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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte HILA EPSTEIN-BARASH and
DANIEL S. KOHANE¹

Appeal 2015-002920
Application 13/263,804
Technology Center 1600

Before DEMETRA J. MILLS, JOHN G. NEW, and RYAN H. FLAX,
Administrative Patent Judges.

NEW, *Administrative Patent Judge.*

¹ Appellants state the real parties-in-interest are Children's Medical Corporation and Massachusetts Institute of Technology. App. Br. 2.

DECISION ON APPEAL

Appellants file this appeal under 35 U.S.C. § 134(a) from the Examiner's Final Rejection of claims 1–8 and 17–21. Specifically, claims 1–6 and 17–19 stand rejected as unpatentable under 35 U.S.C. § 103(a) as being obvious over the combination of Kohane et al. (US 6,326,020 B1, December 4, 2001) (“Kohane ’020”) and Kohane et al. (US 2005/0202093 A1, September 15, 2005) (“Kohane ’093”).

Claims 1–8 and 17–21 stand rejected as unpatentable under 35 U.S.C. § 103(a) as being obvious over the combination of Kohane ’020, Kohane ’093, Lim et al. (US 5,858,397, January 12, 1999) (“Lim”) and J. Wu et al., *Lipid-Based Nanoparticulate Drug Delivery Systems*, NANOPARTICULATE DRUG DELIVERY SYSTEMS, (D. Thassu et al., eds.), 89–98 (2007) (“Wu”).

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

We AFFIRM.

NATURE OF THE CLAIMED INVENTION

Appellants' invention is directed to compositions containing site I sodium channel blockers for use as local anesthetics with rapid nerve block, improved potency and efficacy, and no local toxicity. Liposomes were employed for increased loading of the site I sodium channel blocker.

Abstract.

REPRESENTATIVE CLAIM

Claim 1 is representative of the claims on appeal and recites:

1. An injectable composition for rapid onset nerve blockade, consisting of between 28 and 2800 micrograms of a site I sodium

channel blocker, in a liposome, wherein the composition is effective to provide reliable prolonged nerve blockade in the absence of local toxicity relative to the site I sodium channel blocker encapsulated in a polymeric microparticle.

App. Br. 18.

ISSUES AND ANALYSES

We agree with, and adopt, the Examiner’s findings and conclusion that the appealed claims are *prima facie* obvious over the references cited by the Examiner. We address the arguments raised by Appellants below.

A. Claims 1, 2, 5–8, and 17

Issue

Appellants argue the Examiner erred because a person of ordinary skill would have had no reasonable expectation of success in combining the references and because Appellants have demonstrated unexpected results. App. Br. 13–14.

Analysis

Appellants rely upon three prior art references in their effort to rebut the Examiner’s *prima facie* conclusion of obviousness: (1) D.S. Kohane et al., *A Re-examination of Tetrodotoxin for Prolonged Duration Local Anesthesia*, 89(1) ANESTHESIOLOGY 119–131 (July 1998) (“Kohane 1998”); (2) D.S. Kohane et al., *Prolonged Duration Local Anesthesia from Tetrodotoxin-enhanced Local Anesthetic Microspheres*, 104 PAIN 415–421 (2003) (“Kohane 2003”); and (3) C.S. Barnet et al., *Tissue Injury from Tricyclic Antidepressants Used as Local Anesthetics*, 101(6) ANESTH. &

ANALG. 1838–1843 (2005) (“Barnet 2005”). Appellants argue that these references, and the prior art cited by the Examiner, teach away from Appellants claimed invention and, therefore, a person of ordinary skill in the art would have had no reasonable expectation of successfully modifying the prior art to arrive at the claimed subject matter. App. Br. 13.

