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Paper 70
Entered: February 23, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS X LLC,
Petitioner,

v.

ANACOR PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2015-01776
Patent 7,582,621 B2

Before GRACE KARAFFA OBERMANN and MICHAEL P. TIERNEY, *Vice Chief Administrative Patent Judges*, and TINA E. HULSE, *Administrative Patent Judge*.

HULSE, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Coalition for Affordable Drugs X LLC ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–12 of U.S. Patent No. 7,582,621 B2 (Ex. 1001, "the '621 patent"). Paper 1 ("Pet."). Anacor Pharmaceuticals, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 17 ("Prelim. Resp.").

On February 23, 2016, we instituted an *inter partes* review of claims 1–12 of the '621 patent on two grounds of obviousness. Paper 24 ("Dec. Inst."), 15. Patent Owner filed a Response to the Petition. Paper 32 ("PO Resp."). Petitioner filed a Reply to Patent Owner's Response. Paper 47 ("Pet. Reply").

Patent Owner filed a motion to exclude certain exhibits. Paper 57. Petitioner filed an opposition (Paper 63) and Patent Owner filed a reply (Paper 65). Pursuant to authorization from the Board, Patent Owner also filed an Identification of New Arguments and Evidence in Petitioner's Reply (Paper 53) and Petitioner filed a response (Paper 60).[1]

Patent Owner filed observations on the cross-examinations of Petitioner's declarants, Stephen B. Kahl, Ph.D. (Paper 55) and S. Narasimha Murthy, Ph.D. (Paper 56). Petitioner filed responses to Patent Owner's observations. Paper 61 (Kahl); Paper 62 (Murthy).

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[1] We do not find the arguments identified by Patent Owner to be impermissible new arguments and evidence in the Reply. Rather, we determine that the arguments were each in response to those set forth by Patent Owner in its Response, for the reasons stated by Petitioner. Paper 60, 1–3; 37 C.F.R. § 42.23(b) ("A reply may only respond to arguments raised in the corresponding opposition or patent owner response.").

An oral hearing was held on November 3, 2016, a transcript of which has been entered in the record. Paper 69 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

For the reasons that follow, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–12 of the '521 patent are unpatentable.

A. Related Proceedings

Petitioner has filed concurrently two other petitions for *inter partes* review of the claims of related U.S. Patent No. 7,767,657 B2 in IPR2015-01780 and IPR2015-01785. Pet. 5.

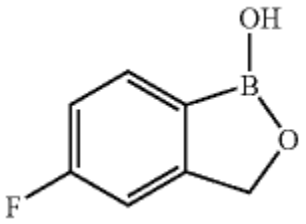
B. The '621 Patent

The '621 patent relates to boron-containing compounds useful for treating fungal infections, including infections of the nail and hoof known as ungual and/or periungual infections. Ex. 1001, Abstract, 1:12–13. One type of ungual and/or periungual fungal infection is onychomycosis. *Id.* at 1:15–17. According to the Specification, current treatment for ungual and/or periungual infections generally falls into three categories: systemic administration of medicine; surgical removal of the nail or hoof followed by topical treatment of the exposed tissue; or topical application of medicine with bandages to keep the medication in place on the nail or hoof. *Id.* at 1:17–24.

Each of the approaches have major drawbacks. Systemic administration of medicine typically requires long-term, high-dose therapy, which can have significant adverse effects on, for example, the liver and testosterone levels. *Id.* at 1:28–45. Surgical treatment is painful and undesirable cosmetically (or not realistic for animals such as horses). *Id.* at

1:46–52. And topical dosage forms cannot keep the drug in contact with the infected area for therapeutically effective periods of time. Moreover, because of the composition of the nail, topical therapy for fungal infections have generally been ineffective. *Id.* at 1:53–2:11. Accordingly, the Specification states that "there is a need in the art for compounds which can effectively penetrate the nail. There is also need in the art for compounds which can effectively treat ungual and/or periungual infections." *Id.* at 2:36–39.

The '621 patent claims a method of treating an infection using 1,3-dihydro-5-fluoro-l-hydroxy-2, 1-benzoxaborole, which is referred to as either compound 1 (*see id.* at 32:10–17) or compound C10 (*see id.* at 51:55–61) in the Specification, and has the following chemical structure:



C. Illustrative Claim

Petitioner challenges claims 1–12 of the '621 patent. Claim 1 is illustrative and is reproduced below:

> 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-l-hydroxy-2, 1-benzoxaborole, or a pharmaceutically acceptable salt thereof, sufficient to treat said infection.

Claims 2–4 and 10 depend directly or indirectly from claim 1 and further recite specific infections that are treated with the claimed method. Claims 5 and 7 depend from claim 1 and further recite specific animals that are treated,

including humans. Claims 8 and 9 depend from claim 1 and further recite the site of administration of the drug. And claims 11 and 12 are independent claims that are similar to claim 1, but recite a method of treating onychomycosis in a human (claim 11) and a method of inhibiting growth of a fungus in a human (claim 12).

D. Grounds of Unpatentability Instituted for Trial

We instituted trial based on the following grounds of unpatentability:

References	**Basis**	**Claim(s) challenged**
Austin[2] and Brehove[3]	§ 103	1–12
Austin and Freeman[4]	§ 103	1–12

II. ANALYSIS

A. Person of Ordinary Skill in the Art

The level of ordinary skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966) and *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner asserts that a person of ordinary skill in the art at the time the '621 patent was filed would have had an advanced degree (Master's or Ph.D.) or equivalent experience in chemistry, pharmacology, or biochemistry, and at least two years of experience with the research, development, or production of pharmaceuticals. Pet. 23 (citing Ex. 1006

[2] Austin et al., WO 95/33754, published Dec. 14, 1995 (Ex. 1002).
[3] Brehove, US 2002/0165121 A1, published Nov. 7, 2002 (Ex. 1003).
[4] Freeman et al., WO 03/009689 A1, published Feb. 6, 2003 (Ex. 1004).

¶ 21; Ex. 1008 ¶ 34). Patent Owner asserts that a person of ordinary skill in the art would have "needed knowledge and experience in several areas: medicinal chemistry; the development of potential drug candidates suitable for treating onychomyosis; and in assessing, together with others, the toxicology, pharmacology, and clinical utility of such candidates, including parameters relating to transungual penetration." PO Resp. 21–22 (citing Ex. 2034 ¶ 108). Patent Owner further asserts that Petitioner's definition is incorrect because it excludes "necessary expertise in mycology and in clinical dermatology." *Id.* at 22.

Based on the record presented, we hold that the cited prior art is representative of the level of ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)). The cited prior art is consistent with Petitioner's broader description of the level of ordinary skill in the art. We are not persuaded that additional experience in mycology, clinical dermatology, medicinal chemistry, the development of drug candidates for treating onychomycosis, and the assessment of the toxicology, pharmacology, and clinical utility of drug candidates is required, as Patent Owner suggests, as it is unclear as to why the claimed subject matter is beyond the abilities of someone that has Petitioner's proposed qualifications.

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 100(b);

Cuozzo Speed Techs., LLC v. Lee, 136 S. Ct. 2131, 2144–46 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

In our Decision to Institute, we determined that the broadest reasonable interpretation of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole includes "5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole" and "tavaborole." Dec. Inst. 6. Neither party contested this construction during trial. Accordingly, because nothing in the full record developed during trial persuades us to deviate from our prior construction, we adopt the construction for purposes of this Decision. For ease of reference, we refer to the claimed compound as "tavaborole" in this Decision.

1. "therapeutically effective amount"

Each of the claims of the '621 patent recites administering a "therapeutically effective amount of tavaborole." According to Petitioner, "therapeutically effective amount" means "an amount of the claimed compound needed to reach the desired therapeutic result." Pet. 12. Patent Owner asserts the claim phrase should be construed as expressly defined in the '621 patent specification: "'therapeutically effective' amount refers to the amount of drug needed to effect the desired therapeutic result." PO Resp. 25; Ex. 1001, 9:57–58.

