

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENE COMPANY PTY LTD,
Petitioner,

v.

THE TRUSTEES OF COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK,

Patent Owner.

Case No. IPR2024-00313
U.S. Patent No. RE47,045

PATENT OWNER'S SUR-REPLY

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I. Introduction

The Petition started from a flawed and now abandoned premise that the 1,5-shift was “likely rate limiting.” Its new “any step” theory fails as Petitioner cannot show the 1,5-shift was even “slow enough” relative to other steps in the A2E pathway to expect a KIE. Further undermining any motivation or expectation, Petitioner does not meaningfully contest that *Roth*—its sole evidence of a KIE—is limited to a reaction mechanism fundamentally different from A2E formation.

Nor does Petitioner justify its misplaced reliance on *Mata* for motivation to administer vitamin A when—as admitted by Petitioner’s declarants—*Mata* teaches away from the “diametrically opposed” use of vitamin A supplementation. And Petitioner nowhere addresses that by 2007 the art as whole likewise taught away from therapeutic vitamin A supplementation, especially for Stargardt’s disease. Having abandoned its unqualified general practice ophthalmologist (Dr. Calman), Petitioner provided no rebuttal to Dr. Del Priore’s expert opinions that vitamin A supplementation was to be avoided.

Ample objective indicia further expose Petitioner’s hindsight analysis. The invention has demonstrated unexpected efficacy without the visual side effects that Petitioner acknowledges plagued prior approaches. Petitioner’s quibbles with the clinical trials and nexus rest solely on attorney argument that fails to consider the novel combination as a whole.

The Board should reject all challenged grounds.

II. Petitioner Fails to Show an Expectation of a KIE

Dr. Guengerich disavowed—and Petitioner does not rehabilitate—his core premise that “the (1,5)-sigmatropic rearrangement *is likely to be the rate-limiting step*....”¹ EX1002 ¶178; Reply, 5-6; POR, 26.² Nor does Petitioner dispute that slowing of end product formation cannot be expected from a mere *intrinsic* isotope effect (slowing an individual bond breaking step) not involved in the rate limiting step. EX1047, 3; EX2084, 3 (“[T]he kinetic isotope effect obtains *only when* a bond to a hydrogen atom is broken (or formed) *in the rate controlling step* of a reaction.”); EX2052 ¶¶130-137; POR, 26-35. Petitioner further fails to meaningfully contest that *Roth* was limited to an intrinsic isotope effect in a reaction mechanism having no relevance to A2E formation. The Petition thus fails on its own terms and in view of the art.

Changing tact, Petitioner advances new opinions from Dr. Guengerich claiming “C-20 deuteration was likely to inhibit the 1,5-sigmatropic rearrangement and thereby favorably inhibit A2E formation, *regardless of*’ the rates of subsequent steps. EX1080 ¶19. The Board should reject this “entirely new

¹ All *bold italic* emphasis is added.

² Paper 31 (“Reply”); Paper 23 (“POR”).

rationale” and “requir[e] [Petitioner] to prove the facts that it alleged.” 2019 Trial Practice Guide (“TPG”), 74-75; *Arctic Cat Inc. v. Polaris Industries, Inc.*, 795 Fed. Appx. 827, 833 (Fed. Cir. 2019). Petitioner’s unsupported “slow enough” rationale is further irreconcilable with the absence of motivation or reasonable expectation of success (“REOS”) due to “the presence of other possible rate-limiting steps....” *Neptune Generics LLC v. Auspex Pharms., Inc.*, IPR2015-01313, Paper 25, 15 (PTAB Dec. 9, 2015); POR, 28-29. Lacking any prior art support, Petitioner cannot hide behind “no guarantee, just a reasonable expectation.” Reply, 12.

A. Petitioner Fails to Show the 1,5 Shift was “Slow Enough”

Petitioner’s claim that “PO’s entire argument hinges on arguing the 1,5-shift must be the slowest step to be rate limiting” mischaracterizes the POR. Reply, 6. As explained, the Petition failed to establish that the 1,5 shift was rate-limiting in any sense (POR, 37 n.9) and the Reply likewise fails to show that it was “slow enough” (Reply, 5-6).

Petitioner cannot establish that the 1,5 step would have been expected to be rate-limiting in any sense where the prior art provided no information about the relative rates of any steps in this reaction—except to teach *others* as slow. EX2052 ¶¶81-111; 183-188; EX2103, 59:11-25, 64:15-65:14. This is dispositive since, as Dr. Guengerich testified, C-H bond breaking must at least “contribute significantly” to the overall rate in order to be “partially rate limiting.” EX2009,

44:8-18. If other steps are significantly slower, the C-H bond breaking will not be at least “partially rate limiting” and “there will be no effect” from deuterium substitution. EX2009, 188:1-189:10; EX1080 ¶¶43, 12 (“deuterium substitution to slow C-H bond breakage... *where the C-H bond breakage was at least partially rate-limiting*”); EX1002 ¶178; EX2022, 49-50 (“if the second step is the slower one, the rate of production” is *not* controlled by the first step). Petitioner’s obfuscations—running from the testimony of its own declarant—should be rejected.

