

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	MAIL STOP AF
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R. Yongxin ZHAO	)	Group Art Unit: 1643
	)	
Application No.: 14/432,073	)	Examiner: Canella, Karen A
	)	
Filed: March 27, 2015	)	Confirmation No.: 6938
	)	
For: HYDROPHILIC LINKERS AND	)	
THEIR USES FOR CONJUGATION	)	
OF DRUGS TO A CELL BINDING	)	
MOLECULES	)	

AMENDMENT UNDER 37 C.F.R. § 1.116

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

In response to the Official Action dated July 10, 2018, please amend the above identified application as follows.

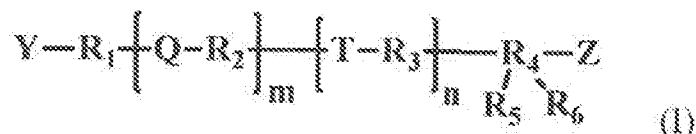
Certification and Request for Consideration under the After-Final Consideration Pilot program 2.0 is being filed concurrently.

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (Previously Presented) A hydrophilic linker of formula (I)



wherein:

Y represents a functional group that enables reaction of the hydrophilic linker with a cell-binding agent;

Q and T are either -P(=O)(OM)-, or -S(O₂)-, or -S(O)-;

m and n are integer from 0 to 5, but not 0 at the same time; provided that when m=1, n=0, Q is not -P(=O)(OM)-; when n=1, m=0, T is not -P(=O)(OM)-; and when Q or T is -S(O₂)-, m and n are not 0;

Z represents a functional group that enables linkage of the hydrophilic linker to a cytotoxic drug via a disulfide, thioether, thioester, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxy or amide bond;

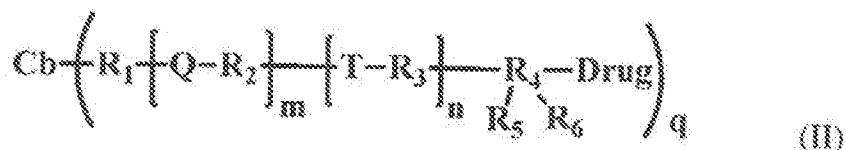
R₁, R₂, R₃, and R₄, are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof,

or R₁, R₂, R₃ and R₄ are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R₁, R₂, R₃ and R₄);

R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt.

2. (Currently Amended) A cell-binding agent-drug conjugate of formula (II):



wherein:

Cb represents a cell-binding agent;

Drug represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, cycloheteroalkane, heteroaromatic, alkoimine or amide bond;

Q and T are either $-P(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$;

m and n are integer from 0 to 5, but not 0 at the same time; provided that when $m=1$, $n=0$, Q is not $-P(=O)(OM)-$; ~~and~~ when $n=1$, $m=0$, T is not $-P(=O)(OM)-$; and when Q or T is $-S(O)-$, m and n are not 0;

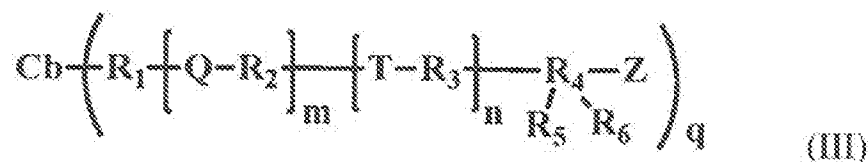
R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof,

or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4);

R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt.

3. (Previously Presented) A compound of formula (III):



wherein:

Cb represents a cell-binding agent;

Q and T are either $-P(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$;

m and n are integer from 0 to 5, but not 0 at the same time; provided that when $m=1$, $n=0$,

Q is not $-P(=O)(OM)-$; and when $n=1$, $m=0$, T is not $-P(=O)(OM)-$;

q is an integer from 1 to 20;

Z represents a functional group that enables linkage of the compound to a cytotoxic drug via a disulfide, thioether, thioester, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

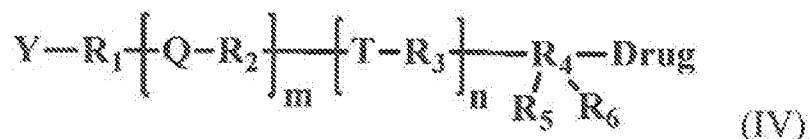
R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof,

or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4);

R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt.