Because the '621 patent specification defines the phrase with clarity, deliberateness, and precision, we determine the broadest reasonable interpretation of "therapeutically effective amount" is "the amount of drug needed to effect the desired therapeutic result." *See In re Paulsen*, 30 F.3d at 1480.

C. Credibility of Petitioner's Experts

As an initial matter, Patent Owner contends that we should not credit the testimony of Petitioner's declarants because they are not qualified to opine from the perspective of a person of ordinary skill in the art. PO Resp. 21–24. For the reasons that follow, we are not persuaded.

Petitioner relies on the testimony of two declarants: S. Narasimha Murthy, Ph.D. and Stephen Kahl, Ph.D. Both Dr. Murthy and Dr. Kahl provide their background and experience in their respective declarations, along with a curriculum vitae, which provides further detail regarding each declarant's experience. Ex. 1008 (Murthy) ¶¶ 4–8; Ex. 1009 (Murthy CV); Ex. 1006 (Kahl) ¶¶ 4–8; Ex. 1007 (Kahl CV). For example, Dr. Murthy has a Ph.D. in pharmaceutics, has been an assistant professor of pharmaceutics at various universities, and has received research grants relating to the topical administration of therapeutics, including ungual nail delivery, which has resulted in 85 publications in peer-reviewed journals. Ex. 1008 ¶¶ 4–8. Dr. Kahl has a Ph.D. in chemistry, is a professor in the department of pharmaceutical chemistry at the University of California, San Francisco, has served as an ad hoc reviewer for 20 journals, and has conducted research related to bioactive boron molecules that are specifically targeted to biological systems, which has resulted in over 65 publications in books and peer-reviewed journals. Ex. 1006 ¶¶ 4–8. Based on these qualifications, we

determine that the Drs. Murthy and Kahl are competent to opine on the matters in this proceeding.

Patent Owner contends that there are "huge holes" in the expertise of Petitioner's declarants. PO Resp. 23. For example, Patent Owner argues that Dr. Murthy's testimony should be disregarded because he allegedly conceded he is not a chemist. *Id.* We are persuaded by Dr. Murthy's testimony in response that, although he is not a synthetic chemist by profession, he is an expert in pharmaceutics with extensive coursework in various fields of chemistry. Ex. 1044 ¶ 10. Patent Owner also argues that neither declarant is a mycologist or has expertise in treating patients. PO Resp. 23. As explained above, we do not agree with Patent Owner's argument that a person of ordinary skill in the art is required to have expertise in mycology or clinical dermatology.

Thus, we are not persuaded by Patent Owner's argument that we should uphold the challenged claims because Petitioners' declarants are not qualified to opine from the perspective of a person of ordinary skill in the art in this proceeding. *Id.* at 24.

D. Principles of Law

To prevail in this *inter partes* review of the challenged claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying

factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does." *Id.* Moreover, a person of ordinary skill in the art must have had a reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014).

We analyze the instituted grounds of unpatentability in accordance with the above-stated principles.

E. Obviousness over Austin and Brehove

Petitioner asserts that claims 1–12 are unpatentable as obvious over Austin and Brehove. Pet. 23–42. Petitioner relies on the Declarations of Stephen Kahl, Ph.D (Ex. 1006) and S. Narasimha Murthy, Ph.D. (Ex. 1008). Patent Owner opposes Petitioner's assertion, relying on the Declarations of Paul J. Reider, Ph.D. (Ex. 2034), Mahmoud A. Ghannoum, Ph.D., E.M.B.A. (Ex. 2035), Majella Lane, Ph.D. (Ex. 2036), and Howard I. Maibach, M.D., Ph.D. (Ex. 2037). PO Resp. 35–54. Based on the full trial record, we determine that Petitioner has established by a preponderance of the evidence that claims 1–12 are unpatentable as obvious over Austin and Brehove.

1. Austin (Ex. 1002)

Austin relates to the use of oxaboroles as industrial biocides, and especially as fungicides for the protection of plastic materials. Ex. 1002,

Abstract. The Abstract further states that "[p]referred compounds are 5- and 6-fluoro or bromo-1,3-dihydro-1-hydroxy-2,1-benzoxaborole including O-esters thereof." *Id.* Austin notes that it has been found that compounds containing an oxaborole ring are "particularly effective against micro-organisms such as bacteria, algae, yeasts and particularly fungi, especially fungi which cause degradation of plastics materials." *Id.* at 1:35–38.

Along with a number of different preferred oxaboroles, Austin discloses tavaborole as Example 64, as well as the results of a study showing tavaborole has effective antifungal activity against five different fungi: *Aspergillus niger*, *Aureobasidium pullulans*, *Candida albicans* ("*C. albicans*"), *Gliocladium roseum*, and *Penicillium pinophylum*. *Id.* at 37 (Table 9).

2. Brehove (Ex. 1003)

Brehove relates to the topical treatment of nail infections such as onychomycosis caused by bacteria, fungi, and other pathogens. Ex. 1003 ¶ 3. Brehove explains that onychomycosis is a nail disease typically caused by *C. albicans*, *Trichophyton mentagrophytes*, *Trichophyton rubrum* ("*T. rubrum*"), or *Epidermpophyton floccusum*. *Id.* ¶ 5. Brehove states that *C. albicans* is the most common pathogen causing onychomycosis. *Id.* ¶ 18. Brehove teaches that to be effective for onychomycosis, the topical treatment should exhibit a powerful potency for pathogens, be permeable through the nail barrier, and be safe for patient use. *Id.* ¶ 6. According to Brehove, "[t]here exists a need in the art for a topical application that combines these traits in high degree." *Id.*

Brehove states that the "safety and non-toxicity of organo-boron compounds has been questioned." *Id.* ¶ 13. On the one hand, Brehove describes one reference that states that boron compounds are "very toxic,"

while on the other hand, Brehove describes references that found the toxicity of a certain boron-containing compound to be "very low" and another industrial fungicide compound called Biobor® JF to cause "mild irritation." *Id.* ¶¶ 14–15.

Biobor® JF contains a combination of 2,2'-(1-methyltrimethylene dioxy) bis-(4-methyl-1, 3, 2-dioxaborinane) (referred to by Brehove as "S1") and 2,2'-oxybis (4, 4, 6-trimethyl-1, 3, 2-dioxaborinane) (referred to by Brehove as "S2"). Ex. 1003 ¶¶ 15, 30. Brehove describes the results of both in vitro testing of the antifungal activity of S1 and S2 against *C. albicans* and in vivo treatment of patients with onychomycosis using S1 and S2. *Id.* ¶¶ 30–38.

3. Analysis

a. Whether Austin Is Analogous Art

Patent Owner first argues that Petitioner's arguments fail because Austin is not analogous art. PO Resp. 27–32. Prior art is analogous if it either (1) "is from the same field of endeavor, regardless of the problem addressed," or (2) "is reasonably pertinent to the particular problem with which the inventor is involved." *Unwired Planet, LLC v. Google Inc.*, 841 F.3d 995, 1000 (Fed. Cir. 2016) (quoting *In re Clay*, 966 F.2d 656, 658–59 (Fed. Cir. 1992)). "A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem." *In re ICON Health & Fitness, Inc.*, 496 F.3d 1374, 1380–81 (Fed. Cir. 2007).

Patent Owner argues that medicinal chemists would not look to industrial biocides for pharmaceutical leads because the requirements for a useful biocide are different from the requirements for a useful drug. PO

Resp. 31 (citing Ex. 2034 ¶¶ 121–126). Patent Owner further asserts that a person of ordinary skill in the art would have sought out compounds with at least low in vivo toxicity, high in vivo activity against medicinally relevant targets, high selectivity, and chemical and metabolic stability. *Id.* Accordingly, Patent Owner contends that a person of ordinary skill in the art "would have learned from *Austin* that these characteristics are not relevant to an industrial biocide." *Id.* We are not persuaded.

