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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte PAUL TARDI, SHARON JOHNSTONE, and LAWRENCE MAYER[1]

Appeal 2018-002052
Application 14/931,679
Technology Center 1600

Before DEBORAH KATZ, TAWEN CHANG, and JOHN E. SCHNEIDER, *Administrative Patent Judges*.

CHANG, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a composition for administering a platinum-based drug and an additional therapeutic agent, which have been rejected as obvious and on the ground of nonstatutory obviousness-type double patenting. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

[1] Appellants identify the Real Party in Interest as Celator Pharmaceuticals, Inc. (Appeal Br. 2.)

STATEMENT OF THE CASE

The Specification states that "platinum-based compounds are . . . anticancer drugs" but have the drawback of toxicity. (Spec. ¶¶ 3–4.) According to the Specification, "[a]lthough improvements have been reported in the art, an ideal formulation which successfully balances platinum drug encapsulation and release as well as reduced toxicity and increased efficacy has not been disclosed." (*Id.* ¶ 10.) Further according to the Specification, the invention relates to compositions that "allow for adequate drug loading, optimized drug release, reduced toxicity and superior efficacy," comprising "[b]lended lipid-based delivery vehicles . . . comprised of a mixture of phosphatidylcholine lipids with varying acyl chain lengths." (*Id.* ¶ 14.)

Claims 1–4 and 6–17 are on appeal. Claim 1 is illustrative and reproduced below:

> 1. A composition for administering a platinum-based drug and an additional therapeutic agent which composition comprises blended liposomes encapsulating said platinum-based drug wherein said blended liposomes comprise an equimolar mixture of DSPC and DPPC, 5–13 mol % cholesterol, and 5–20 mol% phosphatidyl glycerol.

(Appeal Br. 10 (Claims App.).)

The Examiner rejects claims 1–4 and 6–17 under pre-AIA 35 U.S.C. § 103(a) as being unpatentable over Iga,[2] Kudoh,[3] and Tardi.[4] (Ans. 2–3.)

The Examiner provisionally rejects claims 1–4 and 6–17 on the ground of non-statutory obviousness-type double patenting as being unatentable over claims 10–19, 21, and 29 of copending Application No. 14/990,167[5] in view of Iga and Tardi. (Ans. 6.)

The Examiner rejects claims 1–4 and 6–17 on the ground of non-statutory obviousness-type double patenting as being unatentable over claims 1–12 of U.S. Patent No. 7,850,990 in view of Iga and Tardi. (Ans. 8.)

The Examiner rejects claims 1–4 and 6–17 on the ground of non-statutory obviousness-type double patenting as being unatentable over claims 1–8 of U.S. Patent No. 9,271,931 in view of Iga and Tardi. (Ans. 9.)

I.

Issue

The Examiner has rejected claims 1–4 and 6–17 as obvious over Iga, Kudoh, and Tardi. The Examiner finds that Iga teaches a composition comprising cisplatin, a platinum-based drug, encapsulated into thermosensitive liposomes consisting of DPPC and DSPC at an equimolar

[2] Katsumi Iga et al., *Rates of Systemic Degradation and Reticuloendothelial System (RES) Uptake of Thermosensitive Liposome Encapsulating Cisplatin in Rats*, 10 PHARMACEUTICAL RES. 1332 (1993).
[3] Shinzoh Kudoh et al., *Enhanced Antitumor Efficacy of a Combination of CPT-11, a New Derivative of Camptothecin, and Cisplatin against Human Lung Tumor Xenografts*, 84 JAPANESE J. CANCER RES. 203 (1993).
[4] Tardi et al., WO 2004/093795 A2, published Nov. 4, 2002.
[5] Application No. 14/990,167 issued as U.S. Patent No. 10,058,507 B2 on Aug. 28, 2018.

ratio. (Ans. 3.) The Examiner finds that Iga does not teach an additional therapeutic agent or incorporation of cholesterol and phosphatidyl glycerol into the liposomes. (*Id.*) However, the Examiner finds that Tardi teaches "compositions comprising synergistic combinations of cisplatin with other anti-cancer agents such as carboplatin." (*Id.*) The Examiner also finds that Tardi teaches incorporating 20% DSPG, a phosphatidyl glycerol, and 10% cholesterol into liposomes, in order to improve, respectively, circulation longevity and incorporation and controlled release of drugs. (*Id.*)

The Examiner concludes that, based on Tardi's teachings, it would have been obvious to incorporate 20% of DSPG and 10% cholesterol into Iga's thermosensitive liposomes and to modify Iga's composition by further including another drug such as carboplatin to arrive at the claimed invention. (*Id.* at 3–4.) The Examiner finds that a skilled artisan would be motivated to make these modifications to Iga's liposomes and compositions in order to "increase the circulating life [of the liposomes] and obtain a narrow phase transition temperature needed for the controlled release of the encapsulated drugs," and to obtain a composition suitable to treat cancer. (*Id.*)

Appellants contend that the subject matter of the claims exhibit unexpected results. (Appeal Br. 6–8.)