4. (Previously Presented) A compound of formula (IV):



wherein:

Y represents a functional group that enables reaction of the compound with a cell-binding agent;

Q and T are either $-P(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$;

m and n are integer from 0 to 5, but not 0 at the same time; provided that when $m=1$, $n=0$, Q is not $-P(=O)(OM)-$; and when $n=1$, $m=0$, T is not $-P(=O)(OM)-$;

"Drug" represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof,

or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4);

R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt.

5. (Currently Amended) The conjugate of claim 2, wherein Drug is selected from the group consisting of:

1). therapeutic agents comprising a). Alkylating agents comprising Nitrogen mustards comprising chlorambucil, chlornaphazine, cyclophosphamide, dacarbazine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, mannomustine, mitobronitol, melphalan, mitolactol, pipobroman, novembichin, phenesterine, prednimustine, thiotepa, trofosfamide, uracil mustard; CC-1065 and adozelesin, carzelesin and bizelesin; duocarmycin, KW-2189 and CBI-TMI; benzodiazepine dimers comprising dimers of pyrrolbenzodiazepine or tomaymycin, indolinbenzodiazepines, imidazobenzothiadiazepines, or oxazolidinobenzodiazepines; Nitrosoureas comprising carmustine, lomustine, chlorozotocin, fotemustine, nimustine, ranimustine; Alkylsulphonates comprising busulfan, treosulfan, improsulfan and piposulfan; Triazenes; dacarbazine; Platinum containing compounds comprising carboplatin, cisplatin, oxaliplatin; aziridines comprising benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate and trimethylolomelamine; b). Plant Alkaloids comprising Vinca alkaloids comprising vincristine, vinblastine, vindesine, vinorelbine, navelbin; Taxoids comprising paclitaxel, and docetaxol, Maytansinoids comprising DM1, DM2, DM3, DM4, ~~DM5~~DM5, DM6, DM7, maytansine and ansamitocins, cryptophycins comprising cryptophycin 1 and cryptophycin 8; epothilones, eleutherobin, discodermolide, bryostatins, dolostatins, auristatins, tubulysins, cephalostatins; pancratistatin; a sarcodictyin; spongistatin; c). DNA Topoisomerase Inhibitors comprising Epipodophyllins comprising 9-aminocamptothecin, camptothecin, crisnatol, daunomycin, etoposide, etoposide phosphate, irinotecan, mitoxantrone,

novantrone, retinoic acids, retinols, teniposide, topotecan, 9-nitrocamptothecin; mitomycins; d). Anti-metabolites comprising Anti-folate comprising DHFR inhibitors comprising methotrexate, trimetrexate, denopterin, pteropterin, and aminopterin; IMP dehydrogenase Inhibitors comprising mycophenolic acid, tiazofurin, and ribavirin, EICAR; Ribonucleotide reductase Inhibitors comprising hydroxyurea and deferoxamine; Pyrimidine compounds comprising uracil compounds comprising ancitabine, azacitidine, 6-azauridine, capecitabine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, 5-Fluorouracil, floxuridine, and ratitrexed; Cytosine compounds comprising cytarabine, cytosine arabinoside, and fludarabine; Purine compounds comprising azathioprine, fludarabine, mercaptopurine, thiamiprine, and thioguanine; folic acid replenisher; e). Hormonal therapies comprising Receptor antagonists comprising anti-estrogen selected from the group consisting of megestrol, raloxifene, and tamoxifen; LHRH agonists comprising goserelin, and leuprolide acetate; anti-androgens comprising bicalutamide, flutamide, calusterone, dromostanolone propionate, epitio stanol, goserelin, leuprolide, mepitiostane, nilutamide, testolactone, and trilostane; Vitamin D3 compounds comprising CB 1093, EB 1089, KH 1060, cholecalciferol, and ergocalciferol; photodynamic therapies comprising verteporfin, phthalocyanine, photo sensitizer Pc4, and demethoxy-hypocrellin A; cytokines comprising Interferon-alpha, Interferon-gamma, tumor necrosis factor, and human proteins containing a TNF domain; f). Kinase inhibitors comprising anti-EGFR/Erb2, imatinib, gefitinib, pegaptanib, sorafenib, dasatinib, sunitinib, erlotinib, nilotinib, lapatinib, axitinib, pazopanib, vandetanib, anti-VEGFR2, mubritinib, ponatinib, bafetinib, bosutinib, cabozantinib, vismodegib, iniparib, ruxolitinib, CYT387, axitinib, tivozanib, sorafenib, bevacizumab, cetuximab, Trastuzumab, Ranibizumab, Panitumumab, and ispinesib; g). antibiotics comprising enediyne antibiotics comprising calicheamicins comprising calicheamicin γ 1, δ 1, α 1 and β 1; dynemicin selected from the group consisting of dynemicin A and deoxydynemicin; esperamicin, kedarcidin, C-1027, maduropeptin, neocarzinostatin chromophore and chromoprotein enediyne antiobiotic chromomophores, aclacinomysins, actinomycins, anthramycin, azaserine, bleomycins, cactinomycin, carabycin, carminomycin, carzinophilin; chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-

