >1K >1K 1 >1K Targeted mAb A 24 (8 load) >1K >1K >1K <0.004 0.01 0.3 1 >1K >1K 1 >1K Targeted mAb A 24 (4 load) >1K >1K >1K 0.01 0.01 1 4 >1K >1K 11 >1K Targeted mAb B 24 (8 load) >1K >1K >1K <0.004 0.01 0.03 0.5 >1K >1K 1 >1K Targeted mAb B 24 (4 load) >1K >1K >1K <0.004 0.01 0.2 2 >1K >1K 4 >1K Targeted mAb A 23 (8 load) >1K >1K >1K 0.01 0.03 1 1 >1K >1K 1 >1K Targeted mAb A 23 (4 load) >1K >1K >1K 0.02 0.05 4 5 >1K >1K 8 >1K Targeted mAb B 23 (8 load) >1K >1K >1K <0.004 0.01 0.1 0.2 >1K >1K 0.3 >1K Targeted mAb B 23 (4 load) >1K >1K >1K 0.002 0.02 0.3 0.3 >1K >1K 2 >1K Compound X50 (nM)) Compound 1 >1K >1K >1K 2 16 >1K 31 >1K >1K 42 >1K Compoud 12a >1K >1K >1K 3 111 >1K 83 >1K >1K 87 >1K Compound 16 >1K >1K >1K 4 7 >1K 29 >1K >1K 27 >1K

[1742] Multiple additional compounds were synthesized and evaluated for their ability activate THP1-Dual™ reporter cells. Several compounds were active with EC50 values ranging from 1.3 nM (compound 27e) to 6337 nM (compound 126a, Table 3). Compounds with minimal activity up to 10 μM are listed in Table 3 as having an EC59 value of >10,000 nM. Several compounds were conjugated to targeted (Table 1) and non-binding antibodies (not shown) via cleavable or non-cleavable drug linkers and the resulting ADCs were assessed for their ability to activate THP1-Dual™ reporter cells. Conjugates with drug linkers 25-27, 105, 108, 111-112, 121-125, 131-134, 150, and 152 were active with EC51 values ranging from 1.4 to 307 ng/mL (Table 1). All other conjugates tested were not active up to 10 μg/mL in this assay, including conjugates with drug linkers derived from active small molecules (Table 3, Table 1) thus highlighting the challenges of developing active ADCs targeting the STING pathway.

TABLE-US-00010 TABLE 3 Activity of STING agonist small molecules in THP1-DualTM reporter cells. Compound EC.sub.50 (nM)** A 3 1 5 12 37 12a 21 15b 5.8 16 52/34 17 66.28 19 190.2 20 53.91 21 2632 23 62.55 24 83.29 25f 12 25g 1576 26e 5 26f 69 27e 1.3 27f 38 28 954 29 52 30 87 31 175.6 32 44.5 33 >10,000 35 >10,000 37 >10,000 38 >10,000 39 >10,000 40 >10,000 41 >10,000 42 >10,000 43 >10,000 44 >10,000 45 >10,000 46 >10,000 47 >10,000 48 >10,000 49 >10,000 50 >10,000 51 >10,000 52 >10,000 53 >10,000 54 >10,000 55 >10,000 56 >10,000 57 >10,000 58 >10,000 59 >10,000 60 >10,000 62 >10,000 63 2508 64/65 388.3 66b 1159 68a 2238 70 1.6 71 70.11 72 275.3 73 216.25 74 35.98 75 57.73 76 58.8 79 >10,000 80 >10,000 81 >10,000 82 >10,000 83 >10,000 84 >10,000 85 >10,000 86 2465 87 >10,000 88 394 89 1324 90 >10,000 91 350 92 1190 93 >10,000 94 132.8 95 12.9 114 9.4 115 17.4 116 11.6 117 14.6 118 23.6 119 49.9 120 5.2 126a 6337 126b >10,000 127 301 128a >10,000 129 836 130 2260 132 37.4 135 2011 136 >5,000 137 1685 138 >5,000 139 >4,000 140 1793 141 159 142 1123 143 155 154 >10,000 155 94 156 1561 157 51 **For some compounds, EC50 values comprise the average value from multiple experiments

[1743] Compound 1 was conjugated to a non-binding antibody as well as antigen C and PD-L1-

targeted mAbs using the cleavable linker 11 and the resulting ADCs were assessed for their ability to induce cytokine production and direct cytotoxicity by SU-DHL-1 cells. Conjugates targeting antigen C and PD-L1, but not the non-binding conjugate, induced robust production of the cytokine MIP-1α and led to SU-DHL-1 cell death (FIG. **6**A and FIG. **6**B).

[1744] The ability of conjugates to activate THP1 dual reporter immune cells in a bystander manner was evaluated. Conjugates consisting of an antibody targeting antigen C with a hIgG1 LALAPG Fc backbone conjugated to compound 12, 13, and 14 demonstrated some bystander activity when THP1 dual cells were co-cultured with HEK 293T cells engineered to express antigen C (FIG. **7**). Conjugates consisting of the h1C1 antibody targeting EphA2 with a mIgG2a WT or LALAPG Fc backbone (see, e.g., Schlothauer et al., Protein Engineering, Design and Selection, 2016, 29(10):457-466; and Hezareh et al., Journal of Virology, 2001, 75(24):12161-12168, each of which is incorporated herein by reference in its entirety) conjugated to compound 12 also demonstrated bystander activity when THP1 dual cells were co-cultured with murine Renca tumor cells. Markedly enhanced bystander activity was observed with conjugates with an intact WT Fc backbone (FIG. **8**).

[1745] The ability of compound 12-mAb conjugates to elicit immune-mediated tumor cell killing in vitro compared to compound 16 was evaluated by co-culturing RFP+ MDA-MB-468 tumor cells and human peripheral blood mononuclear cells (PBMCs). Tumor cell killing was measured by quantifying the RFP confluence, and immune activation was evaluated by quantifying the number of CD8 T cells in each culture as well as IP-10 cytokine secretion. All compounds led to tumor cell killing (FIG. **9**A), with the B7-H4-targeted conjugates demonstrating more potent tumor cell killing compared to the non-binding conjugates and compound 16. Moreover, the B7-H4-targeted conjugates with a WT Fc backbone demonstrated more potent tumor cell killing compared to the same conjugates with an Fc effector function null LALA-KA backbone (FIGS. **9**A and **10**). B7-H4-targeted conjugates with a WT Fc backbone also led to increased CD8 T cell counts (FIG. **9**B) and secretion of the cytokine IP-10 (FIG. **9**C) compared to the other conjugates and compound 16. αvβ6-targeted conjugates were also evaluated and demonstrated greater tumor cell killing activity than compound 16 (FIG. **10**). Finally, αvβ6-targeted and CD228-targeted conjugates demonstrated more potent tumor cell killing compared to compound 16 when used to treat co-cultures of RFP+ HCT15 (FIG. **11**) or HT 1080 (FIG. **12**) tumor cells and PBMCs, respectively. CD228-targeted conjugates with a WT Fc backbone demonstrated more potent tumor cell killing compared to the same conjugates with an Fc effector function null LALAKA backbone (FIG. **13**). This suggests that targeted conjugates with a WT Fc backbone (FIG. **9**A, 10, and 13) drive increased tumor cell killing in vitro compared to conjugates with an Fc effector function null LALAKA backbone.

[1746] The ability of CD228-targeted conjugates of compound 12 (non-cleavable linker) to elicit tumor cell killing in vitro was also evaluated compared to CD228-targeted conjugates of compounds 11, 13, and 14 (cleavable linkers) as well as compound 25. Similar to experiments described above, CD228-targeted conjugates with a WT Fc backbone elicited more potent cell killing compared to conjugates with an Fe effector function null LALAKA backbone (FIG. **35**). Consistent with the reduced potency of conjugates of 11 and 25 in the THP1 dual assay (FIG. **3** and Table 1), CD228-targeted conjugates of 11 and 25 elicited reduced tumor cell killing in the tumor/PBMC co-culture assay compared to CD228-targeted conjugates of compound 12 (FIG. **35**). However, interestingly, in contrast to the modest decrease in potency of conjugates of 13 and 14 in the THP1 dual assay (FIG. **3** and Table 1), CD228-targeted conjugates of 13 and 14 elicited similar tumor cell killing in the tumor/PBMC coculture assay compared to CD228-targeted conjugates of compound 12 (FIG. **35**).

Example 3

In Vivo Evaluation of Anti-Tumor Immune Responses Induced by Sting Agonist ADCS

Experimental Procedures for In Vivo Studies

In Vivo Cytokine Assay

[1747] Cytokines were measured in mouse plasma harvested at 3, 6, 24, or 48 hours after treatment with compounds or ADCs using a Milliplex MAP mouse cytokine/chemokine magnetic bead panel assay kit (MCYTOMAG-70k custom 11-plex kit: MCP1, MIP1a, MIP1(3, TNFα, IFNγ, IL-10, IL-12p70, IL-6, IL-1β, IP10, RANTES) and analyzed using a Luminex™ MAGPIX™ Instrument System. Values that were outside of the standard curve range (<3.2 or >10,000 μg/mL) were either excluded from calculation of the mean values or, when indicated, converted to 3.2 or 10,000 μg/mL for calculation of the mean values.

In Vivo Anti-Tumor Activity Studies

Renca Cancer Cells

[1748] Renca cancer cells (ATCC) were cultured in RPMI-1640 (ATCC) with 10% heat-inactivated fetal bovine serum, Pen-Strep (100 U/mL-100 μg/mL), MEM non-essential amino acids (1×), sodium pyruvate (1 mM), and L-glutamine (2 mM). Renca cancer cells were implanted (2*10.sup.6 cells in 200 μL 25% Matrigel) subcutaneously into Balb/c female mice. In some experiments, Renca tumor cells were engineered to express the indicated murine or human target antigen.

[1749] When tumor volumes reached 100 mm.sup.3, the mice were dosed with either compounds or ADCs by intraperitoneal or intravenous injection at the indicated dosing schedule and tumor volumes were monitored twice weekly. Compounds were formulated in 40% PEG400 in saline.

CT26 Cancer Cells

[1750] CT26 cancer cells (ATCC) were cultured in RPMI 1640 modified with 1 mM Sodium Pyruvate, 10 mM HEPES, 2.8 mL 45% Glucose (1.25 g) and supplemented with 10% fetal bovine serum and 1% Pen/Strep/Glutamine. CT26 cancer cells were implanted (0.5*10.sup.6 cells in 200 uL serum-free RPMI 1640) subcutaneously into Balb/c mice.

MC38 Cancer Cells

[1751] MC38 cancer cells (Kerafast) were cultured in DMEM with 10% heat-inactivated fetal bovine serum, Pen-Strep (100 U/mL-100 g/mL), MEM non-essential amino acids (1×), sodium pyruvate (1 mM), and L-glutamine (2 mM). MC38 cancer cells were implanted (1*10.sup.6 cells in 100 uL 25% Matrigel) subcutaneously into C57BL/6 mice.

[1752] In some experiments, tumor-bearing mice that achieved complete tumor regression following ADC treatment were “rechallenged” with MC38 tumor cells; MC38 cancer cells were implanted (1*10.sup.6 cells in 100 uL 25% Matrigel) subcutaneously into the opposite flank of C57BL/6 mice.