First, Petitioner’s speculation that there *could* be multiple rate-limiting steps does not show that there was, much less that the 1,5-shift was among them. Reply, 6 (“multiple steps *can* be rate-limiting”); EX1080 ¶21 (contending not “necessarily” one rate-limiting step); EX2209, 52:18-53:8; *Duke Univ. v. BioMarin Pharm. Inc.*, 685 F. App’x 967, (Fed. Cir. 2017) 977-979 (“the evidence of record does not establish the conditions precedent”). Nor can Petitioner shift its burden to Patent Owner to prove that some other step was rate limiting. EX1080 ¶21 (“no good reason to assume”), ¶41 (“no reason C20 deuteration would be unable” to slow), ¶43 (“none of the literature... describe A2PE conversion to A2E as being slower... than the [1,5]-shift”); *Fanduel, Inc. v. Interactive Games LLC*, 966 F.3d 1334, 1341 (Fed. Cir. 2020). Indeed, Dr. Guengerich’s complaint that nothing showed the “A2PE conversion to A2E as being slower... than the [1,5]-shift”

(EX1080 ¶43) underscores this evidentiary gap—if the art didn’t show A2PE conversion was slower, it equally failed to show the 1,5-shift was slow enough to be rate-limiting. EX2052 ¶¶183-188.

Second, Petitioner’s analogy to visual cycle inhibitors to argue “[r]educing the 1,5-shift reduces reactant concentration for subsequent reactions” (Reply, 6-7) simply *assumes* that the 1,5 step “contribute[s] significantly” and that other steps are not significantly slower. EX2009, 44:8-18,188:1-189:10. Moreover, reducing ATR starting material (by inhibiting e.g., RPE65) fundamentally differs from slowing the rate of a step in the A2E pathway. *Compare* EX1080 ¶21 with EX2209, 51:9-52:12, 54:4-9 (“those are two different things”); EX2052 ¶119; EX2066, 2. Whether changes to intermediates affect product formation rate depends on both the concentrations and reaction rates (EX2052 ¶¶184-185; EX2022, 49-50)—neither of which, as Dr. Guengerich concedes, were known. EX2103, 68:15-69:4 (concentration), 59:9-25, 66:20-67:13 (“I don’t think anybody would know the specific rate”), 72:15-25.

Third, Petitioner argues that “forced conditions” used by *Roth* and *Mowery/Verdegem* show the 1,5 shift was slow. Reply, 6-8; EX1080 ¶20. But this fails to connect the abstract notion of “slow” with slow *relative* to other steps in the A2E reaction. POR, 40; EX2052 ¶¶130-137, 259-262; EX2103, 70:4-72:5 (can’t conclude 1,5 step is slow from overall slow lipofuscin formation).

Fourth, Petitioner’s contention that the 1,5 shift was a “desirable” or “best” target due to its upstream position (Reply, 7-10) does not demonstrate it was “slow enough” or “partially rate limiting” to affect A2E formation. Mere identification of what is “desired fails to illuminate” what would have been reasonably expected. *In re Stepan Co.*, 868 F.3d 1342, 1347 (Fed. Cir. 2017). It is also pure hindsight. The art unambiguously taught that the “first and best point for intervention” (Reply, 10) was reducing production of ATR, as *all* prior art attempts had done. EX2003, 14 (“Several approaches have been tested or proposed to slow accumulation of A2E. *All*... ultimately limit the formation of [ATR]”); §III.C.

Fifth, Petitioner claims *Mata* “presented information sufficient to reasonably expect the 1,5-shift was a rate-limiting step” but fails to identify any disclosure in *Mata* addressing its rate in the A2E pathway. Reply, 7-8. Instead, Petitioner relies on conclusory testimony from Dr. Guengerich that parrots the Reply nearly *verbatim* and is contradicted by his admissions that nothing in *Mata* or *Fishkin* show the step is slow. EX1080 ¶¶25-27, 38-40; EX 2103, 121:6-16, 123:8-20.

Finally, Petitioner cannot invoke inherency (“natural result”) as a substitute for motivation to use deuterated vitamin A to slow A2E formation or REOS of the claimed “effective amount.” Reply, 8-9, 15-17; §V.A; *Honeywell Intl. Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1354 (Fed. Cir. 2017) (“The Board committed legal error by improperly relying on inherency to find

obviousness and in its analysis of motivation to combine the references.”).

Petitioner’s *Hospira, Inc. v. Fresenius Kabi USA, LLC* is inapposite, as it did not address motivation, “was not a method claim,” and involved a claimed property (shelf life) that “was necessarily present in the prior art” and thus not entitled to patentable weight. 946 F.3d 1322, 1331-1332 (Fed. Cir. 2020). Here, both the preamble and “effective amount” limitations have patentable weight,³ and rather than being “necessarily in the prior art,” no prior art “suggest[ed] that deuteration of carbon-20 would slow the formation of A2E” or treat MD, or taught using it for this purpose. EX2103, 119:9-17; POR, 12-14, 33-34.

B. Roth’s KIE is Irrelevant to the A2E Reaction

Petitioner continues to rely on *Roth* (Reply, 11-13) as its sole basis for expecting a “large KIE” but fails to address that (1) *Roth* studied a different reaction mechanism than the A2E pathway and (2) its single-step reaction provides no indication of the 1,5 step’s relative rate in the multistep A2E pathway (POR, 40-44, 48).

Petitioner’s argument that *Mowery/Verdegem* used “non-physiological conditions” (Reply, 11-12) misses the point. These studies show the A2E pathway involves base-catalyzed tautomerization, not *Roth*’s sigmatropic rearrangement.

