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DRINKER BIDDLE & REATH (DC)
1500 K STREET, N.W.
SUITE 1100
WASHINGTON, DC 20005-1209

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KOSTURKO, GEORGE W	

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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Ex parte JOHN A. FLYGARE, JANET L. GUNZER-TOSTE, THOMAS PILLOW, PHILIP WILSON HOWARD, and LUKE MASTERSON

_____

Appeal 2017-008476
Application 13/650,277
Technology Center 1600

_____

Before DEMETRA J. MILLS, JEFFREY N. FREDMAN, and DAVID COTTA, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON REQUEST FOR REHEARING

Appellants request rehearing of the decision entered July 9, 2019 ("Decision") that entered a new ground of rejection under 35 U.S.C. § 103(a).

We deny the requested relief.

DISCUSSION

Appellants "disagree that the Kamal reference 'teaches the chemistry of asymmetric attachment of a conjugate to a PBD dimer to the N10 position'" (Req. 3). Appellants contend "the synthesis route in Kamal starts with an *asymmetric compound* (5a) and finishes with an asymmetric compound" (Req. 5). Appellants contend "Kamal discloses only the

inclusion of a protecting group. There are no conjugates disclosed or even remotely suggested in the Kamal reference" (Req. 5).

We are not persuaded. Appellants argue Kamal alone without reference to Hartley's teaching that "the rationally designed pyrrolobenzodiazepine dimer, SJG-136, is the lead clinical candidate" (Dec. 11, FF 11) and to Chari's teaching to make conjugates using pyrrolobenzodiazepine dimers (Dec. 11, FF 12–13). It is the combination of these references that renders a conjugated PBD dimer obvious, not Kamal alone. Prior art "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., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986).

In addition, Kamal evidences that asymmetric conjugate dimers can be synthesized (Dec. 14, FF 22) as even Appellants acknowledge (*see* Req. 5 "finishes with an asymmetric compound"). However, Appellants do not require any particular route of synthesis in this product claim. Appellants provide no persuasive evidence that there would not have been a reasonable expectation, based on the teachings of Kamal, of successfully synthesizing an asymmetric SJG-136 PBD compound consistent with the teachings of Hartley and Kamal, and containing conjugates as suggested by Chari (Dec. 11, FF 12–13). "Obviousness does not require absolute predictability of success . . . *all that is required is a reasonable expectation of success*." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009).

Appellants "disagree that Vlahov is sufficient to form the suggestion relied upon by the Board in formulating a rejection based on a combination of four references" (Req. 5). Appellants contend "chemical mechanisms are necessarily different in light of the hydrazide being used in the Vlahov

reference, thus providing no indication for use of the same linking mechanism on an imine bond and no reasonable expectation of success in the combination of the two references" (Req. 5).

We are not persuaded because this argument fails to combine the teachings of the prior art. *See In re Keller*, 642 F.2d 413, 425 (CCPA 1981) ("The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.")

As to Appellant's argument that the ordinary artisan would not have expected success in linking the known linker of Vlahov to the known N10 linker position disclosed in Kamal because the chemical mechanisms differ, we note that Chari discloses that chemotherapeutic drugs that may be linked to crosslinkers include ethyleneimines as well as 2-ethylhydrazide (Chari ¶ 148). Appellants provide no persuasive evidence that there would be any difficulty in crosslinking either compound using the known crosslinker of Vlahov and "Attorney's argument in a brief cannot take the place of evidence." *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974). No persuasive evidence rebutting the Examiner's position is currently of record in this application.

Appellants contend the "specific combination would not have been suggested to the skilled artisan without the benefit of the instant specification. Therefore, for at least this added reason reconsideration of the new ground for rejection is respectfully requested" (Req. 6). Appellants

contend "there is no indication in any of those references even as to *how* an asymmetrically modified symmetric PBD dimer such as required herein *could* be made, let alone why such a substitution *should* be made" (Req. 6). Appellants note that we cited the Examiner in the related 13/641,198[1] application including a statement that "other methods of synthesizing asymmetric PBD dimers were known, because US 7,429,658 and US 7,049,311 disclose such asymmetric PBD dimers" (Req. 7). Appellants contend that "those references do not actually show the skilled artisan how to make such asymmetric modifications, let alone provide suggestion to do so, while leaving a free imine bond on one side" (Req. 7).

We do not find these arguments persuasive because our reasoning "takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure." *In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971). As discussed in the Decision:

> Hartley's PBD dimer named SJG-136 is reasonably considered a "lead clinical candidate" (FF 11). Chari teaches targeting cancer compounds including PBD dimers (FF 13–14) by conjugation to antibodies for "greater potency" and "greater aqueous solubility" (FF 12) and in order to treat cancer (FF 16). Thus, Chari provided the ordinary artisan reason to conjugate antibodies to PBD dimers such as SJG-136.
>
> Chari teaches that the ordinary artisan would have been able to conjugate "the cytotoxic agents described herein", including PBD dimers (FF 13–14), "in such a manner that the resulting compound still retains the specificity and/or activity of the starting compound" (FF 17). In the previous appeal, Appellants noted that based on the patents cited by Chari regarding PBD dimers, "there may be a suggestion to modify

[1] We note that this application is now abandoned.

> both N10 positions based on the configuration of protecting groups used in the synthesis of SJG-136" (Appeal 2017-001647; App. Br. 10).
>
> Vlahov teaches linkage using a linker consistent with claim 1 (FF 20) and Kamal teaches the chemistry of asymmetric attachment of a conjugate to a PBD dimer to the N10 position (FF 21–22), demonstrating that the N10 position is a site that would "give one skilled in the relevant chemical art the motivation to make close relatives (homologs, analogs, isomers, etc.) of the prior art" SJG-136 compound. *In re Dillon*, 919 F.2d 688, 696 (Fed. Cir. 1990).

(Dec. 14–15). The logic in the decision provides reasons why the substitution should be made, and Kamal demonstrates that asymmetric dimers could be made.

As to the citation to the related case, we were simply pointing out how that Examiner had, in our view, persuasively addressed Declarations filed in the related 13/641,198 application. The only point relevant to the prima facie case of obviousness here is the recognition that the prior art disclosed that asymmetric PBD dimers were known to the ordinary artisan, a point not disputed by Appellants. We have already explained that Kamal provides a reasonable expectation of success in generating an asymmetric PBD dimer. As noted in the Decision, Eigenbrot, cited in the instant application, recognizes that U and U' linked to the PBD dimer at the N10 positions may be "the same or different" and one of the two may simply be an H, resulting in an asymmetric PBD dimer (*see* Eigenbrot 6). And because only attorney argument, not evidence, rebuts that position based on the express disclosure in Kamal, we find the argument unpersuasive.

CONCLUSION

We have reviewed the original opinion in light of Appellants' request, but we find no point of law or fact which we overlooked or misapprehended in arriving at our decision. Therefore, Appellants' request is denied with respect to making any modifications to the decision entering a new ground of rejection.

Outcome of Decision on Rehearing:

Claim	35 U.S.C. §	Basis	Granted	Denied
1	103	Hartley, Chari, Vlahov, Kamal		1

Final Outcome of Appeal after Rehearing

Claim	35 U.S.C. §	Basis	Affirmed	Reversed	New Ground
1	103	Hartley, Chari, Vlahov, Kamal			1

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

REHEARING DENIED