Appellants point to their Specification, which discloses that both tetrodotoxin and saxitoxin, both site I sodium channel antagonists, are too toxic to be used alone. App. Br. 13 (citing Spec. ¶¶ 22–23). Appellants assert that Kohane 1998 teaches that administration of TTX without epinephrine has been shown to produce sciatic nerve block, but with considerable toxicity at the most effective doses. *Id.* at 13–14 (Kohane 1998 Abstr.). Appellants argue this teaches away from using a site I sodium channel blocker alone in a liposomal formulation, as required by claim 1. *Id.* at 14. According to Appellants, the prior art neither teaches nor suggests that, by putting the formulations into polymeric microparticles, one could obtain greater duration of the blockade and less toxicity by incorporating the formulation into liposomes. *Id.* Appellants argue a person of ordinary skill in the art, with knowledge of the teachings of Kohane 1998, would have concluded that a liposomal formulation containing only a type I sodium channel blocker would result in toxicity. *Id.*

Appellants argue further that Kohane 2003 teaches that polymeric microspheres containing tetrodotoxin alone were lethal at 0.1% w/w and ineffective in blockading pain at 0.05%. App. Br. 14 (citing Kohane 2003 Abstr.). Furthermore, Appellants assert, almost all of the test animals demonstrated local muscle injury after administration. *Id.* (citing Kohane 2003 418). Furthermore, Appellants argue, Barnet 2005 and Kohane 1998

both teach that it is difficult to encapsulate effective amounts of potent local anesthetics in polymeric particles because the local anesthetics are hydrophilic and the systemic toxicity from their initial rapid release is dose-limiting. *Id.* Consequently, Appellants assert, in view of the teachings of Kohane 1998, Kohane 2003, and Barnet 2005, one of ordinary skill in the art would not have been motivated to modify the cited references to arrive at Appellants' claimed invention because to do so would result in a formulation that caused local toxicity, contrary to the express requirements of claim 1. *Id.* at 15.

Appellants also dispute the Examiner's finding that the recited range of site I sodium channel blocker would be the result of routine optimization. App. Br. 15. Appellants contend that the prior art teaches the use of toxins alone resulted in local toxicity and injury. *Id.* Therefore, Appellants contend, a person of ordinary skill in the art would not be motivated to optimize the dosage of site I sodium channel blocker because such formulations would nevertheless result in a formulation that causes local toxicity and injury. *Id.*

The Examiner responds that Kohane 1998 teaches that there were effective doses of tetrodotoxin alone that were not toxic. Ans. 9 (citing Kohane 21; Fig. 1; Table 1). The Examiner finds Kohane 1998 does not explicitly teach away from administration of tetrodotoxin alone, and that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Id.* (citing *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989)).

With respect to Appellants' argument that reading the Specification in combination with Kohane 1998 would lead a person of ordinary skill to conclude that liposomal formulations containing only a type I sodium channel blocker would result in toxicity, the Examiner finds Kohane 1998 is quite clear that there are effective doses of tetrodotoxin alone that were not toxic. Ans. 9 (citing Kohane 1998 21; Fig. 1; Table 1).

The Examiner also finds Appellants' Specification does not teach or suggest that formulations containing only a type I sodium channel blocker would result in toxicity. *Id.* The Examiner finds Appellants' Specification acknowledges that it was known at the time of filing that “[t]etrodotoxin alone is too toxic to be used as an anesthetic” and “[s]axitoxin is too toxic to be used alone as a local anesthetic” does not necessarily convey that the Specification teaches or suggests that all site I sodium channel blockers cannot be administered alone. *Id.* (*see* Spec. 5). The Examiner finds that it was known that tetrodotoxin and saxitoxin are two species of a larger genus of “type I sodium channel blockers,” and the Specification makes no such claims about any other type I sodium channel blocker. *Id.*; *see* Spec. 5.

The Examiner also finds the Specification is not specific as to whether the site I sodium channel blockers are administered “alone” (i.e., outside of a carrier) or “alone” (i.e., in a carrier without any co-administered with other agents such as local anesthetics, vasoconstrictors, glucocorticoids, or adrenergic drugs). *Id.* The Examiner therefore finds that a person of ordinary skill would not reasonably conclude that the instant specification would lead one to conclude that liposomal formulations containing only a type I sodium channel blocker with no carrier would result in toxicity. *Id.* at 9–10.