³ Petitioner does not dispute that all three preambles are limiting (POR, 12-14).

EX2078, 1; EX2077, 3. As KIE depends on reaction mechanism⁴ and no prior art reports a KIE for base-catalyzed tautomerization, Petitioner has no basis to predict *any* KIE in the A2E pathway. EX2052 ¶¶268-281. That all studies used artificial conditions is irrelevant. Petitioner does not dispute *Mowery/Verdegem*'s solution-phase studies of retinoids are more analogous to the A2E pathway than *Roth*'s gas-phase study of a structurally distinct compound. *See* EX2078, 1; EX2209, 127:16-128:7 (ATR is a α,β -unsaturated aldehyde with β -methyl substitution); EX1011, 2, 5-6 (citing *Verdegem* Ref. 35).

Petitioner's reliance on *Doering* (Reply, 7-8), which studied the same sigmatropic rearrangement as *Roth*, does nothing to cure Petitioner's reliance on the incorrect reaction mechanism. Moreover, rather than "corroborate" *Roth* (Reply, 8), *Doering* concludes that *Roth*'s methods were unreliable and that its own KIE was "highly problematic." EX2025, 1, 4-5.

Even if the 1,5 shift was understood to be a sigmatropic rearrangement, Petitioner fails to justify relying on *Roth*'s pentadiene study to predict a KIE for a different compound *in vivo*. EX2052 ¶¶295-299. Contrary to Petitioner's assertions (Reply, 12), Dr. Guengerich acknowledged transition state symmetry is "generally

⁴ EX2103, 128:20-129:20, 130:19-131:24.

not predictable” and depends on the structure of the reactants and products.

EX2209, 14:5-22, 16:2-20.

Petitioner’s new arguments—that base catalyzed tautomerizations were *also* “‘prone’ to a strong KIE,” and that a POSA would have been motivated to “measur[e] the KIE”—are prejudicial and should not be considered as PO has no opportunity for rebuttal evidence. *Compare* Reply, 12-13, *with* Pet., 41-42; TPG at 74-75. Moreover, Petitioner’s argument that base-catalyzed reactions were prone to KIEs rests solely on Dr. Guengerich’s unsupported one-sentence assertion, which carries no weight and fails to even purport to address relative rates within the A2E reaction. *Compare* EX1002 ¶¶116-122, 178, 262 *with* EX1080 ¶57; *see Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9, 15 (PTAB Aug. 24, 2022); 37 C.F.R. § 42.65(a). And, even if the prior art did invite “measuring”—which Petitioner has not shown—this provides neither motivation nor REOS for the claimed methods. *Bayer Schering Pharma AG v. Barr Laboratories, Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009) (“[A]n invention is not obvious to try where vague prior art does not guide an inventor toward a particular solution.”).

Petitioner’s KIE arguments were flawed from the start and cannot be salvaged at this late stage with misdirection and unsupported testimony.

III. Petitioner Fails to Establish Obviousness

A. Petitioner Fails to Resolve its Conflicting Motivation

Petitioner does not address the fundamental conflict between its motivation based on *Mata* and its proposed combination to administer vitamin A. POR, 16-17. *Mata* is relied upon for suggesting “pharmacological *inhibition*” of A2E (Pet., 2, 41-42) and teaches that the undesirable A2E formation depends “on the *availability* of [ATR]” generated from vitamin A. EX1010, 6. This is the opposite of administering *more* vitamin A (deuterated or not), which could only be expected to promote ATR and A2E. EX2192 ¶¶180-183.

Nor does Petitioner address the testimony from its declarants confirming this fundamental conflict. Dr. Calman testified that *Mata* “is certainly one of the bases for” recommending against vitamin A supplementation for Stargardt’s patients, explaining that “the more substrate you’re inputting into the visual cycle, potentially that’s exacerbating the buildup of ATR, which is the lipofuscin precursor.” EX2104, 14:4-16:2, 18:16-20:9; *see also id.*, 13:3-11, 20:17-21:7, 22:11-17. Similarly, Dr. Guengerich acknowledged *Ortho*’s supplementation approach is “diametrically opposed” to both *Mata*’s teaching that A2E formation depends on vitamin A availability and the *Widder* (asserted in Ground 3) strategy of reducing serum retinol levels. EX2103, 155:2-25, 172:23-177:20; EX2003, 14.

Without reconciling these opposing therapeutic strategies, Petitioner cannot establish the required motivation to combine. *Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1067 (Fed. Cir. 2020) (affirming no motivation to combine where “a POSA would be dissuaded from selecting or combining the components as claimed”).

B. Petitioner Fails to Rebut Art Teaching Away from Vitamin A

Petitioner’s assertion that “PO provides no evidence these vitamin A serum levels were associated with increased lipofuscin formation” (Reply, 5) is demonstrably false. *E.g.*, EX2113, 11 (“[I]ncreasing... vitamin A had increasingly more lipofuscin in their retinal pigment epithelium (Fig. 7). This dose-related response suggests a close relationship between dietary vitamin A and lipofuscin formation.”). Dr. Calman confirmed this relationship, acknowledging that increased vitamin A “potentially [] exacerbat[es] the buildup of ATR, which is the lipofuscin precursor.” EX2104, 14:9-22; *see* POR, 16-17; EX2192 ¶¶64-69, 109-127, 210-222; Pet., 10.

