

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 IPR2015-01780

Patent 7,767,657 B2

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

TIERNEY, *Vice Chief Administrative Patent Judge*.

FINAL WRITTEN DECISION
Inter Partes Review
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 1–24 of U.S. Patent 7,767,657 B2 (Ex. 1001, “the ’657 patent”). Paper 3 (“Pet.”). Patent Owner, Anacor Pharmaceuticals Inc. (“Patent Owner”), filed a Preliminary Response. Papers 7 and 17 (“Prelim. Resp.”). We determined that there was a reasonable likelihood that Petitioner would prevail in challenging those claims as unpatentable. Pursuant to 35 U.S.C. § 314, we authorized an *inter partes* review to be instituted on February 23, 2016. Paper 24 (“Dec. on Inst.”).

After institution, Patent Owner filed a Patent Owner Response. Paper 32 (“PO Resp.”). Petitioner filed a Reply. Paper 47 (“Reply”). Patent Owner filed Motions for Observations Regarding the Cross-Examination Testimony of Stephen B. Kahl, Ph.D. (Paper 55) and S. Narasimha Murthy, Ph.D. (Paper 56), and Petitioner filed Responses (Papers 61 and 62, respectively). With Board authorization, Patent Owner filed an Identification of New Arguments and Evidence in Petitioner’s Reply (Paper 53), and Petitioner filed a Response (Paper 60).¹ Patent Owner also filed a Motion to Exclude Evidence (Paper 57), Petitioner filed a Response (Paper 63), and Patent Owner filed a Reply (Paper 65).

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; see 37 C.F.R. § 42.23(b) (“A reply may only respond to arguments raised in the corresponding . . . patent owner response.”).

An oral hearing was held on November 3, 2016. A transcript of the hearing has been entered into the record of the proceedings as Paper 69 (“Tr.”).

We have jurisdiction under 35 U.S.C. § 6. 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 1–24 are unpatentable.

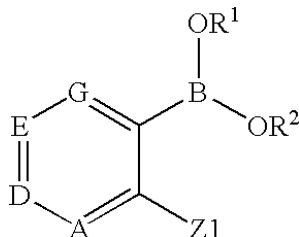
A. Related Proceeding

The claims of the ’657 patent have been challenged in related *inter partes* review proceeding IPR2015-01785. Additionally, the ’657 patent claims to be a continuation-in-part of U.S. Patent 7,582,621, which is involved in *inter partes* review IPR2015-01776. Pet. 4.

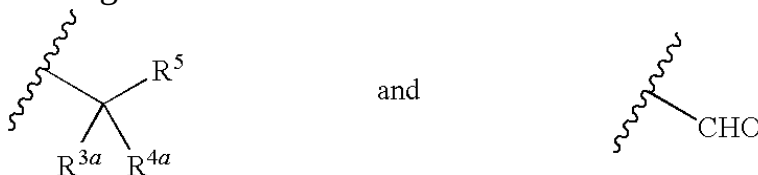
B. The ’657 Patent

The ’657 patent is titled “Boron-Containing Small Molecules.” Ex. 1001. The ’657 patent describes compounds useful for treating fungal infections, in particular, for topical treatment of onychomycosis and/or cutaneous fungal infections. *Id.* at Abstract. The compounds are said to have physiochemical properties that help facilitate the penetration of the nail plate. *Id.*

The ’657 patent describes pharmaceutical formulations that include a pharmaceutically acceptable excipient and a compound of said invention. *Id.* at 139:35–37. According to the ’657 patent “Summary of the Invention,” said invention provides a structure that is described as having the following formula:



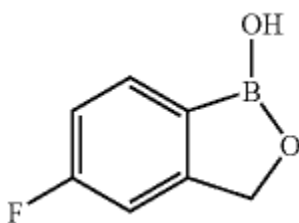
in which R1 and R2 are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R1 and R2, together with the atoms to which they are attached, can be optionally joined to form a 4- to 7-membered ring. Z1 is a member selected from



R3a and R4a are members independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R5 is a member selected from halogen and OR8. R8 is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. A is a member selected from CR9a and N. D is a member selected from CR10a and N. E is a member selected from CR11a and N. G is a member selected from CR12a and N. R9a, R10a, R11a and R12a are members independently selected from H, OR*, NR*R**, SR*, —S(O)R*, —S(O)2R*, —S(O)2NR*R**, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,

substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. Each R* and R** are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R9a and R10a, along with the atoms to which they are attached, are optionally joined to form a ring. R10a and R11a, along with the atoms to which they are attached, are optionally joined to form a ring. R11a and R12a, along with the atoms to which they are attached, are optionally joined to form a ring. The combination of nitrogens (A+D+E+G) is an integer selected from 0 to 3.

Id. at 4:6–5:2. Example 4.2.j identifies the compound 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole as “C10,” which has the following structure:



Id. at 180:20–27. The '657 patent provides several examples describing the antifungal activity of compound C10 and its ability to penetrate human nails. *Id.* at 189:15–196:46.

The '657 patent states that preferred compounds will have desirable pharmacological properties, including oral bioavailability, low toxicity, low serum binding, and desirable in vitro and in vivo half-lives. *Id.* at 165:66–166:2. According to the '657 patent, “[a]ssays may be used to predict these desirable pharmacological properties.” *Id.* at 166:6–7. For example, “[t]oxicity to cultured hepatocytes may be used to predict compound toxicity.” *Id.* at 166:9–10.

C. Illustrative Claim

The '657 patent contains twenty-four claims, all of which are challenged by Petitioner. All twenty-four claims are directed to a pharmaceutical formulation. Claim 1 is the sole independent claim. Claim 1 is illustrative of the challenged claims and is reproduced below:

1. A pharmaceutical formulation, comprising:
 - (a) 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a salt thereof; and
 - (b) a pharmaceutically acceptable excipientwherein said pharmaceutical formulation is for topical administration to an animal suffering from an infection by a microorganism.

D. Prior Art Relied Upon

Petitioner relies upon the following prior art:

U.S. 6,143,794 Chaudhuri	Nov. 4, 2000	(Ex. 1004)
U.S. 6,224,887 Samour	May 1, 2001	(Ex. 1005)
U.S. 7,074,392 Friedman	Jul. 11, 2006	(Ex. 1006)
U.S. 5,498,407 Atlas	Mar. 12, 1996	(Ex. 1007)
U.S. 3,816,472 Shapiro	June 11, 1974	(Ex. 1008)
US 2002/0165121 A1 Brehove	Nov. 7, 2002	(Ex. 1003)
WO 95/33754 Austin	Dec. 14, 1995	(Ex. 1002)

Petitioner contends that the challenged claims are unpatentable under 35 U.S.C. § 103 based on the following specific grounds (Pet. 21–60):

References	Basis	Claim(s) challenged
Austin and Brehove	§ 103	1–5, 10–16, and 18–24
Austin, Brehove, and Chaudhuri	§ 103	6
Austin, Brehove, and Samour	§ 103	7
Austin, Brehove, Friedman, and Atlas	§ 103	8
Austin, Brehove, Friedman, and Samour	§ 103	9
Austin, Brehove, and Shapiro	§ 103	17

E. Level of Ordinary Skill in the Art

Factors that may be considered in determining the level of ordinary skill in the art include, but are not limited to, the types of problems encountered in the art, the sophistication of the technology, and the educational level of active workers in the field. In a given case, one or more factors may predominate. *In re GPAC*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). Here, the challenged claims are directed to pharmaceutical compositions for topical administration to an animal suffering from an infection by a microorganism that comprise 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole and a pharmaceutically acceptable excipient. The '657 patent provides examples of lacquer and solvent formulations, and states that “the preparation of these formulations is well known in the art.” Ex. 1001, 188:25–50.

Petitioner contends that a person of ordinary skill in the art “would have 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. 22 (citing Ex. 1009 ¶¶ 20–22, Ex. 1011 ¶¶ 35–37). Patent Owner argues that Petitioner’s proposed definition “excludes necessary expertise in mycology and in clinical dermatology.” PO Resp. 20. According to Patent Owner, a person of ordinary skill in the art “would have needed knowledge and experience in several areas,” including “medicinal chemistry; the development of potential drug candidates suitable for treating onychomycosis; and in assessing, together with others, the toxicology, pharmacology, and clinical utility of such candidates, including parameters relating to transungual penetration.” *Id.* (citing Ex. 2034 ¶ 108).

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). 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.

II. ANALYSIS

A. Claim Interpretation

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). 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).

For purposes of the Decision on Institution, we interpreted the claim term “1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole” to include “5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole” and “tavaborole.” Dec. on Inst. 9. The parties do not dispute this interpretation, and we see no reason to modify it in light of the record developed at trial. Accordingly, for ease of reference, we refer to the claimed compound as “tavaborole” in this Final Written Decision.

Patent Owner contends that the claim term “wherein said pharmaceutical formulation is for topical administration to an animal suffering from an infection by a microorganism” should be construed to mean that the formulation must be suitable for administration to an animal suffering from the type of infection recited in a given claim. PO Resp. 23. We agree with Patent Owner’s construction that certain challenged claims, for example, claims 18, 20 and 22, are directed compositions where the composition is suitable for use in topical administration of specific infections.

Based on our review of the complete record, and the claim construction arguments raised by the parties, for purposes of this Final Written Decision we determine that it is unnecessary to construe explicitly any other claim terms. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (“[C]laim terms need only be construed ‘to the extent necessary to resolve the controversy.’”) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

B. Expert Qualifications to Testify as to the
Knowledge of One of Ordinary Skill in the Art

In support of the Petition, Petitioner submitted the Declarations of Stephen Kahl, Ph.D. (Ex. 1009 and Ex. 1069) and S. Narasimha Murthy, Ph.D. (Ex. 1011 and Ex. 1070). Patent Owner asserts that “there are huge holes in the expertise of Petitioner’s declarations,” in particular, that Dr. Murthy is not a chemist, and neither Dr. Kahl nor Dr. Murthy is a mycologist. PO Resp. 21–22. Patent Owner’s argument is based on its contention that a person of ordinary skill in the art “would have needed knowledge and experience in several areas,” including “medicinal chemistry; the development of potential drug candidates suitable for treating onychomycosis; and in assessing, together with others, the toxicology, pharmacology, and clinical utility of such candidates, including parameters relating to transungual penetration.” *Id.* at 20.

