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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
08/15/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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EX1018
SYNAFFIX B.V.
IPR2022-01531

Office Action Summary	Application No. 14/432,073	Applicant(s) ZHAO, R. YONGXIN	
	Examiner KAREN CANELLA	Art Unit 1643	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 5/18/17.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 1-12 and 14-20 is/are pending in the application.
5a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 1-12 and 14-20 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) ☒ Notice of References Cited (PTO-892) | 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date ____. | 4) ☐ Other: ____. |

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Acknowledgement is made of applicant's election of the species -P(=O)(OM)-, and applicant's indication that claims 1-20 read on the elected species. Claim 13 has been canceled. Claims 1-12, 14-20 have been amended. Claims 1-12 and 14-20 are pending and examined to the extent that they read on the elected species.

Claim Objections

Claim 13 is objected to for:

reciting "doxorubicin" twice: the first instance on page 9, line 6 from the bottom of the page, and the second instance being on page 10, line 6

reciting "dactinomycin" twice: the first instance on page 9, line 6 from the bottom and the second instance on page 10, line 5;

reciting spectinomycin twice: page 9, section 3a and page 10, section 3k;

reciting "f)" twice: page 7, last line and page 8, line 18;

reciting glycylicyclines twice: page 10, section 3f and page 11, section 3t;

reciting bacitracin twice: page 10, section 3o and page 11, section 3u;

reciting rifampicin three times: page 10, section 3k, page 11, section 3u and page 11, section 4f;

reciting diarylpyrimidines twice: page 11, section 4f and page 12, section 4h;

reciting hydroxyurea twice: page 7, section 1d and page 9, section 1f;

reciting ribavirin twice" page 7, section 1d and page 11, section 4e;

reciting tobramycin twice: page 8, section 3a;

reciting tacrolimus twice: page 9, section 2 and page 10, section 3k.

Claim 5 is objected to for the typographical error of "dimmers of pyrrolobenzodiazepine" rather than "dimers of pyrrolobenzodiazepine".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 and 14-20 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

(A) Claims 1-4 present a structure wherein the moiety represented as [T-R3] is associated with the moiety represented as [Q-R2], the moiety represented by R4 is associated with both the [T-R3] moiety and Z or Drug, and Y-R1 is associated with the [Q-R2] moiety. It is unclear if “T” is required to be directly bonded to R2, R3 is required to be directly bonded to R4, R1 is required to be directly bonded to Q, Y or Cb is directly bonded to R1 and Z is directly bonded to R4, and R5 and R6 are directly bonded to R4 because the claims permit R1 and R4 to be “H” which would not allow for further bonding to either “Z”, “Drug”, “Y” and “Cb”. The claims also permit R2 to be “H” which would not allow for further bonding to the [T-R3] moiety and thus elimination of the inclusion of the “Z” and “Drug” moieties. Likewise, the claims permit R3 to be “H” which would not allow for further bonding to R4 and exclusion of the “Z” and “Drug” moieties. Thus, it appears that inclusion of “H” for R1, R2, R3 and/or R4 is not consistent with the interpretation of the claims wherein Y or Cb is directly attached to R1, R1 is directly attached to Q which is directly attached to R2 which is directly attached to T which is directly attached to R3 which is directly attached to R4 which is directly attached to either Z or Drug.

(B) Claim 1 recites “Z represents a functional group that enables linkage of the hydrophilic linker to a cytotoxic drug via a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, secondary or tertiary or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoximine or amide bond”. It is unclear if the recited

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species of disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, secondary or tertiary or quaternary amine, imine, cycloheteroalkylene, heteroaromatic, alkoximine or amide bond are required as part of the “Z” moiety, or if the recited species are intended to be part of the cytotoxic drug.

Claim 3 recites “Z represents a functional group that is capable of reacting with a cytotoxic drug via a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, secondary or tertiary or quaternary amine, imine, cycloheteroalkylene, heteroaromatic, alkoximine or amide bond”. It is unclear if the recited species of disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, secondary or tertiary or quaternary amine, imine, cycloheteroalkylene, heteroaromatic, alkoximine or amide bond are required as part of the “Z” moiety, or if the recited species are intended to be part of the cytotoxic drug.

For purpose of examination, the elected species will be examined within the context of the compounds described by the specification.

(C) A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by “such as” and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

In the present instance,

claims 1 and 3 recite the broad recitation that Z represents a functional group that enables linkage of the hydrophilic linker compound to a cytotoxic drug via an amide bond, and the claim also recites that Z represents a functional group that enables linkage of the hydrophilic linker compound to a cytotoxic drug via a peptide bond which is the narrower statement of the range/limitation;

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claim 5 recites the broad recitation “retinols” (page 7, 1c), and the claim also recites retinoic acids which is the narrower statement of the range/limitation;

claim 5 recites the broad recitation “retinols”, and the claim also recites CB1093, RB1089, KH1060, cholecalciferol and ergocalciferol (page 7, 1e) which is the narrower statement of the range/limitation;

claim 5 recites the broad recitation anti-EGFR/ErbB2, and the claim also recites BIBW 2992 (page 8, first line) which is the narrower statement of the range/limitation

claim 5 recites the broad recitation anti-VEGFR2, and the claim also recites E7080 (page 8, 3rd line) which is the narrower statement of the range/limitation;

claim 5 recites the broad recitation polyketides (page 8, section f), and the claim also recites acetogenins which is the narrower statement of the range/limitation;

claim 5 recites the broad recitation actinomycin on page 8, line 11, and the claim also recites actinomycin D on page 8, line 24 which are the narrower statements of the range/limitation;

claim 5 recites the broad recitation bleomycins on page 8, line 12, and the claim also recites bleomycin A2, bleomycin B2 and peplomycin on page 8, line 25 which are the narrower statements of the range/limitation;

claim 5 recites the broad recitation CA²⁺ ATPase inhibitors (page 8, line 27), and the claim also recites thapsigargin (page 9, line 1) which is the narrower statement of the range/limitation;

claim 5 recites the broad recitation bactoprenol inhibitors, and the claim also recites Bacitracin (page 11, line 8) which is the narrower statement of the range/limitation;

claim 5 recites the broad recitation DADAL/AR inhibitors, and the claim also recites cycloserine (page 11, line 8) which is the narrower statement of the range/limitation;

claim 5 recites the broad recitation diarylpyrimidines, and the claim also recites etravirine and rilpivirine (page 11, section f) which are the narrower statements of the range/limitation;

claim 8 recites the broad limitation of integrins, and the claim also recites $\alpha v \beta 3$, $\alpha 5 \beta 1$, $\alpha 6 \beta 4$, $\alpha 11 \beta 3$, $\alpha 5 \beta 5$, $\alpha v \beta$ which are the narrower statements of the range/limitation.

claim 15 recites the broad recitation benzodiazepine dimers, and the claim also recites dimers of pyrrolbenzodiazepine, tomaymycin, indolinobenzodiazepines,

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imidazobenzothiadiazepines, or oxazolidinobenzodiazepines which are the narrower statements of the range/limitation;

claim 15 recites the broad recitation dolastatins/auristatins and the claim also recites monomethyl auristatin E, MMAE, MMAF, auristatin PYE, auristatin TP, Auristatins 2-AQ, 6-AQ, EB (AEB), and EFP which are the narrower statement of the range/limitation.

(D) It is unclear how the subheadings a)-f) under “Chemotherapeutic agents in claim 5 limit the subject matter of the claim. For instance subsection e) “Hormonal Therapies” (starting on line 19 of page 7 continues until the bottom of the page) includes a multitude of diverse agents unrelated to “hormonal therapies” such as vitamin D3 analogs, photodynamic “therapies”, and cytokines.

(E) Claim 5 (page 11 section 4), recites “Anti-Viral drugs comprising a) Entry/fusion inhibitors” including gp41 and CD4. However, gp41 and CD4 are the targets of the entry/fusion inhibitors, not the inhibitors per se;

(F) Claim 5 recites various radioisotopes as drugs on page 12, and also recites “derivatives of any of the above drugs”. It is unclear what applicant is intending for a radioisotope derivative, as the radioisotopes are atomic species not compounds.

(G) Claim 15 recites “...esperamicins, and analogues and derivatives thereof”. It is unclear if applicant is claiming analogues and derivatives of the entire Markush group of claim 15, or if analogues and derivatives refers only to esperamicins. For purpose of examination, the claims will be read as encompassing analogues and derivatives of all the species of the Markush group of claim 15.

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person

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skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 6 and 15 are 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. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 5 requires "derivatives of any of the above drugs". Claim 6 requires "derivatives of any of the above". Claim 15 requires "analogues and derivatives thereof". The instant specification has failed to describe any analog or derivative originating from the large genus of chemotherapeutic, anti-autoimmune, anti-infectious, or anti-viral compounds or radioisotopes recited in the specification to be analogs or derivatives. One of skill in the art would reasonably conclude that applicant was not in possession of the compounds of claim 2 requiring the large genus of analogs and derivatives of the recited drug species of claims 5, 6 and 15 at the time of filing.

Claims 13 and 30-32 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) Claim 5 requires the compound of any one of claim 2 wherein the "Drug" is selected from the group consisting of a multitude of agents unrelated in structure. It is clear that the biological activity of the Drug incorporated into the compound must be preserved in order for the claimed compounds to be used by one of skill in the art.

The specification has described conjugation the synthesis of bi-functional mono, bi, tri and tetraphosphinate linkers enabling conjugation to a drug via reaction of a thiol group on a drug moiety and conjugation of a protein or antibody via a maleimido group on the opposite end of the linker. The use of the maleimido group in protein and antibody conjugation is well known in the art. However, claim 5 is not limited to drugs or biologically active proteins having a free thiol group, but includes a plethora of drug molecules, nucleosides and nucleotides, siRNA and anti-sense drugs in addition to multi-component substances, such as Stimuvax (also known as BLP25, see Sangha and Butts, Clinical Cancer Research, 2007, Vol. 13, suppl. 15, pp. 4652s-4654s, see page 4653s, first paragraph under the heading "Liposomal MUC1 Vaccine BLP25"), Allovectin-7 (Stopeck et al, (Clinical Cancer Research, 2001, Vol. 7, pp. 2285-2291, see page 2286, first column, lines 1-6 of the second paragraph) and Provenge (Harzstark and Small, Expert Opinion on Biological Therapy, 2007, Vol. 7, pp. 1275-1280) which is an antigen-loaded antigen presenting cell. The specification provides no teaching or guidance on the modification of the multitude of drugs, including multi-component products and cells, to provide a free thiol group for conjugation to the linker such that the modification and/or the conjugation of the drug, products or cells preserves the required function of the drug, multicomponent products or cells. Thus, one of skill in the art would be required to determine how to modify all the drugs and multicomponent products required in claims 5 such that the expected biological functions of the drugs and products are maintained and if such modification was possible. Based on this requirement, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make and use the broadly claimed compounds of claim 5.

(B) As drawn to the conjugates of the invention comprising anti-infectious disease agent and anti-viral drugs.

Claim 5 is drawn in part to the cell-binding agent drug conjugate of claim 2 wherein the "drug" includes an anti-infectious disease agent or an anti-viral agent. Claim 20 is included with this rejection because a pharmaceutical composition comprising a therapeutically effective amount of the conjugate of claim 2 and additionally, an anti-infectious agent is presumably used to treat an infectious disease. The specification does not teach any binding agent specific for the treatment of a patient with a viral or bacterial infection. The art teaches that the vast majority of therapeutic mAb are administered for a the treatment of cancer, autoimmune disorder and

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transplantation (Irani et al, Molecular Immunology, 2015, Vol. 67, pp. 171-182, see page 171, second column, lines 14-17) but that the development of monoclonal therapeutic antibodies against specific infectious diseases has been slow (page 171, first column, lines 5-8). Irani et al note that antibodies developed to HIV target HIV envelop glycoproteins, antibodies developed to West Nile virus target domain III of the virus, antibodies developed to gram positive Staph aureus target poly N-acetyl glucosamine, and antibodies targeting gram negative bacteria target Serogroup O6 LPS, and Shiga toxin 2 (Table 4). It is noted that antibodies targeting bacteria bind directly to the infectious agent, and that with the exception of lentivirus infected cells and retrovirus infected cells, antibodies which bind to viruses also bind directly to the virus rather than the cell infected with the virus (Pelegrin et al, Trends in Microbiology, 2015, Vol. 23, pp. 653-665, see page 653, lines 1-3 and page 654, lines 9-10). The conjugate of the instant invention requires a cell binding agent, but for recognition of non-retroviral or non-lentiviral viral infections, the virus itself will be bound, rather than the cell harboring the virus. As a free virus is not a cell per se, the targeting of a free virus cannot be carried out by a "cell-binding agent" required by the conjugate of instant claim 2. Further, there are no teachings in the specification of a "Drug" active against a free virus which is not capable of autonomous replication outside of a host cell.

Targeting of free bacteria by the conjugate of the invention could be carried out with a cell binding agent which is a monoclonal antibody recognizing the bacteria cells. Bacterial cells are in possession of a cell wall which is not a feature of a eukaryotic cell. The instant specification provides no guidance as to the ability of the a bacterial cell bound to an antibody to internalize the antibody through the cell wall in order that the Drug attached to the conjugate can be internalized and exert a toxic affect against the targeted bacterial cell. There is no art of record or teachings in the specification to support the notion that antibody-drug conjugates are effective at targeting bacterial cells to exert the effect of the drug on the bacterial cells.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Brixner (U.S. 5,094,848).