Petitioner’s argument that administering vitamin A would not risk increasing lipofuscin formation because of “highly regulated” vitamin A concentrations is similarly misleading. Reply, 3. Studies administering preformed vitamin A reported “constant elevation of the serum level.” EX2151, 4; EX1040, 6 (“Serum retinol values were significantly elevated ($P<.001$) for those receiving vitamin A”);

EX1042, 6; EX2113, 11; EX2150, 1 (“absorption... of *preformed vitamin A* occur[s] very efficiently until a pathologic condition develops”). That “[t]he *cleavage* of provitamin A carotenoids [e.g., beta-carotene] to retinal” *is regulated* only undermines Petitioner’s reliance on the AREDS beta-carotene formulations since it did not result in and does not support therapeutically administering vitamin A.⁵ EX1004 ¶¶142, 204; EX1022, 42 (AREDS study Table 9 showing increase of beta carotene but no increase in vitamin A at 1 and 5 years); EX1069, 76:1-20.

Ignoring context and the 2007 state of art, Petitioner mischaracterizes Dr. Del Priore’s testimony to argue that “vitamin A was safely administered to treat retinitis pigmentosa patients, Sorsby’s fundus patients, and even Stargardt patients” (Reply, 3 (citing EX1069)).

⁵ Petitioner’s Centrum argument fails as no evidence shows the non-prior art label (EX1065) matches the formulation AREDS patients received “containing a study ingredient,” which vitamin A was not. EX1022, 3, 10; EX1069, 15-70:10.

Moreover, Petitioner never claims Centrum was suitable for treating AMD or reducing lipofuscin formation.

The cited testimony, however, discusses two studies from 1993 and 1995,⁶ predating recognition that vitamin A exacerbates lipofuscin formation. As Dr. Del Priore explained, “[p]eople tried a variety of things, you know, for Stargardt’s... *before it was recognized that it was actually a problem with vitamin A.*” EX1069, 123:13-124:5, 124:20-125:2 (old Stargardt’s study “did not see a beneficial effect”). Contrary to Petitioner’s reliance on these out-of-date studies to support therapeutically administering vitamin A, by 2007 the art recognized that the opposite—“reducing the level of the vitamin A cycle”—may have “beneficial consequences for Stargardt, RP, CRD, and some AMD patients” (EX2110, 5) and consensus warned “Stargardt patients should avoid a diet high in vitamin A” (EX2164, 12) and “Vitamin A should not be given to RP patients with mutations in ABCA4” (EX2158, 8). EX2192 ¶¶135-143.

Further, these outdated studies say nothing of reducing lipofuscin accumulation—the central concern by 2007 and Petitioner’s thesis—and at most reported an absence of general “toxic side effects” like “liver disease.” EX1041, 11. In fact, however, vitamin A supplementation according to *Berson* was deemed ineffective and unsafe. EX2153, 1 (“fails to [] establish a significant beneficial

⁶ EX1069, 123:2-129:22, 131:10-132:6, 164:15- 167:14 (discussing EX1040 (*Berson*); EX1041 (*Jacobson*); EX2153 (criticizing *Berson*); EX2154 (same)).

effect for vitamin A in the treatment of RP”); EX2153, 3 (“cost me much in time, money, and I believe, health”); EX2154, 2 (“high dosages of vitamin A for retinitis pigmentosa are detrimental to visual acuity”). As Dr. Del Priore explained, *Berson* “did not provide the basis for vitamin A supplementation to become standard clinical practice even for RP patients, let alone for patients with other retinal disorders.” EX2192 ¶¶107, 142-143; EX2160, 12.

C. Petitioner’s Generalizations Fail to Support Obviousness

Petitioner’s broad generalizations about the desirability of treating macular degeneration without side effects and the general existence of the KIE are not substitutes for the missing motivation or REOS. Reply, 4-5, 25 14-15. *Abbott Lab’ys*, 544 F.3d at 1352. The known side effects of available treatments and understanding of the KIE only underscores the non-obviousness of the invention. EX2052 ¶¶300-306; *Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265, 1273 (Fed. Cir. 2018) (reversing obviousness where “[d]espite the extensive study, this improvement over the then-available treatments [was] not proposed or suggested in the references”).

These arguments also fail on the facts. The art focused exclusively on reducing A2E formation by limiting ATR formation from the visual cycle—*not* on inhibiting steps within the A2E pathway itself. EX2003, 14; EX1030, 1-2; EX1035, 1; EX2209, 50:11-22, 54:16-55:4, 56:4-18. Petitioner recasts this