As set forth above, we are not persuaded that the additional qualifications enumerated by Patent Owner are necessary, and determined that the level of ordinary skill in the art is reflected by the cited prior art. Dr. Murthy has a Ph.D. in pharmaceuticals, has been an assistant professor of

pharmaceutics at various universities, and has received research grants relating to the topical administration of therapeutics, including ungual delivery, which has resulted in 85 publications in peer-reviewed journals. Ex. 1011 ¶¶ 4–8; Ex. 1012; Ex. 1070 ¶¶ 6–9. We also note that, although Dr. Murthy acknowledges that he is “not a synthetic chemist by profession,” he does have “extensive course work in the fields of organic chemistry, physical chemistry, medicinal chemistry and pharmaceuticals.” Ex. 1070 ¶ 10. 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. 1009 ¶¶ 4–8; Ex. 1010. Based on the facts in this record, we determine that Drs. Murthy and Kahl are qualified to testify as to the knowledge of a person of ordinary skill in the art in this proceeding.

C. Section 103 Obviousness Challenge

Petitioner contends that the challenged claims represent a combination of known prior art elements (tavaborole and topical formulations), used for their known purpose (antifungal treatment and topical delivery formulation) to achieve a predictable result (treat or inhibit the growth of fungus in an animal). Pet. 21–60. In support of its contentions, Petitioner relies on the Declarations of Dr. Kahl and Dr. Murthy. *Id.* Patent Owner disagrees with Petitioner’s contentions, and relies 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. 28–64.

1. Background on Obviousness

A claimed invention is not patentable under 35 U.S.C. § 103 if it is obvious. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007). In *Graham v. John Deere, Co.*, the Supreme Court established the factors underlying an obviousness inquiry:

Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.

383 U.S. 1, 17 (1966). In addressing the findings of fact, “[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR*, 550 U.S. at 416.

As explained in *KSR*:

If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.

Id. at 417. Accordingly, a central question in analyzing obviousness is “whether the improvement is more than the predictable use of prior art elements according to their established functions.” *Id.*

2. Scope and Content of the Prior Art

a. Austin

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 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.

Austin tested three compounds falling within the scope of its preferred 5- and 6-fluoro or bromo-1,3-dihydro-1-hydroxy-2,1-benzoxaboroles, including tavaborole. Specifically, Austin discloses tavaborole as Example 64, along with the results of a study showing tavaborole has effective antifungal activity against five different fungi: *Aspergillus niger*, *Aureobasidium pullulans*, *Candida albicans*, *Gliocladium roseum*, and *Penicillium pinophylum*. *Id.* at 37 (Table 9). Of the three preferred compounds tested, tavaborole demonstrated the lowest Minimum Inhibitory Concentration (“MIC”) values against several pathogens, including *Candida albicans*. *Id.* In other words, tavaborole inhibited the visible growth of *Candida albicans* at the lowest level of concentration of the three preferred compounds tested. Ex. 1009 ¶ 35.

Austin teaches that its compounds may be used with water-miscible organic solvents such as ethanol or glycols, including propylene glycol. Ex. 1002, 6:34–37. According to Austin, the concentration of the oxaborole in its biocide composition may range from 10 to 20% by weight relative to

the total weight of the biocide composition, which for tavaborole an ethanol solution would be 7.9%–15.8% w/v. Ex. 1011 ¶¶ 167–169.

b. Brehove

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 *Candida albicans*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, or *Epidermophyton floccusum*. *Id.* ¶ 5. Brehove states that *Candida 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,” and may be considered an industrial poison. *Id.* ¶ 14. On the other hand, Brehove describes references that found the toxicity of a certain boron-containing compound to be “very low,” and a boron containing antifungal fuel additive called Biobor JF, when combined with naptha, is said to cause “mild irritation.” *Id.* ¶¶ 14–15 and 23.

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.

Brehove describes several topical treatment formulations including one that is applied nightly in a petroleum jelly or mineral oil base and another formulation that is applied once per week in a cellulose acetate lacquer base. *Id.* ¶ 18. Brehove teaches that its active ingredient may be used in combination with penetration enhancers to increase the permeability of the skin to a drug. *Id.* ¶ 27. According to Brehove, its formulations achieve efficacy in treating onychomycosis without skin irritation or noticeable side effects. *Id.* ¶ 18. For example, Brehove states that a male volunteer with onychomycosis on both feet applies the solution to his entire toenail and 250 days later, the nail is fully-grown and completely free of infection with no skin irritation observed. *Id.* ¶ 35.

c. Chaudhuri

Chaudhuri is directed to topical formulations for treating nail fungal diseases. Ex. 1004. Chaudhuri states that treating onychomycosis can be difficult and that it would be advantageous to have a topical formulation capable of penetrating the nail barrier and treating nail fungal diseases. *Id.* at 1:55–65. Chaudhuri states that suitable solvents for its composition include lower alkanols, such as ethanol, and dihydroxyalcohols, such as propylene glycol. *Id.* at 6:2–7. In particular, Chaudhuri provides an example containing 5–20% weight propylene glycol, 20–80% weight ethanol, and 0.5 to 15% weight antifungal. *Id.* at 8:57–9:10, Table B. One

skilled in the art would have understood Chaudhuri's Table B proportions as equating to a ratio of 1:4 propylene glycol to ethanol and 1:10 weight per volume of antifungal. Ex. 1011, ¶¶ 100, 193.

d. Samour

Samour describes a nail lacquer formulation that is effective for the treatment or prevention of fungal infections, such as onychomycosis. Samour's nail lacquer formulation incorporates an antifungal agent and, when applied to nails, yields a hard, durable, substantially clear, long-lasting film that is effective in treating fungal infestations associated with nails. Ex. 1005, 3:5–13. Samour teaches that an effective amount of active antifungal agent preferably ranges from 1 to 10% by weight of the composition. *Id.* at 12:9–14. Suitable film-forming polymers for the composition include acrylic polymers such as Gantrez ES-425 (poly(vinyl methyl ether-alt-maleic acid monobutyl ester)). *Id.* at 7:54–62; Ex. 1011 ¶¶ 103, 208; Ex. 1035, 5. Samour teaches that an effective amount of film-forming polymer is preferably 15 to about 50%, and especially from 20 to 40% by weight of composition. *Id.* at 8:38–44; Ex. 1011 ¶¶ 103, 208. Samour exemplifies a number of lacquer formulations including a formulation having 71% ethanol, 24% film-forming polymer and 5% antifungal. Ex. 1005, 9:31–49, 22:20–36.

e. Friedman

Friedman describes a topical sustained release composition for delivery of antifungal agents to nails. Friedman describes a number of methacrylic polymers for use as a film-forming polymer and describes

plasticizers, such as dibutyl sebacate, with a preferable weight ratio of plasticizer to polymer of about 0.4:1 to about 0.3:1. Ex. 1006, 5:51–64. Friedman teaches that a suitable solvent includes ethanol, preferably about 60 to 90% w/w of the composition. *Id.* at 6:1–9. Dr. Murthy testifies that 60% to about 90% w/w ethanol corresponds to 47.4% to about 71.1% w/v ethanol. Ex. 1011 ¶ 225 n.8.

f. Atlas

Atlas describes the use of hydrogel polymers as excellent carriers for the release of drugs. Ex. 1007, 1:5–14. Atlas states that poly(2-hydroxyethyl methacrylate) (“P-HEMA”) was the most widely used hydrogel. *Id.* at Abstract. Atlas teaches that the P-HEMA hollow fibers act as a reservoir and matrix for diffusion-controlled delivery to skin and nails. *Id.* at 2:58–64. Atlas Example 4 describes a cosmetic nail polish composition having P-HEMA. *Id.* at 3:57–4:7.

g. Shapiro

Shapiro describes antifungal compounds for treating fungal infections. Ex. 1008, 1:15–16. Shapiro teaches that its antifungal compounds are effective against fungi including *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton verrucosum*, and *Microsporum gypseum*. *Id.* at 2:3–14.

3. Austin and Brehove: Claims 1–5, 10–16 and 18–24

Petitioner contends that Austin teaches tavaborole “as a preferred fungicide” that “has significant antifungal activity against *Candida albicans*

(CA), a fungus often associated with onychomycosis, at the lowest concentration tested (5 parts per million).” Pet. 30. Petitioner notes that Austin “identifies a number of organic solvents to form solvates with” tavaborole, including ethanol and polyethylene glycol. *Id.* Petitioner further contends that Brehove teaches “the topical application of boron compounds to ‘treat and prevent the spread of nail infections or onychomycosis caused by bacteria, fungi and other pathogens.’” *Id.* (quoting Ex. 1003 ¶ 3). Petitioner notes that Brehove states that onychomycosis typically is caused by *Candida albicans*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum*, and that “boron-based topical formulations have ‘powerful potency against *Candida albicans* . . . effectively kill[ing] the most common pathogen causing onychomycosis.’” *Id.* at 30–31 (quoting Ex. 1003 ¶ 18). Petitioner also contends that Brehove describes boron-based topical formulations that effectively cure onychomycosis without skin irritation and apparent side effects. *Id.* at 31.

Petitioner contends that a person of ordinary skill in the art “would have had several reasons to combine” Austin and Brehove “with a reasonable expectation of success.” Pet. 32. According to Petitioner, both Austin and Brehove “teach the use of boron-based compounds as fungicides,” both also “disclose the use of boron-based compounds to specifically inhibit *Candida albicans*,” and Austin describes “the claimed boron-based compound having a lower molecular weight than the successful compounds” described in Brehove, which is “more likely to effectively penetrate the nail barrier in similar topical formulations.” *Id.* at 32–33. Petitioner contends that a person of ordinary skill in the art “seeking to develop a therapeutic treatment for onychomycosis before February 2005

would have understood that boron compounds were effective fungicides safely applied to humans,” and “would have also understood from *Brehove* that boron-based industrial fungicides had successfully treated onychomycosis with little skin irritation or side effects.” *Id.* at 33.