doxorubicin and deoxydoxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; h). polyketides comprising bullatacin and bullatacinone; gemcitabine, epoxomicins, bortezomib, thalidomide, lenalidomide, pomalidomide, tosedostat, ZYBRESTATfosbretabulin, PLX4032vemurafenib, STA-9090Ganetespib, STIMUVAXtecemotide, ALLOVECTIN-7@, XGEVAdenosumab, PROVENGEsipuluncel-T, YERVOYipilimumab, Isoprenylation inhibitors, Dopaminergic neurotoxins, Cell cycle inhibitors, Actinomycin D, bleomycin A2, bleomycin B2, and peplomycin, Anthracyclines comprising daunorubicin, adriamycin, idarubicin, epirubicin, pirarubicin, zorubicin, and mitoxantrone, MDR inhibitors, Ca^{2+} ATPase inhibitors, Histone deacetylase inhibitors comprising Vorinostat, ROMIDEPSIN, Panobinostat, Valproic acid, Mocetinostat, Belinostat, PCI-24781, Entinostat, SB939, Resminostat, Givinostat, AR-42, CUDC-101, sulforaphane, and Trichostatin A; Celecoxib, glitazones, epigallocatechin gallate, Disulfiram, Salinosporamide A.; Anti-adrenals comprising aminogluthethimide, mitotane, and trilostane; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; arabinoside, bestabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; eflornithine, elfomithine; elliptinium acetate, etoglucid; gallium nitrate; gacytosine, ibandronate, lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK@; razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes comprising T-2 toxin, verrucarins A, roridin A and anguidine; urethane, siRNA, antisense drugs;

2). anti-autoimmune disease agents comprising cyclosporine, cyclosporine A, aminocaproic acid, azathioprine, bromocriptine, chlorambucil, chloroquine, cyclophosphamide, corticosteroids comprising amcinonide, betamethasone, budesonide, hydrocortisone, flunisolide, fluticasone propionate, flucortolone danazol, dexamethasone, Triamcinolone acetonide, and beclometasone dipropionate, DHEA, enanercept, hydroxychloroquine, infliximab, meloxicam, methotrexate, mofetil, mycophenylate, prednisone, sirolimus, tacrolimus;

3). anti-infectious disease agents comprising a). Aminoglycosides comprising amikacin, astromycin, gentamicin comprising netilmicin, sisomicin and isepamicin, hygromycin B, kanamycin comprising amikacin, arbekacin, bekanamycin, dibekacin, and tobramycin, neomycin comprising framycetin, paromomycin, and ribostamycin, netilmicin, spectinomycin, streptomycin, and verdamicin; b). Amphenicols comprising azidamfenicol, chloramphenicol, florfenicol, and thiamphenicol; c). Ansamycins comprising geldanamycin, and herbimycin; d). Carbapenems comprising biapenem, doripenem, ertapenem, imipenem/cilastatin, meropenem, and panipenem; e). Cephems comprising carbacephem, cefacetrile, cefaclor, cefradine, cefadroxil, cefalonium, cefaloridine, cefalotin or cefalothin, cefalexin, cefaloglycin, cefamandole, cefapirin, cefatrizine, cefazaflur, cefazedone, cefazolin, cefbuperazone, cefcapene, cefdaloxime, cefepime, cefminox, cefoxitin, cefprozil, cefroxadine, ceftezole, cefuroxime, cefixime, cefdinir, cefditoren, cefepime, cefetamet, cefmenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, cefozopran, cephalixin, cefpimizole, cefpiramide, cefpirome, cefpodoxime, cefprozil, cefquinome, cefsulodin, ceftazidime, cefteram, ceftibuten, ceftiolene, ceftizoxime, ceftobiprole, ceftriaxone, cefuroxime, cefuzonam, cephamycin comprising cefoxitin, cefotetan, and cefinetazole, and oxacephem comprising flomoxef, and latamoxef; f). Glycopeptides comprising bleomycin, vancomycin, teicoplanin, and ramoplanin; g). Glycylcyclines; h). β -Lactamase inhibitors comprising penam, and clavam; i). Lincosamides comprising clindamycin, and lincomycin; j). Lipopeptides comprising daptomycin, A54145, and calcium-dependent antibiotics; k). Macrolides comprising azithromycin, cethromycin, clarithromycin, dirithromycin, erythromycin, flurithromycin, josamycin, ketolide, midecamycin, miocamycin, oleandomycin, rifamycins, rokitamycin, roxithromycin, spiramycin, troleandomycin, and telithromycin; l). Monobactams comprising aztreonam, and tigemonam; m). Oxazolidinones; n). Penicillins comprising amoxicillin, ampicillin, azidocillin, azlocillin, benzylpenicillin, benzathine benzylpenicillin, benzathine phenoxymethylpenicillin, clometocillin, procaine benzylpenicillin, carbenicillin, cloxacillin, dicloxacillin, epicillin, flucloxacillin, mecillinam, mezlocillin, meticillin, nafcillin, oxacillin, penamecillin, penicillin, pheneticillin, phenoxymethylpenicillin, piperacillin, propicillin, sulbenicillin, temocillin, and ticarcillin; o). Polypeptides comprising bacitracin, colistin, and

