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(54) **Title:** CYCLIC PEPTIDE CONJUGATES AND METHODS OF USE

(57) **Abstract:** The present invention concerns cyclic compounds, compositions comprising the cyclic compounds, linkers, a method of preparing a carrying agentcyclic compound adduct, a method for treating disorders such as proliferation disorders (*e.g.*, malignancies), bone deficiency diseases, and autoimmune diseases, and a method for suppressing the growth of, or inducing apoptosis in, cells (*e.g.*, malignant cells).



DESCRIPTION

CYCLIC PEPTIDE CONJUGATES AND METHODS OF USE

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CROSS-REFERENCE TO RELATED APPLICATION

The present application claims the benefit of U.S. Provisional Application Serial No. 61/883,910, filed September 27, 2013, which is hereby incorporated by reference herein in its entirety, including any figures, tables, nucleic acid sequences, amino acid sequences, or drawings.

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GOVERNMENT SUPPORT

This invention was made with government support under Grant number 1R43CA180308-01 awarded by the National Institutes of Health (NIH). The government has certain rights in the invention.

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BACKGROUND OF THE INVENTION

Multiple myeloma is a disease characterized by the homing and uncontrolled growth of malignant plasma cells within the confines of the bone marrow. Despite the recent advances in therapy, multiple myeloma remains an incurable disease. 14,000 new cases of multiple myeloma are diagnosed each year in the United States with a five year survival rate of 37%. Although standard therapy will typically cause an initial response, myeloma patients ultimately develop drug resistance and become unresponsive to a variety of anti-cancer agents, a phenomenon known as multidrug resistance (MDR). Clinical observations indicate that despite divergent genetic changes typical of myeloma, current therapy is not curative in any subset of patients. The bone marrow microenvironment presents a rich source of extracellular matrices, cytokines and growth factors produced by constituents residing in the bone marrow stroma, including mesenchymal stem cells, fibroblast and mature osteoblasts, suggesting that the bone marrow microenvironment may contribute to the resistant phenotype and the failure of standard chemotherapy. It has been reported that adhesion of myeloma and leukemia cells

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to components of the extracellular matrix is sufficient to cause drug resistance. Targeting interactions between the microenvironment and myeloma cells may be an attractive strategy for increasing the efficacy of standard therapy.

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BRIEF SUMMARY OF THE INVENTION

The development of drug-resistant malignancies presents significant challenges when treating multiple myeloma (MM) within the bone marrow microenvironment. By utilizing necrosis as an alternative cytotoxic pathway and blocking MM-induced bidirectional stromal cell signaling, a cyclic, peptidomimetic drug (MTI-101) has recently been produced with near nM IC₅₀ potency. Still, with rapid blood clearance of the small molecule and the hazard of localized inflammation due to a necrotic mechanism, it is favorable to pursue half-life and specificity augmenting strategies via antibody engineering. In combination with selenocysteine incorporation techniques, the inventors generated two mAb fragments, both IgG-derived Fc-Sec-His6 and scFv- α CD138-Fc-Sec-His6. Selective conjugation with MTI-101 then yielded ADCs with defined 1:1 drug:antibody ratios. Strong mono-affinity to targeted CD44 and bispecific CD44/CD138 binding with improved cytotoxic profiles *in vitro* were demonstrated, as well as improved survival *in vivo*. These results provide compelling data for the applicability of ADCs as therapeutics with the potential for even higher efficacy *in vivo* from additional effector mediation functions.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows an MTI-101 iodoacetamide adduct of the invention.

Figure 2 shows a mechanism and strategy for selenocysteine incorporation.

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Figure 3 shows results of Fc-Sec-His6 purification via recombinant Protein G column and IMAC HisTrap column. This demonstrates that the correct Fc-Sec-His6 mAb (with selenocysteine incorporation) was isolated with high fidelity.

Figure 4 shows scFv-Fc- α CD138-Sec-His6 purification via recombinant Protein G column and IMAC HisTrap column. This demonstrates that the correct scFv-Fc-

α CD138-Sec-His6 mAb (with selenocysteine incorporation) was isolated with high fidelity.

Figure 5 shows SDS-PAGE analysis of reduced and non-reduced mAbs and mAb drug conjugates. The reducing lanes (with disulfide bridges broken) run further in their corresponding lanes (R = reducing; NR = non-reducing). Furthermore, the ADCs show slightly less movement down the lane than their selenocysteine counterparts. This shows that they are slightly heavier (since MTI-101 = 1.7 kDa) and verifies selective, 1:1 drug:antibody conjugation. The binding confirmation analysis also shows that the mAbs were correctly characterized.

Figures 6A-6B show binding of Fc-Sec-His/MTI-101 to the MM cell surface (U266 cells in Figure 6A; H929 cells in Figure 6B). Dashed, unstained cells; dotted gray, Fc-Sec-His (0.3 μ g); solid gray, Fc-Sec-His (3 μ g); dotted black, Fc-Sec-His/MTI-101 (0.3 μ g); solid black, Fc-Sec-His/MTI-101 (3 μ g). APC-conjugated goat anti-human IgG (Fc γ -specific) was used for detection.

Figure 7 shows ELISA binding to CD44 target.

Figures 8A-8B show binding of scFv-Fc-Sec-His/MTI-101 to the MM cell surface (U266 cells in Figure 8A; H929 cells in Figure 8B). dashed, unstained cells; dotted, scFv-Fc-Sec-His (3 μ g); solid, scFv-Fc-Sec-His/MTI-101 (3 μ g). APC-conjugated goat anti-human IgG (Fc γ -specific) was used for detection.

Figure 9 shows ELISA binding to CD138 target.

Figure 10 shows normalized viability of H929 multiple myeloma cells across antibody drug conjugates (ADCs) and drug titrations.

Figure 11 shows a comparison of H929 multiple myeloma cells under microscopy.

Figure 12A-12H show cytotoxicity of Fc-Sec-His/MTI-101 as revealed by flow cytometry. FSC/SSC scatter densities distinguished live cells (right population) and dead cells (left population). This was confirmed by PI staining.

Figure 13 shows concentration-dependent cytotoxicity of Fc-Sec-His/MTI-101 and anti-CD138-scFv-Fc-Sec-His/MTI-101 toward H929 cells. Blue columns (left bar at each concentration) show the cytotoxicity of the indicated MTI-101 conjugates; red columns (right bar at each concentration) show the corresponding stop proteins at the same concentrations.

Figures 14A-14D show cytotoxicity of anti-CD138-scFv-Fc-Sec-His/MTI-101 as revealed by flow cytometry.

Figure 15 shows concentration-dependent cytotoxicity of Fc-Sec-His/MTI-101 and anti-CD138-scFv-Fc-Sec-His/MTI-101 toward U266 cells. Blue columns (left bar at each concentration) show the cytotoxicity of the indicated MTI-101 conjugates; red columns (right bar at each concentration) show the corresponding stop proteins at the same concentrations.

Figure 16 shows an example of a reaction scheme for producing conjugates of the invention. Specifically, Figure 16 depicts site-selective conjugation of MTI-101-iodoacetamide to Fc fragments with an engineered C-terminal selenocysteine (Sec) residue using slightly reducing and acidic conditions.

Figure 17 shows an example of a reaction scheme for producing conjugates of the invention. Specifically, Figure 17 depicts site-selective conjugation of MTI-101-iodoacetamide to an anti-CD138 mAb in scFv-Fc format with an engineered C-terminal selenocysteine (Sec) residue using slightly reducing and acidic conditions.

Figures 18A-18B show cytotoxicity of Fc-Sec-His/MTI-101 *in vivo* and tumor burden over time. One million 5TGM1 cells were injected intravenously (i.v.) in C57BL6/KaLwRij mice. Mice injected i.v. were treated once weekly for 3 weeks with 10 mg/kg Fc-Sec-MTI-101, 10 mg/kg Fc-stop, or an equal payload of MTI-101 (0.3285 mg/kg). The mice were monitored daily and euthanized if they exhibited hind leg paralysis, lethargy, or tumor masses exceeding 2 cm long. Medium survival was 35 days for control and MTI-101 IV equal payload, 26 days for FC-Sec-MTI-101 and 62 days for Fc-Sec-MTI-101 (n=5 animals per group), as shown in Figure 18B. IgG2b levels were measured by ELISA 28 days following tumor inoculation. Mice treated with Fc-Sec-MTI-101 demonstrate a significant reduction in IgG2b levels compared to control and Fc-Stop.

DETAILED DESCRIPTION OF THE INVENTION

MTI-101 is an anti-CD44 targeting circular peptide (Gebhard, A.W., *et al.*, "MTI-101 (cyclized HYD1) binds a CD44 containing complex and induces necrotic cell death in multiple myeloma," *Mol Cancer Ther*, 2013, 12, 2446-2458; cyclic peptide 16 in PCT Application No. PCT/US2011/000512, published as WO 2011/115688 ("Integrin

Interaction Inhibitors for the Treatment of Cancer” on September 22, 2011), which are each incorporated herein by reference its entirety. An iodoacetamide derivative of MTI-101 is shown in Figure 1.

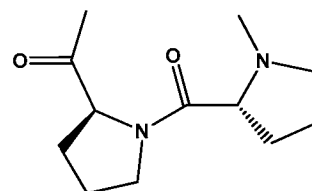
With the goals of improving both the circulatory half-life and selectivity of the MTI-101 peptide and similar circular peptides for disease treatment (*e.g.*, multiple myeloma treatment), the inventors have applied antibody engineering and conjugation strategies (Hofer, Thomas, *et al.* “An engineered selenocysteine defines a unique class of antibody derivatives.” *Proceedings of the National Academy of Sciences*. 105.34 (2008): 12451-12456; Hofer, T., *et al.*, “Molecularly defined antibody conjugation through a selenocysteine interface,” *Biochemistry*, 2009, 48, 12047-12057; and Li, X., *et al.*, “Antibody conjugation via one and two C-terminal selenocysteines,” *Methods* 2014, 65, 133-138, which are each incorporated herein by reference in its entirety) to develop a cyclic peptide conjugate bearing a carrying agent.

Under certain conditions (Palioura, Sotiria, *et al.* “The human SepSecS-tRNA^{Sec} complex reveals the mechanism of selenocysteine formation.” *Science* 325.5938 (2009): 321-325, which is incorporated herein by reference in its entirety) as shown in Figure 2, monoclonal antibodies and antigen binding fragments thereof (“antibody fragments”) can be equipped with a C-terminal selenocysteine residue, the 21st natural amino acid, with unique chemical properties.

These conditions include a selenol pK_a of about 5.2, which allows for selective conjugation in a 1:1 defined carrier:payload ratio. Compared to conventional cysteine and lysine conjugation technologies with heterogeneous drug:antibody ratios (DARs), defined DARs increase therapeutic indices, as these antibody-drug conjugates (ADCs) lack large batch-to-batch variability and the potential for undesired toxicity. Most importantly, this methodology provides a strategy to adjoin small molecules to mAbs and antibody fragments, which should increase the circulatory half-life of the small molecule owing to both increased size and FcRn-mediated recycling (Roopenian DC, Akilesh S. “FcRn: The neonatal Fc receptor comes of age.” *Nat Rev Immunol* 7:715725. (2007), which is incorporated herein by reference in its entirety), and augment the potency of the small molecule by equipping it with the cytotoxic effector functions of the antibody molecule.

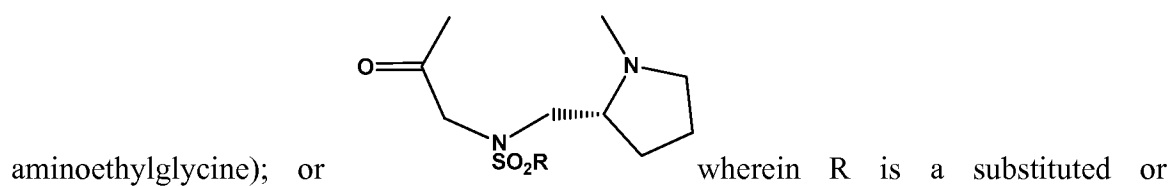
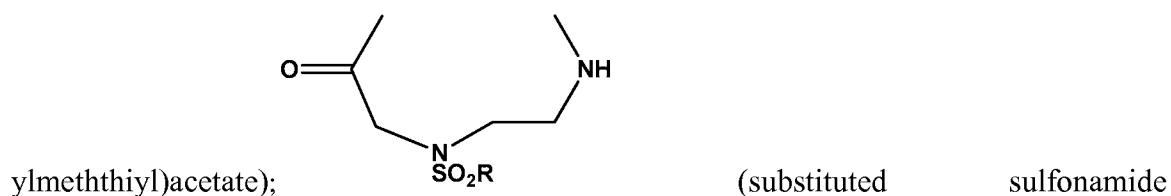
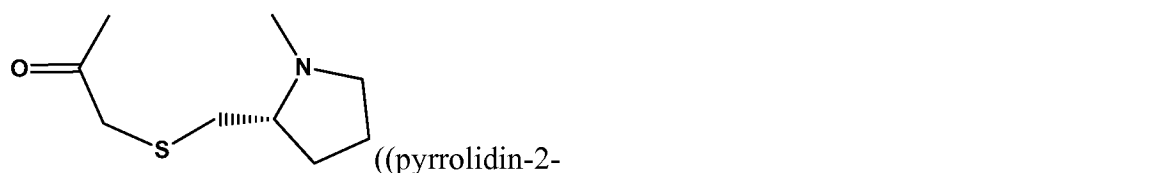
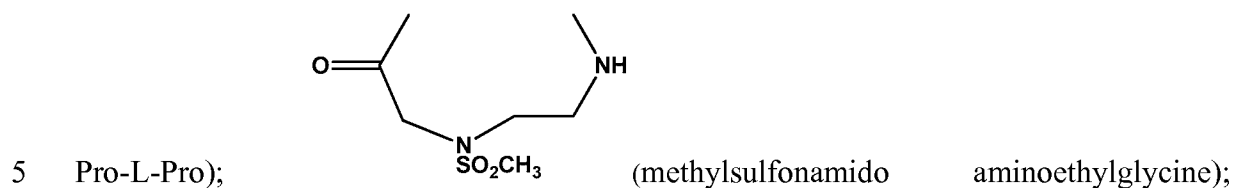
An aspect of the invention concerns a cyclic compound (a conjugate), comprising a recognition sequence and a non-recognition sequence, wherein the recognition sequence

comprises at least four amino acids, wherein the non-recognition sequence comprises at least four amino acids, and wherein the recognition sequence is joined to the non-recognition sequence by a first linker and a second linker, wherein the first linker and the

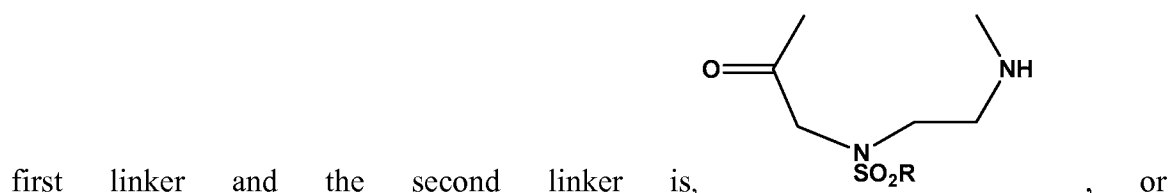


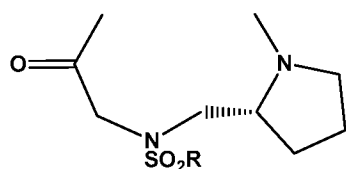
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second linker are independently selected from the structures:



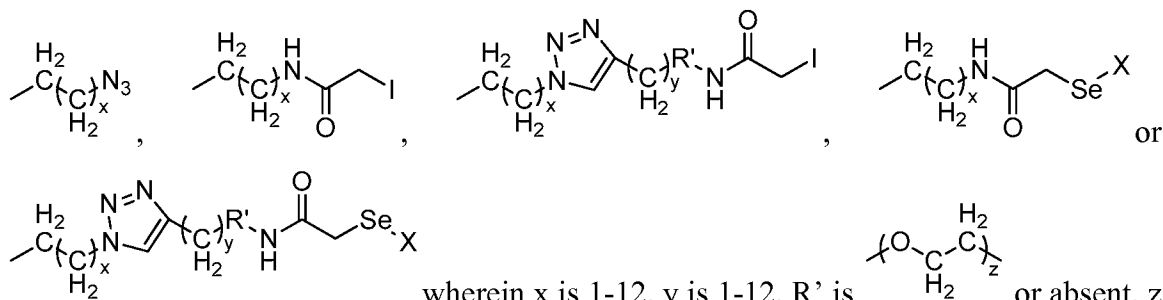
10 unsubstituted C₂-C₃₀ alkyl, aryl, alkylaryl, or arylalkyl group; wherein at least one of the





(*N*-(pyrrolidin-2-ylmethyl substituted sulfamido glycine), ,

wherein at least one R is:



5 is 1 to 20, and X comprises a carrying agent.

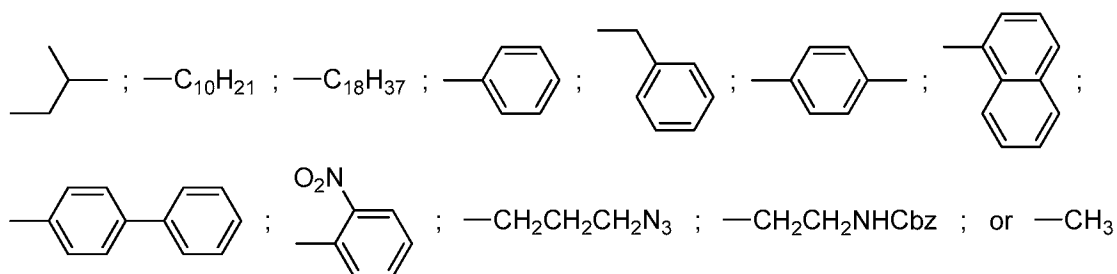
As used herein, the terms “cyclic compound”, “cyclic peptide conjugate”, “antibody drug conjugate”, “ADC”, “carrying agent:cyclic compound adduct” and “conjugate” refer to compounds of the invention.

In some embodiments, the non-recognition sequence is five amino acids selected from KLQLK (SEQ ID NO:1), QLKLK (SEQ ID NO:2), KQKLK (SEQ ID NO:3), KXXKK (SEQ ID NO:4), or ELKLK (SEQ ID NO:5) wherein X = sarcosine and the recognition sequence is five amino acids selected from WAVAW (SEQ ID NO:6), WAVAA (SEQ ID NO:7), WAVAM (SEQ ID NO:8), WAVAN* (SEQ ID NO:9), WAVVN* (SEQ ID NO:10), WAVSN* (SEQ ID NO:11), WAAAW (SEQ ID NO:12), WAAAA (SEQ ID NO:13), WAAAM (SEQ ID NO:14), WAAAN* (SEQ ID NO:15), WAAVW (SEQ ID NO:16), WAAVA (SEQ ID NO:17), WAAVM (SEQ ID NO:18), WAAVN* (SEQ ID NO:19), WAASN* (SEQ ID NO:20), WVVAW (SEQ ID NO:21), WVVAA (SEQ ID NO:22), WVVAM (SEQ ID NO:23), WVVAN* (SEQ ID NO:24), WVVVW (SEQ ID NO:25), WVVVA (SEQ ID NO:26), WVVVM (SEQ ID NO:27), WVVVN* (SEQ ID NO:28), WVVSN* (SEQ ID NO:29), WVAAN* (SEQ ID NO:30), WVAVW (SEQ ID NO:31), WVAVA (SEQ ID NO:32), WVAVM (SEQ ID NO:33), WVAVN* (SEQ ID NO:34), WVASN* (SEQ ID NO:35), WSVAW (SEQ ID NO:36), WSVAA (SEQ ID NO:37), WSVAM (SEQ ID NO:38), WSVAN* (SEQ ID NO:39), WSVVW (SEQ ID NO:40), WSVVA (SEQ ID NO:41), WSVVM (SEQ ID NO:42), WSVVN* (SEQ ID NO:43), WSVSW (SEQ ID NO:44), WSVSA (SEQ ID NO:45), WSVSM (SEQ ID NO:46), WSVSN* (SEQ ID NO:47), WSAAW (SEQ ID NO:48),

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5 WYVAA (SEQ ID NO:61), WYVAM (SEQ ID NO:62), WYVAN* (SEQ ID NO:63),
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10 WYAVW (SEQ ID NO:76), WYAVA (SEQ ID NO:77), WYAVM (SEQ ID NO:78),
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WYASM (SEQ ID NO:82), WYASN* (SEQ ID NO:83), AAVAA (SEQ ID NO:84),
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15 AAAAN* (SEQ ID NO:91), AAAVW (SEQ ID NO:92), AAAVA (SEQ ID NO:93),
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AVVAM (SEQ ID NO:100), AVVAN* (SEQ ID NO:101), AVVVA (SEQ ID NO:102),
AVVVM (SEQ ID NO:103), AVVVN* (SEQ ID NO:104), AVVSN* (SEQ ID NO:105),
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25 NO:215), MYAAW (SEQ ID NO:216), MYAAA (SEQ ID NO:217), MYAAM (SEQ ID
NO:218), MYAAN* (SEQ ID NO:219), MYAVW (SEQ ID NO:220), MYAVA (SEQ ID
NO:221), MYAVM (SEQ ID NO:222), MYAVN* (SEQ ID NO:223), MYASW (SEQ ID
NO:224), MYASA (SEQ ID NO:225), MYASM (SEQ ID NO:226), or MYASN* (SEQ
ID NO:227), wherein N* = norleucine, and wherein either end of the recognition
30 sequence can be a N-terminus.

In some embodiments of the cyclic compound, R is:



In some embodiments of the cyclic compound, R is H, C₁-C₃₀ alkyl, C₂-C₃₀ alkenyl, C₂-C₃₀ alkynyl, C₆-C₁₄ aryl, C₇-C₃₀ arylalkyl, C₈-C₃₀ arylalkenyl, C₈-C₃₀ arylalkynyl, hydroxy, C₁-C₃₀ alkoxy, C₆-C₁₄ aryloxy, C₇-C₃₀ arylalkyloxy, C₂-C₃₀ alkenyloxy, C₂-C₃₀ alkynyloxy, C₈-C₃₀ arylalkenyloxy, C₈-C₃₀ arylalkynyloxy, CO₂H, C₂-C₃₀ alkylester, C₇-C₁₅ aryylester, C₈-C₃₀ alkylaryylester, C₃-C₃₀ alkenylester, C₃-C₃₀ alkynylester, NH₂, C₁-C₃₀ alkylamino, C₆-C₁₄ arylamino, C₇-C₃₀ (arylalkyl)amino, C₂-C₃₀ alkenylamino, C₂-C₃₀ alkynylamino, C₈-C₃₀ (arylalkenyl)amino, C₈-C₃₀ (arylalkynyl)amino, C₂-C₃₀ dialkylamino, C₁₂-C₂₈ diarylamino, C₄-C₃₀ dialkenylamino, C₄-C₃₀ dialkynylamino, C₇-C₃₀ aryl(alkyl)amino, C₇-C₃₀ di(arylalkyl)amino, C₈-C₃₀ alkyl(arylalkyl)amino, C₁₅-C₃₀ aryl(arylalkyl)amino, C₈-C₃₀ alkenyl(aryl)amino, C₈-C₃₀ alkynyl(aryl)amino, C(O)NH₂ (amido), C₂-C₃₀ alkylamido, C₇-C₁₄ arylamido, C₈-C₃₀ (arylalkyl)amido, C₂-C₃₀ dialkylamido, C₁₂-C₂₈ diarylamido, C₈-C₃₀ aryl(alkyl)amido, C₁₅-C₃₀ di(arylalkyl)amido, C₉-C₃₀ alkyl(arylalkyl)amido, C₁₆-C₃₀ aryl(arylalkyl)amido, thiol, C₁-C₃₀ hydroxyalkyl, C₆-C₁₄ hydroxyaryl, C₇-C₃₀ hydroxyarylalkyl, C₃-C₃₀ hydroxyalkenyl, C₃-C₃₀ hydroxyalkynyl, C₈-C₃₀ hydroxyarylalkenyl, C₈-C₃₀ hydroxyarylalkynyl, C₃-C₃₀ polyether, C₃-C₃₀ polyetherester, C₃-C₃₀ polyester, C₃-C₃₀ polyamino, C₃-C₃₀ polyaminoamido, C₃-C₃₀ polyaminoether, C₃-C₃₀ polyaminoester, C₃-C₃₀ polyamidoester, C₃-C₃₀ alkylsulfonic acid, C₃-C₃₀ alkylsulfonate salt, C₁-C₃₀ carboxylate salt, C₁-C₃₀ thiocarboxylate salt, C₁-C₃₀ dithiocarboxylate salt, or C₃-C₃₀ alkylC₁-C₄ trialkylammonium salt, wherein any carbon can be further substituted with any carbon can be substituted with a hydroxy, chloro, bromo, iodo, nitro, or carboxylic acid.

In some embodiments of the cyclic compound, the carrying agent comprises an amino acid, oligo(amino acid), poly(amino acid) or protein. For example, the carrying agent may comprise an antibody, or an Fc portion of an antibody, or an antigen-binding fragment of an antibody. In some embodiments, the carrying agent is a monoclonal antibody (mAb), or an Fc portion of a mAb, or an antigen binding fragment of a mAb,

comprising a selenocysteine residue. In some embodiments, the carrying agent is a monoclonal antibody (mAb), or antigen binding fragment thereof, comprising a C-terminal selenocysteine residue.

Optionally, the carrying agent selected may be one that has the capacity to
5 function as a targeting agent, targeting the cyclic compound to a desired site. A “targeting agent” as used herein refers to a moiety that recognizes, binds or adheres to a target moiety of a target molecule located for example in or on a cell, tissue (*e.g.*, extracellular matrix), fluid, organism, or subset thereof. Thus, the term “carrying agent” is inclusive of targeting agents; therefore, every targeting agent is a carrying agent but a
10 carrying agent is not necessarily a targeting agent.

Accordingly, in some embodiments, the carrying agent does not function as a targeting agent. For example, in some embodiments, the carrying agent is an Fc portion of an antibody (the Fc portion does not target any antigens). Selenocysteine-mediated site-specific and covalent linkage of the cyclic compound to the Fc-Sec-His protein
15 prolongs the circulatory half-life of the cyclic compound, and, without wishing to be bound by theory, equips it with effector functions and bulkiness.

A targeting agent and its target molecule represent a binding pair of molecules, which interact with each other through any of a variety of molecular forces including, for example, ionic, covalent, hydrophobic, van der Waals, and hydrogen bonding, so that the
20 pair have the property of binding specifically to each other. Specific binding means that the binding pair exhibit binding with each other under conditions where they do not bind to another molecule. Examples of binding pairs are biotin-avidin, hormone-receptor, receptor-ligand, enzyme-substrate, IgG-protein A, antigen-antibody, and the like. The targeting agent and its cognate target molecule exhibit a significant association for each
25 other. This association may be evaluated by determining an equilibrium association constant (or binding constant) according to methods well known in the art. Affinity is calculated as $K_d = k_{off}/k_{on}$ (k_{off} is the dissociation rate constant, k_{on} is the association rate constant and K_d is the equilibrium constant. Examples of targeting agents that may be used are disclosed in U.S. Patent Publication 20130171074 (Barbas, C.F. *et al.*,
30 “Targeting Compounds”, assigned to The Scripps Research Institute, published July 4, 2013, which is incorporated herein by reference in its entirety). Preferably, the target molecule (*e.g.*, an antigen) is abundant in or on a target cell or tissue, relative to other

cells or tissues. For example, the target molecule may be an antigen that is overexpressed in or on one or more tumors.

Carrying agents include, but are not limited to, small molecule organic compounds of 5,000 daltons or less such as drugs, proteins, peptides, peptidomimetics, glycoproteins, proteoglycans, lipids glycolipids, phospholipids, lipopolysaccharide, nucleic acids, proteoglycans, carbohydrates, and the like. Carrying agents may include well known therapeutic compounds including anti-neoplastic agents. Anti-neoplastic targeting agents may include targpaclitaxel, daunorubicin, doxorubicin, carminomycin, 4'-epiadriamycin, 4-demethoxy-daunomycin, 11-deoxydaunorubicin, 13-deoxydaunorubicin, adriamycin-14-benzoate, adriamycin-14-octanoate, adriamycin-14-naphthaleneacetate, vinblastine, vincristine, mitomycin C, N-methyl mitomycin C, bleomycin A₂, dideazatetrahydrofolic acid, aminopterin, methotrexate, cholchicine and cisplatin, and the like. Anti-microbial agents include aminoglycosides including gentamicin, antiviral compounds such as rifampicin, 3'-azido-3'-deoxythymidine (AZT) and acyclovir, antifungal agents such as azoles including fluconazole, plyre macrolides such as amphotericin B, and candicidin, anti-parasitic compounds such as antimonials, and the like. Hormone targeting agents include toxins such as diphtheria toxin, cytokines such as CSF, GSF, GMCSF, TNF, erythropoietin, immunomodulators or cytokines such as the interferons or interleukins, a neuropeptide, reproductive hormone such as HGH, FSH, or LH, thyroid hormone, neurotransmitters such as acetylcholine, and hormone receptors such as the estrogen receptor.

In some embodiments, the carrying agent is an Fc portion of an antibody (which does not target any antigen), which does not function as a targeting agent.

In some embodiments, the carrying agent is an antibody or antigen-binding fragment thereof, which functions as a targeting agent.

The immunoglobulin may be a native immunoglobulin or modified immunoglobulin. In other embodiments, the targeting agent is not an antibody or antigen-binding fragment. For example, the targeting agent may be a small molecule. The carrying agent, including any linking moiety necessary for linking the carrying agent to an amino acid residue of the antibody combining site, may be about 300 daltons in size, and preferably may be at least about 400, 500, 600, 700, 800, 900, 1,000, 1,100, 1,200,

1,300, 1,400, 1,500, 1,600, 1,700, 1,800, 1,900, 2,000, 2,500, 3,000, 3,500, 4,000, 4,500 or even 5,000 daltons in size, with even larger sizes possible.

Suitable carrying agents in the invention can be a protein or peptide. “Polypeptide”, “peptide,” and “protein” are used interchangeably to refer to a polymer of amino acid residues (oligo(amino acid) or poly(amino acid)). As used herein, these terms are inclusive of amino acid polymers in which one or more amino acid residue is an artificial chemical analogue of a corresponding naturally occurring amino acid. These terms are also inclusive of naturally occurring amino acid polymers. Amino acids can be in the L or D form as long as the binding function of the peptide is maintained. Peptides can be of variable length, but are generally between about 4 and 200 amino acids in length. Peptides may be cyclic, having an intramolecular bond between two non-adjacent amino acids within the peptide, *e.g.*, backbone to backbone, side-chain to backbone and side-chain to side-chain cyclization. Cyclic peptides can be prepared by methods well known in the art. See *e.g.*, U.S. Patent No. 6,013,625.

The term “protein” is also inclusive of antibodies and portions (*i.e.*, fragments) of antibodies which or may not bind an antigen. For example, in some embodiments, the carrying agent comprises an antibody or antigen-binding portion thereof. In other embodiments, the carrying agent comprises an Fc portion of an antibody. In some embodiments, the antibodies are human antibodies. In some embodiments, the antibodies are non-human animal antibodies. Optionally, antibodies and antibody portions may be humanized.

Protein targeting agents that exhibit binding activity for a target molecule are well known in the art. For example, a targeting agent may be a viral peptide cell fusion inhibitor. This may include the T-20 HIV-1 gp41 fusion inhibitor which targets fusion receptors on HIV infected cells (for T-20, see U.S. Patent Nos. 6,281,331 and 6,015,881 to Kang *et al.*; Nagashima *et al. J. Infectious Diseases* 183:1121, 2001; for other HIV inhibitors see U.S. Patent No. 6,020,459 to Barney and WO 0151673A2 to Jeffs *et al.*), RSV cell fusion inhibitors (see WO 0164013A2 to Antczak and McKimm-Breschkin, *Curr. Opin. Invest. Drugs* 1:425-427, 2000 (VP-14637)), pneumovirus genus cell fusion inhibitors (see WO 9938508A1 by Nitz *et al.*), and the like. Targeting agents also include peptide hormones or peptide hormone analogues such as LHRH, bombesin/gastrin releasing peptide, somatostatin (*e.g.*, RC-121 octapeptide), and the like, which may be

used to target any of a variety of cancers, such as ovarian, mammary, prostate small cell of the lung, colorectal, gastric, and pancreatic. See, *e.g.*, Schally *et al.*, *Eur. J. Endocrinology*, 141:1-14, 1999.

Peptide targeting agents suitable for use in targeting compounds of the invention
5 also may be identified using in vivo targeting of phage libraries that display a random library of peptide sequences (see, *e.g.*, Arap *et al.*, *Nature Medicine*, 2002 8(2):121-7; Arap *et al.*, *Proc. Natl. Acad. Sci. USA* 2002 99(3):1527-1531; Trepel *et al.* *Curr. Opin. Chem. Biol.* 2002 6(3):399-404).

In some embodiments, the carrying agent specifically binds to a cell surface
10 antigen, functioning as a targeting agent.

In some embodiments, the carrying agent specifically binds to a tumor associated antigen, functioning as a targeting agent.

In some embodiments, the targeting agent is specific for an integrin, such as alpha4 integrin, alpha3 integrin, and alpha6 integrin. In addition to antibodies and
15 antigen-binding fragments thereof, suitable targeting agents for integrins include RGD peptides or peptidomimetics or non-RGD peptides or peptidomimetics. As used herein, reference to "Arg-Gly-Asp peptide" or "RGD peptide" is intended to refer to a peptide having one or more Arg-Gly-Asp containing sequence which may function as a binding site for a receptor of the "Arg-Gly-Asp family of receptors", *e.g.*, an integrin. The term
20 RGD peptide also includes amino acids that are functional equivalents (*e.g.*, RLD or KGD) thereof provided they interact with the same RGD receptor. Peptides containing RGD sequences can be synthesized from amino acids by means well known in the art, using, for example, an automated peptide synthesizer, such as those manufactured by Applied Biosystems, Inc., Foster City, Calif. As used herein, "non-RGD" peptide refers
25 to a peptide that is an antagonist or agonist of integrin binding to its ligand (*e.g.*, fibronectin, vitronectin, laminin, collagen *etc.*) but does not involve an RGD binding site. Non-RGD integrin peptides are known (see, *e.g.*, U.S. Patent Nos. 5,767,071; 5,780,426; 6,365,619; Chang *et al.*, *Bioorganic & Medicinal Chem Lett*, 12:159-163 (2002); Lin *et al.*, *Bioorganic & Medicinal Chem Lett*, 12:133-136 (2002)), and the like.