Petitioner also contends that a person of ordinary skill in the art “would have expected that 5-fluoro benzoxaborole, which shares similar structural features with the compounds of *Brehove*, would likely share similar functional features.” *Id.* at 34.

Patent Owner makes three main arguments in response: (1) Austin is not analogous art to the ’657 patent; (2) a person of ordinary skill in the art would not have been motivated to combine Austin and *Brehove*; and (3) the combination of Austin and *Brehove* does not disclose every element of the challenged claims. We address each in turn below.

a. Whether Austin is Analogous Art

Patent Owner argues that Austin is not analogous art because it is neither from the same field of endeavor nor reasonably pertinent to the problem solved by the ’657 patent. PO Resp. 28–34. The test for determining whether a prior art reference constitutes analogous art to the claimed invention is whether the prior art is from the same field of endeavor, regardless of the problem addressed, or, if the reference is not from the same field of endeavor, whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved. *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). “A reference is reasonably pertinent if . . . 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.” *Innovation Toys, LLC v. MGA Entm’t, Inc.*, 637 F.3d 1314, 1321 (Fed. Cir. 2011). The scope of analogous art is to be construed broadly, because “familiar items may have obvious uses beyond their primary purposes, and a person of ordinary skill often will be able to fit the teachings of multiple patents together like pieces of a puzzle.” *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1238 (Fed. Cir. 2010) (quoting *KSR*, 550 U.S. at 398).

Patent Owner contends that Austin is not reasonably pertinent to the problem solved by the ’657 patent because “[m]edicinal chemists would not look to industrial biocides for pharmaceutical leads.” PO Resp. 32. Patent Owner argues that a person of ordinary skill in the art “would have understood that the requirements for a useful biocide are different from the requirements for a useful drug,” and “would have sought out compounds with at least low *in vivo* toxicity, high *in vivo* activity against medically relevant targets, corresponding high selectivity, and chemical and metabolic stability.” *Id.* at 32–33. According to Patent Owner, a person of ordinary skill in the art reading Austin would have learned “that these characteristics are not relevant to an industrial biocide.” *Id.* at 33.

Based upon our review of the complete record, we find that Austin is reasonably pertinent to the problems the inventors of the ’657 patent sought to solve. Both the inventors and Austin sought to inhibit microorganisms, including *Candida albicans*. Ex. 1001, 128:13–129:28; 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 *Candida albicans*. Pet. 18–20; Ex. 1024 ¶¶ 14–15, 23, 30–38; Ex. 1025, 2:9–15, 3:12–16, 6:45–50; Ex. 1026, 1:18–26, 13:32–48; Ex. 1027, 1:25–40, 3:73–4:36; Ex. 1028,

12:52–54, 16:63–17:46; Ex. 1029, Abstract, 15:12–16:16. For example, Pfiffner² 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 *Candida albicans* in vitro. Ex. 1028, 12:52–54, 17:9–46. As another example, Grier describes its compounds as suitable for the treatment of fungal infections caused by *Candida albicans* and *T. rubrum*, as well as for industrial applications, such as mildew-proofing paint. Ex. 1026, 1:18–26, 13:32–48, 17:38–18:45. Moreover, Brehove describes the topical use of an industrial fungicide to treat onychomycosis “without skin irritation or noticeable side effects.” Ex. 1003 ¶ 24; Ex. 1070 ¶¶ 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).” Ex. 1003 ¶ 15.

Patent Owner contends that Brehove mischaracterizes the dangers associated with Biobor. Specifically, Patent Owner states that Brehove omitted highly relevant safety warnings from Biobor JF’s product label and material safety data sheet. PO Resp. 39; Ex. 2034 ¶ 161. We do not find these warnings to be inconsistent with or outweigh the warning stated in Brehove that Biobor may cause skin irritation.

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 Sci. Plastic Products, Inc. v. Biotage AB*, 766 F.3d 1355 (Fed. Cir. 2014); *see also In re ICON Health & Fitness, Inc.*, 496 F.3d 1374,

² Albert Pfiffner, US 4,202,894, issued May 13, 1980 (Ex. 1028).

1379–80 (Fed. Cir. 2007) (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).³

b. Reason to Combine Austin and Brehove

Second, Patent Owner argues that Petitioner failed to meet its burden to show that a person of ordinary skill in the art would have combined Austin and Brehove in the manner recited in the claims with a reasonable expectation of success. PO Resp. 37–51. In that regard, Patent Owner first argues that a person of ordinary skill in the art would not have selected tavaborole from the compounds disclosed in Austin. *Id.* at 34–36. A reference, however, may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art. *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989).

³ Petitioner points to a paper published in 2006 by the inventors of the ’657 patent that “announced their ‘discovery’ of a ‘new’ boron-based compound (tavaborole) for the treatment of onychomycosis,” and “also reported the synthesis of benzoxaborole derivatives, including the 7-fluoro derivative,” which was synthesized using a scheme disclosed in Austin. Reply 10–11 (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 find *Austin* directly relevant, and at minimum, analogous art.” *Id.* at 11. Additionally, the examiner of the ’657 patent application “also identified *Austin* and rejected the pending claims” over Austin. *Id.* at 12. While we do not rely upon the inventors’ citation to Austin or the examiner’s rejection over Austin in finding that Austin is analogous art, we note that the citation by the inventors and the examiner’s reliance on Austin are both consistent with our finding.

As Petitioner notes, Austin discloses 5-fluoro benzoxaboroles as preferred fungicides in the Abstract, and tavaborole as one of three preferred compounds tested that effectively inhibits *Candida albicans*, which is a cause of onychomycosis. Pet. 23 (citing Ex. 1002, Abstract, 36–37, Table 9); Ex. 1011 ¶¶ 189–190. Additionally, of the tested preferred compounds, tavaborole demonstrated the lowest MIC values (5 ppm) against several pathogens, including *Candida albicans*. Pet. 30 (citing Ex. 1002, 36–37, Table 9; Ex. 1009 ¶¶ 32, 35; Ex. 1011 ¶¶ 84, 85, 87, 88, 174–176). In other words, tavaborole inhibited the visible growth of *Candida albicans* at the lowest level of concentration of the three preferred compounds tested. Ex. 1009 ¶ 35. Accordingly, evaluating Austin for all that it teaches, we hold that one of ordinary skill in the art would have recognized that tavaborole is a preferred fungicide for inhibiting *Candida albicans*, which is a cause of onychomycosis.

Patent Owner disagrees, and argues that Austin teaches “tens of thousands” of preferred compounds, with a stated preference for any benzoxaborole with a fluoro or bromo group in the 5 or 6 positions. PO Resp. 35. Patent Owner further argues that the benzoxaborole O-esters in Table 8 have different structures but “are potent at the lowest concentrations tested,” which is “in stark contrast to the substantially lower potencies in Table 9 for 1-hydroxy benzoxaboroles.” *Id.* According to Patent Owner, a person of ordinary skill in the art would understand that “the benzoxaborole O-esters of Formula 4, which includes the compounds of Table 8, are specifically identified” by Austin as being particularly preferred, and that “this group of ‘particularly preferred’ compounds does not include tavaborole.” *Id.* at 36.

We are not persuaded by Patent Owner's arguments. As Petitioner points out, Dr. Reider agrees that Austin only reports the results of tests on "sixteen of the 'thousands' of compounds identified in the abstract as 'preferred compounds,'" nine of which are the O-esters in Table 8 and the other seven, including tavaborole, "were simpler benzoxaboroles listed in Table 9." Reply 14 (citing Ex. 1074, 304:4–308:11). We also credit Dr. Kahl's testimony that a person of ordinary skill in the art would select the simplest molecule when more than one molecule shares similar activity (Ex. 1069 ¶ 10), and Dr. Murthy's testimony that it was well known in the art in 2005 that "low molecular weight compounds were preferred for penetration through the nail" (Ex. 1070 ¶ 47). *See also* Ex. 1011 ¶ 149 ("It was well known to a [person of ordinary skill in the art] before February 16, 2005 that lower molecular weight compounds are more effective at crossing the nail plate following topical administration."). Accordingly, we agree with Petitioner that a person of ordinary skill in the art would have looked to the 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. Reply 12–15; Ex. 1069 ¶¶ 10–11; Ex. 1070 ¶¶ 46–49; *see also* Pet. 35 (A person of ordinary skill in the art would have been "motivated to select 5-fluoro benzoxaborole as disclosed by *Austin* for its relatively small molecular weight." (citing Ex. 1011 ¶ 149)).

During oral argument, Patent Owner argued that because almost all of the "particularly preferred" compounds of Table 8 have the lowest MIC for *Candida albicans* and an average molecular weight of 219 Daltons, which is less than the molecular weights of the compounds of Brehove, 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. 24:11–7. 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*, 874 F.2d at 807 (“That the [prior art] discloses a multitude of effective combinations does not render any particular formulation less obvious.”). That Austin also points to the compounds of Table 8 does not preclude a person of ordinary skill in the art from also 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 *Candida albicans* of the preferred compounds in Table 9. Accordingly, we find that a person of ordinary skill in the art would have understood that tavaborole was suitable for treating onychomycosis. Reply 14–15; Ex. 1069 ¶¶ 10–11; Ex. 1070 ¶¶ 44–47.

Patent Owner also argues that a person of ordinary skill in the art “would simply disregard” Brehove because it “stands in such stark contrast to the entire rest of the prior art concerning boron-containing compounds, and is riddled with so many demonstrably unreliable and incredible assertions.” PO Resp. 37. In particular, Patent Owner argues that Brehove omits details about its described in vivo tests, omits safety warnings, is contradicted by an FAA study that shows Biobor is ineffective in the same kind of in vitro experiments where Brehove claims success, and incorrectly identifies *Candida albicans* as the most common cause of onychomycosis.