polymyxin B; p). Quinolones comprising alatrofloxacin, halofloxacin, ciprofloxacin, clinafloxacin, danofloxacin, difloxacin, enoxacin, enrofloxacin, floxin, garenoxacin, gatifloxacin, gemifloxacin, grepafloxacin, kano trovafloxacin, levofloxacin, lomefloxacin, marbofloxacin, moxifloxacin, nadifloxacin, norfloxacin, orbifloxacin, ofloxacin, pefloxacin, trovafloxacin, grepafloxacin, sitafloxacin, sparfloxacin, temafloxacin, tosufloxacin, and trovafloxacin; q). Streptogramins comprising pristinamycin, and quinupristin/dalfopristin; r). Sulfonamides comprising mafenide, prontosil, sulfacetamide, sulfamethizole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim, and trimethoprim-sulfamethoxazole; s). Steroid antibacterials; t). Tetracyclines comprising doxycycline, chlortetracycline, clomocycline, demeclocycline, lymecycline, meclocycline, metacycline, minocycline, oxytetracycline, penimepicycline, rolitetracycline, and tetracycline; u). antibiotics comprisingannonacin, arspenamine, bactoprenol inhibitors, DADAL/AR inhibitors, dictyostatin, discodermolide, eleutherobin, epothilone, ethambutol, etoposide, faropenem, fusidic acid, furazolidone, isoniazid, laulimalide, metronidazole, mupirocin, mycolactone, NAM synthesis inhibitors, nitrofurantoin, paclitaxel, platensimycin, pyrazinamide, quinupristin/dalfopristin, rifampin, tazobactam tinidazole, and uvaricin;

4). anti-viral drugs comprising a). Entry/fusion inhibitors comprising aplaviroc, maraviroc, vicriviroc, enfuvirtide, PRO 140, and ibalizumab; b). Integrase inhibitors comprising raltegravir, elvitegravir, and globoidnan A; c). Maturation inhibitors comprising bevirimat, and vivecon; d). Neuraminidase inhibitors comprising oseltamivir, zanamivir, and peramivir; e). Nucleosides & nucleotides comprising abacavir, aciclovir, adefovir, amdoxovir, apricitabine, brivudine, cidofovir, clevidine, dextelvucitabine, didanosine, elvucitabine, emtricitabine, entecavir, famciclovir, fluorouracil, 3'-fluoro-substituted 2',3'-dideoxynucleoside compounds comprising 3'-fluoro-2',3'-dideoxythymidine and 3'-fluoro-2',3'-dideoxyguanosine, fomivirsen, ganciclovir, idoxuridine, lamivudine, 1-nucleosides comprising β -1-thymidine and β -1-2'-deoxycytidine, penciclovir, racivir, stampidine, stavudine, taribavirin, telbivudine, tenofovir, trifluridine valaciclovir, valganciclovir, zalcitabine, and zidovudine; f). non-nucleosides comprising amantadine, ateviridine, capravirine, diarylpyrimidines, delavirdine, docosanol, emivirine, efavirenz, foscarnet, imiquimod, interferon alfa, loviride, lodenosine, methisazone,

