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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MORTEN JUST PETERSEN,
FREDRIK MELANDER, ANDERS FALK VIKBJERG,
SUNE ALLAN PETERSEN, and MOGENS WINKEL MADSEN

Appeal 2018-008985[1]
Application 13/497,031
Technology Center 1600

Before FRANCISCO C. PRATS, JEFFREY N. FREDMAN, and MICHAEL J. FITZPATRICK, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge.*

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims to a liposome that contains cisplatin and a specific mixture of lipids. The Examiner rejected the claims for obviousness.

We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

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[1] Appellants state that "[t]he real parties in interest for this appeal are Bio-Bedst ApS and LiPlasome Pharma." Appeal Br. 4.

STATEMENT OF THE CASE

The following rejections are before us for review:

(1) Claims 11, 13, 15, 17, 26, and 30–46, under 35 U.S.C. § 103(a) as being unpatentable over Takagi,[2] Tardi '250,[3] Lim,[4] and Ansell[5] (Ans. 2–3);

(2) Claims 11, 13, 15, 17, 26, and 30–46, under 35 U.S.C. § 103(a) as being unpatentable over Tardi '945,[6] Takagi, Tardi '250, Lim, and Ansell (Ans. 3–5); and

(3) Claims 11, 13, 15, 17, 26, and 30–46, under 35 U.S.C. § 103(a) as being unpatentable over Andresen,[7] Takagi, Tardi '250, Lakkaraju,[8] Lim, and Ansell (Ans. 5–7).

Claim 11, the sole independent claim on appeal, is representative, and reads as follows:

> 11. A secretory phospholipase A2 (sPLA2) hydrolyzable liposome comprising distearoyl phosphatidyl glycerol (DSPG) in an amount of about 25% (mol/mol), distearoyl phosphatidyl choline (DSPC) in an amount of about 70% (mol/mol), [poly(ethylene glycol)]-distearoyl phosphatidyl ethanolamine (DSPE-PEG) in an amount of about 5% (mol/mol), less than 1% cholesterol, and cisplatin.

Appeal Br. 22.

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[2] US 2007/0286898 A1 (published Dec. 13, 2007).
[3] US 2005/0118250 A1 (published June 2, 2005).
[4] US 5,858,397 (issued Jan. 12, 1999).
[5] US 6,027,726 (issued Feb. 22, 2000).
[6] US 2003/0147945 A1 (published Aug. 7, 2003).
[7] Thomas L. Andresen et al., *Advanced strategies in liposomal cancer therapy: Problems and prospects of active and tumor specific drug release*, 44 PROGRESS IN LIPID RESEARCH 68–97 (2005).
[8] US 2003/0026831 A1 (published Feb. 6, 2003).

OBVIOUSNESS—
TAKAGI, TARDI '250, LIM, AND ANSELL

The Examiner's Prima Facie Case

The Examiner cited Takagi as disclosing "liposomal compositions containing DSPC, DSPG and PEG-lipid in percentages which fall within the claimed percentages. The amounts of neutral lipids, anionic lipid and polymer conjugated lipids are 72 %, 22 % and 5.4 % respectively." Ans. 2. The Examiner cited Takagi as disclosing cisplatin as an active agent suitably contained within the liposomes, as recited in Appellants' claim 11. *Id.*

The Examiner conceded, however, that Takagi's liposomes differ from the liposome recited in claim 11 in that "Takagi's liposomes . . . contain cholesterol in more than [the] claimed amounts and PEG in Takagi is complexed with cholesterol and not with DSPE." *Id.*

As evidence that the liposome recited in claim 11 would nonetheless have been obvious, the Examiner cited Tardi '250 as teaching that "the presence of . . . negatively charged phospholipids increase[s] the blood stability of liposomes and decreased concentration of cholesterol in PG containing liposomes increases the retention of antineoplastic agent." *Id.*; *see also id.* at 3 (citing Examples 1–3 of Tardi '250). The Examiner also cited Tardi '250 as disclosing the use of PEG-conjugated phospholipid in its liposomes, including in its examples. *Id.* at 3.