Id. at 38–39. Patent Owner further argues that a person of skill in the art would have understood that all of Brehove’s examples “are prophetic and do not constitute ‘data’ that could provide a reasonable expectation of success.” *Id.* at 40. According to Patent Owner, a person of ordinary skill in the art “would give no weight” to Brehove because “[f]ungal contaminants in jet fuel have no relevance to onychomycosis” and Brehove’s statements that the compounds “would be able to treat onychomycosis” are unsupported. *Id.* at 38.

We are not persuaded that a person of ordinary skill in the art would have disregarded Brehove as Patent Owner contends. As an initial matter, we note 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. There is no requirement, as Patent Owner suggests, that Brehove provide details regarding reports of control experiments, and long-term toxicity reports in order to be credited as results by a person of ordinary skill in the art. *See* PO Resp. 38 (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 for the purposes of an obviousness inquiry.⁴

⁴ As noted in the Decision to Institute, Patent Owner’s allegations that Brehove lacks credibility are inconsistent with its specification and prosecution history. Dec. to Inst. 15. Specifically, Patent Owner described and claimed millions of boron-containing compounds for pharmaceutical formulations and methods of treating fungus using therapeutically effective amounts of the compounds. Ex. 1013, 98-109. Patent Owner’s

Upon review of the complete record, we find that Brehove suggests administering an industrial boron-based biocide to a human to treat onychomycosis. We credit Dr. Murthy's testimony that it is reasonable to assume that Brehove's statement "that a volunteer 'has onychomycosis'" indicates that "the volunteer was diagnosed by some suitable means prior to the treatment." Ex. 1070 ¶ 53 (citing Ex. 1003 ¶¶ 34–38). Dr. Murthy supports his testimony by pointing to Brehove's description of the volunteers' symptoms as those that are associated with onychomycosis, such as detachment from the nail bed. *Id.* We also credit Dr. Murthy's testimony that Brehove describes an effective onychomycosis treatment because Brehove

described evidence of the effectiveness of the treatment, such as describing the size of the clear zone in the treated nail, describing the clear nail as "closely attached" in contrast to the infected nail which is "more detached," and describing the boundary between the infected and clear portion as "not smooth and shows structure." (See [Ex. 1003], ¶¶ [0034]–[0038].) These types of observations of effective treatment are similar to the observations described by one of the inventors, Stephen Baker, and Dr. Maibach, who state that "clinical cure is defined by the extent of new nail growth at the proximal fold which is visibly clear of infection." (Ex. 1092, at 2). Other references cited by the Patent Owner describe similar indications of clinical cure. (See Ex. 2001, at 5 (describing "Completely Clear Nail" as "no clinical evidence of onychomycosis as evidence by a normal toenail plate, no onycholysis, and no subungual hyperkeratosis"); Ex. 2065, at 943 ("A proximal area of normal-appearing nail,

specification, however, does not provide the long-term toxicity reports for these compounds, compositions and methods that Patent Owner states are necessary in order to be credited as results by a person of ordinary skill in the art. PO Resp. 38. As noted by Dr. Murthy, the '657 patent does not report toxicity data, much less selective toxicity data. Ex. 1070, ¶ 48.

representing newly formed nail plate that is devoid of infection, may be present. Visible clearance of the infection will occur after the process of nail-plate turnover is complete.”.)

Id. ¶ 54. As such, we are not persuaded that the alleged deficiencies identified by Patent Owner detract from these teachings of Brehove.

Patent Owner further argues that because Austin and Brehove “disclose distinct classes of boron-containing 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.” PO Resp. 42; *see also id.* at 11 (A person of ordinary skill in the art “would not have expected two structurally different compounds to have similar functional properties.” (citing Ex. 2034 ¶¶ 90–93, 178–181, 192–194)). Patent Owner also argues that because transungual penetration “is a notoriously difficult endeavor,” and because neither Austin nor Brehove disclose “nail penetration data, or any data bearing on propensity to achieve nail penetration,” the goal of transungual delivery does not establish a reason to combine Austin and Brehove with a reasonable expectation of success. *Id.* at 43–46.

Based on the record presented, we find that a person of ordinary skill in the art would have had reason to use Austin’s tavaborole in Brehove’s formulation for topical treatment of nail infections such as onychomycosis. Although we recognize the differences between Brehove’s dioxaborinanes and Austin’s benzoxaboroles, we credit the testimony of Dr. Kahl and Dr. Murthy that the combination of the structural similarities and the similar fungicidal activity against *Candida albicans* would have led a person of ordinary skill in the art to modify Brehove’s topical formulation for treating onychomycosis with tavaborole as described in Austin. Ex. 1009 ¶¶ 32–40,

Ex. 1011 ¶¶ 153–156. Likewise, while we acknowledge Patent Owner’s argument that small structural differences can cause different biological actions and activities (PO Resp. 12 (citing Ex. 2034 ¶ 90; Ex. 2033, 143:25–144:8, 149:9–11), 42 (citing Ex. 2034 ¶ 90)), we determine that a person of ordinary skill in the art would have been less concerned with the possibility of differences in biological function given that the boron compounds described in Austin and Brehove have similar fungicidal activity against *Candida albicans*.

Patent Owner further 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 low molecular weight, which would increase the likelihood of penetrating the nail barrier. PO Resp. 44–46. Patent Owner argues that “Petitioner’s argument represents a gross oversimplification of the many factors that govern whether a given compound will achieve effective penetration through the nail.” *Id.* at 44. In particular, Patent Owner argues that Petitioner’s focus on molecular weight “ignores other factors that make a given compound more or less likely to penetrate the nail,” including keratin binding and the vehicle being used to deliver the compound. *Id.* at 44–45 (citing Ex. 2036 ¶¶ 21–29). Because neither Austin nor Brehove disclose nail penetration data, or data regarding the tendency of the compounds to bind with keratin, Patent Owner contends that a person of ordinary skill in the art would not have identified tavaborole as a possible transungual candidate. *Id.* at 45–46. Additionally, Patent Owner argues that a person of ordinary skill in the art 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 46.

We determine, based on the entirety of the evidence, 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 Daltons, and the parties agree the compounds in Brehove that were effective at treating onychomycosis have molecular weights in the range of 260-290 Daltons. Ex. 1011 ¶¶ 149–150; 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. 1009 ¶¶ 157–158; 1070 ¶¶ 59–67. Dr. Murthy cites various references that demonstrate that molecular size is inversely related to penetration into the nail plate. *See, e.g.*, Ex. 1070 ¶ 63 (quoting Ex. 1032, 9); Ex. 1070 ¶ 64 (citing Ex. 1091, 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 ’657 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. 1090 ¶ 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 contends that a person of ordinary skill in the art would not have had a reasonable expectation of success in combining Austin and Brehove because “the overwhelming evidence is that boron-containing compounds were thought unsuitable for pharmaceuticals (other than end-stage cancer) because of serious toxicity concerns encountered in several different contexts.” PO Resp. 47. Patent Owner contends that Austin “does nothing to change the conventional wisdom in 2005 concerning boron’s toxicity” because it does not discuss toxicity, or otherwise indicate that the described compounds would be safe for therapeutic use. *Id.* According to Patent Owner, Austin “is consistent with the conventional wisdom” because it “shows an apparent lack of selective toxicity,” and “notes that a desirable property of an industrial biocide is a ‘wider spectrum of activity.’” *Id.* at 47–48 (quoting Ex. 1002, 1:7). Patent Owner further contends that Brehove omits “highly relevant safety warnings” and “notes that ‘the safety and non-toxicity of organo-boron compounds has been questioned.’” *Id.* at 48 (quoting Ex. 1003 ¶ 13).

Based upon review of the complete record, we determine that toxicity concerns would not have deterred a person of ordinary skill in the art from combining Austin and Brehove as proposed by Petitioner. Groziak’s⁵ 2001 review article contradicts Patent Owner’s contentions regarding the “conventional wisdom in 2005” regarding boron’s toxicity when it states

⁵ Michael P. Groziak, *Boron Therapeutics on the Horizon*, 8 AM. J. THERAPEUTICS 321–28 (2001) (Ex. 1031).

that “[b]oronic acids are fairly common and easily prepared synthetic organic compounds,” and that no commercially available boronic acid compound has been found to be “unusually toxic” to date. Ex. 1031, 322. Groziak also states that “boron-based agents [are] clearly visible on the therapeutic horizon.” *Id.* at Abstract. Patent Owner criticizes Petitioner for failing “to report Groziak’s observations that ‘[n]o pharmaceutical based on boron has yet made it to market’; and that one reason boron has not been used is because it often forms complexes that are ‘highly toxic to both bacteria and mammalian cells.’” PO Resp. 15 (quoting Ex. 1031, Abstract, 321). 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. 1031, 321. The reason those boron-containing natural products are poor models is 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.

We also credit 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 Grassberger⁶

⁶ Grassberger et al., *Preparation and Antibacterial Activities of New 1,2,3-Diazaborine Derivatives and Analogues*, 27 J. Med. Chem. 947–953 (1984).

(Ex. 2009), (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. 1069 ¶¶ 12–23. We also note that some of the inventors of the '657 patent published a review article in 2009 (“Baker”), citing mostly pre-2005 prior art, which concluded that “boron is not an inherently toxic element.” Ex. 1082,⁷ 1; Ex. 1069 ¶¶ 27–30. And, like Dr. Kahl, the inventors also 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 be used clinically because of the “inherent toxicity of boron-containing compounds.”

Ex. 1082, 3.

Moreover, boron’s allegedly “promiscuous” behavior would 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. Therefore, we credit Dr. Murthy’s testimony that broad-spectrum activity would be preferred over limited-spectrum antifungals to treat the various potential causes of onychomycosis. Ex. 1070 ¶ 49. Accordingly, we determine that a person of ordinary skill in the art in

⁷ Baker et al., *Therapeutic Potential of Boron-Containing Compounds*, 1 FUTURE MED. CHEM. 1275–88 (2009). The cited page numbers in Exhibit 1082 refer to the numbers added by Petitioner at the bottom of each page.

2005 would have understood that boron-containing compounds generally were not considered inherently toxic such that they would be excluded from consideration for topical therapeutic purposes.