Based on our review of the complete record, we find that Austin is reasonably pertinent to the particular problem the inventors sought to solve. Both the inventors and Austin sought to inhibit microorganisms, including *C. albicans*. Ex. 1001, 25:5–55; Ex. 1002, 33:7–38:2. Further, as noted by Petitioner, a person of ordinary skill in the art would have recognized that industrial fungicides may have therapeutic uses, including in some cases, topically treating a human for *C. albicans*. Pet. 15–17; *see, e.g.*, Ex. 1003 ¶¶ 14–15, 23, 30–38; Ex. 1021, 2:9–15, 3:12–16, 6:45–50; Ex. 1022, 1:18–26, 13:32–48; Ex. 1023, 1:25–40, 3:73–4:36; Ex. 1026, 12:52–54, 16:63–17:46; Ex. 1029, Abstract, 15:12–16:16. For example, Pfiffner[5] describes its antifungal compounds as suitable for combating fungi in agriculture and horticulture, but also as suitable for use in ointments where the active compound completely prevented the growth of *C. albicans* in vitro. Ex. 1026, 12:52–54, 17:9-46. As another example, Grier describes its compounds as suitable for the treatment of fungal infections caused by *C. albicans* and *T. rubrum*, as well as for industrial applications, such as mildew-proofing paint. Ex. 1022, 1:18–26, 13:32–48, 17:38–18:45.

[5] Albert Pfiffner, US 4,202,894, issued May 13, 1980 (Ex. 1026).

Moreover, Brehove describes the topical use of an industrial fungicide, BioBor, to treat onychomycosis "without skin irritation or noticeable side effects." Ex. 1003 ¶ 24; Ex. 1044 ¶¶ 50, 52. Brehove also notes that the materials safety data sheet of BioBor states, "Skin Contact: May cause slight to mild irritation. Prolonged or repeated contact may dry the skin and lead to irritation (i.e. dermatitis)." *Id.* ¶ 15. Patent Owner and its declarant assert that Brehove mischaracterizes the dangers associated with contacting the skin with BioBor based on the product label and other warnings in the safety data sheet to wear protective clothing and clean the skin if contact occurs. PO Resp. 32; Ex. 2034 ¶ 155. We do not find those other warnings identified by Dr. Reider to be inconsistent with or to outweigh the warning stated in Brehove that BioBor may cause skin irritation.

Thus, based on the record presented, we find that Austin logically would have commended itself to the problem facing the inventors of the '657 patent. *See Scientific Plastic Products, Inc. v. Biotage AB*, 766 F.3d 1355 (Fed. Cir. 2014); *see also In re ICON Health*, 496 F.3d at 1379–80 (holding that reference may be reasonably pertinent as analogous art where the matter it deals with logically would have commended itself to the inventor's attention).[6]

[6] Petitioner points to a paper published in 2006 by the inventors of the '657 patent that published "their 'discovery' of a 'new' boron-containing compound (tavaborole) for the treatment of onychomycosis," and "also reported on the synthesis of benzoxaborole derivatives, including the 7-fluoro derivative," which was synthesized using a scheme disclosed in Austin. Reply 11–12 (citing Ex. 2157, 3, 6). Petitioner argues that the inventors' citation to Austin as a reference relied upon during the drug discovery process "prov[es] that a [person of ordinary skill in the art] would

b. Independent Claims

Petitioner provides a claim chart identifying where each limitation is taught in the cited references. Pet. 38–42. We have considered the claim chart and find that the combination of Austin and Brehove teaches each limitation of independent claims 1, 11, and 12. For example, regarding claim 1, Brehove teaches a method of treating an infection in an animal by disclosing that the invention relates to the treatment of human fingernails and toenails to cure or prevent the spread of nail infections such as onychomycosis, caused by bacteria, fungi and other pathogens. Ex. 1003 ¶ 3. Brehove also teaches administering a therapeutically effective amount of a pharmaceutical composition to the toenail of a patient suffering from onychomycosis in an amount sufficient to treat the infection. *Id.* ¶ 35. Finally, Austin teaches that tavaborole is effective against *C. albicans*. Ex. 1002, Abstract, 37 (Example 64).

Patent Owner argues that there is no basis to conclude that a person of ordinary skill in the art would have selected tavaborole from among the millions of compounds disclosed in Austin. PO Resp. 33–35. As Petitioner notes, however, Austin discloses tavaborole (i.e., 5-fluoro benzoxaborole) as a preferred fungicide. Pet. 27 (citing Ex. 1002, Abstract); Ex. 1006 ¶ 34; Ex. 1008 ¶ 61. Moreover, of the preferred compounds tested, tavaborole demonstrated the lowest Minimum Inhibitory Concentration ("MIC") tested

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find *Austin* directly relevant, and at minimum, analogous art." *Id.* at 11. Additionally, the examiner of the '621 patent application "also independently identified *Austin* in 2008 and rejected the pending claims over *Austin*." *Id.* at 12. Although we do not rely on the inventors' citation to Austin or the examiner's rejection over Austin in finding that Austin is analogous art, we note that both facts are consistent with our finding.

(5 ppm) against several pathogens, including *C. albicans*. Pet. 28; Ex. 1002, 37 (Table 9, Example 64); Ex. 1006 ¶ 34; Ex. 1008 ¶ 63. That is, tavaborole inhibited the growth of *C. albicans*—which is a cause of onychomycosis—at the lowest level of concentration. Ex. 1008 ¶¶ 63–64. Accordingly, evaluating Austin for all that it teaches, we determine that one of ordinary skill in the art would have recognized that tavaborole is a preferred fungicide for effectively inhibiting *C. albicans*, which causes onychomycosis.

Patent Owner contends that Petitioner's argument is flawed because Austin describes tens of thousands of structures as "preferred" and "particularly preferred," including the O-esters of 5- and 6-fluoro or bromo-1,3-dihydro-1-hydroxy-2,1-benzoxaborole. PO Resp. 33–34 (citing Ex. 2034 ¶¶ 114, 148, 150); Ex. 1002, Abstract. Patent Owner also asserts that a person of ordinary skill in the art would not select tavaborole among the many disclosed compounds given that Table 8 identifies numerous benzoxaborole O-esters with the same MIC of 5 ppm as tavaborole. PO Resp. 34 (citing Ex. 1002, 5; Ex. 2034 ¶ 151).

We are not persuaded by Patent Owner's argument. Although Austin may encompass millions of compounds, Patent Owner's declarant, Dr. Reider, testifies that Austin disclosed test results for only sixteen compounds identified as "preferred compounds"—nine O-esters from Table 8 and seven simple benzoxaboroles, including tavaborole, from Table 9. Ex. 1048, 304:4–308:11. We are persuaded that a person of ordinary skill in the art would have looked to compounds in Table 9 over the O-esters of Table 8 because the Table 9 compounds have a lower molecular weight that is more likely to penetrate the nail. Pet. Reply 14–15; Ex. 1043 ¶¶ 10–11; Ex. 1044 ¶¶ 44–45.

During oral argument, Patent Owner argued that because almost all of the "particularly preferred" compounds of Table 8 have the lowest MIC for *C. albicans* and an average molecular weight of 219 Da, which is less than the molecular weights of the compounds of Brehove and Freeman, a person of ordinary skill in the art would turn to the compounds of Table 8, rather than Table 9, when reading Austin as a whole. Tr. 24:11–29:16. Even if true, we do not find Patent Owner's argument detracts from what Austin reasonably suggests to a person of ordinary skill in the art. *See Merck & Co. v. Biocraft Labs, Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) ("That the [prior art] discloses a multitude of effective combinations does not render any particular formulation less obvious."). In other words, that Austin also points to the compounds of Table 8 does not preclude a person of ordinary skill in the art from considering tavaborole when reading Austin as a whole. *See id.* ("[I]n a section 103 inquiry, 'the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.'") (quoting *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976)). This is particularly true where tavaborole has a lower molecular weight than the compounds of Table 8 and was the most effective against *C. albicans* of the preferred compounds in Table 9.