Brixner discloses the compound of "A-bridge-targeting moiety" (column 2, lines 52-68) for targeting of an active agent in vitro or in vivo, wherein the bridging moiety is the diphosphate linker $-L^1_n-DP-L^2-$, wherein L^1 is an optional spacer group between the active agent and the diphosphate and L^2 is a linking group connecting the diphosphate with the targeting moiety (column 3, lines 1-14). Brixner discloses that the targeting moiety includes polypeptides such as antibodies and fragments thereof (column 10, lines 27-36). Brixner discloses radiolabeled molecules as the active agent (column 13, line 58 to column 15, line 45). Brixner discloses antitumor agents as the active agent, such as ARA-C, cyclophosphamide, diethylstilbestrol diphosphate, polyestradiol phosphate, estrmustine, cytarabine (column 16, lines 40-62) and active agents comprised within polymers, such as methotrexate, daunomycin, doxorubicin, mitomycin, bleomycin and mitoxantrone in addition to ribosomal inactivating toxins (column 17, lines 3-29). Brixner discloses that the polymeric substrate can be conventionally derivatized for conjugation to the targeting group using an HNS or other active ester (column 3, lines 61-67). Brixner disclose the targeting of tumor with a diagnostic or therapeutic agent using the targeting agent of NR-Lu-10 Fab conjugated to anti-breast cancer agents (column 17, lines 61-68). The compound of Brixner comprising the diphosphate meet the limitation of the instant claims 1-4 wherein Q and T are both $-P=O(OM)-$, $m=1$, $n=1$, wherein R_2 is "O" that covalently connects the phosphinate group to the second phosphinate group. Brixner discloses the structure in example 1 wherein Y is the functional group enabling reaction of the linker with the cell binding agent and Z is the functional group enabling a link of the agent to the "cytotoxic drug" which is a radionuclide via a hydrogen bond with the amide nitrogen (column 13, lines 60-68). The structure of Brixner meets the limitation of claims 1-4 wherein R_5 and R_6 are "H".

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KAREN CANELLA whose telephone number is (571)272-0828. The examiner can normally be reached on 9:30-6:00 M-F.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571)272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KAREN CANELLA/
Primary Examiner, Art Unit 1643

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In re Patent Application of	)	MAIL STOP AMENDMENT
	)	
Zhao, R. Yongxin	)	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

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

Commissioner:

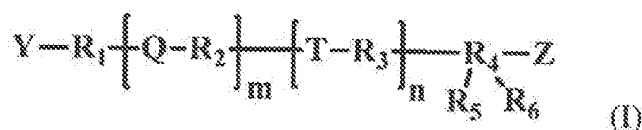
In response to the Official Action dated August 15, 2017, please amend the above identified application as follows.

AMENDMENTS TO THE CLAIMS:

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

LISTING OF CLAIMS:

1. (Currently Amended) 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)-; and when n=1, m=0, T is not -P(=O)(OM)-;

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

R₁, R₂, R₃, and R₄, ~~R₅ and R₆~~, are the same or different and are 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 esters, 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,

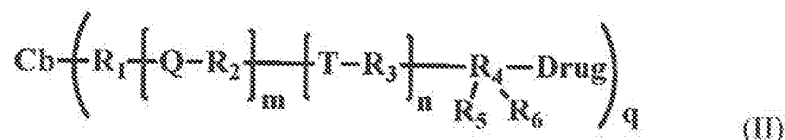
or R₁, R₂, R₃ and R₄ are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R₁, R₂, R₃ and R₄);

R₅ and R₆ are the same or different and are 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ 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, alkoxime or amide bond;

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

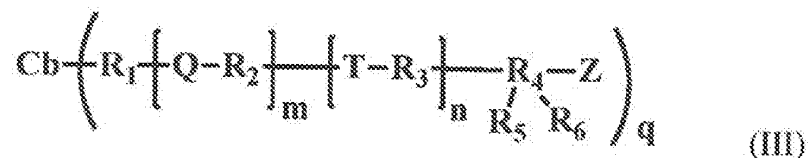
R₁, R₂, R₃, and R₄, ~~R₅ and R₆~~, are the same or different and are H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or esters, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula (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);

R₅ and R₆, are the same or different and are 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 (OCH₂CH₂)_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. (Currently Amended) 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, ~~peptide~~, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or ~~quaternary~~ quaternary amine, imine, cycloheteroalkyane, heteroaromatic, alkoxime or amide bond;

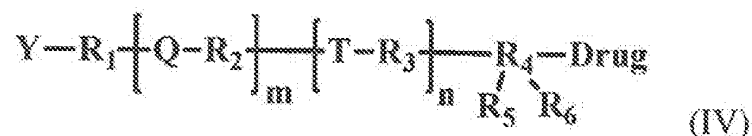
R_1 , R_2 , R_3 , and R_4 , ~~R_5 and R_6~~ are the same or different and are ~~H~~, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or esters, ether or amide having 2-6 carbon atoms, or polyethyleneoxy 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 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. (Currently Amended) 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, cycloheteroalkylene, heteroaromatic, alkoxime or amide bond;

R_1 , R_2 , R_3 , and R_4 , ~~R_5 and R_6~~ are the same or different and are 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 esters, 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 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 the Drug is selected from the group consisting of:

1). ~~chemotherapeutic agents selected from the group consisting of~~comprising a). Alkylating agents ~~selected from the group consisting of~~comprising Nitrogen mustards ~~selected from the group consisting of~~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 ~~synthetic analogues thereof~~; duocarmycin, ~~and synthetic analogues of~~ KW-2189 and CBI-TMI; benzodiazepine dimers ~~selected from the group consisting of~~comprising ~~dimers~~ dimers of pyrrolbenzodiazepine (PBD) or tomaymycin, indolinobenzodiazepines, imidazobenzothiadiazepines, or oxazolidinobenzodiazepines; Nitrosourea ~~selected from the group consisting of~~comprising carmustine, lomustine, chlorozotocin, fotemustine, nimustine, ranimustine; Alkylsulphonates ~~selected from the group consisting of~~comprising busulfan, treosulfan, improsulfan and piposulfan; Triazines~~[[:]]~~; (dacarbazine); Platinum containing compounds ~~selected from the group consisting of~~comprising carboplatin, cisplatin, oxaliplatin; aziridines ~~selected from the group consisting of~~comprising benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide triethylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine; b). Plant Alkaloids ~~selected from the group consisting of~~comprising Vinca alkaloids ~~selected from the group consisting of~~comprising vincristine, vinblastine, vindesine, vinorelbine, navelbin; Taxoids ~~selected from the group consisting of~~comprising paclitaxel, ~~and docetaxol and analogs thereof~~, Maytansinoids ~~selected from the group consisting of~~comprising DM1, DM2, DM3, DM4, DMS, DM6, DM7, maytansine and ansamitocins ~~and analogs thereof~~, cryptophycins ~~selected from the group consisting of~~comprising cryptophycin 1 and cryptophycin 8; epothilones, eleutherobin, discodermolide, bryostatins, dolostatins, auristatins, tubulysins, cephalostatins; pancratistatin; a sarcodictyin; spongistatin; c). DNA Topoisomerase Inhibitors ~~selected from the group consisting of~~comprising Epipodophyllins ~~selected from the group consisting of~~comprising 9-aminocamptothecin, camptothecin, crisnatol, daunomycin, etoposide, etoposide phosphate, irinotecan, mitoxantrone, novantrone, retinoic

acids, (retinols), teniposide, topotecan, 9-nitrocamptothecin (RFS 2000); mitomycins[[]]; d). ~~Anti-metabolites selected from the group consisting of comprising~~ Anti-folate ~~selected from the group consisting of comprising~~ DHFR inhibitors ~~selected from the group consisting of comprising~~ methotrexate, trimetrexate, denopterin, pteropterin, and aminopterin (4-aminopteroic acid) ~~or the other folic acid analogues thereof~~; IMP dehydrogenase Inhibitors ~~selected from the group consisting of comprising~~ mycophenolic acid, tiazofurin, and ribavirin, EICAR; Ribonucleotide reductase Inhibitors ~~selected from the group consisting of comprising~~ hydroxyurea and deferoxamine; Pyrimidine analogs ~~compounds U selected from the group consisting of compounds comprising uracil-analogs compounds selected from the group consisting of comprising~~ ancitabine, azacitidine, 6-azauridine, capecitabine (Xeloda), carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, 5-Fluorouracil, floxuridine, and ratitrexed (Tomudex); Cytosine-analogs ~~compounds selected from the group consisting of comprising~~ cytarabine, cytosine arabinoside, and fludarabine; Purine-analogs ~~compounds selected from the group consisting of comprising~~ azathioprine, fludarabine, mercaptopurine, thiamiprine, and thioguanine; folic acid replenisher; e). Hormonal therapies ~~selected from the group consisting of comprising~~ Receptor antagonists ~~selected from the group consisting of comprising~~ anti-estrogen selected from the group consisting of megestrol, raloxifene, and tamoxifen; LHRH agonists ~~selected from the group consisting of comprising~~ goserelin, and leuprolide acetate; anti-androgens ~~selected from the group consisting of comprising~~ bicalutamide, flutamide, calusterone, dromostanolone propionate, epitiostanol, goserelin, leuprolide, mepitiostane, nilutamide, testolactone, and trilostane; ~~Retinoids/Deltoids selected from the group consisting of~~ Vitamin D3 ~~analogs compounds selected from the group consisting of comprising~~ CB 1093, EB 1089, KH 1060, cholecalciferol, and ergocalciferol; photodynamic therapies ~~selected from the group consisting of comprising~~ verteporfin, phthalocyanine, photo sensitizer Pc4, and demethoxyhypocrellin A; cytokines ~~selected from the group consisting of comprising~~ Interferon-alpha, Interferon-gamma, tumor necrosis factor (TNFs), and human proteins containing a TNF domain; f). Kinase inhibitors ~~selected from the group consisting of comprising~~ BIBW-2992 (anti-EGFR/Erb2), imatinib, gefitinib, pegaptanib, sorafenib, dasatinib, sunitinib, erlotinib, nilotinib, lapatinib, axitinib, pazopanib[[]], vandetanib, E7080 (anti-VEGFR2), mubritinib, ponatinib (AP24534), bafetinib (INNO-406), bosutinib (SKI-606), cabozantinib, vismodegib, iniparib,

ruxolitinib, CYT387, axitinib, tivozanib, sorafenib, bevacizumab, cetuximab, Trastuzumab, Ranibizumab, Panitumumab, and ispinesib; g). antibiotics selected from the group consisting of comprising enediyne antibiotics selected from the group consisting of comprising calicheamicins selected from the group consisting of 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 chromomorphores, 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, nitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; fh). polyketides (acetogenins) selected from the group consisting of comprising bullatacin and bullatacinone; gemcitabine, epoxomicins, bortezomib, thalidomide, lenalidomide, pomalidomide, tosedostat, zybrestat, PLX4032, STA-9090, Stimuvax, allovectin-7, Xegeva, Provenge, Yervoy, Isoprenylation inhibitors, Dopaminergic neurotoxins, Cell cycle inhibitors, Actinomycins selected from the group consisting of Actinomycin D, and dactinomycin, Bleomycins selected from the group consisting of bleomycin A2, bleomycin B2, and peplomycin, Anthracyclines selected from the group consisting of comprising daunorubicin, doxorubicin (adriamycin), idarubicin, epirubicin, pirarubicin, zorubicin, and mitoxantrone, MDR inhibitors, Ca^{2+} ATPase inhibitors, Histone deacetylase inhibitors selected from the group consisting of comprising Vorinostat, Romidepsin, Panobinostat, Valproic acid, Mocetinostat (MGCD0103), Belinostat, PCI-24781, Entinostat, SB939, Resminostat, Givinostat, AR-42, CUDC-101, sulforaphane, and Trichostatin A; Thapsigargin, Celecoxib, glitazones, epigallocatechin gallate, Disulfiram, Salinosporamide A.; Anti-adrenals selected from the group consisting of comprising aminoglutethimide, mitotane, and trilostane; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; arabinoside, bestabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; eflornithine (DFMO), elfomithine; elliptinium acetate, etoglucid; gallium nitrate; gacytosine, hydroxyurea, 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 ~~selected from the group consisting of comprising~~ T-2 toxin, verrucarín A, roridin A and anguidine; urethane, siRNA, antisense drugs;

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

3). anti-infectious disease agents ~~selected from the group consisting of comprising~~ a). Aminoglycosides ~~selected from the group consisting of comprising~~ amikacin, astromicin, gentamicin (netilmicin, sisomicin, isepamicin), hygromycin B, kanamycin (amikacin, arbekacin, bekanamycin, dibekacin, tobramycin), neomycin (framycetin, paromomycin, ribostamycin), netilmicin, spectinomycin, streptomycin, ~~tobramycin~~, and verdamicin; b). Amphenicols ~~selected from the group consisting of comprising~~ azidamfenicol, chloramphenicol, florfenicol, and thiamphenicol; c). Ansamycins ~~selected from the group consisting of comprising~~ geldanamycin, and herbimycin; d). Carbapenems ~~selected from the group consisting of comprising~~ biapenem, doripenem, ertapenem, imipenem/cilastatin, meropenem, and panipenem; e). Cepheims ~~selected from the group consisting of comprising~~ carbacephem (loracarbef), 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, ceftazopran, cephalixin, cefpimizole, cefpiramide, cefpirome, cefpodoxime, cefprozil, cefquinome, cefsulodin, ceftazidime, cefteram, ceftibuten, ceftiolene, ceftizoxime, ceftobiprole, ceftriaxone, cefuroxime, cefuzonam, cephamycin (cefoxitin, cefotetan, cefmetazole), and oxacephem (flomoxef, latamoxef); f).