4T1 Cancer Cells

[1753] 4T1 cancer cells (ATCC) were cultured in RPMI with 10% heat-inactivated fetal bovine serum and implanted (0.02*10.sup.6 cells in 200 uL plain RPMI) subcutaneously into Balb/c mice.

mαvβ6-CT26 Tumor Cells

[1754] CT26 cancer cells (ATCC) were engineered using lentiviral transduction to express murine integrin αvβ6. CT26 cells were cultured in RPMI 1640 modified with MEM Non-essential amino acids (1×), 1 mM Sodium Pyruvate, 2 mM Glutamax, 10 mM HEPES, beta mercaptoethanol (55 μM) and supplemented with 10% fetal bovine serum. CT26 cancer cells were implanted (0.1×10.sup.6 cells in 100 μL 25% Matrigel in serum-free RPMI 1640) subcutaneously into Balb/c mice. When tumor volumes reached 100 mm3, the mice were dosed with either compounds or ADCs by intraperitoneal or intravenous injection at the indicated dosing schedule and tumor volumes were monitored twice weekly.

mB7-H4-Renca Tumor Cells

[1755] Renca cancer cells were engineered using lentiviral transduction to express murine B7-H4. Renca cells were cultured in High glucose RPMI-1640 (ATCC) with 10% heat-inactivated fetal bovine serum, MEM non-essential amino acids (1×), sodium pyruvate (1 mM), and L-glutamine (2 mM). Renca cancer cells were implanted (2×10.sup.6 cells in 200 μL 25% Matrigel in RPMI 1640 medium) subcutaneously into Balb/c female mice. When tumor volumes reached 100 mm3, the mice were dosed with either compounds or ADCs by intraperitoneal or intravenous injection at the

indicated dosing schedule and tumor volumes were monitored twice weekly.

mB7-H4-EMT6 Tumor Cells

[1756] EMT6 cancer cells were engineered using lentiviral transduction to express murine B7-H4. EMT6 cells were cultured in Dulbecco's Modified Eagle Medium with MEM Non-essential Amino Acids (1×), Sodium Pyruvate (1 mM), Glutamax (2 mM), HEPES (10 mM), beta mercaptoenthanol (55 μM) and supplemented with 10% heat-inactivated fetal bovine serum. EMT6 cancer cells were implanted (0.5×10.sup.6 cells in 100 μL 25% Matrigel in serum-free RPMI 1640) subcutaneously into Balb/c female mice. When tumor volumes reached 100 mm.sup.3, the mice were dosed with either compounds or ADCs by intraperitoneal or intravenous injection at the indicated dosing schedule and tumor volumes were monitored twice weekly.

hCD228-LL2 Tumor Cells

[1757] LL2 cancer cells were engineered using lentiviral transduction to express human CD228. LL2 cells were cultured in DMEM (ATCC) with 10% heat-inactivated fetal bovine serum. Female C57BL/6 mice were implanted with 1×106 hCD228-LL2 tumor cells in 100 μL 25% Matrigel in RPMI 1640 medium subcutaneously. Once tumor volumes reached 100 mm.sup.3, mice were randomized into treatment groups and dosed as indicated. Tumor volumes were measured twice per week, and animals were euthanized when tumor volumes reached 750-1000 mm.sup.3. Stock concentrations of mAb or conjugates were diluted to a desired concentration (with 20 mM His, 6% Trehalose or 0.01% Tween20 in PBS) and injected intraperitoneally (i.p.) or intravenously (i.v.) as indicated. The small molecule was formulated in 40% PEG400 in saline and injected i.v.

Evaluation of Conjugate Pk in Lewis Lung Tumor Model

[1758] Pharmacokinetic profiles were analyzed following administration of a single 1, 5, or 10 mg/kg dose of ADCs comprising a CD228-targeted mAb (WT hIgG1 Fc) conjugated to compound 12, 13, or 14 (delivered intravenously or intraperitoneally, as indicated) to female C57BL/6 mice bearing hCD228-expressing LL2 tumors. Plasma was collected and analyzed for generic total antibody (gTAb) by immunoassay. TAb concentrations in mouse K2EDTA plasma were determined by a Gyros flow-through immunoassay platform. Samples and standards were diluted in assay buffer and incubated with a solution containing biotinylated murine anti-human kappa light chain antibody and fluorescent goat anti-human IgG Fcg F(ab′).sub.2 antibody fragment in a sandwich format. The resulting immunocomplexes were bound to the streptavidin-coated beads in the affinity column of the compact disc (CD). The CD was read by a laser that excites the fluorescent detection reagent, producing a signal that is directly proportional to the concentration of test article in the C57BL/6 female mouse plasma sample. Non-compartmental analysis was applied to pooled animal plasma concentration data (serial (FIG. **31**) or sparse (FIG. **33**) sampling) using Phoenix WinNonlin 8.2 (Certara, USA). Concentration values below the limit of quantitation (BLQ) were treated as zero for analysis. Nominal doses and sampling times were used.

MDAMB468 Tumor Model

[1759] MDA-MB-468 cells were cultured in RPMI with 10% fetal bovine serum (FBS) and sodium pyruvate. Female Nude mice were implanted with 1×10.sup.6 MDA-MB-468 cells in 25% Matrigel HC (Corning #354248) subcutaneously. Once tumor volumes reached 100 mm.sup.3, mice were randomized into treatment groups of 8-10 mice each and dosed with a single 3 mg/kg dose of ADCs. Tumor volumes were measured twice per week; animals were euthanized when tumor volume reached 700-1000 mm.sup.3. Tumors were harvested from some animals 3 days post-dose at necropsy and processed for immunohistochemical staining. Stock concentrations of ADC were diluted to desired concentration (with 0.01% Tween20 in PBS) and injected i.p. into each treatment group.

Results from In Vivo Studies

Renca Cancer Cells

[1760] A syngeneic system was used to assess the ability of the STING agonist ADCs to induce immune responses in vivo and drive an anti-tumor immune response. The Renca system is a

subcutaneous, mouse renal adenocarcinoma model. Female Balb/c mice were implanted with 2×10.sup.6 Renca cells subcutaneously in the flank on day 0. When mean tumor size of 100 mm.sup.3 (measured by using the formula Volume (mm.sup.3)=0.5*Length*Width.sup.2 where length is the longer dimension) was reached mice were randomized into treatment groups of ≥5 mice per group. Animals were then treated intraperitoneally (ADCs or compounds) or intravenously (compounds) with the indicated treatment every 7 days, for 3 doses total (or as indicated). Tumor length and width and the weight of the animals was measured throughout the study and tumor volume was calculated using the formula above. Animals were followed until the tumor volume reached ˜1000 mm.sup.3; animals were then euthanized.

[1761] The anti-tumor activity of compound 1 compared to the cleavable linker 11 conjugated to a non-binding or EphA2-targeted mAb (mIgG2a LALAPG backbone; see, e.g., Schlothauer et al., Protein Engineering, Design and Selection, 2016, 29(10):457-466; and Hezareh et al., Journal of Virology, 2001, 75(24):12161-12168, each of which is incorporated herein by reference in its entirety) was evaluated; note that all EphA2-targeted mAb conjugates described herein consist of the h1C1 mIgG2a mAb conjugated to various drug linker compounds. When animals were treated with the Compound 1 or the non-binding mAb conjugate of 11, some tumor growth delay was observed; however, tumor growth delay was significantly enhanced with the EphA2-targeted mAb conjugate of 11, especially at the higher 12 mg/kg dose (FIG. **14**A), clearly demonstrating the anti-tumor benefit of delivering STING agonists using a targeted ADC.

[1762] In the next in vivo study, the anti-tumor activity of the non-cleavable linker compound 12 conjugated to a non-binding or EphA2-targeted mAb (mIgG2a LALAPG backbone) was evaluated. The EphA2-targeted mAb conjugate of 12 exhibited robust anti-tumor activity and was surprisingly more active than the ADC of 11 conjugated to the same EphA2-targeted mAb (FIG. **15**A). In the next in vivo study, the anti-tumor activity of the non-cleavable linker 15 conjugated to a non-binding or EphA2-targeted mAb (mIgG2a WT backbone) was evaluated. EphA2-targeted mAb conjugates of 15 exhibited robust anti-tumor activity that was similar to the corresponding ADC of 12 (FIG. **16**A). In this study, the activity of 12 conjugated to an EphA2-targeted antibody with a mIgG2a WT and LALAPG backbone was also evaluated, and both conjugates were similarly active. This was a surprising finding, given that the in vitro bystander assay indicates that an intact WT Fc backbone significantly enhances bystander immune cell activation compared to LALAPG Fc backbone (FIG. **8**).

[1763] Compound 1 and all antibody conjugates of 11 and 12 on a mIgG2a LALAPG backbone were well tolerated—average weight loss was <−5% after the 1.sup.st and 2.sup.nd dose of the treatment. The STING agonist compound A was less well tolerated—with mice exhibiting on average 6.2% weight loss after the 2.sup.nd dose (FIG. **14**B, **15**B, and **16**B). Moreover, EphA2-targeted mAb conjugates of 12 and 15 with a mIgG2a WT backbone at the 3 mg/kg dose level were less well tolerated than the conjugate of 12 with a LALAPG backbone—with mice treated with targeted WT backbone ADCs exhibiting ˜8% weight loss (FIG. **16**B).

[1764] In the next in vivo study, the anti-tumor activity of the non-cleavable linker compound 12 conjugated to an EphA2-targeted mAb (mIgG2a LALAPG backbone) as well as unconjugated Compound 12a was evaluated. The EphA2-targeted mAb conjugates of 12 exhibited robust anti-tumor activity at doses of 1 mg/kg and 3 mg/kg, while Compound 12a had limited anti-tumor efficacy (FIG. **17**). Collectively, this suggests that STING agonist compounds (e.g., compounds 1 and 12a) that are minimally active in vivo in tumor models can be converted into active therapeutics by conjugation to an antibody (e.g., targeted mAb conjugates of 11 and 12).

[1765] Systemic cytokine production in response to the free drugs and conjugates was measured as a proxy for systemic activity. Compound 1 and all antibody conjugates of 11, 12 and 15 induced very little pro-inflammatory cytokine (IL-6 and TNF) production. On the other hand, compound A and compound 12a induced robust production of IL-6 and TNF (Table 4, Table 5, and Table 6). Moreover, EphA2-targeted conjugates of 11 and 12 with a WT Fc backbone induced more systemic

MIP1α, MIP1β, and MCP-1 expression than the conjugate of 12 with a LALAPG Fc backbone. This indicates that, in the Renca tumor model with the specific EphA2-targeted antibodies described in FIGS. **15**A-**17** dosed at 3 mg/kg q7dx3, a LALAPG Fc backbone may reduce on-target toxicity (systemic cytokines/weight loss), without impacting anti-tumor efficacy. This also indicates that conjugation of a STING agonist compound (e.g., compound 12a vs. the targeted mAb conjugate of 12) may improve both efficacy and safety (reduce systemic cytokines).

TABLE-US-00011 TABLE 4 Cytokine production in peripheral blood (plasma) in Renca tumor-bearing mice upon treatment with various ADCs comprising a non- binding or EphA2-targeted mAb with a mIgG2a LALAPG backbone conjugated to compound 11 or 12, or compound 1 or Compound A. 3 mg/kg 3 mg/kg 2.4 mg/kg non- non- 3 mg/kg 3 mg/kg non- 2.4 mg/g 12 mg/kg 1.48 mg/kg 1.86 mg/kg Time binding binding targeted targeted binding targeted targeted Compound Compound (h) control mAb 11 mAb 12 mAb 11 mAb 12 control mAb 11 mAb 11 mAb 11 1 A IFNγ 3 <3.2 1.1 0.4 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 0.3 6 <3.2 15.6 7.1 8.5 22.6 <3.2 <3.2 1.3 4.3 0.2 71.8 24 <3.2 <3.2 1.4 <3.2 3.0 <3.2 <3.2 <3.2 0.9 <3.2 <3.2 IL1β 3 3.2 5.3 4.3 4.3 5.3 0.4 0.3 0.5 0.3 0.7 1.5 6 3.2 4.3 4.3 5.3 6.4 0.3 1.7 0.3 1.8 1.5 0.6 24 3.2 4.3 4.8 4.3 5.8 0.3 0.3 0.3 0.3 0.8 0.3 IL-6 3 9.2 120.1 23.8 150.5 109.5 154.7 14.3 5.5 37.7 95.7 3553.0 6 26.9 472.1 176.6 305.6 404.4 0.7 162.2 81.9 303.4 6.8 731.9 24 33.2 12.0 58.6 28.0 75.3 7.7 19.6 4.8 27.0 13.5 16.4 IL-10 3 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 1.5 48.8 0.5 6 <3.2 3.9 4.3 4.8 6.4 <3.2 <3.2 <3.2 <3.2 0.8 <3.2 24 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 0.8 34.6 <3.2 IL12p70 3 <3.2 5.9 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 17.6 174.5 0.2 6 <3.2 <3.2 <3.2 <3.2 3.1 <3.2 <3.2 <3.2 <3.2 <3.2 0.2 24 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 23.4 140.0 <3.2 IP10 3 235.3 973.2 402.4 1069.7 1094.1 59.8 176.7 80.5 295.4 702.8 4785.0 6 179.7 2976.0 2783.5 2963.1 3037.2 37.0 3977.4 4205.6 7374.2 3391.5 4976.1 24 192.3 1129.0 2329.0 1019.3 2564.0 71.5 559.7 358.1 1524.0 551.1 889.6 MCP-1 3 50.2 138.6 97.6 152.5 166.5 67.8 21.6 10.0 65.2 167.8 14494.4 6 35.8 1168.1 615.0 1727.0 7542.0 19.7 3822.7 1811.8 10211.9 795.6 10776.8 24 50.2 157.0 2374.8 284.9 7777.1 26.9 238.0 161.9 1486.0 332.6 539.5 MIP1α 3 <3.2 26.1 <3.2 26.1 <3.2 24.1 3.0 13.9 10.0 55.6 1300.3 6 <3.2 36.4 44.5 38.4 67.1 10.0 49.1 24.0 108.5 38.9 208.8 24 <3.2 <3.2 62.9 62.9 36.4 33.9 10.0 49.4 29.9 69.9 41.7 MIP1β 3 <3.2 78.2 40.4 66.6 53.3 6.4 11.3 6.4 45.4 362.3 6365.1 6 <3.2 736.5 697.0 657.3 1267.3 <3.2 469.0 197.9 1170.5 168.7 2153.8 24 <3.2 61.8 439.4 35.9 705.5 <3.2 35.6 26.4 270.7 70.7 35.5 RANTES 3 4.4 6.4 1.3 7.8 5.3 2.9 2.2 1.7 3.4 10.6 91.6 6 <3.2 14.9 3.4 13.2 34.1 2.7 19.9 11.9 57.3 18.4 736.9 24 4.3 25.5 186.5 22.3 239.1 3.5 18.2 11.9 90.6 15.6 113.2 TNFa 3 <3.2 3.2 <3.2 <3.2 <3.2 1.6 1.4 1.3 2.5 3.6 57.0 6 <3.2 12.9 7.2 10.2 4.6 0.8 3.8 2.1 6.2 1.9 17.3 24 <3.2 <3.2 3.2 <3.2 8.2 1.3 1.4 1.3 3.1 2.0 1.3