30 In some embodiments, the carrying agent is a monoclonal antibody (mAb), or an Fc portion of a mAb, or an antigen binding fragment of a mAb, comprising a selenocysteine residue. In some embodiments, the carrying agent is a monoclonal

antibody (mAb), or Fc portion of a mAb, or antigen binding fragment thereof, comprising a C-terminal selenocysteine residue. In some embodiments, the targeting agent specifically binds to a cell surface antigen. In some embodiments, the carrying agent is a polyclonal antibody, or an Fc portion thereof, or an antigen-binding fragment thereof.

5 In some embodiments, the carrying agent specifically binds (targets) molecules, the abundance of which is associated with the disorder to be treated. Thus, a carrying agent can (optionally) be selected to target a molecule associated with a disease state, such as cancer. For example, a carrying agent that targets CD44 can be used for treatment of myeloma and other cancers. A carrying agent that targets alpha4 integrin
10 can be used for treatment of hematopoietic cancers or metastatic solid tumors that home to bone.

In some embodiments, the targeting agent specifically binds to a tumor associated antigen. For example, the tumor associated antigen that is the target of the targeting agent may be an antigen overexpressed in tumors, hematopoietic differentiation antigen, cell
15 surface differentiation antigen, growth factor receptor, angiogenesis or stromal antigen, *etc.* Non-limiting examples of antigens that may be targeted are disclosed in Carter P. *et al.*, "Identification and validation of cell surface antigens for antibody targeting in oncology", *Endocrine-Related Cancer*, 2004, 11:659-687; Alonso-Camino V. *et al.*, "CARbodies: Human Antibodies Against Cell Surface Tumor Antigens Selected from
20 Repertoires Displayed on T Cell Chimeric Antigen Receptors", *Molecular Therapy-Nucleic Acids*, 2013:2:e93; Scott A.M. *et al.*, "Tumour Antigens Recognized by Antibodies," *Encyclopedia of Life Sciences*, 2001, pp. 1-7; Part One: Tumor-associated Antigens (TAAs): Subclasses of TAAS, in *Tumor-Associated Antigens*, Edited by Olivier Gires and Barbara Seliger, 2009; Kiessling A. *et al.*, "Tumor-Associated Antigens for
25 Specific Immunotherapy of Prostate Cancer," *Cancers*, 2012, 4:193-217, which are incorporated herein by reference in their entirety.

In some embodiments, the targeting agent specifically binds to one or more antigens selected from among CD138, CD44, alpha4 integrin, alpha3 integrin, alpha6 integrin, EGFR, tumor suppressor cell antigen, cytotoxic T cell antigen, 17-1A, 707-AP,
30 AFP, Annexin II, ART-4, BAGE, BAGE-1, β -catenin, BCG, bcr/abl, Bcr/abl e14a2 fusion junction, bcr-abl (b3a2), bcr-abl (b3a2), bcr-abl p190 (e1a2), bcr-abl p210 (b2a2), bcr-abl p210 (b3a2), bcr-abl p210 (b3a2), bullous pemphigoid antigen-1, CA19-9,

CA125, CA215, CAG-3, CAMEL, Cancer-testis antigen, Caspase-8, CCL3, CCL4, CD16, CD20, CD3, CD30, CD55, CD63, CDC27, CDK-4, CDR3, CEA, cluster 5, cluster-5A, cyclin-dependent kinase-4, Cyp-B, DAM-10, DAM-6, Dek-cain, E7, EGFRvIII, EGP40, ELF2 M, EpCAM, FucGM1, G250, GA733, GAGE, GAGE-1-8, 5 gastrin cancer associated antigen, GD2, GD3, globoH, glycophorin, GM1, GM2, GM3, GnTV, Gn-T-V, gp100, Her-2/neu, HERV-K-ME, high molecular weight-associated antigen, high molecular weight proteo-glycan (HMPG), HPV-16 E6, HPV-16 E7, HPVE6, HSP70-2M, HST-2, hTERT, human chorionic gonadotropin (HCG), Human milk fat globule (HMFG), iCE, KIAA0205, KK-LC-1, KM-HN-1, L6, LAGE-1, 10 Lcose4Cer, LDLR/FUT, Lewis A, Lewis v/b, M protein, MAGE-1, MVC, MAGE-A1-12, MAGE-C2, MAHGE-3, MART-1/Melan-A, MC1R, ME491, MUC1, MUC2, mucin, MUM-1, MUM-2, MUM-3, mutated p53, Myosin, MZ2-E, N9 neuraminidase, NA88, NA88-A, nasopharyngeal carcinoma antigen, NGA, NK1/c-3, Novel bcr/ablk fusion BCR exons 1, 13, 14 with ABL exons 4, NY-ESO-1/LAGE-2, NY-ESO-1b, OC125, 15 osteosarcoma associated antigen-1, P15, p190 mimor bcr-abl (e1a2), p53, Pml/RAR α , Polysialic acid, PRAME, PSA, PSM, RU1, RU2, SAGE, SART-1, SART-2, SART-3, Sialyl LeA, Sp17, SSX-2, SSX-4, surface immunoglobulin, TAG-1, TAG-2, TEL/AML1, TPI, TRAG-3, TRP-1(gp75), TRP-2, TRP2-INT2, hTERT, tumor associated glycoprotein-72 (TAG-72), tyrosinase, u-PA, WT1, and XAGE-1b, or an immunogenic fragment of 20 any of the foregoing antigens.

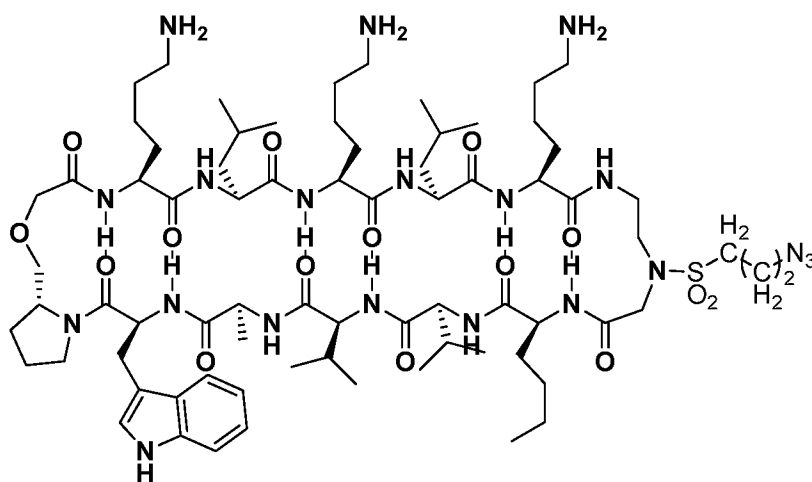
In some embodiments, the tumor associated antigen is identified by the SEREX (serological analysis of recombinant expression cloning) approach or based on the serological screening of cDNA expression library generated from tumor tissues of various origin or cancer cell lines, and identifying immunogenic tumor proteins based on their 25 reactivity with autologous patient sera.

Cyclic peptides, which may be used for making conjugates of the invention, and methods for making such cyclic peptides, are described in International Publication No. WO 2011/115688 (Hazlehurst *et al.*, "Integrin Interaction Inhibitors for the Treatment of Cancer", published September 22, 2011), which is incorporated by reference herein in its 30 entirety.

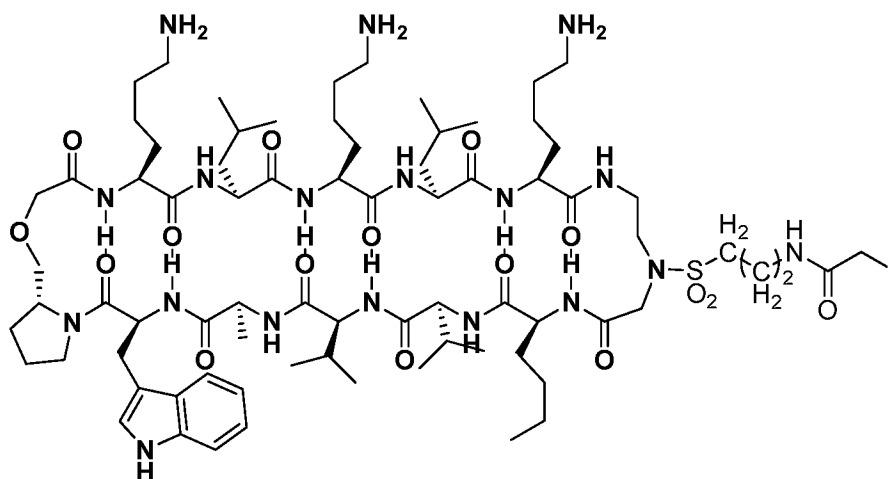
Selenocysteine technology for making selenocysteine mediated hybrid antibody molecules is disclosed in U.S. Patent Publication 2010/0104510 (Rader C. *et al.*), published April 29, 2010, which is incorporated by reference herein in its entirety.

The amino acid sequences of the mouse anti-human CD138 monoclonal antibody
5 are disclosed in U.S. Patent Publication 2009/0169570 (Daelkin B. *et al.*), published July 2, 2009, which is incorporated herein by reference in its entirety.

In some embodiments, the structure of the cyclic compound is:

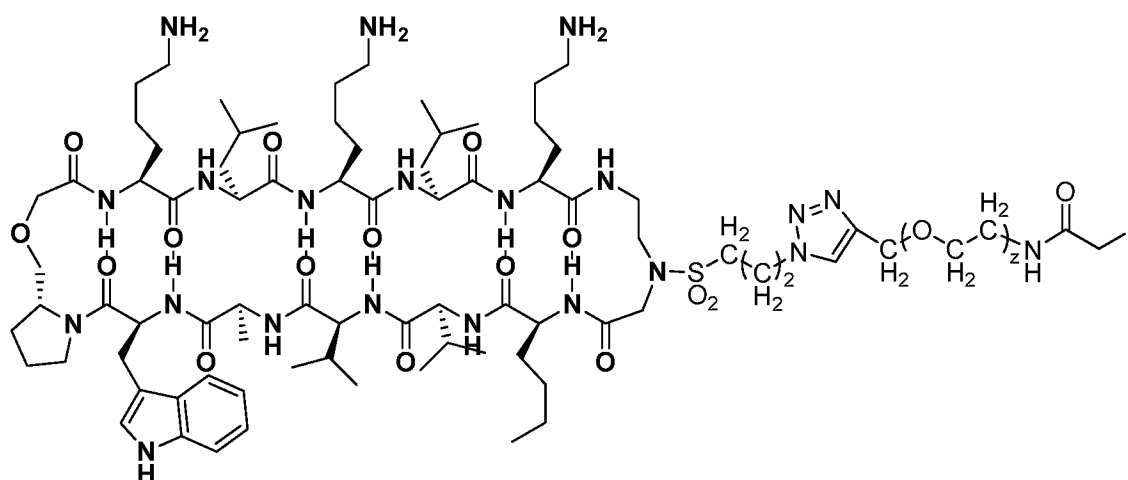


10 In some embodiments, the structure of the cyclic compound is:

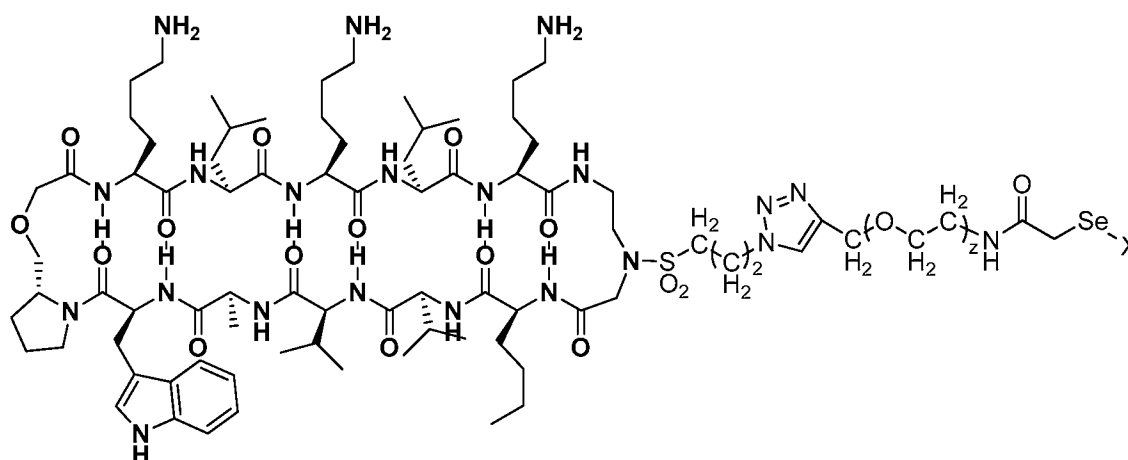


In some embodiments, the structure of the cyclic compound is:

18

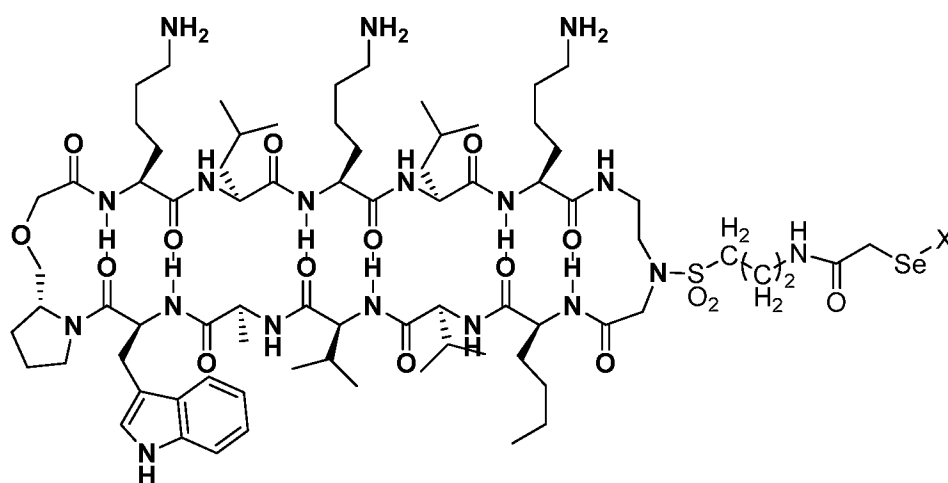


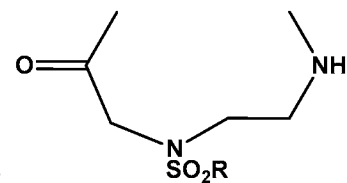
In some embodiments, the structure of the cyclic compound is:



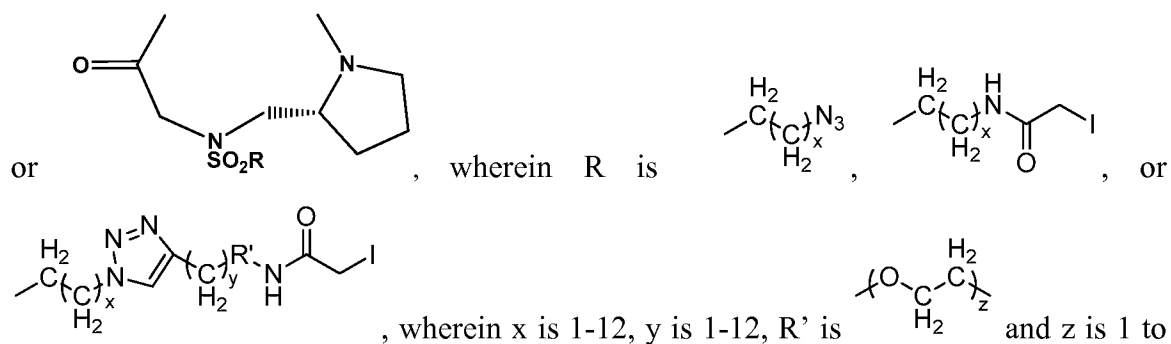
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In some embodiments, the structure of the cyclic compound is:





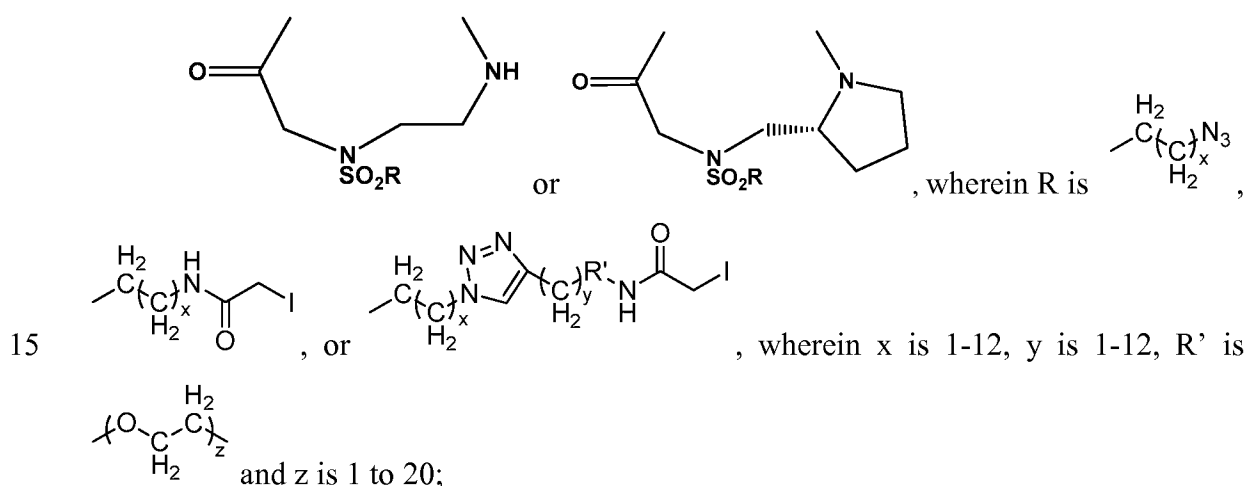
Another aspect of the invention is a linker, comprising:



5 20.

Another aspect of the invention is a method of preparing a carrying agent:cyclic compound adduct, comprising:

10 providing a cyclic compound comprising a recognition sequence and a non-recognition sequence, wherein the recognition sequence comprises at least four amino acids, wherein the non-recognition sequence comprises at least four amino acids, and wherein the recognition sequence is joined to the non-recognition sequence by a first linker and a second linker, wherein at least one of the first linker and the second linker is:



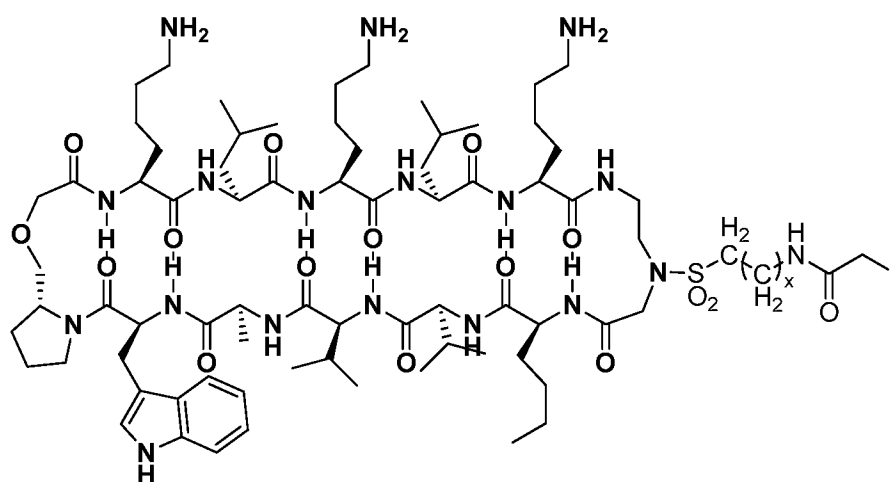
15

providing a carrying agent X comprising a selenocysteine residue; and
combining the carrying agent and the cyclic compound in an aqueous solution.

In some embodiments of the method of preparing a carrying agent:cyclic compound adduct, the aqueous solution comprises dithiothreitol (DTT) and the aqueous solution has an acidic pH.

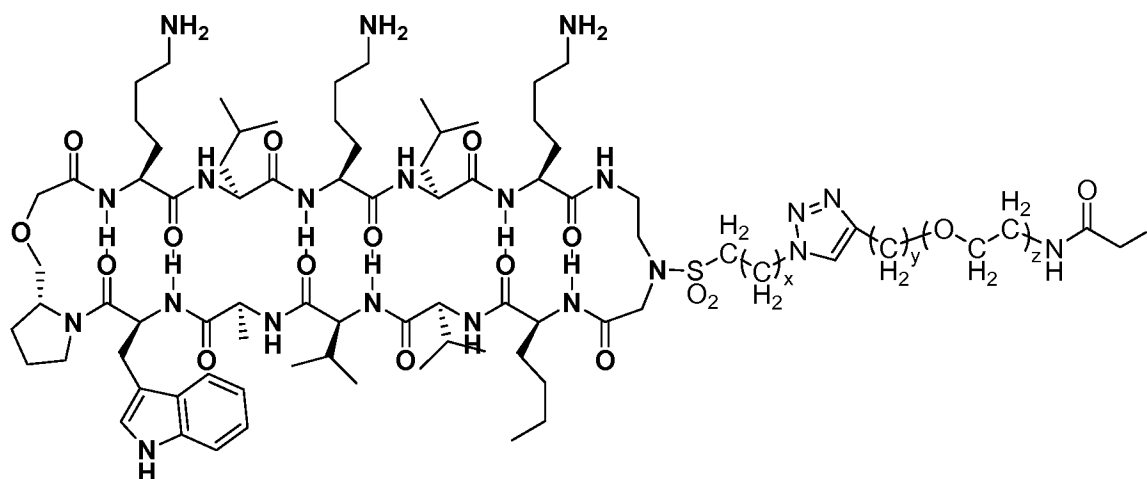
- 5 In some embodiments of the method of preparing a carrying agent:cyclic compound adduct, wherein the pH is 4-6 and the concentration of DTT is 0.1-1 mM.

In some embodiments of the method of preparing a carrying agent:cyclic compound adduct, the cyclic compound comprises:



10

or



,

wherein x is 1-12, y is 1-12, and z is 1.

- 15 In some embodiments of the method of preparing a carrying agent:cyclic compound adduct, the carrying agent comprises an oligo(amino acid), poly(amino acid) or protein comprising a selenocysteine residue.

In some embodiments of the method of preparing a carrying agent:cyclic compound adduct, the carrying agent X is a monoclonal antibody (mAb) comprising a selenocysteine residue.

In some embodiments of the method of preparing a carrying agent:cyclic compound adduct the carrying agent X is the modified antibody Fc-Sec-His having the sequence:

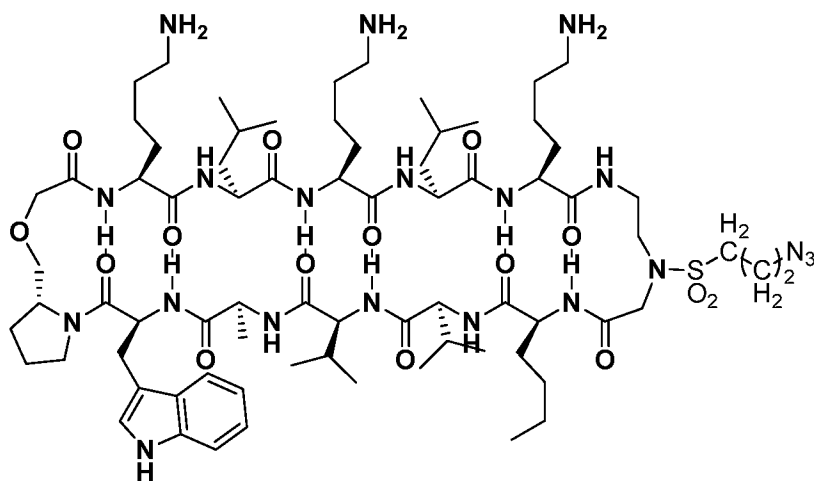
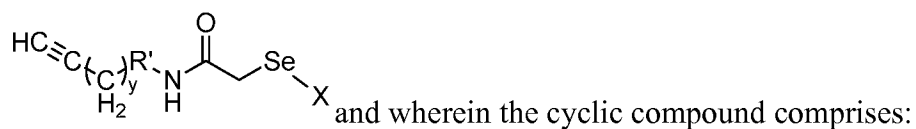
EPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSVCSVMHEALH
NHYTQKSLSLSPGAUHHHHHH (SEQ ID NO:228) where U is the single letter amino
acid code for selenocysteine.

In some embodiments of the method of preparing a carrying agent:cyclic compound adduct, the carrying agent X is a targeting agent that is the modified antibody Anti-CD138-scFv-Fc-Sec-His having the sequence:

DIQMTQSTSSLSASLGDRVTISCSASQGINNYLNWYQQKPDGTVELLIYYTSTLQS
GVPSRFSGSGSGTDYSLTISNLEPEDIGTYYCQQYSKLPRTFGGGTKLEIKGGGGS
GGGGSGGGGSQVQLQQSGSELMMPGASVKISCKATGYTFSNYWIEWVKQRPGH
GLEWIGEILPGTGRTIYNEKFKGKATFTADISSNTVQMQLSSLTSEDSAVYYCARR
DYYGNFYFAMDYWGQGTSTVTSSEPKSSDKTHTCPPCPAPELLGGPSVFLFPPK
KDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR
DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKL
TVDKSRWQQGNVFSVCSVMHEALHNHYTQKSLSLSPGAUHHHHHH (SEQ ID

NO:229) where U is the single letter amino acid code for selenocysteine. This sequence lacks the signal peptide sequence of the anti-CD138 antibody (MDWTWRILFLVAAATGAHS (SEQ ID NO:230)), which is the first 19 amino acid sequence that will typically be cleaved off during antibody purification, prior to combining with the cyclic compound.

In some embodiments of the method of preparing a carrying agent:cyclic compound adduct, the carrying agent X comprises a residue of selenocysteine having a



Another aspect of the invention concerns a method for treating a disorder in a subject, comprising administering an effective amount of a cyclic compound (conjugate) disclosed herein to the subject. In some embodiments, the subject is human. In other embodiments, the subject is a non-human animal.

10 In some embodiments, the disorder is a proliferation disorder, bone deficiency, or autoimmune disease.

In some embodiments, the proliferation disorder is myeloma or another malignancy.

15 In some embodiments, the cyclic compound is administered in a composition further comprising a pharmaceutically acceptable carrier.

Another aspect of the invention concerns a method of suppressing the growth of, or inducing apoptosis in, cells, comprising contacting the cells with an effective amount of a cyclic compound (conjugate) disclosed herein. In some embodiments, the cyclic compound is in a composition further comprising a pharmaceutically acceptable carrier.

20 In some embodiments, the contacting is carried out *in vivo*. In other embodiments, the contacting is carried out *in vitro*.

In some embodiments, the cells are human cells. In other embodiments, the cells are non-human animal cells. In some embodiments, the cells are mammalian cells.

In some embodiments, the cells are myeloma cells or other malignant cells.

Another aspect of the invention concerns a composition comprising a cyclic compound disclosed herein; and a pharmaceutically acceptable carrier. The composition may include additional agents, such as anti-cancer agent.

5 In some embodiments, the proliferation disorder to be treated is a cancer. In some embodiments, the proliferation disorder to be treated is a cancer producing a tumor characterized by $\beta 1$ integrin signaling or $\beta 1$ integrin mediated adhesion.

Examples of susceptible cancer types include, but are not limited to, cancer of the breast, pancreas, prostate, melanoma, myeloma, acute myeloid leukemia (AML), and
10 lung. In some embodiments, the proliferation disorder to be treated is a cancer producing a tumor characterized by the CAM-DR phenotype. In some embodiments, the proliferation disorder to be treated is a cancer that exhibits elevated levels of the cleaved form of $\alpha 4$ integrin. In some embodiments, the proliferation disorder to be treated is a hematopoietic cancer. In some embodiments, the proliferation disorder to be treated is a
15 metastatic solid tumor that homes to bone.

In some embodiments, the treatment methods further include determining whether the proliferation disorder exhibits the aforementioned characteristics ($\beta 1$ integrin signaling or $\beta 1$ integrin mediated adhesion; CAM-DR phenotype; elevated $\alpha 4$ integrin level) prior to administration of the one or more compounds of the invention.

20 In some embodiments, the proliferation disorder to be treated is characterized by a proliferation of T-cells such as autoimmune disease, *e.g.*, type 1 diabetes, lupus and multiple sclerosis, and pathological states such as graft rejection induced by the presentation of a foreign antigen such as a graft in response to a disease condition (*e.g.*, kidney failure). Other non-malignant diseases characterized by proliferation of cells
25 include cirrhosis of the liver and restenosis.

The methods of the present invention can be advantageously combined with at least one additional treatment method, including but not limited to, chemotherapy, radiation therapy, or any other therapy known to those of skill in the art for the treatment and management of proliferation disorders such as cancer.

30 While compounds of the invention can be administered to cells *in vitro* and *in vivo* as isolated agents, it is preferred to administer these compounds as part of a pharmaceutical composition. The subject invention thus further provides compositions

comprising a compound of the invention in association with at least one pharmaceutically acceptable carrier. The pharmaceutical composition can be adapted for various routes of administration, such as enteral, parenteral, intravenous, intramuscular, topical, subcutaneous, and so forth. Administration can be continuous or at distinct intervals, as
5 can be determined by a person of ordinary skill in the art.

The compounds of the invention can be formulated according to known methods for preparing pharmaceutically useful compositions. Formulations are described in a number of sources which are well known and readily available to those skilled in the art. For example, *Remington's Pharmaceutical Science* (Martin, E.W., 1995, Easton
10 Pennsylvania, Mack Publishing Company, 19th ed.) describes formulations which can be used in connection with the subject invention. Formulations suitable for administration include, for example, aqueous sterile injection solutions, which may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient; and aqueous and nonaqueous sterile suspensions which may
15 include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the condition of the sterile liquid carrier, for example, water for injections, prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powder, granules, tablets, *etc.* It
20 should be understood that in addition to the ingredients particularly mentioned above, the compositions of the subject invention can include other agents conventional in the art having regard to the type of formulation in question.

Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids that form a physiological acceptable anion, for example, tosylate,
25 methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, alpha-ketoglutarate, and alpha-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts of compounds may be obtained using standard procedures well known in the art, for example, by reacting a sufficiently basic compound
30 such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

As used herein, the term “analogs” refers to compounds which are substantially the same as another compound but which may have been modified by, for example, adding side groups, oxidation or reduction of the parent structure. Analogs of the specifically disclosed compounds, and other agents disclosed herein, can be readily prepared using commonly known standard reactions. These standard reactions include, but are not limited to, hydrogenation, alkylation, acetylation, and acidification reactions. Chemical modifications can be accomplished by those skilled in the art by protecting all functional groups present in the molecule and deprotecting them after carrying out the desired reactions using standard procedures known in the scientific literature (Greene, T.W. and Wuts, P.G.M. “Protective Groups in Organic Synthesis” John Wiley & Sons, Inc. New York. 3rd Ed. pg. 819, 1999; Honda, T. *et al. Bioorg. Med. Chem. Lett.*, 1997, 7:1623-1628; Honda, T. *et al. Bioorg. Med. Chem. Lett.*, 1998, 8:2711-2714; Konoike, T. *et al. J. Org. Chem.*, 1997, 62:960-966; Honda, T. *et al. J. Med. Chem.*, 2000, 43:4233-4246; each of which are hereby incorporated herein by reference in their entirety).
Analog, fragments, and variants of the compounds exhibiting the desired biological activity (such as induction of cell death, cytotoxicity, cytostaticity, induction of cell cycle arrest, *etc.*) can be identified or confirmed using cellular assays or other *in vitro* or *in vivo* assays.

The compounds of the invention are useful for various non-therapeutic and therapeutic purposes. The compounds may be used for reducing aberrant cell growth in animals and humans. Because of such anti-proliferative properties of the compounds, they are useful in reducing unwanted cell growth in a wide variety of settings including *in vitro* and *in vivo*. In addition to their use in treatment methods, the compounds of the invention are useful as agents for investigating the role of integrin signaling and/or integrin mediated adhesion in cellular metabolism, and controlling integrin mediated malignant or non-malignant cell growth *in vitro* or *in vivo*.

Therapeutic application of the compounds and compositions comprising them can be accomplished by any suitable therapeutic method and technique presently or prospectively known to those skilled in the art. Further, the compounds of the invention can be used as starting materials or intermediates for the preparation of other useful compounds and compositions.

Compounds of the invention may be locally administered at one or more anatomical sites, such as sites of unwanted cell growth (such as a tumor site, *e.g.*, injected or topically applied to the tumor), optionally in combination with a pharmaceutically acceptable carrier such as an inert diluent. Compounds of the invention may be systemically administered, such as intravenously or orally, optionally in combination with a pharmaceutically acceptable carrier such as an inert diluent, or an assimilable edible carrier for oral delivery. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the compounds may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, aerosol sprays, and the like.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac, or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the compounds may be incorporated into sustained-release preparations and devices.

The active agent (*e.g.*, the compounds (conjugates) of the invention) may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active agent can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and

mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations can contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the compounds of the invention which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. The ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. Optionally, the prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the inclusion of agents that delay absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the compounds of the invention in the required amount in the appropriate solvent with various other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the compounds may be applied in pure-form, *i.e.*, when they are liquids. However, it will generally be desirable to administer them topically to the skin as compositions, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

The compounds of the subject invention can be applied topically to a subject's skin to reduce the size (and may include complete removal) of malignant or benign

growths. The compounds of the invention can be applied directly to the growth. Preferably, the compound is applied to the growth in a formulation such as an ointment, cream, lotion, solution, tincture, or the like. Drug delivery systems for delivery of pharmacological substances to dermal lesions can also be used, such as that described in
5 U.S. Patent No. 5,167,649 (Zook).

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the peptide can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants.
10 Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers, for example.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty
15 alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user. Examples of useful dermatological compositions which can be used to deliver the peptides to the skin are disclosed in Jacquet *et al.* (U.S. Patent No. 4,608,392), Geria (U.S. Patent No. 4,992,478), Smith *et al.*
20 (U.S. Patent No. 4,559,157) and Woltzman (U.S. Patent No. 4,820,508).