The Examiner cited Lim and Ansell as evidence that, in liposomal drug delivery formulations, "PEG-cholesterols and PEG-phosphatidylethanolamine are both suitable steric barriers." *Id.*

Based on the references' combined teachings, the Examiner concluded that it would have been obvious to decrease the amount of cholesterol in Takagi's liposomes "since the negatively charged

phospholipid in Takagi's liposomes would by itself increase the blood stability and decreased amounts of cholesterol would enable the liposome to retain the anti-neoplastic agent more within the liposomes as taught by Tardi ['250]." *Id.*

The Examiner also concluded that the "use of PEG-DSPE instead of PEG-cholesterol taught by Takagi would have been obvious to one of ordinary skill in the art because Lim and Ansell teach that both PEG-derivatives are steric barriers." *Id.*

Analysis

As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992):

> [T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . .
>
> After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

Having carefully considered the evidence and arguments advanced by Appellants and the Examiner, Appellants do not persuade us that the preponderance of the evidence fails to support the Examiner's conclusion of obviousness as to representative claim 11 over Takagi, Tardi '250, Lim, and Ansell.

As the Supreme Court explained in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), "when a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." *Id.* at 417 (quoting *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282 (1976)).

In the present case, claim 11 recites a liposome that contains less than 1% cholesterol. Appeal Br. 22. The liposome of claim 11 must contain four ingredients: (1) DSPG in an amount of "***about*** 25%" (mol/mol), (2) DSPC in an amount of "***about*** 70%" (mol/mol), (3) DSPE-PEG in an amount of "***about*** 5%" (mol/mol), and (4) cisplatin. *Id.* (emphasis added).

As Appellants acknowledge (Appeal Br. 8), Example 1 of Tardi '250, expressly cited by the Examiner (Ans. 3), discloses a liposome that contains no cholesterol, daunorubicin as the active agent contained within the liposome, 20 mole % DSPG, and 80 mole % DSPC. Tardi '250 ¶ 102. Example 1 of Tardi also discloses a liposome having the same ingredients, but with the DSPG and DSPC at a 30:70 molar ratio. *See id.*

In analyzing the *in vivo* properties of the liposomes prepared in Example 1, Tardi '250 discloses that the "[r]esults depicted in **FIG. 1B** indicate that plasma blood levels of daunorubicin also increased with increasing levels of DSPG. ***This data thus demonstrates that in addition to decreasing the elimination of liposomes from the blood compartment, the DSPG containing liposomes exhibit excellent drug retention properties in vivo.***" *Id.* ¶ 106 (emphasis added); *see also id.* ¶ 107 ("DSPG was incorporated into DSPC liposomes at 20 mole % as this level of PG was found to confer to the liposomes optimal circulation longevity as demonstrated in Example 1.").

We note, moreover, that Figure 1B of Tardi '250 shows similar *in vivo* drug retention properties of the cholesterol-free 30% DSPG/70% DSPC liposomes, as compared to the "optimal" cholesterol-free 20% DSPG/80% DSPC liposomes. *Id.* ¶ 107; *id.* at Fig. 1B.

Rather than requiring precise amounts of DSPG and DSPC, Appellants' claim 11 requires only that the claimed liposomes contain "***about*** 25%" (mol/mol) DSPG and "***about*** 70%" (mol/mol) DSPC. Appeal Br. 22 (emphasis added). Given Tardi '250's teaching that its cholesterol-free 30% DSPG/70% DSPC liposomes and cholesterol-free 20% DSPG/80% DSPC liposomes "exhibit excellent drug retention properties in vivo" (Tardi '250 ¶ 106), as well as Tardi '250's teaching that its cholesterol-free 20% DSPG/80% DSPC liposomes possess "optimal circulation longevity" *in vivo* (*id.* ¶ 107), Appellants do not persuade us (*see* Appeal Br. 7–12; Reply Br. 2–4) that the Examiner erred in finding that an ordinary artisan had a good reason for, and a reasonable expectation of success in, preparing cholesterol-free liposomes having molar percentages of DSPG and DSPC encompassed by Appellants' claim 11.

Although the liposomes in Tardi '250 described as having advantageous circulation properties contain daunorubicin rather than the cisplatin required by Appellants' claim 11, Tardi '250 discloses that a variety of therapeutic compounds, including anti-neoplastic agents, may be incorporated into its liposomes (Tardi '250 ¶ 72), and the remaining references cited in this rejection provide evidence that it was desirable to incorporate cisplatin, a known anti-neoplastic agent, into liposomes of the type described in Tardi '250. *See* Takagi ¶ 34; Lim at 6:17–31; Ansel at 8:23–36.