TABLE-US-00012 TABLE 5 Cytokine production in peripheral blood (plasma) in engineered Renca tumor- bearing mice upon treatment with various ADCs comprising a non-binding or EphA2-targeted mAb with either a mIgG2a wild type (WT) or a mIgG2a 3 mg/kg 3 mg/kg 3 mg/kg non- non- 3 mg/kg 3 mg/kg non- 3 mg/kg targeted targeted targeted targeted targeted targeted Time mAb 12 mAb 12 mAb 12 mAb 12 mAb 15 mAb 15 (h) control (LALAPG) (WT) (LALAPG) (WT) (WT) (WT) IFNγ 3 1.1 1.2 2.2 0.7 1.2 1.3 1.8 6 0.8 8.9 5.2 12.1 19.3 8.5 17.5 24 1.3 7.1 6.1 18.8 27.0 6.6 21.1 48 2.0 1.5 2.0 2.1 2.0 1.8 2.0 IL1β 3 8.8 12.7 26.0 19. 7.8 15.9 30.3 6 8.8 35.5 14.7 <3.2 27.0 27.3 19.0 24 10.7 12.2 22.7 4.9 10.7 10.8 7.8 48 <3.2 4.9 22.7 7.8 2.1 13.7 10.7 IL-6 3 5.1 12.7 12.6 71.6 61.6 12.0 105.8 6 5.5 55.3 47.3 327.4 279.5 82.4 475.4 24 3.5 33.4 25.2 61.1 80.8 41.3 63.0 48 2.3 5.0 5.8 29.9 15.6 11.5 17.9 IL-10 3 2.6 4.0 4.4 4.1 2.2 5.9 5.1 6 2.5 8.2 4.8 5.2 9.6 8.4 6.3 24 1.6 3.2 2.7 4.9 5.5 4.9 7.3 48 0.6 0.6 2.7 1.7 1.0 2.6 2.1 IL12p70 3 12.1 5.0 31.9 26.6 <3.2 23.3 12.5 6 0.9 48.9 13.7 <3.2 23.5 29.0 10.3 24 0.9 10.5 7.1 4.0 0.9 10.5 4.0 48 <3.2 0.9 20.1 <3.2 0.9 7.1 0.9 IP10 3 99.4 134.0 104.9 335.5 371.9 185.4 637.3 6 71.0 2469.9 2651.6 2757.9 3219.0 2885.3 3422.1 24 86.3 1798.9 1652.7 2219.9 2004.1 2616.0 2324.1 48 127.6 738.5 822.9 824.4 819.2 1052.2 935.8 MCP-1 3 63.2 120.4 165.9 135.5 96.9 142.7 276.1 6 72.1 1368.6 1195.0 915.2 4492.9 1764.0 6594.8 24 57.0 2083.8 1878.0 6406.5 8018.1 9546.4 15026.1 48 42.1 285.6 599.9 794.1 934.2 1629.3 2234.6 MIP1α 3 137.3 142.9 205.0 166.4 101.3 187.3 163.7 6

101.3 178.8 130.0 61.4 284.3 133.8 271.9 24 133.8 120.7 153.3 101.3 227.0 193.7 205.2 48 <3.2 101.3 140.2 101.3 101.3 140.2 166.4 MIP1β 3 <3.2 <3.2 78.1 <3.2 349.4 49.8 942.0 6 <3.2 578.4 850.5 735.3 2898.1 677.8 4342.5 24 <3.2 425.4 456.2 661.8 1493.2 1561.0 1387.7 48 <3.2 178.9 227.9 221.2 309.4 567.1 378.3 RANTES 3 5.6 8.0 11.0 9.1 6.7 10.1 11.0 6 6.6 24.5 18.9 14.4 168.0 37.5 206.6 24 5.6 77.1 52.5 338.9 174.8 335.7 772.2 48 6.6 21.3 43.9 69.6 59.2 140.4 190.4 TNFα 3 4.6 6.2 6.8 7.7 4.3 11.0 9.8 6 2.7 15.0 5.8 3.5 16.5 9.9 22.9 24 5.4 7.7 7.7 6.6 8.8 13.3 11.0 48 1.9 5.4 6.5 5.4 5.4 6.6 7.6

TABLE-US-00013 TABLE 6 Cytokine production in peripheral blood (plasma) in Renca tumor-bearing mice upon treatment with ADCs comprising an EphA2-targeted mAb with mIgG2a LALAPG backbone conjugated to compound 12 or compound 12a. 0.3 mg/kg 1.0 mg/kg 3.0 mg/kg 0.2 mg/kg 0.6 mg/kg 1.8 mg/kg targeted targeted targeted Dose Time Compound Compound Compound mAb 12 mAb 12 mAb 12 # (h) Untreated Vehicle 12a 12a 12a (LALAPG) (LALAPG) (LALAPG) IFNg 1 3 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 1 6 <3.2 <3.2 4.6 18.3 36.4 <3.2 <3.2 9.4 1 24 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 5.8 5.3 1 48 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 2 6 <3.2 <3.2 16.5 41.5 80.4 0.0 1.7 20.1 IL-1b 1 3 0.7 0.7 0.7 0.7 7.5 3.2 0.7 0.7 1 6 0.7 <3.2 0.7 5.7 0.7 3.2 11.0 5.7 1 24 7.0 3.2 3.2 1.6 3.2 2.4 0.7 3.2 1 48 3.2 5.7 0.7 5.7 3.2 3.2 3.2 5.8 2 6 <3.2 <3.2 2.7 5.8 4.6 2.7 2.7 <3.2 IL-6 1 3 3.3 16.6 780.0 1899.7 4314.6 5.8 13.9 17.8 1 6 0.4 4.9 266.1 424.0 543.0 25.0 28.3 152.1 1 24 2.8 1.5 4.1 6.1 6.8 8.6 22.5 74.1 1 48 0.9 0.9 5.6 1.8 1.5 1.9 1.8 26.3 2 6 2.2 5.1 410.9 516.9 1681.6 13.6 53.2 130.1 IL-10 1 3 <3.2 <3.2 15.6 30.4 27.3 <3.2 <3.2 <3.2 1 6 <3.2 <3.2 <3.2 3.8 9.9 <3.2 <3.2 3.8 1 24 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 3.8 1 48 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 2 6 <3.2 <3.2 1.2 <3.2 7.7 <3.2 1.2 <3.2 IL12p70 1 3 <3.2 9.4 <3.2 <3.2 3.1 <3.2 <3.2 9.4 1 6 <3.2 <3.2 <3.2 3.1 <3.2 <3.2 <3.2 <3.2 1 24 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 3.1 1 48 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 2 6 <3.2 <3.2 <3.2 28.4 28.4 <3.2 <3.2 12.1 IP10 1 3 88.9 124.3 1989.6 4826.2 8222.7 122.1 200.3 278.0 1 6 95.4 116.3 8985.4 8828.3 7589.2 4294.0 5279.6 6945.6 1 24 102.2 78.1 257.9 381.8 595.6 1123.5 1703.4 4251.8 1 48 80.8 85.1 172.8 218.4 223.5 317.8 566.2 1631.2 2 6 139.5 191.4 >10000 3996.6 4151.5 1451.7 2590.8 2963.6 MCP-1 1 3 17.3 65.0 333.3 1547.8 5805.3 21.8 48.1 50.2 1 6 11.9 62.8 7790.8 12898.6 13861.5 518.9 311.8 1080.9 1 24 24.4 2.0 53.0 141.5 143.9 283.5 694.9 5104.5 1 48 29.3 19.4 56.8 40.0 2.0 118.0 108.0 530.5 2 6 51.7 87.7 5244.6 9761.2 17185.9 175.5 338.2 592.4 MIP1a 1 3 <3.2 <3.2 10.3 251.5 1052.6 <3.2 <3.2 10.3 1 6 <3.2 10.3 101.9 137.2 172.2 10.3 10.3 100.5 1 24 10.3 <3.2 <3.2 <3.2 10.3 <3.2 <3.2 92.5 1 48 <3.2 <3.2 10.3 10.3 <3.2 10.3 <3.2 <3.2 2 6 32.6 32.6 104.9 115.5 209.9 52.2 32.6 99.2 MIP1b 1 3 <3.2 <3.2 727.2 2471.0 7438.6 <3.2 <3.2 <3.2 1 6 <3.2 <3.2 670.7 1050.0 1162.7 155.7 256.7 695.2 1 24 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 497.5 1 48 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 <3.2 157.8 2 6 <3.2 <3.2 718.6 837.6 1407.7 <3.2 216.1 449.7 RANTES 1 3 <3.2 <3.2 <3.2 20.1 51.2 <3.2 5.0 <3.2 1 6 20.3 <3.2 130.3 255.0 526.2 14.7 17.1 23.2 1 24 <3.2 <3.2 3.2 46.2 48.8 11.3 34.5 131.7 1 48 9.2 <3.2 <3.2 5.0 <3.2 7.9 17.1 79.4 2 6 8.2 2.9 133.8 621.6 892.1 12.5 15.6 45.8 TNFa 1 3 <3.2 4.3 9.1 21.0 46.4 3.2 3.2 4.5 1 6 <3.2 3.2 8.1 15.6 21.2 3.2 10.6 7.3 1 24 7.3 3.2 3.2 5.2 3.2 5.2 5.9 15.2 1 48 <3.2 5.4 4.3 <3.2 3.2 5.2 7.3 8.9 2 6 <3.2 <3.2 10.0 16.7 46.4 3.2 3.2 3.2

[1766] The anti-tumor activity of the cleavable linker 11 conjugated to a non-binding mAb, PD-L1-targeted mAb (tumor and/or immune cell-targeted), or antigen C-targeted mAb (immune cell-targeted) was also evaluated in Renca tumor-bearing mice. All conjugates demonstrated tumor growth delay compared to untreated tumors. The PD-L1-targeted mAb conjugate of 11 demonstrated enhanced anti-tumor activity compared to an unconjugated PD-L1-targeted mAb. This demonstrates the anti-tumor benefit of delivering STING agonists using an ADC targeting antigens C and PD-L1 (FIG. **18**). The anti-tumor activity of the non-cleavable linker 12 conjugated to a PD-L1-targeted mAb was also evaluated in Renca tumor-bearing mice; these conjugates induced tumor growth delay, though were less well tolerated than PD-L1 targeted mAb conjugates of 11.