nevirapine, NOV-205, peginterferon alfa, podophyllotoxin, rimantadine, resiquimod, and tromantadine; g). protease inhibitors comprising amprenavir, atazanavir, boceprevir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, pleconaril, ritonavir, saquinavir, telaprevir, and tipranavir; h). anti-virus drugs comprising ABZYME, ~~ARBIDOL~~ lumifenovir, calanolide a, ceragenin, cyanovirin-n, epigallocatechin gallate, foscarnet, griffithsin, hydroxyurea, KP-1461, miltefosine, pleconaril, portmanteau inhibitors, RIBAVIRIN, and seliciclib;

5). a radioisotope of ^3H , ^{11}C , ^{14}C , ^{18}F , ^{32}P , ^{35}S , ^{64}Cu , ^{68}Ga , ^{86}Y , $^{99\text{m}}\text{Tc}$, ^{111}In , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{133}Xe , ^{177}Lu , ^{211}At , or ^{213}Bi ; and

6). pharmaceutically acceptable salts or acids of any of 1) to 5).

6. (Previously Presented) The conjugate of claim 2, wherein Drug is selected from the group consisting of tubulysins, calicheamicins, auristatins, maytansinoids, CC-1065 compounds, morpholinos doxorubicins, taxanes, cryptophycins, epothilones, and benzodiazepine dimers, siRNA or a combination thereof, and pharmaceutically acceptable salts or acids of any of the above.

7. (Previously Presented) The conjugate of claim 2, wherein the cell binding agent is selected from the group consisting of antibodies, proteins, vitamins, peptides, polymeric micelles, liposomes, lipoprotein-based drug carriers, nano-particle drug carriers, dendrimers, and combination thereof.

8. (Canceled)

9. (Previously Presented) The conjugate of claim 2, wherein the cell-binding agent is an antibody, a single chain antibody, an antibody fragment that binds to a target cell, a monoclonal antibody, a single chain monoclonal antibody, or a monoclonal antibody fragment that binds the target cell, a chimeric antibody, a chimeric antibody fragment that binds to the target cell, a domain antibody, a domain antibody fragment that binds to the target cell, a resurfaced antibody, a resurfaced single chain antibody, or a resurfaced antibody fragment that binds to the target cell,

a humanized antibody or a resurfaced antibody, a humanized single chain antibody, or a humanized antibody fragment that binds to the target cell, a lymphokine, a hormone, a vitamin, a growth factor, a colony stimulating factor, or a nutrient-transport molecule.

10. (Canceled)

11. (Previously Presented) A pharmaceutical composition comprising a therapeutically effective amount of the conjugate of claim 2, and a pharmaceutically acceptable salt, carrier, diluent, or excipient therefor.

12. (Previously Presented) The conjugate of claim 2, wherein the drug is selected from the group consisting of a toxin, a chemotherapeutic agent, a drug moiety, an antibiotic, a radioactive isotope, and a nucleolytic enzyme.

13. (Canceled)

14. (Previously Presented) The conjugate of claim 2, wherein the conjugate comprises one or more linker components of 6-maleimidocaproyl, maleimidopropanoyl, valine-citrulline, alanine-phenylalanine, p-aminobenzyloxycarbonyl, 4-thio-pentanoate, 4-(N-maleimidomethyl)cyclohexane-1-carboxylate, 4-thio-butyrate, maleimidoethyl, 4-thio-2-hydroxysulfonyl-butyrate and (4-acetyl)aminobenzoate.

15. (Previously Presented) The conjugate of claim 2, wherein Drug is selected from the group consisting of tubulysins, maytansinoids, taxanoids, CC-1065 compounds, daunorubicin and doxorubicin compounds, benzodiazepine dimers, calicheamicins and the enediyne antibiotics, actinomycin, azaserines, bleomycins, epirubicin, tamoxifen, idarubicin, dolastatins/auristatins, duocarmycins, thiotepa, vincristine, hemiasterlins, and esperamicins.

16. (Previously Presented) The conjugate of claim 2, having in vitro, in vivo or ex vivo cell

killing activity.

17. (Previously Presented) The conjugate of claim 2, wherein the conjugate comprises either a peptide of 1-20 units of natural or unnatural amino acids, or a p-aminobenzyl unit, or a 6-maleimidocaproyl unit, or a disulfide unit, or a thioether unit, or a hydrozone unit, or an alkoxime unit.