As to the DSPE-PEG recited in Appellants' claim 11, required to be present in the claimed liposome at a molar percentage of about 5% (Appeal Br. 22), both Lim and Ansell disclose that polyethylene glycol lipid conjugates function as steric barrier components which inhibit liposome-to-

liposome interaction and aggregation, as the Examiner found. *See* Ans. 3; *see also* Lim at 7:33–41 ("The purpose of steric barrier components is to inhibit liposome-liposome interactions and thereby reduce aggregation of the liposome systems formed. Suitable steric barrier components are modified derivatives of lipids and cholesterol, such as polyethylene glycol derivatives of cholesterol (PEG-cholesterols) ***and PEG-lipids (e.g., phosphatidylethanolamine-polyoxyethylene conjugates*** and phosphatidic acid-polyoxyethylene conjugates)." (emphasis added)); Ansell at 6:54–58 ("Suitable steric barrier components are modified derivatives of lipids and cholesterol, such as polyethylene glycol derivatives of cholesterol (PEG-cholesterols) ***and PEG-lipids (e.g., phosphatidylethanolamine-polyoxyethylene conjugates*** . . .)." (emphasis added)).

Tardi '250, moreover, discloses that including 5% DSPE-PEG2000, encompassed by Appellants' claim 11, in DSPC-containing liposomes, inhibits liposome aggregation, measured as freezing-induced size increase, a desirable property not exhibited by similar cholesterol-containing liposomes. *See* Tardi '250 ¶ 128 ("[A]s exemplified in **FIG. 14**, pH gradient liposomes consisting of DSPC/DSPE-PEG2000 (95:5 mol %) did not demonstrate changes in size subsequent to freezing whereas DSPC/cholesterol/DSPE-PEG2000 liposomes did."). Thus, Tardi '250, particularly when viewed alongside Lim and Ansell, suggests not only that it would have been desirable to incorporate the amount of DSPE-PEG recited in Appellants' claim 11 into agents carrying therapeutic agents such as cisplatin, but also provides an additional teaching suggesting that it would have been desirable to exclude cholesterol from such liposomes.

In sum, given the teachings discussed above in the cited references, Appellants do not persuade us that the Examiner erred in finding that an ordinary artisan had a good reason for, and a reasonable expectation of success in, preparing a liposome having all of the ingredients required by Appellants' claim 11, in amounts encompassed by the claim.

We acknowledge, as Appellants contend (Appeal Br. 7–8; Reply Br. 2–3), that Takagi is directed to the use of a PEG cholesterol ether as a lipid component in liposomes to enhance drug delivery, rather than the DSPE-PEG recited in Appellants' claim 11, and that Takagi uses cholesterol in its liposomes at molar concentrations higher than the 1% recited in claim 11:

> [T]he present inventors have conducted extensive studies on the method for improving delivery of a drug encapsulated in a liposome into a target organ or cell, and found as a result that polyethylene glycol cholesteryl ether, whose action has so far been revealed only about its retention in the circulating blood, has the effect to improve drug efficacy in the target organ and cell.

Takagi ¶ 20; *see also id.* ¶ 50 (Example 1).

We acknowledge also that Lim and Ansell disclose the desirability of using amounts of cholesterol higher than the 1% limit recited in Appellants' claim 11. *See* Lim at 3:41–48 (disclosing preferred liposomes as containing about 30% to 50% cholesterol); Ansell at 6:47–49 (disclosing preferred liposomes as containing phospholipid and cholesterol, at molar ratios of from 0.1 to 1.0 (cholesterol: phospholipid)).

It is well settled, however, that "[n]on-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [The 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 discussed above, Tardi '250 teaches that cholesterol-free liposomes having DSPG: DSPC in molar percentages encompassed by claim 11 have excellent *in vivo* drug retention properties. Tardi '250 ¶ 106. As discussed above, Tardi '250 also teaches that including 5% DSPE-PEG in DSPG liposomes confers anti-aggregation properties to the liposomes (*id.* ¶ 128), as suggested by both Lim and Ansell (*see* Lim at 7:33–41; Ansell at 6:54–58). And Tardi '250 teaches that the anti-aggregation properties conferred by DSPE-PEG are not present when cholesterol is present in the liposomes in a significant amount. *See* Tardi '250 ¶ 128.