CT26 Cancer Cells

[1767] The anti-tumor activity of compound 1 compared to the cleavable linker 11 conjugated to a non-binding mAb, antigen C-targeted mAb, PD-L1-targeted mAb, or EphA2-targeted mAb was evaluated in CT26 tumor-bearing mice. When animals were treated with compound 1 or the unconjugated PD-L1-targeted mAb, minimal tumor growth delay was observed. Modest tumor growth delay was observed with the non-binding mAb conjugate of 11. In contrast, significant tumor growth delay was observed following treatment with all three targeted mAb conjugates of 11. This demonstrates the anti-tumor benefit of delivering STING agonists using an ADC targeting a variety of antigens, including an immune cell-targeted conjugate (antigen C), immune and/or tumor-targeted conjugate (PD-L1), and tumor-targeted conjugate (EphA2) (FIG. **19**). Results of cytokine production in peripheral blood plasma is presented in Table 7.

TABLE-US-00014 TABLE 7 Cytokine production in peripheral blood (plasma) in CT26 tumor-bearing mice upon treatment with various ADCs comprising a mAb conjugated to compound 11. 12 mg/kg EphA2-targeted Time 1.86 mg/kg mAb 11 (h) Untreated Compound 1 (mIgG2a LALAPG) IL-6 3 0.5 3.2 3.2 622.1 781.4 1128.3 185.8 0.5 217.7 6 2.7 3.2 0.2 2652.5 2393.5 2412.7 2677.9 1790.2 2777.7 24 5.7 5.4 0.6 44.5 31.8 36.5 72.8 0.2 67.6 48 26.5 262.8 7.6 47.8 142.7 29.2 214.1 61.7 80.4 IL-10 3 3.2 3.2 3.2 0.2 2.3 1.2 3.2 3.2 1.2 6 3.2 3.2 3.2 7.8 9 4.4 7.2 2 4.3 24 3.2 3.2 3.2 3.2 3.2 3.2 3.2 3.2 1.5 48 3.2 3.2 3.2 3.2 3.2 3.2 3.2 3.2 3.2 IP-10 3 242.4 109.7 200.2 1439.4 1501.7 1160.7 592.6 125.9 377.2 6 174.7 117.4 188.2 2610.8 2133.6 2473.4 2039.3 2711.3 2008.6 24 272.5 134.4 201.1 1121.6 1025.3 696.2 1468.5 145 1900.5 48 122.9 155.8 74.7 560.1 398.8 560 1293.4 541.3 716.9 MCP-1 3 2.7 3.2 3.2 73.7 78.6 110.3 36.4 2.7 23.1 6 7.2 7.2 3.2 3185.3 2816.3 1634.8 6186.6 3754.5 3698.6 24 3.2 3.2 3.2 397.7 294.7 305.9 765.3 3.2 821 48 13.5 18.6 3.2 93.1 20.9 41.4 207.4 85.1 108.7 MIP-1a 3 3.2 3.2 3.2 3.9 3.2 3.2 3.9 3.2 3.2 6 3.9 3.2 3.2 94.6 93.6 73.9 222.1 127.3 261.8 24 3.2 3.2 3.2 12.7 25.1 3.2 21.7 3.2 21.7 48 3.2 3.2 3.2 3.9 12.7 3.2 3.9 3.2 3.9 MIP1b 3 3.2 1.6 3.2 297.7 336.8 224 311.6 3.2 185.9 6 3.2 3.2 3.2 925.8 369.7 1161.4 1679.2 1460.7 1237.9 24 3.2 3.2 3.2 127.6 125.3 55.3 268.8 3.2 356.8 48 3.2 14.8 3.2 61.1 10.8 57.6 66.7 26.9 56.9 TNFa 3 3.2 3.2 3.2 3.2 4.9 4.3 1.4 3.2 3.2 6 3.2 3.2 3.2 16.9 16.6 10 29.1 26.2 34.8 24 3.2 3.2 3.2 0.4 0.7 3.2 4.3 3.2 3.2 48 3.2 3.2 3.2 1.1 3.2 3.2 1.4 3.2 3.2 2.4 mg/kg 2.4 mg/kg 2.4 mg/kg EphA2-targeted Antigen C-targeted Non-binding Time mAb 11 mAb 11 mAb 11 (h) (mIgG2a LALAPG) (mIgG2a LALAPG) (mIgG2a LALAPG) IL-6 3 17.8 27.7 23.4 483.9 182.4 442.5 1.4 100.6 56.5 6 168.7 303.4 304.8 1821.4 2769.8 2324.8 123.7 151.3 266.9 24 16.2 143.2 16.1 9.4 34.4 126.9 5 16.9 3.2 48 6.5 39.1 7.8 48.9 32.2 19.5 2.9 2.9 2.3 IL-10 3 3.2 3.2 3.2 0.9 3.2 0.4 3.2 3.2 3.2 6 4 1.2 1.6 1.2 3.7 4.3 0.4 0.4 2 24 3.2 3.2 3.2 0.4 3.2 3.2 3.1 3.2 3.2 48 3.2 3.2 3.2 3.2 3.2 3.2 3.2 3.2 3.2 IP-10 3 198.1 190.9 196.9 1271.3 629.1 627.8 109.4 450 308.7 6 2327.7 2740.5 1949.2 2062.9 2328 2713.5 1779.6 1376.6 2092 24 1189.9 1094.8 1089 2565 1994.5 1329.8 246.4 693.7 3.2 48 307.2 167.2 250.2 448.8 273.5 378 107.3 235.9 319.2 MCP-1 3 3.2 10.5 2.7 393.2 69.9 78.6 3.2 46.2 2.7 6 656.5 578.3 382.2 10207.3 4960.7 37687.1 162 556.2 425 24 99.1 99.1 99.1 1009.2 637.8 194 3.2 55.1 3.2 48 27.2 10.5 13.5 39.8 34.7 365.9 3.2 2.7 20.9 MIP-1a 3 3.2 3.2 3.2 217.7 103.1 139.8 3.2 3.2 3.2 6 12.7 3.9 3.2 144 152.7 82.1 17.7 12.7 3.9 24 3.2 3.2 3.2 17.7 21.7 12.7 3.2 3.2 3.2 48 3.2 3.2 3.2 3.2 3.2 17.7 3.2 3.2 3.2 MIP1b 3 26.9 19.7 5.4 1600.5 682.1 991.5 3.2 31.2 7.2 6 367.2 264.6 356.3 1377.1 1236.6 1740.4 137.2 215.4 203.6 24 84.9 63.2 51.3 197.4 142.2 127.5 3.2 26.9 3.2 48 11.4 3.2 8.8 13.8 13.2 69 3.2 3.2 3.2 TNFa 3 3.2 3.2 3.2 31 25.6 27.6 3.2 3.2 3.2 6 6.2 3.8 2.6 31 45.5 39.5 3.2 4.3 3.2 24 3.2 2.9 8.5 2 7 3.8 3.2 1.4 3.2 48 3.2 3.2 3.2 3.2 3.2 1.7 3.2 3.2 3.2 2.4 mg/kg 2.4 mg/kg Time PD-L1-targeted PD-L1-targeted (h) mAb 11 mAb IL-6 3 18.1 56.9 3.3 25.6 0.6 5.8 6 119.4 72.6 162.5 3.2 3.2 1 24 23.8 21.8 5.2 21.2 6.5 216.8 48 26.6 26.8 89.7 1.4 3.2 12.2 IL-10 3 3.2 3.2 3.2 33.8 3.2 3.2 6 0.4 0 0 3.2 3.2 3.2 24 3.2 3.2 3.2 26.2 3.2 3.2 48 3.2 3.2 0.4 3.2 3.2 3.2 IP-10 3 163.9 154.4 178.3 105.7 190.4 96.1 6 1814.4 1744 1389.4 130.6 151.9 110.7 24 717.5 1002.6 833.1 247.7 689.9 166.7 48 748.1 599.3 580.4 128.1 183.3 135.9 MCP-1 3 18.9 13.8 3.2 169.8 3.2 3.2 6 143.3 133 252 3.1 7.5 7.5 24 129.2 191.4 98 129.2 7.5 3.2 48 135.9 127.3 253.1 7.5 13.8 16.4 MIP-1a 3 3.2 3 3.2 3 3 3 6 11.2 3 3 3 3 11.2 24 3 3 3 3 11.2 24 48 11.2 11.2 3 3 7.9 3 MIP1b 3 3.2 5.4 9.9 3.2 3.2 3.2 6 70 61.7 85.7 3.2 3.2 3.2 24

3.2 19.3 32 3.2 3.2 46.1 48 26.5 23.5 30 3.2 3.2 3.2 TNFa 3 5.8 3.2 3.2 75.5 3.2 3.2 6 3.2 3.2 3.2 3.2 3.2 3.2 24 6.4 3.2 3.2 58.6 3.2 3.2 48 3.6 3.2 3.2 3.2 3.2 3.2

MC38 Cancer Cells

[1768] The anti-tumor activity of the cleavable linker 12 conjugated to a non-binding mAb or EphA2-targeted mAb with a LALAPG mIgG2a Fc backbone was evaluated in MC38-tumor bearing wild type (WT) or STING-deficient (Tmem173.sup.gt) mice. Animals treated with 3 weekly doses of 1 mg/kg non-binding conjugates of 12 or 0.1 mg/kg targeted conjugates of 12 demonstrated modest and minimal tumor growth delay, respectively, in WT but not STING-deficient tumor bearing mice. Animals treated with 3 weekly doses of 1 mg/kg targeted conjugates of 12 demonstrated robust tumor growth delay in WT but not STING-deficient tumor bearing mice. This demonstrates that in MC38 tumor-bearing mice STING signaling is required in non-tumor cells in the tumor microenvironment for anti-tumor activity (FIGS. **20**A and **20**C).

[1769] Animals treated with a single dose of 1 mg/kg EphA2-targeted conjugates of 12 also demonstrated robust tumor growth delay in WT tumor bearing mice, demonstrating that a single dose of EphA2-targeted conjugates of 12 is sufficient to drive complete tumor regression (FIG. **20**A).

[1770] Mice that achieved complete tumor regression in response to a single dose or 3 weekly doses of ADC were rechallenged with MC38 tumor cells on the opposite flank and tumor growth was monitored. All rechallenged mice—but not all naïve untreated mice challenged with MC38 tumor cells—were protected from rechallenge, suggesting that targeted conjugates of 12 elicit immune memory (FIG. **20**D).

4T1 Cancer Cells

[1771] The anti-tumor activity of the cleavable linker 12 conjugated to a non-binding or EphA2-targeted mAb with a LALAPG mIgG2a Fc backbone was evaluated in 4T1 tumor-bearing mice. All conjugates of compound 12 led to significant tumor growth delay at the doses tested, with the targeted mAb conjugate of compound 12 demonstrating enhanced tumor growth delay compared to the non-binding conjugate (FIG. **21**A), with minimal weight loss observed (FIG. **21**B). This demonstrates that EphA2-targeted mAb conjugates of compound 12 are active in multiple tumor models (FIGS. **17**-**21**B).

B7-H4-Targeted Conjugates

[1772] B7-H4-targeted conjugates were evaluated in a Renca tumor model engineered via lentiviral transduction to express murine B7-H4 (mB7-H4). mB7-H4-expressing Renca tumor-bearing mice were treated with 3 weekly doses of 1 mg/kg of unconjugated mAb or ADC. Non-binding mAb conjugates of compound 12 led to modest tumor growth delay, while the B7-H4-targeted mAb conjugates of compound 12 led to robust tumor growth delay. B7-H4-targeted conjugates with a WT mIgG2a Fe backbone led to slightly enhanced tumor growth delay compared to those with a Fc effector function null LALA-KA mIgG2a Fc backbone (see, e.g., Schlothauer et al., Protein Engineering, Design and Selection, 2016, 29(10):457-466; and Hezareh et al., Journal of Virology, 2001, 75(24):12161-12168, each of which is incorporated herein by reference in its entirety). This suggests that the B7-H4-targeted ADCs elicit robust anti-tumor responses. Moreover, this suggests that in the Renca tumor model, B7-H4-targeted mAb conjugates with a WT Fe backbone drive slightly more robust anti-tumor responses than those with a LALA-KA Fe null backbone (FIG. **22**A). Importantly, all conjugates were tolerated, though slightly more weight loss was observed following treatment with ADCs with a WT Fe backbone (FIG. **22**B). Cytokine production is provided in Table 8.

