

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 OPPOSITION TO
PETITIONER'S MOTION TO EXCLUDE**

I. Introduction

Petitioner's Motion to Exclude ("Mot.") misstates that certain exhibits are uncited post-institution, misrepresents that Patent Owner did not serve supplemental evidence, misinterprets the content of exhibits and supplemental evidence, and misunderstands Dr. Del Priore's testimony. As such, Patent Owner respectfully requests that the Board deny Petitioner's Motion.

II. Exhibits 2001, 2002, 2004, 2005, 2007, 2010-2013, 2018, 2020, 2021, 2024-2026, 2033, 2036, and 2037

Petitioner moves to exclude the Sessler Declaration (EX2036)¹ and Exhibits 2001, 2002, 2004, 2005, 2007, 2010-2013, 2018, 2020, 2021, 2024-2026, 2033, and 2037 under FRE 401 and 402 for having been cited only pre-institution. Mot. 1-3. Patent Owner opposes.

First, Petitioner is wrong with respect to EX2004, EX2005, EX2007, EX2018, EX2025, EX2033, EX2036. EX2025 is cited in Petitioner's Reply and Patent Owner's Sur-Reply. Reply, 7-8; Sur-Reply, 8. EX2018, EX2025, and EX2033 are cited by Petitioner's declarant in paragraphs that Petitioner relies on in its Reply. EX1080, ¶¶52-53, 62; Reply, 7-8, 11-13, 17. The Board further cited at least EX2004, EX2005, EX2007, and EX2036 in its Institution Decision. Paper 13,

¹ Patent Owner confirms that it is not relying on the declaration of Dr. Sessler.

11, 20-21, 28, 38. These exhibits are thus cited post-institution and/or relied upon in the Board's institution decision.

Second, to preserve the record, none of the exhibits should be excluded, regardless of whether they were cited in or after the institution decision. Indeed, Petitioner provides no justification for departing from the Board's routine practice of preserving the record, including uncited exhibits. *See, e.g., SK Hynix v. Netlist*, IPR2017-00561, Paper 36 at 60 (PTAB July 5, 2018) ("the better course is to have a complete record of the evidence to facilitate public access as well as appellate review"); *see also Eli Lilly v. Teva*, IPR2018-01424, Paper 78 at 168-69 (PTAB Feb. 18, 2020) ("the decision is by an administrative agency, rather than a jury, there is a diminished concern that such exhibits would be prejudicial"); *Corning Inc. v. DSM IP Assets*, IPR2013-00053, Paper 66 at 19 (PTAB May 1, 2014).

Third, allegations of prejudice and inclusion being "improper under the rules of these proceedings, including the APA" are without merit. Mot. 3 (citing *Nike, Inc. v. Adidas AG*, 955 F.3d 45, 52-53 (Fed. Cir. 2023)). This case is distinguishable from *Nike* at least because there are no amended claims at issue here. 955 F.3d at 52-53. Moreover, should the Board rely on these exhibits in its Final Written Decision, Petitioner has had knowledge that these exhibits relate to the state of the art and ample opportunity to respond to them throughout this proceeding.

Accordingly, Patent Owner asserts that these exhibits should not be excluded as they are relevant under FRE 401 and 402.

III. Hussain (EX2015)

Petitioner moves to exclude Hussain (EX2015) for lack of authenticity. Mot. 3-4. Patent Owner opposes.

By way of context, Patent Owner relies on EX2015 for the proposition that “[l]ipofuscin accumulation was understood to be accelerated in Stargardt’s disease, where its early onset affects ‘children age 6 to 12 years causing rapid severe decline in visual acuity over 12 to 24 months.’” POR, 5; *see also id.*, 49; EX2192, ¶281. This point is not materially in dispute. *E.g.*, EX1004 (“Lipofuscin accumulation in the RPE is also associated with Stargardt’s disease (STGD1) and fundus flavimaculatus (FFM), recessive forms of macular degeneration that affect children. . . .” (quoting EX1010, 7154)).