In the present case, Appellants' consideration, in isolation, of the disclosures of Takagi, Lim, and Ansell regarding the use of cholesterol in liposomes improperly fails to take into account the disclosures in Tardi '250 identified by the Examiner teaching that, as an alternative to cholesterol-containing liposomes, a cholesterol-free liposome containing DSPG, DSPC, and DSPE-PEG, in amounts encompassed by Appellants' claim 11, would be useful as a carrier for a therapeutic agent such as the cisplatin recited in claim 11. Appellants do not persuade us, therefore, that when the cited references are properly viewed in combination, an ordinary artisan lacked motivation for, or a reasonable expectation of success in, preparing a liposome encompassed by representative claim 11, or that the claimed combination of elements would have been arrived at solely through improper hindsight.

Appellants argue:

> None of the cited publications describe sPLA2-mediated hydrolysis of lipids, nor do they provide any reason to expect that certain lipids or lipid amounts would produce a liposome exhibiting release of cisplatin at the site of sPLA2-expressing tumors. Thus, one of skill in the art would have had no reasonable expectation of success in improving retention and sPLA2-targeted delivery of cisplatin to tumors by modifying the lipid content and/or ratio of Takagi, Tardi, Lim, or Ansell's liposomes.

Appeal Br. 10.

To establish obviousness, however, the prior art need only provide a reasonable expectation of practicing the subject matter actually recited in the claim at issue. *See Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) ("[O]ne must have a motivation to combine accompanied by ***a reasonable expectation of achieving what is claimed in the patent-at-issue***.") (emphasis added).

In the present case, Appellants' claim 11 does not expressly recite a liposome that exhibits release of cisplatin at the site of sPLA2-expressing tumors, nor does claim 11 recite a liposome that exhibits improved retention and sPLA2-targeted delivery of cisplatin to tumors as compared to some other liposome. Rather, Appellants' claim 11 recites only an sPLA2-hydrolyzable liposome composed of the four ingredients discussed above, and containing less than 1% cholesterol.

As discussed above, the combined teachings of the cited references provide a reasonable expectation of preparing a cholesterol-free liposome containing those four ingredients in the claimed amounts. Appellants identify no persuasive evidence of record suggesting that, following the cited references' teachings, an ordinary artisan lacked a reasonable expectation of preparing a liposome having the ingredients recited in claim 11.

And, Appellants identify no persuasive evidence of record suggesting that the recitation in claim 11's preamble regarding sPLA2-hydrolyzability requires the presence of any ingredients other than those recited in claim 11. *See Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997) ("[W]here a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation.").

To the contrary, on the current record, as discussed above, claim 11 recites a liposome containing ingredients known in the prior art to be suitable for use in therapeutic liposomes, in amounts known to be useful in such liposome formulations. As noted above, "when a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR*, 550 U.S. at 417 (quoting *Sakraida v. Ag Pro*, 425 U.S. at 282).

In the present case, we are not persuaded that Appellants have shown that the claimed combination of prior art elements provides unexpected results sufficient to outweigh the evidence of obviousness in the prior art, discussed above, advanced by the Examiner. *See* Appeal Br. 20 (citing Spec. 8; also citing Spec. 21–29 (Example 6)).

As to unexpected results, Appellants state:

> As is shown in Example 6 of Appellant's specification, the Maximum Tolerated Dose (MTD) of cisplatin increased when cisplatin was administered to rats and mice encapsulated within a liposome within the scope of the claims (LiPlaCis). These results demonstrate that LiPlaCis releases cisplatin at the tumor site and not at a non-tumor site, because of the liposome's sPLA2 hydrolyzable properties and stability *in vivo*.

Appeal Br. 20.

Appellants' Example 6 appears at pages 21–29 of the Specification, and appears to be a proposal for a human clinical trial, as opposed to an experiment showing selective release of cisplatin at a tumor site in rats and/or mice. *See* Spec. 21–29. Although some results in human patients appear to be presented for the study described in Appellants' Example 6, none of those disclosures mentions anything about results in mice or rats, nor do the disclosures include any statement alleging that the human results obtained were unexpected or surprising. *See* Spec. 29 (citing Figs. 8–16).

Other than the unpersuasive citations to the Specification, Appellants point to no other evidence to support their assertion that the liposome formulation of representative claim 11 provided unexpected results. It is well settled that unsupported assertions in a party's briefing regarding the unexpectedness of results is insufficient to show nonobviousness. *See In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997). Thus, on the current record, Appellants do not persuade us that the results disclosed in Example 6 are sufficient to show that the liposome of Appellants' claim 11 provides unexpected benefits.

