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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JOHN A. FLYGARE, JAGATH R. JUNUTULA,
and THOMAS HARDEN PILLOW¹

Appeal 2015-002728
Application 13/297,408
Technology Center 1600

Before DEMETRA J. MILLS, ULRIKE W. JENKS,
and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner rejected the pending claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

STATEMENT OF THE CASE

Appellants' "invention relates generally to antibodies conjugated to maytansinoid drug moieties to form antibody-drug conjugates with therapeutic or diagnostic applications." (Spec. 1, ll. 12–13.)

¹ Appellants identify the Real Party in Interest as Genentech, Inc. (Br. 2.)

As background, the Specification discloses

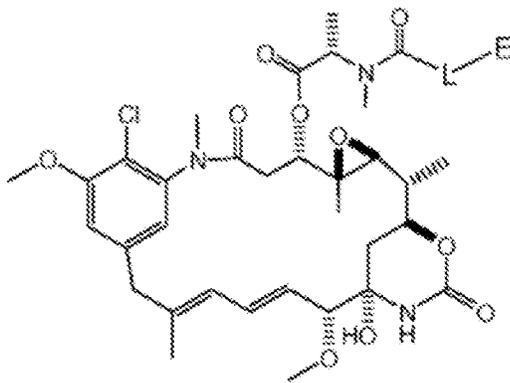
[a]ntibody drug conjugates (ADC) are targeted chemotherapeutic molecules combining the ideal properties of both antibodies and cytotoxic drugs by targeting potent cytotoxic drugs to the antigen-expressing tumor cells The successful ADC development for a given target antigen depends on optimization of antibody selection, linker design and stability, cytotoxic drug potency and mode of drug and linker conjugation to the antibody. . . . Linker stability plays an important role in both the efficacy and toxicity of ADC Stable linkers such as mcc are more efficacious and safer than unstable, disulfide linkers, widening the therapeutic window.

(*Id.* at 1, 1. 19 to 2, 1. 3.)

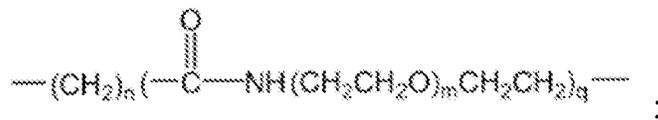
Claims 1–9 are on appeal. Claim 1 is illustrative:

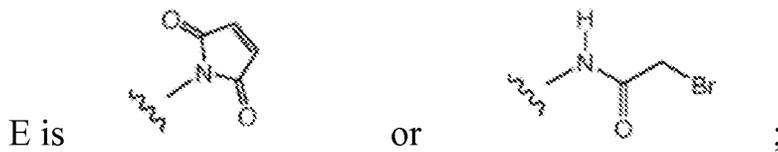
1. A compound of Formula I:

wherein:



L is





n is 2, 3, 4, 5, or 6;
m is 2, 3, or 4; and
q is 0 or 1.

(Br. 9 (Claims App'x).)

The claims stand rejected as follows:

- I. Claims 1–3, 6, and 7 under 35 U.S.C. § 103(a) over Ho² and Alley³ (“Rejection I”).
- II. Claims 1, 4, 5, 8, and 9 under 35 U.S.C. § 103(a) over Singh⁴ and Alley (“Rejection II”).

REJECTION I

Issue

Has the Examiner established by a preponderance of the evidence that claims 1–3, 6, and 7 would have been obvious over Ho and Alley?

Findings of Fact (FF)

FF 1. The Examiner’s findings of fact and statement of Rejection I may be found at pages 2–4 of the Examiner’s Answer dated November 6, 2014. (*See also* Final Act. 2–9.) We adopt the Examiner’s findings

² Ho et al., US 7,598,375 B2, issued Oct. 6, 2009 (“Ho”).