TABLE-US-00015 TABLE 8 Cytokine production in peripheral blood (plasma) in mB7-h4-expressing Renca tumor- bearing mice upon treatment with various ADCs comprising a mAb with either a mIgG2a wild type (WT) or mIgG2a LALAPG or LALAKA backbone conjugated to compound 12. 1 mg/kg 1 mg/kg 1 mg/kg 1 mg/kg 1 mg/kg 1 mg/kg non- B7-h4- non- B7-h4- EphA2- B7-h4- binding targeted binding targeted targeted Time targeted mAb 12 mAb 12 mAb 12

mAb 12 mAb 12 (h) control mAb (WT) (WT) (LALAPG) (LALAKA) (LALAPG) IFNγ 3 3.5 0.5 3.2 4.3 2.0 1.2 2.1 6 3.4 1.2 5.8 6.3 1.6 1.8 2.9 IL1β 3 56.7 25.4 50.5 58.5 48.5 23.9 27.9 6 50.9 62.3 66.1 38.4 15.9 27.7 51.0 IL-6 3 12.6 12.3 19.9 35.1 15.0 11.4 27.7 6 138.4 64.3 85.2 206.2 153.5 135.4 71.1 IL-10 3 17.3 24.8 32.8 26.8 23.4 11.2 9.4 6 23.4 35.0 35.0 23.0 14.8 12.8 11.0 IL12p70 3 44.9 53.6 55.1 44.8 42.0 33.4 24.3 6 60.8 79.4 79.5 38.5 19.7 33.4 35.8 IP10 3 158.7 100.3 172.0 205.7 167.7 132.6 308.9 6 108.8 72.5 630.2 1498.6 1134.8 617.0 1295.5 MCP-1 3 101.5 122.3 175.8 171.3 146.5 97.1 81.7 6 142.1 192.9 297.2 863.5 213.6 146.5 180.9 MIP1α 3 150.5 161.6 171.4 200.8 179.9 136.8 118.3 6 223.3 268.0 221.6 151.7 98.9 131.8 84.1 MIP1β 3 29.4 30.4 80.8 66.4 52.0 18.0 30.8 6 39.6 65.9 86.1 164.4 43.2 40.4 47.2 RANTES 3 14.5 13.9 13.6 17.5 14.2 12.1 6.6 6 15.0 16.5 18.8 20.7 9.3 11.5 11.7 TNFα 3 16.6 13.5 16.8 18.0 13.0 3.8 4.7 6 12.2 21.4 24.1 13.3 6.3 16.6 12.3

[1773] B7-H4-targeted ADCs were also evaluated in an EMT6 tumor model engineered via lentiviral transduction to express murine B7-H4 (mB7-H4). mB7-H4-expressing EMT6 tumor-bearing mice were treated with 3 weekly doses of 1 or 0.5 mg/kg of STING ADCs or a single dose of 1 mg/kg of ADCs. Non-binding mAb conjugates of compound 12 led to modest tumor growth delay, while the B7-H4-targeted mAb conjugates of compound 12 led to robust tumor growth delay in a dose-dependent manner (FIG. **23**A). B7-H4-targeted conjugates with a WT mIgG2a Fc backbone led to enhanced tumor growth delay compared to those with a Fc effector function null LALA-KA mIgG2a Fc backbone. This suggests that B7-H4-targeted ADCs elicit robust anti-tumor responses in this mB7-H4-expressing EMT6 tumor model. Moreover, these data demonstrate that B7-H4-targeted ADCs with a WT Fc backbone drive more robust anti-tumor responses than those with a LALA-KA Fc null backbone. Importantly, all conjugates were tolerated, as there was no significant weight loss observed in any treatment group (FIG. **23**B).

αvβ6-Targeted ADCs

[1774] Integrin αvβ6-targeted ADCs were evaluated in a CT26 tumor model engineered via lentiviral transduction to express murine integrin αv and β6 (mαvβ6). Murine αvβ6-expressing CT26 tumor bearing mice were treated with 3 weekly doses of 0.5, 1, or 3 mg/kg of ADCs or a single dose of 1 mg/kg of ADCs. Non-binding mAb conjugates of compound 12 led to modest tumor growth delay, while the αvβ6-targeted conjugates of compound 12 led to robust tumor growth delay in a dose-dependent manner (FIG. **24**). αvβ6-targeted ADCs with a WT mIgG2a Fc backbone elicited similar tumor growth delay compared to those with an Fc effector function null LALA-KA mIgG2a Fc backbone, though there was a slight trend towards modestly enhanced anti-tumor activity with the WT backbone (FIG. **24**). There was no significant weight loss observed in any treatment group. Overall, this demonstrates that αvβ6-targeted ADCs are active in this murine αvβ6-expressing CT26 tumor model.

Evaluation of CD228-Targeted ADCs in hCD228-LL2 Tumor-Bearing Mice

[1775] CD228-targeted ADCs were evaluated in a LL2 tumor model engineered via lentiviral transduction to express human CD228 (hCD228). hCD228-expressing LL2 tumor-bearing mice were treated with non-binding or CD228-targeted mAb conjugates of compound 12 (5 mg/kg single dose, 3 mg/kg Q4Dx2, or 3 mg/kg Q7Dx3), compound A (0.08 or 1.5 mg/kg Q4Dx3), or an anti-PD1 mAb (10 mg/kg Q4Dx3) alone or in combination when tumors were 100 mm.sup.3. Tumor volume was measured twice weekly. Some ADCs were prepared using antibodies with a human IgG1 backbone; therefore, shortened dosing schedules were selected to avoid anti-drug antibody (ADA) responses that can occur in immunocompetent mice upon repeat dosing.

[1776] Treatment with the CD228-targeted ADCs, but not the non-binding ADCs, resulted in robust tumor growth delay (FIG. **25**, FIG. **26**). Moreover, while treatment with an anti-PD1 mAb alone was inactive, combination of an anti-PD1 mAb with CD228-targeted ADCs resulted in enhanced tumor growth delay compared to either alone (FIG. **26**). All ADCs were tolerated; no significant weight loss was observed in any treatment group.

[1777] CD228-targeted ADCs with a mIgG2a backbone were also evaluated and demonstrated

more robust anti-tumor activity compared to those on a hIgG1 backbone (FIG. **26** and FIG. **27**A). Moreover, CD228-targeted STING IDCs with a mIgG2a WT Fe backbone demonstrated significantly more antitumor activity than those with an Fc effector function null LALAKA Fc backbone (FIG. **28**A), without impacting weight loss or increasing systemic cytokine levels after the 1.sup.st or 2.sup.nd dose (FIG. **28**B and Table 9). Thus, consistent with in vitro data (FIG. **13**), CD228-targeted STING IDCs with a WT Fe backbone drive enhanced anti-tumor activity compared to those with a LALAKA Fc null backbone. Finally, intravenous dosing of CD228-targeted STING IDCs led to more robust anti-tumor activity compared to intraperitoneal dosing, suggesting that the route of IDC delivery impacts antitumor activity (FIG. **28**A).

[1778] The ability of CD228-targeted conjugates of compound 12 (non-cleavable linker) to elicit antitumor activity was then evaluated compared to conjugates of compounds 13 and 14 (cleavable linkers). Although CD228-targeted conjugates of compounds 12, 13, and 14 elicited similar tumor cell killing in vitro in a tumor/PBMC co-culture assay (FIG. **35**), in vivo CD228-targeted conjugates of compound 12 elicited more robust antitumor activity compared to conjugates of compounds 13 or 14 (FIG. **30**). All three conjugates had a similar Pk profile, with comparable exposures over the first 4 days after intravenous dosing (FIG. **31**). Moreover, the reduced antitumor activity of conjugates of compounds 13 and 14 was accompanied by a trend towards higher levels of several cytokines 6 hours after dosing (e.g. IFNg, IL-6, IP10, MIP1a, MIP1b, RANTES) and a slight reduction in cytokines 24 hours after dosing. This suggests that the kinetics of the systemic cytokine response to IDCs may vary depending on the drug linker properties—independent of the Pk profile—and this in turn may impact antitumor activity (Table 10). Moreover, this suggests that the antitumor activity of conjugates in vivo cannot be predicted simply based on in vitro potency.

[1779] The antitumor activity and pharmacokinetic profile of CD228-targeted conjugates of compound 12 were also evaluated across a range of dose levels. Antitumor activity increased with increasing dose of ADC (FIG. **32**). Consistent with dose-dependent antitumor activity, systemic exposure was also dose-dependent (FIG. **33**), with the maximum observed concentration (C.sub.max) increasing proportionally with increasing dose of ADC. The area under the concentration time curves from time 0 to 7 days (AUC.sub.0-7d) and from time 0 to 10 days (AUC.sub.0-10d) increased less than proportionally with increasing dose of ADC, potentially due to anti-drug antibodies elicited by the human Fc backbone in immunocompetent mice.

TABLE-US-00016 TABLE 9 Cytokine production in peripheral blood (plasma) in engineered LL2 tumor-bearing mice upon treatment with various ADCs comprising a non- binding, CD228-targeted, or EphA2-targeted mAb with either a mIgG2a wild type (WT) or a mIgG2a LALAKA backbone conjugated to compound 12. CD228- CD228- CD228- CD228- EphA2- Non- targeted targeted targeted targeted targeted binding mAb 12 mAb 12 mAb 12 mAb 12 mAb 12 mAb 12 (WT (WT (WT (LALAKA (WT (WT Compound A Compound A Time hIgG1 Fc) mIgG2a Fc) mIgG2a Fc) mIgG2a Fc) mIgG2a Fc) mIgG2a Fc) (1.5 mg/kg (0.08 mg/kg Dose (h) Q4Dx2 i.p. Q7dx3 i.v. Q7dx3 i.p. Q7dx3 i.p. Q7dx3 i.p. Q7dx3 i.p. Q7Dx3 i.v.) Q7Dx3 i.v.) IFNg 1 3 3.2 1 6 6.0 62.8 9.9 5.4 29.2 <3.2 392.4 9.8 2 3 8.7 2 6 12.2 59.2 8.0 21.4 22.3 33.0 1550.6 11.7 1 24 10.2 3 6 11.5 25.2 17.6 38.1 2.5 1236.8 21.9 1 3 32.0 IL1b 1 6 33.4 38.3 22.1 16.0 24.8 12.1 38.0 12.1 2 3 12.1 2 6 24.8 32.0 54.0 33.1 37.3 2670.8 57.4 26.2 1 24 38.3 3 6 64.9 1006.6 29.1 42.3 11.0 36.8 66.6 IL-6 1 3 79.9 1 6 689.2 2388.9 450.3 398.7 1671.2 108.9 10532.0 346.7 2 3 70.1 2 6 166.5 363.0 478.0 892.5 2984.4 848.6 22725.1 936.6 1 24 306.6 3 6 209.0 684.8 685.8 1750.7 133.6 14635.1 1494.7 IL-10 1 3 9.8 1 6 41.5 24.8 27.9 33.5 41.7 9.8 71.5 15.8 2 3 12.8 2 6 24.5 36.4 27.2 35.4 49.5 294.1 92.3 9.5 1 24 20.4 3 6 73.8 305.7 36.0 76.2 26.6 62.8 36.3 IL-12p70 1 3 2.8 1 6 34.3 28.5 9.3 3.0 16.1 3.0 32.3 3.0 2 3 15.5 2 6 15.3 9.3 99.6 15.0 21.8 3005.9 75.4 9.7 1 24 32.9 3 6 43.9 1537.3 15.5 12.9 2.8 43.9 220.3 IP10 1 3 459.9 1 6 6335.8 9573.5 6777.7 8402.9 8605.7 3525.7 >10000 7501.0 2 3 1192.3 2 6 1323.4 8091.7 3979.4 6251.2 6699.0 2025.2 >10000 9045.3 1 24 2189.6 3 6 3410.9 6519.3 4653.6 7420.3 1435.8 >10000 7718.5 MCP-1 1 3 258.6 1 6 5512.0 8936.7 5632.5 3576.4 6704.7 3335.2 10000.0 3780.5 2 3 776.5 2 6 808.2 2864.3 2355.9 4122.0