We acknowledge, consistent with Appellants' argument, that the rat experiment described in Appellants' Example 3 "revealed that LiPlaCis [a liposome encompassed by claim 11] is a long-circulating liposomal form of cisplatin with a T1/2 of about 20–23 h compared to the 15 minutes for free cisplatin. The area under the curve (AUC) for LiPlaCis was at least 50 times that of cisplatin." Spec. 19.

We acknowledge also the disclosure in Appellants' Example 4 of an experiment in which cisplatin-containing liposomes were administered to

mice with induced tumors. *See id.* at 19–20. Consistent with Appellants' argument, the Specification discloses that "LiPlaCis is long-circulating liposomal form of cisplatin. LiPlaCis accumulates in tumors and also in kidneys and spleen. Cisplatin can be released from LiPlaCis in the tumor microenvironment." *Id.* at 20.

Again, however, neither Example 3 nor Example 4 includes any statement or assertion alleging that the results presented therein would have been unexpected. As noted above, the unsupported assertions in Appellants' briefing regarding the unexpectedness of those results are insufficient to show nonobviousness. *See In re Geisler*, 116 F.3d at 1471.

It is well settled, moreover, that "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). In the present case, Appellants do not identify in the record any comparison of the properties of the liposome of representative claim 11 to any prior art liposome formulation, much less one identified as being the closest prior art.

We acknowledge the disclosures on page 25 of the Specification identified by Appellants regarding the conversion factor for cisplatin dosages in rats as compared to humans. Appeal Br. 20 (citing Spec. 25). We acknowledge the statement in the Specification identified by Appellants (*see id.*) that "[t]he MTD (maximum tolerated dose) of LiPlaCis [a liposome encompassed by claim 11] given every 3 weeks was determined to be above 80 mg per treatment cycle, which is surprising in view of the MTD predicted from animal experiments." Spec. 8.

Appellants, however, fail to explain specifically which animal experiments were used to demonstrate the allegedly unexpected MTD, and more importantly, whether those animal experiments involved the use of prior art liposomes in any of the cited prior art, or in the closest prior art. In the absence of identifying a suitable specific comparative basis for establishing unexpectedness, we are not persuaded that the assertion regarding an unexpected MTD in the Specification is sufficient to show that the liposome of Appellants' claim 11 possesses unexpected properties sufficient to demonstrate nonobviousness. *See In re Baxter-Travenol Labs.*, 952 F.2d at 392.

In sum, for the reasons discussed, Appellants do not persuade us that the preponderance of the evidence shows that Examiner erred in concluding that the liposome recited in Appellants' claim 11 would have been obvious. We, therefore, affirm the Examiner's rejection of claim 11 over Takagi, Tardi '250, Lim, and Ansell. Because they were not argued separately, claims 13, 15, 17, 26, and 30–46 fall with claim 11. 37 C.F.R. § 41.37(c)(1)(iv).

OBVIOUSNESS—
TARDI '945, TAKAGI, TARDI '250, LIM, AND ANSELL

The Examiner's Prima Facie Case

In rejecting claims 11, 13, 15, 17, 26, and 30–46 over Tardi '945, Takagi, Tardi '250, Lim, and Ansell, the Examiner cited Tardi '945 as disclosing "various liposomal preparations containing cisplatin, a neutral phospholipid (DSPC) an anionic lipid (DSPS) and PEG-DSPE (Examples). The amounts of DSPC: Chol:DSPS: DSPE-PEG-2000 in Example 19 are 35:45:10:10." Ans. 4.

The Examiner conceded that Tardi '945's liposomes differed from the claimed liposomes in that the "amounts of anionic lipid taught by Tardi ['945] are lower than the claimed amounts." *Id.*

As evidence that the claimed liposomes nonetheless would have been obvious, the Examiner again cited Takagi and Tardi '250 as evidence that it would have been desirable to prepare cholesterol-free, cisplatin-containing liposomes having the claimed combination of lipid components, in the claimed amounts. *Id.*

In particular, the Examiner reasoned:

> To use anionic lipid, DSPG in instant amounts with a reasonable expectation of success would have been obvious to one of ordinary skill in the art since the inclusion of amounts of 22 % of the anionic lipid in liposomes is a common practice in the art for the encapsulation of cisplatin as taught by Takagi. To decrease the amount of cholesterol in the liposomes would have also been obvious to one of ordinary skill in the art since the negatively charged phospholipid in liposomes would by itself increase the blood stability and decreased amounts of cholesterol would enable the liposome to retain the anti-neoplastic agent more within the liposomes as taught by Tardi.