18. (Previously Presented) The conjugate of claim 2, wherein the conjugate is cleavable by a protease.

19. (Previously Presented) A pharmaceutical composition comprising the conjugate of claim 2, and a pharmaceutically acceptable carrier.

20. (Previously Presented) A pharmaceutical composition comprising a therapeutically effective amount of the conjugate of claim 2, and a chemotherapeutic agent, radiation therapy agent, immunotherapy agent, autoimmune disorder agent, or anti-infectious agent.

21. (Previously Presented) The hydrophilic linker of claim 1, wherein Z comprises a thiol, disulfide, amino, carboxy, aldehydes, maleimido, haloacetyl, hydrazine or hydroxyl group.

22. (Previously Presented) The conjugate of claim 2, wherein the drug is derived from a drug containing a -SH, -CONHNH₂, -≡, -COR'' or -NHR'', wherein R'' is H, CH₃, Et, Pr, Bu, or Ph; and/or the cell-binding agent is an antibody or protein.

23. (Previously Presented) The conjugate of claim 3, wherein the cytotoxic drug is a drug containing a -SH, -CONHNH₂, -≡, -COR'' or -NHR'', wherein R'' is H, CH₃, Et, Pr, Bu, or Ph; and/or the cell-binding agent is an antibody or protein.

24. (Previously Presented) The conjugate of claim 4, wherein the drug is derived from a drug containing a -SH, -CONHNH₂, -≡, -COR'' or -NHR'', wherein R'' is H, CH₃, Et, Pr, Bu, or Ph; and/or the cell-binding agent is an antibody or protein.

REMARKS

In the present Amendment, claim 2 has been amended to further define Q, T, m and n. Support for these amendments can be found throughout the Specification, particularly, the Examples (see, e.g., Examples 208, 218 and 230). Claim 5 has been amended to further improve its form. Claims 8 and 10 have been canceled without prejudice or disclaimer. Claim 13 was previously cancelled. No new matter has been added.

Applicant respectfully submits that entry of the amendments, after final, is proper, at least because they place the application either in condition for allowance or in better form for appeal. See M.P.E.P. § 714.12. Upon entry of the Amendment, claims 1-7, 9, 11, 12 and 14-24 will be all the claims pending in the application.

Applicant notes with appreciation that claims 1 and 21 are allowed.

I. Response to Claim Objection

Claim 5 was objected to for informalities. Applicant respectfully submits that claim 5 as amended does not contain informalities.

In the Amendment, claim 5 has been amended to correct a typographical error, by replacing "DMS" with "--DM5--", as suggested by the Examiner. Accordingly, reconsideration and withdrawal of the objection are respectfully requested.

II. Response to Rejections under 35 U.S.C. § 112

a. Claims 5 and 8 were rejected under 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite. Applicant respectfully submits that the claims as amended are not indefinite.

In the Amendment, claim 5 has been amended to replace various tradenames with chemical names. Specifically, ZYBRESTAT, PLX4032, STA-9090, STIMUVAX, ALLOVECTIN-7, XGEVA, PROVENGE, YERVOY and RIBAVIRIN have been replaced with fosbretabulin, vemurafenib, ganetespib, tecemotide, Allovectin-7®, denosumab, sipuleucel-T, ipilimumab and umifenovir, respectively:

ZYBRESTAT (fosbretabulin, combretastatin A4 phosphate made by OXiGENE Co.);

PLX4032 (vemurafenib, marketed as Zelboraf, by Plexxikon (now part of Daiichi-Sankyo) and Genentech);

STA-9090 (ganetespib);

STIMUVAX (tecemotide, by Oncothyreon and Merck KGaA);

Allovectin-7[®], developed by Vical, Inc., is a DNA plasmid containing the genes coding for foreign human HLA-B7 (an allogeneic MHC class I protein) heavy chain and β 2-microglobulin, inserted into a simplified eukaryotic expression vector (pBR322). No other name is provided. For more details, see <https://en.wikipedia.org/wiki/Allovectin-7>; and Bedikian, et al., Allovectin-7 therapy in metastatic melanoma, Expert Opin. Biol Ther., 2008, 8(6), pp839-843 (a copy is attached hereto).

XGEVA (denosumab by Amgen);

PROVENGE (sipuleucel-T by Dendreon Co., now Valeant Pharmaceuticals);

YERVOY (ipilimumab by Medarex, now Bristol-Myers Squibb);

ARBIDOL (umifenovir by JSC Pharmstandard).