4369.8 3250.3 >10000 7114.6 1 24 4295.5 3 6 2776.1 7830.5 2043.7 7114.1 383.7 >10000 5009.1 MIP1a 1 3 158.2 1 6 170.4 343.8 135.7 193.2 512.4 114.4 574.2 107.1 2 3 102.7 2 6 102.7 231.5 232.0 311.5 366.4 515.7 846.6 206.0 1 24 145.3 3 6 230.0 333.6 264.0 423.0 80.8 743.4 270.0 MIP1b 1 3 49.9 1 6 903.3 2671.2 1074.9 1126.5 3471.4 193.5 4253.1 474.6 2 3 51.7 2 6 124.2 1435.1 887.2 1461.3 1765.7 453.7 5235.4 1550.3 1 24 325.2 3 6 703.1 1415.0 743.6 2507.7 205.1 4517.1 1009.6 RANTES 1 3 11.0 1 6 14.4 161.6 29.1 16.8 43.6 4.7 1705.3 33.9 2 3 20.6 2 6 11.2 80.7 44.7 103.8 95.5 313.0 1906.1 236.6 1 24 109.0 3 6 102.9 264.4 57.5 275.4 19.5 2533.7 172.9 TNFa 1 3 18.2 1 6 16.0 46.3 18.8 13.3 41.2 3.3 95.7 11.0 2 3 8.5 2 6 8.5 29.9 38.5 37.3 54.2 204.1 204.0 18.4 1 24 22.7 3 6 43.3 176.8 16.8 58.7 11.0 195.3 29.6 *Values out of standard curve range (e.g. >10,000 or <3.2) were converted to 10,000 or 3.2 pg/mL respectively to calculate mean cytokine; if all 3 values were out of range, they are plotted as <10,000 or <3.2 pg/mL.

TABLE-US-00017 TABLE 10 Cytokine production in peripheral blood (plasma) in human CD228-LL2 tumor-bearing mice upon treatment with various ADCs comprising a CD228- targeted mAb (hIgG1 WT) conjugated to compounds 12, 13, or 14. CD228- CD228- CD228- CD228- targeted targeted targeted targeted mAb-12 mAb-13 mAb-14 mAb-12 (WT (WT (WT (WT Untreated hIgG1, i.v.) hIgG1, i.v.) hIgG1, i.v.) hIgG1, i.p.) IFNg 6 h 3.2 53.4 138.9 166.9 26.0 24 h 3.2 16.5 11.2 8.0 14.9 IL1b 6 h 18.9 31.6 44.4 50.8 38.0 24 h 18.9 22.1 25.3 25.3 34.8 IL-6 6 h 78.5 1939.1 3407.3 2422.3 886.8 24 h 27.9 459.6 197.2 117.4 339.9 IL-10 6 h 3.8 26.1 49.1 23.4 26.2 24 h 3.2 3.2 14.5 9.2 6.8 IL12p70 6 h 7.0 25.6 35.8 33.1 30.8 24 h 8.9 5.0 25.2 17.1 22.1 IP10 6 h 206.8 7593.2 9554.3 9735.5 6691.1 24 h 197.2 2894.2 2013.7 1426.2 2193.4 MCP-1 6 h 135.5 12716.4 17729.6 24776.7 5414.8 24 h 109.8 4183.4 1962.1 1979.7 4222.1 MIP1a 6 h 69.4 315.3 791.1 622.8 369.9 24 h 116.5 205.8 221.5 139.5 273.1 MIP1b 6 h 3.2 2692.2 4311.9 4274.3 1586.3 24 h 17.4 503.8 313.4 219.4 370.0 RANTES 6 h 7.5 178.1 627.4 609.8 43.5 24 h 6.0 264.6 203.2 154.6 153.3 TNFa 6 h 6.4 41.3 67.6 69.1 24.4 24 h 8.6 7.8 12.5 13.8 15.6 *Values out of standard curve range (e.g. >10,000 or <3.2) were converted to 10,000 or 3.2 pg/mL respectively to calculate mean cytokine.

Evaluation of STING IDCs in a Xenograft Model of Breast Cancer

[1780] The ability of B7-H4 and αvβ6-targeted conjugates of compound 12 to elicit antitumor activity in immunodeficient Nude mice bearing MDA-MB-468 tumors was then evaluated. B7-H4-targeted conjugates of 12 (with both a WT and LALAKA Fe backbone) elicited robust anti-tumor activity. Similarly, human αvβ6-targeted conjugates of compound 12 (h2A2 mAb with both a WT and aglycosylated Fc backbone that reduces FcγR binding) elicited strong tumor growth delay. Finally, the human/mouse αvβ6-targeted conjugates of compound 12 (h15H3 mAb with both a WT and LALAKA Fe backbone) elicited modest tumor growth delay, similar to the non-binding conjugate of compound 12. This demonstrates the ability of tumor-targeted conjugates of compound 12 to elicit antitumor activity in the absence of cytotoxic T cells and independent of engagement of innate immune cells via FcγR binding. Systemic cytokines elicited by these conjugates was also evaluated and is shown in Table 11.

TABLE-US-00018 TABLE 11 Cytokine production in peripheral blood (plasma) inhuman MDA-MB-468 tumor-bearing mice upon treatment with various ADCs comprising a B7-H4 or αvβ6-targeted mAb conjugated to compound 12. B7-H4- αvβ6- αvβ6- αvβ6- Non- B7-H4- targeted targeted targeted αvβ6- targeted binding targeted mAb-12 mAb-12 mAb-12 targeted mAb-12 mAb-12 mAb-12 mAb-12 (LALAKA (h15H3 (h15H3 mAb-12 (h2A2 (WT (WT Fc WT LALAKA (h2A2 WT aglycosylated Untreated mIgG2a) mIgG2a) mIgG2a) mIgG2a) mIgG2a) mIgG2a) mIgG2a) IFNg 3 h 2.9 3.2 3.2 3.2 3.2 3.2 3.2 3.2 6 h 3.2 11.6 5.8 10.1 30.5 40.7 2.9 6.0 IL1b 3 h 10.5 16.6 16.5 19.4 27.5 23.5 24.4 18.6 6 h 5.6 13.7 20.5 35.7 27.6 26.5 15.4 11.7 IL-6 3 h 12.3 30.9 29.0 24.6 25.3 34.3 16.3 24.4 6 h 762.2 768.5 581.3 895.9 900.3 924.9 1001.9 505.5 IL-10 3 h 10.4 131.0 10.4 25.9 15.9 5.8 11.7 10.4 6 h 3.2 97.1 33.2 46.9 50.2 30.9 54.4 3.2 IL12p70 3 h 16.4 20.5 16.4 25.1 27.2 16.4 18.4 16.7 6 h 3.2 14.3 16.4 33.4 31.5 20.5 7.4 3.2 IP10 3 h 172.7 221.9 217.3 185.5 342.3 189.0 238.1 187.7 6 h 135.7 5612.7 5400.7 5730.7 6171.4 6085.6 5496.7 2627.5 MCP-1 3 h 125.2

131.4 161.8 165.7 274.0 169.8 213.1 145.6 6 h 73.1 2015.6 1195.0 2487.6 3820.9 3180.1 2250.2 368.4 MIP1a 3 h 150.7 184.1 174.7 155.0 226.1 206.2 208.0 176.7 6 h 98.3 197.1 221.0 230.8 411.5 259.2 279.5 168.8 MIP1b 3 h 16.7 3.2 17.8 28.8 459.9 34.9 31.3 3.2 6 h 3.2 560.1 716.0 853.8 2526.3 1171.0 1233.5 244.8 RANTES 3 h 3.2 2.1 3.5 3.2 2.5 2.8 2.5 1.7 6 h 3.2 6.4 9.9 11.2 49.3 19.4 9.5 3.5 TNFa 3 h 9.6 4.8 4.8 14.4 18.2 7.1 8.7 3.2 6 h 3.2 12.8 12.8 29.0 26.2 21.9 21.7 3.2

Rat Tolerability Study:

[1781] The nonclinical safety profile of compound 12 conjugated to non-binding antibodies with a WT Fc backbone, non-binding antibodies with an Fe null backbone, targeted antibodies with a WT Fe backbone, and targeted antibodies with an Fe null backbone was evaluated in non-GLP rat toxicology studies. All conjugates with the compound 12 drug linker (both non-binding and targeted, WT and null Fc backbone) were tolerated in rat at doses higher than the minimally efficacious dose in mouse tumor models.

Example 4

In Vivo Pharmacokinetic Study

Methods

[1782] Pharmacokinetic profiles were analyzed following administration of two weekly 1 mg/kg doses of an ADC comprising a [deglycosylated]non-binding mAb conjugated to compound 12 to male C57BL/6 mice. Plasma was collected and analyzed for generic total antibody (gTAb) by immunoassay. TAb concentrations in mouse K2EDTA plasma were determined by a Gyros flow-through immunoassay platform. Samples and standards were diluted in assay buffer and incubated with a solution containing biotinylated murine anti-human kappa light chain antibody and fluorescent goat anti-human IgG Fcg F(ab′).sub.2 antibody fragment in a sandwich format. The resulting immunocomplexes were bound to the streptavidin-coated beads in the affinity column of the compact disc (CD). The CD was read by a laser that excites the fluorescent detection reagent, producing a signal that is directly proportional to the concentration of test article in the C57BL/6 male mouse plasma sample. Non-compartmental analysis was applied to pooled animal plasma concentration data (sparse sampling) using Phoenix WinNonlin 8.2 (Certara, USA). Concentration values below the limit of quantitation (BLQ) were treated as zero for analysis. Nominal doses and sampling times were used.

Results

[1783] Pharmacokinetic profiles were analyzed following administration of two weekly 1 mg/kg doses of an ADC comprising a [deglycosylated]non-binding mAb conjugated to compound 12 to male C57BL/6 mice. The maximum observed concentration (Cmax) after the first and second dose was 40500 and 52400 ng/mL, respectively. The area under the concentration-time curve from time 0 through 7 days (AUC0-7d) was 85600 d*ng/mL. This suggests that the total antibody exposure for the non-binding conjugate of compound 12 was higher than the small molecule exposure of published small molecule STING agonists (FIG. **29**) (See, e.g., Ramanjulu et al., 2018, Nature 564, 439-443).

[1784] The contents of each of the references cited in the present disclosure are hereby incorporated by reference in their entirety.

[1785] A number of embodiments of the present disclosure have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the present disclosure. Accordingly, other embodiments are within the scope of the following claims.