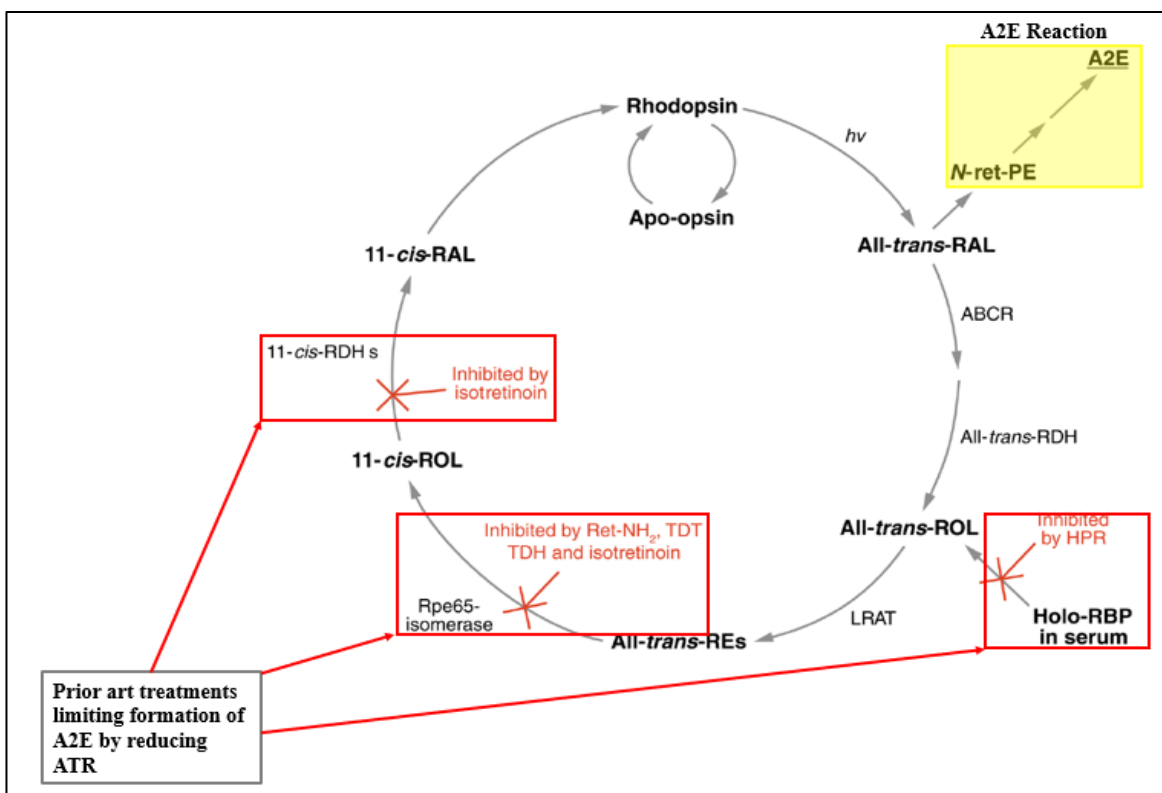
exclusive focus on reducing ATR as motivation to target the A2E pathway itself through misleading reliance on Dr. Del Priore's discussion of EX2111.⁷ As Dr. Guengerich admitted, EX2111 focused solely on reducing ATR and said nothing about directly targeting individual steps in the A2E pathway. EX2209, 63:3-65:2; *compare* EX1080 ¶29. Similarly, *Kim 2007*'s generic statement that an "[i]mproved understanding... of A2E and other RPE lipofuscin compounds could facilitate... yet other novel approaches to therapy"⁸ is a far from "an express suggestion to specifically inhibit the A2E byproduct pathway itself."⁹ Like *Mata*¹⁰, this is, at best, a broad invitation "to explore a new technology or general approach" without any guidance "to the particular form of the claimed invention or how to achieve it." *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 997 (Fed. Cir. 2009).

⁷ Reply, 5 (quoting EX1069, 203:6-14 (discussing EX2111)).

⁸ Reply, 5 (quoting EX2019, 7 and citing EX1080 ¶¶28-32, 35).

⁹ EX1080 ¶31.

¹⁰ *Mata*'s "inhibition" (EX1010, 6) also did not suggest deuterium substitution. EX2103, 192:11-25; *cf.* Reply, 10-11.



EX2003, Fig. 5 (annotated)

As for the KIE, neither Petitioner's attorney argument nor Dr. Guengerich's testimony identify any prior art showing deuterium used to create novel therapeutic interventions in non-enzymatic processes, as here. Reply, 14-15; EX1080 ¶¶47-50. Instead Petitioner relies on Dr. Guengerich's declaration from another case,¹¹ which only confirms Dr. Prestwich's testimony that deuterium was at best used to improve drug metabolic properties. Compare EX2008 ¶¶49-50, 54-56 (Guengerich

¹¹ Reply, 15 (citing EX2008).

deuterium to improve enzymatic metabolism) *with* EX2052 ¶¶139-157 (Prestwich same); EX2104 56:17-57:19.

IV. Objective Indicia Reinforce Nonobviousness

Where, as here, Petitioner has not disputed that “[PO’s] asserted objective evidence is tied to a specific product and that product is the invention disclosed and claimed by the patents-in-suit,” a presumption of nexus applies.¹² *Medtronic, Inc. v. Teleflex Innovations S.a.r.l.*, 70 F.4th 1331, 1337 (Fed. Cir. 2023). The Board should further find the challenged claims nonobvious in view of PO’s objective evidence as Petitioner’s attorney argument fails to rebut this presumption or the underlying evidence. Reply, 18-25.

A. Nexus and Commensurate in Scope Were Established

Petitioner attempts to attribute PO’s objective evidence to “a prior-art feature” and the “natural[] results from C₂₀-deuteration” (Reply, 18), but errs by (1) arguing inherency where the method entails a unique combination of elements and (2) dissecting the claim “on a ‘limitation-by-limitation’ basis” rather than

¹² For example, Petitioner does not dispute that the TEASE and SAGA trials practice claims 1, 2, 4-15, 18, 19, 26, 28-30, 32-42, 45, 46, and 53; that the patent and pre-clinical studies practice the claims; or that efficacy in treating Stargardt and GA is reflective of efficacy in other MDs. POR, 51-52, 55-57; Reply, 18-25.