In sum, Austin teaches that tavaborole was known as a preferred fungicide that was effective against *C. albicans*. Although Austin describes a broad class of preferred compounds, Austin tested only sixteen of its preferred compounds where nine of the sixteen compounds were "O-esters" in Table 8 and seven of the sixteen compounds, including tavaborole, were listed in Table 9. Ex. 1002, Abstract, Tables 8 and 9; Ex. 1048, 304:4–308:11. Of the preferred compounds tested with the most potent activity,

tavaborole was the simplest and lowest molecular weight compound, which, as explained further below, is the most important factor in predicting whether a molecule will penetrate a nail plate. Ex. 1043 ¶¶ 10–11; Ex. 1044 ¶¶ 44–45. Accordingly, we find that a person of ordinary skill in the art would have chosen tavaborole as a potential candidate for treating onychomycosis. Pet. Reply 15; Ex. 1043 ¶¶ 10–11; Ex. 1044 ¶¶ 44–47.

Patent Owner also argues that neither reference discloses "administering to the animal [or human] a therapeutically effective amount of [tavaborole]," as required by each claim. PO Resp. 35–36. We are not persuaded. Patent Owner attacks each reference separately and does not acknowledge what the art fairly teaches in combination. *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (stating the prior art "must be read, not in isolation, but for what it fairly teaches in combination with the prior art as whole"). Here, Austin and Brehove together suggest administering to a human a therapeutically effective amount of tavaborole.

The parties also dispute whether a person of ordinary skill in the art would have had a reason to combine Austin and Brehove to reach the claimed invention with a reasonable expectation of success. We determine that Petitioner has shown that it would.

In particular, we are persuaded by Petitioner's detailed explanation supported by the testimony of its two declarants as to why a person of ordinary skill in the art would have administered Austin's tavaborole in Brehove's method of treating onychomycosis with a reasonable expectation of success. Pet. 31–38. Specifically, Petitioner asserts that a person of ordinary skill in the art would have combined Austin and Brehove because:

> (1) both references teach the use of boron-based compounds as fungicides; (2) both references also disclose the use of boron-

> based compounds to specifically inhibit *Candida albicans*, which is one of the fungi responsible for onychomycosis; and (3) *Austin* discloses boron-based compounds that have lower molecular weight than the successful compounds of *Brehove* and are therefore likely to effectively penetrate the nail barrier.

Pet. 31 (citing Ex. 1006 ¶¶ 33-34, 36; Ex. 1008 ¶¶ 86, 93-96, 116).

In response, Patent Owner first argues that an ordinary artisan would not have found Brehove credible and, therefore, would not have combined it with Austin with a reasonable expectation of success. PO Resp. 36–40. Specifically, Patent Owner criticizes Brehove for failing to provide further details regarding the in vivo tests and data described in Brehove. *Id.* at 37–39. For example, Patent Owner argues that Brehove does not confirm the clinical diagnosis of onychomycosis through laboratory analysis of the microorganisms causing the onychomycosis. *Id.* at 37. Nor does Brehove discuss the facts that, according to Patent Owner and its declarants, jet fuel additives have no relevance to onychomycosis, BioBor has safety warnings on its label and materials safety data sheet, and BioBor was shown to be ineffective in vitro in a different study. *Id.* at 37–38 (citing Ex. 2035 ¶¶ 26–27, 106–108, 113). Moreover, Patent Owner argues that Brehove inaccurately reports the toxicity of another boron-containing dioxaborinane called tolboxane, and is incorrect when it stated *C. albicans* is "the most common pathogen causing onychomycosis." *Id.* at 38–39. Finally, Patent Owner asserts that a person of ordinary skill in the art would have understood Brehove's examples to be prophetic and do not constitute data that would provide a reasonable expectation of success. *Id.* at 39–40.

We are not persuaded that a person of ordinary skill in the art would not have considered Brehove to be a credible reference. There is no requirement, as Patent Owner suggests, that Brehove provide details

regarding background tests, data, and long-term toxicity reports, to be credited as results by a person of ordinary skill in the art. *See* PO Resp. 37 (pointing to Dr. Murthy's testimony that he would ask for underlying data "if one of his graduate students were to hand him the *Brehove* disclosure as a draft academic paper") (citing Ex. 2032, 599:9–15). Brehove is a patent application that does not need to meet the standard of a peer-reviewed academic article. It is well settled that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art. *Merck*, 874 F.2d at 807.

Having reviewed the complete record, we find that Brehove reasonably suggests administering Biobor to treat onychomycosis. We are persuaded by Dr. Murthy's testimony that it is reasonable to assume that where Brehove states a volunteer "has onychomycosis," that the volunteer was diagnosed before treatment. Ex. 1044 ¶ 51 (citing Ex. 1003 ¶¶ 34–38). Dr. Murthy explains why this belief is reasonable, stating Brehove describes symptoms in the patients that are associated with onychomycosis, such as detachment of the nail from the nail bed. *Id.* Similarly, we credit Dr. Murthy's testimony that where Brehove states the compositions "are effective in curing the onychomycosis without skin irritation and evidence side effects," he takes those statements to be true. *Id.* ¶ 52. Dr. Murthy's belief is reasonable in light of Brehove's description of the "clear zone in the treated nail," which is similar to observations made by others, including the inventors. *Id.* (citing Ex. 1003 ¶¶ 34–38; Ex. 1066, 2; Ex. 2001, 5; Ex. 2065, 943). As such, we are not persuaded that the alleged inaccuracies, unexplained data, and prophetic examples identified by Patent Owner (PO Resp. 37–39) detract from these teachings of Brehove.

Patent Owner then argues that there would have been no reason to combine Austin and Brehove. PO Resp. 41–50. Specifically, Patent Owner contends that because Austin and Brehove concern structurally different compounds, a person of ordinary skill in the art "would not assume (without reliable tests) that data generated in connection with one class of compounds would be applicable to a different compound class." *Id.* at 41–42. Patent Owner also argues that neither reference provides guidance about treating onychomycosis caused by dermatophytes, which represents over 90% of onychomycosis cases. *Id.* at 43–47. Patent Owner further argues that because transungual penetration is difficult, and because Austin and Brehove do not provide any guidance on transungual penetration, a person of ordinary skill in the art would not have had a reason to combine the references or a reasonable expectation of success in doing so. *Id.* at 47–50.

Taken as a whole, the evidence of record persuades us that a person of ordinary skill in the art would have had a reason to combine Austin and Brehove. Petitioner's declarant, Dr. Kahl agrees that there are obviously structural differences between the dioxaborinanes of Brehove and the benzoxaboroles of Austin. Ex. 1043 ¶ 25. We are persuaded, however, by Dr. Murthy and Dr. Kahl's testimony 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 BioBor. Ex. 1008 (Murthy) ¶¶ 93–95; Ex. 1006 (Kahl) ¶¶ 38, 43. We acknowledge Patent Owner's argument that small structural differences can cause different biological actions and activities. PO Resp. 41–42 (citing Ex. 2034 ¶ 90); *see also* Ex. 2034 ¶¶ 91–93. But we are persuaded 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 BioBor and tavaborole have similar fungicidal activity against *C. albicans*. In that regard, Austin's disclosure of tavaborole as a fungicide effective against *C. albicans* would have recommended its use for that purpose in treating onychomycosis. Of the seven preferred compounds tested in Austin's Table 9, tavaborole had the lowest tested anti-fungal activity against *C. albicans* and had the lowest molecular weight, which made it the first and best compound to select for treatment of onychomycosis. Ex. 1043 ¶¶ 10–11; Ex. 1044 ¶¶ 44–45.

