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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	
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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.

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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the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention is withdrawn in light of applicant's amendments.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 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 (Pelegri 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.

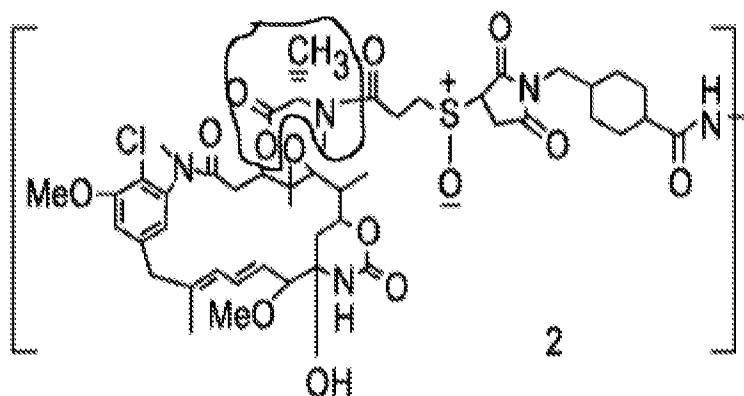
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the 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 with 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