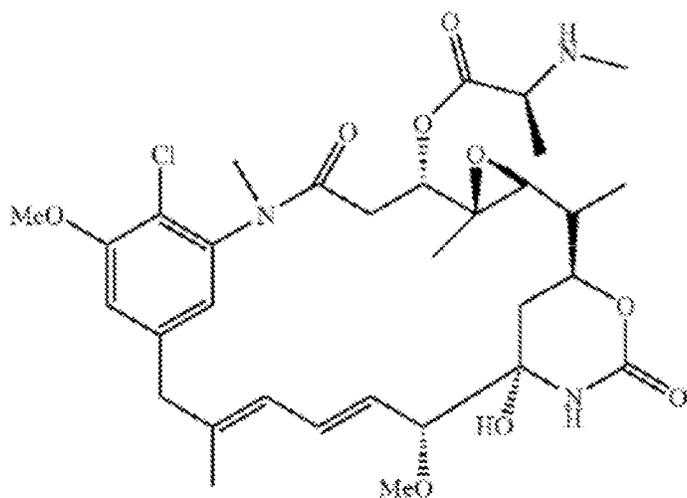
³ Alley et al., *Contribution of Linker Stability to the Activities of Anticancer Immunoconjugates*, 19 BIOCONJUGATE CHEM. 759–65 (2008) (“Alley”).

⁴ Singh et al., US 2010/0129314 A1, published May 27, 2010 (“Singh”).

concerning the scope and content of the prior art and provide the following for emphasis.

FF 2. Ho teaches “maytansinoids having a chiral amino acid side chain, such as DM1 and DM4 that are used to treat cancer.” (Ho Abstract.) Ho teaches “[m]aytansinoids are potent anti-cancer compounds, the use of which is limited by their toxicity. One approach for managing the toxicity of these agents is to link the maytansinoid to an antibody that specifically targets the tumor.” (*Id.* at col. 1, ll. 20–24.)

FF 3. Ho teaches methods of making maytansinoids by formation of an intermediate compound “Aa” having the following structure:



Aa (*N*-methylalanine ester)

(*Id.* at col. 7, ll. 20–39; *see also id.* at col. 3, ll. 10–30, col. 4, ll. 16–44, and col. 12 (claim 1).) With respect to compound Aa, Ho discloses “[m]aytansinol 3-(*S*)- α -*N*-methylaminopropionate (Aa) is a useful intermediate for making other maytansinoids such as DM4.” (*Id.* at col. 8, ll. 45–47; Ans. 2–3.) For example, compound Aa may be further reacted

with 3-(2-methyldisulfanyl)propanoic acid resulting in a disulfide linkage.

(*See, e.g.*, col. 7, ll. 19–55; Ans. 3.)

FF 4. Alley teaches

[t]he linker component of antibody-drug conjugates (ADC) is a key feature in developing optimized therapeutic agents that are highly active at well tolerated doses. For maximal intratumoral drug delivery, linkers are required that are highly stable in the systemic circulation, yet allow for efficient drug release at the target site. In this respect, amide bond-based technologies constitute a technological advancement, since the linker half-lives in circulation ($t_{1/2} \sim 7$ days) are much longer than earlier generation linkers that break down within 1–2 days. The amide linkers, some of which contain peptides, are appended to mAb carriers through thioether/maleimide adducts. Here, we describe that use of bromoacetamidocaproyl (bac) in place of maleimidocaproyl (mc) increases the plasma stability of resulting thioether ADCs. . . . [D]ata indicate that new linkers can be obtained with improved in vivo stability by replacing the maleimide with an acetamide, but the resulting ADCs had similar tolerability and activity profiles.

(Alley Abstract.)

FF 5. Alley teaches “[e]arly generation ADC linkers were commonly derived from disulfides and acid-labile hydrazones, both of which were designed to be cleaved inside target cancer cells, but inevitably underwent cleavage at nontarget sites.” (*Id.* at 759.) Alley also teaches “[e]arly generation ADCs often contained unstable linkers with short half-lives (1–2 days) such as disulfides.” (*Id.* at 763.) Alley describes prior studies to improve linker stability in “ADCs composed of the potent cytotoxin maytansine” where it was found that “[c]onjugates with sterically hindered

disulfides displayed potent antitumor activity and had improved biological stability compared to their less hindered counterparts.” (*Id.* at 759.)