We are also not persuaded that a person of ordinary skill in the art would not look to Austin because it only reports activity against *C. albicans*, which causes a very small percentage of onychomycosis cases. PO Resp. 43–47. Although dermatophytes cause about 90% of onychomycosis cases, the parties agree that onychomycosis can be caused by yeast (such as *C. albicans*). Ex. 1008 ¶ 49; Ex. 2035 ¶¶ 22, 28. We are not persuaded by Dr. Ghannoum's testimony that a person of ordinary skill in the art seeking to develop a formulation for the treatment of onychomycosis "would have been interested *only* in antifungal agents having demonstrated efficacy against dermatophytes, particularly *T. rubrum*, and efficacy only against *C. albicans* would have been inconsequential." Ex. 2035 ¶ 35 (emphasis added); *see also id.* ¶¶ 108–114. Brehove belies Dr. Ghannoum's assertion, as it relates to the treatment of onychomycosis and focuses on inhibiting *C. albicans* rather than the dermatophyte *T. rubrum*. Ex. 1003 ¶ 18 (describing the compositions of the invention as having "powerful potency against *Candida albicans*"). Accordingly, we are persuaded that Petitioner has shown sufficiently that a person of ordinary skill in the art would have had a reason

to combine Austin's tavaborole with Brehove's method of treating onychomycosis.

Patent Owner also argues that there would have been no reasonable expectation of success in combining Austin and Brehove. PO Resp. 47–52. In particular, Patent Owner contests Petitioner's argument that a person of ordinary skill in the art would have had a reasonable expectation that tavaborole would be an effective treatment because of its lower molecular weight, which would increase the likelihood of penetrating the nail barrier. *Id.* at 47–48. Patent Owner characterizes Petitioner's arguments as a "gross oversimplification of the many factors that govern whether a given compound will achieve effective penetration through the nail." *Id.* at 48. For example, Patent Owner asserts that a person of ordinary skill in the art would have recognized that a good candidate for transungual delivery would need to have a low affinity for keratin binding. *Id.* at 49 (citing Ex. 2036 ¶ 27). Because neither Austin nor Brehove provides any data on keratin binding, Patent Owner argues that a person of ordinary skill would not have identified tavaborole as a possible transungual candidate. *Id.* Moreover, Patent Owner argues that an ordinary artisan would not have expected the formulations described in Brehove to be effective in transungual delivery, particularly without information regarding the lipophilicity of tavaborole. *Id.* at 49–50 (citing Ex. 2036 ¶¶ 51–52).

Having considered the full trial record, we determine that Petitioner has shown that a person of ordinary skill in the art would have had a reasonable expectation of success in combining Austin and Brehove. Tavaborole has a molecular weight of 151.93 Da. Ex. 1008 ¶ 102. The parties agree the compounds in Brehove that were effective at treating onychomycosis are in the range of 260–290 Da. *Id.*; Tr. 26:1–3. Although

other factors such as lipophilicity, keratin binding, and potency of the compound may influence transungual drug delivery, we are persuaded by the well-supported testimony of Dr. Murthy that low molecular weight is the most important factor in predicting whether a molecule will penetrate the nail plate, and that the remaining factors described by Patent Owner's declarant, Dr. Lane, are of less importance, particularly with a low molecular weight and low MIC molecule such as tavaborole. Ex. 1008 ¶ 102; Ex. 1044 ¶¶ 63–64, 78–81. Dr. Murthy cites various references explaining that, "As expected, molecular size has an inverse relationship with penetration into the nail plate." Ex. 1008 ¶ 102 (citing Ex. 1028, "Murdan"); *see also* Ex. 1044 ¶ 68 (citing Ex. 1065, "Mertin", 3) ("There was a linear relationship with a negative slope between the permeability coefficient and the molecular weight for both the nail plate (generally lower P-values) and the hoof membrane."). Dr. Murthy's testimony is consistent with the specification of the provisional application to which the '621 patent claims priority, where the inventors state that "[c]ompounds with a molecular weight of less than 200 Da penetrate the nail plate in a manner superior to the commercially available treatment for onychomycosis." Ex. 1064 ¶ 6. Accordingly, we determine that a person of ordinary skill in the art would have had a reasonable expectation that administering tavaborole topically would penetrate the nail.

Patent Owner also asserts that concerns about tavaborole's toxicity preclude a reasonable expectation of success. PO Resp. 50–52. In light of the alleged "conventional wisdom" regarding boron's toxicity and without any evidence regarding tavaborole's safety in humans, Patent Owner contends that a person of ordinary skill in the art would have had no reasonable basis to believe tavaborole could be used as a pharmaceutical

formulation. *Id.* at 51. According to Patent Owner, this is particularly true where Austin teaches that tavaborole has a wider spectrum of activity against multiple organisms such as bacteria and algae in addition to fungi. *Id.* (citing Ex. 2034 ¶¶ 119, 124–125); *see also id.* at 7.

Although the parties have presented ample arguments and evidence conveying contrary opinions regarding the inherent toxicity of boron-containing compounds (Pet. 15–21; PO Resp. 7–15; Pet. Reply. 3–10), we find the weight of the evidence favors Petitioner. For example, we are persuaded by the 2001 review article by Groziak stating "boron-based agents [are] clearly visible on the therapeutic horizon," thereby suggesting such compounds are not inherently toxic. Ex. 1027,[7] Abstract. Groziak also states that "[b]oronic acids are fairly common and easily prepared synthetic organic compounds" and that no commercially available boronic acid has been found to be "unusually toxic" to date. *Id.* at 322. Patent Owner criticizes Petitioner for failing to report that Groziak also states that "one of the reasons boron has not been used is because it often forms complexes that are 'highly toxic to both bacteria and mammalian cells.'" PO Resp. 15 (citing Ex. 1027, Abstract, 321). But we disagree with Patent Owner's characterization of Groziak. Read in its entirety, Groziak states that one reason boron has been underutilized in therapeutic agents is because "very few boron-containing natural products are available to serve as an intellectual spark for medicinal chemists in their drug-design efforts, and to make matters worse, these turn out to be rather poor models." Ex. 1027, 321. The reason those boron-containing natural products are poor models is

[7] Michael P. Groziak, *Boron Therapeutics on the Horizon*, 8 AM. J. THERAPEUTICS 321–28 (2001) (Ex. 1027).

because they form complexes that are highly toxic to bacteria and mammalian cells. *Id.* Thus, Groziak does not state that all boron-containing compounds are highly toxic, as Patent Owner asserts; Groziak simply explains why it has been difficult for medicinal chemists to design drugs using natural boron-containing products as a model.

Moreover, we are persuaded by Dr. Kahl's testimony that many of the references cited by Patent Owner and Dr. Reider as demonstrating the toxicity of boron-containing compounds can be discounted because they (1) rely on discredited statements regarding toxicity in a 1984 article by Grassberger[8] (Ex. 2008), (2) are outdated papers that have been refuted by more recent research, or (3) relate to administering boron-containing compounds orally or intravenously, as opposed to topically, as indicated in Brehove. Ex. 1043 ¶¶ 12–26. We also note the inventors of the '621 patent published a review article in 2009 ("Baker"), citing mostly pre-2005 prior art, in which they concluded that "boron is not an inherently toxic element." Ex. 1056,[9] 1; Ex. 1043 ¶¶ 27–30. And, like Dr. Kahl, the inventors discredited Grassberger's assertions regarding boron toxicity:

> Grassberger *et al.* cautioned against the potential toxicity associated with this class and openly speculated that boron could be involved. However, no toxicity data were published and no proof (or testable hypothesis) that boron was the origin of toxicity was offered. A retrospective on Grassberger's work then misinterpreted these comments as proof that boron can not

[8] Grassberger et al., *Preparation and Antibacterial Activities of New 1,2,3-Diazaborine Derivatives and Analogues*, 27 J. Med. Chem. 947–953 (1984) (Ex. 2008).
[9] Baker et al., *Therapeutic Potential of Boron-Containing Compounds*, 1 FUTURE MED. CHEM. 1275–88 (2009) (Ex. 1056).

> be used clinically because of the "inherent toxicity of boron-containing compounds."

Ex. 1056, 3.

Moreover, boron's allegedly "promiscuous" behavior does not dissuade a person of ordinary skill in the art from considering boron-containing compounds generally, or tavaborole in particular. Onychomycosis has multiple causes, such as dermatophytes, yeast, and molds. Ex. 2035 ¶ 22. As such, we credit the testimony of Dr. Murthy that broad-spectrum activity would be preferred over limited-spectrum antifungals to treat the various potential causes of onychomycosis. Ex. 1044 ¶ 47 (citing Ex. 2070, 422 ("Griseofulvin['s] . . . effectiveness in onychomycosis proved a disappointment since its spectrum of activity is limited to dermatophytes only . . . .")).