The Examiner next addresses Appellants' argument that none of the cited prior art would have led a person of ordinary skill to substitute liposomes for polymeric carriers would provide prolonged nerve blockade in the absence of local toxicity. Ans.10. The Examiner finds that a person of ordinary skill in the art would have had a reasonable expectation of success of creating a composition substituting liposomes for polymeric carriers because liposomes and polymeric carriers are both explicitly taught for encapsulating site I sodium channel blockers. *Id.* (citing Kohane '093 ¶¶ 8; 30; 35–37; 43; Kohane '020 Abstr., col. 8, ll. 65–67; col. 9, ll. 28–30). The Examiner finds these compositions are functional equivalents in the art as delivery vehicles, and concludes that substituting one for the other would have been obvious at the time of the invention. *Id.* (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007)).

The Examiner further finds Appellants' submitted rebuttal art, Kohane 1998, Kohane 2003, and Barnet 2005, do not overcome the Examiner's *prima facie* case of obviousness. Ans. 11. The Examiner finds the data presented in Kohane 2003, Barnet 2005, and Kohane 1998 does not adequately represent the entire scope of the claimed invention, and it does not present truly unexpected and unobvious results that are both statistically and practically significant. *Id.*

We are not persuaded by Appellants' arguments. We agree with the Examiner that the cited prior art references, as combined, teach or suggest the limitations of claim 1. Kohane '020, for example, teaches the use of liposomes as a carrier of tetrodotoxin and the concentration ranges recited in claim 1. Kohane '020 col. 9, ll. 28–35; col. 10, ll. 19–29. Similarly, Kohane '093 teaches:

Any type of microparticle known in the art can be used to deliver the desired pharmaceutical agent to the diseased tissue or site with the unwanted electrical activity. The type of microparticles useful in the inventive system include *liposomes*, spray-dried particles, microspheres formed by single- and double-emulsion techniques, microparticles produced off of a micropatterned surface, and microparticles formed by spray drying, coacervation, or spontaneous emulsification.

Kohane '093 ¶ 30 (emphasis added).² The Examiner has thus provided evidence to support a prima facie case of obviousness.

In their Reply Brief, Appellants dispute the Examiner's finding that the claim limitation reciting "[w]herein the amount of the site I sodium channel blocker is effective to: [p]rovide reliable prolonged nerve blockade[;] [i]n the absence of local toxicity relative to the site I sodium channel blocker," is not a structural limitation of the claimed composition and is given no weight. Reply Br. 2; *see* Ans. 8. Appellants argue the claim term "amount of the site I sodium channel blocker is effective to," i.e., the "effective amount" must be construed by the Board in light of the Specification and be accorded weight as a limitation of the claim. *Id.* at 4. According to Appellants, their Specification clearly defines what effective dosages are and how to test for efficacy and toxicity. *Id.* at 5. Appellants assert the dosages taught by the prior art must be different in polymeric particles as compared to liposomes due to the greater toxicity and lower efficacy in the polymeric particles. *Id.* at 5.

² At oral argument, Appellants' counsel intimated that the liposomes disclosed by Kohane '093 were somehow different from the liposomes required of the invention; however, neither the appealed claims themselves nor the Specification distinguish the claimed liposomes in any way, other than being either solid or fluid in nature. *See, e.g.*, Spec. 3:25–29, 6:10–21.

However, even if we find, *arguendo*, that Appellants are correct with respect as to whether the disputed limitation must be given weight in a composition claim, we are not persuaded by Appellants that the prior art would fail to teach or suggest the limitation. The “effective amount” recited in claim 1 must consist of “between 28 and 2800 micrograms of a site I sodium channel blocker” as required by the claim. Kohane ’020 teaches the use of liposomes and further teaches:

Dosage ranges are between 5 and 175 mg for bupivacaine alone, *between 28 and 2800 micrograms for tetrodotoxin alone*, between 7 and 2800 micrograms tetrodotoxin alone or in combination with bupivacaine in combination with between 1:200,000 and 1:5,000,000 epinephrine, 7 and 700 micrograms saxitoxin alone or in combination with bupivacaine, one to 700 micrograms saxitoxin alone or in combination with bupivacaine with between 1:200,000 and 1:5,000,000 epinephrine, and any of these combinations with between 0.05 and 1 mg dexamethasone/mg.