FF 6. In researching further improved ADC linkers, Alley examined conjugates comprising the cytotoxic drug monomethyl auristatin F (MMAF), and maleimidocaproyl (mc) or bromoacetamidocaproyl (bac) linkers. (*Id.* at Abstract; *see also id.* at 761 (Fig. 1) (disclosing the structures of the MMAF and mc or bac linker compounds); Ans. 3–4.) Alley teaches, for example, “IF6-C4v2-mc-MMAF lost drug with a half-life of 7 days In contrast, the IF6-C4v2-bac-MMAF conjugate [that did not contain a maleimide/thioether adduct] was more stable in vivo, with no apparent drug loss throughout the 14 day assay period.” (Alley 762.) Alley teaches “[t]he results reported here provide the first direct evidence that maleimide/thioether fragmentation can lead to conjugate instability.” (*Id.* at 764.)

FF 7. Alley teaches “simply by replacement of the maleimide with an acetamide, ADC stability can be significantly increased. . . . [I]n spite of the stability difference between the bromoacetamide and alkyl-maleimide based ADCs, their efficacy, potency, and toxicity characteristics were indistinguishable.” (*Id.* at 764.) Alley concludes “we have demonstrated that ADCs with linker half-lives in the range of 7 days in mice result in nearly optimal safety and efficacy profiles. Attachment of the drug/linker derivatives to mAb thiols through acetamides extends the half-lives significantly by circumventing maleimide transfer.” (*Id.*)

Principles of Law

“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). “[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious,” the answer depends on “whether the improvement is more than the predictable use of prior art elements according to their established functions.” *Id.* at 417.

Analysis

Appellants argue the patentability of claims 1–3, 6, and 7 as a group. We select claim 1 as representative.

The Examiner concludes “[i]t would have been obvious . . . to react Aa (N-methylalanine ester) [as taught in Ho] with bromoacetamidocaproyl or maleimidocaproyl [as taught in Alley] forming a compound” encompassed by claim 1. (Ans. 4.)⁵ The Examiner reasons the skilled artisan “would have been motivated to do so because antibody-drug conjugates to treat cancer were known to utilize more stable linkers such as bromoacetamidocaproyl or maleimidocaproyl as taught by Alley [] . . . [and] reacting Aa (N-methylalanine ester) with bromoacetamidocaproyl or

⁵ The Examiner finds that the proposed combination would “form[] [a] compound of Formula 1 whereby L of the presently claimed compound would be $-(CH_2)_n$ where n is 5 (note that q is 0) and E would be either a maleimide or a bromoacetamide group.” (Ans. 4.)

maleimidocaproyl would support the treatment of cancer by utilizing a more stable linker.” (Ans. 4.)

Appellants argue “Ho teaches only thioether and disulfide containing drug compounds, DM1 and DM4 maytansinoids . . . [and] does not teach compounds with a [mc] or [bac] group.” (Br. 5.) Appellants further argue “Alley teaches only antibody drug conjugates (ADC) composed of the MMAF auristatin drug moiety . . . [and] does not teach maytansinoid drug linkers or specific solutions to the problem of linker stability.” (*Id.* at 6.) Thus, Appellants contend, “Ho provides no motivation, by itself or in combination with Alley, to remove the sulfur, thioether linkage to make the maytansinoid drug-linker compounds of the invention.” (*Id.*)

Appellants’ contentions are unpersuasive and amount to arguing the teachings of Ho and Alley individually. “Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [Each reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole.” *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986).

As concluded by the Examiner, the skilled person would have predictably applied the teachings of Alley — particularly those concerning advantages of mc and bac linker groups compared to other linkers like disulfides — in designing ADCs that include maytansinoid as the cytotoxic agent. (Ans. 4; FF 3–7.) Alley’s specific reference to prior-art efforts to improve linker stability in ADCs comprising “the potent cytotoxin maytansine” reinforces the Examiner’s conclusion. (FF 5.) We are also not

persuaded that the skilled artisan would read Alley's teachings as limited to only the particular cytotoxic drug Alley tested (MMAF auristatin).⁶ To the contrary, "Alley does discuss the importance of linker stability in ADCs in a general manner." (Ans. 10.) Alley's discussion of the results is similarly broad and reasonably understood as extending to ADCs with other cytotoxic drugs. (FF 4, 7.) We thus agree with the Examiner that it would have been prima facie obvious to design a compound comprising a maytansinoid and a bromoacetamidocaproyl or maleimidocaproyl linker to produce an ADC-precursor with improved linker half-life and stability. (Ans. 4; FF 2–7.)