Further, Applicant provides the following explanation:

ROMIDEPSIN, also known as Istodax (brand name by Gloucester Pharmaceuticals, now a part of Celgene). It was initially codenamed FK228 and FR901228. See <https://en.wikipedia.org/wiki/Romidepsin>;

An abzyme (from antibody and enzyme), also called catmab (from catalytic monoclonal antibody), and most often called catalytic antibody, is a monoclonal antibody with catalytic activity. See <https://en.wikipedia.org/wiki/Abzyme>;

Ribavirin is the INN and USAN, also known as tribavirin; its brand name is Copegus, Ribasphere, Rebetol. See <https://en.wikipedia.org/wiki/Ribavirin>.

Claim 8 has been canceled.

Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

b. Claim 8 was rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. Applicant respectfully submits that this rejection is moot because claim 8 has been canceled.

c. Claims 2-12, 14-20, and 22-24 were rejected under 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the enablement requirement. Applicant respectfully traverses the rejection for the reasons of record and the following additional reasons.

Applicant respectfully submits that it is well known in the art to use antibiotic drugs and anti-viral drugs for conjugation. For the Examiner's convenience, Applicant attaches hereto copies of some publications.

For example, Fletcher, et al. describes Peptide-IgG Conjugate in A Novel Peptide-IgG Conjugate, CAPI8₁₀₆₋₁₃₈-IgG, that Binds to and Neutralizes Endotoxin and Kills Gram-Negative Bacteria, *The Journal of Infectious Disease*, 1997, 175, pp. 621-32.

Paulik, et al. describes antibody-brefeldin A conjugates and antibody-glaucarubolone conjugates in Drug-Antibody Conjugates with Anti-HIV Activity, *Biochemical Pharmacology*, 1999, Vol. 58, pp. 1781-1790.

Zhou et al. describes THIOMAB antibody antibiotic conjugate in Pharmacokinetics and pharmacodynamics of DSTA4637A: A novel THIOMAB antibody antibiotic conjugate against *Staphylococcus aureus* in mice, *MABS*, 2016, vol. 8, no. 8, pp. 1612-1619. See, also, Lehar, et al., Novel antibody-antibiotic conjugate eliminates intracellular *S. aureus*, *Nature*, 2015, 527, 323-328, a copy of which was previously submitted.

Strong et al. describes ED and DC conjugates in Antibody-targeted Photolysis, *Annals New York Academy of Sciences*, pp. 297-320:

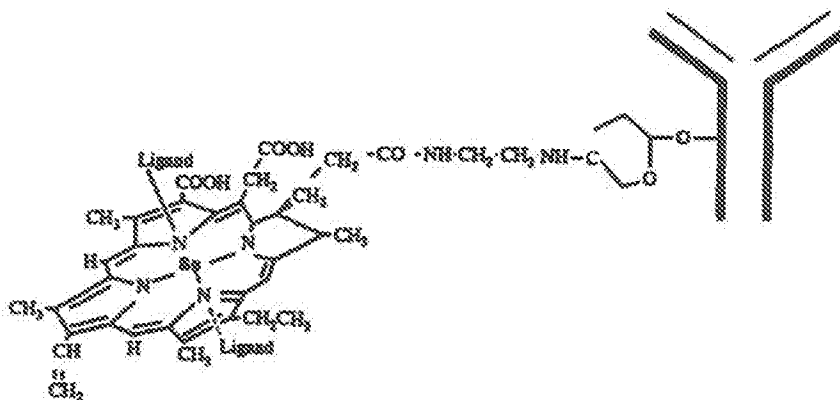


FIGURE 2a. Schematic structure of ED immunoconjugate.