Kohane ’020 col. 10, ll. 19–28 (emphasis added). Kohane ’020 thus teaches the same range for a site I sodium channel blocker (tetrodotoxin) as is recited in claim 1. Furthermore, means of assessing the duration and effectiveness of sensory blockade and myotoxicity were well known in the art at the time of invention, as taught, at least, by Appellants’ submitted references. *See, e.g.*, Kohane 1998 121; Kohane 2003 416. We conclude that a person of ordinary skill in this highly-skilled art, upon learning the teachings of Kohane ’020 and understanding methods of determining sensory blockade and assessment of toxicity that were well known in the art, would have been able, as a matter of optimization, to determine an effective amount of site I sodium channel blocker. *See In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955) (“[W]here the general conditions of a claim are disclosed in

the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.”); *see also In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980) (“[D]iscovery of an optimum value of a result effective variable ... is ordinarily within the skill of the art”).

Appellants’ primary argument in their Appeal Brief relies upon their submitted rebuttal prior art as allegedly demonstrating that a person of ordinary skill in the art would have been discouraged or deterred from combining the references in the manner explained by the Examiner. *See* App. Br. 14. However, none of Appellants’ submitted prior art references address the use of liposomes or different types of liposomes as carriers. Kohane 1998, for instance, teaches that direct injection of tetrodotoxin alone to the region of the sciatic nerve resulted in blockade of thermal nociception but, in effective doses, also exhibited significant toxicity. Kohane 1998 123.

Kohane 2003 studies the efficiency of using “microparticles composed of poly (lactic-co-glycolic) acid (PLGA)” in effecting sensory blockade when used as a carrier for tetrodotoxin alone, tetrodotoxin combined with either bupivacaine or dexamethasone, or a combination of all three. Kohane 2003 415–416; *see also* Fig. 1. Kohane 2003 teaches that the encapsulated combination of tetrodotoxin, bupivacaine, and dexamethasone has a synergistic effect in producing longer-lasting sensory blockade, but that all animals tested exhibited some level of local anesthetic myotoxicity. *Id.* at 419–420.

Finally Barnet 2005 teaches that use of the tricyclic antidepressants doxepin and amitriptyline caused significant tissue injury at concentrations less than what would be required to provide clinical effectiveness and more toxicity than bupivacaine. Barnet 2005 1842. Barnet 2005 is silent with

respect to site I sodium channel blockers such as tetrodotoxin and saxitoxin as well as the use of liposomes as a carrier. Appellants argue that Kohane 1998 and Barnet 2005 teach that it is extremely difficult to encapsulate effective amounts of potent local anesthetics in polymeric particles because the local anesthetics are hydrophilic and the systemic toxicity from their initial rapid release is dose-limiting. *See* App. Br. 14. However, we do not see the relevance of these teachings to the use of liposomes as carriers.

A “teaching away” requires a reference to actually criticize, discredit, or otherwise discourage the claimed solution. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). Given that all three rebuttal references relied upon by Appellants are silent with respect to the use of liposomes, and that one is silent as well with respect to the use of the site I sodium channel blockers taught by the Examiner’s cited art (i.e., tetrodotoxin and saxitoxin), and given that all three references demonstrate a degree of success, even if incomplete, we cannot agree with Appellants’ contention that these references constitute a teaching away from Appellants’ claimed invention. *See In re Dunn*, 349 F.2d 433, 438 (C.C.P.A. 1965) (Teaching an alternative or equivalent method does not teach away from the use of a claimed method). Indeed, it is possible that the lack of complete success recited in Appellants’ rebuttal references could have motivated a person of ordinary skill in the art to attempt to employ an alternative carrier, such as a liposome, as taught by Kohane ’020 and Kohane ’093. Consequently, we find that Appellants’ submitted rebuttal references do not teach away from the claimed invention.