Patent Owner further argues that Freeman⁸ undermines Petitioner's argument that boron-containing compounds share similar functional features. PO Resp. 49–51. Patent Owner argues that Freeman “demonstrates that PBAs [phenylboronic acids] are hardly effective, if at all, in inhibiting or killing microorganisms, even at dosage concentrations hundreds if not thousands of times higher than the highest concentrations that would be acceptable in pharmaceuticals.” *Id.* at 50 (citing Ex. 2035 ¶¶ 131–134). Patent Owner also argues that Freeman “predicts toxicity of PBA that is not selective to the target microorganism or host.” *Id.* (citing Ex. 2034 ¶ 99). According to Patent Owner, “based on Petitioner's theory of functionality,” a person of ordinary skill in the art would have expected that Brehove's dioxaborinanes would be “ineffective for pharmaceutical antifungal purposes” and “highly toxic to animals.” *Id.* at 50–51. We disagree.

Brehove explicitly teaches a dioxaborinane that is effective for treating onychomycosis. As explained above, prior art in an obviousness analysis may be relied upon for all that it reasonably would have suggested to a person of ordinary skill in the art. *Merck*, 874 F.2d at 807. Moreover, Petitioner's theory is based on the combination of structural similarity and functional similarity (in that both are active against *Candida albicans*). We determine, therefore, that a person of ordinary skill in the art would not have

⁸ Freeman, WO 03/009689 A1, published Feb. 6, 2003 (Ex. 1024).

expected Brehove's dioxaborinanes to be unsafe and ineffective for therapeutic antifungal use based on the disclosures in Freeman.

With respect to claims 18 and 19, in which the microorganism causing the infection is a dermatophyte (claim 18), or is selected from *Tinea unguium*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes* (claim 19), Patent Owner argues that a person of ordinary skill in the art would not have combined Austin and Brehove to arrive at these claims "because they provide no guidance about treating dermatophyte infections, including onychomycosis, which is overwhelmingly caused by dermatophytes." PO Resp. 51. Specifically, Patent Owner argues that a person of ordinary skill in the art "would not have sought to develop a pharmaceutical formulation for treating dermatophyte infections by starting with a reference" like Austin "that has no teaching concerning dermatophytes." *Id.* at 52 (citing Ex. 2035 ¶ 95; Ex. 2049, 641; Ex. 2040, 301; Ex. 2032, 116:22–118:9). According to Patent Owner, even if a person of ordinary skill in the art were motivated to try an Austin compound to treat an infection caused by a dermatophyte, that person "could not have predicted activity against dermatophytes based on activity against a yeast such as *C. albicans*." *Id.* (citing Ex. 2035 ¶ 127).

We disagree with Patent Owner's arguments. Although dermatophytes cause about 90% of onychomycosis cases, the parties agree that onychomycosis can be caused by a yeast, such as *Candida albicans*. Ex. 1011 ¶ 63; 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.” *Id.* ¶ 35 (emphasis added); see also *id.* ¶¶ 108–114. Brehove contradicts Dr. Ghannoum’s testimony, as it describes a treatment for onychomycosis with “powerful potency against *Candida albicans*.” Ex. 1003 ¶ 18. Moreover, as Dr. Murthy notes, Brehove recognizes that onychomycosis is “typically caused by the organisms *Candida albicans*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, or *Epidermophyton floccusum*.” Ex. 1070 ¶ 51 (quoting Ex. 1003 ¶ 5).

As discussed in the Decision to Institute, Claims 18 and 19 are composition claims, not method claims. Dec. on Inst. at 18. On this record, Patent Owner has not explained sufficiently how its composition claims for treating infections caused by dermatophytes, *Tinea unguium*, *Trichophyton rubrum* and *Trichophyton mentagrophytes* differ from a composition for treating onychomycosis caused by *Candida albicans*. Specifically, Patent Owner does not provide sufficient and credible evidence of record to demonstrate that a tavaborole composition formed following the teachings of Austin and Brehove to treat *Candida albicans* would not likewise be suitable for use against dermatophytes, such as *Trichophyton rubrum*.

At oral hearing, in response to questions regarding differences between compositions suitable for use in treating *Candida albicans* and compositions that are suitable for use in treating dermatophytes, counsel for Patent Owner stated that the differences can be seen in Figures 2A and 2B of the ’657 patent. Tr. 68:1–17. On this record, however, Patent Owner does not explain sufficiently how the figures demonstrate a meaningful difference in the compositions. For example, Figure 2A shows that for a RPMI cell culture medium, C10 (tavaborole) had an MIC against *C. albicans* ATC

90028 of 1 µg/ml and an MIC against *C. albicans* F56 of .5 µg/ml. Ex. 1001, Fig. 2A. Similarly, for *T. rubrum* F296, tavaborole had an MIC of 1 µg/ml for a culture medium of RPMI and MOPS and 2 µg/ml for a medium of RPMI, MOPS and 5% keratin powder. *Id.* To the extent the recited examples in Figure 2A are meaningful, Figure 2A demonstrates that the MIC was the same or lower for the tested tavaborole compositions against *C. albicans* as compared to *T. rubrum*.

Additionally, Brehove is not limited to treating onychomycosis caused by *Candida albicans*, but instead describes its invention as curing or preventing the spread of nail infections, such as onychomycosis, caused by bacteria, fungi, or other pathogens by treating with a boron-containing compound. Ex. 1003 ¶¶ 1, 17–18. As set forth above, we credit the testimony of Dr. Kahl and Dr. Murthy that the combination of the structural similarities and the similar fungicidal activity against *Candida albicans* would have led a person of ordinary skill in the art to modify Brehove's topical formulation for treating onychomycosis with tavaborole as described in Austin. Ex. 1009 ¶¶ 32–40; Ex. 1011 ¶¶ 153–156. Because Brehove describes treating onychomycosis caused by a number of different yeast and fungi, we find that person of ordinary skill in the art would have expected that Austin's tavaborole would share similar functional features with the compounds in Brehove that effectively treat onychomycosis caused by microorganisms other than *Candida albicans*, and thus would have had a reasonable expectation of success in combining Austin and Brehove to effectively treat infections as recited in claims 18 and 19.

Accordingly, after considering Petitioner's and Patent Owner's positions, as well as the evidence of record, we determine that Petitioner has

shown, by a preponderance of the evidence, that a person of ordinary skill in the art would have had a reason to combine the teachings of Austin and Breck to arrive at the claimed subject matter, and would have had a reasonable expectation of success in doing so.

c. Whether Austin and Brehove Disclose Every
Limitation of the Challenged Claims

Patent Owner contends that the combination of Austin and Brehove does not disclose every limitation of challenged claims. PO Resp. 36–37. Specifically, Patent Owner contends that “[n]either reference discloses a tavaborole-based pharmaceutical formulation that ‘is for topical administration to an animal suffering from an infection by a microorganism,’ as required by every claim of the ’657 Patent.” *Id.* at 36. Patent Owner contends that Austin does not disclose in vivo experiments or that the described compounds can be administered to an animal, and that Brehove “does not disclose the administration of tavaborole.” *Id.* at 36–37. Patent Owner’s argument is based on what each reference teaches separately, and not on the teachings of the combined references. The test for obviousness, however, is whether the combinations of references, taken as a whole, would have suggested the patentees’ invention to a person of ordinary skill in the art. *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”); *In re Keller*, 642 F.2d 413, 425 (CCPA 1981). Patent Owner’s argument is not persuasive because it does not address the combination proposed by Petitioner.

Petitioner has presented sufficient evidence showing that the combination of Austin and Brehove teaches each limitation of claims 1–5,

10–16, and 18–24. Pet. 22–32. For instance, with respect to claim 1, Petitioner relies upon Austin’s teaching that tavaborole is a compound that is effective in inhibiting *Candida albicans* and Brehove’s teaching that topical formulations, such as lacquers, are effective in treating *Candida albicans*. Ex. 1002, 37 (Table 9); Ex. 1003 ¶¶ 18 and 30–38.

4. Austin, Brehove, and Chaudhuri: Claim 6

Claim 6 depends from claim 1, and additionally requires that the pharmaceutical composition of claim 1 comprise propylene glycol and ethanol in a ratio of about 1:4 and about 1:10 weight per volume of tavaborole. Petitioner asserts that the combination of Austin and Brehove discloses all of the limitations of claim 1, relying on the explanation set forth respect to Petitioner’s challenge of claim 1. Pet. 38. Petitioner further asserts that Austin describes organic solvents, such as ethanol and propylene glycol in combination with a biocide, with preferably 10 to 20% by weight concentration of biocide. *Id.* Petitioner relies upon Chaudhuri for its teaching that an effective nail treatment formulation for onychomycosis would employ a 1:4 ratio of propylene glycol to ethanol and 1:10 weight per volume antifungal. *Id.* at 40. Petitioner contends that a person of ordinary skill in the art “would have had a reason to combine the disclosures in *Austin*, *Brehove* and *Chaudhuri* for all the reasons discussed” with respect to the combination of Austin and Brehove, and because Chaudhuri “describes topical formulations for effectively delivering antifungal compounds (e.g., butenafine) of higher molecular weight (e.g., 317.47 Daltons) than 5-fluoro benzoxaborole (151.93 Daltons) through the nail barrier to treat onychomycosis.” *Id.* (citing Ex. 1011 ¶ 194, 197, 198; Ex. 1040, 1).

Patent Owner argues that a person of ordinary skill in the art “would have recognized structural dissimilarities of” the butenafine compounds described in Chaudhuri, Austin’s benzoxaboroles, and Brehove’s dioxaborinanes “that would preclude a finding of a reason to combine.” PO Resp. 56 (citing Ex. 2034 ¶¶ 178–181, 191–194). Patent Owner further contends that Petitioner’s argument that Chaudhuri’s description of topical formulations that deliver higher molecular weight compounds than tavaborole “[s]hows Petitioner’s use of hindsight,” because “Petitioner elsewhere contends that low molecular weight is key to nail penetration.” *Id.* at 56–57.