“consider[ing] the invention as a whole.” *Volvo Penta of the Americas, LLC v. Brunswick Corp.*, 81 F.4th 1202, 1211-12 (Fed. Cir. 2023) (citing *Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1377-1378 (Fed. Cir. 2021) (“Concluding otherwise would mean that nexus could never exist where the claimed invention is a unique combination of known elements from the prior art.”). Here, un rebutted evidence shows that PO’s objective indicia result from the novel methods of treatment, providing “previously unknown and unexpected properties.” *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1307 (Fed. Cir. 2015) (rejecting “argument that the unexpected results do not support nonobviousness because they are merely the inherent properties”); POR, 51-57; EX2192 ¶¶264-270, 289-317. This is distinct from Petitioner’s cases (Reply, 18) where the evidence “relate[d] entirely” to prior art features. *Yita LLC v. MacNeil IP LLC*, 69 F.4th 1356, 1364 (Fed. Cir. 2023); *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008).

Unable to establish that PO’s evidence is not at least “due in part to the claimed invention,” which is all that is required, Petitioner nevertheless speculates that it could be attributable to unclaimed clinical protocol or formulation features. *Ex Parte Whirlpool Corp.*, Appeal 2013-008232, 15-16 (PTAB Oct. 30, 2013) (informative); Reply, 18-19, 22-24; But objective evidence cannot be rebutted “with argument alone—it must present evidence.” *WBIP, LLC v. Kohler Co.*, 829

F.3d 1317, 1329 (Fed. Cir. 2016). Nor can Petitioner meet its burden by complaining of inadequate discovery (Reply, 18-19) where it failed to seek authorization (37 C.F.R. § 42.51) or guidance (EX1079, 68:18-71:19) from the Board. *Arctic Cat Inc.*, 795 F. App'x at 831-832.

Petitioner also argues that “[m]ost claims are not directed to Stargardt or ABCR-linked disease” like the TEASE inclusion criteria (Reply, 18), but nowhere contests that demonstrated efficacy in these conditions represents efficacy across other macular degenerations. POR, 51-52; EX2192 ¶¶103, 274-275, 278-280, 294. Similarly, Petitioner’s speculation about formulation effects ignores evidence of efficacy across multiple formulations and administration routes. EX2006, 2-3; EX2061, 2; EX2181, 1-2; *Cadence Pharms. Inc. v. Exela PharmSci Inc.*, 780 F.3d 1364, 1376 (Fed. Cir. 2015) (affirming reliance on secondary considerations from related formulation where “there [was] no reason to believe that” they would not extend to claimed formulations).

Petitioner also argues that “the unmet need for an *oral* AMD treatment... is not commensurate with the challenged claims, which are not limited to an oral AMD.” Reply, 23. However, neither the long-felt need nor PO’s evidence are limited to oral AMD treatments. POR, 49-52, 55-57; see EX2192 ¶¶304-317; EX1001, 19:40-21:22; EX2006, 2-3, 7; EX2061, 7; EX2181, 1-2 (efficacy via oral

and injection administrations); EX2192 ¶¶276, 283 (other injection and oral treatments failed).

B. Petitioner Fails to Rebut Unexpected Results

Petitioner's unexpected results reply is limited to attorney argument and conclusory declarant assertions irreconcilable with record evidence. *See, e.g.*, Reply, 25 (citing EX1004 ¶¶76-79, 243; EX1080 ¶¶28-36); *Xerox Corp.*, Paper 9, at 15-16.

First, no prior art evidence supports Petitioner's assertion that reducing lipofuscin accumulation without visual cycle side effects would have been expected. §III; POR, 49-50, 55-57. Indeed, the side effects were previously unavoidable. POR, 6, 55-57; EX1069, 217:12-24.

Second, Petitioner fails to address the art relied on by Dr. Del Priore showing why rapid replacement of vitamin A was surprising. EX2192 ¶316; EX2181, 1; EX2090.

C. TEASE and SAGA Evidence Nonobviousness

The TEASE and SAGA trials demonstrated unexpected results and fulfilled the long-felt need despite failure and skepticism. POR, 55-56; EX2192 ¶¶271-299.

The evidence shows that SAGA demonstrated clinically meaningful benefits for GA, meeting the long-felt need. POR, 51-52, 56. For example, it is undisputed that treatment "was associated with slower growth of [geographic atrophy] lesions

and improved visual acuity” without visual side effects. EX2192 ¶278 (citing EX2094, 1). Neither primary endpoints (Reply, 20-22) nor FDA approval is a prerequisite for meeting a long-felt need. *Argentum Pharm. LLC v. Research Corp. Techs., Inc.*, No. IPR2016-00204, 2017 WL 1096590, at *17–18 (P.T.A.B. Mar. 22, 2017), *aff’d sub nom. Mylan Pharm. Inc. v. Research Corp. Techs., Inc.*, 914 F.3d 1366 (Fed. Cir. 2019).

Petitioner’s attorney arguments that that TEASE did not use qualified image readers (Reply, 19-23) are inaccurate and “not evidence.” *Icon Health & Fitness, Inc. v. Strava, Inc.*, 849 F.3d 1034, 1043 (Fed. Cir. 2017). The TEASE readers were qualified professionals blinded from the treatment. EX1079, 89:9-13, 91:18-21, 215:14-25. Their results were independently confirmed. EX1079, 216:1-218:9. Petitioner’s attorney inuendo provides no basis to dispute this evidence, especially when the TEASE results were vetted publicly and the FDA awarded “Breakthrough Therapy Designation”. EX2107, 1; EX2108, 1.