Claims

1.-**3**. (canceled)

4. An antibody-drug conjugate comprising an antigen-binding protein or an antigen-binding

fragment thereof that binds CD228, wherein the antibody-drug conjugate is represented by the structure: ##STR00556## or a pharmaceutically acceptable salt thereof, wherein: Ab is the antigen-binding protein or an antigen-binding fragment thereof, each S* is a sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof; subscript p is an integer from 2 to 8; R.sup.1C is hydrogen, hydroxyl, C.sub.1-6 alkoxy, —(C.sub.1-6 alkyl) C.sub.1-6 alkoxy, —(CH.sub.2).sub.n—NR.sup.AR.sup.B, or PEG2 to PEG4; R.sup.2C is —CO.sub.2R.sup.M, —(C═O)NR.sup.CR.sup.D, —S(O).sub.2NR.sup.CR.sup.D, —S(O).sub.2R.sup.M, —(CH.sub.2).sub.q—NR.sup.ER.sup.F, —(CH.sub.2).sub.q—OR.sup.M, —O(C═O)—NR.sup.ER.sup.F, or —NR.sup.M(C═O)—NR.sup.ER.sup.F, wherein R.sup.2C is attached at any one of positions labeled 1, 2, or 3; R.sup.3C is —CO.sub.2R.sup.M, —(C═O)NR.sup.CR.sup.D, —S(O).sub.2NR.sup.CR.sup.D, —S(O).sub.2R.sup.M, —(CH.sub.2).sub.q—NR.sup.ER.sup.F, —(CH.sub.2).sub.q—OR.sup.M, —O(C═O)—NR.sup.ER.sup.F, or —NR.sup.M(C═O)—NR.sup.ER.sup.F, wherein R.sup.3C is attached at any one of positions labeled 1′, 2′, or 3′; each R.sup.A, R.sup.B, R.sup.C, R.sup.D, R.sup.E, R.sup.F, and R.sup.M are independently hydrogen or C.sub.1-6 alkyl; each subscript n is independently an integer from 0 to 6; each subscript q is independently an integer from 0 to 6; L.sup.E is —(C═O)— or —S(O).sub.2—; L.sup.C is —(CR.sup.IR.sup.J).sub.1-3— each R.sup.I and R.sup.J are independently hydrogen or C.sub.1-3 alkyl; subscript s is 0 or 1; each Cy.sup.1 is independently a 4-6 membered heterocycle, a 5-6 membered heteroaryl, or a C.sub.3-6 cycloalkyl, each optionally substituted with one or more R.sup.K; each R.sup.K is independently selected from the group consisting of: C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, ═O, —NR.sup.d2R.sup.e2, —C(O)NR.sup.d2R.sup.e2, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl); each R.sup.d2 and R.sup.e2 are independently hydrogen or C.sub.1-3 alkyl; L.sup.AA is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, —C(O)NR.sup.L(CH.sub.2).sub.1-6—, —(CH.sub.2).sub.1-6O—, —C(O)(CH.sub.2).sub.1-6O—, or —C(O)NR.sup.L(CH.sub.2).sub.1-6O—; R.sup.L is hydrogen or C.sub.1-3 alkyl; Cy.sup.2 is C.sub.3-6 cycloalkyl, 4-6 membered heterocycle, 5-6 membered heteroaryl, or phenyl, each optionally substituted with one or more R.sup.U; each R.sup.U is independently selected from the group consisting of —CO.sub.2R.sup.j1, —(C═O)NR.sup.d3R.sup.e3, —S(O).sub.2NR.sup.d3R.sup.e3, —(CH.sub.2).sub.q1—NR.sup.g1R.sup.h1, —(CH.sub.2).sub.q1—OR.sup.j1, and —(CH.sub.2).sub.q1—(OCH.sub.2CH.sub.2).sub.1-8OH; each R.sup.d3, R.sup.e3, R.sup.g1, R.sup.h1, and R.sup.j1 are independently hydrogen or C.sub.1-6 alkyl; subscript q1 is an integer from 0 to 6; subscripts t1 and t2 are independently 0 or 1, wherein at least one of t1 and t2 is 1; L.sup.D is —(CH.sub.2).sub.1-6—; subscript u is 0 or 1; Z is —N(R.sup.HH)— or —N.sup.+(C.sub.1-6 alkyl)(R.sup.HH)—; R.sup.HH is hydrogen, C.sub.1-6 alkyl, C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.1-3 alkoxy, —(CH.sub.2).sub.1-3 4-6 membered heterocycle, or —(CH.sub.2).sub.1-3 5-6 membered heteroaryl; Y is a self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety; subscript y is 0 or 1; W is a chain of 1-12 amino acids or has the structure: ##STR00557## wherein Su is a Sugar moiety; —O.sup.A— represents a glycosidic bond; each R.sup.9 is independently hydrogen, halogen, —CN, or —NO.sub.2; W.sup.1 is absent or —O—C(═O)—; custom-character represents covalent attachment to L.sup.BB; * represents covalent attachment to Y, L.sup.D, NR.sup.HH, or Cy.sup.2; subscript w is 0 or 1; L.sup.BB is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, or —[NHC(O)(CH.sub.2).sub.1-4].sub.1-3—; and each subscript b is independently an integer from 1 to 6.

5. The antibody-drug conjugate of claim 4, wherein the antibody-drug conjugate is represented by the structure: ##STR00558## or a pharmaceutically acceptable salt thereof.

6. The antibody-drug conjugate of claim 4, wherein the antigen-binding protein or antigen-binding fragment thereof is hL49 HALC hIgG1.

7. The antibody-drug conjugate of claim 4, wherein the antigen-binding protein or antigen-binding

fragment thereof comprises the following 6 CDRs: an CDR-H1 comprising the amino acid sequence of SEQ ID NO: 29; an CDR-H2 comprising the amino acid sequence of SEQ ID NO: 30; an CDR-H3 comprising the amino acid sequence of SEQ ID NO: 31; an CDR-L1 comprising the amino acid sequence of SEQ ID NO: 32; an CDR-L2 comprising the amino acid sequence of SEQ ID NO: 33; and an CDR-L3 comprising the amino acid sequence of SEQ ID NO: 34.

8. The antibody-drug conjugate of claim 4, wherein the antigen-binding protein or antigen-binding fragment thereof comprises a VH and a VL, wherein the VH has at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 35 and the VL has at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 36.

9. The antibody-drug conjugate of claim 4, wherein the antigen-binding protein or antigen-binding fragment thereof comprises a VH and a VL, wherein the VH comprises the amino acid sequence of SEQ ID NO: 35 and the VL comprises the amino acid sequence of SEQ ID NO: 36.

10. The antibody-drug conjugate of claim 4, wherein the antigen-binding protein or antigen-binding fragment thereof comprises an HC comprising the amino acid sequence of SEQ ID NO: 37 or SEQ ID NO: 38 and an LC comprising the amino acid sequence of SEQ ID NO: 39.

11. The antibody-drug conjugate of claim 4, wherein the antigen-binding protein or antigen-binding fragment thereof comprises an HC comprising the amino acid sequence of SEQ ID NO: 40 or SEQ ID NO: 41 and an LC comprising the amino acid sequence of SEQ ID NO: 42.

12.-**14**. (canceled)

15. An antibody-drug conjugate comprising an antigen-binding protein or an antigen-binding fragment thereof that binds αvβ6, wherein the antibody-drug conjugate is represented by the structure: ##STR00559## or a pharmaceutically acceptable salt thereof, wherein: Ab is the antigen-binding protein or an antigen-binding fragment thereof, each S* is a sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof; subscript p is an integer from 2 to 8; R.sup.1C is hydrogen, hydroxyl, C.sub.1-6 alkoxy, —(C.sub.1-6 alkyl) C.sub.1-6 alkoxy, —(CH.sub.2).sub.n—NR.sup.AR.sup.B, or PEG2 to PEG4; R.sup.2C is —CO.sub.2R.sup.M, —(C═O)NR.sup.CR.sup.D, —S(O).sub.2NR.sup.CR.sup.D, —S(O).sub.2R.sup.M, —(CH.sub.2).sub.q—NR.sup.ER.sup.F, —(CH.sub.2).sub.q—OR.sup.M, —O(C═O)—NR.sup.ER.sup.F, or —NR.sup.M(C═O)—NR.sup.ER.sup.F, wherein R.sup.2C is attached at any one of positions labeled 1, 2, or 3; R.sup.3C is —CO.sub.2R.sup.M, —(C═O)NR.sup.CR.sup.D, —S(O).sub.2NR.sup.CR.sup.D, —S(O).sub.2R.sup.M, —(CH.sub.2).sub.q—NR.sup.ER.sup.F, —(CH.sub.2).sub.q—OR.sup.M, —O(C═O)—NR.sup.ER.sup.F, or —NR.sup.M(C═O)—NR.sup.ER.sup.F, wherein R.sup.3C is attached at any one of positions labeled 1′, 2′, or 3′; each R.sup.A, R.sup.B, R.sup.C, R.sup.D, R.sup.E, R.sup.F, and R.sup.M are independently hydrogen or C.sub.1-6 alkyl; each subscript n is independently an integer from 0 to 6; each subscript q is independently an integer from 0 to 6; L.sup.E is —(C═O)— or —S(O).sub.2—; L.sup.C is —(CR.sup.IR.sup.J).sub.1-3— each R.sup.I and R.sup.J are independently hydrogen or C.sub.1-3 alkyl; subscript s is 0 or 1; each Cy.sup.i is independently a 4-6 membered heterocycle, a 5-6 membered heteroaryl, or a C.sub.3-6 cycloalkyl, each optionally substituted with one or more R.sup.K; each R.sup.K is independently selected from the group consisting of: C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, ═O, —NR.sup.d2R.sup.e2, —C(O)NR.sup.d2R.sup.e2, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl); each R.sup.d2 and R.sup.e2 are independently hydrogen or C.sub.1-3 alkyl; L.sup.AA is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, —C(O)NR.sup.L(CH.sub.2).sub.1-6—, —(CH.sub.2).sub.1-6O—, —C(O)(CH.sub.2).sub.1-6O—, or —C(O)NR.sup.L(CH.sub.2).sub.1-6O—; R.sup.L is hydrogen or C.sub.1-3 alkyl; Cy.sup.2 is C.sub.3-6 cycloalkyl, 4-6 membered heterocycle, 5-6 membered heteroaryl, or phenyl, each optionally substituted with one or more R.sup.U; each R.sup.U is independently selected from the group consisting of —CO.sub.2R.sup.j1, —(C═O)NR.sup.d3R.sup.e3, —

S(O).sub.2NR.sup.d3R.sup.e3, —(CH.sub.2).sub.q1—NR.sup.g1R.sup.h1, —(CH.sub.2).sub.q1—OR.sup.31, and —(CH.sub.2).sub.q1—(OCH.sub.2CH.sub.2).sub.1-8OH; each R.sup.d3, R.sup.e3, R.sup.g1, R.sup.h1, and R.sup.j1 are independently hydrogen or C.sub.1-6 alkyl; subscript q1 is an integer from 0 to 6; subscripts t1 and t2 are independently 0 or 1, wherein at least one of t1 and t2 is 1; L.sup.D is —(CH.sub.2).sub.1-6—; subscript u is 0 or 1; Z is —N(R.sup.HH)— or -N+(C.sub.1-6 alkyl)(R.sup.HH)—; R.sup.HH is hydrogen, C.sub.1-6 alkyl, C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.1-3 alkoxy, —(CH.sub.2).sub.1-3 4-6 membered heterocycle, or —(CH.sub.2).sub.1-3 5-6 membered heteroaryl; Y is a self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety; subscript y is 0 or 1; W is a chain of 1-12 amino acids or has the structure: ##STR00560## wherein Su is a Sugar moiety; —O.sup.A— represents a glycosidic bond; each R.sup.g is independently hydrogen, halogen, —CN, or —NO.sub.2; W.sup.1 is absent or —O—C(═O)—; custom-character represents covalent attachment to L.sup.BB; * represents covalent attachment to Y, L.sup.D NR.sup.HH or Cy.sup.2; subscript w is 0 or 1; L.sup.BB is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, or —[NHC(O)(CH.sub.2).sub.1-4].sub.1-3—; and each subscript b is independently an integer from 1 to 6.

16. The antibody-drug conjugate of claim 15, wherein the antibody-drug conjugate is represented by the structure: ##STR00561## or a pharmaceutically acceptable salt thereof.

17. The antibody-drug conjugate of claim 15, wherein the antigen-binding protein or antigen-binding fragment thereof is h2A2 HCLG hIgG1.

18. The antibody-drug conjugate of claim 15, wherein the antigen-binding protein or antigen-binding fragment thereof comprises the following 6 CDRs: an CDR-H1 comprising the amino acid sequence of SEQ ID NO: 43; an CDR-H2 comprising the amino acid sequence of SEQ ID NO: 44; an CDR-H3 comprising the amino acid sequence of SEQ ID NO: 45; an CDR-L1 comprising the amino acid sequence of SEQ ID NO: 46; an CDR-L2 comprising the amino acid sequence of SEQ ID NO: 47; and an CDR-L3 comprising the amino acid sequence of SEQ ID NO: 48.

19. The antibody-drug conjugate of claim 15, wherein the antigen-binding protein or antigen-binding fragment thereof comprises a VH and a VL, wherein the VH has at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 49 and the VL has at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 50.

20. The antibody-drug conjugate of claim 15, wherein the antigen-binding protein or antigen-binding fragment thereof comprises a VH and a VL, wherein the VH comprises the amino acid sequence of SEQ ID NO: 49 and the VL comprises the amino acid sequence of SEQ ID NO: 50.