Furthermore, we do not agree with Appellants’ argument that a person of ordinary skill in the art would not have had a reasonable expectation of

success. All of Appellants' submitted prior art references show a certain degree of success in sensory blockade, and not all of the references necessarily show toxicity. Kohane 1998, for instance, teaches that toxicity can be significantly mitigated by co-administration of epinephrine and/or bupivacaine. Kohane 1998 126. The fact that the employment of liposomes as a carrier did not predictably provide long-term sensory blockade and "absence of local toxicity relative to the site I sodium channel blocker encapsulated in a polymeric microparticle" does not preclude a conclusion of obviousness. Only a reasonable expectation of success, not absolute predictability, is necessary for a conclusion of obviousness. *In re Longi*, 759 F.2d 887, 897 (Fed. Cir. 1985). We find nothing in Appellants' submitted rebuttal prior art references that demonstrates that the teachings of the Examiner's cited prior art, Kohane '020 and Kohane '093, would persuade a person of ordinary skill in the art that there was no reasonable expectation of success in combining the teachings of the references.

"[W]hen a *prima facie* case is made, the burden shifts to the applicant to come forward with evidence and/or argument supporting patentability." *In re Glaug*, 283 F.3d 1335, 1338 (Fed. Cir. 2002). Appellants argue that their invention provided unexpected results. However, in neither their Appeal Brief nor in their Reply Brief do Appellants point to evidence disclosed in their Specification that compares the alleged unexpected results to the closest prior art to show that the results are unexpected or surprising. Instead, Appellants' argument is that:

The specification discloses that both tetrodotoxin (TIX) and [s]axitoxin are too toxic to be used alone. [Kohane 1998] discloses that TTX without epinephrine has been shown to produce sciatic nerve block, but with considerable toxicity at the

most effective doses.... Kohane 1998 teaches that TTX produces injury when used alone. This is a clear teaching away from using a site I sodium channel blocker alone as required by claim 1 in a liposomal formulation that has no local toxicity. The prior art does not disclose that putting the formulations into polymeric microparticles prolongs nerve blockade without toxicity, much less that one could obtain greater prolongation and less toxicity by incorporating into liposomes. Reading the specification in combination with Kohane et al. would lead one of ordinary skill in the art to conclude that liposomal formulations containing only a type I sodium channel blocker would result in toxicity.

App. Br. 13–14. This is the single direct reference to the disclosures of Appellants’ Specification with respect to Appellants’ alleged unexpected results in either the Appeal or the Reply Brief. *See also* Reply Br. 9. That is to say, Appellants make an assertion, unsupported by data from their Specification, of unexpected results and then immediately pivot to the teachings of their submitted rebuttal prior art, arguing that a person of ordinary skill would not have had a reasonable expectation of success in combining the Examiner’s cited prior art. Essentially, Appellants make no substantive argument, supported by evidence of record, in either brief that their results actually *were* unexpected or surprising, but argue only that the submitted references teach away from their invention and that a person of ordinary skill would have had no reasonable expectation of success. That is insufficient to either sustain their argument of unexpected results or overcome the Examiner’s *prima facie* conclusion of obviousness.³ It is well

³ At oral argument, counsel for Appellants argued extensively that data disclosed in the Specification, when compared with the data in their submitted rebuttal references provided unexpected and surprising results. Dr. Daniel S. Kohane, co-inventor of the claimed invention, also testified

settled that arguments of counsel cannot take the place of factually supported objective evidence. *See, e.g., In re Huang*, 100 F.3d 135, 139-40 (Fed. Cir. 1996); *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984).

Consequently, we affirm the Examiner's rejection of the claims.