Useful dosages of the pharmaceutical compositions of the present invention can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Patent No. 4,938,949.

25 Accordingly, the present invention includes a pharmaceutical composition comprising compound of the invention in combination with a pharmaceutically acceptable carrier. Pharmaceutical compositions adapted for oral, topical or parenteral administration, comprising an amount of a compound of the invention constitute a preferred embodiment of the invention. The dose administered to a patient, particularly a
30 human, in the context of the present invention should be sufficient to achieve a therapeutic response in the patient over a reasonable time frame, without lethal toxicity, and preferably causing no more than an acceptable level of side effects or morbidity. One

skilled in the art will recognize that dosage will depend upon a variety of factors including the condition (health) of the subject, the body weight of the subject, kind of concurrent treatment, if any, frequency of treatment, therapeutic ratio, as well as the severity and stage of the pathological condition. Advantageously, in some embodiments,
5 administration of the compounds of the invention does not induce weight loss or overt signs of toxicity in the subject.

Depending upon the disorder or disease condition to be treated (*e.g.*, a proliferation disorder, bone deficiency, or autoimmune disorder), a suitable dose(s) may be that amount that will reduce proliferation or growth of the target cell(s), or induce cell
10 death. In the context of cancer, a suitable dose(s) is that which will result in a concentration of the active agent (one or more compounds of the invention) in cancer tissue, such as a malignant tumor, which is known to achieve the desired response. The preferred dosage is the amount which results in maximum inhibition of cancer cell growth, without unmanageable side effects. Administration of a compound of the
15 invention can be continuous or at distinct intervals, as can be determined by a person of ordinary skill in the art.

To provide for the administration of such dosages for the desired therapeutic treatment, in some embodiments, pharmaceutical compositions of the invention can comprise between about 0.1% and 45%, and especially, 1 and 15%, by weight of the total
20 of one or more of the compounds of the invention based on the weight of the total composition including carrier or diluents. Illustratively, dosage levels of the administered active ingredients can be: intravenous, 0.01 to about 20 mg/kg; intraperitoneal, 0.01 to about 100 mg/kg; subcutaneous, 0.01 to about 100 mg/kg; intramuscular, 0.01 to about 100 mg/kg; orally 0.01 to about 200 mg/kg, and preferably about 1 to 100 mg/kg;
25 intranasal instillation, 0.01 to about 20 mg/kg; and aerosol, 0.01 to about 20 mg/kg of animal (body) weight.

Mammalian species which benefit from the disclosed methods include, but are not limited to, primates, such as apes, chimpanzees, orangutans, humans, monkeys; domesticated animals (*e.g.*, pets) such as dogs, cats, guinea pigs, hamsters, Vietnamese
30 pot-bellied pigs, rabbits, and ferrets; domesticated farm animals such as cows, buffalo, bison, horses, donkey, swine, sheep, and goats; exotic animals typically found in zoos, such as bear, lions, tigers, panthers, elephants, hippopotamus, rhinoceros, giraffes,

antelopes, sloth, gazelles, zebras, wildebeests, prairie dogs, koala bears, kangaroo, opossums, raccoons, pandas, hyena, seals, sea lions, elephant seals, otters, porpoises, dolphins, and whales. Other species that may benefit from the disclosed methods include fish, amphibians, avians, and reptiles. As used herein, the terms “patient”, “subject”, and
5 “individual” are used interchangeably and are intended to include such human and non-human species. Likewise, *in vitro* methods of the present invention can be carried out on cells of such human and non-human species.

Patients in need of treatment using the methods of the present invention can be identified using standard techniques known to those in the medical or veterinary
10 professions, as appropriate.

The terms “cancer” and “malignancy” are used herein interchangeably to refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. The cancer may be multi-drug resistant (MDR) or drug-sensitive. Examples of cancer include but are not limited to, carcinoma, lymphoma,
15 blastoma, sarcoma, and leukemia. More particular examples of such cancers include breast cancer, prostate cancer, colon cancer, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, cervical cancer, ovarian cancer, peritoneal cancer, liver cancer, *e.g.*, hepatic carcinoma, bladder cancer, colorectal cancer, endometrial carcinoma, kidney cancer, and thyroid cancer. In some
20 embodiments, the cancer is multiple myeloma or another hematologic malignancy.

In some embodiments, the cancer or malignancy is one that expresses CD44. In some embodiments, the methods of the invention further comprise obtaining a sample of the cancer cells and determining whether the cells express one or more biomarkers, such as CD44, prior to administration of a peptide of the invention. Optionally, the methods
25 may further comprise administering the peptide if the cancer sample expresses CD44.

Other non-limiting examples of cancers that may be treated are basal cell carcinoma, biliary tract cancer; bone cancer; brain and CNS cancer; choriocarcinoma; connective tissue cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer; intra-epithelial neoplasm; larynx cancer; lymphoma including Hodgkin’s
30 and Non-Hodgkin’s lymphoma; melanoma; myeloma; neuroblastoma; oral cavity cancer (*e.g.*, lip, tongue, mouth, and pharynx); retinoblastoma; rhabdomyosarcoma; rectal cancer; cancer of the respiratory system; sarcoma; skin cancer; stomach cancer; testicular

cancer; uterine cancer; cancer of the urinary system, as well as other carcinomas and sarcomas. Examples of cancer types that may potentially be treated using the compounds of the present invention are also listed in Table 1.

5 Table 1. Examples of Cancer Types

Acute Lymphoblastic Leukemia, Adult	Hairy Cell Leukemia
Acute Lymphoblastic Leukemia, Childhood	Head and Neck Cancer
Acute Myeloid Leukemia, Adult	Hepatocellular (Liver) Cancer, Adult (Primary)
Acute Myeloid Leukemia, Childhood	Hepatocellular (Liver) Cancer, Childhood (Primary)
Adrenocortical Carcinoma	Hodgkin's Lymphoma, Adult
Adrenocortical Carcinoma, Childhood	Hodgkin's Lymphoma, Childhood
AIDS-Related Cancers	Hodgkin's Lymphoma During Pregnancy
AIDS-Related Lymphoma	Hypopharyngeal Cancer
Anal Cancer	Hypothalamic and Visual Pathway Glioma, Childhood
Astrocytoma, Childhood Cerebellar	
Astrocytoma, Childhood Cerebral	
Basal Cell Carcinoma	Intraocular Melanoma
Bile Duct Cancer, Extrahepatic	Islet Cell Carcinoma (Endocrine Pancreas)
Bladder Cancer	Kaposi's Sarcoma
Bladder Cancer, Childhood	Kidney (Renal Cell) Cancer
Bone Cancer, Osteosarcoma/Malignant	Kidney Cancer, Childhood
Fibrous Histiocytoma	
Brain Stem Glioma, Childhood	Laryngeal Cancer
Brain Tumor, Adult	Laryngeal Cancer, Childhood
Brain Tumor, Brain Stem Glioma, Childhood	Leukemia, Acute Lymphoblastic, Adult
Brain Tumor, Cerebellar Astrocytoma, Childhood	Leukemia, Acute Lymphoblastic, Childhood
Brain Tumor, Cerebral	Leukemia, Acute Myeloid, Adult
Astrocytoma/Malignant Glioma, Childhood	Leukemia, Acute Myeloid, Childhood
Brain Tumor, Ependymoma, Childhood	Leukemia, Chronic Lymphocytic
Brain Tumor, Medulloblastoma, Childhood	Leukemia, Chronic Myelogenous
Brain Tumor, Supratentorial Primitive Neuroectodermal Tumors, Childhood	Leukemia, Hairy Cell
Brain Tumor, Visual Pathway and Hypothalamic Glioma, Childhood	Lip and Oral Cavity Cancer
Brain Tumor, Childhood	Liver Cancer, Adult (Primary)
Breast Cancer	Liver Cancer, Childhood (Primary)
Breast Cancer, Childhood	Lung Cancer, Non-Small Cell
Breast Cancer, Male	Lung Cancer, Small Cell
Bronchial Adenomas/Carcinoids, Childhood	Lymphoma, AIDS-Related
	Lymphoma, Burkitt's
	Lymphoma, Cutaneous T-Cell, see Mycosis Fungoides and Sézary Syndrome
	Lymphoma, Hodgkin's, Adult
	Lymphoma, Hodgkin's, Childhood
	Lymphoma, Hodgkin's During Pregnancy
	Lymphoma, Non-Hodgkin's, Adult

Burkitt's Lymphoma	Lymphoma, Non-Hodgkin's, Childhood
Carcinoid Tumor, Childhood	Lymphoma, Non-Hodgkin's During Pregnancy
Carcinoid Tumor, Gastrointestinal	Lymphoma, Primary Central Nervous System
Carcinoma of Unknown Primary	Macroglobulinemia, Waldenström's
Central Nervous System Lymphoma, Primary	Malignant Fibrous Histiocytoma of Bone/Osteosarcoma
Cerebellar Astrocytoma, Childhood	Medulloblastoma, Childhood
Cerebral Astrocytoma/Malignant	Melanoma
Glioma, Childhood	Melanoma, Intraocular (Eye)
Cervical Cancer	Merkel Cell Carcinoma
Childhood Cancers	Mesothelioma, Adult Malignant
Chronic Lymphocytic Leukemia	Mesothelioma, Childhood
Chronic Myelogenous Leukemia	Metastatic Squamous Neck Cancer with Occult Primary
Chronic Myeloproliferative Disorders	Multiple Endocrine Neoplasia Syndrome, Childhood
Colon Cancer	Multiple Myeloma/Plasma Cell Neoplasm
Colorectal Cancer, Childhood	Mycosis Fungoides
Cutaneous T-Cell Lymphoma, see	Myelodysplastic Syndromes
Mycosis Fungoides and Sézary Syndrome	Myelodysplastic/Myeloproliferative Diseases
Endometrial Cancer	Myelogenous Leukemia, Chronic
Ependymoma, Childhood	Myeloid Leukemia, Adult Acute
Esophageal Cancer	Myeloid Leukemia, Childhood Acute
Esophageal Cancer, Childhood	Myeloma, Multiple
Ewing's Family of Tumors	Myeloproliferative Disorders, Chronic
Extracranial Germ Cell Tumor, Childhood	Nasal Cavity and Paranasal Sinus Cancer
Extragonadal Germ Cell Tumor	Nasopharyngeal Cancer
Extrahepatic Bile Duct Cancer	Nasopharyngeal Cancer, Childhood
Eye Cancer, Intraocular Melanoma	Neuroblastoma
Eye Cancer, Retinoblastoma	Non-Hodgkin's Lymphoma, Adult
Gallbladder Cancer	Non-Hodgkin's Lymphoma, Childhood
Gastric (Stomach) Cancer	Non-Hodgkin's Lymphoma During Pregnancy
Gastric (Stomach) Cancer, Childhood	Non-Small Cell Lung Cancer
Gastrointestinal Carcinoid Tumor	Oral Cancer, Childhood
Germ Cell Tumor, Extracranial, Childhood	Oral Cavity Cancer, Lip and Oropharyngeal Cancer
Germ Cell Tumor, Extragonadal	Osteosarcoma/Malignant Fibrous Histiocytoma of Bone
Germ Cell Tumor, Ovarian	Ovarian Cancer, Childhood
	Ovarian Epithelial Cancer
	Ovarian Germ Cell Tumor
	Ovarian Low Malignant Potential Tumor
	Pancreatic Cancer
	Pancreatic Cancer, Childhood
	Pancreatic Cancer, Islet Cell
	Paranasal Sinus and Nasal Cavity Cancer

Gestational Trophoblastic Tumor Glioma, Adult Glioma, Childhood Brain Stem Glioma, Childhood Cerebral Astrocytoma Glioma, Childhood Visual Pathway and Hypothalamic Skin Cancer (Melanoma) Skin Carcinoma, Merkel Cell Small Cell Lung Cancer Small Intestine Cancer Soft Tissue Sarcoma, Adult Soft Tissue Sarcoma, Childhood Squamous Cell Carcinoma, see Skin Cancer (non-Melanoma) Squamous Neck Cancer with Occult Primary, Metastatic Stomach (Gastric) Cancer Stomach (Gastric) Cancer, Childhood Supratentorial Primitive Neuroectodermal Tumors, Childhood T-Cell Lymphoma, Cutaneous, see Mycosis Fungoides and Sézary Syndrome Testicular Cancer Thymoma, Childhood Thymoma and Thymic Carcinoma Thyroid Cancer Thyroid Cancer, Childhood Transitional Cell Cancer of the Renal Pelvis and Ureter Trophoblastic Tumor, Gestational Unknown Primary Site, Carcinoma of, Adult Unknown Primary Site, Cancer of, Childhood Unusual Cancers of Childhood Ureter and Renal Pelvis, Transitional Cell Cancer Urethral Cancer Uterine Cancer, Endometrial Uterine Sarcoma Vaginal Cancer Visual Pathway and Hypothalamic Glioma, Childhood Vulvar Cancer	Parathyroid Cancer Penile Cancer Pheochromocytoma Pineoblastoma and Supratentorial Primitive Neuroectodermal Tumors, Childhood Pituitary Tumor Plasma Cell Neoplasm/Multiple Myeloma Pleuropulmonary Blastoma Pregnancy and Breast Cancer Pregnancy and Hodgkin's Lymphoma Pregnancy and Non-Hodgkin's Lymphoma Primary Central Nervous System Lymphoma Prostate Cancer Rectal Cancer Renal Cell (Kidney) Cancer Renal Cell (Kidney) Cancer, Childhood Renal Pelvis and Ureter, Transitional Cell Cancer Retinoblastoma Rhabdomyosarcoma, Childhood Salivary Gland Cancer Salivary Gland Cancer, Childhood Sarcoma, Ewing's Family of Tumors Sarcoma, Kaposi's Sarcoma, Soft Tissue, Adult Sarcoma, Soft Tissue, Childhood Sarcoma, Uterine Sézary Syndrome Skin Cancer (non-Melanoma) Skin Cancer, Childhood
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Waldenström's Macroglobulinemia Wilms' Tumor	
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As used herein, the term “tumor” refers to all neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues. For example, a particular cancer may be characterized by a solid mass tumor or non-solid tumor. The solid tumor mass, if present, may be a primary tumor mass. A primary tumor mass refers to a growth of cancer cells in a tissue resulting from the transformation of a normal cell of that tissue. In most cases, the primary tumor mass is identified by the presence of a cyst, which can be found through visual or palpation methods, or by irregularity in shape, texture or weight of the tissue. However, some primary tumors are not palpable and can be detected only through medical imaging techniques such as X-rays (*e.g.*, mammography) or magnetic resonance imaging (MRI), or by needle aspirations. The use of these latter techniques is more common in early detection. Molecular and phenotypic analysis of cancer cells within a tissue can usually be used to confirm if the cancer is endogenous to the tissue or if the lesion is due to metastasis from another site. The treatment methods of the invention can be utilized for early, middle, or late stage disease, and acute or chronic disease. In some embodiments, the tumor is characterized as one exhibiting the CAM-DR phenotype.

In some embodiments, the disorder to be treated is a proliferation disorder, bone deficiency, or autoimmune disease. In addition to cancer, the proliferation disorder may be a disorder involving an aberrant number of activated T-cells. Thus, administration of the compounds may be used to reduce the number of activated T-cells in a subject.

In some embodiments, the disorder to be treated is a bone deficiency or autoimmune disease, and the carrying agent is a non-targeting agent, such as an Fc portion of an antibody.

In some embodiments, the disorder to be treated is a bone deficiency caused by an osteopenic disorder, such as osteoporosis, Paget's disease, lytic bone metastases, periodontitis, rheumatoid arthritis, and bone loss due to immobilization.

In some embodiments, the subject has a cancer that increases osteoclast activity and/or induces bone resorption.

In some embodiments, the subject does not have a proliferation disorder, such as cancer.

The compounds of the invention may also be administered to treat an autoimmune disorder. In some embodiments, the autoimmune disorder selected from among: AIDS-associated myopathy, AIDS-associated neuropathy, Acute disseminated encephalomyelitis, Addison's Disease, Alopecia Areata, Anaphylaxis Reactions, Ankylosing Spondylitis, Antibody-related Neuropathies, Antiphospholipid Syndrome, Arthritis (*e.g.*, rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis), Autism, Autoimmune Atherosclerosis, Autoimmune Diabetes Insipidus, Autoimmune Endometriosis, Autoimmune Eye Diseases, Autoimmune Gastritis, Autoimmune Hemolytic Anemia, Autoimmune Hemophilia, Auto immune Hepatitis, Auto immune Interstitial Cystitis, Auto immune Lym pho proliferative Syndrome, Autoimmune Myelopathy, Autoimmune Myocarditis, Autoimmune Neuropathies, Autoimmune Oophoritis, Autoimmune Orchitis, Autoimmune Thrombocytopenia, Autoimmune Thyroid Diseases, Autoimmune Urticaria, Autoimmune Uveitis, Autoimmune Vasculitis, Behcet's Disease, Bell's Palsy, Bullous Pemphigoid, CREST, Celiac Disease, Cerebellar degeneration (paraneoplastic), Chronic Fatigue Syndrome, Chronic Rhinosinusitis, Chronic inflammatory demyelinating polyneuropathy, Churg Strauss Syndrome, Connective Tissue Diseases, Crohn's Disease, Cutaneous Lupus, Dermatitis Herpetiformis, Dermatomyositis, Diabetes Mellitus, Discoid Lupus Erythematosus, Drug-induced Lupus, Endocrine Orbitopathy, Glomerulonephritis, Goodpasture Syndrome, Goodpasture's Syndrome, Graft-versus-Host Disease (GVHD), Graves Disease, Guillian-Barre Syndrome, Miller Fisher variant of the Guillian Barre Syndrome, axonal Guillian Barre Syndrome, demyelinating Guillian Barre Syndrome, Hashimoto Thyroiditis, Herpes Gestationis, Human T-cell lymphomavirus-associated myelopathy, Huntington's Disease, IgA Nephropathy, Immune Thrombocytopenic Purpura, Inclusion body myositis, Interstitial Cystitis, Isaacs syndrome, Lambert Eaton myasthenic syndrome, Limbic encephalitis, Lower motor neuron disease, Lyme Disease, MCTD, Microscopic Polyangiitis, Miller Fisher Syndrome, Mixed Connective Tissue Disease, Mononeuritis multiplex (vasculitis), Multiple Sclerosis (relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), primary-progressive MS (PPMS), and progressive-relapsing MS (PRMS)), Myasthenia Gravis, Myxedema, Meniere Disease, Neonatal LE, Neuropathies

with dysproteinemias, Opsoclonus-myoclonus, PBC, POEMS syndrome, Paraneoplastic Autoimmune Syndromes, Pemphigus, Pemphigus Foliaceus, Pemphigus Vulgaris, Pernicious Anemia, Peyronie's Disease, Plaque Psoriasis, Plasmacytoma/myeloma neuropathy, Poly-Dermatomyositis, Polyarteritis Nodosa, Polyendocrine Deficiency Syndrome, Polyendocrine Deficiency Syndrome Type 1, Polyendocrine Deficiency Syndrome Type 2, Polyglandular Autoimmune Syndrome Type I, Polyglandular Autoimmune Syndrome Type II, Polyglandular Autoimmune Syndrome Type III, Polymyositis, Primary Biliary Cirrhosis, Primary Glomerulonephritis, Primary Sclerosing Cholangitis, Psoriasis, Psoriatic Arthritis, Rasmussen's Encephalitis, Raynaud's Disease, Relapsing Polychondritis, Retrobulbar neuritis, Rheumatic Diseases, Rheumatoid Arthritis, Scleroderma, Sensory neuropathies (paraneoplastic), Sjogren's Syndrome, Stiff-Person Syndrome, Subacute Thyroiditis, Subacute autonomic neuropathy, Sydenham Chorea, Sympathetic Ophthalmitis, Systemic Lupus Erythematosus, Transverse myelitis, Type 1 Diabetes, Ulcerative Colitis, Vasculitis, Vitiligo, Wegener's Granulomatosis, acrocyanosis, anaphylactic reaction, autoimmune inner ear disease, bilateral sensorineural hearing loss, cold agglutinin hemolytic anemia, cold-induced immune hemolytic anemia, idiopathic endolymphatic hydrops, idiopathic progressive bilateral sensorineural hearing loss, immune-mediated inner ear disease, and mixed autoimmune hemolysis.

In some embodiments, the subject has graft-versus-host disease (GVHD), and the compound is administered to treat the GVHD in the subject. In some embodiments, the compound is administered before, during, and/or after a transplant to delay the onset of graft-versus-host disease (GVHD). In some embodiments, the transplant comprises an allograft or xenograft. In some embodiments, the transplant comprises an allogeneic stem cell, bone marrow, or organ transplant.

Combination Treatments

According to the method of the subject invention, a compound disclosed herein (a conjugate) can be administered to a subject by itself, or co-administered with one or more other agents such as another compound of the invention (another conjugate), or a different agent or agents. In some embodiments, the additional agent is one or more anti-cancer

agents. Anti-cancer agents include but are not limited to the chemotherapeutic agents listed Table 3.

Co-administration can be carried out simultaneously (in the same or separate formulations) or consecutively with the additional agent administered before and/or after one or more compounds disclosed herein. Furthermore, according to the method of the subject invention, peptides of the invention can be administered to a subject as adjuvant therapy. For example, peptides of the invention can be administered to a patient in conjunction with chemotherapy.

Thus, the compounds of the invention, whether administered separately, or as a pharmaceutical composition, can include various other components as additives. Examples of acceptable components or adjuncts which can be employed in relevant circumstances include antioxidants, free radical scavenging agents, peptides, growth factors, antibiotics, bacteriostatic agents, immunosuppressives, anticoagulants, buffering agents, anti-inflammatory agents, anti-angiogenics, anti-pyretics, time-release binders, anesthetics, steroids, and corticosteroids. Such components can provide additional therapeutic benefit, act to affect the therapeutic action of the compounds of the invention, or act towards preventing any potential side effects which may be posed as a result of administration of the compounds. The compounds of the subject invention can be further conjugated to a therapeutic agent, as well.

Additional agents that can be co-administered to target cells *in vitro* or *in vivo*, such as in a subject, in the same or as a separate formulation, include those that modify a given biological response, such as immunomodulators. The additional agents may be, for example, small molecules, polypeptides (proteins, peptides, or antibodies or antibody fragments), or nucleic acids (encoding polypeptides or inhibitory nucleic acids such as antisense oligonucleotides or interfering RNA). For example, proteins such as tumor necrosis factor (TNF), interferon (such as alpha-interferon and beta-interferon), nerve growth factor (NGF), platelet derived growth factor (PDGF), and tissue plasminogen activator can be administered. Biological response modifiers, such as lymphokines, interleukins (such as interleukin-1 (IL-1), interleukin-2 (IL-2), and interleukin-6 (IL-6)), granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), or other growth factors can be administered. In one embodiment, the methods and compositions of the invention incorporate one or more

anti-cancer agents, such as cytotoxic agents, chemotherapeutic agents, anti-signaling agents, and anti-angiogenic agents.

In some embodiments, the compositions of the invention include at least one additional anti-cancer agent (*e.g.*, a chemotherapeutic agent). In some embodiments of the methods of the invention, at least one additional anti-cancer agent is administered with the compound of the invention. In some embodiments, the anti-cancer agent is selected from among suberoylanilide hydroxamic acid (SAHA) or other histone deacetylase inhibitor, arsenic trioxide, doxorubicin or other anthracycline DNA intercalating agent, and etoposide or other topoisomerase II inhibitor.

In some embodiments, the compositions of the invention include one or more proteasome inhibitors (*e.g.*, bortezomib), inhibitors of autophagy (*e.g.*, chloroquine), alkylating agents (*e.g.*, melphalan, cyclophosphamide), MEK inhibitors (*e.g.*, PD98509), FAK/PYK2 inhibitors (*e.g.*, PF562271), or EGFR inhibitors (*e.g.*, erlotinib, gefitinib, cetuximab, panitumumab, zalutumumab, nimotuzumab, matuzumab), or a combination of two or more of the foregoing. Likewise, the methods of the invention include administration of one or more proteasome inhibitors, inhibitors of autophagy, alkylating agents, MEK inhibitors, FAK/PYK2 inhibitors, EGFR inhibitors, or a combination of two or more of the foregoing to cancer cells *in vitro* or to a subject before, during (in the same composition or separate compositions), or after administration of a compound (conjugate) disclosed herein.

In some embodiments, the compounds of the invention are administered before, during, or after:

(a) an agent for treatment of a bone deficiency, selected from among bisphosphonate (*e.g.*, alendronate, risedronate, ibandronate, zoledronic acid), teriparatide, denosumab, and calcitonin; or

(b) an agent for treatment of an autoimmune disorder, selected from among a corticosteroid (such as prednisone), nonsteroid drug such as azathioprine, cyclophosphamide, methotrexate, mycophenolate, mofetil, sirolimus, rituximab, tacrolimus, cyclosporine, or other immunosuppressive agent. The agent may be administered in the same composition as the compound of the invention or separately.

Compounds as described herein may include residues of L-amino acids, D-amino acids, or any combination thereof. In some embodiments, all amino acids of the peptide

are D-amino acids. Amino acids may be from natural or non-natural sources. The 20 L-amino acids commonly found in proteins are identified herein by the conventional one-letter abbreviations known in the art, and the corresponding D-amino acids are generally designated by a lower case one letter symbol. Compounds of the invention may also

5 contain one or more rare amino acids (such as 4-hydroxyproline or hydroxylysine), organic acids or amides and/or derivatives of common amino acids, such as amino acids having the C-terminal carboxylate esterified (*e.g.*, benzyl, methyl or ethyl ester) or amidated and/or having modifications of the N-terminal amino group (*e.g.*, acetylation or alkoxy-carbonylamino), with or without any of a wide variety of side chain modifications

10 and/or substitutions (*e.g.*, methylation, benzylation, t-butylation, tosylation, alkoxy-carbonylamino, and the like). Such modifications and derivatives of an amino acid sequence, and others known to those of skill in the art, are herein termed “variants”. Some derivatives include amino acids having an N-acetyl group (such that the amino group that represents the N-terminus of the peptide is acetylated) and/or a C-terminal

15 amide group (*i.e.*, the carboxy terminus of the peptide is amidated). Residues other than common amino acids that may be present include, but are not limited to, penicillamine, tetramethylene cysteine, pentamethylene cysteine, mercaptopropionic acid, pentamethylene-mercaptopropionic acid, 2-mercaptobenzene, 2-mercaptoaniline, 2-mercaptoproline, ornithine, diaminobutyric acid, aminoadipic acid, m-

20 aminomethylbenzoic acid, and diaminopropionic acid.

Functional fragments according to the subject invention can comprise a contiguous span of at least 4 consecutive amino acids of a recognition sequence (also referred to as the recognition portion) and/or a non-recognition sequence (also referred to as the non-recognition portion) of the compounds disclosed herein. Peptides fragments

25 according to the subject invention can be any integer in length from at least 4 consecutive amino acids to 1 amino acid less than a full length peptide (*e.g.*, 1 amino acid less than the full length peptide). Thus, in some embodiments, functional fragments may be 4, 5, 6, 7, 8, or 9 amino acids in length (*e.g.*, a span of 4, 5, 6, 7, 8, or 9 consecutive amino acids).

30 Each fragment of the subject invention can also be described in terms of its N-terminal and C-terminal positions. For example, combinations of N-terminal to C-terminal fragments of 6 contiguous amino acids to 1 amino acid less than the full length

peptide of are included in the present invention. Thus, a 6 consecutive amino acid fragment could occupy positions selected from the group consisting of 1-6, 2-7, 3-8, 4-9, 5-10, *etc.* It is noted that all ranges used to describe any embodiment of the present invention are inclusive unless specifically set forth otherwise and that fragments of a given peptide can be any integer in length, provided that the length of the peptide fragment is at least one amino acid shorter than the full-length peptide from which the fragment is derived.

Fragments, as described herein, can be obtained by cleaving the peptides of the invention with a proteolytic enzyme (such as trypsin, chymotrypsin, or collagenase) or with a chemical reagent, such as cyanogen bromide (CNBr). Alternatively, peptide fragments can be generated in a highly acidic environment, for example at pH 2.5. Such peptide fragments may be equally well prepared by chemical synthesis or using hosts transformed with an expression vector according to the invention.

In certain preferred embodiments, fragments of the peptides disclosed herein retain at least one property or activity of the full-length peptide from which the fragments are derived.

Various detectable moieties may be attached to the compounds of the invention, such as at a nitrogen atom on one or more linkers. Such moieties that may find use with the compounds of the present invention can include but not be limited to sugars, lectins, antigens, intercalators, chelators, biotin, digoxigenin and combinations thereof. The particular choice of a dye as a labeling agent or cell uptake facilitator may depend upon physical characteristics such as absorption maxima, emission maxima, quantum yields, chemical stability and solvent solubility. A large number of fluorescent and chemiluminescent compounds have been shown to be useful for labeling proteins and nucleic acids. Examples of compounds that may be used as the dye portion can include but not be limited to xanthene, anthracene, cyanine, porphyrin and coumarin dyes. Examples of xanthene dyes that may be coupled to the peptides of the present invention can include but not be limited to fluorescein, 6-carboxyfluorescein (6-FAM), 5-carboxyfluorescein (5-Fam), 5- or 6-carboxy-4,7,2',7'-tetrachlorofluorescein (TET), 5- or 6-carboxy-4'5'2'4'5'7' hexachlorofluorescein (HEX), 5' or 6'-carboxy-4',5'-dichloro-2',7'-dimethoxyfluorescein (JOE), 5-carboxy-2',4',5',7'-tetrachlorofluorescein (ZOE) rhodol, rhodamine, tetramethylrhodamine (TAMRA), 4,7-dichlorotetramethyl rhodamine

(DTAMRA), rhodamine X (ROX) and Texas Red. Examples of cyanine dyes that may find use with the peptides of the present invention can include but not be limited to Cy 3, Cy 3.5, Cy 5, Cy 5.5, Cy 7 and Cy 7.5. Other dyes that may find use with the peptides of the present invention can include but not be limited to energy transfer dyes, composite dyes and other aromatic compounds that give fluorescent signals. Chemiluminescent compounds that may be used with the peptides of the present invention can include but not be limited to dioxetane and acridinium esters. It should also be understood that ligands and dyes are not mutually exclusive groups. For instance, fluorescein is a well known example of a moiety that has been used as a fluorescent label and also as an antigen for labeled antibodies. Detectable moieties may be detected using devices and methodologies appropriate for the label in question.

The compounds expressly provided herein, as well as the fragments thereof, may further comprise linker elements that facilitate the attachment of the fragments to other molecules, amino acids, or polypeptide sequences. The linkers can also be used to attach the peptides, or fragments thereof, to solid support matrices for use in affinity purification protocols. Non-limiting examples of “linkers” suitable for the practice of the invention include chemical linkers (such as those sold by Pierce, Rockford, IL), or peptides that allow for the connection combinations of peptides (see, for example, linkers such as those disclosed in U.S. Patent Nos. 6,121,424, 5,843,464, 5,750,352, and 5,990,275, hereby incorporated by reference in their entirety).

In other embodiments, the linker element can be an amino acid sequence (a peptide linker). In some embodiments, the peptide linker has one or more of the following characteristics: a) it allows for the free rotation of the peptides that it links (relative to each other); b) it is resistant or susceptible to digestion (cleavage) by proteases; and c) it does not interact with the peptides it joins together. In various embodiments, a multimeric construct according to the subject invention includes a peptide linker and the peptide linker is 5 to 60 amino acids in length. More preferably, the peptide linker is 10 to 30, amino acids in length; even more preferably, the peptide linker is 10 to 20 amino acids in length. In some embodiments, the peptide linker is 17 amino acids in length.

A “variant” or “variant peptide” (or peptide variant) is to be understood to designate peptides exhibiting, in relation to the peptides disclosed herein, certain

modifications. These modifications can include a deletion, addition, or substitution of at least one amino acid (*e.g.*, one, two, three or more amino acids), a truncation, an extension, a chimeric fusion (fusion protein), a mutation, or polypeptides exhibiting post-translational modifications. These modifications can occur anywhere in the peptide, *e.g.*, one or both ends and/or in the middle. Among these homologous variant peptides, are those comprising amino acid sequences exhibiting between at least (or at least about) 20.00% to 99.99% (inclusive) identity to the full length, native, or naturally occurring polypeptide are another aspect of the invention. The aforementioned range of percent identity is to be taken as including, and providing written description and support for, any fractional percentage, in intervals of 0.01%, between 20.00% and, up to, including 99.99%. These percentages are purely statistical and differences between two polypeptide sequences can be distributed randomly and over the entire sequence length. Thus, variant peptides can have 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 percent identity with the peptide sequences of the instant invention. In a preferred embodiment, a variant or modified peptide exhibits at least 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 percent identity to the reference peptide. The percent identity is calculated with reference to the full-length polypeptide or the length of the fragment of a particular SEQ ID NO: that is identified. Preferably, the variant peptides retain at least one of the biological activities associated with the reference peptide.

For example, one or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity which acts as a functional equivalent, resulting in a silent alteration. In one aspect of the present invention, conservative substitutions for an amino acid within the sequence may be selected from other members of the class to which the amino acid belongs (see Table 2). Conservative substitutions also include substitutions by amino acids having chemically modified side chains that do not eliminate the biological function of the resulting variant.

Table 2.