Taken together, we determine that a person of ordinary skill in the art in 2005 would have understood that boron-containing compounds generally were not considered inherently toxic such that they would be excluded from consideration from topical therapeutic purposes.

Finally, Patent Owner argues that Freeman undermines Petitioner's argument that boron-containing compounds with similar structure share similar functional features. PO Resp. 53–54. According to Patent Owner, Freeman teaches that phenylboronic acids (PBAs) are ineffective at inhibiting microorganisms because the disclosed MICs of 3–10 mg/ml are thousands of times higher than the maximum acceptable concentrations for potential pharmaceutical products. PO Resp. 53 (citing Ex. 2035 ¶¶ 127–131). Thus, Patent Owner argues that, under Petitioner's theory of functional similarity, a person of ordinary skill in the art would have reasonably expected the dioxaborinanes to be ineffective for pharmaceutical

purposes. *Id.* at 53–54. To the extent we understand Patent Owner's argument, we are not persuaded. Brehove teaches that dioxaborinanes are effective in inhibiting *C. albicans* and treating onychomycosis. Ex. 1003 ¶¶ 33–38. And, as explained above, for an obviousness analysis, prior art may be relied on for all that it reasonably would have suggested to one of ordinary skill in the art. *Merck*, 874 F.2d at 807. Moreover, Petitioner's theory is not based on structural similarities alone. Petitioner's theory is based on the combination of structural similarity and functional similarity (i.e., both are active against *C. albicans*). Thus, we are not persuaded by Patent Owner's argument.

Accordingly, having considered the full trial record, we determine that the combination of Austin and Brehove teaches each limitation of independent claims 1, 11, and 12, and 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.

c. Dependent Claims

For 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. *See* Pet. 39–42; Ex. 1008 ¶¶ 107–117. For the same reasons stated above, we determine 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 response, Patent Owner argues that, at a minimum, Petitioner has a complete failure of proof as to dependent claim 4, which is limited to treating onychomycosis, and dependent claim 6, which is further limited to treating tinea unguium (i.e., onychomycosis caused by a dermatophyte). PO Resp. 64. As explained above, however, we determine that Brehove teaches treating onychomycosis.

Thus, we reject Patent Owner's argument as to dependent claim 4. The question remains, however, whether the combination of Brehove and Austin teaches or suggests treating onychomycosis caused by a dermatophyte, as required by dependent claim 6. We determine that it does.

It is undisputed that neither Austin nor Brehove expressly teaches whether the disclosed compounds exhibit any activity against dermatophytes. The parties dispute centers on whether a person of ordinary skill in the art would have understood that the combination of Austin and Brehove teaches or suggests administering tavaborole to treat onychomycosis caused by a dermatophyte with a reasonable expectation of success.

Petitioner asserts that because both references disclose the inhibition of *C. albicans* by boron heterocycles, 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." Pet. 35 (citing Ex. 1008 ¶ 101). Brehove discloses that onychomycosis is typically caused by *C. albicans* and *T. rubrum*, among others. Ex. 1003 ¶ 5. Brehove also teaches the effective treatment of patients suffering from onychomycosis. *Id.* ¶¶ 34–38. Thus, Dr. Murthy contends that the in vitro testing together with the effective treatment of onychomycosis would have led a person of ordinary skill in the art to reasonably assume that the boron-containing compounds were effective against both *C. albicans* and dermatophytes. Ex. 1044 ¶ 53. Patent Owner responds that a person of ordinary skill in the art could not have predicted activity against dermatophytes based on activity against a yeast such as *C. albicans*. PO Resp. 44 (citing Ex. 2035 ¶ 123).

We determine that the weight of the evidence favors Petitioner's argument. For example, a 1996 paper by Segal[10] shows that terbinafine, which is highly potent against dermatophytes, is also active (albeit less so) against *C. albicans*. Ex. 2050, 960. Patent Owner's declarant Dr. Ghannoum cites Nimura[11] to show that a person of ordinary skill in the art would have known that ketoconazole has potent antifungal activity against *C. albicans* but has poor activity against dermatophytes. Ex. 2035 ¶ 64. But, as confirmed by Dr. Murthy and Dr. Ghannoum, Nimura also teaches that amorolfine "exhibited potent antifungal activity against all fungal species tested," which included both *C. albicans* and *T. rubrum*. Ex. 2105, 175; *see also* Ex. 1044 ¶ 91; Ex. 1046, 101:5–14. Moreover, although it does not expressly identify *C. albicans* as the yeast tested, Mertin[12] teaches that "[d]ermatophytes are usually more sensitive towards antimycotics than yeasts." Ex. 1065, 6.

We note that conclusive proof of efficacy is not required to show obviousness. *See Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) ("Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success."). As such, in light of the evidence of record, we determine that a

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[10] Segal et al., *Treatment of Candida Nail Infection with Terbinafine*, 35 J. AM. ACAD. DERMATOL. 958–61 (1996) (Ex. 2050).
[11] Nimura et al., *Comparison of In Vitro Antifungal Activities of Topical Antimycotics Launched in 1990s in Japan*, 18 Intl. J. Antimicrobial Agents 173–78 (2001) (Ex. 2105).
[12] Mertin & 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. Pharm. Pharmacol. 866–72 (1997) (Ex. 1065).

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, particularly given the teaching that dermatophytes are usually more sensitive to antimycotics than yeast.

Thus, having considered the full trial record, we determine that the combination of Austin and Brehove teaches each limitation of claims 2–10 and 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.

d. Secondary Considerations of Nonobviousness

Factual inquiries for an obviousness determination include secondary considerations based on evaluation and crediting of objective evidence of nonobviousness. *Graham*, 383 U.S. at 17–18. The totality of the evidence submitted, including objective evidence of nonobviousness, may lead to a conclusion that the challenged claims would not have been obvious to one of ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984).

Patent Owner argues that the nonobviousness of the claims is supported by objective evidence of unexpected results, the satisfaction of a long-felt need, and industry praise. PO Resp. 60–64. As explained further below, we are not persuaded by Patent Owner's argument and evidence.

i. Unexpected Results

Patent Owner argues that a person of ordinary skill in the art would not have had any basis for an expectation of success, thereby making the success of tavaborole unexpected. Patent Owner asserts that the selective toxicity of tavaborole—i.e., its ability to kill the fungus but not be toxic to the human host—is over 1000-fold. PO Resp. 60 (citing Ex. 2035 ¶ 139). Dr. Ghannoum testifies that this is remarkable given the similarities between

fungal and human cells and the expectation in the art that the oxaboroles of Austin would be toxic. Ex. 2035 ¶ 139.

We are not persuaded that Patent Owner has demonstrated that the selective toxicity of tavaborole was an unexpected result. In particular, based on Patent Owner's argument and Dr. Ghannoum's testimony, we are unable to ascertain that the results are unexpected. Specifically, Dr. Ghannoum testifies that a person of ordinary skill in the art would have understood that a new compound identified as a potential antifungal would have been expected to be toxic to host cells, unless proven otherwise. Ex. 2035 ¶ 139. Dr. Ghannoum, however, does not direct our attention to any credible evidence to support this proposition. For example, although Dr. Ghannoum cites Alley[13] (Ex. 2113) for its teaching of tavaborole selectivity, Alley does not mention this particular selectivity as surprising or unexpected but, at best, mentions that specific fungal inhibitors are "less common." Ex. 2113, 163 ("Although eukaryotic protein synthesis inhibitors are common . . ., specific fungal inhibitors are less common because of the similarity between the fungal and human enzymes involved in protein synthesis.").

Further, Dr. Ghannoum does not provide a sufficient explanation as to how this selectivity represents an alleged unexpected result in light of the closest prior art of record. That is, "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Kao Corp. v. Unilever United States, Inc*., 441 F.3d 963, 970 (Fed. Cir. 2006) (*quoting In re Baxter Travenol*

[13] Alley et al., *Recent Progress on the Topical Therapy of Onychomycosis*, 16 EXPERT OPIN. INVESTIG. DRUGS 157–67 (2007) (Ex. 2113).