Appellants also argue the Examiner included a "nonsensical and incorrect" statement in the July 31, 2014 Office Action that "must be discounted." (Br. 6.) Appellants point out that "[t]he [prior art] DM1 and DM4 maytansinoid compounds do not have an *electrophilic* functional group. DM1 and DM4 have a *nucleophilic* sulfide group. An antibody is not an *electrophilic* functional group." (Br. 6 (emphasis added).) The Examiner has since recognized and corrected the "misnomer . . . that the moiety was conjugated to an antibody via an electrophilic functional group," but otherwise maintained the rejection. (Ans. 8–9.) Appellants did not further argue this point (no Reply brief filed) and so we consider it moot.

⁶ Singh teaches "[a]ntibodies against various cancer cell-surface antigens have been conjugated with different cytotoxic agents that inhibit various essential cellular targets such as microtubules (maytansinoids, auristatins, . . . []).]" (Singh ¶ 3; *see also id.* at ¶ 165 (listing maytansinoids and auristatins as suitable drugs to use with Singh's linkers).) This grouping of maytansinoids and auristatins in the art further suggests the skilled person would have considered the two drugs as alternatives in designing ADCs.

Appellants also argue “[t]he patentability of the claimed compounds is further supported by the unexpectedly superior stability and efficacy of the antibody-drug conjugates made from the maytansinoid drug-linker intermediate of the invention.” (Br. 7.) In support, Appellants rely on the April 7, 2014 declaration of co-inventor Thomas Pillow, Ph.D., (“Pillow Decl.”) as showing, for example, “that removing the maleimide group from the LC-Tmab-MPA-May antibody-drug conjugate of the invention improves linker stability *in vivo* and improves efficacy because the efficacy of the LC-Tmab-MPA-May is similar to the efficacy of Tmab-MCC-DM1 at half the dose.” (Br. 7 (citing slide 13 from a presentation attached to the Pillow Decl.)) According to Appellants, the Pillow Decl. shows “thioether functionality in linkers known in the art cause instability,” “[t]he invention includes new linkers that solve the problem of stability while preserving [ADC] efficacy,” and ADCs “made with the linkers of the invention show potent activity which could not have been predicted.” (Br. 5.) Appellants thus contend it was “not predictable that from the many possible combinations of drug moieties and linkers known in the art that the antibody-drug conjugates (withdrawn claims 10-25), made by conjugating the claimed maytansinoid drug-linker intermediates (claims 1-9) with antibodies, would have the surprising and unexpected properties and biological activities they possess.” (Br. 7.)

We have considered Appellants’ evidence but, like the Examiner, do not find it sufficiently persuasive to overcome the Examiner’s *prima facie* case. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007) (“[W]e hold that even if Pfizer showed that amlodipine besylate exhibits

unexpectedly superior results, this secondary consideration does not overcome the strong showing of obviousness in this case. Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion.”)

First, we agree with the Examiner that “the features upon which applicant relies in the Declaration (i.e. unexpected results of the antibody-drug conjugates having improved stability) are not recited in the rejected claims.” (Ans. 8.) As the Examiner noted, “claims 1-9 are drawn to an intermediate compound without an antibody . . . [and] [a]s such, the unexpected results illustrated in the Declaration are not commensurate in scope” with the claims. (*Id.*) *In re Lindner*, 457 F.2d 506, 508 (CCPA 1972) (“It is well established that the objective evidence of nonobviousness must be commensurate in scope with the claims.”). Appellants withdrew claims directed to antibody-drug conjugates, such as encompassed by the testing described in the Pillow Declaration. (Ans. 8; Br. 7.)