Id. at 5.

Analysis

Having carefully considered the evidence and arguments advanced by Appellants and the Examiner, Appellants do not persuade us that the preponderance of the evidence fails to support the Examiner's conclusion of obviousness as to representative claim 11 over Tardi '945, Takagi, Tardi '250, Lim, and Ansell.

We acknowledge, as Appellants contend (Appeal Br. 13–14; Reply Br. 4–5), that Tardi '945's Example 19 uses a significant percentage of cholesterol, and also that Tardi '945 discloses that including cholesterol in

liposomes used as vehicles for therapeutic agents such as cisplatin can be advantageous in certain circumstances. *See* Tardi '945 ¶ 286 (Tardi '945's Example 19 using 45 mole % cholesterol); *id.* ¶ 150 ("[I]mproved pharmacokinetics may be achieved by encapsulating the second drug in a liposome composition with lipids of increased acyl chain length (e.g., DSPC/Chol).").

As discussed above, however, Tardi '250 teaches that cholesterol-free liposomes having DSPG: DSPC in molar percentages encompassed by claim 11 have excellent *in vivo* drug retention properties. Tardi '250 ¶ 106. As also discussed above, Tardi '250 also teaches that including 5% DSPE-PEG in DSPG liposomes confers anti-aggregation properties to the liposomes (*id.* ¶ 128), as suggested by both Lim and Ansell (*see* Lim at 7:33–41; Ansell at 6:54–58). And Tardi '250 teaches that the anti-aggregation properties conferred by DSPE-PEG are not present when cholesterol is present in the liposomes in a significant amount. *See* Tardi '250 ¶ 128.

Thus, similar to the position advanced by Appellants in the rejection discussed above, Appellants' consideration of the isolated disclosures of Tardi '945, Takagi, Lim, and Ansell regarding the use of cholesterol in liposomes improperly fails to take into account the disclosures in Tardi '250 identified by the Examiner teaching that, as an alternative to cholesterol-containing liposomes, a cholesterol-free liposome containing DSPG, DSPC, and DSPE-PEG, in amounts encompassed by Appellants' claim 11, would be useful as a carrier for a therapeutic agent such as the cisplatin recited in claim 11. Appellants do not persuade us, therefore, that when the cited references are properly viewed in combination, an ordinary artisan lacked motivation for, or a reasonable expectation of success in, preparing a

liposome encompassed by representative claim 11, or that the claimed combination of elements would have been arrived at solely through improper hindsight.

As discussed above, we are also not persuaded that Appellants have shown sufficiently that the liposome recited in representative claim 11 exhibits unexpected properties sufficient to establish the claimed liposome's nonobviousness when weighed against the disclosures in the cited references.

In sum, for the reasons discussed above, Appellants do not persuade us that the preponderance of the evidence shows that Examiner erred in concluding that the liposome recited in Appellants' claim 11 would have been obvious. We, therefore, affirm the Examiner's rejection of claim 11 over Tardi '945, Takagi, Tardi '250, Lim, and Ansell. Because they were not argued separately, claims 13, 15, 17, 26, and 30–46 fall with claim 11. 37 C.F.R. § 41.37(c)(1)(iv).

OBVIOUSNESS—ANDRESEN, TAKAGI, TARDI '250, LAKKARAJU, LIM, AND ANSELL

The Examiner's Prima Facie Case

In rejecting claims 11, 13, 15, 17, 26, and 30–46 over Andresen, Takagi, Tardi '250, Lakkaraju, Lim, and Ansell, the Examiner cited Andresen as disclosing "sPLA2 hydrolysable liposomes containing DSPC/DSPG/DSPE-PEG 2000 and cisplatin (3.4)," that is, liposomes containing each of the ingredients required by representative claim 11. Ans. 5.