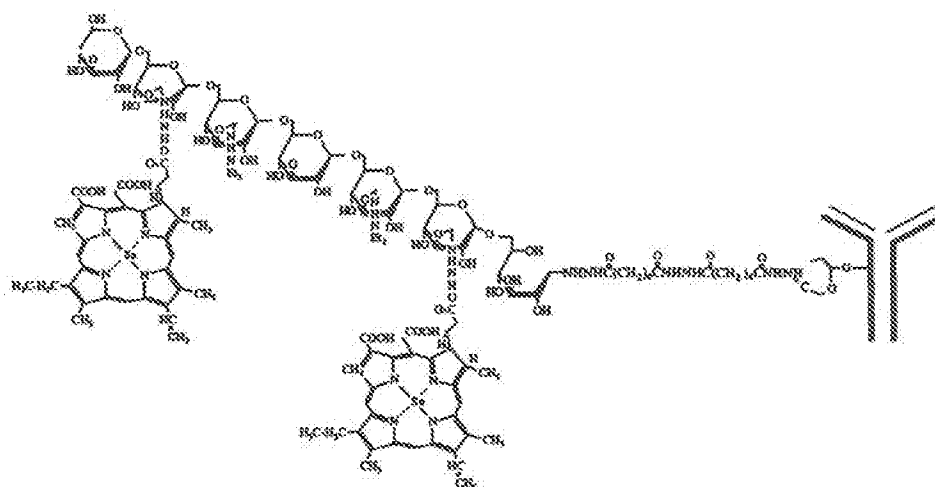


FIGURE 2b. Schematic structure of DC immunoconjugate. Axial ligands are presumed to be either OH⁻ or Cl⁻.

Nature Reviews Drug Discovery describes Antibody-antibiotic conjugate tracks down hidden *S. aureus*, December 31, 2015, www.nature.com/nrd.

Zarling, et al. describes PAP and PAP-mAb conjugates (PAP-anti CD4, PAP-anti CD7 and PAP-anti CD5) in Inhibition of HIV-1 Replication in Seropositive Patients' CD4⁺ T-Cells by Pokeweed Antiviral Protein-Monoclonal Antibody Conjugates, *Int. J. Immunopharmac.*, 1991, Vol. 13, Suppl. 1, pp. 63-68.

Neurath, et al. describes peptide- β -lactamase conjugates in Detection of Antiviral Antibodies with Predetermined Specificity Using Synthetic Peptide- β -Lactamase Conjugates: Application to Antibodies Specific for the preS Region of the Hepatitis B Virus Envelop Proteins, *J. gen. Virol.*, 1986, 67, 453-461.

Touti, et al. describes antibody-bacterial macrocyclic peptide conjugates in Antibody-Bacterial Macrocyclic Peptide Conjugates to Target Gram-Negative Bacteria, *ChemBioChem* 10.1002/cbic.201800295.

Pincus, et al. describes in Design and *in Vivo* Characterization of Immunoconjugates Targeting HIV gp160, *Journal of Virology*, February 2017, Vol. 91, Issue 3, pp. 1-16, various cytotoxic ICs consisting of a MAb or other targeting agent linked to a moiety that is toxic to cells wherein the toxic moiety is a protein toxin derived from bacteria or plants (IT), a small drug (ADC) or a high-energy radionuclide (Radio-IC). See, also, Pincus, et al., *Design and In Vivo Characterization of Immunoconjugates Targeting HIV gp160*, *Journal of*

Virology, online publication, October 19, 2016 (51 pages), a copy of which was previously submitted.

Therefore, one of ordinary skill in the art would be able to make and use the claimed invention, based on the teachings of the present application and common knowledge in the art.

In view of the foregoing, reconsideration and withdrawal of the rejection are respectfully requested.

III. Response to Rejection under 35 U.S.C. § 102

Claims 2, 5-12, 14-17, 19, 20, and 22 under pre-AIA 35 U.S.C. 102(a) and pre-AIA 35 U.S.C. 102(e) as being anticipated by WO2012145112 to Fishkin as evidenced by Kovtun et al., Cancer Research, 2010, vol. 70, pp. 2528-2537 and Widdison et al., Journal of Medicinal Chemistry, 2006, Vol. 49, pp. 4392-4408. Applicant respectfully submits that the claims as amended are patentable over the cited references for at least the following reasons.

In the Amendment, claim 2, from which claims 5-7, 9, 11, 12, 14-17, 19, 20, and 22 depend directly, has been amended to recite that in Formula (II), when Q or T is -S(O)-, m and n are not 0, thereby excluding compound 2 described in Fishkin. Kovtun et al. and Widdison et al. do not rectify the deficiencies of Fishkin.

In view of the above, reconsideration and withdrawal of the rejection are respectfully requested.

IV. Conclusion

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order and such action is earnestly solicited. If there are any questions concerning this paper or the application in general, the Examiner is invited to telephone the undersigned at his earliest convenience.

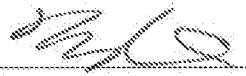
The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.20(d) and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: July 24, 2018

By:



Fang Liu

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