Appellants contend in the Summary of Claimed Subject Matter Section of the Appeal Brief that claims 3 and 9 should be considered separately from independent claims 1 and 7 because "they require the exact liposomes that were demonstrated in the application to exhibit the optimal properties on which patentability depends." (Appeal Br. 2.) Appellants do not separately argue the remaining claims. Accordingly, we limit our analysis to claims 1 and 3 as representative. The issue with respect to this

rejection is whether the subject matter of claims 1 and 3 exhibit unexpected results.

Analysis

We agree with the Examiner that claims 1 and 3 are obvious over the combination of at least Iga and Tardi and address Appellants' arguments below. *See generally In re Bush*, 296 F.2d 491, 496 (CCPA 1961) (the Board may rely on less than all of the references relied upon by Examiner). Only those arguments timely made by Appellants in the briefs have been considered; arguments not so presented in the briefs are waived. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2015); *see also Ex parte Borden*, 93 USPQ2d 1473, 1474 (BPAI 2010) (informative) ("Any bases for asserting error, whether factual or legal, that are not raised in the principal brief are waived.").

In the Appeal Brief, Appellants do not appear to dispute that the Examiner has established a prima facie case of obviousness. However, citing the Mayer Declaration,[6] Appellants contend that the claimed subject matter exhibits unexpected results. (Appeal Br. 6; *see also* Reply Br. 1.) In particular, Appellants contend that the data referred to in the Mayer Declaration, including Figure 1 of the Specification, shows the "surprising result" that "half-life and optimal efficacy do not track" and that "[t]he claimed liposomes show half-lives substantially less than those of liposomes with less efficacy." (Appeal Br. 7; *see also* Reply Br. 4.)

We agree that "[o]ne way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of 'unexpected results,' i.e., to

[6] Declaration of Lawrence Mayer under 37 C.F.R. § 1.132 (May 9, 2017).

show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). However, "the burden of showing unexpected results rests on he who asserts them. Thus it is not enough to show that results are obtained which differ from those obtained in the prior art: that difference must be shown to be an *unexpected* difference." *In re Klosak*, 455 F.2d 1077, 1080 (CCPA 1972).

We are not persuaded that Appellants have shown that the subject matter of claims 1 and 3 exhibit unexpected results. In particular, while Example 1 and Figure 1 of the Specification purports to show that "there is a peak formulation for efficacy which corresponds to an intermediate half-life for cisplatin release," which formulation comprises DSPC/DPPC/DSPG/Cholesterol (35:35:20:10) liposomes, Appellants have not provided persuasive evidence that this result is unexpected. *In re Klosak*, 455 F.2d at 1080.

We acknowledge that Dr. Mayer states in his declaration that the results shown in Figure 1 is surprising. (Mayer Decl. ¶¶ 2, 3, 8.) However, these statements are conclusory, and Dr. Mayer does not provide any reasoning to support his conclusion. We thus accord the statements little weight. *Perreira v. Secretary of the Dept. of HHS*, 33 F.3d 1375, 1377 (Fed. Cir. 1994) (explaining that "[a]n expert opinion is no better than the soundness of the reasons supporting it"); *Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1329 (Fed. Cir. 2001) (stating that "[b]road conclusory statement offered by . . . experts are not evidence"); *In re American Acad. of Science Tech Ctr.*, 367 F.3d 1359, 1368 (Fed. Cir. 2004) ("The Board has broad discretion as to the weight to give to declarations

offered in the course of prosecution. *See Velander v. Garner*, 348 F.3d 1359, 1371 (Fed. Cir. 2003) ('[A]ccord[ing] little weight to broad conclusory statements [in expert testimony before the Board] that it determined were unsupported by corroborating references [was] within the discretion of the trier of fact to give each item of evidence such weight as it feels appropriate.').") (alterations in original). Likewise, attorney arguments in Appellants' briefs cannot take the place of evidence. *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974).