Glycopeptides ~~selected from the group consisting of~~comprising bleomycin, vancomycin (oritavancin, telavancin), teicoplanin (dalbavancin), and ramoplanin; g). Glycylcyclines; h). β -Lactamase inhibitors ~~selected from the group consisting of~~comprising penam (sulbactam, tazobactam), and clavam (clavulanic acid); i). Lincosamides ~~selected from the group consisting of~~comprising clindamycin, and lincomycin; j). Lipopeptides ~~selected from the group consisting of~~comprising daptomycin, A54145, and calcium-dependent antibiotics (CDA); k). Macrolides ~~selected from the group consisting of~~comprising azithromycin, cethromycin, clarithromycin, dirithromycin, erythromycin, flurithromycin, josamycin, ketolide (telithromycin, cethromycin), midecamycin, miocamycin, oleandomycin, rifamycins (rifampicin, rifampin, rifabutin, rifapentine), rokitamycin, roxithromycin, ~~spectinomycin~~, spiramycin, ~~tacrolimus (FK506)~~, troleandomycin, and telithromycin; l). Monobactams ~~selected from the group consisting of~~comprising aztreonam, and tigemonam; m). Oxazolidinones; n). Penicillins ~~selected from the group consisting of~~comprising amoxicillin, ampicillin (pivampicillin, hetacillin, bacampicillin, metampicillin, talampicillin), azidocillin, azlocillin, benzylpenicillin, benzathine benzylpenicillin, benzathine phenoxymethylpenicillin, clometocillin, procaine benzylpenicillin, carbenicillin (carindacillin), cloxacillin, dicloxacillin, epicillin, flucloxacillin, mecillinam (pivmecillinam), mezlocillin, meticillin, nafcillin, oxacillin, penamecillin, penicillin, pheneticillin, phenoxymethylpenicillin, piperacillin, propicillin, sulbenicillin, temocillin, and ticarcillin; o). Polypeptides ~~selected from the group consisting of~~comprising bacitracin, colistin, and polymyxin B; p). Quinolones ~~selected from the group consisting of~~comprising alatrofloxacin, balofloxacin, 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 ~~selected from the group consisting of~~comprising pristinamycin, and quinupristin/dalfopristin; r). Sulfonamides ~~selected from the group consisting of~~comprising mafenide, prontosil, sulfacetamide, sulfamethizole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim, and trimethoprim-sulfamethoxazole (co-trimoxazole); s). Steroid antibacterials; t). Tetracyclines ~~selected from the group consisting of~~comprising doxycycline, chlortetracycline, clomocycline, demeclocycline, lymecycline,

meclocycline, metacycline, minocycline, oxytetracycline, penimepicycline, rolitetracycline, and tetracycline; and glycylcyclines; u). antibiotics selected from the group consisting of comprising amoniacin, arspenamine, bactoprenol inhibitors (~~Bacitracin~~), DADAL/AR inhibitors (~~eyeloserine~~), dictyostatin, discodermolide, eleutherobin, epothilone, ethambutol, etoposide, faropenem, fusidic acid, furazolidone, isoniazid, laulimalide, metronidazole, mupirocin, mycolactone, NAM synthesis inhibitors, nitrofurantoin, paclitaxel, platensimycin, pyrazinamide, quinupristin/dalfopristin, ~~rifampicin~~ (~~rifampin~~), tazobactam tinidazole, and uvaricin;

4). anti-viral drugs selected from the group consisting of comprising a). Entry/fusion inhibitors selected from the group consisting of comprising aplaviroc, maraviroc, vicriviroc, ~~gp41~~ (enfuvirtide), PRO 140, and ~~CD4~~ (ibalizumab); b). Integrase inhibitors selected from the group consisting of comprising raltegravir, elvitegravir, and globoidnan A; c). Maturation inhibitors selected from the group consisting of comprising bevirimat, and vivecon; d). Neuraminidase inhibitors selected from the group consisting of comprising oseltamivir, zanamivir, and peramivir; e). Nucleosides & nucleotides selected from the group consisting of comprising abacavir, aciclovir, adefovir, amdoxovir, apricitabine, brivudine, cidofovir, clevudine, dexelvucitabine, didanosine (ddI), elvucitabine, emtricitabine (FTC), entecavir, famciclovir, fluorouracil (5-FU), 3'-fluoro-substituted 2',3'-dideoxynucleoside ~~analogues compounds comprising (e.g. 3'-fluoro-2',3'-dideoxythymidine (FLT) and 3'-fluoro-2',3'-dideoxyguanosine (FLG), fomivirsen, ganciclovir, idoxuridine, lamivudine (3TC), 1-nucleosides selected from the group consisting of comprising β -1-thymidine and β -1-2'-deoxycytidine), penciclovir, racivir, ~~ribavirin~~, stampidine, stavudine (d4T), taribavirin (viramidine), telbivudine, tenofovir, trifluridine valaciclovir, valganciclovir, zalcitabine (ddC), and zidovudine (AZT); f). non-nucleosides selected from the group consisting of comprising amantadine, ateviridine, capravirine, diarylpyrimidines (~~etravirine, rilpivirine~~), delavirdine, docosanol, emivirine, efavirenz, foscarnet (phosphonoformic acid), imiquimod, interferon alfa, loviride, lodenosine, methisazone, nevirapine, NOV-205, peginterferon alfa, podophyllotoxin, ~~rifampicin~~, rimantadine, resiquimod (R-848), and tromantadine; g). protease inhibitors selected from the group consisting of comprising amprenavir, atazanavir, boceprevir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, pleconaril, ritonavir, saquinavir, telaprevir (VX-950), and tipranavir; h). anti-virus drugs selected from the group consisting of comprising abzyme, arbidol,~~

calanolide a, ceragenin, cyanovirin-n, diarylpyrimidines, epigallocatechin gallate (EGCG), foscarnet, griffithsin, taribavirin (viramidine), hydroxyurea, KP-1461, miltefosine, pleconaril, portmanteau inhibitors, ribavirin, and seliciclib;

5). any of 1) to 4) having a radioisotopes selected from of (radionuclides) ^3H , ^{11}C , ^{14}C , ^{18}F , ^{32}P , ^{35}S , ^{64}Cu , ^{68}Ga , ^{86}Y , ^{99}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[$[\cdot]$] or acids ~~or derivatives~~ of any of the above ~~drugs 1) to 5).~~

6. (Currently Amended) The conjugate of claim 2, wherein "Drug" is selected from the group consisting of tubulysins, calicheamicins, auristatins, maytansinoids, CC-1065 ~~analogues~~ compounds, morpholinos doxorubicins, taxanes, cryptophycins, epothilones, and benzodiazepine dimers, siRNA or a combination thereof, and pharmaceutically acceptable salts[$[\cdot]$] or acids ~~or derivatives~~ 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. (Previously Presented) The conjugate of claim 2, wherein the cell-binding agent is configured to bind to target cells which are selected from the group consisting of tumor cells, virus infected cells, microorganism infected cells, parasite infected cells, autoimmune cells, activated cells, myeloid cells, activated T-cells, B cells, or melanocytes; cells expressing the CD19, CD20, CD22, CD30, CD33, CD37, CD38, CD40, CD51, CD52, CD56, CD66, CD70, CD74, CD79, CD80, CD98, CD125, CD221, CD227, CD262, CD309, CD326, CEACAM3, CEACAM5 (carcinoembryonic antigen), DLL4 (Δ -like-4), EGFR, CTLA4, CXCR4 (CD184), Endoglin (CD105), EPCAM (epithelial cell adhesion molecule), ERBB2 (Epidermal Growth Factor Receptor 2), FCGR1, FOLR (folate receptor), GD2 ganglioside, G-28 (a cell surface antigen glyvolipid), GD3 idiotypic, Heat shock proteins, HER1, HER2, HLA-DR10, HLA-DRB, human chorionic gonadotropin, IGF1R (insulin-like growth factor 1 receptor), IL-2 receptor

(interleukin 2 receptor), IL-6R (interleukin 6 receptor), Integrins ($\alpha v\beta 3$, $\alpha 5\beta 1$, $\alpha 6\beta 4$, $\alpha 11\beta 3$, $\alpha 5\beta 5$, $\alpha v\beta 5$), MAGE-1, MAGE-2, MAGE-3, MAGE 4, anti-transferrin receptor, p97, MS4A1 (membrane-spanning 4-domains subfamily A member 1), MUC1 or MUC1-KLH, MUC16 (CA125), CEA, gp100, MART1, MPG, MS4A1 (membrane-spanning 4-domains subfamily A), Nucleolin, Neu oncogene product, P21, Paratope of anti-(N-glycolylneuraminic acid), PLAP-like testicular alkaline phosphatase, PSMA, PSA, ROBO4, TAG 72 (tumor associated glycoprotein 72), T cell transmembrane protein, Tie (CD202b), TNFRSF10B (tumor necrosis factor receptor superfamily member 10B), TNFRSF13B (tumor necrosis factor receptor superfamily member 13B), TPBG (trophoblast glycoprotein), TRAIL-R1 (Tumor necrosis apoptosis Inducing ligand Receptor 1), VCAM-1 (CD106), VEGF, VEGF-A, VEGF-2 (CD309), CanAg, CALLA, and cells expressing insulin growth factor receptor, or epidermal growth factor receptor.

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. (Previously Presented) The conjugate of claim 8, wherein the tumor cells are selected from the group consisting of lymphoma cells, myeloma cells, renal cells, breast cancer cells, prostate cancer cells, ovarian cancer cells, colorectal cancer cells, gastric cancer cells, squamous cancer cells, small-cell lung cancer cells, testicular cancer cells, and cells that grow and divide at an unregulated, quickened pace to cause cancers.

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 (MC), maleimidopropanoyl (MP), valine-citrulline (val-cit), alanine-phenylalanine (ala-phe), p-aminobenzoyloxycarbonyl (PAB), 4-thio-pentanoate (SPP), 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (MCC), 4-thio-butyrate (SPDB), maleimidoethyl containing (ME), 4-thio-2-hydroxysulfonyl-butyrate (2-Sulfo-SPDB) and (4-acetyl)aminobenzoate (SIAB).

15. (Currently Amended) The conjugate of claim 2, wherein Drug is selected from the group consisting of tubulysins, maytansinoids, taxanoids (taxanes), CC-1065-analogs compounds, daunorubicin and doxorubicin compounds, benzodiazepine dimers (e.g., dimers of pyrrolbenzodiazepine (PBD), tomaymycin, anthramycin, indolinbenzodiazepines, imidazobenzothiadiazepines, or oxazolidinbenzodiazepines), calicheamicins and the enediyne antibiotics, actinomycin, azaserines, bleomycins, epirubicin, tamoxifen, idarubicin, dolastatins/auristatins (e.g., monomethyl auristatin E, MMAE, MMAF, auristatin P/E, auristatin TP, Auristatins 2-AQ, 6-AQ, EB (AEB), and EEP (AEEP)), duocarmycins, thiotepa, vincristine, hemiasterlins, and esperamicins, and analogues and derivatives thereof.

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

REMARKS

Entry of the foregoing, reconsideration of the subject matter identified in caption, as amended, pursuant to and consistent with 37 C.F.R. §1.111, and in light of the remarks which follow, are respectfully requested.

In the Amendment, claims 1-6 and 15 have been amended to further improve their form and/or clarity. New claim 21 has been added. Support for claim 21 can be found in the specification, for example, page 12, lines 17-21. Claim 13 was previously cancelled. No new matter has been added. Upon entry of the Amendment, claims 1-12 and 14-21 will be all the claims pending in the application.

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 address the issues raised in the Office Action. Accordingly, withdrawal of the objection is respectfully requested.

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

a. Claims 1-12 and 14-20 were rejected under 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite. Applicant respectfully submits that the claims as amended are in compliance with the § 112 requirements.

In the Amendment, the claims have been amended to address various issues raised in the Office Action. Particularly, R₁, R₂, R₃, and R₄, as defined are not H.

(B) The Office Action asserts that:

Claim 1 recites "Z represents a functional group that enables linkage of the hydrophilic linker to a cytotoxic drug via a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, secondary or tertiary or quaternary amine, imine, cycloheteroalkylene, heteroaromatic, alkoximine or amide bond". It is unclear if the recited species of disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, secondary or tertiary or quaternary amine, imine, cycloheteroalkylene, heteroaromatic, alkoximine or amide bond are required as part of the "Z" moiety, or if the recited species are intended to be part of the cytotoxic drug. (Office Action at pages 3-4)

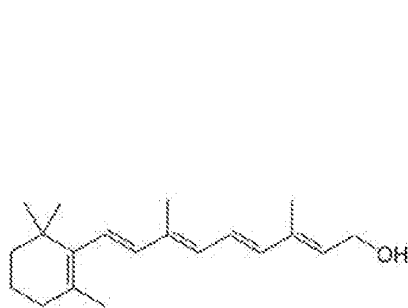
Applicant respectfully submits that the definition of Z is clear and understood by one of ordinary skill in the art. As correctly understood by the Examiner, Z is only required to enable linkage of the hydrophilic linker to a cytotoxic drug via a specified bond. That is, there is no requirement that the specified bond be, either entirely or partially, contained in Z or in the cytotoxic drug.

Further, it is well established that breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971); *In re Gardner*, 427 F.2d 786, 788, 166 USPQ 138, 140 (CCPA 1970).

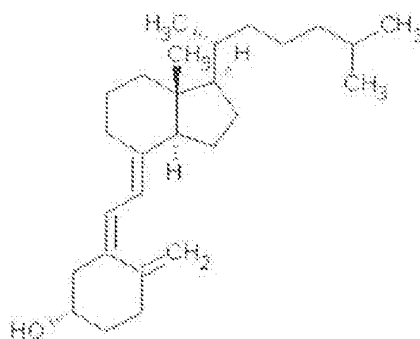
(C) The Office Action asserts that:

claim 5 recites the broad recitation "retinols", and the claim also recites CB1093, RB1089, KH1060, cholecalciferol and ergocalciferol (page 7, 1e) which is the narrower statement of the range/limitation. (Office Action at page 4)

Applicant respectfully disagrees. Specifically, as shown in the formulae below (see <https://www.thoughtco.com/vitamin-chemical-structures-4064208>), Vitamin A (Retinol) is different from Vitamin D3 which analog CB1093, RB1089, KH1060, cholecalciferol and ergocalciferol belong to.