21. The antibody-drug conjugate of claim 15, wherein the antigen-binding protein or antigen-binding fragment thereof comprises an HC comprising the amino acid sequence of SEQ ID NO: 51 or SEQ ID NO: 52 and an LC comprising the amino acid sequence of SEQ ID NO: 53.

22. The antibody-drug conjugate of claim 15, wherein the antigen-binding protein or antigen-binding fragment thereof comprises an HC comprising the amino acid sequence of SEQ ID NO: 54 or SEQ ID NO: 55 and an LC comprising the amino acid sequence of SEQ ID NO: 56.

23.-**25**. (canceled)

26. An antibody-drug conjugate comprising an antigen-binding protein or an antigen-binding fragment thereof that binds B7-H4, wherein the antibody-drug conjugate is represented by the structure: ##STR00562## or a pharmaceutically acceptable salt thereof, wherein: Ab is the antigen-binding protein or an antigen-binding fragment thereof, each S* is a sulfur atom from a cysteine residue of the antigen-binding protein or an antigen-binding fragment thereof; subscript p is an integer from 2 to 8; R.sup.1C is hydrogen, hydroxyl, C.sub.1-6 alkoxy, —(C.sub.1-6 alkyl) C.sub.1-6 alkoxy, —(CH.sub.2).sub.n—NR.sup.AR.sup.B, or PEG2 to PEG4; R.sup.2C is —CO.sub.2R.sup.M, —(C═O)NR.sup.CR.sup.D, —S(O).sub.2NR.sup.CR.sup.D, —S(O).sub.2R.sup.M, —(CH.sub.2).sub.q—NR.sup.ER.sup.F, —(CH.sub.2).sub.q—OR.sup.M, —

O(C═O)—NR.sup.ER.sup.F, or —NR.sup.M(C═O)—NR.sup.ER.sup.F, wherein R.sup.2C is attached at any one of positions labeled 1, 2, or 3; R.sup.3C is —CO.sub.2R.sup.M, —(C═O)NR.sup.CR.sup.D, —S(O).sub.2NR.sup.CR.sup.D, —S(O).sub.2R.sup.M, —(CH.sub.2).sub.q—NR.sup.ER.sup.F, —(CH.sub.2).sub.q—OR.sup.M, —O(C═O)—NR.sup.ER.sup.F, or —NR.sup.M(C═O)—NR.sup.ER.sup.F, wherein R.sup.3C is attached at any one of positions labeled 1′, 2′, or 3′; each R.sup.A, R.sup.B, R.sup.C, R.sup.D, R.sup.E, R.sup.F, and R.sup.M are independently hydrogen or C.sub.1-6 alkyl; each subscript n is independently an integer from 0 to 6; each subscript q is independently an integer from 0 to 6; L.sup.E is —(C═O)— or —S(O).sub.2—; L.sup.C is —(CR.sup.IR.sup.J).sub.1-3— each R.sup.I and R.sup.J are independently hydrogen or C.sub.1-3 alkyl; subscript s is 0 or 1; each Cy.sup.1 is independently a 4-6 membered heterocycle, a 5-6 membered heteroaryl, or a C.sub.3-6 cycloalkyl, each optionally substituted with one or more R.sup.K; each R.sup.K is independently selected from the group consisting of: C.sub.1-6 alkyl, C.sub.1-6 haloalkyl, C.sub.1-6 alkoxy, C.sub.1-6 haloalkoxy, halogen, —OH, ═O, —NR.sup.d2R.sup.e2, —C(O)NR.sup.d2R.sup.e2, —C(O)(C.sub.1-6 alkyl), and —C(O)O(C.sub.1-6 alkyl); each R.sup.d2 and R.sup.e2 are independently hydrogen or C.sub.1-3 alkyl; L.sup.AA is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, —C(O)NR.sup.L(CH.sub.2).sub.1-6—, —(CH.sub.2).sub.1-6O—, —C(O)(CH.sub.2).sub.1-6O—, or —C(O)NR.sup.L(CH.sub.2).sub.1-6O—; R.sup.L is hydrogen or C.sub.1-3 alkyl; Cy.sup.2 is C.sub.3-6 cycloalkyl, 4-6 membered heterocycle, 5-6 membered heteroaryl, or phenyl, each optionally substituted with one or more R.sup.U; each R.sup.U is independently selected from the group consisting of —CO.sub.2R.sup.j1, —(C═O)NR.sup.d3R.sup.e3, —S(O).sub.2NR.sup.d3R.sup.e3, —(CH.sub.2).sub.q1—NR.sup.g1R.sup.h1, —(CH.sub.2).sub.q1—OR.sup.1, and —(CH.sub.2).sub.q1—(OCH.sub.2CH.sub.2).sub.1-8OH; each R.sup.d3, R.sup.e3, R.sup.g1, R.sup.h1, and R.sup.j1 are independently hydrogen or C.sub.1-6 alkyl; subscript q1 is an integer from 0 to 6; subscripts t1 and t2 are independently 0 or 1, wherein at least one of t1 and t2 is 1; L.sup.D is —(CH.sub.2).sub.1-6—; subscript u is 0 or 1; Z is —N(R.sup.HH)— or -N+(C.sub.1-6 alkyl)(R.sup.HH)—; R.sup.HH is hydrogen, C.sub.1-6 alkyl, C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.3-6 cycloalkyl, —(CH.sub.2).sub.1-3C.sub.1-3 alkoxy, —(CH.sub.2).sub.1-3 4-6 membered heterocycle, or —(CH.sub.2).sub.1-3 5-6 membered heteroaryl; Y is a self-immolative moiety, a non-self-immolative releasable moiety, or a non-cleavable moiety; subscript y is 0 or 1; W is a chain of 1-12 amino acids or has the structure: ##STR00563## wherein Su is a Sugar moiety; —O.sup.A— represents a glycosidic bond; each R.sup.g is independently hydrogen, halogen, —CN, or —NO.sub.2; W.sup.1 is absent or —O—C(═O)—; custom-character represents covalent attachment to L.sup.BB; * represents covalent attachment to Y, L.sup.D NR.sup.HH or Cy.sup.2; subscript w is 0 or 1; L.sup.BB is —(CH.sub.2).sub.1-6—, —C(O)(CH.sub.2).sub.1-6—, or —[NHC(O)(CH.sub.2).sub.1-4].sub.1-3—; and each subscript b is independently an integer from 1 to 6.

27. The antibody-drug conjugate of claim 26, wherein the antibody-drug conjugate is represented by the structure: ##STR00564## or a pharmaceutically acceptable salt thereof.

28. The antibody-drug conjugate of claim 26, wherein the antigen-binding protein or antigen-binding fragment thereof is B7H41001 hIgG1.

29. The antibody-drug conjugate of claim 26, wherein the antigen-binding protein or antigen-binding fragment thereof comprises the following 6 CDRs: an CDR-H1 comprising the amino acid sequence of SEQ ID NO: 57; an CDR-H2 comprising the amino acid sequence of SEQ ID NO: 58; an CDR-H3 comprising the amino acid sequence of SEQ ID NO: 59; an CDR-L1 comprising the amino acid sequence of SEQ ID NO: 60; an CDR-L2 comprising the amino acid sequence of SEQ ID NO: 61; and an CDR-L3 comprising the amino acid sequence of SEQ ID NO: 62.

30. The antibody-drug conjugate of claim 26, wherein the antigen-binding protein or antigen-binding fragment thereof comprises a VH and a VL, wherein the VH has at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence of SEQ ID

NO: 63 and the VL has at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 64.

31. The antibody-drug conjugate of claim 26, wherein the antigen-binding protein or antigen-binding fragment thereof comprises a VH and a VL, wherein the VH comprises the amino acid sequence of SEQ ID NO: 63 and the VL comprises the amino acid sequence of SEQ ID NO: 64.

32. The antibody-drug conjugate of claim 26, wherein the antigen-binding protein or antigen-binding fragment thereof comprises an HC comprising the amino acid sequence of SEQ ID NO: 65 or SEQ ID NO: 66 and an LC comprising the amino acid sequence of SEQ ID NO: 67.

33. The antibody-drug conjugate of claim 26, wherein the antigen-binding protein or antigen-binding fragment thereof comprises an HC comprising the amino acid sequence of SEQ ID NO: 68 or SEQ ID NO: 69 and an LC comprising the amino acid sequence of SEQ ID NO: 70.

34. The antibody-drug conjugate of claim 26, wherein the antigen-binding protein or antigen-binding fragment thereof is selected from the group consisting of B7H4-15461, B7H4-20500, B7H4-20501, B7H4-20502.1, B7H4-22208, B7H4-15462, B7H4-22213, B7H4-15465, B7H4-20506, B7H4-15483, B7H4-20513, B7H4-22216, B7H4-15489, B7H4-20516, B7H4-15472, B7H4-15503, B7H4-15495, B7H4-15478, B7H4-15441, and B7H4-20496.

35. The antibody-drug conjugate of claim 26, wherein the antigen-binding protein or antigen-binding fragment thereof comprises VH CDR1, VH CDR2, VH CDR3 and VL CDR1, VL CDR2, and VL CDR3 sequences selected from the group consisting of: (a) SEQ ID NOs: 71-76, respectively; (b) SEQ ID NOs: 79-84, respectively; (c) SEQ ID NOs: 87-92, respectively; (d) SEQ ID NOs: 95-100, respectively; (e) SEQ ID NOs: 103-108, respectively; (f) SEQ ID NOs: 111-116, respectively; (g) SEQ ID NOs: 119-124, respectively; (h) SEQ ID NOs: 127-132, respectively; (i) SEQ ID NOs: 135-140, respectively; (j) SEQ ID NOs: 143-148, respectively; F (k) SEQ ID NOs: 151-156, respectively; (l) SEQ ID NOs: 159-164, respectively; (m) SEQ ID NOs: 167-172, respectively; (n) SEQ ID NOs: 175-180, respectively; (o) SEQ ID NOs: 183-188, respectively; (p) SEQ ID NOs: 191-196, respectively; (q) SEQ ID NOs: 199-204, respectively; (r) SEQ ID NOs: 207-212, respectively; (s) SEQ ID NOs: 215-220, respectively; and (t) SEQ ID NOs: 223-228, respectively.

36. The antibody-drug conjugate of claim 26, wherein the antigen-binding protein or antigen-binding fragment thereof comprises a VH and a VL, wherein the VH has at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 77, 85, 93, 101, 109, 117, 125, 133, 141, 149, 157, 165, 173, 181, 189, 197, 205, 213, 221, and 229 and the VL has at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% amino acid sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174, 182, 190, 198, 206, 214, 222, and 230, respectively.

37. The antibody-drug conjugate of claim 26, wherein the antigen-binding protein or antigen-binding fragment thereof comprises a VH and a VL, wherein the VH has an amino acid sequence selected from the group consisting of SEQ ID NOs: 77, 85, 93, 101, 109, 117, 125, 133, 141, 149, 157, 165, 173, 181, 189, 197, 205, 213, 221, and 229 and the VL has an amino acid sequence selected from the group consisting of SEQ ID NOs: 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174, 182, 190, 198, 206, 214, 222, and 230, respectively.

38. The antibody-drug conjugate of claim 26, wherein the antigen-binding protein or antigen-binding fragment thereof comprises an HC having an amino acid sequence selected from the group consisting of SEQ ID NOs: 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, and 269 and an LC having an amino acid sequence selected from the group consisting of SEQ ID NOs: 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, and 270, respectively.

39.-**42**. (canceled)

43. A pharmaceutical composition comprising the antibody-drug conjugate of claim 4 and a

pharmaceutically acceptable carrier.

44. A method of treating a CD228-expressing cancer in an individual comprising administering to an individual in need thereof an effective amount of the antibody-drug conjugate of claim 4.

45. A method of treating αvβ6-expressing cancer in an individual comprising administering to an individual in need thereof an effective amount of the antibody-drug conjugate of claim 15.

46. A method of treating a B7-H4-expressing cancer in an individual comprising administering to an individual in need thereof an effective amount of the antibody-drug conjugate of claim 26.

47. A pharmaceutical composition comprising the antibody-drug conjugate of claim 15 and a pharmaceutically acceptable carrier.

48. A pharmaceutical composition comprising the antibody-drug conjugate of claim 26 and a pharmaceutically acceptable carrier.