We are not persuaded by Patent Owner’s arguments. As Dr. Murthy notes, the ’657 patent recognizes that “formulating pharmaceutical compositions was well known in the art of cosmetics and topical pharmaceuticals.” Ex. 1011 ¶ 195; *see also* Ex. 1001, 188:49–51 (“The preparation of these formulations is well known in the art and is found in references such as *Remington: The Science and Practice of Pharmacy*, *supra*.”). Dr. Murthy further testifies that

the ’657 Patent does not provide any guidance regarding why the particular claimed formulations were chosen, but instead states that the formulation were “well known in the art.” (Ex. 1001, col. 11:27–35; col. 163:34–43; col. 173:7–9; col. 188:29–51). The ’657 Patent did not attribute any importance or unexpected results to the claimed quantities of excipients or active agents, nor were the claimed quantities added or otherwise limited to avoid the prior art. The ’657 Patent identifies the purpose of a “pharmaceutically acceptable carrier” as “any formulation or carrier medium that provides the appropriate delivery of an effective amount of a[n] active agent . . . does not interfere with the effectiveness of the biological activity of the active agent, and that is sufficiently non-toxic to the host or patient.” (*Id.* at col.

11:21–27). The prior art discloses a variety of topical formulations that combine different amounts of various pharmaceutically acceptable carriers and active agents to effectively treat onychomycosis.

Ex. 1011 ¶ 124. We also credit Dr. Murthy’s testimony that “[f]ormulating compositions involves nothing more than routine experimentation based on well-known protocols,” particularly in light of the fact that the ’657 patent “does not describe any new or unexpected results attributable to the claimed pharmaceutical formulation of claim 6, nor was the claim formulation added to avoid prior art during prosecution.” *Id.* ¶ 195.

With respect to Patent Owner’s argument regarding the structural dissimilarities between Brehove’s dioxaborinanes, Austin’s benzoxaboroles, and Chaudhuri’s butenafine compounds, as set forth above with respect to the combination of Austin and Brehove, we credit the testimony of Dr. Kahl and Dr. Murthy that the combination of the structural similarities and the similar fungicidal activity against *Candida albicans* would have led a person of ordinary skill in the art to modify Brehove’s topical formulation for treating onychomycosis with tavaborole as described in Austin. Ex. 1009 ¶¶ 32–40; Ex. 1011 ¶¶ 153–156. We also credit Dr. Murthy’s testimony that a person of ordinary skill in the art would be further motivated to combine Chaudhuri with Austin and Brehove because Chaudhuri, like Brehove, teaches a “formulation proven capable of delivering antifungal through the nail barrier for treatment of onychomycosis.” *Id.* ¶ 196.

As explained above with respect to the combination of Austin and Brehove, we also credit 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. Ex. 1009 ¶¶ 157–158; Ex. 1070

¶¶ 59–67. Dr. Murthy’s testimony is consistent with the specification of the provisional application to which the ’657 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. 1090 ¶ 6. Therefore, we are persuaded by Dr. Murthy’s testimony that a person having ordinary skill in the art “would be motivated to substitute the higher molecular weight compound disclosed in the *Chaudhuri* formulation with the smaller 5-fluoro benzoxaborole disclosed by *Austin* to arrive at a pharmaceutical formulation to topically treat onychomycosis in a human,” and “would expect that the smaller 5-fluoro benzoxaborole would more effectively penetrate the nail barrier following topical administration because *Chaudhuri*’s compound has a substantially higher molecular weight.” Ex. 1011 ¶¶ 199–200; Ex. 1070 ¶ 99.

5. Austin, Brehove, and Samour: Claim 7

Claim 7 depends from claim 1, and additionally requires that the pharmaceutical composition of claim 1 comprises about 70% ethanol, about 20% poly(vinyl methyl ether-alt-maleic acid monobutyl ester) and about 10% tavaborole. Petitioner cites Austin for its description of organic solvents, such as ethanol and propylene glycol in combination with a biocide, with preferably 10 to 20% by weight concentration of biocide. Pet. 40–41. Petitioner relies upon Brehove for its teaching that onychomycosis treatments can be formulated with evaporating solvents, such as alcohols. *Id.* at 41. Petitioner cites Samour for teaching one skilled in the art that an effective nail treatment formulation for onychomycosis can be formulated

using 20 to 40% film-forming polymer such as Gantrez ES-425, a solvent such as ethanol in an amount of about 71% and an antifungal agent in an amount of from 1 to 10% of the composition. *Id.* at 41–44. Petitioner contends that a person of ordinary skill in the art “would have had a reason to combine the disclosures in *Austin*, *Brehove* and *Samour* for all the reasons discussed” with respect to the combination of *Austin* and *Brehove*, and because *Samour* describes topical lacquer formulations with improved physical properties and improved diffusion characteristics for active antifungals that have a higher molecular weight than tavaborole for treating onychomycosis in humans. *Id.* at 44 (citing Ex. 1011 ¶¶ 211, 213, 214).

Patent Owner counters that *Samour* focuses on formulations that contain little or no water that rely on “a specific class of penetration enhancers” to enhance penetration of active ingredients into skin and nail tissues. PO Resp. 57. Patent Owner argues that “*Samour*’s teaching of the importance of penetration enhancers undercuts Petitioner’s insistence that low molecular weight of the active ingredient is the sole basis for reasonably expecting successful nail penetration.” *Id.* (citing Ex. 2036 ¶ 66; Ex. 1005, 22:21–23:10).

We disagree with Patent Owner. For the same reasons set forth above with respect to claim 6, we credit Dr. Murthy’s testimony that “[f]ormulating pharmaceutical compositions involves nothing more than routine experimentation based on well-known protocols,” and the ’657 patent does not “describe any unexpected results attributable to the claimed pharmaceutical formulation of claim 7.” Ex. 1011 ¶¶ 211–212. We also credit Dr. Murthy’s testimony, for the reasons set forth above with respect to the combinations of *Austin* and *Brehove*, and *Austin*, *Brehove*, and

Chaudhuri, that “lower molecular weight compounds are more effective at crossing the nail plate following topical administration” and, therefore, because the topical formulations described in Samour “effectively delivered compounds of higher molecular weight” than tavaborole through the nail barrier, a person of ordinary skill in the art would be motivated to substitute tavaborole for the higher molecular weight compound in Samour to arrive at the pharmaceutical formulation recited in claim 7, and would have a reasonable expectation of success in doing so. *Id.* ¶¶ 213–216; Ex. 1070 ¶ 101.

Moreover, Dr. Murthy notes that the ’657 patent states that “topical pharmaceutical compositions may also comprise suitable nail enhancers,” and the provisional application to which the ’657 patent claims priority states that “the presence of penetration enhancing agents in the formulation are likely to increase penetration of the active agent when compared to similar formulations containing no penetration enhancing agent.” Ex. 1070 ¶ 98 (citing Ex. 1001, 171:34–37; Ex. 1090 ¶ 22). Samour states that “the reason for the enhanced transungual diffusion” in the described formulations “has not yet been fully elucidated,” while hypothesizing that the skin penetration enhancing agents function as solubilizing agents for the antifungal agent. Ex. 1005, 5:55–65. Dr. Murthy also correctly notes that “neither the specification nor the claims of the ’657 Patent excludes additional excipients and ingredients” such as penetration enhancers. Ex. 1070 ¶ 104. We therefore also credit Dr. Murthy’s testimony that “the fact that” Samour “disclose[s] additional excipients or additives does not render the disclosed formulations incompatible with the claims of the ’657 patent.” *Id.*

6. Austin, Brehove, Friedman, and Atlas: Claim 8

Claim 8 depends from claim 1, and additionally requires that the pharmaceutical composition comprises about 56% ethanol; about 14% water; about 15% poly(2-hydroxyethyl methacrylate); about 5% dibutyl sebacate and about 10% of tavaborole. Petitioner relies on Austin's description of tavaborole and Brehove's description of the topical application of boron-based compounds to treat onychomycosis, as set forth with respect to claim 1 above. Pet. 47. Petitioner relies on Friedman's description of "a [s]ustained release' nail varnish for delivery of antifungal agents to fingernails or toenails for treating fungal infections caused by '*Trichophyton rubrum*, *Trichophyton mentagrophytes* . . . [and] *Candida albicans*' to effectively treat onychomycosis" that comprises less than about 7.5% (w/w) methacrylic polymers, about 0.1% to about 2% w/w plasticizers such as dibutyl sebacate, about 60 to about 90% (w/w) ethanol, and about less than 5% (w/w) water. *Id.* at 48 (citing Ex. 1006, Abstract, 1:28–30, 3:32–59, 5:27–29, 9:3–15, 5:51–58, 62–24, 6:1–9, 8:56–61; Ex. 1011 ¶¶ 109–112, 223–226). Petitioner relies on Atlas's teaching "that hydrogels may be used for controlled drug delivery and that poly(2-hydroxyethyl methacrylate) (i.e., P-HEMA) was 'the most widely used hydrogel.'" *Id.* at 49 (citing Ex. 1007, Abstract; Ex. 1011 ¶¶ 113, 228; Ex. 1036, 4). Petitioner also relies on Atlas's statement that the "biocompatibility of hydrogels is attributed to their ability to simulate natural tissue due to their high water content," and that hydrogels exhibit "high swelling" properties. *Id.* (quoting Ex. 1007, 1:14–16, 2:48–50; citing Ex. 1011 ¶ 228).

According to Petitioner, a person of ordinary skill in the art “would have had a reason to combine the disclosures in *Austin*, *Brehove*, *Friedman* and *Atlas* for all the reasons discussed above for *Austin* and *Brehove*,” and because it “was known in the art before February 16, 2005” that “‘high-swelling polymers’ were ‘preferred’ for pharmaceutical lacquer formulations,” “[o]ne would have had reason to substitute P-HEMA for the methacrylic polymers of *Friedman*.” Pet. 50. Petitioner also contends that person having ordinary skill in the art “would have had further reason to combine *Friedman* because like *Brehove*, *Friedman* discloses treating or inhibiting onychomycosis by administering a topical sustained release nail varnish to the nail of a human.” *Id.* (citing Ex. 1011 ¶¶ 223, 231, 233). Petitioner further contends that *Friedman* provides delivery of compounds with higher molecular weight than tavaborole, and a person of ordinary skill would have reasonably expected that a formulation that successfully delivered antifungal agents having higher molecular weights than tavaborole would likely be effective to delivery tavaborole to treat onychomycosis. *Id.* at 51 (citing Ex. 1011 ¶¶ 229, 235–237).