Labs., 952 F.2d 388, 392 (Fed. Cir. 1991)). Here, Patent Owner has not identified the closest prior art and has therefore not explained sufficiently why the 1000-fold selective toxicity was unexpected as compared to the closest prior art or the statistical and practical significance of the selectivity. Accordingly, we are not persuaded that Patent Owner's evidence of unexpected results supports the nonobviousness of the challenged claims or overcomes the evidence of obviousness presented by Petitioner.

ii. Long-Felt Need

"Evidence of a long felt but unresolved need tends to show non-obviousness because it is reasonable to infer that the need would have not persisted had the solution been obvious." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1332 (Fed. Cir. 2016). "[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem which were, before the invention, unsuccessful." *Tex. Instruments v. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993). In particular, the evidence must show that the need was a persistent one that was recognized by those of ordinary skill in the art. *In re Gershon*, 372 F.2d 535, 539 (CCPA 1967).

Patent Owner argues that there has been a long-felt need for a safe and effective topical treatment for onychomycosis, particularly in light of the serious side effects of oral formulations. PO Resp. 61–62 (citing Ex. 2037 ¶¶ 37–47). According to Patent Owner, Penlac (ciclopirox) was the only topical treatment for onychomycosis that had been approved by the FDA as of 2005, but it was barely more effective than the placebo. *Id.* at 62 (citing Ex. 2037 ¶ 52–57). Patent Owner also contends that Loceryl was available abroad, but was insufficiently effective to gain approval in the United States and exhibited poor transungual penetration. *Id.* at 63 (citing Ex. 2037 ¶¶ 52,

58). Finally, Patent Owner asserts that many other attempts to develop topical onychomycosis treatments by other pharmaceutical companies had failed. *Id.* (citing Ex. 2037 ¶¶ 69–77).

Although Patent Owner contends Kerydin met the long-felt need for a safe and effective topical treatment for onychomycosis, Patent Owner does not provide persuasive evidence to support its contention. In particular, what is missing from Patent Owner's analysis is sufficient and credible evidence to show Kerydin is more effective than, for example, Penlac. Patent Owner criticizes Penlac for being barely more effective than the placebo, but does not say how much more effective Kerydin is. Without that evidence, we cannot ascertain whether Kerydin satisfied that long-felt but unmet need. Indeed, Petitioner notes that a 2016 article by Rosen suggests that Kerydin (tavaborole) has similar efficacy to Penlac (ciclopirox):

TABLE 3. Topical Antifungals: Efficacy in Phase III Pivotal Trials

Medication	Complete Cure Rates*
Ciclopirox 8%[12]	5.5% and 8.5%
Efinaconazole 10%[15]	15% and 18%
Tavaborole 10%[16]	7% and 9%

Regimens: All of these medications are approved for daily application for 48 weeks.

*Results of two phase III trials, respectively.

Ex. 2062,[14] 6. We recognize that the studies reported in Table 3 were not conducted using standardized protocols and that the authors stated "each

[14] Rosen et al., *Antifungal Drugs for Onychomycosis: Efficacy, Safety, and Mechanisms of Action*, 35 Seminars in Cutaneous Medicine and Surgery S51–S55 (2016) (Ex. 2062). We cite the page numbers provided by Patent Owner pursuant to 37 C.F.R. § 42.63(d)(2)(i).

medication must be considered on its own merits in determining which topical agent to choose for an individual patient." *Id.* But even with that limitation, when asked about the Table 3 data during oral argument, Patent Owner did not address the similarity of the cure rates between Kerydin (tavaborole) and Penlac (ciclopirox), or point us to any contrary data indicating that the efficacy of Kerydin was superior to Penlac. Tr. 44:11–45:6. Thus, it remains unclear to us whether Kerydin satisfied a long-felt but unmet need of providing a more effective topical treatment for onychomycosis.I love

Accordingly, we are not persuaded that Patent Owner's evidence of the satisfaction of a long-felt need supports the nonobviousness of the challenged claims or overcomes the evidence of obviousness presented by Petitioner.

iii. Industry Praise

Industry praise for an invention may provide evidence of non-obviousness where the industry praise is linked to the claimed invention. *See Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010); *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008).

Patent Owner asserts that KERYDIN has received industry praise directly related to the administration of tavaborole, as claimed in the '621 patent. PO Resp. 63–64. Patent Owner identifies several examples:

- A 2015 article stating, "[tavaborole] offers an important alternative to [previously] available topical antifungal therapies." (Ex. 2060 at 6189.) The article praised tavaborole's efficacy and "excellent safety profile," and described the emergence of tavaborole as "exciting." (*Id*. at 6188-89.)
- A 2016 article praising tavaborole's nail penetration for being "40-fold greater than that of ciclopirox after 14 days of

treatment." (Ex. 2061 at 27; Ex. 2037 (Maibach) ¶ 85; *see also* Ex. 2063 at 9 (touting tavaborole's improved nail penetration compared to ciclopirox).

- A 2016 article reported that the introduction of tavaborole, along with topical efinoconazole, "expanded the roster of medications available to more effectively manage onychomycosis in a wide range of patients, including those for whom comorbid conditions, concomitant medications, or patient preference limited the use of systemic antifungals." (Ex. 2062 at S53.)

PO Resp. 63–64; *see also* Ex. 2037 ¶¶ 81–88 (Dr. Maibach's testimony identifying and describing similar articles).

We are not persuaded that the evidence presented demonstrates industry praise for the invention, as opposed to praise for another alternative therapy for topical treatment of onychomycosis. The statements cited by Patent Owner that tavaborole offers "an important alternative" (Ex. 2060, 6189) and "expand[s] the roster of medications available" (Ex. 2062, 6) do not persuade us that the industry praised the claimed invention. Moreover, the statement praising tavaborole's improved nail penetration says little about whether tavaborole is more effective than ciclopirox. Indeed, as explained above, from the limited data we have on record, it appears the efficacy of the two drugs is similar.

Accordingly, we are not persuaded that Patent Owner's evidence of industry praise supports the nonobviousness of the challenged claims or overcomes the evidence of obviousness presented by Petitioner.

4. Conclusion as to Obviousness

Having considered the parties' arguments and evidence, we evaluate all of the evidence together to make a final determination of obviousness. *In re Eli Lilly & Co.*, 902 F.2d 943, 945 (Fed. Cir. 1990) ("After a prima facie case of obviousness has been made and rebuttal evidence submitted, all the

evidence must be considered anew."). In doing so, we conclude that Petitioner has shown by a preponderance of the evidence that claims 1–12 are unpatentable as obvious over Austin and Brehove.

F. Obviousness over Austin and Freeman

Petitioner argues that claims 1–12 are unpatentable as obvious over Austin and Freeman. Pet. 43–56. Patent Owner opposes. PO Resp. 54–60. Having considered the full trial record, we determine that Petitioner has established by a preponderance of the evidence that claims 1–12 are unpatentable over Austin and Freeman.

We incorporate here our earlier findings and discussion regarding the disclosure of Austin.

1. Freeman (Ex. 1004)

Freeman discloses phenylboronic acid (PBA) and related boronic acid compounds that are used for treating fungal infections such as onychomycosis. Ex. 1004, Abstract, ¶ 1. Freeman identifies *T. rubrum* as one of the most common dermatophyte causes of onychomycosis. *Id.* ¶ 8. Freeman also identifies non-dermatophytes, "especially *Candida Sp.*," as another cause of onychomycosis. *Id.* According to Freeman, PBAs "have been found to be particularly useful in treating nail fungal infections." *Id.* ¶ 22.