The Examiner conceded, however, that Andresen's liposome differs from the liposome recited in Appellants' claim 11 in that Andresen "is unclear as to the percentages of the lipids in [the disclosed liposomes]." *Id.*

The Examiner reasoned, nonetheless, based on teachings in Andresen, that "[i]t would have been obvious to one of ordinary skill in the art to adjust the amounts of PEG-lipids, neutral phospholipids and negatively charged PG in order to obtain the best possible results based on And[re]sen's teachings." *Id.* at 6.

The Examiner cited Lakkaraju as disclosing cholesterol-free "anionic liposomes containing phosphatidylcholine and phosphatidylglycerol and containing active agents such as anti-neoplastic agents," including lipids similar to those recited in Appellants' claim 11, in amounts comparable to those recited in the claim. *Id.*

The Examiner found that an ordinary artisan would have been motivated to "use the percentages of neutral lipids, anionic lipid and polymer conjugated lipid in [Appellants'] claimed amounts since these amounts are routinely used in the art for the encapsulation of cisplatin as taught by Takagi." *Id.*

The Examiner concluded:

> To increase the amount of negatively charged liposome and decrease the cholesterol in the liposomes would have been obvious to one of ordinary skill in the art since the negatively charged phospholipid in Takagi's liposomes would by itself increase the blood stability and decreased amounts of cholesterol would enable the liposome to retain the anti-neoplastic agent more within the liposomes as taught by Tardi 250. Although Takagi teaches PEG-cholesterol and not PEG-DSPE, one of ordinary skill in the art would be motivated to use PEG-DSPE because Lim and Ansell teach that both PEG-derivatives are steric barriers.

Id. at 6–7.

Analysis

Having carefully considered the evidence and arguments advanced by Appellants and the Examiner, Appellants do not persuade us that the preponderance of the evidence fails to support the Examiner's conclusion of obviousness as to representative claim 11 over Andresen, Takagi, Tardi '250, Lakkaraju, Lim, and Ansell.

Andresen discloses that cholesterol-free liposomes containing each of the three lipids recited in representative claim 11 are hydrolyzed by tumor cells expressing sPLA2 *in vitro*, releasing the drug contained within the liposomes at the cells' location, while also exhibiting drug-retention stability in the absence of the tumor-specific enzyme:

> We have encapsulated doxorubicin and cisplatin in liposomes and found that we can obtain a $sPLA_2$ generated drug release through enzymatic hydrolysis of the liposomal membrane in vitro.
>
> We have analyzed liposomes with different DSPC/DSPG/DSPE-PEG_{2000} lipid composition loaded with doxorubicin for in vitro serum stability and found that the drug is successfully retained in the liposomes in compositions that can be degraded by human $sPLA_2$ type IIA. We have furthermore found that it is possible to release doxorubicin from liposomes incubated with media from $sPLA_2$ secreting colon cancer cells to a high degree within a few hours as shown in Fig. 8. In contrast, the clinically used liposomal doxorubicin formulation, Doxil®, does not release doxorubicin, clearly illustrating that the $sPLA_2$ mediated drug release does not occur for this formulation.

Andresen 87–88.

Andresen discloses that targeted delivery results similar to those described for doxorubicin were also observed in relation to cisplatin:

> We have encapsulated cisplatin in $sPLA_2$ degradable liposomes and tested these against a series of cancer cell lines. We have found that $sPLA_2$ triggers the release of cisplatin from $sPLA_2$ degradable liposomes (Fig. 9(b)) resulting in a pronounced cytotoxic effect in contrast to cisplatin encapsulated in Stealth® liposomes (SPI-077) . . . . We have furthermore investigated the cisplatin loaded $sPLA_2$ degradable liposomes in preclinical studies. Improved drug efficacy was obtained in a mouse breast cancer model (MT-3) (Fig. 10). . . . We are currently optimizing drug dose and liposome formulation to improve this drug delivery system for specific triggering and release of cisplatin at the tumor target site.

Id. at 89–90 (citation omitted).

Andresen, thus, suggests that cholesterol-free liposomes having each of the four ingredients recited in Appellants' claim 11 are advantageous in that the liposomes can provide targeted delivery of the drug to certain tumor cells, thereby improving drug efficacy. Although Andresen differs from claim 11 in not disclosing the specific amounts of the lipids recited in the claim, Tardi '250, as discussed above, teaches that cholesterol-free liposomes having DSPG: DSPC in molar percentages encompassed by claim 11 have excellent *in vivo* drug retention properties. Tardi '250 ¶ 106. As discussed above, Tardi '250 also teaches that including 5% DSPE-PEG in DSPG liposomes confers anti-aggregation properties to the liposomes (*id.* ¶ 128), as suggested by both Lim and Ansell (*see* Lim at 7:33–41; Ansell at 6:54–58). And Tardi '250 teaches that the anti-aggregation properties conferred by DSPE-PEG are not present when cholesterol is present in the liposomes in a significant amount. *See* Tardi '250 ¶ 128.