Patent Owner responds that the structural differences between the compounds of *Austin*, *Brehove*, *Friedman* and *Atlas* would leave a person of ordinary skill in the art with no reason to combine them. PO Resp. 58 (citing Ex. 2034 ¶¶ 178–181, 232–233). Patent Owner also argues that Petitioner does not explain the contradiction between *Friedman*’s hydrophobic methacrylic polymers and *Atlas*’s hydrophilic hydrogels. *Id.* at 58–59.

For the same reasons set forth above with respect to claim 6, we credit Dr. Murthy’s testimony that “formulating pharmaceutical compositions was

well known in the art of cosmetics and topical pharmaceuticals (*see* Ex. 1001, col. 11:21–35), and a number of non-toxic, pharmaceutically acceptable solvents were known, including water and ethanol (*see id.* at col. 163:34–43),” and “[f]ormulating pharmaceutical compositions involves nothing more than routine experimentation based on well-known protocols.” Ex. 1011 ¶ 230. Also, for the same reasons set forth above with respect to claims 1, 6, and 7, we credit Dr. Murthy’s testimony that a person of ordinary skill in the art would have been motivated to combine Austin, Brehove, and Friedman because “[t]he topical formulations described by *Friedman* effectively delivered compounds of higher molecular weight than” tavaborole “through the nail barrier” (Ex. 1011 ¶ 234), and “would have had a high expectation for success in substituting” tavaborole “in the *Friedman* formulation to effectively treat onychomycosis” (*id.* ¶ 237).

We also are persuaded by Dr. Murthy’s testimony that “high swelling polymers” were preferred for use in pharmaceutical lacquer formulations (such as the one disclosed in *Friedman*), and that Atlas teaches that “P-HEMA was a well-known hydrogel capable of ‘diffusion controlled delivery’ of active ingredients to skin and nails, and hydrogels were known to have ‘high water content’ and ‘high swelling . . . properties.’” Ex. 1011 ¶ 232 (citing Ex. 1030, 242, 245; Ex. 1007, Abstract, 1:14–16, 2:45–50, 58–61). We also credit Dr. Murthy’s testimony that, “[w]hile *Friedman* disclosed an effective ‘sustained release’ nail varnish composition for effective topical treatment of onychomycosis,” a person of ordinary skill in the art “would have had a high likelihood of improving the *Friedman* composition by substituting the disclosed methacrylic polymer for another

methacrylic polymer, i.e., P-HEMA, which was a well-known, high-swelling polymer.” *Id.* ¶ 236.

7. Austin, Brehove, Friedman, and Samour: Claim 9

Claim 9 depends from claim 1 and requires that the pharmaceutical composition comprises about 55% ethanol; about 15% ethyl acetate; about 15% poly(vinyl acetate); about 5% dibutyl sebacate; and about 10% tavaborole. Petitioner relies on Samour’s description of a topical formulation for treatment of onychomycosis with about 55% ethanol, about 15% ethyl acetate, about 15% poly(vinyl acetate), and about 10% antifungal. Pet. 55 (citing Ex. 1011 ¶¶ 108, 248). Petitioner relies on Friedman’s “‘sustained release’ nail varnish for delivery of antifungal agents to treat infections of the nail, such as onychomycosis” that includes “plasticizers, such as dibutyl sebacate” in the varnish solution at a concentration of about 0.1% to about 2% (w/w). *Id.* at 55–56 (citing Ex. 1006, Abstract, 1:28–30, 5:51–51; Ex. 1011 ¶¶ 227, 249, 250). Petitioner contends that, in addition to the reasons to combine the disclosures of Austin and Brehove, a person of ordinary skill in the art “would have had reason to modify the sustained release characteristics of the *Samour* formulation by substituting dibutyl sebacate as a plasticizer” as described in Friedman. *Id.* at 56–57 (citing Ex. 1011 ¶¶ 101, 111, 251–253, 255–257, 259). Petitioner also argues that a person of ordinary skill in the art “would have reasonably expected that an improved lacquer formulation for topical delivery of antifungal agents having higher molecular weights than” tavaborole would also effectively deliver tavaborole to treat onychomycosis. *Id.* at 57 (citing Ex. 1011 ¶¶ 254, 258; Ex. 1005, Table 1; Ex. 1006, 13:1–38; Exs. 1041–1043).

Patent Owner responds that Friedman does not disclose a boron-containing compound, Samour emphasizes the use of penetration enhancers, and Friedman says nothing about penetration enhancers. PO Resp. 59. According to Patent Owner, “[t]he Petition does not attempt to explain how a [person of ordinary skill in the art] would have combined *Samour* and *Friedman* to arrive at a pharmaceutical formulation for topical application of tavaborole with any expectation of success.” *Id.* (citing Ex. 2036 ¶¶ 73–75). These arguments are based on what each reference teaches separately, and not on the teachings of all of the combined references (i.e., Austin, Brehove, Samour, and Friedman). The test for obviousness, however, is whether the combination of references, taken as a whole, would have suggested the patentees’ invention to a person of ordinary skill in the art. *Merck*, 800 F.2d at 1097 (stating the prior art “must be read, not in isolation, but for what it fairly teaches in combination with the prior art as whole”); *Keller*, 642 F.2d at 425. Patent Owner’s arguments are not persuasive because they do not address the combination of Austin, Brehove, Samour, and Friedman as proposed by Petitioner.

Patent Owner further argues that none of Austin, Brehove, Samour or Friedman discloses data indicating the compounds disclosed therein would have similar functional activity to each other. PO Resp. 59. For the reasons set forth above with respect to substantially the same argument made regarding the combination of Austin and Brehove, we find that a person of ordinary skill in the art nevertheless would have had reason to use Austin’s tavaborole in Brehove’s formulation for topical treatment of nail infections such as onychomycosis, and would have looked to Samour and Friedman, which also disclose topical treatments of nail infections such as

onychomycosis, to further improve the effectiveness of the formulation. See Ex. 1011 ¶¶ 253–256. We also credit Dr. Murthy’s testimony that a person of ordinary skill in the art would have had a high expectation of success that substituting low-molecular-weight tavaborole into topical formulations that deliver higher-molecular-weight molecules would effectively treat onychomycosis, for the reasons already set forth above. *Id.* ¶ 258.

Further, for the same reasons set forth above with respect to claim 6, we credit Dr. Murthy’s testimony that “formulating pharmaceutical compositions was well known in the art of cosmetics and topical pharmaceuticals (see Ex. 1001, col. 11:21–35), and a number of non-toxic, pharmaceutically acceptable solvents were known, including water and ethanol (see *id.* at col. 163:34–43),” and “[f]ormulating pharmaceutical compositions involves nothing more than routine experimentation based on well-known protocols.” Ex. 1011 ¶ 252. We also credit Dr. Murthy’s testimony that “[f]ormulating pharmaceutical compositions involves nothing more than routine experimentation based on well-known protocols,” and that the ’657 patent does not “describe any unexpected results attributable to the claimed pharmaceutical formulation of claim 9.” *Id.*

8. Austin, Brehove, and Shapiro: Claim 17

Claim 17 depends from claim 14, which depends from claim 1. Claim 17 requires the fungus or yeast be selected from *Trichophyton concentricum*, *Trichophyton violaceum*, *Trichophyton schoenleinii*, *Trichophyton verrucosum*, *Trichophyton soudanense*, *Microsporum gypseum*, *Microsporum equinum*, *Candida guilliermondii*, *Malassezia globosa*, *Malassezia obtuse*, *Malassezia restricta*, *Malassezia slooffiae* and *Aspergillus flavus*.

Petitioner relies on Austin's for its teaching that tavaborole "is an effective antifungal agent against each of the five (5) fungi tested including *Candida albicans* (CA) and on Brehove's description of "a formulation of 10 wt% active agent in mineral oil for treating onychomycosis that is effective against *Candida albicans*." Pet. 59 (citing Ex. 1002, 36–37, Table 9; Ex. 1003 ¶ 32, Table 1; Ex. 1011 ¶¶ 263–265). Petitioner relies on Shapiro's description of "antifungal compounds for treatment of a number of infections of the skin, hair and nails, including *Tinea unguium* (onychomycosis), "caused by one or more of the following genera of fungi: *Trichophyton rubrum* . . . *Trichophyton mentagrophytes* . . . *Trichophyton verrucosum* . . . [and] *Microsporum gypseum*." *Id.* (citing Ex. 1008, 2:3–14; Ex. 1011 ¶¶ 115, 266). In addition to the reasons described above with respect to the combination of Austin and Brehove, Petitioner argues that a person of ordinary skill in the art would have understood from Shapiro that antifungal compounds exhibit cross-activity against a different number of fungi linked to onychomycosis and fungi linked to other fungal infections of the skin, hair and nails, such as *Trichophyton verrucosum* and *Microsporum gypseum*. *Id.* at 60 (citing Ex. 1011 ¶ 272). Patent Owner responds that a person of ordinary skill in the art "would have immediately grasped the structural differences, precluding a reason to combine, between Austin's tavaborole, Brehove's dioxaborinanes, and Shapiro's griseofulvin analogs." PO Resp. 60 (citing Ex. 2034 ¶¶ 271–273).