Second, the Examiner’s proposed combination of Ho and Alley would have been expected to produce potent ADCs with increased stability. As the Examiner determined, “Alley [] found that both the bac and mc ADCs exhibited potent and uniform activities against all cell lines tested . . . [and] teaches that the bac and mc linkers improve stability because of their longer half-life” compared to ADCs comprising, for instance, unstable disulfide linkers. (Ans. 9; FF 4–7.) Just as Appellants contend their data shows that removing thioethers (maleimide, sulfur) in linkers improves ADC stability (*see, e.g.*, Pillow Decl. ¶ 6 and slides 7–8, 15), Alley teaches that ADCs containing maleimide/thioether adducts are more unstable than ADCs

without such structure. (See FF 4, 6–7.) *In re Skoner*, 517 F.2d 947, 950 (CCPA 1975) (“Expected beneficial results are evidence of obviousness of a claimed invention.”). Thus, as concluded by the Examiner, “one of ordinary skill in the art would have a reasonable expectation of success in substituting the disulfide or thioether linkages of Ho . . . for the [bac] and [mc] linkers of Alley given that the [bac] and [mc] linkers improve stability of an antibody-drug conjugate.” (Ans. 9–10.)

Conclusion of Law

For these reasons, we conclude the Examiner established by a preponderance of the evidence that claim 1 would have been obvious over Ho and Alley.

Claims 2, 3, 6, and 7 have not been argued separately and so fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

REJECTION II

Issue

Has the Examiner established by a preponderance of the evidence that claims 1, 4, 5, 8, and 9 would have been obvious over Singh and Alley?

Findings of Fact (FF)

FF 8. The Examiner’s findings of fact and statement of Rejection II may be found at pages 5–7 of the Examiner’s Answer dated November 6, 2014. (See also Final Act. 9–12.) We adopt the Examiner’s findings concerning the scope and content of the prior art and provide the following for emphasis.

FF 9. Singh teaches “new linkers to link drugs (e.g. cytotoxic agents) to cell-binding agents (e.g., antibodies) in such a way that the linker contributes in increasing the activity of the drug.” (Singh ¶ 2.) Singh further teaches “[l]inkers for binding drugs to cell binding agents are modified to hydrophilic linkers by incorporating a polyethylene glycol [PEG] spacer” and Singh teaches the addition of a PEG spacer enhances the potency and efficacy of ADCs in a variety of cancer cell types. (*Id.* at Abstract; *see also id.* at ¶¶ 8–11, 14.) Singh discloses that a suitable cytotoxic agent is a maytansinoid. (*See, e.g., id.* at ¶¶ 12–13, 20–22.) Singh teaches ADCs comprising maytansinoid and linker compounds that form disulfide and thioether bonds. (*See, e.g., id.* at ¶¶ 14–17, Figs. 1 (illustrating maleimide/thioether linkage), Fig. 3 (illustrating disulfide linkage).)

Analysis

Appellants argue the patentability of claims 1, 4, 5, 8, and 9 as a group. We select claim 1 as representative.

We agree with the Examiner’s reasoning and conclusion that claim 1 would have been obvious over Singh and Alley (Ans. 5–7), and address Appellants’ arguments below.

Appellants’ arguments overlap substantially with the arguments discussed above concerning the rejection based on Ho and Alley. (Br. 5–8.)

Appellants contend “Singh teaches only thioether and disulfide containing linker-drug compounds and antibody-drug conjugates” and “Singh provides no motivation, by itself or in combination with Alley, to remove the sulfur, thioether linkage and make the maytansinoid drug-linker intermediate of the invention.” (*Id.* at 6–7.) This argument is unpersuasive.

It overlooks the contribution provided by Alley, which teaches that the addition of mc and bac linkers in ADCs provide potent effect and greater stability compared to linkers comprising a disulfide bond. (FF 4–7.) And, as discussed above, rejections based on obviousness cannot be overcome by attacking the teachings of the references individually. *In re Merck & Co.*, 800 F.2d at 1097.

Insofar as Appellants also rely on alleged unexpected results with respect to the rejection over Singh and Alley (Br. 5, 7–8), Appellants' arguments and evidence is unpersuasive for the reasons previously discussed.

Conclusion of Law

We conclude the Examiner established by a preponderance of the evidence that claim 1 would have been obvious over Singh and Alley.

Claims 4, 5, 8, and 9 have not been argued separately and so fall with claim 1.

SUMMARY

We affirm the rejection of claims 1–9.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED