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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(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 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.

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