Both the Mayer Declaration and Appellants' briefs also assert that prior art does not suggest "that liposomes of the claimed composition would have this surprisingly effective result" (i.e., greater efficacy than liposomes having a different ratio of DSPC and DPPC and either longer or shorter half-lives). (Mayer Decl. ¶¶ 3, 7.)

In particular, the Mayer Declaration states that "[t]he combination of Iga and Tardi would not lead the artisan to the surprising result shown in Figure 1 of the present application" because (1) Iga did not test liposomes having less than 50:50 ratio of DPPC and DSPC and thus "does not show that a 50:50 ratio of DPPC and DSOC is optimal" and (2) Tardi only teaches that PI or PG would enhance half-life, but "this does not lead to the surprising result that a longer half-life is not necessarily advantageous." (*Id.* ¶¶ 7, 8.)

Similarly, Appellants contend in the Appeal Brief that, "although Iga disclosed liposomes with the 1:1 ratio (and indeed the liposomes include cisplatin) . . . , Iga . . . fails to show that extending half-life beyond what is shown by a 1:1 ratio decreases efficacy." (Appeal Br. 8; *see also* Reply Br. 2.) Thus, Appellants contend that "Iga does not suggest the unexpected

results of a 1:1 DSPC, DPPC ratio" while Tardi, which is cited for inclusion of cholesterol and phosphatidyl glycerol in the liposomes, is "simply irrelevant." (Appeal Br. 8; *see also* Reply Br. 2–3.)

We are not persuaded. As discussed above, "the burden of showing unexpected results rests on he who asserts them." *In re Klosak*, 455 F.2d 1077, 1080 (CCPA 1972). That the cited prior art does not teach the allegedly unexpected results does not show what a skilled artisan would have expected with respect to the relationship between molar ratio of DSPC/DPPC, half-life, and efficacy, or show that the results are in fact unexpected. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007) (holding that "evidence [of unexpected results] must fail because the record is devoid of *any* evidence of what the skilled artisan would have expected).

Indeed, as the Examiner points out, the Specification teaches that

> [o]ne of the drawbacks of current platin delivery vehicle is that formulations which are designed to load sufficient amounts of drug and circulate for extended time show little therapeutic activity. Poor bioavailability of the encapsulated platinum-based drug has been proposed to be the reason for the less than optimal activity. In this respect, the drug-containing delivery vehicles are cleared from the body before drug is released from the liposomes at the disease site. Other liposome formulations release the drug rapidly and show some activity yet not optimal. It is likely here that the released drug is cleared from the body before it has adequate time to accumulate at the disease site.

(Spec. ¶ 5; Ans. 12; *see also* Spec. ¶ 6 (explaining with respect to a prior art liposomal cisplatin formulation that, "although the liposomes are able to circulate for extended periods of time, the cisplatin is not released from the

liposomes and is ultimately cleared from the body along with the intact liposomes").)

Appellants contend that this passage merely explains that previous attempts to provide liposomes with extended half-lives did not succeed in achieving an extension sufficient to assure adequate delivery and that the takeaway vis-à-vis maximizing effectiveness would have been to further extend the lifetime of the liposomes in circulation "so that they are not 'cleared from the body before drug is released from the liposomes at the disease site.'" (Reply Br. 4.) However, we find that the above passage at least suggests that a skilled artisan would expect efficacy to be affected by factors other than the drug's half-life, such as its bioavailability, which in turn suggests that efficacy would not be expected to correlate solely with half-life.

In the Reply Brief, Appellants attempt to argue that "the prior art would lead one to believe that efficacy and longer half-life are correlated." (Reply Br. 3.) In particular, Appellants contend that paragraph 72 of Tardi "focusses on extending circulation longevity of liposomes as the goal" and further contend that "[t]his . . . expectation is also implied in Iga." (Reply Br. 4.)

We are not persuaded. We have already discussed why Iga does not imply a correlation between circulation longevity and efficacy. Similarly, paragraph 72 of Tardi simply describes various ways to increase circulation longevity of the carrier without suggesting that such increased circulation longevity is necessarily expected to result in increased efficacy.