Petitioner criticizes the absence of peer-reviewed Phase III trials (Reply, 20), but there is no such requirement. *In re Brana*, 51 F.3d 1560, 1567-68 (Fed. Cir. 1995) (distinguishing patentability and FDA standards). Moreover, the clinical trial publications—most first or co-authored by Dr. Scholl, the CMO of Petitioner’s RPI—were peer reviewed. EX1079, 210:18-211:20, 228:20-230:2; EX2086; EX2087; EX2088; EX2089; EX2090; EX2091; EX2094. And Dr. Guengerich peer

reviewed the inventor’s foundational publications, declaring them to be “novel” and “innovative.” EX2056, 1; EX2057, 1-2.

D. Long-Felt, Unmet Need and Failure of Others Evidence Is Largely Undisputed

Petitioner agrees there were no treatments for lipofuscin-associated MD without “unnecessary” or “blindness inducing” side effects. Reply, 1, 22; POR, 49-50. Petitioner’s evidence and its RPI confirm this unmet need for treating Stargardt and dry-AMD. EX1020, 4 (“no treatments or preventive measures are currently available for patients with dry AMD”); EX1022, 2 (same); EX2190, 4 (no FDA approved treatments); *Procter & Gamble*, 566 F.3d at 998. Petitioner does not dispute that the invention avoids these “blindness-inducing” side effects. Reply, 1, 20-25.

Without addressing the many failed treatments, Petitioner turns to two recently approved GA products. Reply, 19-20, 22; POR, 50. But approved in 2023, these products say nothing of the need in 2007. EX2192 ¶277; *Procter & Gamble*, 566 F.3d at 998 (unmet need assessed “by filing date of the challenged invention”). Moreover, these products “carr[y] a substantial adverse event profile” and present

“enormous treatment burden[s]” without “detectable effect[s] in visual function at 2 years.” EX2192 ¶277; EX2104, 25:11-26:16.¹³

Petitioner also manufactures a requirement that PO had to identify a “technical obstacle” in “using deuterated-vitamin A to retard lipofuscin formulation” or a “technical barrier or oral MD therapies.” Reply, 22-23 (citing no authority). Petitioner’s no “technical barrier” assertion, however, more poignantly reflects “that the [Petition] only traverses the obstacles to this inventive enterprise with a resort to hindsight.” *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1356 (Fed. Cir. 2013). To the extent a “technical obstacle” is required, this is met by evidence that supplemental vitamin A was understood to risk increasing lipofuscin accumulation and exacerbating MD. POR, 37-39, 49-50, 55-56.

E. Skepticism/Praise Evidence Is Relevant to the Claims

Unlike the prior art failures, the claimed method has overcome skepticism and garnered praise. POR, 53-55; EX2192 ¶¶300-303. Petitioner fails to rebut this evidence. Reply, 23-25.

Petitioner’s arguments recognize and do not dispute the skepticism the invention faced related to human efficacy without dietary vitamin A restrictions.

¹³ EX2074 emphasizes deficiencies in treating dry-AMD and any alleged “optimism” does not fulfill a long-felt need. Reply, 22; EX2074, 1, 10-11.

Reply, 23-24. Overcoming this skepticism, TEASE and SAGA demonstrated efficacy without the “tight dietary control” used in mice. EX2180, 14; EX2098, 5-6; EX2099, 4.

As for praise, Petitioner does not dispute a nexus but instead wrongly asserts that Breakthrough Therapy Designation (“BTD”) merely “reflect[s] *a desire* for successful results rather than a conclusion they were already obtained.” Reply, 24. To the contrary, BTD reflects preliminary clinical evidence that *already shows* “a clear advantage over available therapy” and is probative of non-obviousness. EX2107, 1; *Ferring B.V. v. Watson Lab’ys, Inc.-Fla.*, 764 F.3d 1401, 1407 (Fed. Cir. 2014) (FDA recognition probative of non-obviousness).

Nor can Petitioner dismiss the express praise from Dr. Guengerich and his reviewers—that thought “[t]he use of a C20-D3-vitamin A is quite novel and interesting” and thought the papers were “innovative” (EX2056, 1; EX2057, 1-2)—as not “a patentability analysis” or the FDA listening sessions as mere “hopeful patient anecdotes.” Reply, 24-25; EX2149, 14-15, 19-20. Both are probative. *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1333 (Fed. Cir. 2019) (awards and customer satisfaction as evidence of praise).

V. Claim-Specific Deficiencies

A. “Effective Amount” Limitation: All Claims

Petitioner still (POR, 44-47) fails to identify any teaching in the ground references of the “effective amount” limitations. Reply, 15-16. Petitioner instead argues it “encompasses the prior art” and is inherent (“efficacy naturally results”). *Id.* However, Petitioner identifies no art teaching a therapeutic range for deuterated vitamin A or that it “would slow the formation of A2E” or treat MD. EX2103, 119:9-17; POR, 12-14, 33-34; *Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1366 (Fed. Cir. 2016) (missing limitation not supplied by “conclusory statements”). Petitioner thus fails to establish this limitation in any claim.