Petitioner argues that “PO did not serve supplemental evidence regarding EX2015.” Mot. 3-4. This is mistaken. On July 23, 2024, Patent Owner timely served EX2050 (Declaration of Shauna L. Wiest), which provides testimony related to the source of EX2015 (e.g., EX2048, EX2049). *See* EX2210, 8 (Patent Owner’s Updated Exhibit List July 23, 2024); EX2050, 5. Ms. Wiest’s Declaration further testifies to the authenticity of EX2015, stating that “**Exhibit 2015** is a true and correct copy of Hussain, R. M., Ciulla, T. A., Berrocal, A. M., Gregori, N. Z.,

Flynn, H. W., & Lam, B. L. (2018). *Stargardt macular dystrophy and evolving therapies*. Expert Opinion on Biological Therapy, 18(10), pages 1049–1059.” *Id.* (emphasis original). Ms. Wiest’s Declaration thus provides testimony “that an item is what it is claimed to be.” FRE, 901(b)(1). Patent Owner is filing the as-served supplemental evidence (EX2050, EX2048, EX2049, EX2210) contemporaneously with this Opposition. See Trial Practice Guide at 79; 37 C.F.R. § 42.64(b)(2).

Patent Owner has provided sufficient evidence “to support a finding that [EX2015] is what the proponent claims it is” under FRE 901, and therefore, EX2015 should not be excluded.

IV. Mowery (EX2077)

Petitioner moves to exclude Mowery as being irrelevant for lack of legibility or completeness. Mot. 4-6. Patent Owner opposes.

For context, Mowery demonstrates that the 1,5 shift in the A2E pathway takes place through a base-catalyzed tautomerization, rather than a sigmatropic rearrangement. EX2077, 1-3; POR, 41; Sur-Reply, 7-8. Petitioner attempts to exclude Mowery in its entirety for an alleged issue with Figure 5. Mot. 5. In making this argument, Petitioner ignores two aspects of Mowery (EX2077 and EX2203): 1) the chemical names are readily identified in the caption of Figure 5 and 2) the mechanism of Figure 5 is detailed in the “Discussion” section of the

exhibit. See EX2077, 3. Petitioner further discounts how the served copy of Mowery (EX2203) resolves any legibility concerns based on original EX2077.

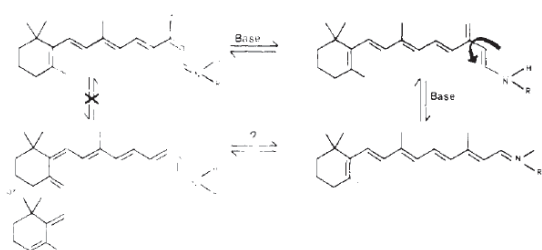


Figure 5. Proposed scheme for the thermal equilibration of 13-*cis*- and *all-trans*-retinylidene-*n*-butylamine.

EX2077, Fig. 5.

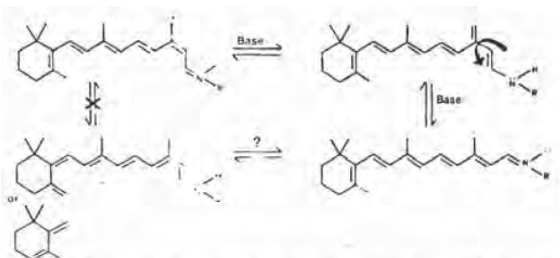


Figure 5. Proposed scheme for the thermal equilibration of 13-*cis*- and *all-trans*-retinylidene-*n*-butylamine.

EX2203, Fig. 5.

Neither version of Figure 5 prevents Petitioner, the Board, or the public from understanding the import of the figure as the information found in it is explained elsewhere in the exhibit. For example, Mowery describes that “13-*cis*-retinylidene-*n*-butylamine was shown to undergo thermodynamic equilibration with the trans isomer by general base catalysis” and that “[i]t is clear that 13-*cis*-retinylidene-*n*-butylamine easily isomerizes to the trans imine by a mechanism involving general base catalysis.” EX2077, 1, 3. Referencing Figure 5 specifically, Mowery further explains:

The simplest hypothesis would therefore consist of general-base-catalyzed thermodynamic equilibration between imines via a 13-methylene enamine intermediate (Figure 5). Such intermediates are usually not encountered in high concentrations, because C=N bonds are more stable than C=C bonds when primary amines

are the reactants,¹⁰ and because enamines of aldehydes are generally not stable.¹¹ It is noteworthy in this respect that the trans imine showed signs of decomposition at 130 min (Figure 2).