Vitamin A (Retinol)



Vitamin D3

As such, CB1093, RB1089, KH1060, cholecalciferol and ergocalciferol are not "the narrower statement of the range/limitation" of "the broad recitation 'retinols,'" contrary to the Examiner's assertion.

Moreover, it is well established that "the double inclusion of an element by members of a Markush group is not, in itself, sufficient basis for objection to or rejection of claims." Therefore, the mere fact that a compound may be embraced by more than one member of a

Markush group recited in the claim does not necessarily render the scope of the claim unclear. For example, the Markush group, "selected from the group consisting of amino, halogen, nitro, chloro and alkyl" should be acceptable even though "halogen" is generic to "chloro." See MPEP 2173.05(h).

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

b. Claims 5, 6 and 15 were rejected under 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement.

The Office Action asserts that:

The instant specification has failed to describe any analog or derivative originating from the large genus of chemotherapeutic, anti-autoimmune, anti-infectious, or anti-viral compounds or radioisotopes recited in the specification to be analogs or derivatives. (Office Action at page 7)

While not conceding the propriety of this rejection, and to expedite prosecution, the claims have been amended to delete the phrases "analogs" and "derivatives." Accordingly, withdrawal of the rejection is respectfully requested.

c. Claims "13 and 30-32" [sic] were rejected under 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the enablement requirement.

The Office Action asserts that:

It is clear that the biological activity of the Drug [recited in claim 5] incorporated into the compound must be preserved in order for the claimed compounds to be used by one of skill in the art.... The specification provides no teaching or guidance on the modification of the multitude of drugs, including multi-component products and cells, to provide a free thiol group for conjugation to the linker such that the modification and/or the conjugation of the drug, products or cells preserves the required function of the drug, multicomponent products or cells.... one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make and use the broadly claimed compounds of claim 5. (Office Action at pages 7-8)

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

In the present case, the drugs recited in claim 5 each have a functional group or can be introduced with a functional group through a chemical reaction. One skilled in the art would be able to synthesize conjugates of the drugs via a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkylene, heteroaromatic, alkoxime or amide bond by using the linkers described in the present application.

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

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

Claims 1-7 were rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,094,848 to Brixner. Applicant respectfully traverses the rejection for the following reasons.

Brixner discloses a pharmaceutical agent covalently bonded via a diphosphate or amidated diphosphate bond, i.e., $-L^1-DP-L^2$ or $-L^1-DP(A)-L^2-$, to a targeting moiety

(abstract). Particularly, Brixner discloses
$$\begin{array}{c} \text{O} & \text{O} \\ || & || \\ -\text{O}-\text{P}-\text{O}-\text{P}-\text{O}- \\ | & | \\ \text{O}^- & \text{O}^- \end{array} \quad \text{and} \quad \begin{array}{c} \text{O} & \text{O} \\ || & || \\ -\text{X}^1-\text{P}-\text{O}-\text{P}-\text{X}^1- \\ | & | \\ \text{O}^- & \text{O}^- \end{array}$$
 wherein one X^1 is O and the other is NH.

The Office Action asserts that:

The compound of Brixner comprising the diphosphate meet [sic] the limitation of the instant claims 1-4 wherein Q and T are both $-P=O(OM)-$, $m=1$, $n=1$, wherein R_2 is "O" that covalently connects the phosphinate group to the second phosphinate group. (Office Action at page 10)

Applicant respectfully disagrees. Specifically, the present claims define, among others, R_2 , to be "a chain of atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects..." It is clear that the "chain of atoms" contains more than one atom. As such, the diphosphate bond disclosed in Brixner does not meet the requirements of the present claims.

Nonetheless, to expedite prosecution, claims 1-4 have been amended to specify "a chain of two or more atoms."

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

IV. New Claim

Newly added claim 21 depends from claim 1 and thus is patentable at least by virtue of its dependency.

V. Conclusion

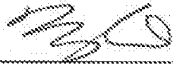
From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order and such action is earnestly solicited. If there are any questions concerning this paper or the application in general, the Examiner is invited to telephone the undersigned at his earliest 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: November 15, 2017

By: 

Fang Liu

Registration No. 51283

Customer No. 21839

703 836 6620

Electronic Acknowledgement Receipt	
EFS ID:	30956881
Application Number:	14432073
International Application Number:	
Confirmation Number:	6938
Title of Invention:	HYDROPHILIC LINKERS AND THEIR USES FOR CONJUGATION OF DRUGS TO A CELL BINDING MOLECULES
First Named Inventor/Applicant Name:	R. Yongxin Zhao
Customer Number:	21839
Filer:	Fang Liu/Sarah Noel
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File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Amendment.pdf	3666228	yes	20
			b62907140ad64fc7cd38e9c5addf548b54264b6		

Multipart Description/PDF files in .zip description			
Document Description		Start	End
Amendment/Req. Reconsideration-After Non-Final Reject		1	1
Claims		2	15
Applicant Arguments/Remarks Made in an Amendment		16	20
Warnings:			
Information:			
Total Files Size (in bytes):		3666228	
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			ART UNIT 1643	PAPER NUMBER
			NOTIFICATION DATE 03/08/2018	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPDOC1@BIPC.com

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

The species of -S(O₂)- has been added to the elected species of -P(=O)(OM)- for examination at this time.

Claims 1-6 and 15 have been amended. Claim 13 has been canceled. Claim 21 has been added. Claims 1-12 and 14-21 are pending and under consideration.

Claim Objections

Claim 5 objected to because of the following informalities: the typographical error of “Xegeva” rather than Xgeva. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 8, 14, 15 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

It is unclear how the parenthetical information included in claims 5, 8, 14, 15 limit the scope of the claims.

Claim 15 is vague and indefinite in the recitation of “maleimidoethyl containing”. It is unclear how a conjugate comprising one or more linker components of maleimidoethyl differs from a conjugate comprising one or more linker components of “maleimidoethyl containing”.

Claim 8 is vague and indefinite in the recitation of the conjugate of claim 2, wherein the cell-binding agent is configured to bind to target cells which are selected from cell expressing

“paratope of anti-(N-glycolylneuraminic acid” (page 13, lines 5-6) because a “paratope” refers to the antigen recognition portion of an antibody which is not consistent with being a target cell required by the claim.

Claim 5 is rejected for the use of Tradenames, such as RFS 2000, Xeloda, Tomudex, zybrestat, Stimuvax, Allovectin-7, “Xegeva” (Xgeva), Provenge, Yervoy, Romidepsin, PSK, viramidine, AZT, abzyme, arbidol, viramidine ,and ribavirin. Tradenames designate the origin of the material but do not suffice to describe the material claimed.

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 is 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. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. Claim 5 has been amended to require that any of the agents listed in 1 through 4 of claim 5 comprise a radioisotope (page 12 of the claims). The originally filed specification does not provide a basis for this requirement. One of skill in the art would reasonably conclude that applicant was not in possession of the claimed invention at the time of filing.

The rejection of claims 2-12 and 14-21 (word processing error in previous action mistakenly indicated claims 13 and 30-32) under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the enablement requirement is maintained for reasons

of record. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) Claim 5 requires the compound of any one of claim 2 wherein the “Drug” is selected from the group consisting of a multitude of agents unrelated in structure. It is clear that the biological activity of the Drug incorporated into the compound must be preserved in order for the claimed compounds to be used by one of skill in the art.

The specification has described conjugation the synthesis of bi-functional mono, bi, tri and tetraphosphinate linkers enabling conjugation to a drug via reaction of a thiol group on a drug moiety and conjugation of a protein or antibody via a maleimido group on the opposite end of the linker. The use of the maleimido group in protein and antibody conjugation is well known in the art. However, claim 5 is not limited to drugs or biologically active proteins having a free thiol group, but includes a plethora of drug molecules, nucleosides and nucleotides, siRNA and anti-sense drugs in addition to multi-component substances, such as Stimuvax (also known as BLP25, see Sangha and Butts, Clinical Cancer Research, 2007, Vol. 13, suppl. 15, pp. 4652s-4654s, see page 4653s, first paragraph under the heading “Liposomal MUC1 Vaccine BLP25”), Allovectin-7 (Stopeck et al, (Clinical Cancer Research, 2001, Vol. 7, pp. 2285-2291, see page 2286, first column, lines 1-6 of the second paragraph) and Provenge (Harzstark and Small, Expert Opinion on Biological Therapy, 2007, Vol. 7, pp. 1275-1280) which is an antigen-loaded antigen presenting cell. The specification provides no teaching or guidance on the modification of the multitude of drugs, including multi-component products and cells, to provide a free thiol group for conjugation to the linker such that the modification and/or the conjugation of the drug, products or cells preserves the required function of the drug, multicomponent products or cells. Thus, one of skill in the art would be required to determine how to modify all the drugs and multicomponent products required in claims 5 such that the expected biological functions of the

drugs and products are maintained and if such modification was possible. Based on this requirement, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make and use the broadly claimed compounds of claim 5.

(B) As drawn to the conjugates of the invention comprising anti-infectious disease agent and anti-viral drugs.

Claim 5 is drawn in part to the cell-binding agent drug conjugate of claim 2 wherein the "drug" includes an anti-infectious disease agent or an anti-viral agent. Claim 20 is included with this rejection because a pharmaceutical composition comprising a therapeutically effective amount of the conjugate of claim 2 and additionally, an anti-infectious agent is presumably used to treat an infectious disease. The specification does not teach any binding agent specific for the treatment of a patient with a viral or bacterial infection. The art teaches that the vast majority of therapeutic mAb are administered for a the treatment of cancer, autoimmune disorder and transplantation (Irani et al, Molecular Immunology, 2015, Vol. 67, pp. 171-182, see page 171, second column, lines 14-17) but that the development of monoclonal therapeutic antibodies against specific infectious diseases has been slow (page 171, first column, lines 5-8). Irani et al note that antibodies developed to HIV target HIV envelop glycoproteins, antibodies developed to West Nile virus target domain III of the virus, antibodies developed to gram positive Staph aureus target poly N-acetyl glucosamine, and antibodies targeting gram negative bacteria target Serogroup O6 LPS, and Shiga toxin 2 (Table 4). It is noted that antibodies targeting bacteria bind directly to the infectious agent, and that with the exception of lentivirus infected cells and retrovirus infected cells, antibodies which bind to viruses also bind directly to the virus rather than the cell infected with the virus (Pelegrin et al, Trends in Microbiology, 2015, Vol. 23, pp. 653-665, see page 653, lines 1-3 and page 654, lines 9-10). The conjugate of the instant invention requires a cell binding agent, but for recognition of non-retroviral or non-lentiviral viral infections, the virus itself will be bound, rather than the cell harboring the virus. As a free virus is not a cell per se, the targeting of a free virus cannot be carried out by a "cell-binding agent" required by the conjugate of instant claim 2. Further, there are no teachings in the specification of a "Drug" active against a free virus which is not capable of autonomous replication outside of a host cell.

Targeting of free bacteria by the conjugate of the invention could be carried out with a cell binding agent which is a monoclonal antibody recognizing the bacteria cells. Bacterial cells

are in possession of a cell wall which is not a feature of a eukaryotic cell. The instant specification provides no guidance as to the ability of the a bacterial cell bound to an antibody to internalize the antibody through the cell wall in order that the Drug attached to the conjugate can be internalized and exert a toxic affect against the targeted bacterial cell. There is no art of record or teachings in the specification to support the notion that antibody-drug conjugates are effective at targeting bacterial cells to exert the effect of the drug on the bacterial cells.

Applicant argues that one of skill in the art , through a chemical reaction, would be able to synthesize conjugates of “the drugs” with a disulfide, thioether, thiester, peptide, hydrazone, ethyl ester, carbamate, carbonate, secondary amine, tertiary amine, quaternary amine, imine, cycloheteroalkyne, heteroaromatic, alkoxime or amide bond by using the linker described in the present application. This has been considered but not found persuasive because the question is one of undue experimentation. Further section 2145 of the M.P.E.P. states:

ARGUMENT DOES NOT REPLACE EVIDENCE WHERE EVIDENCE IS
NECESSARY.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Lees (WO97/41897).

Lees discloses a heterobifunctional linker which is an N-hydroxysuccinimide vinylsulfone (page 22, formula at bottom of page) having substituted or unsubstituted alkyl chain of 1 to 20 carbon atoms (page 23, top formula) or including polyethylglycol (page 23, middle formula). Lees discloses the use of the linker to attach a derivatized polysaccharide to one end and a protein to the other (page 23, lines 17-19). The NHS vinylsulfone or Lees anticipates instant formula 55 shown in Figure 6 of the instant specification. Therefore the NHS portion represents a functional group that enables reaction of the linker with a cell binding agent, and the

vinyl group enables linkage of the linker to a cytotoxic drug as indicated by structure 56 of Figure 6.

All other rejections and objections as set forth in the prior Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KAREN A CANELLA whose telephone number is (571)272-0828. The examiner can normally be reached on M-F 10-6:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on 571-272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KAREN A. CANELLA
Examiner
Art Unit 1643

/Karen A. Canella/
Primary Examiner, Art Unit 1643

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	MAIL STOP AMENDMENT
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. § 1.111

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

Commissioner:

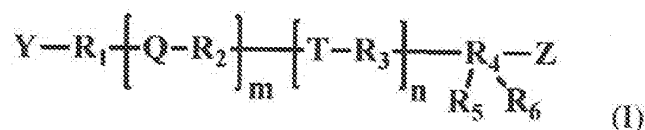
In response to the Official Action dated March 8, 2018, please amend the above identified application as follows.

AMENDMENTS TO THE CLAIMS:

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

LISTING OF CLAIMS:

I. (Currently Amended) 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)-; and 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, cycloheteroalkylene, heteroaromatic, alkoxime or amide bond;

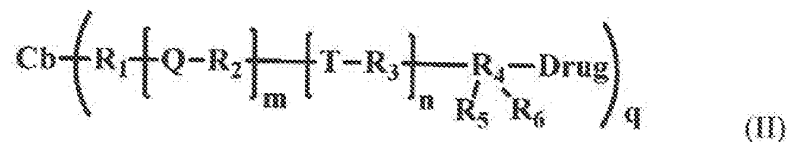
R₁, R₂, R₃, and R₄, are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, 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, alkoxime 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 $-P(=O)(OM)-$;

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,

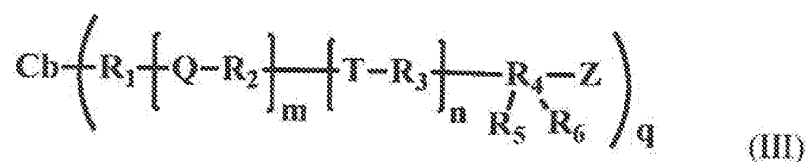
or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4);

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 $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $\text{N}^+\text{R}_1\text{R}_2\text{R}_3$ or a pharmaceutical salt.

3. (Currently Amended) A compound of formula (III):



wherein:

Cb represents a cell-binding agent;

Q and T are either $-\text{P}(=\text{O})(\text{OM})-$, or $-\text{S}(\text{O}_2)-$, or $-\text{S}(\text{O})-$;

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 $-\text{P}(=\text{O})(\text{OM})-$; and when $n=1$, $m=0$, T is not $-\text{P}(=\text{O})(\text{OM})-$;

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, cycloheteroalkylene, 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 $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof,

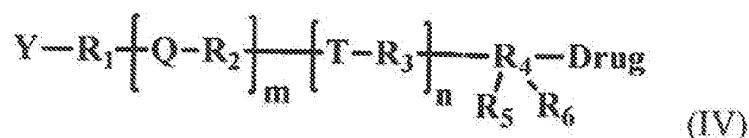
or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4);

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 $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $\text{N}^+\text{R}_1\text{R}_2\text{R}_3$ or a pharmaceutical salt.

4. (Currently Amended) 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 $-\text{P}(=\text{O})(\text{OM})-$, or $-\text{S}(\text{O}_2)-$, or $-\text{S}(\text{O})-$;

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 $-\text{P}(=\text{O})(\text{OM})-$; and when $n=1$, $m=0$, T is not $-\text{P}(=\text{O})(\text{OM})-$;

"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, cycloheteroalkylene, 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 $(\text{OCH}_2\text{CH}_2)_p$, 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 $N^+ R_1 R_2 R_3$ 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 (~~PBD~~) or tomaymycin, indolinobenzodiazepines, 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, DMS, 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 (~~RFS-2000~~); mitomycins; d). Anti-metabolites comprising Anti-folate comprising DHFR inhibitors comprising methotrexate,

trimetrexate, denopterin, pteropterin, and aminopterin (~~4-aminopteroic acid~~); 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 (~~Xeloda~~), carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, 5-Fluorouracil, floxuridine, and ratitrexed (~~Tomodex~~); 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 (~~TNFs~~), 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 (~~AP24534~~), bafetinib (~~INNO-406~~), bosutinib (~~SKI-606~~), 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 antibiotic 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,

nitomycins, 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, zybrestat ZYBRESTAT, PLX4032, STA-9090, Stimuvax STIMUVAX, allovectin-7 ALLOVECTIN-7, Xegeva XGEVA, Provenge PROVENGE, Yervoy YERVOY, 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 ROMIDEPSIN, Panobinostat, Valproic acid, Mocetinostat (MGCD0103), 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 aminoglutethimide, mitotane, and trilostane; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; arabinoside, bestabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; eflornithine (DFMO), elfomithine; elliptinium acetate, etoglucid; gallium nitrate; gacytosine, ibandronate, lentinan; Ionidamine; 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, fluocortolone danazol, dexamethasone, Triamcinolone acetonide, and beclometasone dipropionate, DHEA, enanercept, hydroxychloroquine, infliximab, meloxicam, methotrexate, mofetil, mycophenolate, prednisone, sirolimus, tacrolimus;

3). anti-infectious disease agents comprising a). Aminoglycosides comprising amikacin, astromicin, 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 (~~loracarbef~~), 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, ceftazidime, 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 cefmetazole), and oxacephem (comprising
 flomoxef, and latamoxef); f). Glycopeptides comprising bleomycin, vancomycin (~~oritavanein~~;
~~telavanein~~), teicoplanin (~~dalbavanein~~), and ramoplanin; g). Glycylcyclines; h). β -Lactamase
 inhibitors comprising penam (~~sulbactam~~, ~~tazobactam~~), and clavam (~~clavulanic acid~~); i).
 Lincosamides comprising clindamycin, and lincomycin; j). Lipopeptides comprising
 daptomycin, A54145, and calcium-dependent antibiotics (~~CDA~~); k). Macrolides comprising
 azithromycin, cethromycin, clarithromycin, dirithromycin, erythromycin, flurithromycin,
 josamycin, ketolide (~~telithromycin~~, ~~cethromycin~~), midecamycin, miocamycin, oleandomycin,
 rifamycins (~~rifampicin~~, ~~rifampin~~, ~~rifabutin~~, ~~rifapentine~~), rokitamycin, roxithromycin, spiramycin,
 troleandomycin, and telithromycin; l). Monobactams comprising aztreonam, and tigemonam;
 m). Oxazolidinones; n). Penicillins comprising amoxicillin, ampicillin (~~pivampicillin~~, ~~hetacillin~~,
~~bacampicillin~~, ~~metampicillin~~, ~~talampicillin~~), azidocillin, azlocillin, benzylpenicillin, benzathine
 benzylpenicillin, benzathine phenoxymethylpenicillin, clometocillin, procaine benzylpenicillin,
 carbenicillin (~~carindacillin~~), cloxacillin, dicloxacillin, epicillin, flucloxacillin, mecillinam
 (~~pivmecillinam~~), 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, balofloxacin, 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 (~~co-trimoxazole~~); s). Steroid antibacterials; t). Tetracyclines comprising doxycycline, chlortetracycline, clomocycline, demeclocycline, lymecycline, meclocycline, metacycline, minocycline, oxytetracycline, penimepicycline, rolitetracycline, and tetracycline; u). antibiotics comprising annonacin, arsphenamine, 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, clevudine, dextelvucitabine, didanosine (~~ddI~~), elvucitabine, emtricitabine (~~FTC~~), entecavir, famciclovir, fluorouracil (~~5-FU~~), 3'-fluoro-substituted 2',3'-dideoxynucleoside compounds comprising 3'-fluoro-2',3'-dideoxythymidine (~~FLT~~) and 3'-fluoro-2',3'-dideoxyguanosine (~~FLG~~), fomivirsen, ganciclovir, idoxuridine, lamivudine (~~3TC~~), 1-nucleosides comprising β -1-thymidine and β -1-2'-deoxycytidine), penciclovir, racivir, stampidine, stavudine (~~ddT~~), taribavirin (~~viramidine~~), telbivudine, tenofovir, trifluridine valaciclovir, valganciclovir, zalcitabine (~~ddC~~), and zidovudine (~~AZT~~); f). non-nucleosides comprising amantadine, ateviridine, capravirine, diarylpyrimidines, delavirdine, docosanol, emivirine, efavirenz,

foscarnet (~~phosphonoformic acid~~), imiquimod, interferon alfa, loviride, lodenosine, methisazone, nevirapine, NOV-205, peginterferon alfa, podophyllotoxin, rimantadine, resiquimod (~~R-848~~), and tromantadine; g). protease inhibitors comprising amprenavir, atazanavir, boceprevir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, pleconaril, ritonavir, saquinavir, telaprevir (~~VX-950~~), and tipranavir; h). anti-virus drugs comprising ~~abzyme~~ ABZYME, ~~arbidol~~ ARBIDOL, calanolide a, ceragenin, cyanovirin-n, epigallocatechin gallate (~~EGCG~~), foscarnet, griffithsin, ~~taribavirin~~ (~~viramidine~~), hydroxyurea, KP-1461, miltefosine, pleconaril, portmanteau inhibitors, ~~ribavirin~~ RIBAVIRIN, and seliciclib;

5). any of 1) to 4) having a radioisotope of ^3H , ^{11}C , ^{14}C , ^{18}F , ^{32}P , ^{35}S , ^{64}Cu , ^{68}Ga , ^{86}Y , ^{99}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. (Currently Amended) The conjugate of claim 2, wherein the cell-binding agent is configured to bind to target cells which are selected from the group consisting of tumor cells, virus infected cells, microorganism infected cells, parasite infected cells, autoimmune cells, activated cells, myeloid cells, activated T-cells, B cells, or melanocytes; cells expressing the CD19, CD20, CD22, CD30, CD33, CD37, CD38, CD40, CD51, CD52, CD56, CD66, CD70, CD74, CD79, CD80, CD98, CD125, CD221, CD227, CD262, CD309, CD326, CEACAM3, CEACAM5

(carcinoembryonic antigen), DLL4 (Δ -like-4), EGFR, CTLA4, CXCR4 (CD184), Endoglin (CD105), EPCAM (epithelial cell adhesion molecule), ERBB2 (Epidermal Growth Factor Receptor-2), FCGR1, FOLR (folate receptor), GD2 ganglioside, G-28 (a cell surface antigen glycolipid), GD3 idiotypic, Heat shock proteins, HER1, HER2, HLA-DR10, HLA-DRB, human chorionic gonadotropin, IGF1R (insulin-like growth factor 1 receptor), IL-2 receptor (interleukin 2 receptor), IL-6R (interleukin 6 receptor), Integrins ($\alpha\beta$ 3, α 5 β 1, α 6 β 4, α 11 β 3, α 5 β 5, α 5 β 5), MAGE-1, MAGE-2, MAGE-3, MAGE 4, anti-transferrin receptor, p97, MS4A1 (membrane-spanning 4 domains subfamily A member 1), MUC1 or MUC1-KLH, MUC16 (CA125), CEA, gp100, MART1, MPG, MS4A1 (membrane-spanning 4 domains subfamily A), Nucleolin, Neu oncogene product, P21, Paratope antibody having a paratope of anti-(N-glycolylneuraminic acid), PLAP-like testicular alkaline phosphatase, PSMA, PSA, ROBO4, TAG 72 (tumor associated glycoprotein 72), T cell transmembrane protein, Tic (CD202b), TNFRSF10B (tumor necrosis factor receptor superfamily member 10B), TNFRSF13B (tumor necrosis factor receptor superfamily member 13B), TPBG (trophoblast glycoprotein), TRAIL-R1 (Tumor necrosis apoptosis inducing ligand Receptor 1), VCAM-1 (CD106), VEGF, VEGF-A, VEGF-2 (CD309), CanAg, CALLA, and cells expressing insulin growth factor receptor, or epidermal growth factor receptor.

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. (Previously Presented) The conjugate of claim 8, wherein the tumor cells are selected from

the group consisting of lymphoma cells, myeloma cells, renal cells, breast cancer cells, prostate cancer cells, ovarian cancer cells, colorectal cancer cells, gastric cancer cells, squamous cancer cells, small-cell lung cancer cells, testicular cancer cells, and cells that grow and divide at an unregulated, quickened pace to cause cancers.

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. (Currently Amended) The conjugate of claim 2, wherein the conjugate comprises one or more linker components of 6-maleimidocaproyl-(MC), maleimidopropanoyl-(MP), valine-citrulline-(~~val-cit~~), alanine-phenylalanine-(~~ala-phe~~), p-aminobenzyloxycarbonyl-(PAB), 4-thio-pentanoate-(SPP), 4-(N-maleimidomethyl)cyclohexane-1-carboxylate-(MCC), 4-thio-butyrate-(SPDB), maleimidoethyl ~~containing~~-(ME), 4-thio-2-hydroxysulfonyl-butyrate (~~2-Sulfo-SPDB~~) and (4-acetyl)aminobenzoate-(SIAB).

15. (Currently Amended) The conjugate of claim 2, wherein Drug is selected from the group consisting of tubulysins, maytansinoids, taxanoids-(~~taxanes~~), 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. (New) 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. (New) 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. (New) 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

Entry of the foregoing, reconsideration of the subject matter identified in caption, as amended, pursuant to and consistent with 37 C.F.R. §1.111, and in light of the remarks which follow, are respectfully requested.

In the present Amendment, claim 1 has been amended to further define R_1 - R_6 , Q, T, m and n. Claims 2-4 also have been amended to further define R_1 - R_6 . Support for these amendments can be found throughout the Specification, particularly, the Examples (see, e.g., Examples 69, 75, 86, 116, 122, 128, 135, 138, 142 and 147). Claims 5, 8, 14 and 15 have been amended to further improve their form. New claims 22-24 have been added. Support for claims 22-24 can be found throughout the Specification, particularly, Figs. 6, 7, 11, 13, 15, 16 and 18. Claim 13 was previously cancelled. No new matter has been added. Upon entry of the Amendment, claims 1-12 and 14-24 will be all the claims pending in the application.

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 "Xegeva" with --XGEVA--, 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, 8, 14, and 15 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, claims 5, 8, 14, and 15 have been amended to delete certain parentheses therein. Claim 14 has been amended to delete the word "containing." Claim 8 has been amended to specify "antibody having a paratope." Further, claim 5 has been amended to capitalize trademarks therein. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

b. Claim 5 was rejected under 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. Applicant respectfully submits that claim 5 as amended complies with the written description requirement.

In the Amendment, claim 5 has been amended to recite "a radioisotope." Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

c. Claims 2-12 and 14-21 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 following reasons.