B. Retarding Lipofuscin Accumulation: Claims 1, 2-9, 19-23, 25-26

Petitioner does not contest that none of the ground references disclose retarding lipofuscin accumulation. POR, 58-59; Reply, 15-17, 26. Its conclusory declarant testimony cannot substitute for a missing claim limitation. *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (rejecting “unsupported and inferential theories” as substitute for disclosure of missing limitation).

C. Stargardt’s Disease and ABCA4-Gene Mutation: Claims 11–15, 18, 38-42

Petitioner fails to establish obviousness of these claims, which require, e.g., administering an “effective amount” of deuterated vitamin A to “a patient in need of treatment for Stargardt disease.” EX1001, 25:6-7; Reply, 26. Petitioner does not

dispute that, as confirmed by both clinicians, by 2007 the art unambiguously taught away from administering vitamin A supplements to Stargardt’s patients. EX2133, 2; EX2110, 5; EX2104, 13:3-14:22, 20:17-21:2; EX2192 ¶¶245-249; *see Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1360-63 (Fed. Cir. 2017). Petitioner’s failure to rebut these express teachings forecloses obviousness.

D. Ground 3 (Widder): Claims 16-17, 24, 27, 43-44, 51, and 54

Petitioner fails to articulate a viable motivation to combine *Widder*—premised on “lowering the levels of serum retinol in the body of a patient” (EX1009, 3, 16, 35-37)—with *Ortho*’s vitamin A supplementation that can increase serum retinol. EX2192 ¶¶161-168; EX2150, 1; EX2151, 4; EX1040, 6; EX1042, 6; *AstraZeneca AB v. Mylan Pharms. Inc.*, 19 F.4th 1325, 1337 (Fed. Cir. 2021) (affirming nonobviousness where “the data cut against the very goal a [POSA] would have been trying to achieve”). Petitioner neither addresses these contradictions nor offers any rebuttal to Dr. Del Priore’s corresponding testimony. EX2192 ¶¶184-192. Petitioner failed to establish a motivation to combine and thus failed to establish obviousness of any Ground 3 claim.

VI. Petitioner’s Unqualified Declarants and Concealed RPIs

A. Petitioner’s Declarants Are Unqualified and Unreliable

Petitioner defends Dr. Calman as a general practice ophthalmologist but does not dispute that, as in *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254,

1256-57 (Fed. Cir. 2007), the implicated level of skill is that of a specialist that Dr. Calman is decidedly not. Reply, 26-28; POR, 6-11. Nor does Petitioner dispute that Dr. Calman is a professional witness, having only outdated and irrelevant research experience. POR, 11.

Abandoning Dr. Calman in Reply, Petitioner instead relies on Dr. Guengerich, an enzymologist who, by his own admission, lacks any knowledge or experience in “treating any ophthalmologic disease.” EX2013, 33:1-7, 35:6-37:13. Dr. Guengerich further undermines his own credibility by providing *pages* of quotes from the Del Priore deposition¹⁴—often quoting only *the question*—on clinical ophthalmology where he has neither experience nor training and is not offering independent opinion. EX2103, 35:21-36:20; EX2209, 57:18-58:2; *Dura Auto. Sys. of Indiana, Inc. v. CTS Corp.*, 285 F.3d 609, 614 (7th Cir. 2002) (“A scientist... is not permitted to be the mouthpiece of a scientist *in a different specialty*.”). He did not read the references he second-hand quotes from the transcript (77:6-78:17, 80:12-81:2)¹⁵ and did not address Dr. Del Priore’s

¹⁴ EX1080 ¶¶29, 33-35, 75-77.

¹⁵ See also EX2209, 61:17-62:9 (EX2111), 69:13-70:8 (EX2120), 71:5-20 (EX1041), 75:17-76:14 (EX1042), 82:12-21 (EX1040).

declaration or the majority of references cited therein. EX2209, 84:20-85:10, 87:5-21; EX1080 ¶2.

As for the POSA definition, Petitioner’s attorney argument that PO’s definition “excludes its sole inventor” (Reply, 27) is disproven by the inventor’s publication list and lipofuscin-specific experiments, and ignores binding precedent that “[t]he actual inventor’s skill is not determinative.” EX1083 (at least references 1, 4, 9); EX1001, 18:45-21:22 (at least Examples 1-6); *Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 962-63 (Fed. Cir. 1986). Petitioner’s response on its “team” definition ignores the fundamental problem—which Petitioner does not dispute—that it seeks to piece together *separate* obviousness allegations from different perspectives. POR, 9.

B. Petitioner’s Concealed RPIs

Petitioner does not dispute that it violated the non-discretionary statutory requirement of 35 U.S.C. §312(a)(2) by concealing the involvement of related and commonly represented parties having a vested interest in this Petition. POR, 63-64.

VII. Conclusion

The Board should confirm the patentability of all claims.

Respectfully submitted,

Dated: February 3, 2025

/Mark J. Feldstein/

Mark J. Feldstein

Reg. No. 46,693

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I, Mark J. Feldstein, certify that **PATENT OWNER'S SUR-REPLY** contains **5,592** words, excluding those portions identified in 37 C.F.R. § 42.24(c), as measured by the word-processing system used to prepare this paper.

Dated: February 3, 2025

/Mark J. Feldstein/

Mark J. Feldstein

Reg. No. 46,693

CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **PATENT OWNER'S SUR-REPLY** was served electronically via email on February 3, 2025, in its entirety on the following:

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