Class of Amino Acid	Examples of Amino Acids
Nonpolar	Ala, Val, Leu, Ile, Pro, Met, Phe, Trp
Uncharged Polar	Gly, Ser, Thr, Cys, Tyr, Asn, Gln
Acidic	Asp, Glu
Basic	Lys, Arg, His

Fusion proteins according to the subject invention comprise one or more heterologous peptide sequences (*e.g.*, tags that facilitate purification of the peptides of the invention (see, for example, U.S. Patent No. 6,342,362, hereby incorporated by reference in its entirety; Altendorf *et al.* [1999-WWW, 2000] "Structure and Function of the F₀ Complex of the ATP Synthase from *Escherichia Coli*," *J. of Experimental Biology* 203:19-28, The Co. of Biologists, Ltd., G.B.; Baneyx [1999] "Recombinant Protein Expression in *Escherichia coli*," *Biotechnology* 10:411-21, Elsevier Science Ltd.; Eihauer *et al.* [2001] "The FLAGTM Peptide, a Versatile Fusion Tag for the Purification of Recombinant Proteins," *J. Biochem Biophys Methods* 49:455-65; Jones *et al.* [1995] *J. Chromatography* 707:3-22; Jones *et al.* [1995] "Current Trends in Molecular Recognition and Bioseparation," *J. of Chromatography A* 707:3-22, Elsevier Science B.V.; Margolin [2000] "Green Fluorescent Protein as a Reporter for Macromolecular Localization in Bacterial Cells," *Methods* 20:62-72, Academic Press; Puig *et al.* [2001] "The Tandem Affinity Purification (TAP) Method: A General Procedure of Protein Complex Purification," *Methods* 24:218-29, Academic Press; Sassenfeld [1990] "Engineering Proteins for Purification," *TibTech* 8:88-93; Sheibani [1999] "Prokaryotic Gene Fusion Expression Systems and Their Use in Structural and Functional Studies of Proteins," *Prep. Biochem. & Biotechnol.* 29(1):77-90, Marcel Dekker, Inc.; Skerra *et al.* [1999] "Applications of a Peptide Ligand for Streptavidin: the *Strep*-tag", *Biomolecular Engineering* 16:79-86, Elsevier Science, B.V.; Smith [1998] "Cookbook for Eukaryotic Protein Expression: Yeast, Insect, and Plant Expression Systems," *The Scientist*

12(22):20; Smyth *et al.* [2000] "Eukaryotic Expression and Purification of Recombinant Extracellular Matrix Proteins Carrying the Strep II Tag", *Methods in Molecular Biology*, 139:49-57; Unger [1997] "Show Me the Money: Prokaryotic Expression Vectors and Purification Systems," *The Scientist* 11(17):20, each of which is hereby incorporated by
5 reference in their entireties), or commercially available tags from vendors such as such as STRATAGENE (La Jolla, CA), NOVAGEN (Madison, WI), QIAGEN, Inc., (Valencia, CA), or InVitrogen (San Diego, CA).

In other embodiments, peptides of the subject invention can be fused to heterologous polypeptide sequences that have adjuvant activity (a polypeptide adjuvant).
10 Non-limiting examples of such polypeptides include heat shock proteins (hsp) (see, for example, U.S. Patent No. 6,524,825, the disclosure of which is hereby incorporated by reference in its entirety).

Peptides as described herein may be synthesized by methods well known in the art, including recombinant DNA methods and chemical synthesis. Chemical synthesis
15 may generally be performed using standard solution phase or solid phase peptide synthesis techniques, in which a peptide linkage occurs through the direct condensation of the amino group of one amino acid with the carboxy group of the other amino acid with the elimination of a water molecule. Peptide bond synthesis by direct condensation, as formulated above, requires suppression of the reactive character of the amino group of the
20 first and of the carboxyl group of the second amino acid. The masking substituents must permit their ready removal, without inducing breakdown of the labile peptide molecule.

In solution phase synthesis, a wide variety of coupling methods and protecting groups may be used (see Gross and Meienhofer, eds., "The Peptides: Analysis, Synthesis, Biology," Vol. 1-4 (Academic Press, 1979); Bodansky and Bodansky, "The Practice of
25 Peptide Synthesis," 2d ed. (Springer Verlag, 1994)). In addition, intermediate purification and linear scale up are possible. Those of ordinary skill in the art will appreciate that solution synthesis requires consideration of main chain and side chain protecting groups and activation method. In addition, careful segment selection is necessary to minimize racemization during segment condensation. Solubility
30 considerations are also a factor.

Solid phase peptide synthesis uses an insoluble polymer for support during organic synthesis. The polymer-supported peptide chain permits the use of simple

washing and filtration steps instead of laborious purifications at intermediate steps. Solid-phase peptide synthesis may generally be performed according to the method of Merrifield *et al.*, *J. Am. Chem. Soc.*, 1963, 85:2149, which involves assembling a linear peptide chain on a resin support using protected amino acids. Solid phase peptide
5 synthesis typically utilizes either the Boc or Fmoc strategy, which are well known in the art.

Those of ordinary skill in the art will recognize that, in solid phase synthesis, deprotection and coupling reactions must go to completion and the side-chain blocking groups must be stable throughout the synthesis. In addition, solid phase synthesis is
10 generally most suitable when peptides are to be made on a small scale.

Acetylation of the N-terminal can be accomplished by reacting the final peptide with acetic anhydride before cleavage from the resin. C-amidation is accomplished using an appropriate resin such as methylbenzhydrylamine resin using the Boc technology.

The compounds disclosed herein may be modified by attachment of a second
15 molecule that confers a desired property upon the peptide, such as increased half-life in the body, for example, pegylation. Such modifications also fall within the scope of the term "variant" as used herein.

Covalent attachment of a molecule or solid support may generally be achieved by first reacting the support material with a bifunctional reagent that will also react with a
20 functional group, such as a hydroxyl, thiol, carboxyl, ketone or amino group, on the modulating agent. A preferred method of generating a linkage is via amino groups using glutaraldehyde. A peptide may be linked to cellulose via ester linkages. Similarly, amide linkages may be suitable for linkage to other molecules such as keyhole limpet hemocyanin or other support materials.

25 Within certain aspects of the present invention, one or more compounds as described herein may be present within a pharmaceutical composition. A pharmaceutical composition comprises one or more compounds of the invention in combination with one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients. Such compositions may comprise buffers (*e.g.*, neutral buffered saline or phosphate
30 buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (*e.g.*, aluminum hydroxide) and/or preservatives.

Within yet other embodiments, compositions of the present invention may be formulated as a lyophilizate. A compound may, but need not, be encapsulated within liposomes using well known technology. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous, or intramuscular administration. For certain topical applications, formulation as a cream or lotion, using well known components, is preferred.

Various techniques may be utilized to facilitate delivery of the compounds of the invention to the target cells *in vitro* (including *ex vivo*) and *in vivo* (Cellular Drug Delivery: Principles and Practice, edited by Lu, D.R. and Oie, S., Human Press, Totowa, N.J., 2004). Optionally, it may be desirable to facilitate delivery of the compounds of the invention through the outer cell membrane. Various protein carrier molecules may be further coupled to the compounds of the invention to assist penetration through biological membranes. For example, small regions (*e.g.*, 9-16 amino acids) of proteins called protein transduction domains (PTDs) cell penetrating peptides (CPP) possess the ability to traverse biological membranes through protein transduction (Barnett, E.M. *et al.*, *Invest. Ophthalmol. Vis. Sci.*, 2006, 47:2589-2595; Schwarze S.R. *et al.*, *Science*, 1999, 285(5433):1569-1572; Wadia, J.S. and Dowdy, S.F., *Advanced Drug Delivery Reviews*, 2005, 57(4): 579-596; Wadia, J.S. and Dowdy, S.F., *Curr. Opin. Biotechnol.*, 2002, 13(1):52-56; Ho A. *et al.*, *Cancer Research*, 2001, 61:474-477; Futaki *et al.*, *J. Biol. Chem.*, 2001, Feb., 276(8):5836-5840; Cao G. *et al.*, *J. Neurosci.*, 2002, 22(13):5423-5431; Becker-Hapak, M. *et al.*, *Methods*, 2001, 24:247-256; Snyder, E.L. and Dowdy, S.F., *Curr. Opin. Mol. Ther.*, 2001, 3:147-152; Lewin, M. *et al.*, *Nat. Biotechnol.*, 2000, 18:410-414; Tung, C.H. *et al.*, *Bioorg. Med. Chem.*, 2002, 10:3609-3614; Richard, J.P., *et al.*, *J. Biol. Chem.*, Oct. 30, 2002, epub ahead of print). Transduction can occur in a receptor- and transporter-independent fashion that appears to target the lipid bilayer directly. Proteins (peptides) and compounds that are linked to PTDs (*e.g.*, covalently) have the capability to traverse outer cell membranes. Preferably, the delivery peptide is a trans-activating transcriptional activator (TAT) peptide or an Antennapedia (ANT) peptide, or a derivative of either. PTDs can be linked to the peptides of the subject invention for transport across the cell membrane. One well characterized PTD is the human immunodeficient virus (HIV)-1 Tat peptide (see, for example, U.S. Patent Nos.

5,804,604; 5,747,641; 5,674,980; 5,670,617; and 5,652,122). Peptides such as the homeodomain of *Drosophila* antennapedia (ANTP) and arginine-rich peptides display similar properties can be employed. VP22, a tegument protein from Herpes simplex virus type 1 (HSV-1), also has the ability to transport proteins across a cell membrane, and may
5 be coupled to the compounds of the invention.

Definitions

As used herein, the terms “administering” or “administer” are defined as the introduction of a substance into cells *in vitro* or into the body of an individual *in vivo* by
10 any route (for example, oral, nasal, ocular, rectal, vaginal and parenteral routes). Compounds of the invention (conjugates) may be administered individually or in combination with other agents via any route of administration, including but not limited to subcutaneous (SQ), intramuscular (IM), intravenous (IV), intraperitoneal (IP), intradermal (ID), via the nasal, ocular or oral mucosa (IN), or orally. For example, the
15 compounds can be administered by direct injection into or on a tumor, or systemically (*e.g.*, into the circulatory system), to kill circulating tumor cells (CTC).

In the context of the instant invention, the terms “oligopeptide”, “polypeptide”, “peptide” and “protein” can be used interchangeably; however, it should be understood that the invention does not relate to the peptides in natural form, that is to say that they
20 are not in their natural environment but that the peptide may have been isolated or obtained by purification from natural sources or obtained from host cells prepared by genetic manipulation (*e.g.*, the peptides, or fragments thereof, are recombinantly produced by host cells, or by chemical synthesis). Compounds of the invention may also contain non-natural amino acids, as will be described below. The terms “oligopeptide”,
25 “polypeptide”, “peptide” and “protein” are also used, in the instant specification, to designate a series of residues of any length, typically L-amino acids, connected one to the other, typically by peptide bonds between the α -amino and carboxyl groups of adjacent amino acids. Linker elements can be joined to the peptides of the subject invention, for example, through peptide bonds or via chemical bonds (*e.g.*, heterobifunctional chemical
30 linker elements) as set forth below. Additionally, the terms “amino acid(s)” and “residue(s)” can be used interchangeably.

As used herein, the terms “treat” or “treatment” refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as the development or spread of cancer or other proliferation disorder. For purposes of this invention, 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. For example, treatment with a compound of the invention may include reduction of undesirable cell proliferation, and/or induction of apoptosis and cytotoxicity. “Treatment” can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented or onset delayed. Optionally, the patient may be identified (*e.g.*, diagnosed) as one suffering from the disease or condition (*e.g.*, proliferation disorder) prior to administration of the compound of the invention.

As used herein, the term “(therapeutically) effective amount” refers to an amount of the compound of the invention or other agent (*e.g.*, a drug) effective to treat a disease or disorder in a mammal. In the case of cancer or other proliferation disorder, the therapeutically effective amount of the agent may reduce (*i.e.*, slow to some extent and preferably stop) unwanted cellular proliferation; reduce the number of cancer cells; reduce the tumor size; inhibit (*i.e.*, slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (*i.e.*, slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; reduce $\beta 1$ integrin signaling in the target cells, and/or relieve, to some extent, one or more of the symptoms associated with the cancer. To the extent the administered compound prevents growth of and/or kills existing cancer cells, it may be cytostatic and/or cytotoxic. For cancer therapy, efficacy can, for example, be measured by assessing the time to disease progression (TTP) and/or determining the response rate (RR).

As used herein, the term “growth inhibitory amount” of the compound of the invention refers to an amount which inhibits growth or proliferation of a target cell, such as a tumor cell, either *in vitro* or *in vivo*, irrespective of the mechanism by which cell

growth is inhibited (*e.g.*, by cytostatic properties, cytotoxic properties, *etc.*). In a preferred embodiment, the growth inhibitory amount inhibits (*i.e.*, slows to some extent and preferably stops) proliferation or growth of the target cell *in vivo* or in cell culture by greater than about 20%, preferably greater than about 50%, most preferably greater than about 75% (*e.g.*, from about 75% to about 100%).

The terms “cell” and “cells” are used interchangeably herein and are intended to include either a single cell or a plurality of cells, *in vitro* or *in vivo*, unless otherwise specified.

A compound of the invention may be administered before, during, or after administration of one or more other agents, such as an anti-cancer compound. If administered simultaneously, they may be administered within the same composition or separate compositions. As used herein, the term “anti-cancer agent” refers to a substance or treatment (*e.g.*, radiation therapy) that inhibits the function of cancer cells, inhibits their formation, and/or causes their destruction *in vitro* or *in vivo*. Examples include, but are not limited to, cytotoxic agents (*e.g.*, 5-fluorouracil, TAXOL), chemotherapeutic agents, and anti-signaling agents (*e.g.*, the PI3K inhibitor LY). Anti-cancer agents include but are not limited to the chemotherapeutic agents listed Table 3.

As used herein, the term “cytotoxic agent” refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells *in vitro* and/or *in vivo*. The term is intended to include radioactive isotopes (*e.g.*, At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³², and radioactive isotopes of Lu), chemotherapeutic agents, toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, and antibodies, including fragments and/or variants thereof.

As used herein, the term “chemotherapeutic agent” is a chemical compound useful in the treatment of cancer, such as, for example, taxanes, *e.g.*, paclitaxel (TAXOL, BRISTOL-MYERS SQUIBB Oncology, Princeton, N.J.) and doxorubicin (DOXIL, Bristol-Myers Squibb Oncology, Princeton, N.J.) and doxorubicin (DOXIL, Bristol-Myers Squibb Oncology, Princeton, N.J.), chlorambucil, vincristine, vinblastine, anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (FARESTON, GTx, Memphis, TN), and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin, *etc.* Examples of chemotherapeutic agents that may be used in conjunction with the compounds of the invention are listed in

Table 3. In a preferred embodiment, the chemotherapeutic agent is one or more anthracyclines. Anthracyclines are a family of chemotherapy drugs that are also antibiotics. The anthracyclines act to prevent cell division by disrupting the structure of the DNA and terminate its function by: (1) intercalating into the base pairs in the DNA minor grooves; and (2) causing free radical damage of the ribose in the DNA. The anthracyclines are frequently used in leukemia therapy. Examples of anthracyclines include daunorubicin (CERUBIDINE), doxorubicin (ADRIAMYCIN, RUBEX), epirubicin (ELLENCE, PHARMORUBICIN), and idarubicin (IDAMYCIN).

10 Table 3. Examples of Chemotherapeutic Agents

- 13-cis-Retinoic Acid	- Mylocel
-2-Amino-6-Mercaptopurine	- Letrozole
	- Neosar
- 2-CdA	- Neulasta
- 2-Chlorodeoxyadenosine	- Neumega
- 5-fluorouracil	- Neupogen
- 5-FU	- Nilandron
- 6 - TG	- Nilutamide
- 6 - Thioguanine	- Nitrogen Mustard
- 6-Mercaptopurine	- Novaldex
- 6-MP	- Novantrone
- Accutane	- Octreotide
- Actinomycin-D	- Octreotide acetate
- Adriamycin	- Oncospar
- Adrucil	- Oncovin
- Agrylin	- Ontak
- Ala-Cort	- Onxal
- Aldesleukin	- Oprevelkin
- Alemtuzumab	- Orapred
- Alitretinoin	- Orasone

- Alkaban-AQ	- Oxaliplatin
- Alkeran	- Paclitaxel
- All-transretinoic acid	- Pamidronate
- Alpha interferon	- Panretin
- Altretamine	- Paraplatin
- Amethopterin	- Pediapred
- Amifostine	- PEG Interferon
- Aminoglutethimide	- Pegaspargase
- Anagrelide	- Pegfilgrastim
- Anandron	- PEG-INTRON
- Anastrozole	- PEG-L-asparaginase
- Arabinosylcytosine	- Phenylalanine Mustard
- Ara-C	- Platinol
- Aranesp	- Platinol-AQ
- Aredia	- Prednisolone
- Arimidex	- Prednisone
- Aromasin	- Prelone
- Arsenic trioxide	- Procarbazine
- Asparaginase	- PROCRIT
- ATRA	- Proleukin
- Avastin	- Prolifeprospan 20 with Carmustine implant
- BCG	- Purinethol
- BCNU	- Raloxifene
- Bevacizumab	- Rheumatrex
- Bexarotene	- Rituxan
- Bicalutamide	- Rituximab
- BiCNU	- Roveron-A (interferon alfa-2a)
- Blenoxane	- Rubex
- Bleomycin	- Rubidomycin hydrochloride
- Bortezomib	- Sandostatin

- Busulfan	- Sandostatin LAR
- Busulfex	- Sargramostim
- C225	- Solu-Cortef
- Calcium Leucovorin	- Solu-Medrol
- Campath	- STI-571
- Camptosar	- Streptozocin
- Camptothecin-11	- Tamoxifen
- Capecitabine	- Targretin
- Carac	- Taxol
- Carboplatin	- Taxotere
- Carmustine	- Temodar
- Carmustine wafer	- Temozolomide
- Casodex	- Teniposide
- CCNU	- TESPA
- CDDP	- Thalidomide
- CeeNU	- Thalomid
- Cerubidine	- TheraCys
- cetuximab	- Thioguanine
- Chlorambucil	- Thioguanine Tabloid
- Cisplatin	- Thiophosphoamide
- Citrovorum Factor	- Thioplex
- Cladribine	- Thiotepa
- Cortisone	- TICE
- Cosmegen	- Toposar
- CPT-11	- Topotecan
- Cyclophosphamide	- Toremifene
- Cytadren	- Trastuzumab
- Cytarabine	- Tretinoin
- Cytarabine liposomal	- Trexall
- Cytosar-U	- Trisenox

- Cytosan	- TSPA
- Dacarbazine	- VCR
- Dactinomycin	- Velban
- Darbepoetin alfa	- Velcade
- Daunomycin	- VePesid
- Daunorubicin	- Vesanoid
- Daunorubicin hydrochloride	- Viadur
- Daunorubicin liposomal	- Vinblastine
- DaunoXome	- Vinblastine Sulfate
- Decadron	- Vincasar Pfs
- Delta-Cortef	- Vincristine
- Deltasone	- Vinorelbine
- Denileukin diftitox	- Vinorelbine tartrate
- DepoCyt	- VLB
- Dexamethasone	- VP-16
- Dexamethasone acetate	- Vumon
- dexamethasone sodium phosphate	- Xeloda
- Dexasone	- Zanosar
- Dexrazoxane	- Zevalin
- DHAD	- Zinecard
- DIC	- Zoladex
- Diodex	- Zoledronic acid
- Docetaxel	- Zometa
- Doxil	- Gliadel wafer
- Doxorubicin	- Glivec
- Doxorubicin liposomal	- GM-CSF
- Droxia	- Goserelin
- DTIC	- granulocyte - colony stimulating factor
	- Granulocyte macrophage colony stimulating factor

- DTIC-Dome	- Halotestin
- Duralone	- Herceptin
- Efudex	- Hexadrol
- Eligard	- Hexalen
- Ellence	- Hexamethylmelamine
- Eloxatin	- HMM
- Elspar	- Hycamtin
- Emcyt	- Hydrea
- Epirubicin	- Hydrocort Acetate
- Epoetin alfa	- Hydrocortisone
- Erbitux	- Hydrocortisone sodium phosphate
- Erwinia L-asparaginase	- Hydrocortisone sodium succinate
- Estramustine	- Hydrocortone phosphate
- Ethyol	- Hydroxyurea
- Etopophos	- Ibritumomab
- Etoposide	- Ibritumomab Tiuxetan
- Etoposide phosphate	- Idamycin
- Eulexin	- Idarubicin
- Evista	- Ifex
- Exemestane	- IFN-alpha
- Fareston	- Ifosfamide
- Faslodex	- IL - 2
- Femara	- IL-11
- Filgrastim	- Imatinib mesylate
- Floxuridine	- Imidazole Carboxamide
- Fludara	- Interferon alfa
- Fludarabine	- Interferon Alfa-2b (PEG conjugate)
- Fluoroplex	- Interleukin - 2
- Fluorouracil	- Interleukin-11
- Fluorouracil (cream)	- Intron A (interferon alfa-2b)

- Fluoxymesterone	- Leucovorin
- Flutamide	- Leukeran
- Folinic Acid	- Leukine
- FUDR	- Leuprolide
- Fulvestrant	- Leurocristine
- G-CSF	- Leustatin
- Gefitinib	- Liposomal Ara-C
- Gemcitabine	- Liquid Pred
- Gemtuzumab ozogamicin	- Lomustine
- Gemzar	- L-PAM
- Gleevec	- L-Sarcolysin
- Lupron	- Meticorten
- Lupron Depot	- Mitomycin
- Matulane	- Mitomycin-C
- Maxidex	- Mitoxantrone
- Mechlorethamine	- M-Prednisol
-Mechlorethamine Hydrochlorine	- MTC
	- MTX
- Medralone	- Mustargen
- Medrol	- Mustine
- Megace	- Mutamycin
- Megestrol	- Myleran
- Megestrol Acetate	- Iressa
- Melphalan	- Irinotecan
- Mercaptopurine	- Isotretinoin
- Mesna	- Kidrolase
- Mesnex	- Lanacort
- Methotrexate	- L-asparaginase
- Methotrexate Sodium	- LCR
- Methylprednisolone	

As used herein, the term “tumor” refers to all neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues. For example, a particular cancer may be characterized by a solid tumor mass. A primary tumor mass refers to a growth of cancer cells in a tissue resulting from the transformation of a normal cell of that tissue. In most cases, the primary tumor mass is identified by the presence of a cyst, which can be found through visual or palpation methods, or by irregularity in shape, texture, or weight of the tissue. However, some primary tumors are not palpable and can be detected only through medical imaging techniques such as X-rays (e.g., mammography), or by needle aspirations. The use of these latter techniques is more common in early detection. Molecular and phenotypic analysis of cancer cells within a tissue will usually confirm if the cancer is endogenous to the tissue or if the lesion is due to metastasis from another site. The compounds of the invention are capable of inducing apoptosis in tumor cells and reducing tumor cell growth. The compounds of the invention can be administered locally at the site of a tumor (e.g., by direct injection) or remotely. The compounds of the invention can induce cell death in circulating tumor cells (CTC) in a subject, e.g., by administering the compounds intravenously. Furthermore, the compounds of the invention can prevent or reduce onset of metastasis to other tissues, e.g., to the bone.

As used herein, the term “signaling” and “signaling transduction” represents the biochemical process involving transmission of extracellular stimuli, via cell surface receptors through a specific and sequential series of molecules, to genes in the nucleus resulting in specific cellular responses to the stimuli.

As used herein, the term “pharmaceutically acceptable salt or prodrug” is intended to describe any pharmaceutically acceptable form (such as an ester, phosphate ester, salt of an ester or a related group) of a compound of the invention or other agent, which, upon administration to a subject, provides the mature or base compound. Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids. Suitable salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium and magnesium, among numerous other acids well known in the pharmaceutical art. Pharmaceutically acceptable prodrugs refer to a compound that is metabolized, for example hydrolyzed or oxidized, in the host to form the compound of the present invention. Typical examples of prodrugs

include compounds that have biologically labile protecting groups on a functional moiety of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated to
5 produce the active compound.

The terms “link” or “join” refers to any method known in the art for functionally connecting peptides, including, without limitation, recombinant fusion, covalent bonding, disulfide bonding, ionic bonding, hydrogen bonding, and electrostatic bonding.

The terms “comprising”, “consisting of” and “consisting essentially of” are
10 defined according to their standard meaning. The terms may be substituted for one another throughout the instant application in order to attach the specific meaning associated with each term.

The terms “isolated” or “biologically pure” refer to material that is substantially or essentially free from components which normally accompany the material as it is found in
15 its native state. Thus, compounds in accordance with the invention preferably do not contain materials normally associated with the peptides in their *in situ* environment.

As used in this specification, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to “a compound” includes more than one such compound. A reference to “a cell” includes
20 more than one such cell, and so forth.

The practice of the present invention can employ, unless otherwise indicated, conventional techniques of molecular biology, microbiology, recombinant DNA technology, electrophysiology, and pharmacology that are within the skill of the art. Such techniques are explained fully in the literature (see, *e.g.*, Sambrook, Fritsch & Maniatis, *Molecular Cloning: A Laboratory Manual*, Second Edition (1989); DNA Cloning, Vols. I and II (D. N. Glover Ed. 1985); Perbal, B., *A Practical Guide to Molecular Cloning* (1984); the series, *Methods In Enzymology* (S. Colowick and N. Kaplan Eds., Academic Press, Inc.); *Transcription and Translation* (Hames *et al.* Eds. 1984); *Gene Transfer Vectors For Mammalian Cells* (J. H. Miller *et al.* Eds. (1987) Cold Spring Harbor
25 Laboratory, Cold Spring Harbor, N.Y.); *Scopes, Protein Purification: Principles and Practice* (2nd ed., Springer-Verlag); and *PCR: A Practical Approach* (McPherson *et al.*
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Eds. (1991) IRL Press)), each of which are incorporated herein by reference in their entirety.

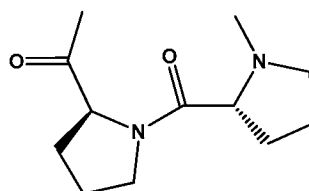
Experimental controls are considered fundamental in experiments designed in accordance with the scientific method. It is routine in the art to use experimental controls in scientific experiments to prevent factors other than those being studied from affecting the outcome.

Exemplified Embodiments

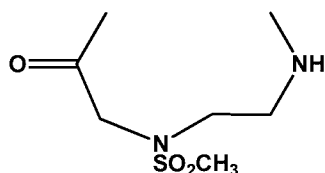
Examples of claimed embodiments of the invention include, but are not limited to:

Embodiment 1. A cyclic compound, comprising a recognition sequence and a non-recognition sequence, wherein said recognition sequence comprises at least four amino acids, wherein said non-recognition sequence comprises at least four amino acids, and wherein said recognition sequence is joined to said non-recognition sequence by a first linker and a second linker, wherein said first linker and said second linker are

independently selected from the structures:

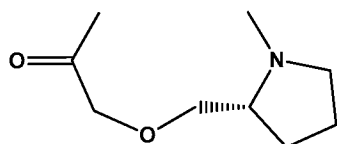


(D-Pro-L-Pro);

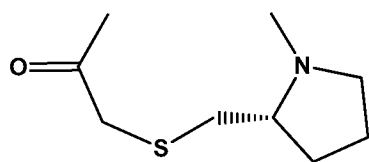


(methylsulfonamido

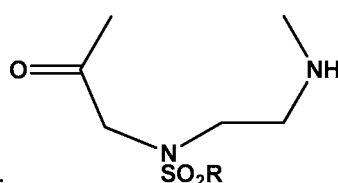
aminoethylglycine);



((pyrrolidin-2-ylmethoxy)acetate),



((pyrrolidin-2-

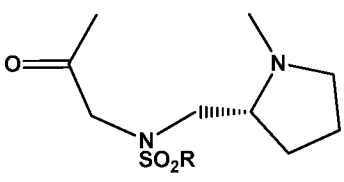


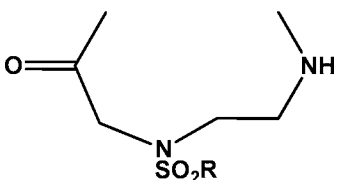
ylmeththiyl)acetate);

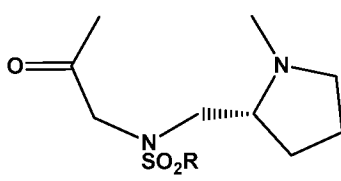
(substituted

sulfonamide

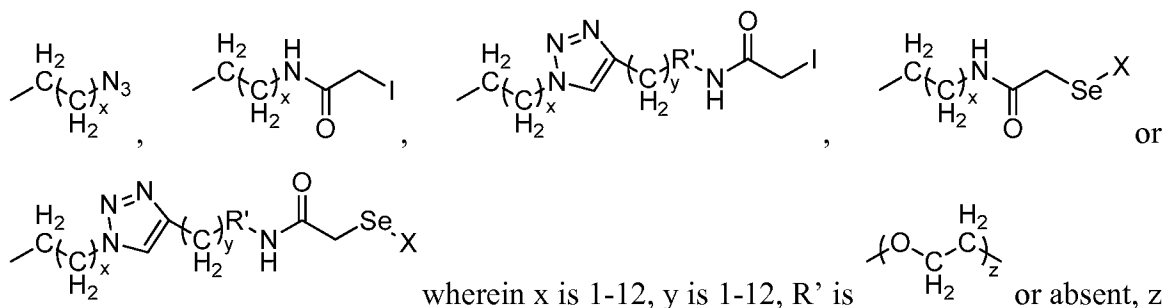
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aminoethylglycine); or  wherein R is a substituted or unsubstituted C₂-C₃₀ alkyl, aryl, alkylaryl, or arylalkyl group; wherein at least one of said

first linker and said second linker is, , or

 (N-(pyrrolidin-2-ylmethyl substituted sulfamido glycine), ,

5 wherein at least one R is:



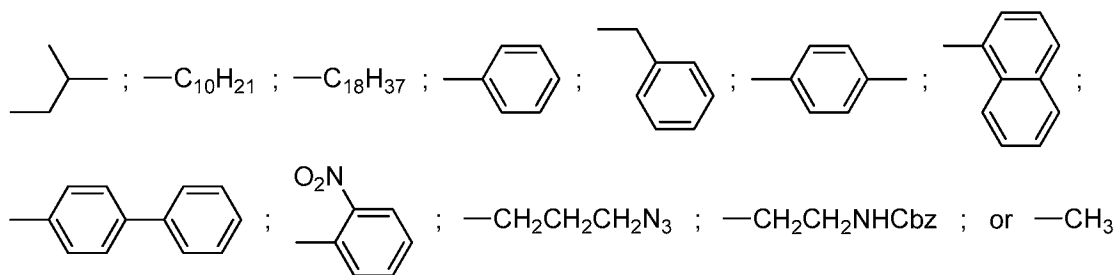
Embodiment 2. The cyclic compound of embodiment 1, wherein said non-
 10 recognition sequence is five amino acids selected from KLQLK (SEQ ID NO:1), QLKLK (SEQ ID NO:2), KQKLK (SEQ ID NO:3), KXXKXK (SEQ ID NO:4), or ELKLK (SEQ ID NO:5) wherein X = sarcosine and the recognition sequence is five amino acids selected from WAVAW (SEQ ID NO:6), WAVAA (SEQ ID NO:7), WAVAM (SEQ ID NO:8), WAVAN* (SEQ ID NO:9), WAVVN* (SEQ ID NO:10), WAVSN* (SEQ ID NO:11), WAAAW (SEQ ID NO:12), WAAAA (SEQ ID NO:13), WAAAM (SEQ ID NO:14), WAAAN* (SEQ ID NO:15), WAAVW (SEQ ID NO:16), WAAVA (SEQ ID NO:17), WAAVM (SEQ ID NO:18), WAAVN* (SEQ ID NO:19), WAASN* (SEQ ID NO:20), WVVAW (SEQ ID NO:21), WVVAA (SEQ ID NO:22), WVVAM (SEQ ID NO:23), WVVAN* (SEQ ID NO:24), WVVVW (SEQ ID NO:25), WVVVA (SEQ ID NO:26), WVVVM (SEQ ID NO:27), WVVVN* (SEQ ID NO:28), WVVSN* (SEQ ID NO:29), WVAAN* (SEQ ID NO:30), WVAVW (SEQ ID NO:31), WVAVA (SEQ ID

NO:32), WVAVM (SEQ ID NO:33), WVAVN* (SEQ ID NO:34), WVASN* (SEQ ID NO:35), WSVAW (SEQ ID NO:36), WSVAA (SEQ ID NO:37), WSVAM (SEQ ID NO:38), WSVAN* (SEQ ID NO:39), WSVVW (SEQ ID NO:40), WSVVA (SEQ ID NO:41), WSVVM (SEQ ID NO:42), WSVVN* (SEQ ID NO:43), WSVSW (SEQ ID NO:44), WSVSA (SEQ ID NO:45), WSVSM (SEQ ID NO:46), WSVSN* (SEQ ID NO:47), WSAAW (SEQ ID NO:48), WSAVA (SEQ ID NO:49), WSAAM (SEQ ID NO:50), WSAAN* (SEQ ID NO:51), WSAVW (SEQ ID NO:52), WSAVA (SEQ ID NO:53), WSAVM (SEQ ID NO:54), WSAVN* (SEQ ID NO:55), WSASW (SEQ ID NO:56), WSASA (SEQ ID NO:57), WSASM (SEQ ID NO:58), WSASN* (SEQ ID NO:59), WYVAW (SEQ ID NO:60), WYVAA (SEQ ID NO:61), WYVAM (SEQ ID NO:62), WYVAN* (SEQ ID NO:63), WYVVW (SEQ ID NO:64), WYVVA (SEQ ID NO:65), WYVVM (SEQ ID NO:66), WYVVN* (SEQ ID NO:67), WYVSW (SEQ ID NO:68), WYVSA (SEQ ID NO:69), WYVSM (SEQ ID NO:70), WYVSN* (SEQ ID NO:71), WYAAW (SEQ ID NO:72), WYAAA (SEQ ID NO:73), WYAAM (SEQ ID NO:74), WYAAN* (SEQ ID NO:75), WYAVW (SEQ ID NO:76), WYAVA (SEQ ID NO:77), WYAVM (SEQ ID NO:78), WYAVN* (SEQ ID NO:79), WYASW (SEQ ID NO:80), WYASA (SEQ ID NO:81), WYASM (SEQ ID NO:82), WYASN* (SEQ ID NO:83), AAVAA (SEQ ID NO:84), AAVAM (SEQ ID NO:85), AAVAN* (SEQ ID NO:86), AAVVN* (SEQ ID NO:87), AAVSN* (SEQ ID NO:88), AAAAA (SEQ ID NO:89), AAAAM (SEQ ID NO:90), AAAAN* (SEQ ID NO:91), AAAVW (SEQ ID NO:92), AAAVA (SEQ ID NO:93), AAAVM (SEQ ID NO:94), AAAVN* (SEQ ID NO:95), AAASM (SEQ ID NO:96), AAASN* (SEQ ID NO:97), AVVAW (SEQ ID NO:98), AVVAA (SEQ ID NO:99), AVVAM (SEQ ID NO:100), AVVAN* (SEQ ID NO:101), AVVVA (SEQ ID NO:102), AVVVM (SEQ ID NO:103), AVVVN* (SEQ ID NO:104), AVVSN* (SEQ ID NO:105), AVAAW (SEQ ID NO:106), AVAAM (SEQ ID NO:107), AVAAN* (SEQ ID NO:108), AVAVA (SEQ ID NO:109), AVAVM (SEQ ID NO:110), AVAVN* (SEQ ID NO:111), AVASN* (SEQ ID NO:112), ASVAW (SEQ ID NO:113), ASVAA (SEQ ID NO:114), ASVAM (SEQ ID NO:115), ASVAN* (SEQ ID NO:116), ASVVW (SEQ ID NO:117), ASVVA (SEQ ID NO:118), ASVVM (SEQ ID NO:119), ASVVN* (SEQ ID NO:120), ASVSA (SEQ ID NO:121), ASVSM (SEQ ID NO:122), ASVSN* (SEQ ID NO:123), ASAAW (SEQ ID NO:124), ASAAA (SEQ ID NO:125), ASAAM (SEQ ID NO:126), ASAAAN* (SEQ ID NO:127), ASAVW (SEQ ID

NO:128), ASAVA (SEQ ID NO:129), ASAVM (SEQ ID NO:130), ASAVN* (SEQ ID
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 NO:137), AYVAN* (SEQ ID NO:138), AYVVW (SEQ ID NO:139), AYVVA (SEQ ID
 5 NO:140), AYVVM (SEQ ID NO:141), AYVVN* (SEQ ID NO:142), AYVSW (SEQ ID
 NO:143), AYVSA (SEQ ID NO:144), AYVSM (SEQ ID NO:145), AYVSN* (SEQ ID
 NO:146), AYAAW (SEQ ID NO:147), AYAAA (SEQ ID NO:148), AYAAAM (SEQ ID
 NO:149), AYAAAN* (SEQ ID NO:150), AYAVW (SEQ ID NO:151), AYAVA (SEQ ID
 NO:152), AYAVM (SEQ ID NO:153), AYAVN* (SEQ ID NO:154), AYASW (SEQ ID
 10 NO:155), AYASA (SEQ ID NO:156), AYASM (SEQ ID NO:157), AYASN* (SEQ ID
 NO:158), MAVAA (SEQ ID NO:159), MAVAM (SEQ ID NO:160), MAVAN* (SEQ ID
 NO:161), MAVVN* (SEQ ID NO:162), MAVSN* (SEQ ID NO:163), MAAAA (SEQ
 ID NO:164), MAAAM (SEQ ID NO:165), MAAAN* (SEQ ID NO:166), MAAVW
 (SEQ ID NO:167), MAAVA (SEQ ID NO:168), MAAVM (SEQ ID NO:169), MAAVN*
 15 (SEQ ID NO:170), MAASN* (SEQ ID NO:171), MVVAW (SEQ ID NO:172), MVVAA
 (SEQ ID NO:173), MVVAM (SEQ ID NO:174), MVVAN* (SEQ ID NO:175),
 MVVVM (SEQ ID NO:176), MVVVN* (SEQ ID NO:177), MVVSN* (SEQ ID
 NO:178), MVAAM (SEQ ID NO:179), MVAAN* (SEQ ID NO:180), MVAVM (SEQ
 ID NO:181), MVAVN* (SEQ ID NO:182), MVASN* (SEQ ID NO:183), MSVAW
 20 (SEQ ID NO:184), MSVAA (SEQ ID NO:185), MSVAM (SEQ ID NO:186), MSVAN*
 (SEQ ID NO:187), MSVVW (SEQ ID NO:188), MSVVA (SEQ ID NO:189), MSVVM
 (SEQ ID NO:190), MSVVN* (SEQ ID NO:191), MSVSM (SEQ ID NO:192), MSVSN*
 (SEQ ID NO:193), MSAAW (SEQ ID NO:194), MSAAA (SEQ ID NO:195), MSAAM
 (SEQ ID NO:196), MSAAN* (SEQ ID NO:197), MSAVW (SEQ ID NO:198), MSAVA
 25 (SEQ ID NO:199), MSAVM (SEQ ID NO:200), MSAVN* (SEQ ID NO:201), MSASM
 (SEQ ID NO:202), MSASN* (SEQ ID NO:203), MYVAW (SEQ ID NO:204), MYVAA
 (SEQ ID NO:205), MYVAM (SEQ ID NO:206), MYVAN* (SEQ ID NO:207),
 MYVVW (SEQ ID NO:208), MYVVA (SEQ ID NO:209), MYVVM (SEQ ID NO:210),
 MYVVN* (SEQ ID NO:211), MYVSW (SEQ ID NO:212), MYVSA (SEQ ID NO:213),
 30 MYVSM (SEQ ID NO:214), MYVSN* (SEQ ID NO:215), MYAAW (SEQ ID NO:216),
 MYAAA (SEQ ID NO:217), MYAAM (SEQ ID NO:218), MYAAN* (SEQ ID NO:219),
 MYAVW (SEQ ID NO:220), MYAVA (SEQ ID NO:221), MYAVM (SEQ ID NO:222),

MYAVN* (SEQ ID NO:223), MYASW (SEQ ID NO:224), MYASA (SEQ ID NO:225), MYASM (SEQ ID NO:226), or MYASN* (SEQ ID NO:227), wherein N* = norleucine, and wherein either end of said recognition sequence can be a N-terminus.