We are also not persuaded that Appellants have provided evidence of unexpected results commensurate with the scope of claims 1 and 3. *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."). Our reviewing court has explained that, "[i]f an applicant demonstrates that an embodiment has an unexpected result and provides an adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner, this will generally establish that the evidence is commensurate with [the] scope of the claims." *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Appellants' argument rests on a single example allegedly showing unexpected results for cisplatin-encapsulating liposomes consisting of DSPC:DPPC:DSPG:Chol or DSPC:DPPC:DPPG:Chol at the molar ratio of 35:35:20:10. However, both claims 1 and 3 encompasses "platinum-based drug" other than cisplatin, and Appellants have not cited to persuasive evidence that all of the platinum-based drugs will behave in the same manner as cisplatin with respect to the relationship between molar ratio of DSPC/DPPC, half-life, and efficacy.

Likewise, claim 1 encompasses liposomes comprising "equimolar mixture of DSPC and DPPC, 5–13 mol% cholesterol, and 5–20 mol% of phosphatidyl glycerol." Appellants also have not cited to persuasive evidence that all liposomes meeting these limitations would behave in the same manner as liposomes consisting of DSPC:DPPC:DSPG:Chol or DSPC:DPPC:DPPG:Chol at the molar ratio of 35:35:20:10, even if they contain different mol% of DSPC/DPPC, cholesterol, and phosphatidyl glycerol. In particular, Dr. Mayer states in his declaration:

> Based on my experience in designing liposomal compositions, I can verify that the behavior of the liposomes *in vivo* will not be affected within the ranges [of

> phosphatidyl glycol and cholesterol set forth in claim 1 – *i.e.*, a range of 5-13 mol% cholesterol would be invariant in the behavior over this range and PG in the range of 5-20 mol% would be invariant over that range. Thus, in my experience, the ranges of PG and cholesterol required do not affect the behavior of the liposomes and thus the specific liposomes tested are indicative of the behavior of the range claimed.

(Mayer Decl. ¶ 10.) Once again, however, these statements are themselves conclusory and do not provide an adequate basis to support the conclusion that other liposomes falling within the claim will behave in the same manner as the liposomes consisting of DSPC:DPPC:PG:Chol (35:35:20:10) that are evaluated in Example 1. *Telemac Cellular Corp.* 247 F.3d at 1329 (stating that "[b]road conclusory statement offered by . . . experts are not evidence").

We have considered other arguments in Appellants' briefs and find them similarly unpersuasive, as discussed below.

Appellants contend the "[t]he relevance of Kudoh is simply not understandable" because "Kudoh does nothing more than to show that the relevant drugs when administered without liposomes at all are useful in treating cancer" while "[t]he invention is directed to liposomes that effect the most favorable type of delivery of the drugs in question." (Appeal Br. 6; *see also* Reply Br. 3.)

While we agree that claims 1 and 3 are obvious over Iga and Tardi alone, inclusion of a prior art reference not necessary to a conclusion of obviousness does not render the rejection erroneous. *See generally In re Bush*, 296 F.2d 491, 496 (CCPA 1961) (the Board may rely on less than all of the references relied upon by Examiner). Moreover, the Examiner cites Kudoh for limitations relating to non-antagonistic ratios of a platinum-based drug and an additional therapeutic agent, as recited in claim 7, as well

as limitations relating to camptothecin, which appear in claims 6 and 10. (Final Act. 11; Ans. 17.) Thus, we do not agree that Kudoh is not relevant to the rejection as a whole.

Appellants argue in the Reply Brief that Kudoh's teaching is misstated in that it does not teach synergistic anti-tumor activity for the combination of irinotecan (a camptothecin) and cisplatin. (Reply Br. 3.) Assuming for the sake of argument that Kudoh does not teach a synergistic effect for the combination of irinotecan and cisplatin, lack of synergism does not render the combination non-obvious.

Appellants argue that the Examiner dismissed Appellants' unexpected results because the Examiner found that "the 1:1 ratio of DSPC:DPPC is the only critical factor demonstrated by the [S]pecification." (Appeal Br. 6–7.) Appellants argue that "this is not a valid reason for rejecting claims that require a 1:1 ratio and have additional limitations." (*Id.*)

Appellants misunderstand the Examiner's point, which is that unexpected results must be shown to be unexpected as compared to the closest prior art, *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991), in this case Iga's liposomes having 5/5 w/w of DSPC/DPPC. (Advisory Act. 2; Ans. 14–15.) The closest Appellants came to with regard to comparing the claimed invention with the closest prior art is the statement in the Appeal Brief (and the similar statement in the Mayer Declaration) that "the optimal half-life that is associated with the optimal efficacy as shown in Figure 1 [of the Specification] is <u>not</u> achieved in Iga where absent [the claimed 5–13 mol% cholesterol and 5–20 mol% phosphatidyl glycerol] half-life of only 1.5 hours is obtained," compared to the half-life of at least 4 hours associated with maximal drug efficacy, as shown in Figure 1. (Appeal

Br. 8; Mayer Decl. ¶ 9.) This result, however, is not *unexpected* because Tardi teaches that phosphatidyl glycerol increases the circulation longevity of a liposome when incorporated into the liposome. (Tardi ¶ 72.)

Finally, Appellants assert for the first time in the Reply Brief that the Examiner has not established a prima facie case of obviousness, arguing that "[t]he combination of documents cited by the Examiner fail to suggest . . . the [claimed] composition" because "Iga does not disclose liposomes with equimolar ratios of components, only 5/5 w/w."[7] (Reply Br. 1–2; *see also* Reply Br. 3.)

This argument is waived because they were not presented in the opening brief, thereby denying the Board the benefit of the Examiner's

[7] Appellants also argue that "Iga does not teach anything at all about the most efficacious ratio for delivery of a platinum based drug and teaches nothing at all about the delivery of a platinum based drug along with an additional component." (Reply Br. 2.) To the extent Appellants are arguing that Iga does not suggest the allegedly unexpected results, we do not find this a reason for reversing the rejection, for the reasons already discussed. To the extent Appellants are arguing that the Examiner has not established a prima facie case, we find that Appellants have waived the arguments for failing to raise it in the Appeal Brief. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2015); *see also Ex parte Borden*, 93 USPQ2d at 1474. We are also not convinced by Appellants' arguments. A composition does not need to be known as the most efficacious in the prior art in order to be obvious. *In re Burckel*, 592 F.2d 1175, 1179 (CCPA 1979) ("[W]e reiterate that 'all disclosures of the prior art, including unpreferred embodiments, must be considered' in determining obviousness.'"). Similarly, the Examiner relies on Tardi for teaching synergistic combinations of cisplatin with other anti-cancer agents, and "[n]on-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986).

response, and no showing of good cause was made by Appellants to explain why the late argument should be considered by the Board. *See* 37 C.F.R. § 41.41(b)(2); *Cf. Optivus Technology, Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 989 (Fed. Cir. 2006) (argument raised for the first time in the Reply Brief that could have been raised in the opening brief is waived). Indeed, Appellants stated in the Appeal Brief that "Iga disclosed liposomes with the 1:1 ratio (and indeed the liposomes include cisplatin) when correctly interpreted," and likewise stated in response to the Final Action that "Iga does describe . . . an equimolar ratio [of DPPC and DSPC], as well as alternatives." (Amendment under 37 C.F.R. § 1.116 7 (May 17, 2017).) Neither did Appellants provide any evidence that DPPC and DSPC have significantly different molecular weights and/or that 5/5 w/w DPPC/DSPC would be significantly different from an equimolar ratio of DPPC/DSPC. *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 783 (Fed. Cir. 1985) (holding that prior art alloys having 0.25% Mo—0.75% Ni and 0.31% Mo—0.94% Ni are so close to the claimed alloy having 0.3% Mo and 0.8% Ni that they render claimed alloy obvious absent evidence rebutting prima facie case).

Accordingly, we affirm the Examiner's rejection of claims 1 and 3 as obvious over Iga and Tardi. Claims 2, 4 and 6–17, which are not separately argued, fall with claims 1 and 3. 37 C.F.R. § 41.37(c)(1)(iv).

II.

The Examiner provisionally rejects claims 1–4 and 6–17 on the ground of non-statutory obviousness-type double patenting as being unatentable over claims 10–19, 21, and 29 of copending Application No.

14/990,167[8] in view of Iga and Tardi. The Examiner rejects claims 1–4 and 6–17 on the ground of non-statutory obviousness-type double patenting as being unpatentable, in view of Iga and Tardi, over claims 1–12 of U.S. Patent No. 7,850,990, and claims 1–8 of U.S. Patent No. 9,271,931. Because we affirm the Examiner's obviousness rejection of claims 1–4 and 6–17, we do not reach the non-statutory obviousness-type double patenting rejections.

SUMMARY

For the reasons above, we affirm the Examiner's decision rejecting claims 1–4 and 6–17.

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

[8] Application No. 14/990,167 issued as U.S. Patent No. 10,058,507 B2 on Aug. 28, 2018.