EX2077, 3. Petitioner does not challenge the context surrounding Figure 5. Patent Owner is filing the as-served supplemental evidence (EX2203) contemporaneously with this Opposition. *See* Trial Practice Guide at 79; 37 C.F.R. § 42.64(b)(2).

Contrary to Petitioner's allegations of illegibility, Dr. Prestwich was further able to fully understand Mowery's disclosure and its relevance to the issues in the case. For example, Dr. Prestwich redraws Mowery Fig. 5 as Figure 13:

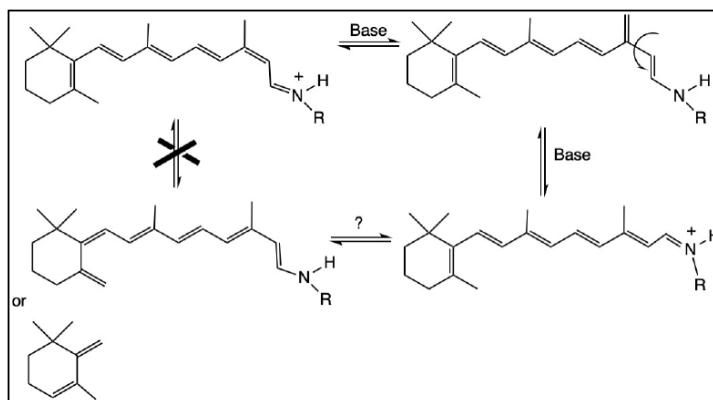


Figure 13. General base catalysis for 13-*cis*-retinylidene-*n*-butylamine. The C13 methyl group, which would be numbered C20) in *Mowery* is the same as Carbon 20 (C20) in NRPE in, e.g., *Mata 2000*, *Fishkin 2005*.
EX2077 (Mowery) at 3, Fig. 5 (redrawn).

EX2052, ¶¶ 279, 291 (explaining that the “reduced acidity at more distant positions explains the “X” across the equilibrium on the left side *Mowery* Figure 5,

indicating that deprotonation of these remote methyl hydrogens is unfavorable.

EX2077 (Mowery) at 3, Fig. 5.”).

Consequently, nothing about Mowery is undiscernible such that it would unfairly prejudice Petitioner. Accordingly, EX2077 should not be excluded.

V. Del Priore Declaration (EX2192)

Petitioner argues that paragraph 62 and “all testimony relying directly or indirectly upon” paragraph 62² in Dr. Del Priore’s Declaration should be excluded under FRE 702 because Dr. Del Priore is purportedly not an expert in enzyme kinetics. Mot. 6-7. Patent Owner opposes.

First, Petitioner has not, and has never, challenged that Dr. Del Priore qualifies as a POSA or that he lacks expertise regarding enzymes as they are relevant in the specific context of the visual cycle. Reply, 26-28. Indeed, Dr. Del Priore has more than 30 years of experience and extensive research related to the visual cycle, including a PhD thesis directed to “light induced changes in

² Patent Owner’s arguments below related to paragraph 62 also apply to Petitioner’s claims that “all testimony relying directly or indirectly upon (e.g., EX2192, ¶¶109, 175, 179, 210-11, 216, 221).” Mot. 7. Moreover, Petitioner’s arguments here are overly broad as paragraphs 109, 175, 179, 210-11, 216, 221 of EX2192 cite to “§ VI.B.” and not paragraph 62 specifically.

rhodopsin, including the transition of 11-cis to all-trans retinal, as well as changes in cyclic nucleotides (cyclic GMP) that occur after light absorption.” EX2192, ¶¶ 5-18; EX2193. Among his more than 500 publications (EX2193), Dr. Del Priore authored EX1027, “Age-Related Changes in Human RPE Cell Density and Apoptosis Proportion In Situ” which was *introduced by Petitioner* and addresses enzyme catalysis in the context of experimental methods and cellular processes. EX1027, 1, 6. And there is no dispute that Dr. Del Priore more than qualifies as an expert under either parties’ POSA definition. POR 7-8; Petition, 7; EX2192, ¶¶ 23-30; EX2193.