Embodiment 3. The cyclic compound of embodiment 1, wherein one R is:



5

Embodiment 4. The cyclic compound of embodiment 1, wherein R is H, C₁-C₃₀ alkyl, C₂-C₃₀ alkenyl, C₂-C₃₀ alkynyl, C₆-C₁₄ aryl, C₇-C₃₀ arylalkyl, C₈-C₃₀ arylalkenyl, C₈-C₃₀ arylalkynyl, hydroxy, C₁-C₃₀ alkoxy, C₆-C₁₄ aryloxy, C₇-C₃₀ arylalkyloxy, C₂-C₃₀ alkenyloxy, C₂-C₃₀ alkynyloxy, C₈-C₃₀ arylalkenyloxy, C₈-C₃₀ arylalkynyloxy, CO₂H, C₂-C₃₀ alkylester, C₇-C₁₅ ary-lester, C₈-C₃₀ alkylarylester, C₃-C₃₀ alkenylester, C₃-C₃₀ alkynylester, NH₂, C₁-C₃₀ alkylamino, C₆-C₁₄ arylamino, C₇-C₃₀ (arylalkyl)amino, C₂-C₃₀ alkenylamino, C₂-C₃₀ alkynylamino, C₈-C₃₀ (arylalkenyl)amino, C₈-C₃₀ (arylalkynyl)amino, C₂-C₃₀ dialkylamino, C₁₂-C₂₈ diarylamino, C₄-C₃₀ dialkenylamino, C₄-C₃₀ dialkynylamino, C₇-C₃₀ aryl(alkyl)amino, C₇-C₃₀ di(arylalkyl)amino, C₈-C₃₀ alkyl(arylalkyl)amino, C₁₅-C₃₀ aryl(arylalkyl)amino, C₈-C₃₀ alkenyl(aryl)amino, C₈-C₃₀ alkynyl(aryl)amino, C(O)NH₂ (amido), C₂-C₃₀ alkylamido, C₇-C₁₄ arylamido, C₈-C₃₀ (arylalkyl)amido, C₂-C₃₀ dialkylamido, C₁₂-C₂₈ diarylamido, C₈-C₃₀ aryl(alkyl)amido, C₁₅-C₃₀ di(arylalkyl)amido, C₉-C₃₀ alkyl(arylalkyl)amido, C₁₆-C₃₀ aryl(arylalkyl)amido, thiol, C₁-C₃₀ hydroxyalkyl, C₆-C₁₄ hydroxyaryl, C₇-C₃₀ hydroxyarylalkyl, C₃-C₃₀ hydroxyalkenyl, C₃-C₃₀ hydroxyalkynyl, C₈-C₃₀ hydroxyarylalkenyl, C₈-C₃₀ hydroxyarylalkynyl, C₃-C₃₀ polyether, C₃-C₃₀ polyetherester, C₃-C₃₀ polyester, C₃-C₃₀ polyamino, C₃-C₃₀ polyaminoamido, C₃-C₃₀ polyaminoether, C₃-C₃₀ polyaminoester, C₃-C₃₀ polyamidoester, C₃-C₃₀ alkylsulfonic acid, C₃-C₃₀ alkylsulfonate salt, C₁-C₃₀ carboxylate salt, C₁-C₃₀ thiocarboxylate salt, C₁-C₃₀ dithiocarboxylate salt, or C₃-C₃₀ alkylC₁-C₄ trialkylammonium salt, wherein any carbon can be further substituted with any carbon can be substituted with a hydroxy, chloro, bromo, iodo, nitro, or carboxylic acid.

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Embodiment 5. The cyclic compound of any preceding embodiment, wherein said carrying agent comprises an amino acid, oligo(amino acid), poly(amino acid) or protein.

Embodiment 6. The cyclic compound of any preceding embodiment, wherein said carrying agent comprises an antibody, or an Fc portion of an antibody, or an antigen-binding fragment of an antibody.

Embodiment 7. The cyclic compound of any preceding embodiment, wherein said carrying agent is a monoclonal antibody (mAb), or an Fc portion of a mAb, or an antigen binding fragment of a mAb, comprising a selenocysteine residue.

Embodiment 8. The cyclic compound of any preceding embodiment, wherein said carrying agent is a monoclonal antibody (mAb), or an Fc portion of a mAb, or antigen binding fragment of a mAb, comprising a C-terminal selenocysteine residue.

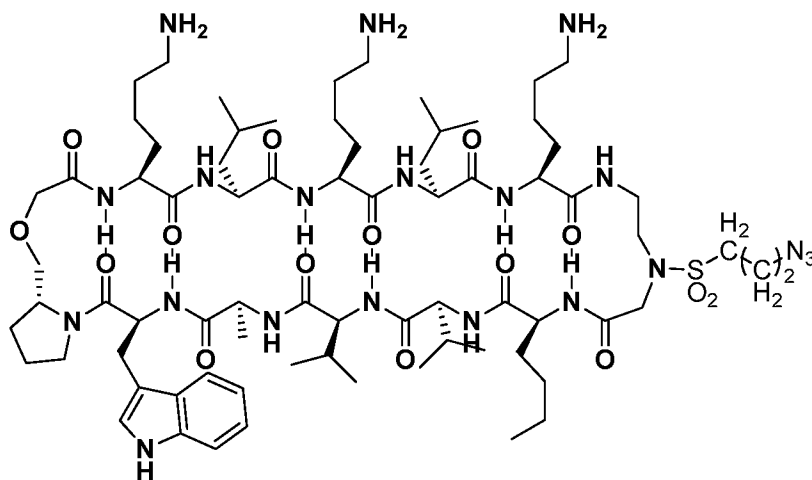
Embodiment 9. The cyclic compound of any preceding embodiment, wherein said carrying agent specifically binds to a cell surface antigen.

Embodiment 10. The cyclic compound of any preceding embodiment, wherein said carrying agent specifically binds to a tumor associated antigen.

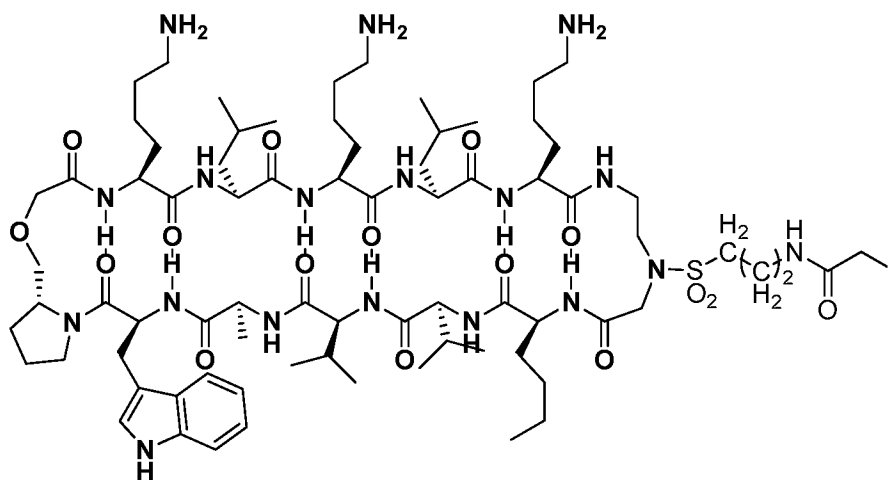
Embodiment 11. The cyclic compound of any preceding embodiment, wherein said carrying agent specifically binds to one or more antigens selected from among CD138, CD44, alpha4 integrin, alpha3 integrin, alpha6 integrin, EGFR, tumor suppressor cell antigen, cytotoxic T cell antigen, 17-1A, 707-AP, AFP, Annexin II, ART-4, BAGE, BAGE-1, β -catenin, BCG, bcr/abl, Bcr/abl e14a2 fusion junction, bcr-abl (b3a2), bcr-abl (b3a2), bcr-abl p190 (e1a2), bcr-abl p210 (b2a2), bcr-abl p210 (b3a2), bcr-abl p210 (b3a2), bullous pemphigoid antigen-1, CA19-9, CA125, CA215, CAG-3, CAMEL, Cancer-testis antigen, Caspase-8, CCL3, CCL4, CD16, CD20, CD3, CD30, CD55, CD63, CDC27, CDK-4, CDR3, CEA, cluster 5, cluster-5A, cyclin-dependent kinase-4, Cyp-B, DAM-10, DAM-6, Dek-cain, E7, EGFRvIII, EGP40, ELF2 M, EpCAM, FucGM1, G250, GA733, GAGE, GAGE-1-8, gastrin cancer associated antigen, GD2, GD3, globoH, glycophorin, GM1, GM2, GM3, GnTV, Gn-T-V, gp100, Her-2/neu, HERV-K-ME, high molecular weight-associated antigen, high molecular weight proteo-glycan (HMPG), HPV-16 E6, HPV-16 E7, HPVE6, HSP70-2M, HST-2, hTERT, human chorionic gonadotropin (HCG), Human milk fat globule (HMFG), iCE, KIAA0205, KK-LC-1, KM-HN-1, L6, LAGE-1, Lcose4Cer, LDLR/FUT, Lewis A, Lewis v/b, M protein, MAGE-1, MVC, MAGE-A1-12, MAGE-C2, MAHGE-3, MART-1/Melan-A, MC1R,

ME491, MUC1, MUC2, mucin, MUM-1, MUM-2, MUM-3, mutated p53, Myosin, MZ2-E, N9 neuraminidase, NA88, NA88-A, nasopharyngeal carcinoma antigen, NGA, NK1/c-3, Novel bcr/ablk fusion BCR exons 1, 13, 14 with ABL exons 4, NY-ESO-1/LAGE-2, NY-ESO-1b, OC125, osteosarcoma associated antigen-1, P15, p190 mimor bcr-abl
 5 (c1a2), p53, Pml/RAR α , Polysialic acid, PRAME, PSA, PSM, RU1, RU2, SAGE, SART-1, SART-2, SART-3, Sialyl LeA, Sp17, SSX-2, SSX-4, surface immunoglobulin, TAG-1, TAG-2, TEL/AML1, TPI, TRAG-3, TRP-1(gp75), TRP-2, TRP2-INT2, hTERT, tumor associated glycoprotein-72 (TAG-72), tyrosinase, u-PA, WT1, and XAGE-1b, or an immunogenic fragment of any of the foregoing antigens.

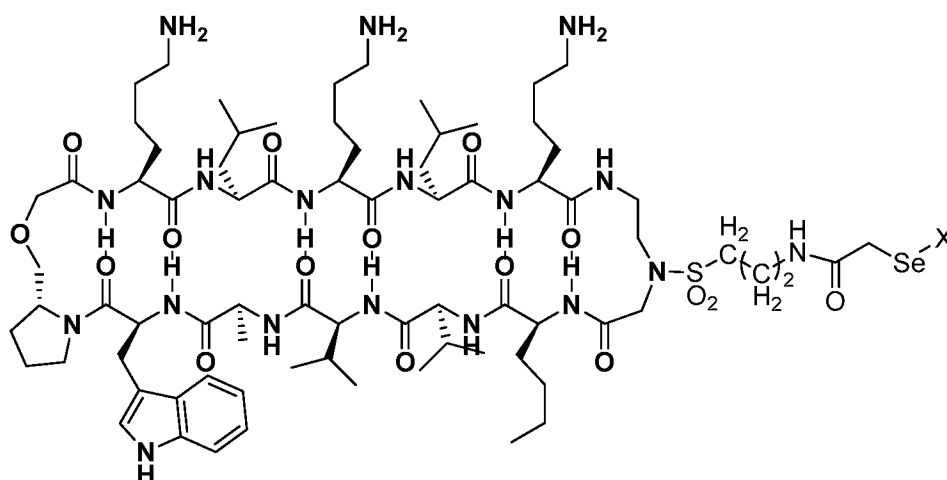
10 Embodiment 12. The cyclic compound of embodiment 1, wherein the structure is:



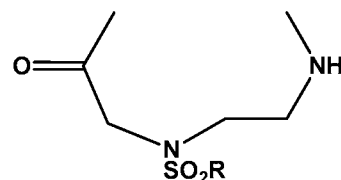
Embodiment 13. The cyclic compound of embodiment 1, wherein the structure is:



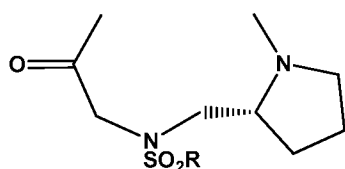
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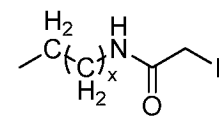
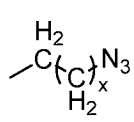
Embodiment 17. A linker, comprising:



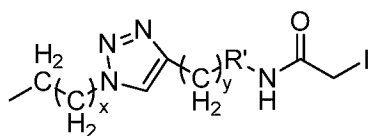
or



, wherein R is

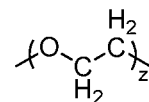


, or



5

, wherein x is 1-12, y is 1-12, R' is



and z is 1 to

20.

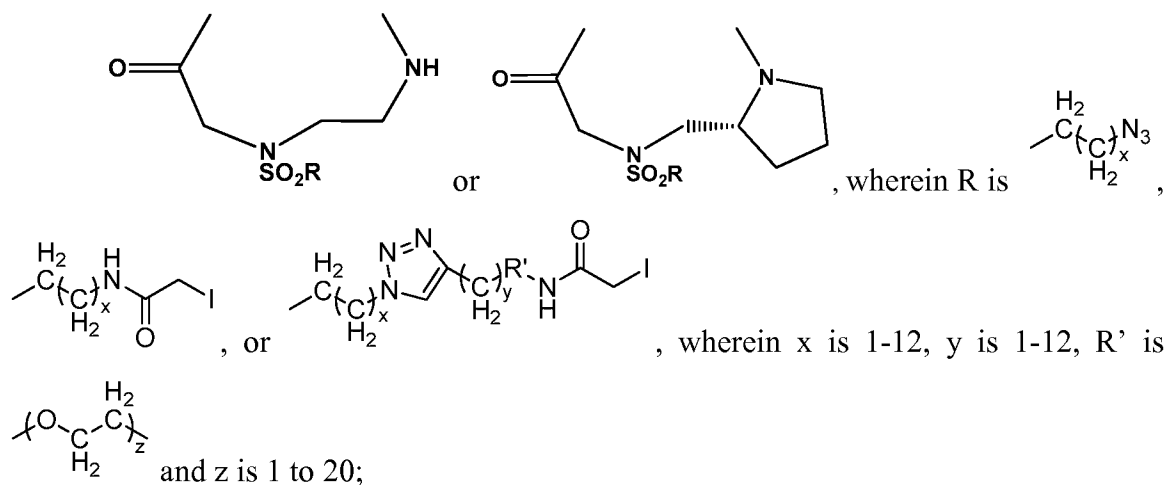
Embodiment 18. A method of preparing a carrying agent:cyclic compound adduct, comprising:

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providing a cyclic compound comprising a recognition sequence and a non-recognition sequence, wherein said recognition sequence comprises at least four amino acids, wherein said non-recognition sequence comprises at least four amino acids, and wherein said recognition sequence is joined to said non-recognition sequence by a first linker and a second linker, wherein at least one of said first linker and said second linker is:

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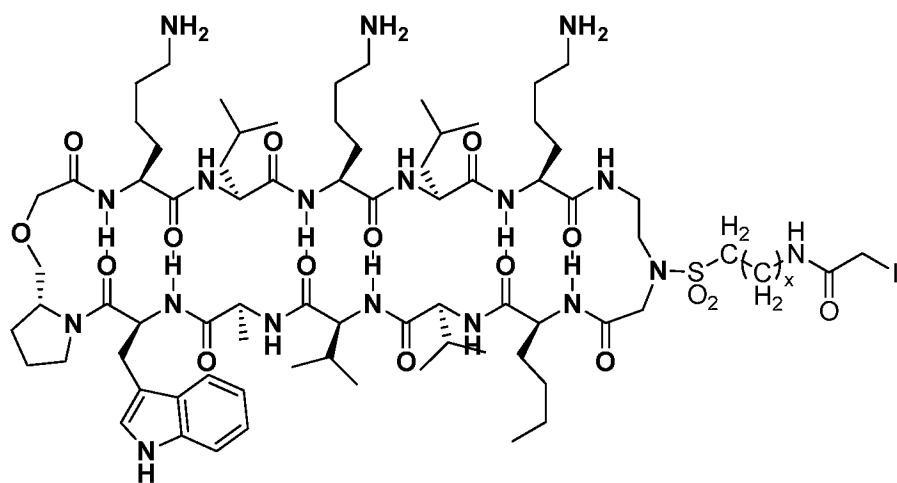


- providing a carrying agent X comprising a selenocysteine residue; and
 5 combining said carrying agent and said cyclic compound in an aqueous solution.

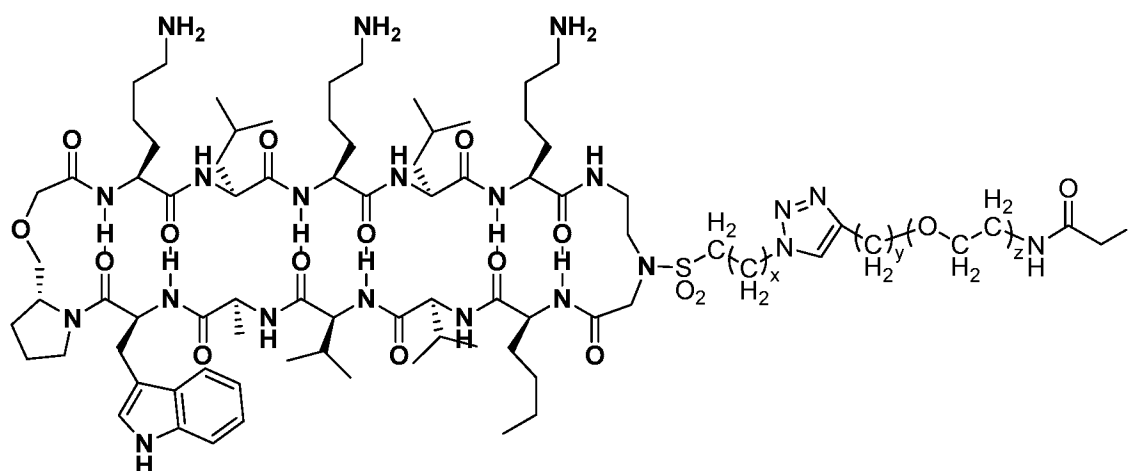
Embodiment 19. The method of preparing a carrying agent:cyclic compound adduct of embodiment 18, wherein said aqueous solution comprises dithiothreitol (DTT)
 10 and wherein said aqueous solution has an acidic pH.

Embodiment 20. The method of preparing a carrying agent:cyclic compound adduct of embodiment 19, wherein said pH is 4-6 and the concentration of DTT is 0.1-1 mM.

Embodiment 21. The method of preparing a carrying agent:cyclic compound
 15 adduct of claim 18, wherein the cyclic compound comprises:



68



wherein x is 1-12, y is 1-12, and z is 1.

Embodiment 22. The method of preparing a carrying agent:cyclic compound adduct according to embodiment 18, wherein the carrying agent comprises an

oligo(amino acid), poly(amino acid) or protein comprising a selenocysteine residue

Embodiment 23. The method of preparing a carrying agent:cyclic compound adduct according to embodiment 18, wherein said carrying agent X is a monoclonal antibody (mAb) comprising a selenocysteine residue

Embodiment 24. The method of preparing a carrying agent:cyclic compound adduct according to embodiment 18, wherein said carrying agent X is the modified antibody Fc-Sec-His having the sequence:

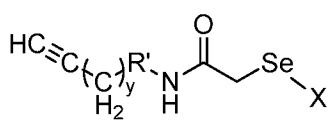
EPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDP
 EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
 SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV
 EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
 NHYTQKSLSLSPGAUHHHHHH (SEQ ID NO:228) where U is the single letter amino acid code for selenocysteine.

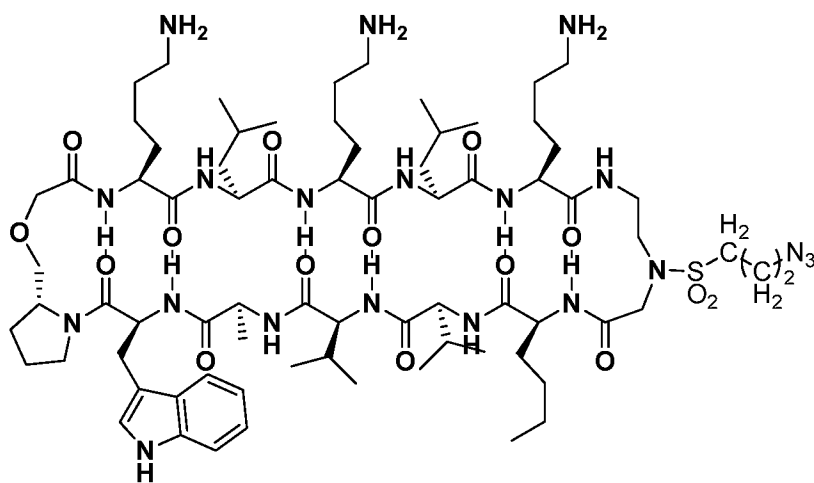
Embodiment 25. The method of preparing a carrying agent:cyclic compound adduct according to embodiment 18, wherein said carrying agent X is a targeting agent that is the modified antibody Anti-CD138-scFv-Fc-Sec-His having the sequence:

DIQMTQSTSSLSASLGDRVTISCSASQGINNYLNWYQQKPDGTVELLIYYTSTLQS
 GVPSRFSGSGSGTDYSLTISNLEPEDIGTYICQQYSKLPRTFGGGTKLEIKGGGGS
 GGGGSGGGGSQVQLQQSGSELMMPGASVKISKATGYTFSNYWIEWVKQRPGH

GLEWIGEILPGTGRTIYNEKFKGKATFTADISSNTVQMQLSSLTSEDSAVYYCARR
 DYYGNFYAMDYWGQGTSTVVSSEPKSSDKTHTCPPCPAPPELLGGPSVFLFPPKP
 KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
 RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR
 5 DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKL
 TVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGAUHHHHHHH (SEQ ID
 NO:229) where U is the single letter amino acid code for selenocysteine.

Embodiment 26. The method of preparing a carrying agent agent:cyclic
 10 compound adduct according to embodiment 18, wherein said carrying agent X comprises

a residue of selenocysteine having a  and wherein said cyclic
 compound comprises:



15 Embodiment 27. A method for treating a disorder in a subject, comprising
 administering an effective amount of a cyclic compound of any one of embodiments 1 to
 16 to the subject.

Embodiment 28. The method of embodiment 27, wherein the subject is human.

Embodiment 29. The method of embodiment 27, wherein the disorder is a
 20 proliferation disorder, bone deficiency, or autoimmune disease.

Embodiment 30. The method of embodiment 28, wherein the proliferation
 disorder is myeloma or another malignancy.

Embodiment 31. The method of any one of embodiments 27 to 30, wherein the cyclic compound is administered in a composition further comprising a pharmaceutically acceptable carrier.

Embodiment 32. A method of suppressing the growth of, or inducing apoptosis
5 in, cells, comprising contacting the cells with an effective amount of a cyclic compound of any one of embodiments 1 to 16.

Embodiment 33. The method of embodiment 32, wherein the cyclic compound is in a composition further comprising a pharmaceutically acceptable carrier.

Embodiment 34. The method of embodiment 32 or 33, wherein said contacting is
10 carried out *in vivo*.

Embodiment 35. The method of any one of embodiments 32 to 34, wherein the cells are human cells.

Embodiment 36. The method of any one of embodiments 32 to 35, wherein the cells are myeloma cells or other malignant cells.

Embodiment 37. A composition comprising a cyclic compound of any one of
15 embodiments 1 to 16; and a pharmaceutically acceptable carrier.

MATERIALS AND METHODS

Outline of Selenocysteine Monoclonal Antibody (mAb) Expression and Purification.

- 20 1. pCEP4-mAb (Fc, α CD138) containing vectors transfected into 293F (Fc only) and 293P (both) HEK cells with Lipofectamine 2000 reagent.
2. Cells cultured in protein-free Freestyle Expression 293 Medium and supplemented with 1 μ M Na₂ SeO₃
3. mAbs were collected (3x) every 3 days.
- 25 4. mAbs concentrated using 10-kDa cutoff ultrafiltration device under nitrogen gas.
5. mAbs purified via recombinant Protein G column and then IMAC HisTrap column.

SDS-PAGE Characterization.

- 30 1. 3 μ g, 20 μ l aliquots diluted in PBS. 1 μ l (v/v) 1% β -mercaptoethanol added to reducing samples
2. Loaded onto NuPAGE Novex Bis-Tris 4-12% gradient gel and stained with SimplyBlue SafeStain.

Binding Confirmation.

Incubations for APC fluorochrome analysis were 30 min for each antibody at rt followed by (2x) PBS washings.

5

All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

10

Following are examples that illustrate procedures for practicing the invention. These examples should not be construed as limiting. All percentages are by weight and all solvent mixture proportions are by volume unless otherwise noted.

Example 1—Production and Characterization of Cyclic Peptide Conjugates

15

Cloning and production of the antibodies were performed with designed expression cassettes in pCEP4 vector, which yielded approximately 2 mg of both Fc-Sec-His6 and scFv-Fc- α CD138 over a period of 3 weeks after a series of pilot studies. Utilizing the selective selenocysteine incorporation methodology (Figure 2), MTI-101 was conjugated to each antibody in a 1:1 DAR with >90% yield. The antibody drug conjugates (ADCs) were then further characterized by reduced and non-reduced SDS-PAGE to verify putative MTI-101 incorporation.

20

The inventors investigated the conjugation of an iodoacetamide derivative of MTI-101 (Figure 1) to two different carrier proteins; (i) the Fc fragment of human IgG1 and (ii) the scFv-Fc format of chimeric mouse/human monoclonal antibody (mAb) B-B4, which binds with high affinity and specificity to human CD138. Conjugate (i) constitutes a chemically programmed antibody (Rader, C., “Chemically programmed antibodies,” *Trends Biotechnol.*, 2014, 32, 186-197), in which the conventional antigen binding site is replaced with a synthetic component. Conjugate (ii) is a chemically programmed bispecific antibody with conventional (anti-CD138) and synthetic (anti-CD44) antigen binding sites.

25

30

As shown in Figures 16 and 17, mAbs and antibody fragments can be equipped with a C-terminal selenocysteine residue, the 21st natural amino acid with unique chemical properties, and stably and site-selectively conjugated to iodoacetamide

derivatives. Conditions for conjugation included a selenol pKa of about 5.2, which allows for selective conjugation in a 1:1 defined carrier:payload ratio. Compared to conventional cysteine and lysine conjugation technologies with heterogeneous drug-to-antibody ratios (DARs), defined DARs increase therapeutic indices, as these ADCs lack large batch-to-batch variability and the potential for undesired toxicity. Most importantly, this methodology provides a strategy to adjoin small molecules to mAbs and antibody fragments, which should increase the circulatory half-life of the small molecule owing to both increased size and FcRn-mediated recycling (Roopenian, D.C. and Akilesh, S., “FcRn: the neonatal Fc receptor comes of age”, *Nat Rev Immunol*, 2007,7, 715-725), and augment the potency of the small molecule by equipping it with the cytotoxic effector functions of the antibody molecule.

As described below, carrier protein Fc-Sec-His (Figure 16), was expressed and purified as described previously (Hofer, T., *et al.*, “An engineered selenocysteine defines a unique class of antibody derivatives”, *Proc Natl Acad Sci USA*, 2008, 105, 12451-12456), and analyzed by SDS-PAGE.

Purification of Fc-Sec-His was performed by tandem Protein G affinity chromatography and immobilized metal affinity chromatography (IMAC). Figure 3 shows the elution profile of Fc-Sec-His on a HisTrap column, which separates Fc-stop (without C-terminal selenocysteine) from Fc-Sec-His.

SDS-PAGE analysis of purified Fc-Sec-His and scFc-Fc-Sec-His was carried out before and after conjugation to MTI-101-iodoacetamide. The proteins and conjugates were separated on a NuPAGE Novex Bis-Tris 4-12% gradient gel. SimplyBlue SafeStain was used to visualize the protein bands. R, reduced with β -mercaptoethanol; NR, non-reduced. Both Fc-Sec-His (~55-kD dimer) and scFv-Fc-Sec-His (~110-kD dimer) reveal the expected sizes. A slight shift is noticeable after conjugation of MTI-101-Iodoacetamide (1.7 kDa), as shown in Figure 5.

Next, the inventors confirmed the binding of the Fc-Sec-His/MTI-101 conjugate to the cell surface of human MM cell lines U266 and H929 by flow cytometry (Figures 6A-6B), demonstrating successful chemical programming. APC flow cytometry (FCM) and human-CD44 ELISA were employed to confirm mono-affinity of Fc-Sec/MTI-101 to CD44. Further APC-FCM and human-CD138 ELISA data confirmed strong mono-affinity of the α CD138 ADC to CD138.

Due to the dual expression of CD44 and CD138 on the myeloma cell surface, demonstrating successful chemical programming of the scFv-Fc-Sec/MTI-101 conjugate by flow cytometry is complicated. However, the inventors showed that both anti-CD138-scFv-Fc-Sec-His and anti-CD138- scFv-Fc-Sec-His/MTI-101 bound equally well to the cell surface of human MM cell lines U266 and H929, which express CD138 at high cell surface densities (Figures 8A-8B). Thus, conjugated MTI-101 does not interfere with CD138 binding. The development of suitable assays demonstrating simultaneous binding of anti-CD138-scFv-Fc-Sec-His/MTI-101 to CD138 and CD44 is ongoing.