B. Claims 3, 4, and 18–21

Issue

Appellants argue the Examiner erred because a person of ordinary skill in the art would not have had a reasonable expectation of success in obtaining “prolonged nerve blockade in the absence of local toxicity relative to the site I sodium channel blocker encapsulated in a polymeric microparticle.” App. Br. 15–16.

before the panel to the same end. However, we are compelled to afford little probative value to evidence and arguments raised in oral argument that were not adduced or argued in the briefs. *See* 37 C.F.R. § 41.47(e)(1) (“At the oral hearing, appellant may only rely on Evidence that has been previously entered and considered by the primary examiner and *present argument that has been relied upon in the brief or reply brief* except as permitted by paragraph (e)(2) of this section”) (emphasis added) (Paragraph (e)(2) of 37 C.F.R. § 41.47 is not relevant to the instant circumstances). Because Appellants provided no substantive argument in either brief comparing the results disclosed in the Specification with data from the nearest prior art, we do not accord Appellants' oral argument probative weight in this respect. If prosecution should continue on this application and if Appellants intend to rely on such evidence, it should be made of record with the Examiner, preferably in the form of a Declaration.

Analysis

Appellants assert that claim 3 requires, *inter alia*, (1) an injectable composition consisting of between 28 and 2800 micrograms of a site I sodium channel blocker; (2) an effective amount equivalent to 0.05 to 1 mg dexamethasone/mg of glucocorticoid selected from the recited list; (3) in a liposome; and (4) that the glucocorticoid enhance nerve block in the absence of local toxicity relative to the site I sodium channel blocker alone.⁴ App. Br. 15.

Appellants state the Examiner acknowledged that the cited art fails to disclose between 28 and 2800 micrograms of a site I sodium channel blocker and an effective amount of a glucocorticoid equivalent to 0.05 to 1 mg dexamethasone/mg of glucocorticoid selected from the recited list. App. Br. 15. However, Appellants assert, the Examiner alleges that it would have been a routine matter of optimization to arrive at the required dosages. Appellants argue that, as argued with respect to the prior claims, their submitted rebuttal prior art references teach the use of toxins to generate nerve blockage resulted in local toxicity and injury. *Id.* at 15–16. Therefore, Appellants argue, a person of ordinary skill in the art would not be motivated to optimize the dosage of site I sodium channel blocker and glucocorticoid because such formulations would still result in a formulation that causes local toxicity and injury. *Id.* at 16.

⁴ Additionally, claim 3 neither recites, nor requires, a liposome, which was argued by Appellants' counsel to be a critical and distinguishing claim element. Counsel for Appellants acknowledged at oral argument that the omission of a limitation reciting a liposome was an oversight, missed by both Appellants and the Examiner during prosecution that would require amendment of the claim.

We are not persuaded by Appellants' argument. As we have related *supra*, the Examiner's cited prior art teaches the limitations of claim 1 which also apply to claim 3. Kohane '020 additionally teaches:

Corticosteroids that are useful to prolong in vivo nerve blockade include glucocorticoids such as dexamethasone, cortisone, hydrocortisone, prednisone, and others routinely administered orally or by injection. Other glucocorticoids include beclomethasone, betamethasone, flunisolide, methyl prednisone, para methasone, prednisolone, triamcinolone, alclometasone, amcinonide, clobetasol, fludrocortisone, diflurosone diacetate, fluocinolone acetonide, fluoromethalone, flurandrenolide, halcinonide, medrysone, and mometasone, and pharmaceutically acceptable salts and mixtures thereof.

Kohane '020 col. 8, ll. 3–13. Kohane also teaches that dexamethasone can be coadministered with 28–2800 micrograms of tetrodotoxin in dosages “[of] between 0.05 and 1 mg dexamethasone/mg.” Kohane '020 col. 10, ll. 27–28. We have further related why we conclude it would be within the skill of an ordinary artisan in this sophisticated art, working from the teachings of the Examiner's and Appellants' cited prior art, to optimize the variables so as to arrive at Appellants' claimed invention.

We have also explained *supra*, our reasoning as to why a person of ordinary skill in the art would be motivated, with a reasonable expectation of success, to combine the teachings of Kohane '020 and Kohane '093. In view of this reasoning with respect to claims 3, 4, and 18–21, we consequently affirm the Examiner's rejection of the claims.

DECISION

The Examiner's rejection of claims 1–8 and 17–21 as unpatentable under 35 U.S.C. § 103(a) is affirmed.

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No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED