United States Court of Appeals for the Federal Circuit

ANACOR PHARMACEUTICALS, INC.,
Appellant

v.

ANDREI IANCU, UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE,
Intervenor

2017-1947

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2015-01776.

Decided: May 14, 2018

MICHAEL N. KENNEDY, Covington & Burling LLP, Washington, DC, argued for appellant. Also represented by EVAN SMITH KRYGOWSKI, ANDREA GAY REISTER.

SARAH E. CRAVEN, Office of the Solicitor, United States Patent and Trademark Office, Alexandria, VA, argued for intervenor. Also represented by NATHAN K. KELLEY, THOMAS W. KRAUSE, LORE A. UNT.

JAMES CARMICHAEL, Carmichael IP, PLLC, Tysons, VA, for amicus curiae FlatWing Pharmaceuticals, LLC.

Before REYNA, BRYSON, and STOLL, *Circuit Judges.*

BRYSON, *Circuit Judge.*

This is an appeal from a decision of the Patent Trial and Appeal Board in an inter partes review proceeding. The Board held all of the claims of a patent owned by Anacor Pharmaceuticals, Inc., to be unpatentable for obviousness. Anacor has appealed with respect to only one of the rejected claims. We affirm.

I

A

The patent in suit, U.S. Patent No. 7,582,621 ("the '621 patent") is entitled "Boron-containing Small Molecules." The patent is directed to the use of 1,3-dihydro-5-fluoro-1-hydroxy-2, 1-benzoxaborole, also known as tavaborole, to treat fungal infections. In particular, the patent teaches the use of tavaborole as a topical treatment for fungal infections that develop under fingernails and toenails. When applied topically, tavaborole can penetrate the nail plate and treat the underlying fungal infection.

The '621 patent teaches that tavaborole can be used to treat a fungal infection known as onychomycosis, which is a disease of the nail that is responsible for approximately half of all nail disorders in humans. '621 patent, col. 28, ll. 18–20. Onychomycosis can be caused by a variety of yeasts and molds, but it is most frequently caused by dermatophytes, a group of fungi that includes the genus *Trichophyton* and the species *Trichophyton rubrum* ("*T. rubrum*"). *Id.*, col. 28, ll. 23–27. Onychomycosis is also

sometimes caused by another fungus, a yeast known as *Candida albicans* ("*C. albicans*").[1]

The single claim of the '621 patent that is at issue in this appeal is claim 6, which depends from claims 1 and 4. The three related claims recite as follows:

> 1. A method of treating an infection in an animal, said method comprising administering to the animal a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof, sufficient to treat said infection.
>
> 4. The method of claim 1, wherein said infection is onychomycosis.
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> 6. The method of claim 4, wherein said onychomycosis is tinea unguium.

Id., col. 67, ll. 34–38; *id.*, col. 68, ll. 20–21; *id.*, col. 68, ll. 25–26. Tinea unguium is the term for onychomycosis that is caused by a dermatophyte. *Id.*, col. 28, ll. 24–25.

B

In 2015, the Coalition for Affordable Drugs X LLC filed a petition requesting inter partes review of all 12 claims of the '621 patent. The Board instituted review and found that the claims would have been obvious in light of the combination of Int'l Pat. Appl. No. PCT/GB95/01206 ("Austin") and U.S. Pat. Appl. No. 10/077,521 ("Brehove"). Both Austin and Brehove teach the use of boron heterocycles as antifungal agents that inhibit *C. albicans*, among other fungi. Boron heterocy-

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[1] The evidence before the Board showed that dermatophytes are responsible for approximately 90 percent of all cases of onychomycosis, while *C. albicans* is responsible for approximately five percent of all such cases.

cles are organic compounds that contain both boron and carbon in a ring structure.[2]

Austin teaches the use of oxaboroles—boron heterocycles that include a five-member ring containing three carbon atoms, one oxygen atom, and one boron atom—as fungicides. Austin discloses tavaborole as one of a small group of oxaboroles that were tested for antifungal activity and teaches that tavaborole is a highly effective agent that inhibits a variety of fungi, including *C. albicans*.

Brehove teaches the use of boron heterocycles in a topical composition to treat onychomycosis. Specifically, two dioxaborinanes—boron heterocycles that include a six-member ring containing three carbon atoms, two oxygen atoms, and one boron atom—were determined through *in vitro* testing to have powerful potency against *C. albicans*. Brehove also reports the results of five *in vivo* tests, each involving a single individual, in which the individual's onychomycosis was successfully treated by the topical application of Brehove's two dioxaborinanes. Brehove does not identify whether each individual's onychomycosis was caused by *C. albicans* or some other microorganism, such as a dermatophyte.

The petition posited that the combination of Austin and Brehove would have rendered all the claims of the

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[2] The Board also instituted review on a second ground, the combination of Austin with Int'l Pat. Appl. No. PCT/US02/23252 ("Freeman"). The Board found that all the claims of the '621 patent were unpatentable for obviousness in light of that combination. Because we affirm the Board's conclusion that claim 6 would have been obvious in light of the combination of Austin and Brehove, we need not address Anacor's additional arguments on appeal challenging the Board's decision on the second ground.

'621 patent obvious. According to the petition, a person of ordinary skill would have had a reason to combine Austin and Brehove because the compounds in both references are boron heterocycles that are effective as fungicides and, in particular, in inhibiting *C. albicans*. The petition argued that a skilled artisan would have expected that those compounds would share other fungicidal activity, such as treating onychomycosis caused by dermatophytes. In addressing claim 6, the petition referred to Brehove's *in vivo* tests, which reported the successful use of Brehove's compounds to treat onychomycosis, a condition that is most often caused by dermatophytes. In addition, the petition pointed out that tavaborole has a lower molecular weight than the Brehove compounds, and would therefore be expected to be more likely than those compounds to penetrate the nail barrier at lower concentrations.

In its patent owner's response, Anacor argued that the combination of Austin and Brehove would not disclose treating onychomycosis caused by a dermatophyte, and that a person of ordinary skill would not have combined Austin and Brehove because they concern structurally different compounds. In addition, Anacor argued that a person of ordinary skill would not have had an expectation of success in treating a dermatophyte infection with tavaborole, because such a person "could not have predicted activity against dermatophytes based on activity against a yeast such as *C. albicans*."

In support of that argument, Anacor cited an article by Dr. Rina Segal ("Segal").[3] Among other things, Anacor noted that the Segal article reported that a compound known as terbinafine was very effective against dermato-

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[3] Rina Segal et al., *Treatment of* Candida *nail infection with terbinafine*, 35 J. Am. Acad. Dermatology 958 (1996).

phytes but had "variable and species-dependent" effectiveness against different species of the *Candida* genus.

The petitioner also relied on Segal, introducing that article during the deposition of the petitioner's expert, Dr. Narasimha Murthy. In his deposition, Dr. Murthy explained that terbinafine was effective against both dermatophytes and various *Candida* species. Dr. Murthy testified that the information in the Segal article supported his opinion that a person of ordinary skill would have understood that "most antifungal drugs are found to be active against different strains over a broad spectrum of organisms."[4]

As part of its patent owner's response, Anacor also included declarations from several experts, including Dr. Marjella Lane and Dr. Mahmoud A. Ghannoum. Dr. Lane addressed whether a person of ordinary skill would have expected tavaborole to be suitable for topical application to a human nail. In the course of her testimony, Dr. Lane cited two installments of a study by Dirk Mertin and Bernhard C. Lippold that was published in 1997 in the *Journal of Pharmacy and Pharmacology*. Dr. Lane argued that those articles supported her view that a person of ordinary skill would not have expected the combination of Austin and Brehove to be successful.

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[4] Dr. Stephen Kahl, another of the petitioner's experts, testified to the same effect. He stated, "I think a [person of ordinary skill] would presume that if a compound showed significant antifungal activity against any of a variety of fungi, would have reasonable reason to look at those against a specific fungus and expect some success. . . . [F]ungi are rather simple organisms. And it's not unusual that a compound that . . . has antifungal activity in one fungus, might be expected or at least evaluated in another fungus."

During the depositions of Anacor's experts, the petitioner introduced the third installment of the study by Mertin and Lippold, which was published in 1997 as part of the same series of articles ("Mertin").[5] The petitioner used the third Mertin article to challenge Dr. Lane's testimony regarding the relationship between a compound's molecular weight and its ability to penetrate the nail plate. When questioned about the study, Dr. Lane explained that she was aware of the article, but that she disagreed with its findings about the inverse relationship between permeability and molecular weight.

The petitioner also used the third Mertin article during Dr. Ghannoum's deposition. Dr. Ghannoum relied on a paper by Kazuhiro Nimura ("Nimura"), which teaches that some antifungals, such as ketoconazole, are effective against *C. albicans* but ineffective against dermatophytes such as *T. rubrum*.[6] Based on Nimura, Dr. Ghannoum testified that a person of ordinary skill would not have predicted activity against dermatophytes based on activity against other microorganisms such as *C. albicans*. In challenging Dr. Ghannoum's testimony on that issue, the petitioner directed his attention to a statement from the third Mertin article that "[d]ermatophytes are usually more sensitive to antimycotics than yeast."[7]

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[5] Dirk Mertin & Bernhard C. Lippold, *In-vitro Permeability of the Human Nail and of a Keratin Membrane from Bovine Hooves: Prediction of the Penetration Rate of Antimycotics Through the Nail Plate and Their Efficacy*, 49 J. Pharmacy & Pharmacology 866 (1997).

[6] Kazuhiro Nimura et al., *Comparison of In Vitro Antifungal Activities of Topical Antimycotics Launched in 1990s in Japan*, 18 Int'l J. Antimicrobial Agents 173 (2001).

[7] The various *Candida* species are fungi that are classified as yeasts.

In its reply brief to the Board, the petitioner responded to Anacor's argument that a person of ordinary skill would not have predicted a compound's activity against dermatophytes based on its activity against *C. albicans*. In the course of that discussion, the petitioner discussed Mertin's conclusion that antimycotics are often more effective against dermatophytes than against yeasts. The petitioner's expert, Dr. Murthy, also noted in his reply declaration that Segal and Nimura teach that a number of antifungal drugs are equally or more effective against dermatophytes than against *C. albicans*.

C

In its final written decision, the Board observed that Austin teaches that tavaborole is a known fungicide with particular potency against *C. albicans*. The Board also found that molecular weight was the most important factor in predicting whether a molecule would penetrate the nail plate. The Board then pointed out that, of the 16 tested compounds listed in Tables 8 and 9 of Austin, tavaborole was the most effective against various fungi, including *C. albicans*, of any of the seven compounds in Table 9 and that it had a lower molecular weight than any of the nine compounds in Table 8. Based on the evidence before it, the Board found that a person of ordinary skill in the art would have considered tavaborole as a promising candidate for treating onychomycosis.

The Board found that Brehove taught the treatment of onychomycosis with boron heterocycles and, in particular, that Brehove's compounds were effective against *C. albicans*, which Brehove characterized as a common cause of onychomycosis. In light of Brehove's test results, the Board concluded that a person of ordinary skill in the art would have used Austin's tavaborole in Brehove's topical treatment of onychomycosis with a reasonable expectation of success. The Board acknowledged that "there are obviously structural differences between the dioxa-

borinanes of Brehove and the benzoxaboroles of Austin," and it recognized that "small structural differences can cause different biological actions and activities." *Coal. for Affordable Drugs X LLC v. Anacor Pharm., Inc.*, No. IPR2015-01776, at 21 (P.T.A.B. Feb. 23, 2017) ("*Final Written Decision*"). Nonetheless, the Board was persuaded by the petitioner's experts that "the combination of the structural similarities *and* the similar fungicidal activity against *C. albicans* would have led a person of ordinary skill in the art to combine Brehove's method of treating onychomycosis using Austin's tavaborole." *Id.* The Board explained that "a person of ordinary skill in the art would have been less concerned about the possibility of differences in biological function given Brehove and Austin's disclosure confirming that [Brehove's compounds] and tavaborole have similar fungicidal activity against *C. albicans*." *Id.* at 21–22.

Addressing claim 6, the Board noted that "neither Austin nor Brehove expressly teaches whether the disclosed compounds exhibit any activity against dermatophytes." *Id.* at 29. Accordingly, the Board identified the question posed by claim 6 as whether "a person of ordinary skill in the art would have expected that tavaborole, which shares functional activity with the compounds of Brehove" against *C. albicans* would also share functional activity against other fungi responsible for onychomycosis, i.e., dermatophytes. *Id.* at 29.

On that issue, the Board concluded that "the weight of the evidence favors Petitioner's argument." *Id.* at 30. In support of that conclusion, the Board cited evidence that included Segal, Nimura, and Mertin. The Board noted that Segal shows that terbinafine, an antifungal, is highly potent against dermatophytes and also active (albeit less so) against *C. albicans*; that although Nimura discloses that ketoconazole has potent antifungal activity against *C. albicans* but poor activity against dermatophytes, another antifungal, amorolfine, exhibits potent antifungal

activity against all fungal species tested, including both *C. albicans* and *T. rubrum*; and that Mertin teaches that dermatophytes are usually more sensitive to antimycotics than yeasts are.

In light of all the evidence of record, the Board concluded that a person of ordinary skill "would have had a reasonable expectation that a compound with activity against *C. albicans* would also have activity against dermatophytes, particularly given the teaching that dermatophytes are usually more sensitive to antimycotics than yeast." *Id.* at 31. The Board therefore held that "the combination of Austin and Brehove teaches each limitation of" the claims and that the claims of the '621 patent, including claim 6, were invalid for obviousness. *Id.*; *see also id.* at 37.

II

A

On appeal, Anacor first argues that the Board violated due process and the procedural requirements of the Administrative Procedure Act ("APA") by failing to provide Anacor with adequate notice of, and an opportunity to respond to, the grounds of rejection ultimately adopted by the Board.

Under the APA, a patent owner involved in an inter partes review is entitled to notice of and a fair opportunity to address the grounds of rejection. 5 U.S.C. §§ 554(b)–(c), 557(c); *Dell Inc. v. Acceleron, LLC*, 818 F.3d 1293, 1301 (Fed. Cir. 2016). Therefore, an agency "may not change theories in midstream without giving respondents reasonable notice of the change and the opportunity to present argument under the new theory." *Genzyme Therapeutic Prod. Ltd. P'ship v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1366 (Fed. Cir. 2016) (quoting *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1080 (Fed. Cir. 2015)).

Anacor argues that the Board's decision violated the APA and due process in two related ways. First, Anacor contends that the petitioner abandoned one prior art reference in its reply (Brehove) and shifted to a new theory of invalidity (relying on Austin in light of Segal and Mertin), and that the Board adopted that new theory without giving Anacor proper notice or an opportunity to respond to it. Second, Anacor argues that, in bolstering this new theory of obviousness, the petitioner impermissibly relied on new evidence, not included in the petition, to satisfy its burden of showing a *prima facie* case of obviousness.

We reject Anacor's argument that the Board violated the APA or due process by adopting a new theory of obviousness not presented in the petition. Unlike in *In re NuVasive, Inc.*, 841 F.3d 966 (Fed. Cir. 2016), on which Anacor relies, the Board's final written decision was based on the same combination of references—Austin and Brehove—and the same series of inferences that the petition proposed.

To demonstrate effectiveness against dermatophytes, the petition cited Brehove's *in vivo* tests to demonstrate that boron heterocycles can be effective against onychomycosis, which is most often caused by dermatophytes. The petition suggested that Brehove's compounds would likely show effectiveness against dermatophytes and that, therefore, Austin's tavaborole would do so also, since the compounds in both references were effective against *C. albicans*.

The Board's final written decision was based on the same combination of references, and it concluded that the weight of the evidence supported the inferences drawn by the petition. The Board stated that "[f]or the reasons stated in the Petition and by Dr. Murthy, we are persuaded that the combination of Austin and Brehove teaches or suggests each limitation of dependent claims 2–10." *Final*

Written Decision, at 28; *see also id.* at 31 (concluding that "a person of ordinary skill in the art would have had a reason to combine Austin and Brehove with a reasonable expectation of success"). In particular, the Board concluded that "a person of ordinary skill in the art would have had a reasonable expectation that a compound with activity against *C. albicans* would also have activity against dermatophytes," *id.* at 30–31, which was the same argument raised in the petition.

We also reject Anacor's argument that the Board improperly relied on new evidence to which Anacor did not have an opportunity to respond. Anacor argues that the Board improperly cited two references—Mertin and Segal—that were not cited in the petition. There is, however, no blanket prohibition against the introduction of new evidence during an inter partes review proceeding. In fact, "the introduction of new evidence in the course of the trial is to be expected in inter partes review trial proceedings and, as long as the opposing party is given notice of the evidence and an opportunity to respond to it, the introduction of such evidence is perfectly permissible under the APA." *Genzyme*, 825 F.3d at 1366; *see also Novartis AG v. Torrent Pharm. Ltd.*, 853 F.3d 1316, 1325–26 (Fed. Cir. 2017) (finding no APA violation because patent owner was not "surprised" where a reference was discussed in patent owner's response, in depositions, and at the hearing, because "it is quite clear that [the patentee] had more than sufficient notice and opportunity to be heard on [the reference's] potential relevance").

In addition, the petitioner in an inter partes review proceeding may introduce new evidence after the petition stage if the evidence is a legitimate reply to evidence introduced by the patent owner, or if it is used "to document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness." *Genzyme*, 825 F.3d at 1369 (quoting *Ariosa*

Diagnostics v. Verinata Health, Inc., 805 F.3d 1359, 1365 (Fed. Cir. 2015)).[8]

It was not improper for the Board to cite Segal and Mertin (along with Nimura) as evidence of the knowledge that a skilled artisan would bring to bear in reading Austin and Brehove, even though those references were not cited in the petition. Anacor argues that Segal, Mertin, and Nimura "surfaced for the first time in Petitioner's Reply," but that is not so. Anacor discussed both Nimura and Segal in its patent owner's response and related submissions; indeed, Anacor spent three pages of its patent owner's response addressing Segal. For that reason, it was not improper for the Board to rely on those references to show what a person of skill in the art would believe about whether a compound effective against a yeast such as *C. albicans* would be likely to be effective against a dermatophyte.

As for Mertin, the first two installments in Mertin and Lippold's three-part series of articles were first introduced and addressed by Anacor in the declaration of Dr.

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[8] *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359 (Fed. Cir. 2016), cited by Anacor, is not to the contrary. In that case, the court upheld the Board's refusal to consider the petitioner's reply brief on the ground that the reply brief presented a new argument for the first time. The Board found that the reply violated a Board regulation, 37 C.F.R. § 42.23(b), which provides that a reply "may only respond to arguments raised in the corresponding opposition or patent owner response." *Id.* at 1369–70. In this case, the reply appropriately responded to arguments made in the patent owner's response and evidence elicited in the course of the proceeding through the depositions of the parties' experts, and the Board accordingly did not refuse to consider the petitioner's reply.

Lane. The third installment was introduced by the petitioner during the deposition of Anacor's experts and was then referred to in the petitioner's reply. But the third installment did not come as a surprise to Anacor. As noted, Dr. Lane admitted she was familiar with the article, which related to the first two installments she had cited in her declaration. Moreover, the third Mertin article was offered in direct response to testimony by Dr. Lane at her deposition: it was brought up in the deposition as part of the petitioner's challenge to Dr. Lane's testimony regarding the relationship between molecular weight and nail permeability.[9]

Following Dr. Lane's deposition, the Mertin article was brought up again during the deposition of Anacor's expert, Dr. Ghannoum. In that proceeding, the petitioner's counsel questioned Dr. Ghannoum about the conclusions reached in the Mertin article as part of the petition-petitioner's challenge to Dr. Ghannoum's assertion, based in part on Nimura, that compounds that showed activity against *C. albicans* often were not particularly effective against dermatophytes. In particular, the petitioner's counsel cross-examined Dr. Ghannoum regarding his opinion on that point by referring to the statement in Mertin that "[d]ermatophytes are usually more sensitive towards antimycotics than yeasts."

Finally, Anacor discussed Mertin extensively at the hearing before the Board, including discussing Mertin's findings with respect to permeability, and arguing that Mertin "highlights the unpredictability of going from predicting the activity of one species and going to another

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[9] In addition, the third Mertin article was cited and discussed at some length in another reference relied on by Dr. Lane and cited in her declaration. *See* Sudaxshina Murdan, *Drug Delivery to the Nail Following Topical Application*, 236 Int'l J. of Pharmaceutics 1, 9–11 (2002).

species." In response to the petitioner's argument that Mertin says that dermatophytes are more sensitive to antimycotics than yeasts, Anacor argued at the hearing that "nowhere in the Mertin article does it talk about Candida albicans. So they are extrapolating much beyond the teachings of Mertin[.]"

Based on this record, we conclude that Anacor was not denied its procedural rights with respect to the theory of obviousness adopted by the Board or any evidence relied on by the Board. The Board did not materially deviate from the theory of obviousness set forth in the petition, and Anacor had ample notice of and an opportunity to respond to the Segal and Mertin references, which in any event were properly offered in reply to arguments made by Anacor and for the purpose of showing the state of the art at the time of the patent application.

B

Anacor next argues that the Board improperly shifted the burden of proof by requiring the patent owner to disprove obviousness. Relying on *In re Magnum Oil Tools International, Ltd.*, 829 F.3d 1364 (Fed. Cir. 2016), Anacor contends that the record provides no basis to conclude that tavaborole's activity against dermatophytes would be expected and that, in adopting the petitioner's position without supporting evidence, the Board necessarily shifted the burden of proof to Anacor.

Unlike in *In re Magnum*, nothing in the Board's final written decision suggests that the Board improperly shifted the burden to the patent owner to disprove obviousness. To the contrary, the Board expressly and repeatedly stated that it was the petitioner's burden to "show[] by a preponderance of the evidence that claims 1–12 of the '521 patent are unpatentable." *Final Written Decision*, at 3; *see also id.* at 9, 10, 18, 22, 23, 37, 42.

Notwithstanding those statements, Anacor argues that the Board effectively shifted the burden of proof to the patent owner because the Board's conclusions rested not on the petitioner's presentation of evidence in support of an argument, but rather on whether Anacor had sufficiently disproved that argument. In particular, Anacor contends that the Board failed to require proof from the petitioner as to the mechanism of action that would lead to the conclusion that tavaborole would kill both *C. albicans* and dermatophytes, and that the Board did not explain why the evidence that dermatophytes are usually more sensitive than yeasts to antimycotics applies to tavaborole.

In substance, Anacor's argument is not that the Board shifted the burden of proof to Anacor, but that the Board improperly relaxed the burden on the petitioner to prove its case. That argument, however, does not suggest that the Board shifted the burden of proof to Anacor, but instead is directed to the question whether there was substantial evidence to support the Board's finding of obviousness.

As to that issue, the Board found that a person of skill in the art would have been motivated to combine Austin and Brehove and would have had a reasonable expectation of success in doing so. Austin disclosed the use of oxaboroles, a subset of boron heterocycles, as fungicides that were effective against five different species of fungi, including *C. albicans*. It stated that compounds containing an oxaborole ring, such as tavaborole, are particularly effective against fungi. Tavaborole, in particular, was identified as being especially potent against the various species of fungi that Austin tested. Austin also disclosed that tavaborole was a low molecular weight compound, which would enable the compound to penetrate the nail plate covering the locus of the infection.

The compounds of Brehove, also boron heterocycles, were shown through *in vitro* testing to be effective against *C. albicans*. The results of Brehove's *in vivo* testing showed that Brehove's compounds were effective against onychomycosis in each of the patients suffering from that condition. In light of the fact that approximately 90 percent of all onychomycosis cases are attributable to dermatophytes, and in the absence of any evidence that patients with dermatophyte-based onychomycosis were excluded from the *in vivo* testing, it is highly likely that at least some of the five cases discussed by Brehove involved dermatophyte infections.

Beyond that, the evidence in the record before the Board showed that persons of skill in the art would have known that antifungal agents that are effective against one species of fungus are typically effective against others, as reported by the petitioner's experts, Dr. Kahl and Dr. Murthy. In addition, one of skill in the art would have appreciated that many antifungal agents are more effective against dermatophytes than against yeasts, as reported by Dr. Murthy and as indicated by data in the Segal, Mertin, and Nimura references.[10] In light of the full record before the Board, we conclude that substantial evidence supports the Board's findings that a person of ordinary skill in the art would have been motivated to combine the pertinent teachings of Austin and Brehove

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[10] As for Anacor's argument that the Board failed to require proof of the mechanism of action that caused the boron heterocycles to be toxic to fungi, no such proof is required, as it has long been settled that "an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests." *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570 (Fed. Cir. 1983) (citing *Diamond Rubber Co. v. Consol. Rubber Tire Co.*, 220 U.S. 428, 435–36 (1911)).

and would have had a reasonable expectation of success in doing so.

C

In its third argument, Anacor challenges what it refers to as the Board's "conclusion that the compounds of *Austin* are 'structurally similar' to the compounds of *Brehove*." Anacor contends that the compounds are structurally dissimilar, and that a person of ordinary skill in the art would have expected that even small structural differences between tavaborole and the Brehove compounds would result in significant differences in their chemical and biological properties.

Anacor's argument is premised on the misapprehension that the Board viewed structural similarity as a binary factor—either present or absent—and that the Board found it was present in this case. That is not an accurate characterization of the Board's assessment of the issue of structural similarity.

In its final written decision, the Board viewed the existence of some structural similarity between the compounds in Austin and Brehove as evidence that the references might be good candidates to be combined. That is, the Board recognized that the structural similarity between the boron heterocycles of Austin and Brehove provides a useful starting point, but it attributed more significance to the functional similarities of the two groups of compounds. As the Board observed, Austin teaches that oxaboroles, a subset of boron heterocycles, are effective fungicides, and Brehove teaches that certain dioxaborinanes, a different subset of boron heterocycles, are likewise effective fungicides. Moreover, notwithstanding the structural differences between the two subsets of compounds, the Board focused on the fact that both were shown to be effective against *C. albicans,* a fungus that was known to cause onychomycosis.

The Board did not regard the structural similarity between the compounds of Austin and Brehove to be sufficient proof, by itself, that tavaborole would be likely to have the same functionality as the compounds in Brehove. The Board correctly acknowledged that there "are obviously structural differences between the dioxaborinanes of Brehove and the benzoxaboroles of Austin," but it concluded that "the combination of the structural similarities *and* the similar fungicidal activity against *C. albicans* would have led a person of ordinary skill in the art to combine Brehove's method of treating onychomycosis using Austin's tavaborole instead of [Brehove's compounds]." *Final Written Decision*, at 21.

It is true that in the case of patents on new chemical compounds, the obviousness inquiry "frequently turns on the structural similarities and differences between the compounds claimed and those in the prior art." *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1352 (Fed. Cir. 2010). In such cases, where the properties of the new chemical compound are not known, structural similarity is often sufficient to create an expectation that the "new compound will have similar properties to the old." *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1007 (Fed. Cir. 2009) (quoting *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008)).

This case, however, does not involve a patent on a new chemical compound. Where the patent is directed to a new treatment using a known compound, it is reasonable to assume that similar compounds that share certain common properties are apt to share other related properties as well. *See In re Merck & Co.*, 800 F.2d 1091, 1096 (Fed. Cir. 1986) (the fact that two similar compounds are both psychotropic drugs and one possesses antidepressive properties suggests that the other may possess antidepressive properties as well); *see also In re Mehta*, 347 F.2d 859, 864 (CCPA 1965) ("The similarity of *properties* of a reference compound as compared with a claimed com-

pound gives rise to an even stronger inference of obviousness than that of structural similarity alone[.]"); *In re Rosselet*, 347 F.2d 847, 850 (CCPA 1965) (referring to a "prima facie showing of obviousness by reason of the admitted 'gross structural similarities' of the art compounds, coupled with the fact those compounds are shown to have utility *in the same area of pharmacological activity*").

To be clear, we recognize that structural similarity is an important factor in assessing the motivation to combine and reasonable expectation of success. It has been long recognized that chemical compounds with similar structures often have similar properties and that similarity in properties can be inferred from structural similarity. *In re Hass*, 141 F.2d 122, 125 (CCPA 1944). Our cases have held that the greater the structural similarity between the compounds, the greater the motivation to combine and reasonable expectation of success. *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1377 (Fed. Cir. 2006) (noting that, for a new chemical compound, finding obviousness requires "structural similarity" and a "reason or motivation to make the claimed compositions" (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc))); *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995) ("Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds."). The opposite is true, too: the less the structural similarity, the less the motivation to combine and the reasonable expectation of success. *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992) (reversing the *prima facie* obviousness finding because of the "lack of close similarity of structure").

At the same time, our cases recognize that the chemical arts are unpredictable and that similar structures do not always result in similar properties. *See Eisai Co.*, 533 F.3d at 1359. The obviousness inquiry often depends on whether there is evidence demonstrating a nexus between

structural similarities (or dissimilarities) and functional similarities (or dissimilarities). In this case, although there is only limited structural similarity between the compounds disclosed in Austin and Brehove, we conclude that, in light of the combination of the structural and functional similarities between the compounds, substantial evidence supports the Board's findings.

The Board understood that the petitioner's theory was "not based on structural similarities alone," but was "based on the combination of structural similarity and functional similarity." *Final Written Decision*, at 28. And the Board agreed with the petitioner that "a person of ordinary skill in the art would have expected that tavaborole, which shares functional activity with the compounds of Brehove, would have shared other activities as well, such as the inhibition of additional fungi responsible for onychomycosis." *Id.* at 29. The Board thus did not disregard the structural differences between the compounds of Austin and Brehove or attribute undue significance to their structural similarities.

For the foregoing reasons, we reject Anacor's challenges to the Board's reasoning and uphold the Board's conclusion that claim 6 of the '621 patent is invalid for obviousness.

AFFIRMED