Despite inconclusive bivalent data from Figures 6A-6B, Figure 11 demonstrates cross-coupling and death of H929 cells analogously to MTI-101 but not the STOP mAb, strongly suggesting dual targeting *in vitro*. It is possible that the large relative size and mass of scFv-Fc- α CD138 against MTI-101 (110 vs. 1.7 kDa) induces steric hindrance from CD44 binding when plated in ELISA.

Significant *in vitro* killing of MM cell lines was shown in the 15-36 μ M range for both ADCs using FCM FSC-A/SSC-A and digital microscopy. When overlaid with free MTI-101 and the iodoacetamide adduct titration data, the ADCs demonstrate increased potency via conjugation. Specifically, the inventors tested the cytotoxicity of Fc-Sec-His/MTI-101 (Figures 12A-12H) and anti-CD138-scFv-Fc-Sec- His/MTI-101 (Figures 14A-14D) toward MM cell lines U266 and H929 *in vitro*. The cells were incubated with the conjugates and negative and positive controls for 1 hour at 37°C followed by propidium iodide (PI) staining and flow cytometry analysis using FSC/SSC scatter densities and fluorescence to distinguish live and dead cells. Whereas Fc-stop and anti-CD138-scFv-Fc-stop revealed no cytotoxicity when compared to medium alone (negative control), Fc-Sec-His/MTI- 101, anti-CD138-scFv-Fc-Sec-His/MTI-101, and free MTI-101 clearly killed both U266 and H929 cells. Light microscopy confirmed the MTI-101-dependent cytotoxicity of both conjugates.

Further experiments revealed that the killing is concentration-dependent with IC50s in the 10-50 μ M range depending on conjugate and cell line (Figures 13 and 15).

The overall potency of the cyclic peptide conjugates showed an increase in cytotoxicity relative to the given MTI-101 iodoacetamide adduct (Figure 10).

Under microscopy (see Figure 11), the ADCs showed cell cross-linking and coagulation, which is in agreement with the action of the drug alone. This confirms both

proper conjugation and can serve as a visual indicator of previous and concurrent cell death. Furthermore, the ADCs showed very potent cytotoxicity with little STOP effects when cell viability was compared via flow cytometry, in Figures 12A-12H, 13, 14A-14D, and 15.

5 The inventors then tested the cytotoxicity of Fc-Sec-His/MTI-101 *in vivo*, utilizing the 5TGM1 murine model (Garrett, I.R., *et al.*, "A murine model of human myeloma bone disease. *Bone*, 1997, 20, 515-520). This is an excellent immune competent MM model in which drug response is monitored in the confines of the bone marrow microenvironment. The model demonstrates tumor burden in the bone and bone
10 lesions typical of the clinical course of the disease. 5TGM1 cells (1×10^6 in 100 μ L of PBS) were injected intravenously (i.v.) into the tail vein of 6-week old C57 BL/KaLwRij mice (Harlen, Netherlands). Tumor was allowed to engraft for 10 days prior to the initiation of drug treatment. Four treatment groups were included: 1) Control animals; 2) MTI-101 (10 mg/kg) administered i.p. 3x weekly for three weeks (*maximum tolerated*
15 *dose*); 3) Fc-Sec-His/MTI-101 conjugate (10 mg/kg) administered i.v. 1x weekly for three weeks; 4) Fc-stop (10 mg/kg) administered i.v. 1x weekly for three weeks; 5) equal payload of MTI-101 (0.3285 mg/kg) administered i.v. 1x weekly for three weeks. Results are shown in Figure 18A.

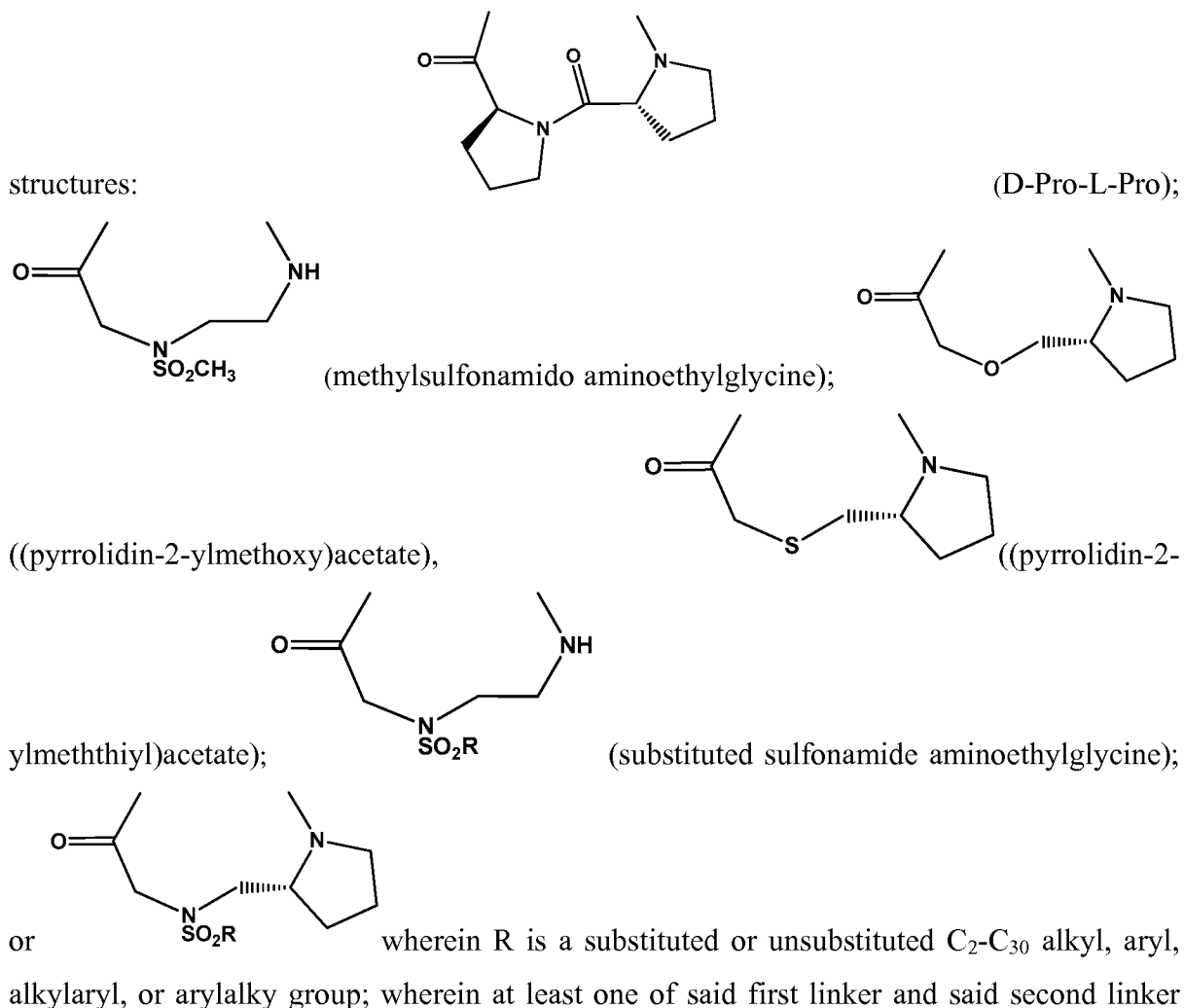
 To quantify tumor burden, blood was collected by submandibular bleeding and
20 mice were monitored weekly by measuring 5TGM1 secreted IgG2b (paraprotein) in the serum by ELISA (Figure 18B). Hind limb paralysis and hunching were considered as additional surrogate markers for morbidity.

 It should be understood that the examples and embodiments described herein are
25 for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims. In addition, any elements or limitations of any invention or embodiment thereof disclosed herein can be combined with any and/or all other elements or limitations (individually or in any
30 combination) or any other invention or embodiment thereof disclosed herein, and all such combinations are contemplated with the scope of the invention without limitation thereto.

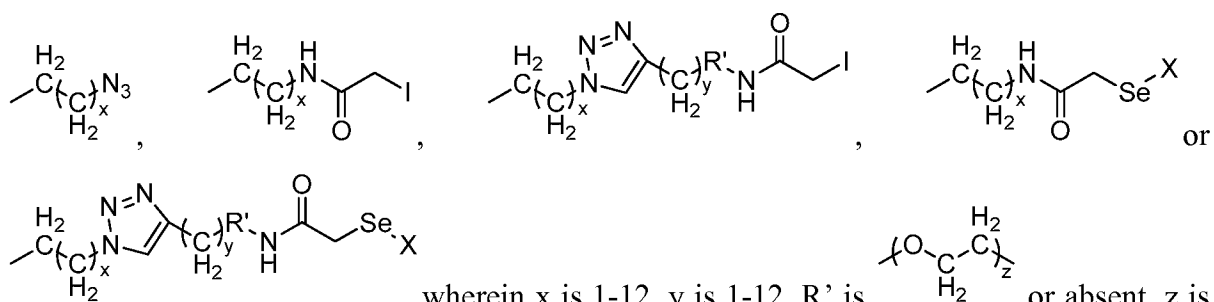
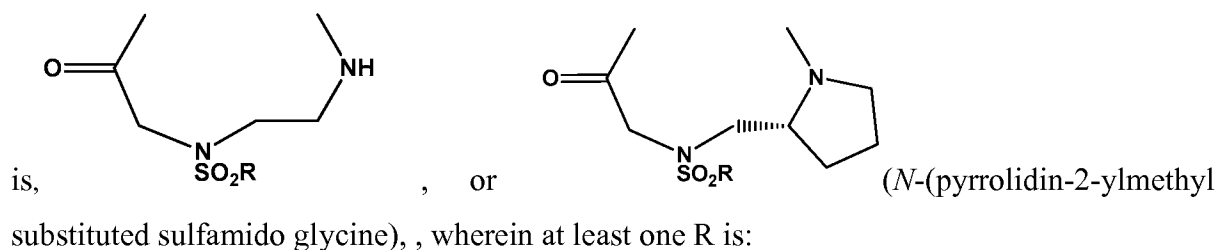
CLAIMS

What is claimed is:

1. A cyclic compound, comprising a recognition sequence and a non-recognition sequence, wherein said recognition sequence comprises at least four amino acids, wherein said non-recognition sequence comprises at least four amino acids, and wherein said recognition sequence is joined to said non-recognition sequence by a first linker and a second linker, wherein said first linker and said second linker are independently selected from the



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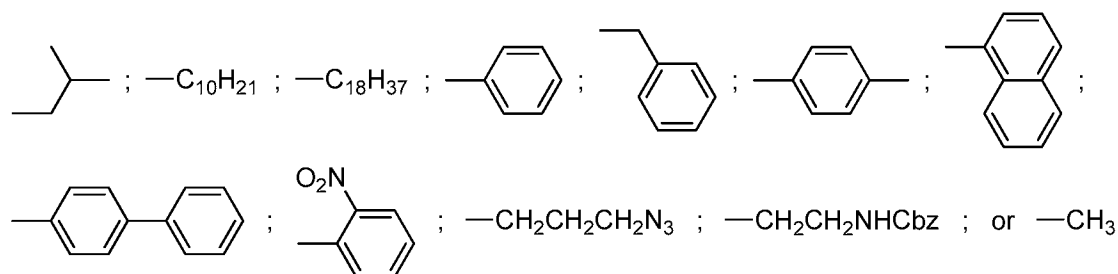


2. The cyclic compound of claim 1, wherein said non-recognition sequence is five amino acids selected from KLQLK (SEQ ID NO:1), QLKLK (SEQ ID NO:2), KQKLK (SEQ ID NO:3), KXXKK (SEQ ID NO:4), or ELKLK (SEQ ID NO:5) wherein X = sarcosine and the recognition sequence is five amino acids selected from WAVAW (SEQ ID NO:6), WAVAA (SEQ ID NO:7), WAVAM (SEQ ID NO:8), WAVAN* (SEQ ID NO:9), WAVVN* (SEQ ID NO:10), WAVSN* (SEQ ID NO:11), WAAAW (SEQ ID NO:12), WAAAA (SEQ ID NO:13), WAAAM (SEQ ID NO:14), WAAAN* (SEQ ID NO:15), WAAVW (SEQ ID NO:16), WAAVA (SEQ ID NO:17), WAAVM (SEQ ID NO:18), WAAVN* (SEQ ID NO:19), WAASN* (SEQ ID NO:20), WVVAW (SEQ ID NO:21), WVVAA (SEQ ID NO:22), WVVAM (SEQ ID NO:23), WVVAN* (SEQ ID NO:24), WVVVW (SEQ ID NO:25), WVVVA (SEQ ID NO:26), WVVVM (SEQ ID NO:27), WVVVN* (SEQ ID NO:28), WVVSN* (SEQ ID NO:29), WVAAN* (SEQ ID NO:30), WVAVW (SEQ ID NO:31), WVAVA (SEQ ID NO:32), WVAVM (SEQ ID NO:33), WVAVN* (SEQ ID NO:34), WVASN* (SEQ ID NO:35), WSVAW (SEQ ID NO:36), WSVAA (SEQ ID NO:37), WSVAM (SEQ ID NO:38), WSVAN* (SEQ ID NO:39), WSVVW (SEQ ID NO:40), WSVVA (SEQ ID NO:41), WSVVM (SEQ ID NO:42), WSVVN* (SEQ ID NO:43), WSVSW (SEQ ID NO:44), WSVSA (SEQ ID NO:45), WSVSM (SEQ ID NO:46), WSVSN* (SEQ ID NO:47), WSAAW (SEQ ID NO:48), WSAAA (SEQ ID NO:49), WSAAM (SEQ ID NO:50), WSAAN* (SEQ ID NO:51), WSAVW (SEQ ID NO:52), WSAVA (SEQ ID NO:53), WSAVM (SEQ ID NO:54),

WSAVN* (SEQ ID NO:55), WSASW (SEQ ID NO:56), WSASA (SEQ ID NO:57), WSASM (SEQ ID NO:58), WSASN* (SEQ ID NO:59), WYVAW (SEQ ID NO:60), WYVAA (SEQ ID NO:61), WYVAM (SEQ ID NO:62), WYVAN* (SEQ ID NO:63), WYVVW (SEQ ID NO:64), WYVVA (SEQ ID NO:65), WYVVM (SEQ ID NO:66), WYVVN* (SEQ ID NO:67), WYVSW (SEQ ID NO:68), WYVSA (SEQ ID NO:69), WYVSM (SEQ ID NO:70), WYVSN* (SEQ ID NO:71), WYAAW (SEQ ID NO:72), WYAAA (SEQ ID NO:73), WYAAM (SEQ ID NO:74), WYAAN* (SEQ ID NO:75), WYAVW (SEQ ID NO:76), WYAVA (SEQ ID NO:77), WYAVM (SEQ ID NO:78), WYAVN* (SEQ ID NO:79), WYASW (SEQ ID NO:80), WYASA (SEQ ID NO:81), WYASM (SEQ ID NO:82), WYASN* (SEQ ID NO:83), AAVAA (SEQ ID NO:84), AAVAM (SEQ ID NO:85), AAVAN* (SEQ ID NO:86), AAVVN* (SEQ ID NO:87), AAVSN* (SEQ ID NO:88), AAAAA (SEQ ID NO:89), AAAAM (SEQ ID NO:90), AAAAN* (SEQ ID NO:91), AAAVW (SEQ ID NO:92), AAAVA (SEQ ID NO:93), AAAVM (SEQ ID NO:94), AAAVN* (SEQ ID NO:95), AAASM (SEQ ID NO:96), AAASN* (SEQ ID NO:97), AVVAW (SEQ ID NO:98), AVVAA (SEQ ID NO:99), AVVAM (SEQ ID NO:100), AVVAN* (SEQ ID NO:101), AVVVA (SEQ ID NO:102), AVVVM (SEQ ID NO:103), AVVVN* (SEQ ID NO:104), AVVSN* (SEQ ID NO:105), AVAAW (SEQ ID NO:106), AVAAM (SEQ ID NO:107), AVAAN* (SEQ ID NO:108), AVAVA (SEQ ID NO:109), AVAVM (SEQ ID NO:110), AVAVN* (SEQ ID NO:111), AVASN* (SEQ ID NO:112), ASVAW (SEQ ID NO:113), ASVAA (SEQ ID NO:114), ASVAM (SEQ ID NO:115), ASVAN* (SEQ ID NO:116), ASVVW (SEQ ID NO:117), ASVVA (SEQ ID NO:118), ASVVM (SEQ ID NO:119), ASVVN* (SEQ ID NO:120), ASVSA (SEQ ID NO:121), ASVSM (SEQ ID NO:122), ASVSN* (SEQ ID NO:123), ASAAW (SEQ ID NO:124), ASAAA (SEQ ID NO:125), ASAAM (SEQ ID NO:126), ASAAN* (SEQ ID NO:127), ASAVW (SEQ ID NO:128), ASAVA (SEQ ID NO:129), ASAVM (SEQ ID NO:130), ASAVN* (SEQ ID NO:131), ASASA (SEQ ID NO:132), ASASM (SEQ ID NO:133), ASASN* (SEQ ID NO:134), AYVAW (SEQ ID NO:135), AYVAA (SEQ ID NO:136), AYVAM (SEQ ID NO:137), AYVAN* (SEQ ID NO:138), AYVVW (SEQ ID NO:139), AYVVA (SEQ ID NO:140), AYVVM (SEQ ID NO:141), AYVVN* (SEQ ID NO:142), AYVSW (SEQ ID NO:143), AYVSA (SEQ ID NO:144), AYVSM (SEQ ID NO:145), AYVSN* (SEQ ID NO:146), AYAAW (SEQ ID NO:147), AYAAA (SEQ ID NO:148), AYAAAM (SEQ ID NO:149), AYAAAN* (SEQ ID NO:150),

AYAVW (SEQ ID NO:151), AYAVA (SEQ ID NO:152), AYAVM (SEQ ID NO:153), AYAVN* (SEQ ID NO:154), AYASW (SEQ ID NO:155), AYASA (SEQ ID NO:156), AYASM (SEQ ID NO:157), AYASN* (SEQ ID NO:158), MAVAA (SEQ ID NO:159), MAVAM (SEQ ID NO:160), MAVAN* (SEQ ID NO:161), MAVVN* (SEQ ID NO:162), MAVSN* (SEQ ID NO:163), MAAAA (SEQ ID NO:164), MAAAM (SEQ ID NO:165), MAAAN* (SEQ ID NO:166), MAAVW (SEQ ID NO:167), MAAVA (SEQ ID NO:168), MAAVM (SEQ ID NO:169), MAAVN* (SEQ ID NO:170), MAASN* (SEQ ID NO:171), MVVAW (SEQ ID NO:172), MVVAA (SEQ ID NO:173), MVVAM (SEQ ID NO:174), MVVAN* (SEQ ID NO:175), MVVVM (SEQ ID NO:176), MVVVN* (SEQ ID NO:177), MVVSN* (SEQ ID NO:178), MVAAM (SEQ ID NO:179), MVAAN* (SEQ ID NO:180), MVAVM (SEQ ID NO:181), MVAVN* (SEQ ID NO:182), MVASN* (SEQ ID NO:183), MSVAW (SEQ ID NO:184), MSVAA (SEQ ID NO:185), MSVAM (SEQ ID NO:186), MSVAN* (SEQ ID NO:187), MSVVW (SEQ ID NO:188), MSVVA (SEQ ID NO:189), MSVVM (SEQ ID NO:190), MSVVN* (SEQ ID NO:191), MSVSM (SEQ ID NO:192), MSVSN* (SEQ ID NO:193), MSAAW (SEQ ID NO:194), MSAAA (SEQ ID NO:195), MSAAM (SEQ ID NO:196), MSAAN* (SEQ ID NO:197), MSAVW (SEQ ID NO:198), MSAVA (SEQ ID NO:199), MSAVM (SEQ ID NO:200), MSAVN* (SEQ ID NO:201), MSASM (SEQ ID NO:202), MSASN* (SEQ ID NO:203), MYVAW (SEQ ID NO:204), MYVAA (SEQ ID NO:205), MYVAM (SEQ ID NO:206), MYVAN* (SEQ ID NO:207), MYVVW (SEQ ID NO:208), MYVVA (SEQ ID NO:209), MYVVM (SEQ ID NO:210), MYVVN* (SEQ ID NO:211), MYVSW (SEQ ID NO:212), MYVSA (SEQ ID NO:213), MYVSM (SEQ ID NO:214), MYVSN* (SEQ ID NO:215), MYAAW (SEQ ID NO:216), MYAAA (SEQ ID NO:217), MYAAM (SEQ ID NO:218), MYAAN* (SEQ ID NO:219), MYAVW (SEQ ID NO:220), MYAVA (SEQ ID NO:221), MYAVM (SEQ ID NO:222), MYAVN* (SEQ ID NO:223), MYASW (SEQ ID NO:224), MYASA (SEQ ID NO:225), MYASM (SEQ ID NO:226), or MYASN* (SEQ ID NO:227), wherein N* = norleucine, and wherein either end of said recognition sequence can be a N-terminus.

3. The cyclic compound of claim 1, wherein one R is:



4. The cyclic compound of claim 1, wherein R is H, $\text{C}_1\text{—C}_{30}$ alkyl, $\text{C}_2\text{—C}_{30}$ alkenyl, $\text{C}_2\text{—C}_{30}$ alkynyl, $\text{C}_6\text{—C}_{14}$ aryl, $\text{C}_7\text{—C}_{30}$ arylalkyl, $\text{C}_8\text{—C}_{30}$ arylalkenyl, $\text{C}_8\text{—C}_{30}$ arylalkynyl, hydroxy, $\text{C}_1\text{—C}_{30}$ alkoxy, $\text{C}_6\text{—C}_{14}$ aryloxy, $\text{C}_7\text{—C}_{30}$ arylalkyloxy, $\text{C}_2\text{—C}_{30}$ alkenyloxy, $\text{C}_2\text{—C}_{30}$ alkynyloxy, $\text{C}_8\text{—C}_{30}$ arylalkenyloxy, $\text{C}_8\text{—C}_{30}$ arylalkynyloxy, CO_2H , $\text{C}_2\text{—C}_{30}$ alkylester, $\text{C}_7\text{—C}_{15}$ aryylester, $\text{C}_8\text{—C}_{30}$ alkylaryylester, $\text{C}_3\text{—C}_{30}$ alkenylester, $\text{C}_3\text{—C}_{30}$ alkynylester, NH_2 , $\text{C}_1\text{—C}_{30}$ alkylamino, $\text{C}_6\text{—C}_{14}$ arylamino, $\text{C}_7\text{—C}_{30}$ (arylalkyl)amino, $\text{C}_2\text{—C}_{30}$ alkenylamino, $\text{C}_2\text{—C}_{30}$ alkynylamino, $\text{C}_8\text{—C}_{30}$ (arylalkenyl)amino, $\text{C}_8\text{—C}_{30}$ (arylalkynyl)amino, $\text{C}_2\text{—C}_{30}$ dialkylamino, $\text{C}_{12}\text{—C}_{28}$ diarylamino, $\text{C}_4\text{—C}_{30}$ dialkenylamino, $\text{C}_4\text{—C}_{30}$ dialkynylamino, $\text{C}_7\text{—C}_{30}$ aryl(alkyl)amino, $\text{C}_7\text{—C}_{30}$ di(arylalkyl)amino, $\text{C}_8\text{—C}_{30}$ alkyl(arylalkyl)amino, $\text{C}_{15}\text{—C}_{30}$ aryl(arylalkyl)amino, $\text{C}_8\text{—C}_{30}$ alkenyl(aryl)amino, $\text{C}_8\text{—C}_{30}$ alkynyl(aryl)amino, C(O)NH_2 (amido), $\text{C}_2\text{—C}_{30}$ alkylamido, $\text{C}_7\text{—C}_{14}$ arylamido, $\text{C}_8\text{—C}_{30}$ (arylalkyl)amido, $\text{C}_2\text{—C}_{30}$ dialkylamido, $\text{C}_{12}\text{—C}_{28}$ diarylamido, $\text{C}_8\text{—C}_{30}$ aryl(alkyl)amido, $\text{C}_{15}\text{—C}_{30}$ di(arylalkyl)amido, $\text{C}_9\text{—C}_{30}$ alkyl(arylalkyl)amido, $\text{C}_{16}\text{—C}_{30}$ aryl(arylalkyl)amido, thiol, $\text{C}_1\text{—C}_{30}$ hydroxyalkyl, $\text{C}_6\text{—C}_{14}$ hydroxyaryl, $\text{C}_7\text{—C}_{30}$ hydroxyarylalkyl, $\text{C}_3\text{—C}_{30}$ hydroxyalkenyl, $\text{C}_3\text{—C}_{30}$ hydroxyalkynyl, $\text{C}_8\text{—C}_{30}$ hydroxyarylalkenyl, $\text{C}_8\text{—C}_{30}$ hydroxyarylalkynyl, $\text{C}_3\text{—C}_{30}$ polyether, $\text{C}_3\text{—C}_{30}$ polyetherester, $\text{C}_3\text{—C}_{30}$ polyester, $\text{C}_3\text{—C}_{30}$ polyamino, $\text{C}_3\text{—C}_{30}$ polyaminoamido, $\text{C}_3\text{—C}_{30}$ polyaminoether, $\text{C}_3\text{—C}_{30}$ polyaminoester, $\text{C}_3\text{—C}_{30}$ polyamidoester, $\text{C}_3\text{—C}_{30}$ alkylsulfonic acid, $\text{C}_3\text{—C}_{30}$ alkylsulfonate salt, $\text{C}_1\text{—C}_{30}$ carboxylate salt, $\text{C}_1\text{—C}_{30}$ thiocarboxylate salt, $\text{C}_1\text{—C}_{30}$ dithiocarboxylate salt, or $\text{C}_3\text{—C}_{30}$ alkyl $\text{C}_1\text{—C}_4$ trialkylammonium salt, wherein any carbon can be further substituted with any carbon can be substituted with a hydroxy, chloro, bromo, iodo, nitro, or carboxylic acid.

5. The cyclic compound of claim 1, wherein said carrying agent comprises an amino acid, oligo(amino acid), poly(amino acid) or protein.

6. The cyclic compound of claim 1, wherein said carrying agent comprises an antibody, or an Fc portion of an antibody, or an antigen-binding fragment of an antibody.

7. The cyclic compound of claim 1, wherein said carrying agent is a monoclonal antibody (mAb), or an Fc portion of a mAb, or an antigen binding fragment of a mAb, comprising a selenocysteine residue.

8. The cyclic compound of claim 1, wherein said carrying agent is a monoclonal antibody (mAb), or an Fc portion of a mAb, or antigen binding fragment of a mAb, comprising a C-terminal selenocysteine residue.

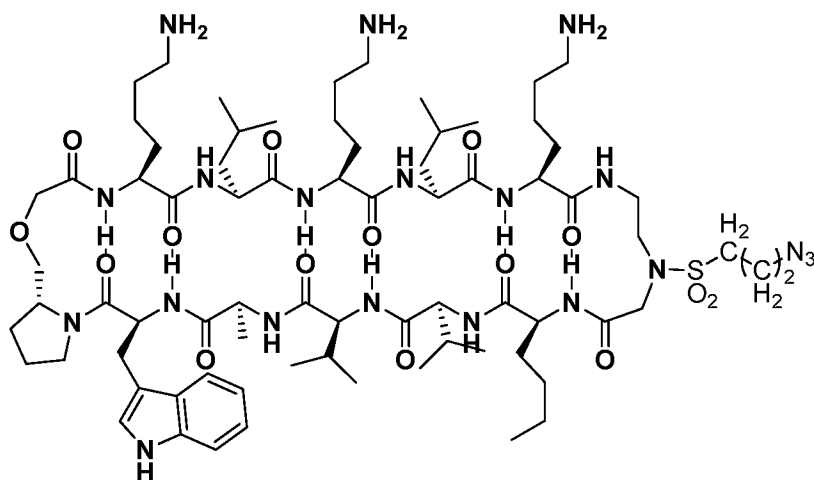
9. The cyclic compound of claim 1, wherein said carrying agent specifically binds to a cell surface antigen.

10. The cyclic compound of claim 1, wherein said carrying agent specifically binds to a tumor associated antigen.

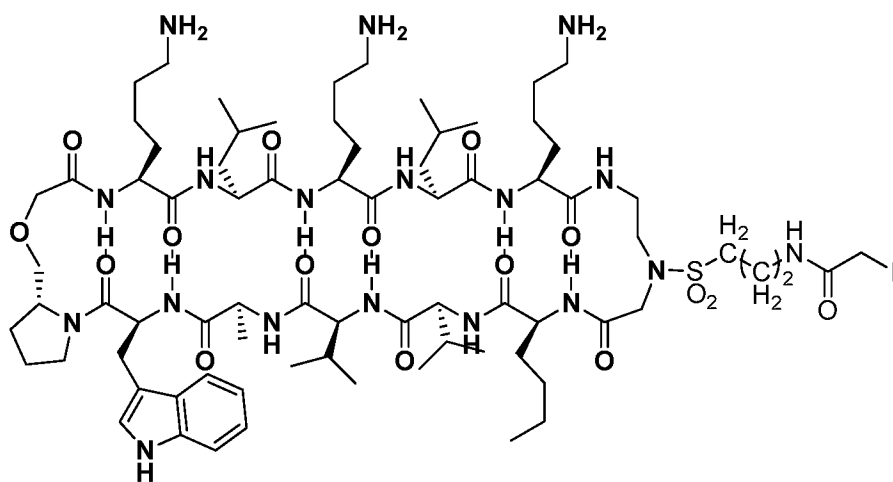
11. The cyclic compound of claim 1, wherein said carrying agent specifically binds to one or more antigens selected from among CD138, CD44, alpha4 integrin, alpha3 integrin, alpha6 integrin, EGFR, tumor suppressor cell antigen, cytotoxic T cell antigen, 17-1A, 707-AP, AFP, Annexin II, ART-4, BAGE, BAGE-1, β -catenin, BCG, bcr/abl, Bcr/abl e14a2 fusion junction, bcr-abl (b3a2), bcr-abl (b3a2), bcr-abl p190 (e1a2), bcr-abl p210 (b2a2), bcr-abl p210 (b3a2), bcr-abl p210 (b3a2), bullous pemphigoid antigen-1, CA19-9, CA125, CA215, CAG-3, CAMEL, Cancer-testis antigen, Caspase-8, CCL3, CCL4, CD16, CD20, CD3, CD30, CD55, CD63, CDC27, CDK-4, CDR3, CEA, cluster 5, cluster-5A, cyclin-dependent kinase-4, Cyp-B, DAM-10, DAM-6, Dek-cain, E7, EGFRvIII, EGP40, ELF2 M, EpCAM, FucGM1, G250, GA733, GAGE, GAGE-1-8, gastrin cancer associated antigen, GD2, GD3, globoH, glycophorin, GM1, GM2, GM3, GnTV, Gn-T-V, gp100, Her-2/neu, HERV-K-ME, high molecular weight-associated antigen, high molecular weight proteoglycan (HMPG), HPV-16 E6, HPV-16 E7, HPVE6, HSP70-2M, HST-2, hTERT, human chorionic gonadotropin (HCG), Human milk fat globule (HMFG), iCE, KIAA0205, KK-LC-1, KM-HN-1, L6, LAGE-1, Lcose4Cer, LDLR/FUT, Lewis A, Lewis v/b, M protein, MAGE-1, MVC, MAGE-A1-12, MAGE-C2, MAHGE-3, MART-1/Melan-A, MC1R, ME491, MUC1, MUC2, mucin, MUM-1, MUM-2, MUM-3, mutated p53, Myosin, MZ2-E, N9

neuraminidase, NA88, NA88-A, nasopharyngeal carcinoma antigen, NGA, NK1/c-3, Novel bcr/ablk fusion BCR exons 1, 13, 14 with ABL exons 4, NY-ESO-1/LAGE-2, NY-ESO-1b, OC125, osteosarcoma associated antigen-1, P15, p190 mimor bcr-abl (e1a2), p53, Pml/RAR α , Polysialic acid, PRAME, PSA, PSM, RU1, RU2, SAGE, SART-1, SART-2, SART-3, Sialyl LeA, Sp17, SSX-2, SSX-4, surface immunoglobulin, TAG-1, TAG-2, TEL/AML1, TPI, TRAG-3, TRP-1(gp75), TRP-2, TRP2-INT2, hTRT, tumor associated glycoprotein-72 (TAG-72), tyrosinase, u-PA, WT1, and XAGE-1b, or an immunogenic fragment of any of the foregoing antigens.