Claim 17, like claims 18 and 19 discussed above, is a composition claim, not a method claim. Patent Owner has not explained sufficiently how its composition claim for treating infections caused by the fungi and yeast enumerated in claim 17 differs from a composition for treating

onychomycosis caused by *Candida albicans*. Further, Petitioner has established on this record that one of ordinary skill in the art, knowing that a composition such as the one that results from the combination of Austin and Brehove would be effective to treat onychomycosis when it is caused by *Candida albicans*, would likewise have reason to combine Austin and Brehove with a reasonable expectation of success to form a composition that treats onychomycosis caused by dermatophytes or other yeast or fungi. Specifically, Brehove is not limited to treating onychomycosis caused by *Candida albicans*, but instead describes its invention as curing or preventing the spread of nail infections, such as onychomycosis, caused by bacteria, fungi, or other pathogens by treating with a boron-containing compound. Ex. 1003 ¶¶ 1, 17–18. As set forth above, we credit the testimony of Dr. Kahl and Dr. Murthy that the combination of the structural similarities and the similar fungicidal activity against *Candida albicans* would have led a person of ordinary skill in the art to modify Brehove’s topical formulation for treating onychomycosis with tavaborole as described in Austin. Ex. 1009 ¶¶ 32–40; Ex. 1011 ¶¶ 153–156. Because Brehove describes treating onychomycosis caused by a number of different yeast and fungi, we find that person of ordinary skill in the art would have expected that Austin’s tavaborole would share similar functional features with the compounds in Brehove that effectively treat onychomycosis caused by microorganisms other than *Candida albicans*, and thus would have had a reasonable expectation of success in combining Austin and Brehove to effectively treat infections as recited in claim 17.

Moreover, we credit Dr. Murthy’s testimony that “it was known to one of skill in the art that antifungal drugs showed cross-activity between

fungi linked to onychomycosis and fungi linked to other fungal infections of the skin, hair and nails, such as *Trichophyton verrucosum* and *Microsporum gypseum*, as shown by *Shapiro*.” Ex. 1011 ¶ 272. Accordingly, we hold that a person of ordinary skill in the art “would have been motivated to apply a topical formulation known to be effective against onychomycosis, as taught by *Austin* in view of *Brehove*, to an infection caused by other fungi, such as *Trichophyton verrucosum* or *Microsporum gypseum*, as taught by *Shapiro*,” and would have had a reasonable likelihood that it would effectively treat infections caused by those other fungi. *Id.* ¶¶ 271–272.

D. Secondary Considerations of Non-obviousness

As part of our obviousness analysis, we consider the evidence and arguments submitted by Patent Owner regarding secondary considerations of non-obviousness. *See Graham*, 383 U.S. 17–18 (secondary considerations include commercial success, long-felt but unsolved needs, failure of others, and unexpected results). Here, Patent Owner raises arguments related to unexpected results, long-felt need, and industry praise. PO Resp. 60–64.⁹

1. Unexpected Results

Patent Owner, based on a post-filing publication, contends 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 ¶ 165, which cites Ex. 2113 at 163). Relying on Dr. Ghannoum’s testimony,

⁹ At oral argument, counsel for Patent Owner noted that the claims that cover the approved product are claims 1, 2, 4–6, 10, 12–16, and 18–24. Tr. 47:22–48:2.

Patent Owner contends “that this is not only unexpected, it is remarkable for any antifungal, let alone an antifungal that contains boron.” *Id.* (citing Ex. 2035 ¶¶ 164–165). According to Patent Owner, “[t]hese unexpected results are the hallmarks of non-obviousness.” *Id.*

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 or their practical significance. 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 ¶ 165. Dr. Ghannoum, however, does not direct our attention to any credible evidence to support this proposition. For example, although Dr. Ghannoum cites Alley et al.¹⁰ (Ex. 2113) for its teaching of tavaborole selectivity, Alley et al. 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.”

¹⁰ Alley et al., *Recent Progress on the Topical Therapy of Onychomycosis*, 16 EXPERT OPIN. INVESTIG. DRUGS 157–67 (2007) (Ex. 2113).

Kao Corp. v. Unilever United States, Inc., 441 F.3d 963, 970 (Fed. Cir. 2006) (quoting *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991)). Here, however, Patent Owner has not explained 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 find that the evidence presented as to unexpected results does not overcome the evidence of obviousness presented by Petitioner.

2. Long-Felt but Unmet Need

Patent Owner contends that “there has been a need for a safe and effective topical treatment for as long as there has been onychomycosis.” PO Resp. 61. Patent Owner contends that, although oral formulations to treat onychomycosis were available in 2005, they “tended to be toxic” and “also tended to adversely interact with other medications.” *Id.* According to Patent Owner, “[b]ecause of the shortcomings of oral treatments, there was a long-felt need for a topical treatment.” *Id.* at 62. Patent Owner also notes that, in 2005, PENLAC (ciclopirox) was the only FDA-approved topical treatment for onychomycosis, but it “is barely more effective than placebo, perhaps because it does not penetrate the nail plate very well.” *Id.*

Petitioner contends that Patent Owner did not satisfy any alleged long-felt need. Reply 23–24, 26. Petitioner states that “Kerydin® was neither the first topical drug approved by the FDA nor the most effective at treating onychomycosis.” *Id.* at 23–24. Petitioner contends that PENLAC “received FDA approval in 2004 and has similar activity to tavaborole (Kerydin®), and efinaconazole (Jublia®) received FDA approval one month (6/6/14) before Kerydin® (7/7/14) and is twice as effective.” *Id.* at 24. According to Petitioner, “[a]ny differences in effectiveness between Kerydin® and

Penlac® is merely one of degree, not kind, and is not probative of non-obviousness.” *Id.*

“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).

Although Patent Owner contends Kerydin met the long-felt need for a safe and effective topical treatment for onychomycosis, Patent Owner does not provide evidence to support this contention. Patent Owner criticizes Penlac for being barely more effective than the placebo, but does not quantify any increased effectiveness of Kerydin over Penlac. Indeed, Petitioner notes that a 2016 article suggests that Kerydin (tavaborole) has similar activity 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. 2062,¹¹ 6. We recognize that the studies reported in Table 3 were not conducted using standardized protocols and that the authors stated “each 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 these 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.

Accordingly, we find that the evidence presented does not amount to a sufficient showing that Patent Owner’s Kerydin met any alleged long felt need as to a safe and effective topical onychomycosis treatment, especially in view of the similar efficacy rates as compared to Penlac (Ciclopirox), which was approved by the FDA in 2004. Pet. Reply 23–24.

¹¹ The cited page numbers in Exhibit 2062 refer to the numbers added by Patent Owner at the bottom of each page.

3. Industry Praise

Patent Owner contends that Kerydin has “received industry praise directly related to the ’657 Patent’s innovative pharmaceutical formulations suitable to treat onychomycosis safely and effectively.” PO Resp. 63 (citing Ex. 2037 ¶¶ 78–88). In support of its contention, Patent Owner identifies several articles, including one from 2015 that “praised tavaborole’s efficacy and ‘excellent safety profile,’ and described the emergence of tavaborole as ‘exciting’” (*id.* (quoting Ex. 2060,¹² 4–5)), an article from 2016 that praises “tavaborole’s nail penetration for being ‘40-fold greater than that of ciclopirox after 14 days of treatment’” (*id.* at 63–64 (quoting Ex. 2061,¹³ 3)), and another article from 2016 that “reported that the introduction of tavaborole, along with the topical efinaconazole, ‘expanded the roster of medications available to more effectively manage onychomycosis in a wide range of patients’” (*id.* at 64 (quoting Ex. 2062, 6)). *See also* Ex. 2037 ¶¶ 81–88 (Dr. Maibach’s testimony identifying and describing similar articles).

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). The evidence presented represents praise for another alternative therapy for topical treatment of onychomycosis. Specifically, the

¹² The cited page numbers in Exhibit 2060 refer to the numbers added by Patent Owner at the bottom of each page.

¹³ The cited page numbers in Exhibit 2061 refer to the numbers added by Patent Owner at the bottom of each page.

statements cited by Patent Owner indicate that tavaborole offers “an important *alternative*” (Ex. 2060, 5) and “expand[s] the roster of medications available” (Ex. 2062, 4). Additionally, although one article praises the 40-fold greater nail penetration of tavaborole over ciclopirox, the evidence of record shows that both treatments have similar cure rates. Ex. 2062, 6.

Evidence that the industry praised a claimed product which embodies the challenged claims weighs against an assertion that the claims would have been obvious. The “praise” for Patent Owner’s product, however, represents recognition of yet another approved treatment regime and, on this record, does not establish that one of ordinary skill in the art would not have had reason to form, and an expectation of success to form, the claimed invention given the teachings of the prior art.

Based on the record presented, we hold that the evidence of secondary considerations, does not overcome the evidence of obviousness presented by Petitioner.

E. 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 1–24 are unpatentable as obvious over the cited references.

III. CONCLUSION

For the foregoing reasons, we determine that Petitioner has demonstrated by a preponderance of the evidence that claims 1–5, 10–16, and 18–24 of the '657 patent are unpatentable as obvious over the combined teachings of Austin and Brehove; claim 6 is unpatentable as obvious over the combined teachings of Austin, Brehove, and Chaudhuri; claim 7 is unpatentable as obvious over the combined teachings of Austin, Brehove, and Samour; claim 8 is unpatentable as obvious over the combined teachings of Austin, Brehove, Friedman, and Atlas; claim 9 is unpatentable as obvious over the combined teachings of Austin, Brehove, Friedman, and Samour; and claim 17 is obvious over the combined teachings of Austin, Brehove, and Shapiro.

IV. PATENT OWNER'S MOTION TO EXCLUDE

Patent Owner moves to exclude Exhibits 1033, 1034, 1048, 1049, 1077, 1093–1095, 1097, 1100, and 1101. Paper 57. Because our Decision does not rely on any of the challenged exhibits, we dismiss Patent Owner's Motion to Exclude as moot.

V. ORDER

In consideration of the foregoing, it is:

ORDERED that claims 1–24 of the '657 patent are held unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude (Paper 57) is *dismissed*; and

FURTHER ORDERED that, because this is a Final Written Decision, 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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PETITIONER:

Jeffrey Blake
Kathleen Ott
MERCHANT & GOULD, P.C.
jblake@merchantgould.com
kott@merchantgould.com

PATENT OWNER:

Andrea Reister
Enrique Longton
COVINGTON & BURLINGTON LLP
areister@cov.com
elongton@cov.com