Given the teachings in Tardi '250 that a cholesterol-free liposome containing DSPG, DSPC, and DSPE-PEG, in amounts encompassed by Appellants' claim 11, would be useful as a carrier for a therapeutic agent

such as the cisplatin recited in claim 11, Appellants do not persuade us (*see* Appeal Br. 15–20; Reply Br. 6–8) that an ordinary artisan, informed by Andresen's teachings regarding the advantageous properties of cholesterol-free liposomes composed of DSPG, DSPC, and DSPE-PEG, lacked a good reason for, or a reasonable expectation of success in, using the amounts of DSPG, DSPC, and DSPE-PEG taught in Tardi '250 in Andresen's liposomes.

It might be true, as Appellants contend (Appeal Br. 17–18; Reply Br. 7–8), that the cited references provide multiple different potential liposome formulations that would be useful for delivering cisplatin. Given Andresen's disclosure of the advantageous properties of the claimed combination of ingredients, however, particularly when viewed in light of the teachings in Tardi '250 regarding the advantageous properties obtained when using the amounts of the claimed lipids recited in claim 11, it is evident that an ordinary artisan would have recognized that the specific combination of ingredients recited in representative claim 11, in the claimed amounts, would be useful for delivering cisplatin. *See KSR*, 550 U.S. at 417 ("[W]hen a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious.") (quoting *Sakraida v. Ag Pro*, 425 U.S. at 282).

As to Appellants' contention that Tardi '250 teaches that "suboptimal results were observed with a liposome containing greater than 20% (mol/mol) of a PG lipid and less than 80% of a PC lipid" (Appeal Br. 18), we first note that Appellants' claim 11 recites DSPG and DSPC in amounts of "***about*** 25% (mol/mol)" and "***about*** 70% (mol/mol)" (Appeal Br. 22

(emphasis added)), and therefore encompasses the 20:80 DSPG: DSPC combination described in Tardi '250 as having "optimal circulation longevity" (Tardi '250 ¶ 107).

As noted above, moreover, the 30:70 DSPG: DSPC combination described in Tardi '250 has circulation properties similar to the optimal 20:80 combination (*see id.* at Fig. 1B), and regarding the results shown in Figure 1B, Tardi '250 discloses more generally that its "DSPG containing liposomes exhibit excellent drug retention properties in vivo." *Id.* ¶ 106.

Thus, that Appellants' claim 11 might not recite the DSPG: DSPC ratio described by Tardi '250 as being the most preferred does not persuade us that an ordinary artisan nonetheless would not have recognized the ratio of lipids recited in claim 11 as being useful when preparing a cisplatin-delivering liposome. *See In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) ("[O]ur case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention.").

In sum, for the reasons discussed, Appellants do not persuade us that the Examiner erred in finding, based in particular on the teachings in Andresen and Tardi '250, that an ordinary artisan had a good reason for, and a reasonable expectation of success in, preparing a liposome having the ingredients required by Appellants' claim 11, in the amounts required by the claim 11. For reasons similar to those discussed above, we are also not persuaded that Appellants have shown sufficiently that the liposome recited in representative claim 11 exhibits unexpected properties sufficient to establish the claimed liposome's nonobviousness when weighed against the disclosures in the cited references, particularly in view of Andresen's

teachings regarding the advantageousness of the claimed combination of ingredients.

Accordingly, for the reasons discussed above, Appellants do not persuade us that the preponderance of the evidence shows that Examiner erred in concluding that the liposome recited in Appellants' claim 11 would have been obvious. We, therefore, affirm the Examiner's rejection of claim 11 over Andresen, Takagi, Tardi '250, Lakkaraju, Lim, and Ansell. Because they were not argued separately, claims 13, 15, 17, 26, and 30–46 fall with claim 11. 37 C.F.R. § 41.37(c)(1)(iv).

SUMMARY

For the reasons discussed, we affirm each of the Examiner's obviousness rejections.

TIME PERIOD

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