12. The cyclic compound of claim 1, wherein the structure is:

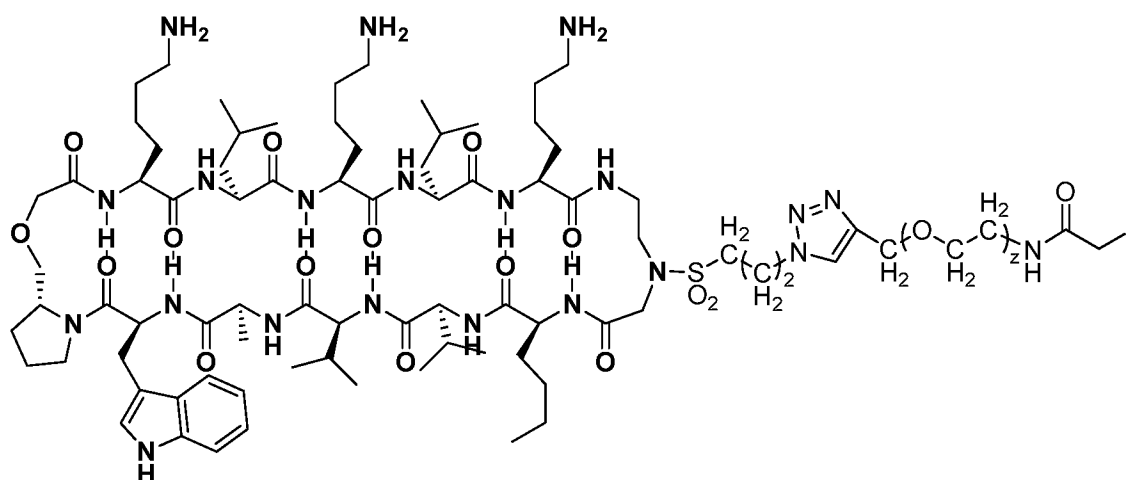


13. The cyclic compound of claim 1, wherein the structure is:

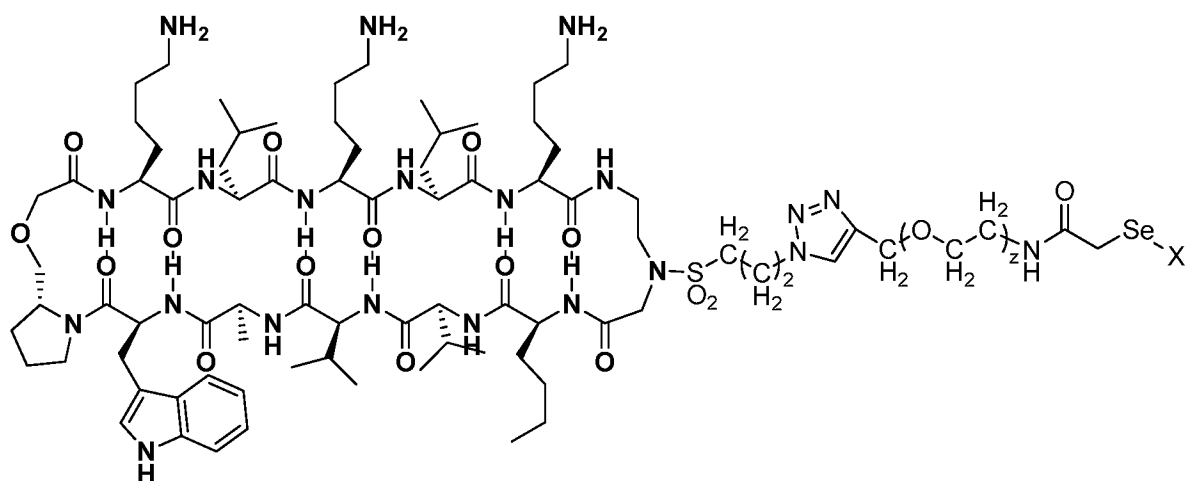


14. The cyclic compound of claim 1, wherein the structure is:

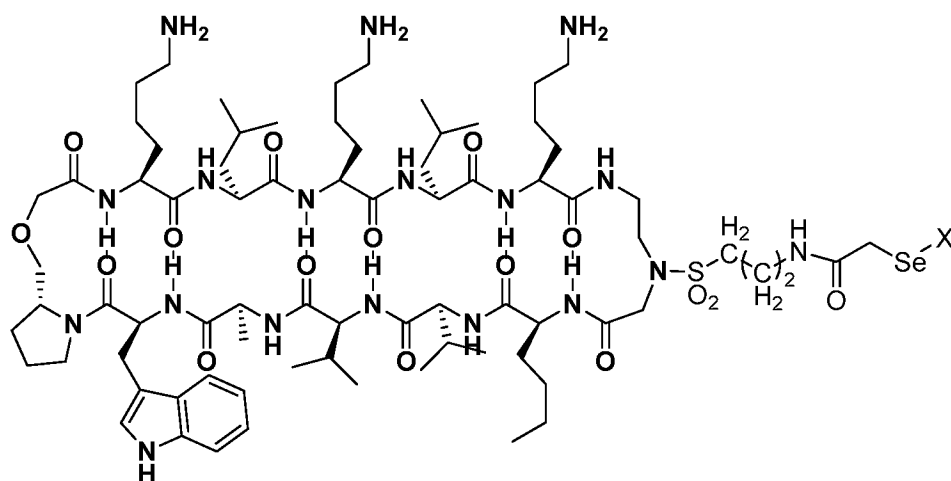
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15. The cyclic compound of claim 1, wherein the structure is:

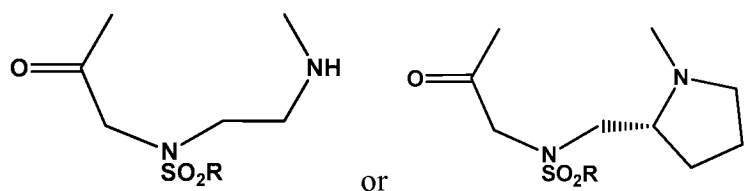


16. The cyclic compound of claim 1, wherein the structure is:



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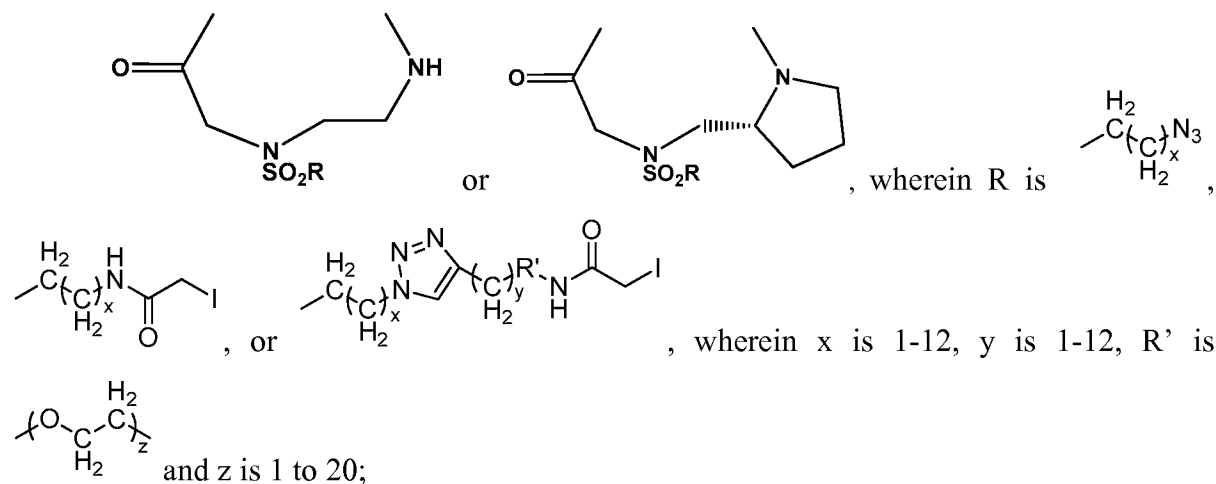
17. A linker, comprising:



wherein R is $\text{C}(\text{H}_2)_x\text{N}_3$, $\text{C}(\text{H}_2)_x\text{N}(\text{H})\text{C}(=\text{O})\text{CH}_2\text{I}$, or $\text{C}(\text{H}_2)_x\text{N}(\text{N}=\text{N})\text{C}(\text{H}_2)_y\text{R}'\text{N}(\text{H})\text{C}(=\text{O})\text{CH}_2\text{I}$, wherein x is 1-12, y is 1-12, R' is $\text{C}(\text{H}_2)_z$ and z is 1 to 20.

18. A method of preparing a carrying agent:cyclic compound adduct, comprising:

providing a cyclic compound comprising a recognition sequence and a non-recognition sequence, wherein said recognition sequence comprises at least four amino acids, wherein said non-recognition sequence comprises at least four amino acids, and wherein said recognition sequence is joined to said non-recognition sequence by a first linker and a second linker, wherein at least one of said first linker and said second linker is:

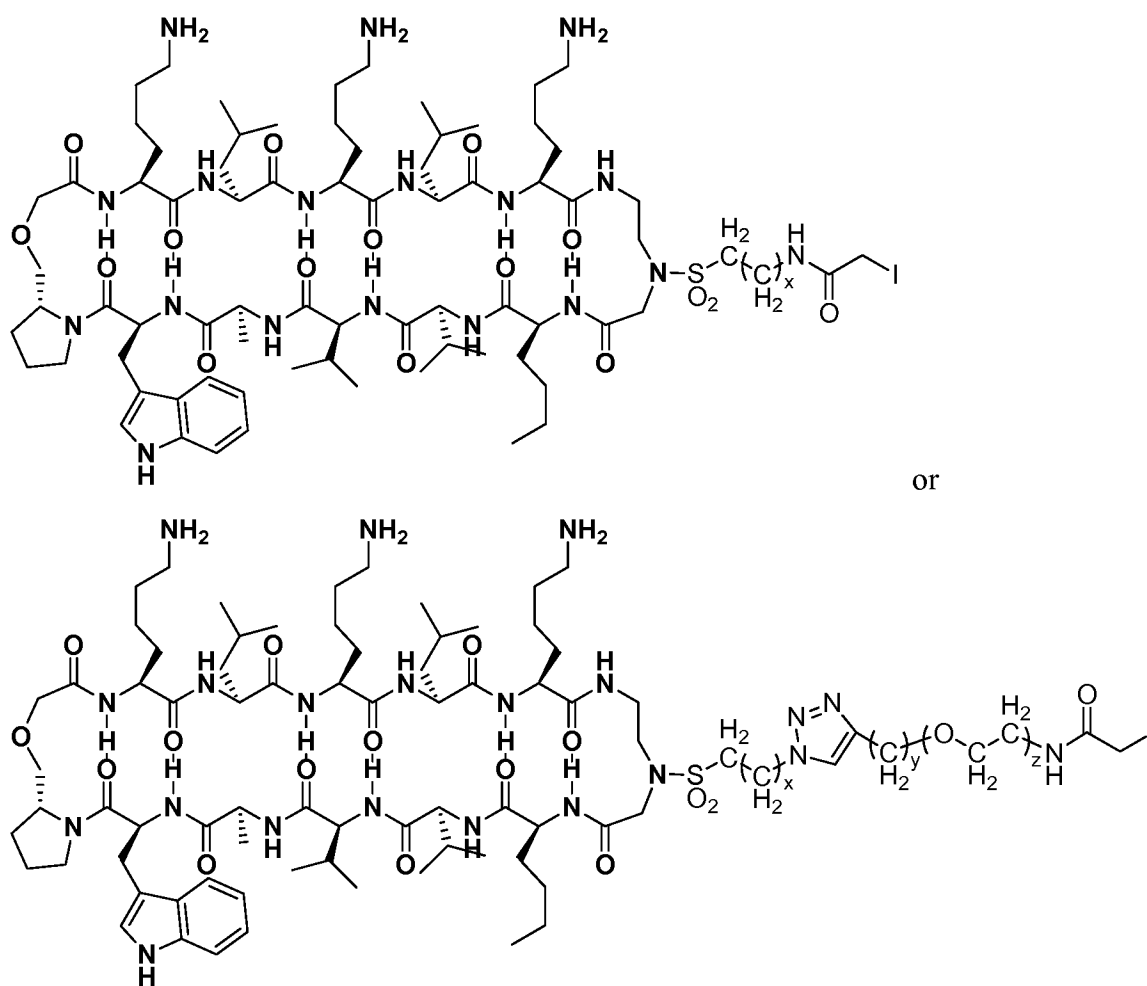


providing a carrying agent X comprising a selenocysteine residue; and
combining said carrying agent and said cyclic compound in an aqueous solution.

19. The method of preparing a carrying agent:cyclic compound adduct of claim 18, wherein said aqueous solution comprises dithiothreitol (DTT) and wherein said aqueous solution has an acidic pH.

20. The method of preparing a carrying agent:cyclic compound adduct of claim 19, wherein said pH is 4-6 and the concentration of DTT is 0.1-1 mM.

21. The method of preparing a carrying agent:cyclic compound adduct of claim 18, wherein the cyclic compound comprises:



wherein x is 1-12, y is 1-12, and z is 1.

22. The method of preparing a carrying agent:cyclic compound adduct according to claim 18, wherein the carrying agent comprises an oligo(amino acid), poly(amino acid) or protein comprising a selenocysteine residue.

23. The method of preparing a carrying agent:cyclic compound adduct according to claim 18, wherein said carrying agent X is a monoclonal antibody (mAb) comprising a selenocysteine residue.

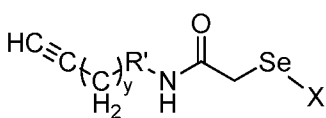
24. The method of preparing a carrying agent:cyclic compound adduct according to claim 18, wherein said carrying agent X is the modified antibody Fc-Sec-His having the sequence:

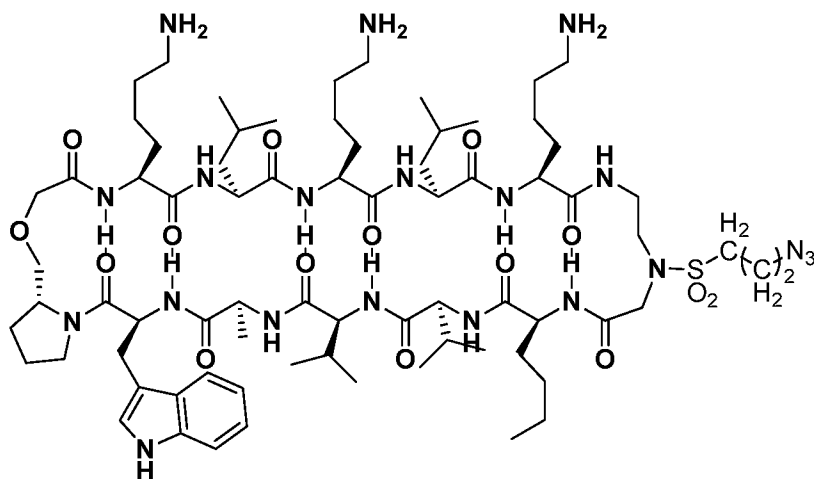
EPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGAUHHHHHH (SEQ ID NO:228) where U is the single letter amino acid code for selenocysteine.

25. The method of preparing a carrying agent:cyclic compound adduct according to claim 18, wherein said carrying agent X is a targeting agent that is the modified antibody Anti-CD138-scFv-Fc-Sec-His having the sequence:

DIQMTQSTSSLSASLGDRVTISCSASQGNNYLNWYQQKPDGTVELLIYYTSTLQSGVPSRFSGSGSGTDYSLTISNLEPEDIGTYYCQQYSKLPRTFGGGTKLEIKGGGGSGGGGSGGGGSQVQLQQSGSELMMPGASVKISCKATGYTFSNYWIEWVKQRPGHGLEWIGELPGTGRTIYNEKFKGKATFTADISSNTVQMQLSSLTSEDSAVYYCARRDYYGNFYAMDYWGQGTSTVTSSEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGAUHHHHHH (SEQ ID NO:229) where U is the single letter amino acid code for selenocysteine.

26. The method of preparing a carrying agent agent:cyclic compound adduct according to claim 18, wherein said carrying agent X comprises a residue of selenocysteine

having a  and wherein said cyclic compound comprises:



27. A method for treating a disorder in a subject, comprising administering an effective amount of a cyclic compound of any one of claims 1 to 16 to the subject.
28. The method of claim 27, wherein the subject is human.
29. The method of claim 27, wherein the disorder is a proliferation disorder, bone deficiency, or autoimmune disease.
30. The method of claim 28, wherein the proliferation disorder is myeloma or another malignancy.
31. The method of claim 27, wherein the cyclic compound is administered in a composition further comprising a pharmaceutically acceptable carrier.
32. A method of suppressing the growth of, or inducing apoptosis in, cells, comprising contacting the cells with an effective amount of a cyclic compound of any one of claims 1 to 16.
33. The method of claim 32, wherein the cyclic compound is in a composition further comprising a pharmaceutically acceptable carrier.

34. The method of claim 32, wherein said contacting is carried out *in vivo*.
35. The method of claim 32, wherein the cells are human cells.
36. The method of claim 32, wherein the cells are myeloma cells or other malignant cells.
37. A composition comprising a cyclic compound of any one of claims 1 to 16; and a pharmaceutically acceptable carrier.

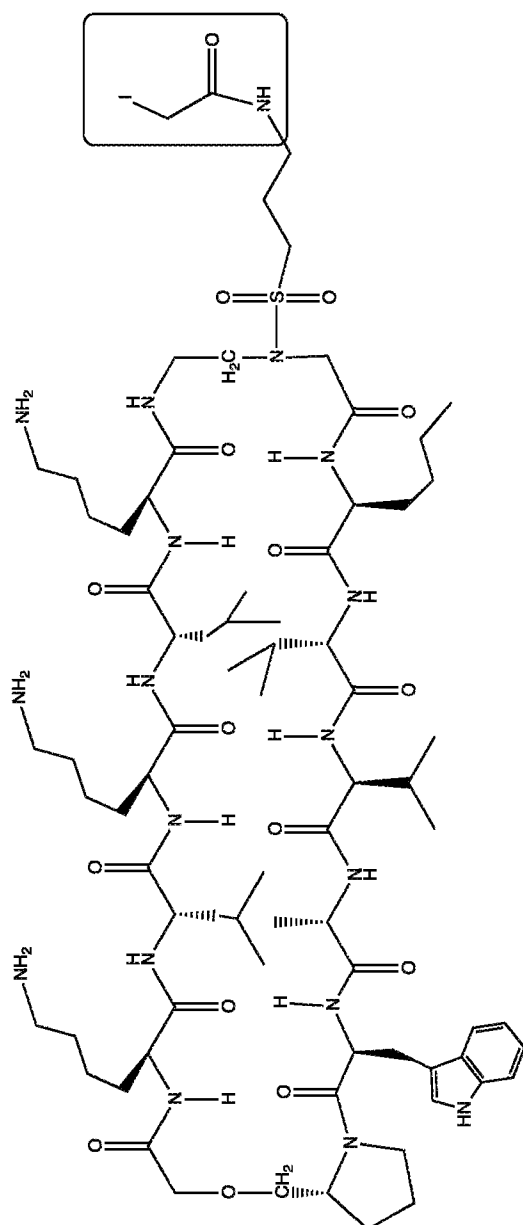


FIG. 1

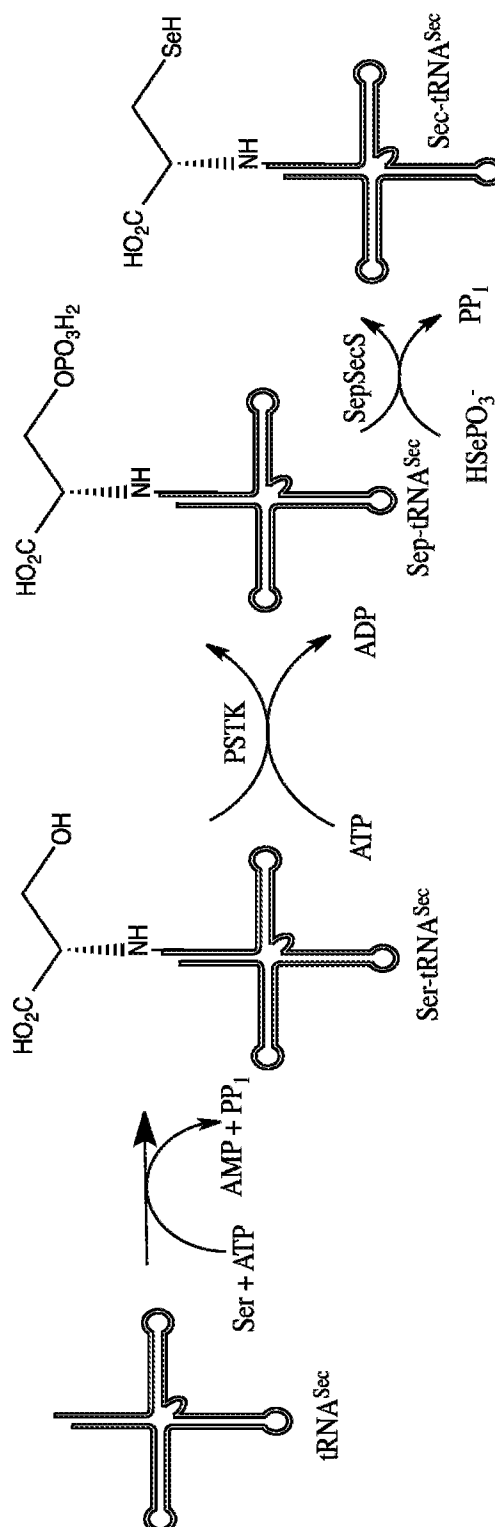


FIG. 2

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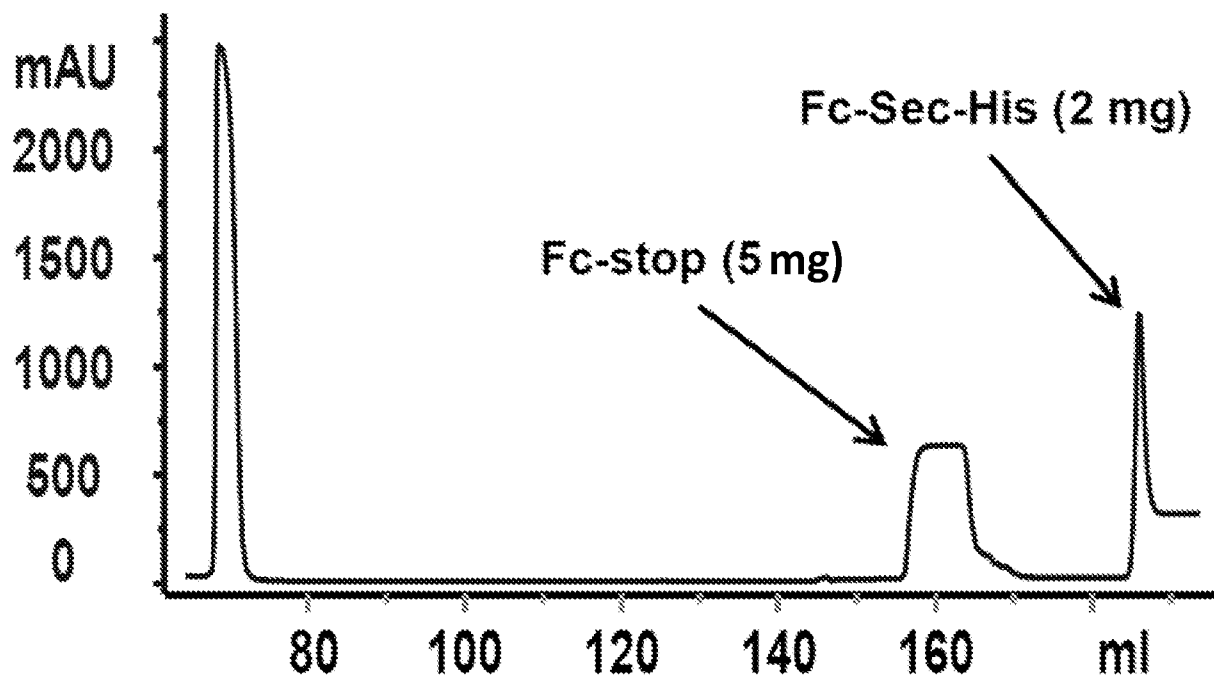


FIG. 3

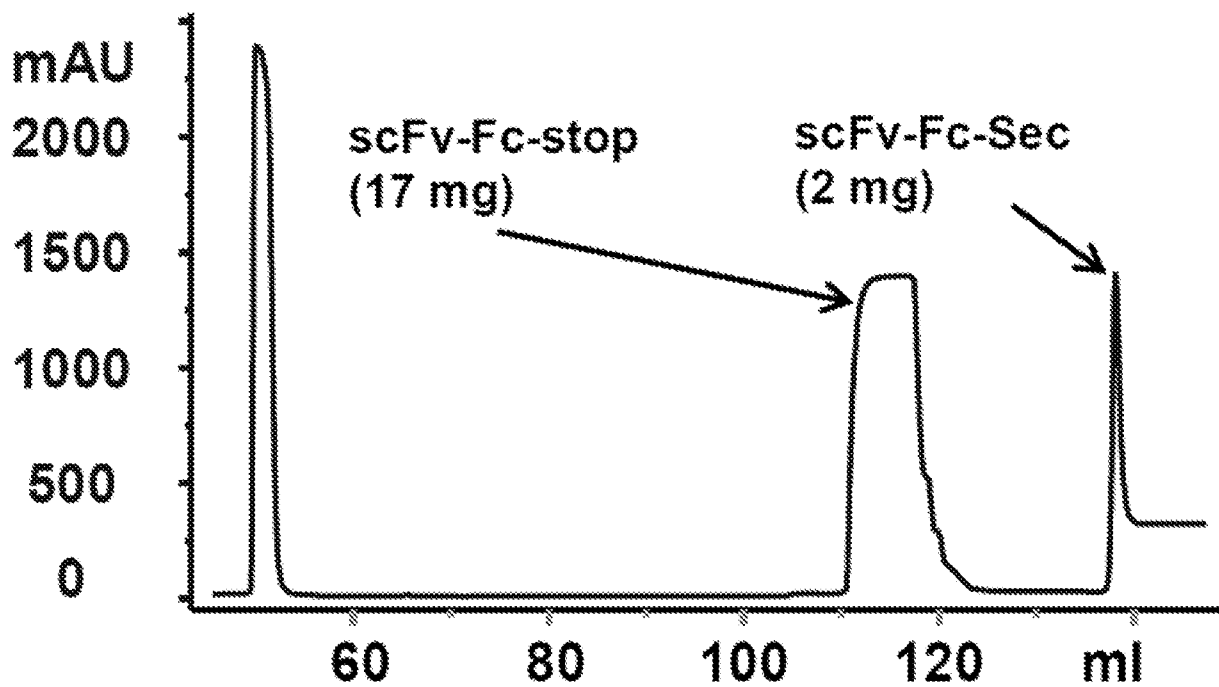
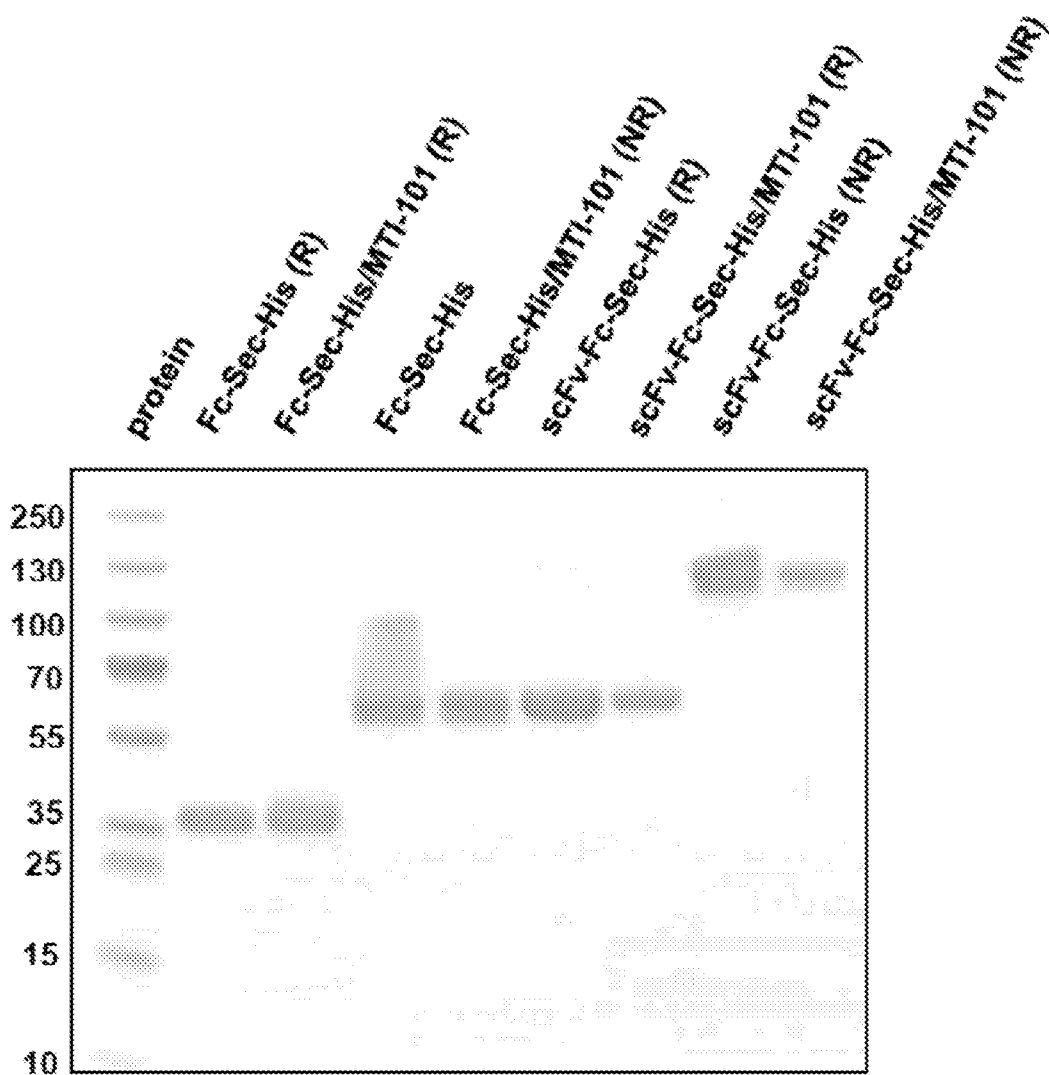
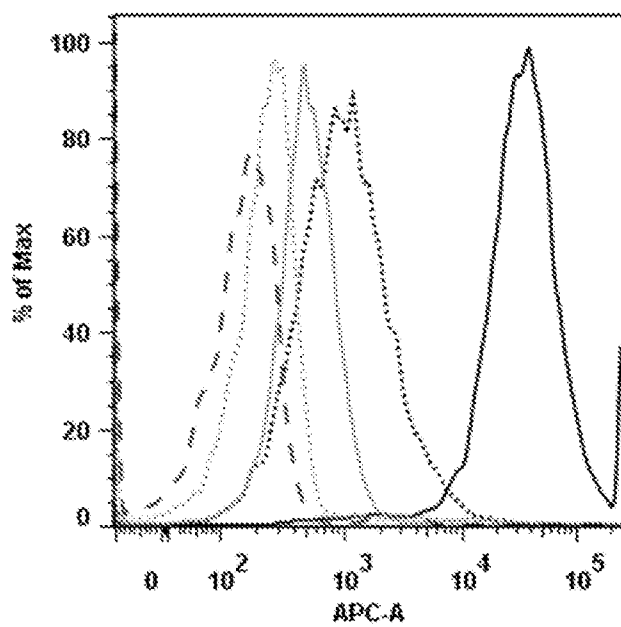
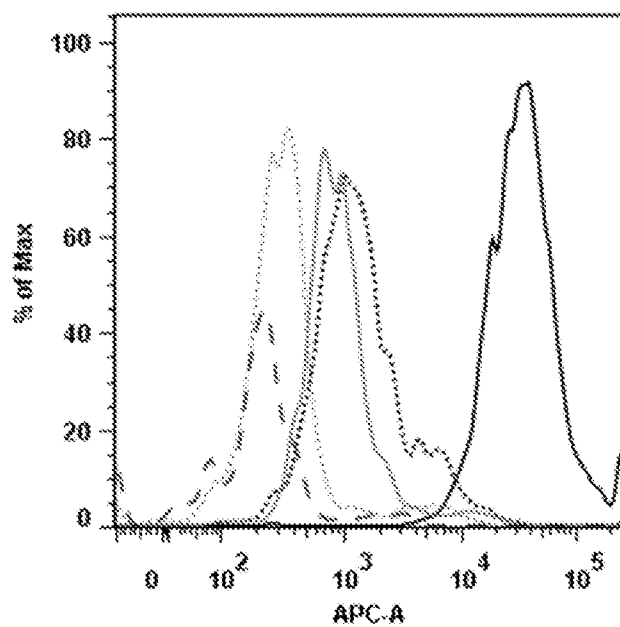


FIG. 4

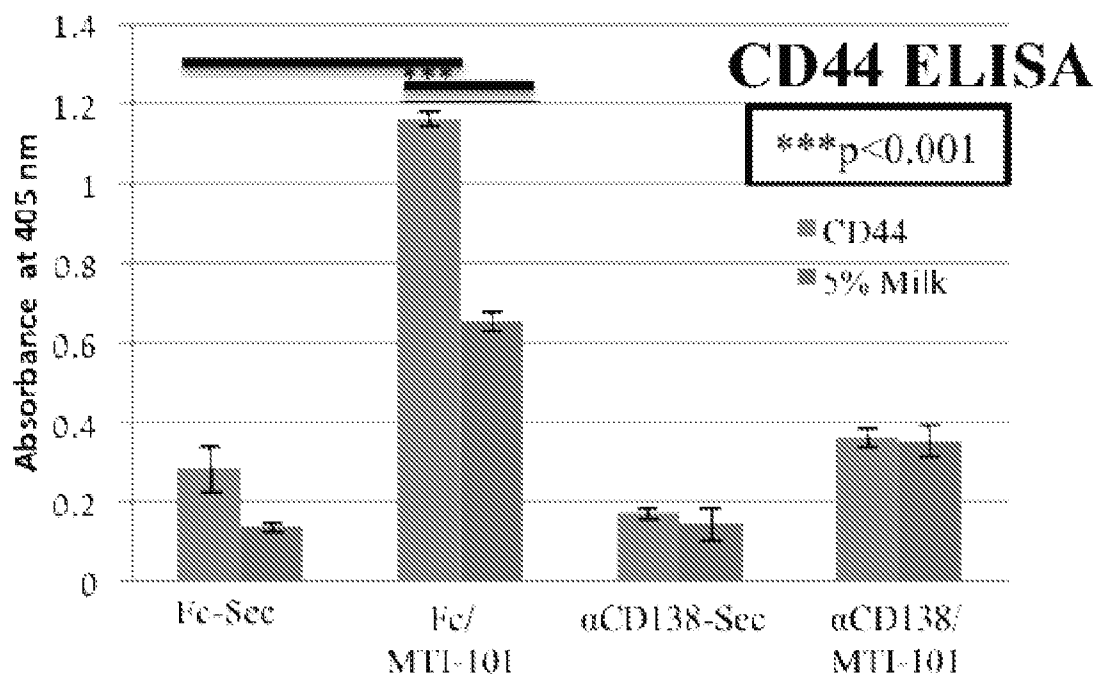
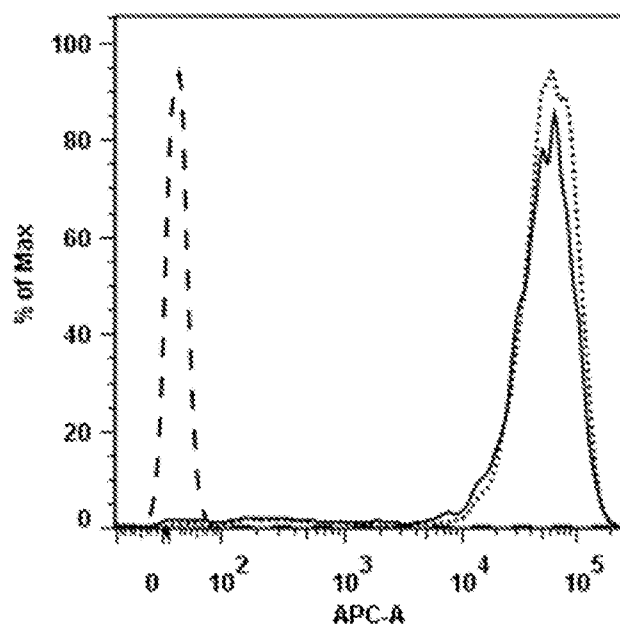
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**FIG. 5**

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**FIG. 6A****FIG. 6B**

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**FIG. 7****FIG. 8A**

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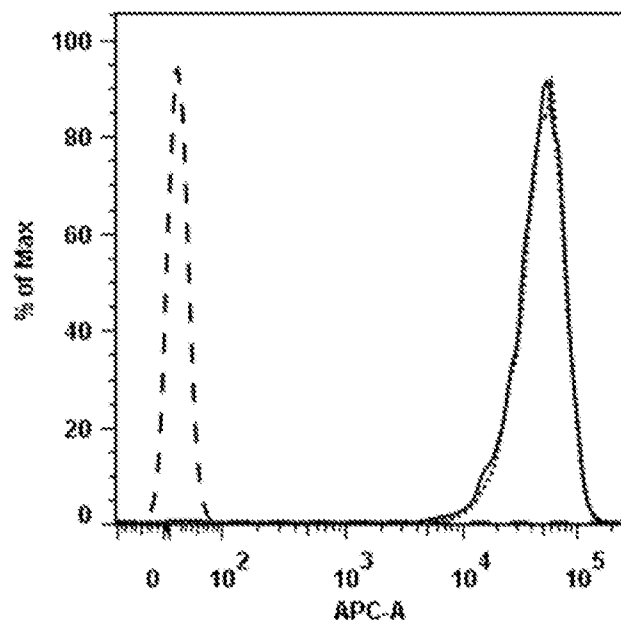


FIG. 8B

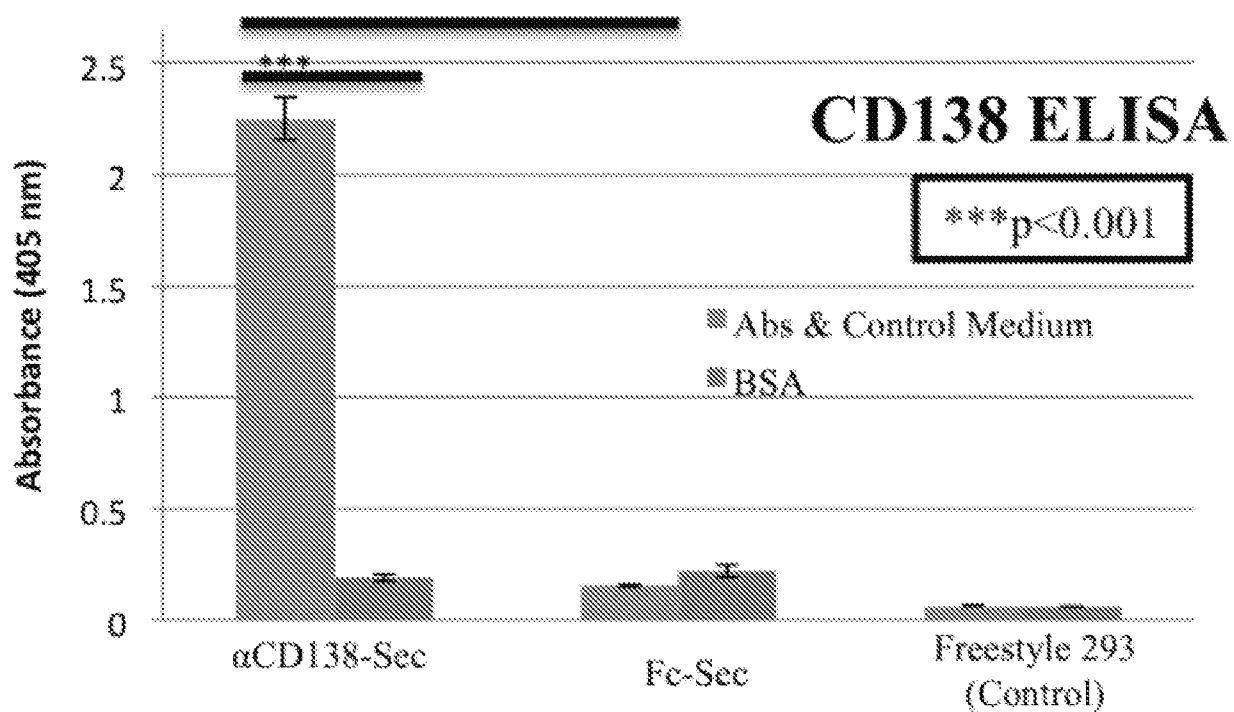


FIG. 9

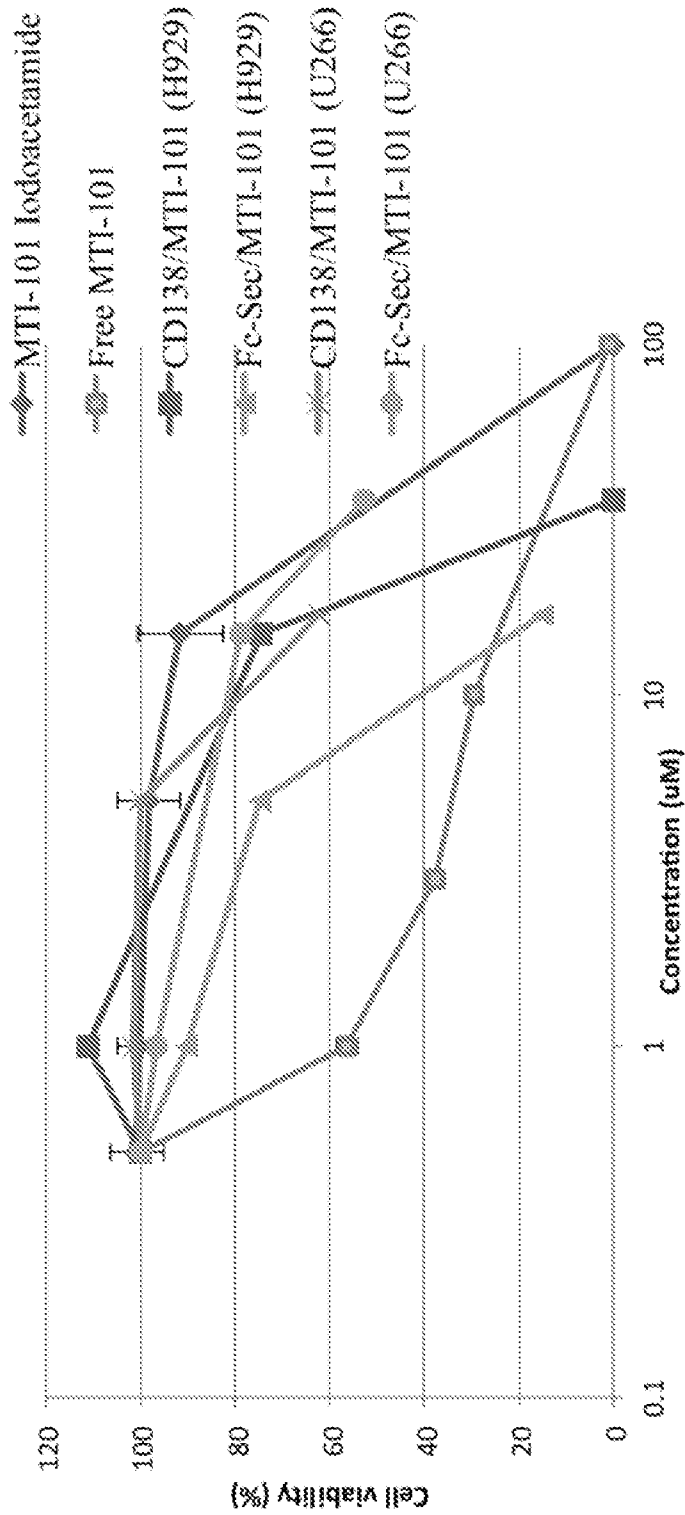


FIG. 10

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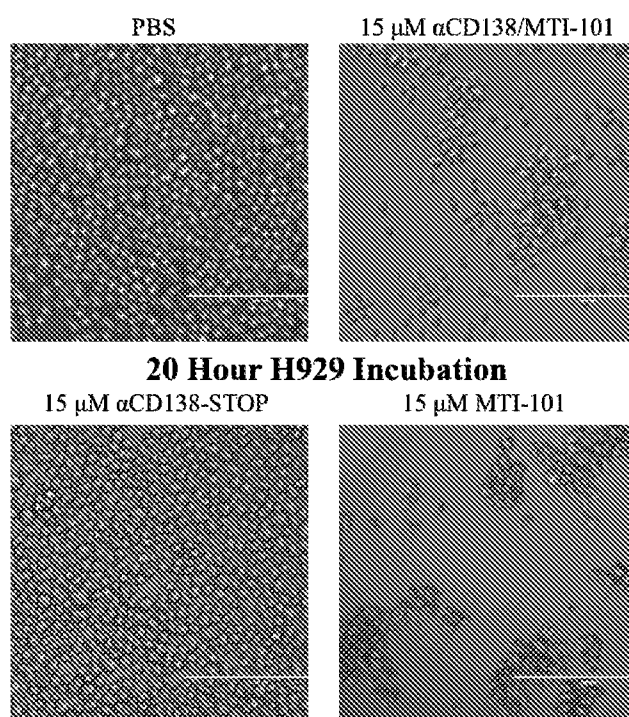
**FIG. 11**

FIG. 12A

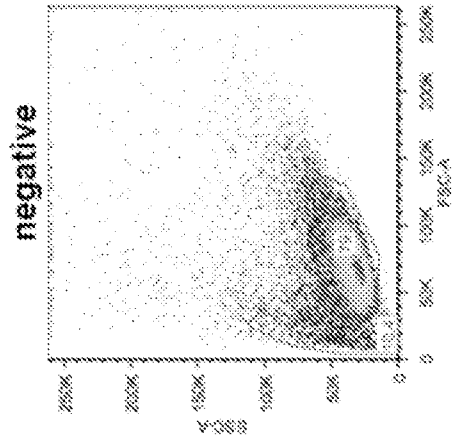


FIG. 12B

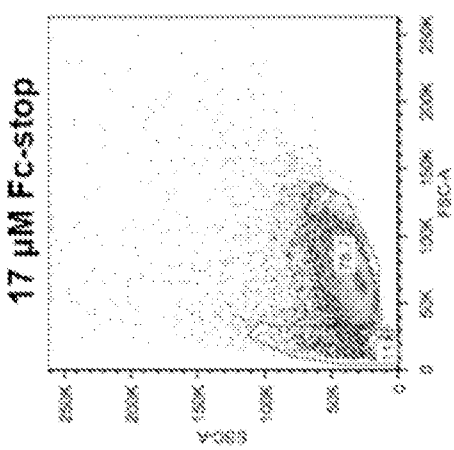


FIG. 12C

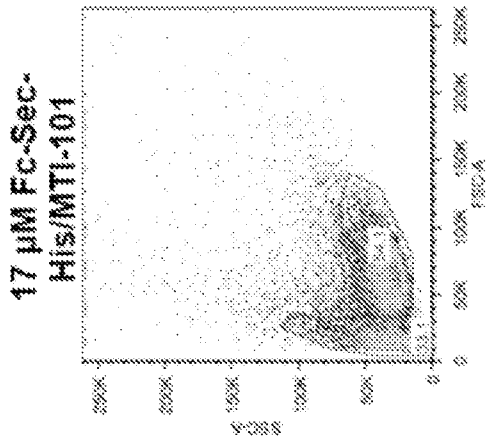


FIG. 12D

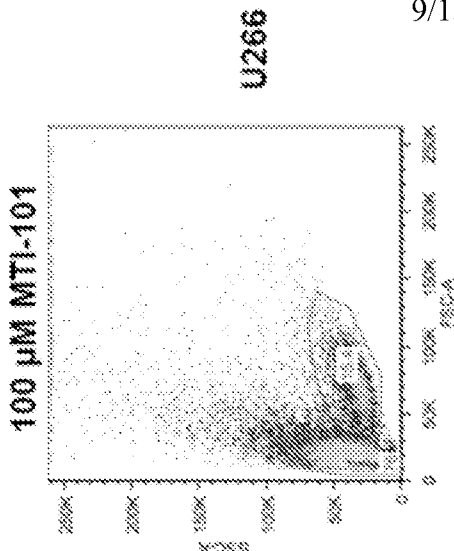


FIG. 12E

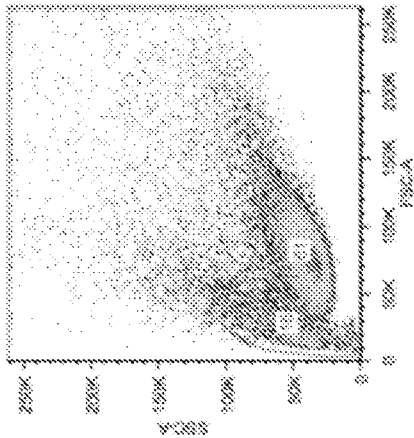


FIG. 12F

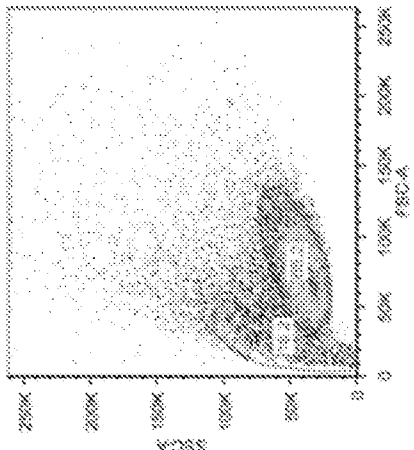


FIG. 12G

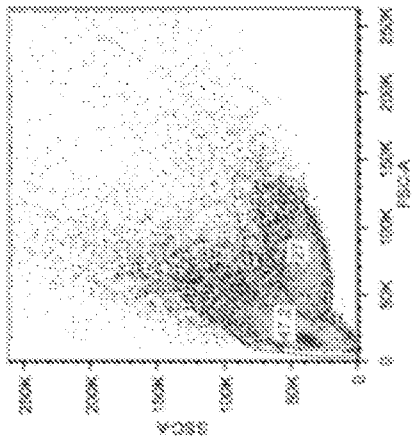
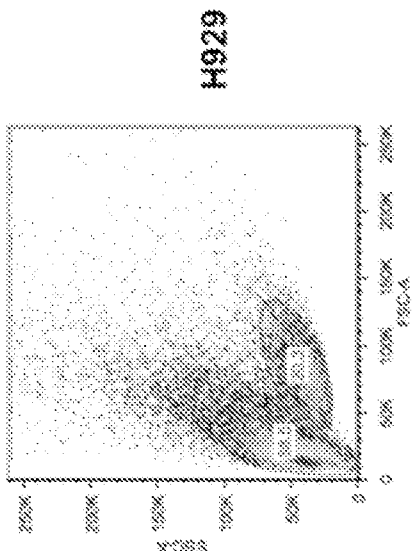


FIG. 12H



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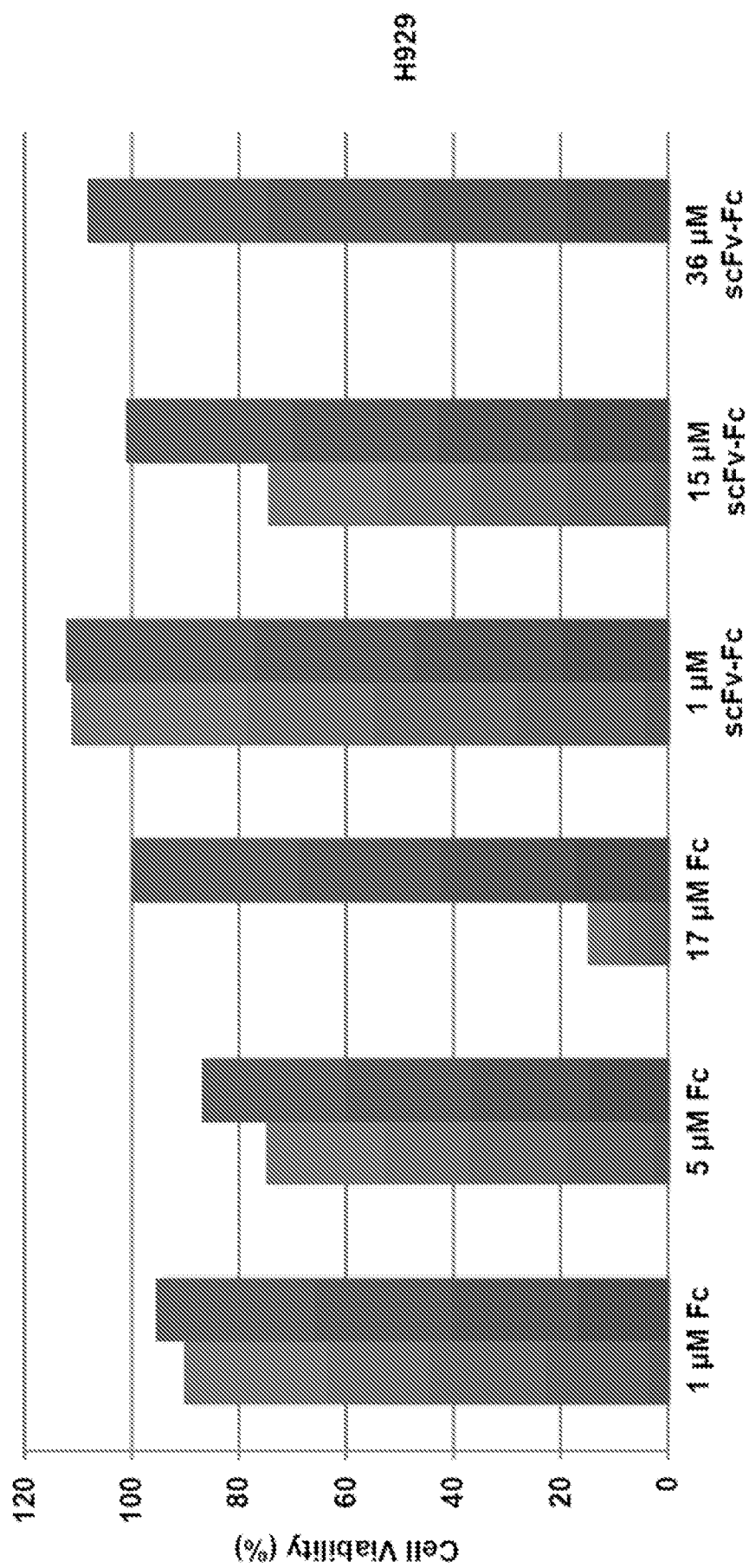


FIG. 13

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FIG. 14A
36 μ M scFv-Fc-
stop

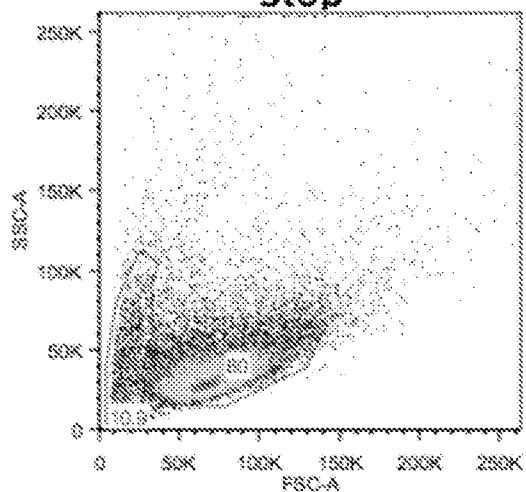
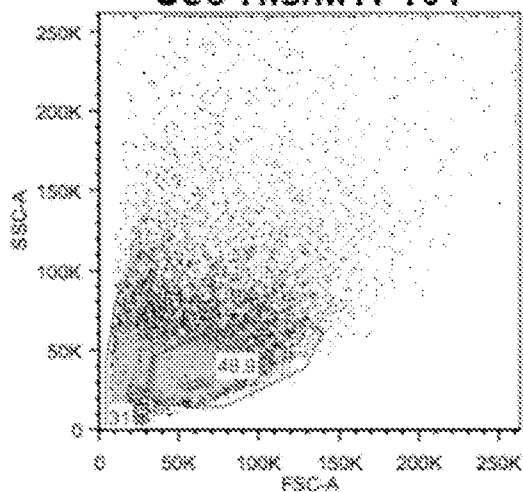


FIG. 14B
36 μ M scFv-Fc-
Sec-His/MTI-101



U266

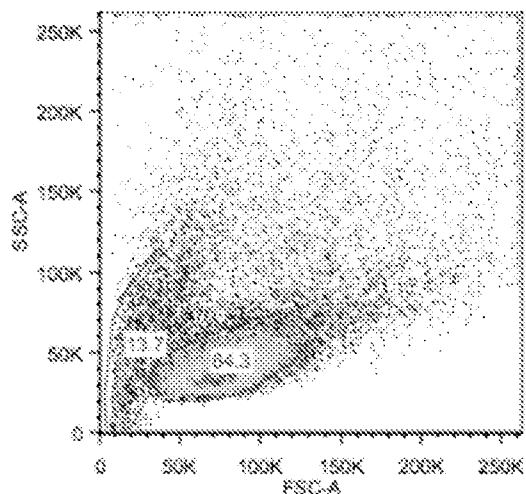
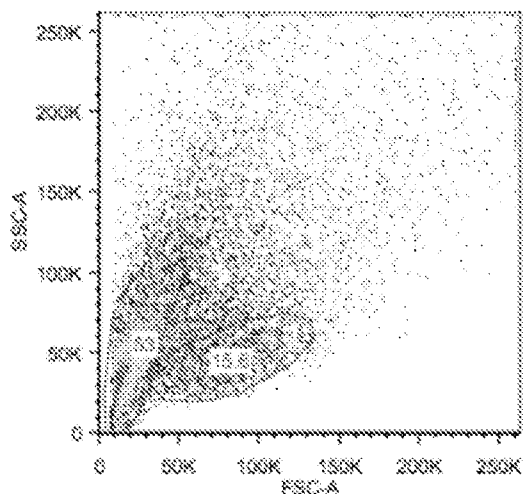


FIG. 14C



H929

FIG. 14D

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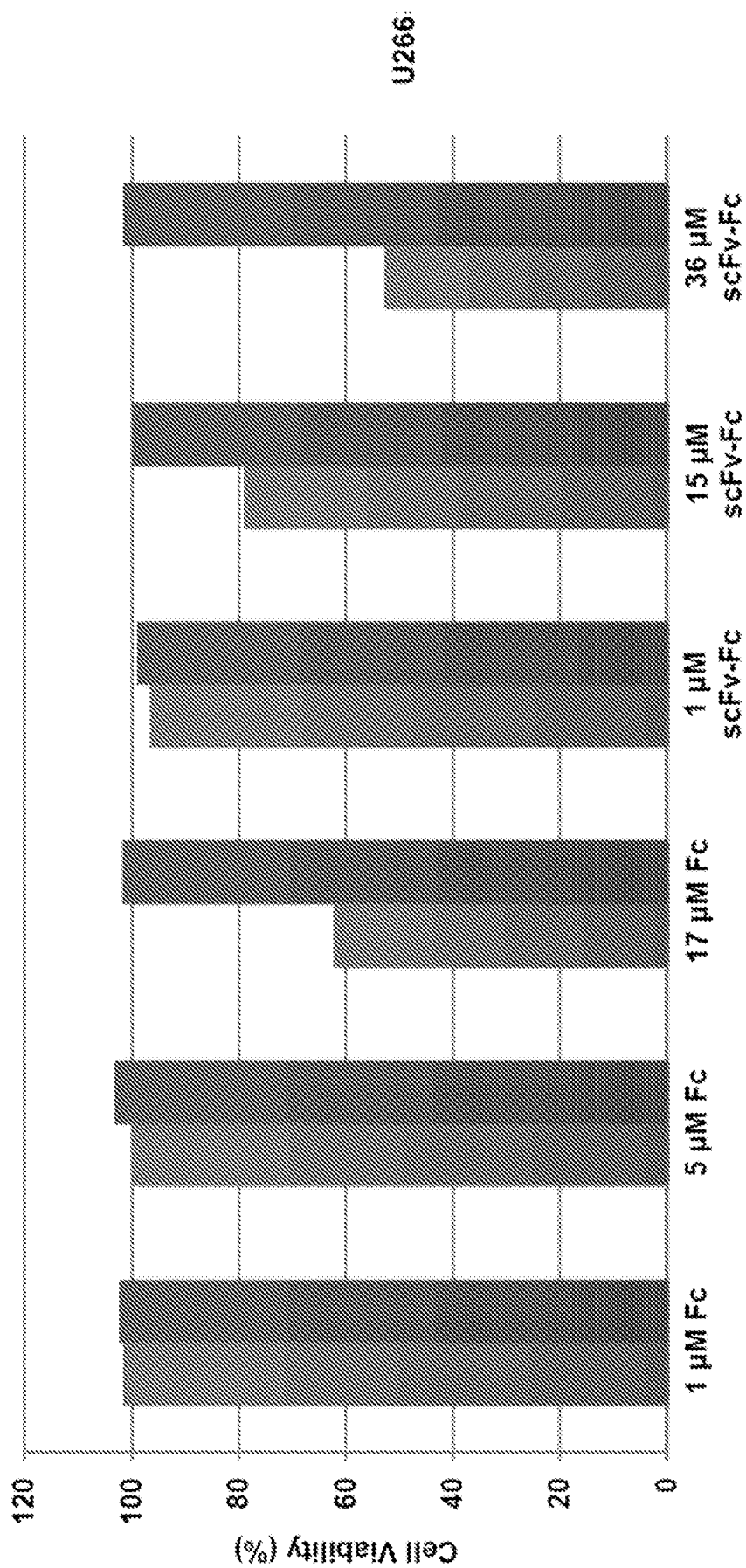


FIG. 15

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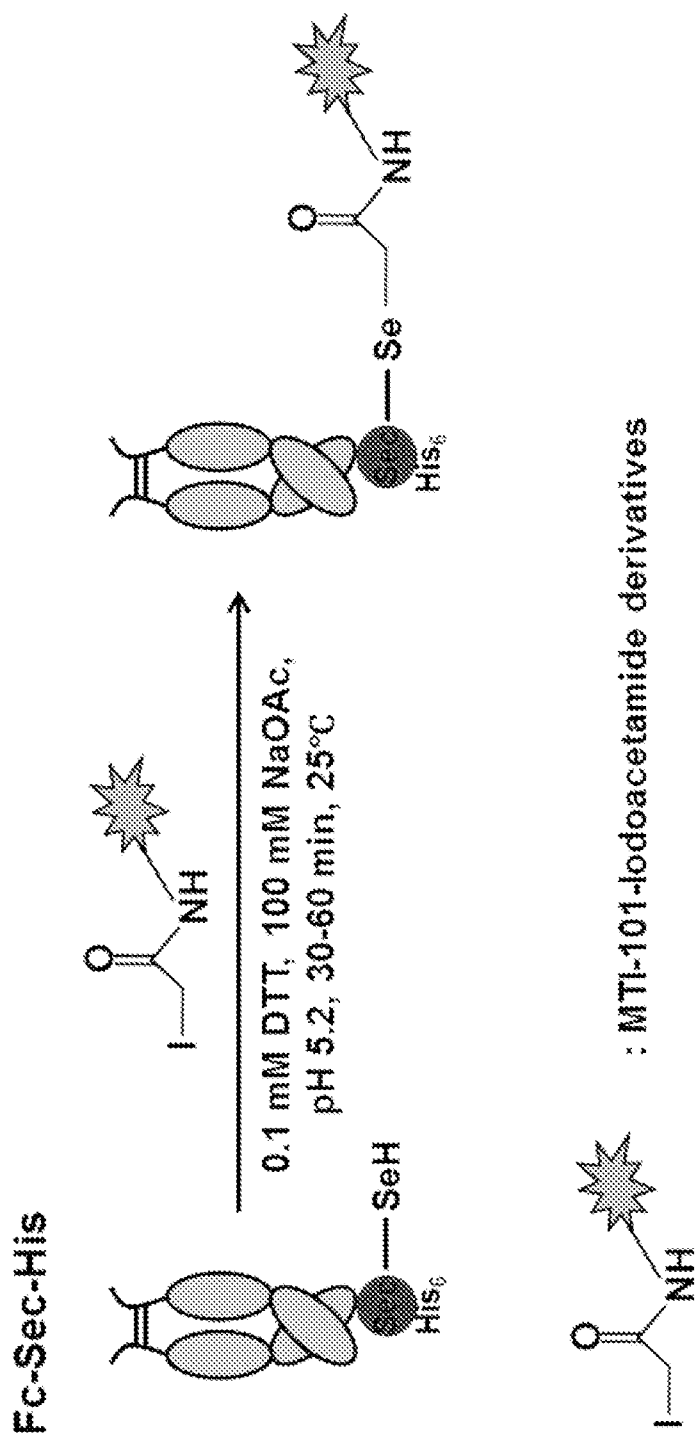
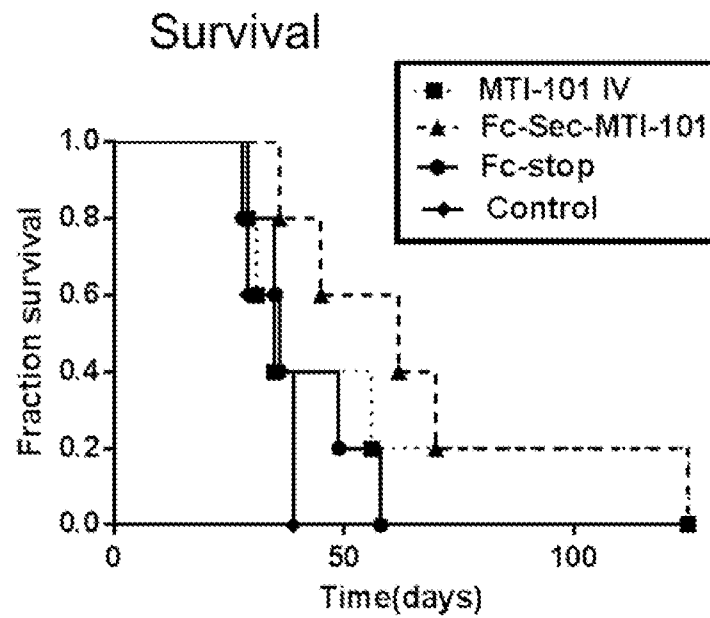
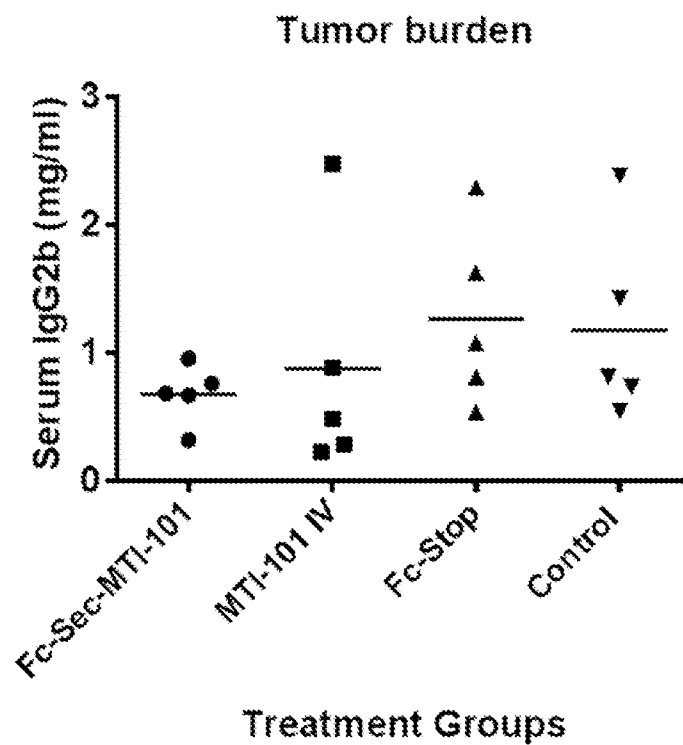


FIG. 16

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**FIG. 18A****FIG. 18B**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/057763**A. CLASSIFICATION OF SUBJECT MATTER****C07K 7/00(2006.01)i, C07K 19/00(2006.01)i, A61K 38/10(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07K 7/00; A61K 39/395; A61K 51/00; A61K 38/12; C07K 7/64; C07K 19/00; A61K 38/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: cyclic compound, recognition sequence, non-recognition sequence, MTI-101

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011-115688 A2 (H. LEE MOFFITT CANCER CENTER & RESEARCH INSTITUTE et al.) 22 September 2011 See abstract; pages 4, 11; table 8; figure 45B; claims 1-2, 5.	1-6, 9-17, 37
Y		7-8, 18-26
Y	HOFER et al., 'Molecularly defined antibody conjugation through a selenocysteine interface' Biochemistry, Vol.48, No.50, pp.12047-12057 (2009) See abstract; page 12050.	7-8, 18-26
A	US 2010-0104510 A1 (RADER et al.) 29 April 2010 See claims 1, 10.	1-26, 37
A	GEBHARD et al., 'MTI-101 (cyclized HYD1) binds a CD44 containing complex and induces necrotic cell death in multiple myeloma' Molecular Cancer Therapeutics, Vol.12, No.11, pp.2446-2458 (Epub. 18 September 2013) See the whole document.	1-26, 37



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

14 January 2015 (14.01.2015)

Date of mailing of the international search report

14 January 2015 (14.01.2015)

Name and mailing address of the ISA/KR

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INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US2014/057763**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 27-36
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 27-36 pertain to methods for treatment of the human body by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv), to search.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2014/057763

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011-115688 A2	22/09/2011	CA 2793838 A1 EP 2547693 A2 EP 2547693 A4 US 2013-0065837 A1 US 8853149 B2 WO 2011-115688 A3	22/09/2011 23/01/2013 28/08/2013 14/03/2013 07/10/2014 16/02/2012
US 2010-0104510 A1	29/04/2010	US 8916159 B2 WO 2008-122039 A2 WO 2008-122039 A3	23/12/2014 09/10/2008 15/10/2009