The Office Action asserts that:

The specification has described conjugation the synthesis of bi-functional mono, bi, tri and tetraphosphinate linkers enabling conjugation to a drug via reaction of a thiol group on a drug moiety and conjugation of a protein or antibody via a maleimido [sic, maleimido] group on the opposite end of the linker. The use of the maleimido group in protein and antibody conjugation is well known in the art. However, claim 5 is not limited to drugs or biologically active proteins having a free thiol group ... The specification provides no teaching or guidance on the modification of the multitude of drugs ... to provide a free thiol group for conjugation to the linker such that the modification and/or the conjugation of the drug, products or cells preserves the required function of the drug, multicomponent products or cells. Thus, one of skill in the art would be required to determine how to modify all the drugs and multicomponent products required in claims [sic, claim] 5 such that the expected biological functions of the drugs and products are maintained and if such modification was possible. Based on this requirement, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make and use the broadly claimed compounds of claim 5. (Office Action at pages 4-5)

Applicant respectfully disagrees. As set forth in the previous Amendment, one skilled in the art would be able to synthesize conjugates of the drugs recited in claim 5, through an appropriate chemical reaction with the linker to form a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond.

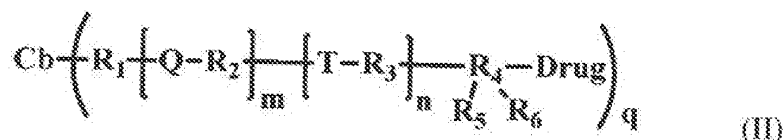
The present specification also provides specific examples of reacting the linker with various drugs, besides the drugs with a -SH group. For example, in Fig. 11, Drug-CO-NHNH₂

is used to convert Compounds 150 and 152 into Compounds 154 and 153, respectively; in Fig. 13, Drug-≡ is used to convert Compound 166 into Compound 167; in Fig. 15, Drug-CO-R" is used to convert Compounds 193 and 196 into Compounds 194 and 195, respectively; in Fig. 16, Drug-CO-R" is used to convert Compounds 201 and 204 into Compounds 202 and 203, respectively; and in Fig. 18, Drug-NH-R" is used to convert Compound 228 into Compound 229.

The Office Action also asserts that:

Claim 5 ... the "drug" includes an anti-infectious disease agent or an anti-viral agent ... The conjugate of the instant invention requires a cell binding agent, but for recognition of non-retroviral or non-lentiviral viral infections, the virus itself will be bound, rather than the cell harboring the virus. As a free virus is not a cell per se, the targeting of a free virus cannot be carried out by a "cell-binding agent" required by the conjugate of instant claim 2.... (Office Action at page 5)

The Examiner appears to misread the claim language. Specifically, claim 2, from which claim 5 depends, recites a cell-binding agent-drug conjugate of formula (II):



Note that Drug and the cell-binding agent Cb are both present in formula (II). Claim 5 further specifies that Drug includes, among others, an anti-infectious disease agent or an anti-viral drug. However, the claim does not require that when Drug is an anti-infectious disease agent or an anti-viral drug, the cell-binding agent bind to the target virus.

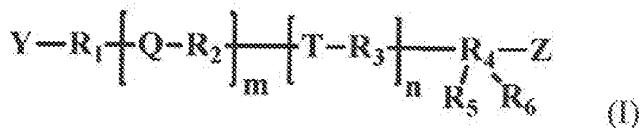
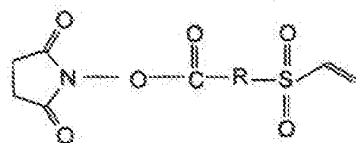
Applicant advises that both bacterial and viral cells express certain antigens on their cell surfaces, the antibody-drug conjugates therefore can bind, be endocytosed and then kill the abnormal cells, the same as for tumor cells. See, e.g., Pincus, et al., *Design and In Vivo Characterization of Immunoconjugates Targeting HIV gp160*, Journal of Virology, online publication, October 19, 2016 (51 pages); and Lehar, et al., Novel antibody-antibiotic conjugate eliminates intracellular *S. aureus*, Nature, 2015, 527, 323-328, copies of which are attached hereto.

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

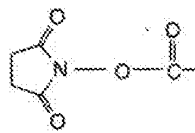
III. Response to Rejection under 35 U.S.C. § 102

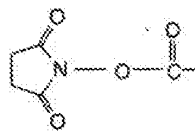
Claim 1 was rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by WO 97/41897 to Lees. Applicant respectfully submits that claim 1 as amended is novel and patentable over Lees for at least the following reasons.

Lees discloses protein/polysaccharide conjugates prepared via a heterobifunctional vinylsulfone, such as an N-hydroxysuccinimide vinylsulfone having the following structure:



This compound corresponds to



recited in claim 1 of the present application, where Y is , Q (or T) is $-S(O_2)-$, m (or n) is 1, n (or m) is 0, $R_2(R_3)$ and R_4-R_6 are absent, and Z is .

On the other hand, claim 1 of the present application recites that when Q or T is $-S(O_2)-$, m and n are not 0, thereby excluding the above noted compound described in Lees.

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

IV. New Claims

Newly added claims 22-24 depend from claim 2, 3 or 4, and thus are patentable at least for the reasons set forth above.

V. 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

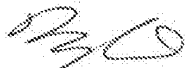
concerning this paper or the application in general, the Examiner is invited to telephone the undersigned at his earliest convenience.

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: March 20, 2018

By: 
Fang Liu
Registration No. 51283

Customer No. 21839
703 836 6620

Electronic Acknowledgement Receipt	
EFS ID:	32100923
Application Number:	14432073
International Application Number:	
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Title of Invention:	HYDROPHILIC LINKERS AND THEIR USES FOR CONJUGATION OF DRUGS TO A CELL BINDING MOLECULES
First Named Inventor/Applicant Name:	R. Yongxin Zhao
Customer Number:	21839
Filer:	Fang Liu/Sarah Noel
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File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Amendment.pdf	5930341	yes	91
			a88c433ba8a5c3f7974e59f909f30b8666c87f16		

Multipart Description/PDF files in .zip description			
Document Description		Start	End
Amendment/Req. Reconsideration-After Non-Final Reject		1	1
Claims		2	15
Applicant Arguments/Remarks Made in an Amendment		16	91
Warnings:			
Information:			
Total Files Size (in bytes):		5930341	
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/432,073	03/27/2015	R. Yongxin Zhao	0088597-000003	6938
21839 7590 07/10/2018 BUCHANAN, INGERSOLL & ROONEY PC POST OFFICE BOX 1404 ALEXANDRIA, VIRGINIA 22313-1404 UNITED STATES OF AMERICA			EXAMINER CANELLA, KAREN A	
			ART UNIT 1643	PAPER NUMBER
			NOTIFICATION DATE 07/10/2018	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPDOC1@BIPC.com

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

The species of -S(O)- has been added to the elected species of -P(=O)(OM)- and -S(O₂)- for examination at this time.

Claims 1-5, 8, 14, and 15 have been amended. Claims 22-24 have been added. Claims 1-12 and 14-24 are pending and under consideration.

Claim Objections

Claim 5 objected to because of the following informalities: the typographical error of “DMS” rather than “DM5”. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 14 and 15 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention is withdrawn in light of applicant’s amendments.

The rejection of claim 5 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention is maintained for partial reasons of record.

Claim 5 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the

invention because of the use of Tradenames, such as zybrestat, Stimuvax, Allovectin-7, Xgeva, Provenge, Yervoy, Romidepsin, PSK, abzyme, arbidol, and ribavirin is maintained. Tradenames designate the origin of the material but do not suffice to describe the material claimed.

Claim 8 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. Claim 8 is vague and indefinite in the recitation of the conjugate of claim 2, wherein the cell-binding agent is configured to bind to target cells which are selected from a group including cells expressing “antibody having a paratope of anti-N-glycolylneuraminic acid. An antibody paratope refers to the three dimensional portion of the antibody responsible for recognition of the epitope bound by the antibody. Thus the antibody epitope can be described by the variable chain sequences of the light and heavy chains of the antibody, but not the epitope bound by the antibody. It is unclear what applicant is attempting to claim with respect to a cell expressing an antibody having a paratope of an antibody that binds to N-glycolylneuraminic acid.

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claim 5 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 due to new matter is withdrawn in light of applicant’s amendment.

Claim 8 is 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. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 8 has been amended to require an antibody having a paratope of anti-N-glycolylneuraminic acid which is interpreted to read on an antibody which binds to an antibody which recognizes an epitope comprising N-glycolylneuraminic acid. The art teaches that antibodies to N-glycolylneuraminic acid (Neu5Gc) can be found in 85% of the human population and that Neu5Gc is an oligosaccharide structure found in therapeutic antibodies produced in mouse myeloma cells, such as SP2 or NS0 cells (Yagi et al, Analytical biochemistry, 2012, Vol. 431, pp. 120-126, see page 120, first column, lines 7-14). The specification provides no written description of a target cell expressing such an antibody, nor the cell binding agent for binding to this target cell. A description of an antibody paratope cannot be met by a description of the epitope to which the antibody binds.

The rejection of claims 2-12 and 14-20 under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the enablement requirement is maintained for reasons of record. Claims 22-24 are also rejected for the same reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) Claim 5 requires the compound of any one of claim 2 wherein the "Drug" is selected from the group consisting of a multitude of agents unrelated in structure. It is clear that the

biological activity of the Drug incorporated into the compound must be preserved in order for the claimed compounds to be used by one of skill in the art.

The specification has described conjugation the synthesis of bi-functional hydrophilic mono, bi, tri and tetraphosphinate linkers as well as bifunctional linkers comprising sulfones and sulfoxides wherein the linkers enable conjugation to a drug via reaction of a thiol group on a drug moiety and conjugation of a protein or antibody via a maleimido group on the opposite end of the linker. The use of the maleimido group in protein and antibody conjugation is well known in the art. However, claim 5 is not limited to drugs or biologically active proteins having a free thiol group, but includes a plethora of drug molecules, nucleosides and nucleotides, siRNA and anti-sense drugs in addition to multi-component substances, such as Stimuvax (also known as BLP25, see Sangha and Butts, *Clinical Cancer Research*, 2007, Vol. 13, suppl. 15, pp. 4652s-4654s, see page 4653s, first paragraph under the heading “Liposomal MUC1 Vaccine BLP25”), Allovectin-7 (Stopeck et al, (*Clinical Cancer Research*, 2001, Vol. 7, pp. 2285-2291, see page 2286, first column, lines 1-6 of the second paragraph) and Provenge (Harzstark and Small, *Expert Opinion on Biological Therapy*, 2007, Vol. 7, pp. 1275-1280) which is an antigen-loaded antigen presenting cell. The specification provides no teaching or guidance on the modification of the multitude of drugs, including multi-component products and cells, to provide a free thiol group for conjugation to the linker such that the modification and/or the conjugation of the drug, products or cells preserves the required function of the drug, multicomponent products or cells. Thus, one of skill in the art would be required to determine how to modify all the drugs and multicomponent products required in claims 5 such that the expected biological functions of the drugs and products are maintained and if such modification was possible. Based on this requirement, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make and use the broadly claimed compounds of claim 5.

Applicant argues that one of skill in the art would be able to synthesize conjugates of the drugs recited in claim 5 through an appropriate chemical reaction, and that the specification also provides specific examples of reacting the linker with various drugs in addition to drugs with a SH group. Applicant points to Figure 11, and the conversion of compounds 150 and 152 into compounds 154 and 153, Figure 13 and the conversion of compound 166 to compound 167; Figure 15 and the conversion of compounds 193 and 196 into compounds 194 and 195; Figure 16 wherein compounds 201 and 204 are converted into compounds 202 and 203 and Figure 18

wherein compound 228 is converted into compound 229. This has been considered but not found persuasive. In all of the aforesaid figures “drug” is simply indicated as a generic “drug” having a required appendage of a desired functional group. This fails to provide enablement for how to make the broad genus of drugs comprising the required functional group wherein the desired activity of the modified drug would not be adversely affected by the chemical reactions required for the structural modification. It is noted that the modification of certain therapeutic agents listed in claim 5, such as the maytansins DM1 and DM4, auristatins, calicheamicins, duocarmycin, doxorubicin, idarubicin, tubulysin, paclitaxel, docetaxel, vinblastine, mitomycin C and methotrexate, (Goldmacher and Kovtun, *Therapeutic Delivery*, 2011, Vol. 2, 397-416; Zhao et al, *Journal of Medicinal Chemistry*, 2011, Vol. 55, pp. 766-782, reference of the IDS filed 2/2/2017; Safavy et al, *Bioconjugate Chemistry*, 2004, Vol. 15, pp. 1264-1274; Ojima et al, *Journal of Medicinal Chemistry*, 2002, Vol. 45, pp. 5620-5623, reference of the IDS filed 2/2/2017; Chari et al, *Advanced Drug Delivery Reviews*, 1998, Vol. 31, pp. 89-104; Friden et al, *PNAS*, 1991, Vol. 88, pp. 4771-4775; Apeltgren et al, *Cancer Research*, 1990, Vol. 50, pp. 3540-3544) which are well-known to form antibody drug conjugates are well known in the art and thus would be enabled in the instant specification because the structure activity relationship of the drug is well known as is the positions of chemical modifications that do not interfere with the structure activity relationship of the cytotoxic drugs.

(B) As drawn to the conjugates of the invention comprising anti-infectious disease agent and anti-viral drugs.