Freeman also discloses results of in vitro testing of the fungicidal activity of PBA. *Id.* ¶¶ 31–34. In particular, Freeman notes that PBA exhibited fungicidal effect on *T. rubrum* within a concentration range of 5-10 mg/ml. *Id.* ¶ 34. Freeman also notes that the compounds tested had a fungicidal effect on *Candida parapsilosis* at 10 mg/ml. *Id.*

2. Analysis

Petitioner asserts that the combination of Austin and Freeman render the subject matter of claims 1–12 obvious. Pet. 43– 56. Through claim charts and Dr. Murthy's testimony, Petitioner asserts that the combination teaches each limitation of the claims. Pet. 51–56; Ex. 1008 ¶¶ 119–24, 138–46. Patent Owner again argues that Petitioner's assertions must fail because (1) Austin is not analogous art, (2) a person of ordinary skill in the art would have been concerned about the toxicity of boron-containing compounds, and (3) Austin provides no basis to choose tavaborole to treat fungal infections. PO Resp. 54–55. For the same reasons stated above, we are not persuaded by Patent Owner's arguments.

a. Independent Claims 1, 11, and 12

We are persuaded that the combination of Austin and Freeman teaches each limitation of independent claims 1, 11, and 12, for the reasons stated by Petitioner and Dr. Murthy. Pet. 51–52, 55–56. Patent Owner contends that the combination of Austin and Freeman does not disclose "administering to the animal [or human] a therapeutically effective amount of [tavaborole]." PO Resp. 55. We do not find Patent Owner's argument persuasive, as Freeman teaches that the present invention relates to methods for treating fungal infections such as onychomycosis. *See* Ex. 1004 ¶¶ 1, 22 ("It has now been discovered that phenyl boronic acid and derivatives thereof as well as related boronic acid compounds have fungicidal properties, and that these compounds are particularly useful in treating fungal infections [and] particularly useful in treating nail fungal infections.").

Petitioner also asserts that a person of ordinary skill in the art would have had a reason to combine Austin's tavaborole with Freeman's method of

treating onychomycosis with a reasonable expectation of success. Pet. 45–51. Specifically, Petitioner asserts:

> (1) both references teach the use of boron-based compounds as fungicides; (2) both references disclose the use of boron-based compounds to specifically inhibit *Candida albicans* or *T. rubrum*, which are fungi responsible for onychomycosis; and (3) *Austin* discloses boron-based compounds that have structural similarity to *Freeman's* preferred compounds for treating and inhibiting onychomycosis in humans.

Id. at 45–46 (citing Ex. 1008 ¶¶ 65, 74, 77, 125–27).

For similar reasons stated above with respect to the challenge over Austin and Brehove, we determine that the weight of the evidence supports Petitioner's argument that a person of ordinary skill in the art would have combined Austin and Freeman to achieve the claimed invention with a reasonable expectation of success. Patent Owner asserts that a person of ordinary skill in the art would not combine Austin and Freeman with a reasonable expectation of success given the structural differences between tavaborole and PBAs. PO Resp. 55–56. Although we agree there are structural differences, as above, we are persuaded that a person of ordinary skill in the art would have had a reason to combine the references in light of the structural similarities (i.e., both are boron heterocycles) *and* the similar functional activity against *Candida* species. Pet. 46.

Patent Owner again argues that a person of ordinary skill in the art would have expected tavaborole to be toxic given reports of clinical studies showing para-fluoro PBA is highly toxic to mice. PO Resp. 57 (citing Ex. 2052, 311). For the same reasons stated above, we are not persuaded. And as noted by Petitioner, the studies in mice are directed to boron neutron capture therapy for cancer, which one would expect to be toxic. Pet. 23; Ex. 1043 ¶¶ 14–17. Moreover, the studies injected the compound

intraperitoneally into the mice, rather than topically. *See* Ex. 2052, 311 (stating the compound was "injected intraperitoneally"). Even Freeman recognizes that PBA "is considered harmful if swallowed," but still teaches administering the compound topically to treat fungal infections. Ex. 1004 ¶¶ 28–29. Thus, we are not persuaded that a person of ordinary skill in the art would have been dissuaded from combining Austin and Freeman because of toxicity concerns over PBAs.

Patent Owner also argues that Freeman reports fungicidal activity of PBAs at concentrations much higher than a person of ordinary skill in the art would have considered to be the upper concentration limits for potential pharmaceuticals. PO Resp. 57—58 (citing Ex. 2035 ¶¶ 127–31). Patent Owner further notes that Dr. Murthy admitted that Freeman teaches poor antifungal effectiveness for its PBAs. *Id.* at 58 (citing Ex. 2032, 594:9–595:4). To start, we disagree with Patent Owner's characterization of Dr. Murthy's testimony. The cited testimony did not specifically address Freeman. Rather, the line of questioning appears to begin with Patent Owner's hypothetical question, "How high is too high?" Ex. 2032, 592:18. Dr. Murthy answered, with the caveat that it depends on the molecular size. *Id.* at 592:23–24. Moreover, Dr. Murthy explained that a person of ordinary skill in the art would expect compounds with similar structure to exhibit a similar spectrum of activity against fungi, but not necessarily at the same concentration. *Id.* at 210:25–211:8.

We are persuaded that a person of ordinary skill in the art would have had a reason to modify Freeman to administer Austin's tavaborole instead of PBA in light of the similar chemical structure and the similar activity against *Candida* species. Patent Owner argues that a person of ordinary skill in the art would have known that *C. parapsilosis* is not a cause of onychomycosis

and is a contaminant normally found on the hands. Ex. 2035 ¶ 31. We note, however, that the '621 patent specification identifies *C. parapsilosis* as a target microorganism of the invention. Ex. 1001, 25:37. Moreover, at oral argument, when asked whether a person of ordinary skill in the art would have expected that a drug that is active against one species of *Candida* would not be active against another species of *Candida*, Patent Owner directed us to Dr. Ghannoum's declaration testifying that an ordinary artisan could not have predicted the activity of a compound against *dermatophytes* based on activity of a different fungal organism, such as a yeast. Tr. 31:14–32:5 (citing Ex. 2035 ¶ 64). That testimony does not answer the question of whether a person of ordinary skill in the art would have expected a compound that is active against one species of *Candida* to be active against another species of *Candida*. Thus, we are not persuaded by Dr. Ghannoum's testimony.

Accordingly, having considered the full trial record, we determine that the combination of Austin and Freeman teaches each limitation of independent claims 1, 11, and 12, and that a person of ordinary skill in the art would have had a reason to combine Austin and Freeman with a reasonable expectation of success.

b. Dependent Claims

For the reasons stated in the Petition and by Dr. Murthy, we are persuaded that the combination of Austin and Freeman teaches or suggests each limitation of dependent claims 2–10. *See* Pet. 52–55; Ex. 1008 ¶¶ 138–146. Patent Owner does not separately address the dependent claims with respect to this ground. Accordingly, for the same reasons stated above, we also determine that a person of ordinary skill in the art would have had a

reason to combine Austin and Freeman with a reasonable expectation of success.

c. Conclusion as to Obviousness

Patent Owner makes no other specific arguments with respect to any other claims and the combination of Austin and Freeman. Accordingly, having considered the record as a whole—including the evidence of secondary considerations of nonobviousness, as explained above—we conclude that Petitioner has established by a preponderance of the evidence that claims 1–12 are unpatentable as obvious over Austin and Freeman.

III. PATENT OWNER'S MOTION TO EXCLUDE

The party moving to exclude evidence bears the burden of proving that it is entitled to the relief requested—namely, that the material sought to be excluded is inadmissible under the Federal Rules of Evidence. *See* 37 C.F.R. §§ 42.20(c), 42.62(a).

Patent Owner filed a Motion to Exclude Exhibits 1024, 1025, 1031, 1032, 1051, 1067, 1068, 1069, 1071, 1074, and 1075. Paper 57. We do not rely on any of the challenged exhibits in rendering this Decision. Accordingly, we dismiss Patent Owner's Motion to Exclude as moot.

IV. CONCLUSION

We conclude that Petitioner has shown by a preponderance of the evidence that claims 1–12 of the '621 patent are unpatentable.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–12 of the '621 patent are held unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude is *dismissed as moot*.

FURTHER ORDERED that, because this is a Final Written Decision, the parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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