Claim 5 is drawn in part to the cell-binding agent drug conjugate of claim 2 wherein the "drug" includes an anti-infectious disease agent or an anti-viral agent. Claim 20 is included with this rejection because a pharmaceutical composition comprising a therapeutically effective amount of the conjugate of claim 2 and additionally, an anti-infectious agent is presumably used to treat an infectious disease. The specification does not teach any binding agent specific for the treatment of a patient with a viral or bacterial infection. The art teaches that the vast majority of therapeutic mAb are administered for a the treatment of cancer, autoimmune disorder and transplantation (Irani et al, *Molecular Immunology*, 2015, Vol. 67, pp. 171-182, see page 171, second column, lines 14-17) but that the development of monoclonal therapeutic antibodies against specific infectious diseases has been slow (page 171, first column, lines 5-8). Irani et al note that antibodies developed to HIV target HIV envelop glycoproteins, antibodies developed to

West Nile virus target domain III of the virus, antibodies developed to gram positive Staph aureus target poly N-acetyl glucosamine, and antibodies targeting gram negative bacteria target Serogroup O6 LPS, and Shiga toxin 2 (Table 4). It is noted that antibodies targeting bacteria bind directly to the infectious agent, and that with the exception of lentivirus infected cells and retrovirus infected cells, antibodies which bind to viruses also bind directly to the virus rather than the cell infected with the virus (Pelegrin et al, Trends in Microbiology, 2015, Vol. 23, pp. 653-665, see page 653, lines 1-3 and page 654, lines 9-10). The conjugate of the instant invention requires a cell binding agent, but for recognition of non-retroviral or non-lentiviral viral infections, the virus itself will be bound, rather than the cell harboring the virus. As a free virus is not a cell per se, the targeting of a free virus cannot be carried out by a "cell-binding agent" required by the conjugate of instant claim 2. Further, there are no teachings in the specification of a "Drug" active against a free virus which is not capable of autonomous replication outside of a host cell.

Targeting of free bacteria by the conjugate of the invention could be carried out with a cell binding agent which is a monoclonal antibody recognizing the bacteria cells. Bacterial cells are in possession of a cell wall which is not a feature of a eukaryotic cell. The instant specification provides no guidance as to the ability of the a bacterial cell bound to an antibody to internalize the antibody through the cell wall in order that the Drug attached to the conjugate can be internalized and exert a toxic affect against the targeted bacterial cell. There is no art of record or teachings in the specification to support the notion that antibody-drug conjugates are effective at targeting bacterial cells to exert the effect of the drug on the bacterial cells.

Applicant argues that in claim 5 it is not required that the cell binding agent bind to the target virus. This has been considered but not found persuasive, as the claims do not limit the cell binding agent to the binding of target mammalian cells.

Applicant argues that because both bacterial cells and viral cells express certain antigens on their cell surfaces, the antibody drug conjugates can bind be endocytosed and then kill the abnormal cells in the same method that is functional against tumor cells. Applicant cites Pincus et al describing the antibody targeting of gp160 of HIV. This has been considered but not found persuasive. As stated in the rejection above,

It is noted that antibodies targeting bacteria bind directly to the infectious agent, and that with the exception of lentivirus infected cells and retrovirus infected cells, antibodies which bind to viruses also bind directly to the virus rather than the cell infected with the virus (Pelegrin et al, Trends in Microbiology, 2015, Vol. 23, pp. 653-665, see page 653, lines 1-3 and page 654, lines 9-10).

However, the claims are not limited to cell binding agents which target lentivirus infected cells and retrovirus infected cells, such as human cells infected with HIV.

Applicant also cites Lehar et al for enablement of treatment of intracellular bacteria. This has been considered but not found persuasive because the claims are not limited in the treatment of a bacterial disease which is intracellular. It is noted that instant claim 8 recites microorganism infected cells and parasite infected cells which does not confine the infection to an intracellular infection because bacteria growing on the surface of a mammalian cell or parasites living on a mammalian cell also constitutes a microorganism or parasite infected cell. Further claim 8 recites “activated cell” which can be interpreted as a proliferating bacterium or proliferating parasite.

The rejection of claim 1 under pre-AIA 35 U.S.C. 102(b) as being anticipated by Lees (WO97/41897) is withdrawn in light of applicant’s amendment requiring that when Q or T is – (SO₂)-, m and n are not zero.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

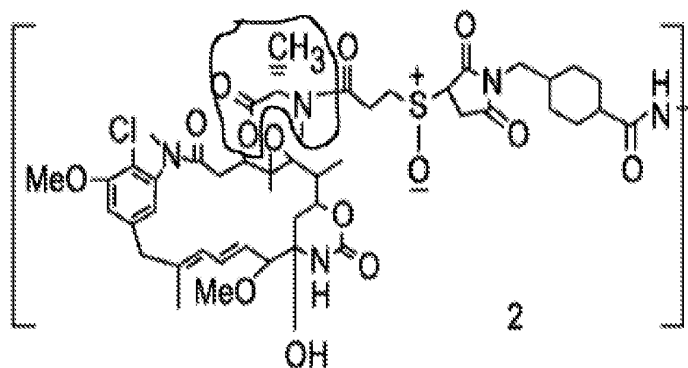
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 2, 5-12, 14-16, 17, 19, 20 and 22 are rejected under pre-AIA 35 U.S.C. 102(a) and pre-AIA 35 U.S.C. 102(e) as being anticipated by Fishkin (WO2012145112, reference of the IDS filed 3/10/2017) 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, reference of the IDS filed 2/2/2017).

Fishkin discloses the maytansinoid cytotoxic agent DM1 conjugated through a linker comprising a sulfoxide to an anti-EpCAM antibody (Figure 1, compound 2) which meets the limitations of claim 2 wherein Cb is the anti-EpCAM antibody; Drug is the DM1 linked to the hydrophilic linker via an oxidized thioether, n=0, m=1, R1 is absent, R2 is a cyclic amide having 4 carbon atoms; R4 is combination of a linear alkyl having one carbon atom, a cyclic alkyl of six carbon atoms and an amide, R5 and R6 are absent and "Drug" is the maytansinoid DM1, and also meets the limitations of claim 5 wherein the drug is DM1; the limitations of claim 6 and 15 wherein the drug is a maytansinoid; the limitations of claim 12 wherein the drug is a toxin; the limitations of claim 7 wherein the cell binding agent is an antibody; the limitations of claim 8; the limitations of claim 9 wherein the cell binding agent is an antibody, and wherein the cell binding agent binds to target cells which are tumor cells and wherein the cell binding agent binds to cells expressing EpCAM; Fishkin discloses that Ab-SMCC-DM1 was prepared by the method of Kovtun et al (page 60, paragraph [0183]). Kovtun et al provides evidence that the antibody was modified with SMCC prior to conjugation with DM1 as described in Widdison et al (page 2529, in the paragraph labeled "Antibody-maytansinoid conjugates"). Widdison et al provide evidence that the maytansinoid, DM1 was obtained by reduction of the corresponding disulfide containing maytansinoid to obtain the thiol containing DM1 (page 4394, Scheme 2, page 4395, second column, second paragraph, page 4396, Scheme 7, compound 25(a)). Thus the conjugate of Fishkin meets the limitation of claim 22 wherein the drug is derived from a drug containing an -SH and/or the cell binding agent is an antibody.

Claim 74 of Fishkin discloses that the cell binding antibodies of the invention include a single chain antibody, an antibody fragment that specifically binds to the target cell, a monoclonal antibody, a single chain monoclonal antibody, or a monoclonal antibody fragment that specifically binds the a target cell, a chimeric antibody, a chimeric antibody fragment that specifically binds to the target cell, a domain antibody, and a domain antibody fragment that specifically binds to the target cell, which meets the remaining limitations in instant claim 9. Fishkin discloses that the anti-EpCAM-sulfoxide -DM1 conjugate is toxic to squamous cell carcinoma in vitro (Figure 1) as well as lung carcinoma cells in vitro (Figure 2) which meets the limitations of claim 10 for squamous cancer cells and cells that grown and divide at a quickened pace to cause cancers and the limitations of claim 16 wherein the conjugate has in vitro, in vivo or ex vivo cell killing activity. The anti-EpCAM-sulfoxide -DM1 of Fishkin meets the limitations of claim 14 wherein the conjugate comprises one or more linker components of 4-(N-maleimidomethyl)cyclohexane-1-carboxylate because the conjugate of Fishkin comprises the linker of succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC). Fishkin discloses pharmaceutical composition comprising conjugates of the invention (page 5, paragraph [10], and that the conjugates of the invention are supplied as a lyophilized sterile powder, and doses are administered in sterile saline (page 57 paragraph [169], page 58, paragraph [174]), that meets the limitations of claim 19 drawn to a pharmaceutical composition comprising a pharmaceutically acceptable carrier. Fishkin discloses the conjugates of the invention optionally in combination with another chemotherapeutic agent (page 5, paragraph [11]), which meets the limitation of instant claim 20.

Figure 1 of Fishkin indicates that the conjugate comprises a peptide having one unit of an unnatural amino acid, N-methyl alanine:



which meets the limitation of claim 17 for a conjugate comprising a peptide of 1 unit of unnatural amino acids

All other rejections and objections as set forth in the prior Office action are withdrawn.

Allowable Subject Matter

Claims 1 and 21 are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KAREN A CANELLA whose telephone number is (571)272-0828. The examiner can normally be reached on M-F 10-6:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on 571-272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KAREN A. CANELLA
Examiner
Art Unit 1643

/Karen A. Canella/
Primary Examiner, Art Unit 1643

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	MAIL STOP AF
	)	
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.

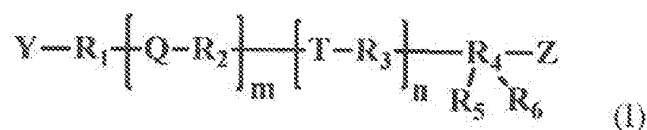
Certification and Request for Consideration under the After-Final Consideration Pilot program 2.0 is being filed concurrently.

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, alkoxime or amide bond;

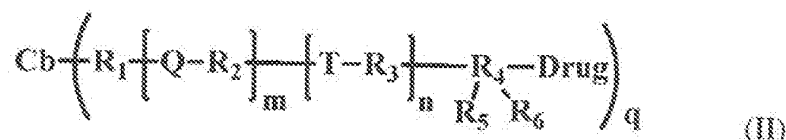
R₁, R₂, R₃, and R₄, are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, 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, alkoxy 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;~~

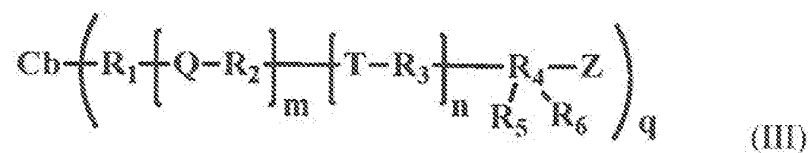
R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula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

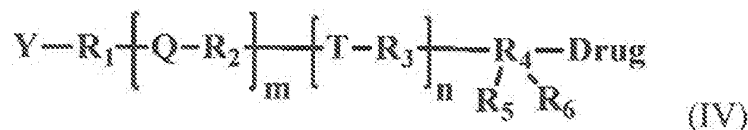
R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, 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 $N^+ R_1 R_2 R_3$ 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, encitabine, 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, mepitio stanol, 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, ivozanib, 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, nitomyces, 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, ZYBRESTATf, foscarnet, PLX4032, vemurafenib, STA-9090, Ganetespib, STIMUVAX, tecemotide, ALLOVECTIN-7, XGEVA, Adenosumab, PROVENGE, sipuluncel-T, YERVOY, ipilimumab, 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 aminoglutethimide, mitotane, and trilostane; aceglutone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; arabinoside, bestabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; eflornithine, elfornithine; 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 beclomethasone dipropionate, DHEA, enantcept, hydroxychloroquine, infliximab, meloxicam, methotrexate, mofetil, mycophenolate, prednisone, sirolimus, tacrolimus;

3). anti-infectious disease agents comprising a). Aminoglycosides comprising amikacin, astromicin, 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, ceflazidime, cefteram, cefibuten, ceftiolene, ceftizoxime, ceftobiprole, ceftriaxone, cefuroxime, cefuzonam, cephamycin comprising cefoxitin, cefotetan, and cefmetazole, 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, balofloxacin, 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 comprising annonacin, 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, dexelvucitabine, didanosine, elvucitabine, emtricitabine, entecavir, fanciclovir, 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~~ umifenovir, calanolide a, ceragemin, 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}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, CAP18₁₀₆₋₁₃₈-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:

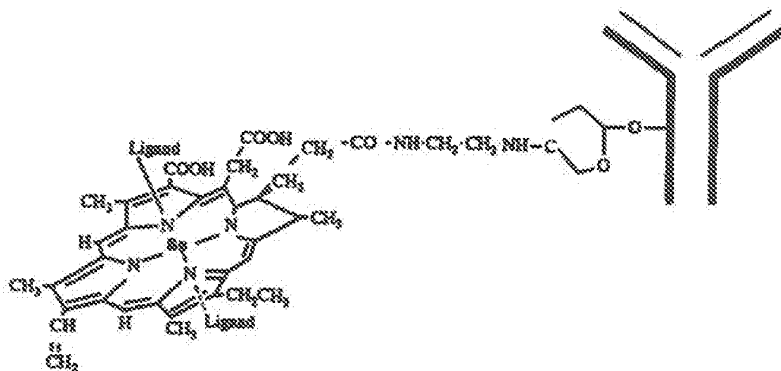


FIGURE 2a. Schematic structure of ED immunoconjugate.

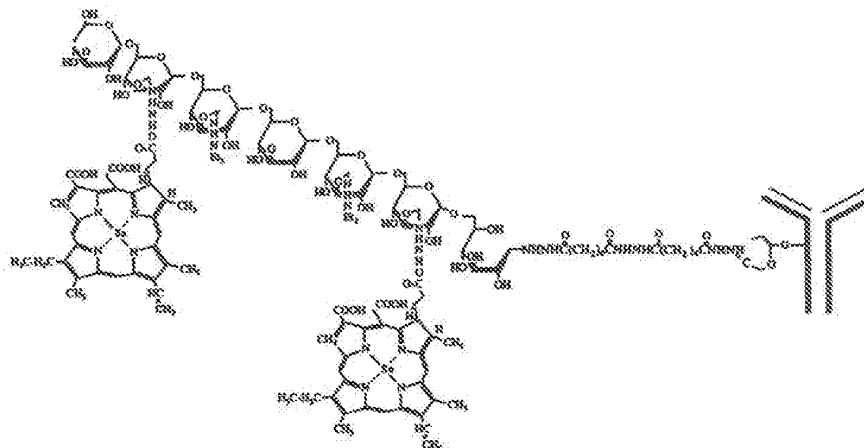


FIGURE 2b. Schematic structure of DC immunocapsule. Axial ligands are presumed to be either OH⁻ or Cl⁻.

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

Registration No. 51283

Customer No. 21839
703 836 6620

OK TO ENTER: /KAC/

PATENT
Attorney Docket No. 0088597-000003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	MAIL STOP AF
	)	
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:

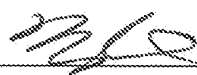
In response to the Official Action dated July 10, 2018, please amend the above identified application as follows.

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

Doc Code: A.NE.AFCP

Document Description: After Final Consideration Pilot Program Request

PTO/SB/434 (05-13)

CERTIFICATION AND REQUEST FOR CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0		
Practitioner Docket No.: 0088597-000003	Application No.: 14/432,073	Filing Date: March 27, 2018
First Named Inventor: R. Yongxin ZHAO	Title: HYDROPHILIC LINKERS AND THEIR USES FOR CONJUGATION OF DRUGS TO A CELL BINDING MOLECULES	
APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0 (AFCP 2.0) OF THE ACCOMPANYING RESPONSE UNDER 37 CFR 1.116. - The above-identified application is (i) an original utility, plant, or design nonprovisional application filed under 35 U.S.C. 111(a) [a continuing application (e.g., a continuation or divisional application) is filed under 35 U.S.C. 111(a) and is eligible under (i)], or (ii) an international application that has entered the national stage in compliance with 35 U.S.C. 371(c). - The above-identified application contains an outstanding final rejection. - Submitted herewith is a response under 37 CFR 1.116 to the outstanding final rejection. The response includes an amendment to at least one independent claim, and the amendment does not broaden the scope of the independent claim in any aspect. - This certification and request for consideration under AFCP 2.0 is the only AFCP 2.0 certification and request filed in response to the outstanding final rejection. - Applicant is willing and available to participate in any interview requested by the examiner concerning the present response. - This certification and request is being filed electronically using the Office's electronic filing system (EFS-Web). - Any fees that would be necessary consistent with current practice concerning responses after final rejection under 37 CFR 1.116, e.g., extension of time fees, are being concurrently filed herewith. [There is no additional fee required to request consideration under AFCP 2.0.] - By filing this certification and request, applicant acknowledges the following: - Reissue applications and reexamination proceedings are not eligible to participate in AFCP 2.0. - The examiner will verify that the AFCP 2.0 submission is compliant, i.e., that the requirements of the program have been met (see items 1 to 7 above). For compliant submissions: - The examiner will review the response under 37 CFR 1.116 to determine if additional search and/or consideration (i) is necessitated by the amendment and (ii) could be completed within the time allotted under AFCP 2.0. If additional search and/or consideration is required but cannot be completed within the allotted time, the examiner will process the submission consistent with current practice concerning responses after final rejection under 37 CFR 1.116, e.g., by mailing an advisory action. - If the examiner determines that the amendment does not necessitate additional search and/or consideration, or if the examiner determines that additional search and/or consideration is required and could be completed within the allotted time, then the examiner will consider whether the amendment places the application in condition for allowance (after completing the additional search and/or consideration, if required). If the examiner determines that the amendment does not place the application in condition for allowance, then the examiner will contact the applicant and request an interview. - The interview will be conducted by the examiner, and if the examiner does not have negotiation authority, a primary examiner and/or supervisory patent examiner will also participate. - If the applicant declines the interview, or if the interview cannot be scheduled within ten (10) calendar days from the date that the examiner first contacts the applicant, then the examiner will proceed consistent with current practice concerning responses after final rejection under 37 CFR 1.116.		
Signature 		Date July 24, 2018
Name (Print/Typed) Fang Liu		Practitioner Registration No. 51,283
<i>Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.</i>		
☐ * Total of _____ forms are submitted.		



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NOTICE OF ALLOWANCE AND FEE(S) DUE

21839 7590 08/30/2018
BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER

CANELLA, KAREN A

ART UNIT

PAPER NUMBER

1643

DATE MAILED: 08/30/2018

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/432,073	03/27/2015	R. Yongxin Zhao	0088597-000003	6938

TITLE OF INVENTION: HYDROPHILIC LINKERS AND THEIR USES FOR CONJUGATION OF DRUGS TO A CELL BINDING MOLECULES

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$500	\$0.00	\$0.00	\$500	11/30/2018

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21839 7590 08/30/2018
BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/432,073	03/27/2015	R. Yongxin Zhao	0088597-000003	6938

TITLE OF INVENTION: HYDROPHILIC LINKERS AND THEIR USES FOR CONJUGATION OF DRUGS TO A CELL BINDING MOLECULES

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$500	\$0.00	\$0.00	\$500	11/30/2018

EXAMINER	ART UNIT	CLASS-SUBCLASS
CANELLA, KAREN A	1643	424-197110

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363). ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached. ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.	2. For printing on the patent front page, list (1) The names of up to 3 registered patent attorneys or agents OR, alternatively, (2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.	1 _____ 2 _____ 3 _____
--	---	-------------------------------

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☐ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☐ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
☐ Applicant asserting small entity status. See 37 CFR 1.27
☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____
Typed or printed name _____ Registration No. _____



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/432,073	03/27/2015	R. Yongxin Zhao	0088597-000003	6938
21839	7590	08/30/2018	EXAMINER	
BUCHANAN, INGERSOLL & ROONEY PC			CANELLA, KAREN A	
POST OFFICE BOX 1404			ART UNIT	
ALEXANDRIA, VA 22313-1404			PAPER NUMBER	

1643

DATE MAILED: 08/30/2018

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b) (2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 14/432,073	Applicant(s) Zhao, R. Yongxin	
	Examiner KAREN A CANELLA	Art Unit 1643	AIA Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to the response file 7/24/2018.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are See Continuation Sheet. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some *c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. ____.

3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: ____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file areply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date ____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892) 2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date ____. 3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material ____. 4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____.	5. ☒ Examiner's Amendment/Comment 6. ☐ Examiner's Statement of Reasons for Allowance 7. ☐ Other _____.
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/Karen A. Canella/ Primary Examiner, Art Unit 1643	
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Continuation of 3. The allowed claim(s) is/are: 1-7,9,11-12 and 14-24

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Fang Liu on August 17, 2018.

The application has been amended as follows:

Claim 5 has been replaced with the following:

The conjugate of claim 2, wherein the 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, bizelesin, duocarmycin, KW-2189, ~~and~~ CBI-TMI[:], ~~benzodiazepine dimers comprising dimers of pyrrolbenzodiazepine dimers, or~~ tomaymycin dimers, indolinbenzodiazepine[s] dimers, imidazobenzothiadiazepine[s] dimers, ~~or~~ oxazolidinobenzodiazepine[s] dimers[:], ~~Nitrosoureas comprising~~ carmustine, lomustine, chlorozotocin, fotemustine, nimustine, ranimustine[:], ~~Alkylsulphonates comprising~~ busulfan, treosulfan, improsulfan ~~and~~ pipsulfan[:], 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~~ or trimethylolomelamine;

b). Plant Alkaloids comprising ~~Vinea alkaloids comprising~~ vincristine, vinblastine, vindesine, vinorelbine, navelbin[:], ~~Taxoids comprising~~ paclitaxel, ~~and~~ docetaxol[:], Maytansinoids comprising DM1, DM2, DM3, DM4, DM5, DM6, or DM7, maytansine, ~~and~~ ansamitocins[:], ~~cryptophycins comprising~~ cryptophycin 1, ~~and~~ cryptophycin 8[:], epothilones,

eleutherobin, discodermolide, bryostatins, dolostatins, auristatins, tubulysins, cephalostatins[;], pancratistatin[;], ~~or~~ sarcodictyin A[;] or 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[;], or mitomycins;

d). Anti-metabolites comprising ~~Anti-folate comprising DHFR inhibitors comprising~~ methotrexate, trimetrexate, denopterin, pteropterin, ~~and~~ aminopterin[;], ~~IMP dehydrogenase Inhibitors comprising~~ mycophenolic acid, tiazofurin, ribavirin, EICAR[;], ~~Ribonucleotide reductase Inhibitors comprising~~ hydroxyurea, 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[;], and a 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, epitiostanol, goserelin, leuprolide, mepitiostane, nilutamide, testolactone, and trilostane;

f). Vitamin D3 compounds comprising CB 1093, EB 1089 KH 1060, cholecalciferol,~~and~~ or ergocalciferol;

g). Photodynamic therapies comprising verteporfin, phthalocyanine, photo sensitizer Pc4, or demethoxy-hypocrellin A;

h). Cytokines comprising Interferon-alpha, Interferon-gamma, tumor necrosis factor (TNFs), or human proteins containing a TNF domain;

[f)] i). Kinase inhibitors comprising ~~anti-EGFR/ErbB2~~, 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~~, or ispinesib;

[g)] ~~j).~~ antibiotics comprising ~~enediynes comprising calicheamicins comprising~~ calicheamicin $\gamma 1$, $\delta 1$, $\alpha 1$ or $\beta 1$ [;], ~~dynemicin, including selected from the group consisting of~~ dynemicin A₂ and deoxydynemicin[;], esperamicin, kedarcidin, C-1027, maduropeptin, neocarzinostatin chromophore, and chromoprotein enediyne antiobiotic chromomophores, aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabacin, 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, nitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, or zorubicin;

[f)] ~~k).~~ Polyketides comprising bullatacin and or bullatacinone; gemcitabine, epoxomicins, bortezomib, thalidomide, lenalidomide, pomalidomide, tosedostat, fosbretabulin, vemurafib, gentespib, tecemotide, ~~allovectin-7, Adenosumab, sipuleucel-T, ipilimumab,~~ Isoprenylation inhibitors, Dopaminergic neurotoxins, Cell cycle inhibitors, Actinomycin D, bleomycin A₂, bleomycin B₂, peplomycin, ~~anthracyclines comprising~~ daunorubicin, adriamycin, idarubicin, epirubicin, pirarubicin, zorubicin, mtoxantrone, MDR inhibitors, Ca⁺² ATPase inhibitors, Vorinostat, Romidepsin, Panobinostat, Valproic acid, Mocetinostat, Belinostat, PCI-24781, Entinostat, SB939, Resminostat, Givinostat, AR-42, CUDC-101, sulforaphane, Trichostatin A[;], Celecoxib, glitazones, epigallocatechin gallate, Disulfiram, Salinosporamide A[;], ~~Anti-adrenals comprising~~ aminoglutethimide, mitotane, trilostane; aceglatone[;], aldophosphamide glycoside; aminolevulinic acid[;], amsacrine[;], arabinoside, bestrabucil[;], bisantrene[;], edatraxate[;], defofamine[;], demecolcine[;], diaziquone[;], eflornithine, elfomithine[;], elliptinium acetate, etoglucid[;], gallium nitrate[;], gacytosine, hydroxyurea[;], 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[;], T-2 toxin, verrucarins, roridin A₂ and anguidine[;], urethane, siRNA, or antisense drugs;

2). Anti-autoimmune disease agents comprising cyclosporine, cyclosporine A, aminocaproic acid, azathioprine, bromocriptine, chlorambucil, chloroquine, cyclophosphamide,

amcinonide, betamethasone, budesonide, hydrocortisone, flunisolide, fluticasone propionate, fluocortolone danazol, dexamethasone, Triamcinolone acetonide, ~~and~~ beclometasone dipropionate, DHEA, enanercept, hydroxychloroquine, ~~infiximab~~, meloxicam, methotrexate, mofetil, mycophenylate, prednisone, sirolimus, or tacrolimus;

3). Anti-infectious disease agents comprising a) ~~Aminoglycosides comprising~~ amikacin, astromicin, ~~gentamicin comprising~~ netilmicin, sisomicin, 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, thiamphenicol[;], c) ~~Ansamyins comprising~~ geldanamycin, ~~and~~ herbimycin[;], d) ~~Carbapenems comprising~~ biapenem, doripenem, ertapenem, imipenem/~~cilastatin~~, meropenem, ~~and~~ panipenem[;], e) ~~Cephems comprising~~ carbacephem, cefacetile, cefaclor, cefradine, cefadroxil, cefalonium, cefaloridine, cefalotin, ~~or~~ cefalothin, cefalexin, cefaloglycin, cefamandole, cefapirin, cefatrizine, cefazaflur, cefazedone, cefazolin, cefbuperazone, cefcapene, cefdaloxime, cefepime, cefminox, cefoxitin, cefprozil, cefroxadine, ceftazole, 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~~ cefmetazole, ~~oxacephem comprising~~ flomoxef, and latamoxef[;], bleomycin, vancomycin, teicoplanin, 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, spectinomycin, 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, balofloxacin, 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 comprising~~ annonacin, 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~~ or uvaricin;

4). Anti-viral drugs comprising a)- ~~Entry/fusion inhibitors comprising~~ aplaviroc, maraviroc, vicriviroc, enfuvirtide, PRO 140, ~~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, dexelvucitabine, 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, ~~ribavirin~~, 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, rifampicin,

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, umifenovir, calanolide-a, ceragenin, cyanovirin-n, epigallocatechin gallate, foscarnet, griffithsin, hydroxyurea, KP-1461, miltefosine, pleconaril, ~~portmanteau inhibitors~~, ribavirin, or seliciclib;

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

6) the pharmaceutically acceptable salts or acids of any of the above drugs.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KAREN A CANELLA whose telephone number is (571)272-0828. The examiner can normally be reached on M-F 10-6:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on 571-272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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