Second, Petitioner’s argument mischaracterizes Dr. Del Priore’s testimony. The challenged paragraph 62 is part of a summary of a POSA’s knowledge of the visual cycle, not a separate discourse on abstract enzyme kinetics. EX2192, ¶62. Indeed, the paragraph recites:

Enzymatic processing within the visual cycle begins with vitamin A as the source or “substrate” for the formation of visual cycle byproducts in the eye. In enzymatic reactions, generally more substrate leads to more product. EX2109 (Harper’s Biochemistry 2003) at 13, 15-16. Further, when the substrate concentration is increased, the output of the reaction can also increase. *Id.* Given these basic principles of enzyme reaction kinetics, it was understood to be beneficial to reduce levels of vitamin A

since increasing vitamin A levels would have been understood to have the potential to increase downstream byproducts of the visual cycle—including all-trans-retinal, which can react to form undesirable A2E and ATR-dimer lipofuscin pigments. . . [citations to EX1030, EX2110, EX2111] . . . Thus, a POSA would have understood that increasing intake of the vitamin A visual cycle substrate could be harmful for macular degeneration patients since it can increase the generation of visual cycle byproducts, thereby increasing accumulation of lipofuscin in the RPE and exacerbating macular degeneration.

EX2192, ¶62. Dr. Del Priore is thus opining on the visual cycle—fully within his expertise. And Dr. Del Priore’s statements related to “basic principles of enzyme reaction kinetics” (*id.*) do not go beyond his opinions about vitamin A’s impact on the visual cycle. Reply, 26-27. Rather, Dr. Del Priore explains that a skilled artisan would have known that increasing vitamin A levels would risk increasing lipofuscin accumulation. *Id.*

None of this is controversial, as both parties agree that 1) the visual cycle is an enzymatic process and 2) adding vitamin A to the visual cycle leads to lipofuscin accumulation. *See, e.g.,* Pet., 8-10 (“The retinoid cycle is a series of light-driven and enzyme-catalyzed reactions.”); POR, 5 (“the art focused on

inhibiting the visual cycle by reducing the levels of retinol (vitamin A) in the blood or by pharmacologically inhibiting visual cycle enzymes to lower ATR production and, in turn, decrease lipofuscin pigments”); EX2104 (Calman Deposition), 14:4-16:2 (“the more substrate you’re inputting into the visual cycle, potentially that’s exacerbating the buildup of ATR, which is the lipofuscin precursor.”).

Third, even reading paragraph 62 as a separate opinion on enzyme kinetics, Dr. Del Priore would still be qualified to opine on visual cycle enzyme kinetics. Prior to 2007, Dr. Del Priore had experience researching and publishing on matters related to the visual cycle enzymes and lipofuscin accumulation in the eye. EX2192, ¶29; EX2193, 14-22. While Dr. Del Priore modestly may not “hold [him]self out as an expert” in a broad category of enzyme kinetics, he has an MD and PhD with 30 years of relevant experience as discussed above. EX1069, 22:16-19; EX2192, ¶¶5-18, 29; EX2193. He has more than the requisite knowledge and expertise to opine on enzyme kinetics in the eye.

Finally, in the objections to the evidence filed September 30, 2024, Petitioner failed to properly object to Dr. Del Priore’s testimony, EX2192, paragraph 62. Paper 25, 8-9. Petitioner’s objection stated: “to the extent his testimony is not providing an opinion within Dr. Del Priore’s knowledge, skill, experience, training, or education that is based on sufficient facts or data and is the product of reliable principles and methods reliably applied to the facts of this case

(F.R.E. 702-703; 37 C.F.R. § 42.65).” *Id.* This objection lacked “sufficient particularity” as it did not list specific paragraphs of EX2192 that Petitioner believed to be based on opinions outside of Dr. Del Priore’s expertise. 37 C.F.R. § 42.64(b)(1). Further, this objection did not explain how Dr. Del Priore was unqualified to opine on any specific topic. Because Petitioner’s objection lacked “sufficient particularity,” Patent Owner was not “allow[ed] correction in the form of supplemental evidence.” *Id.* The Board has found that “[t]he lack of an effective objection is sufficient basis to deny a Motion to Exclude” because overly broad objections like Petitioner’s “r[u]n afoul of Rule 42.64(b)(1), leaving [Patent Owner] without any meaningful sense of the alleged evidentiary flaws in Dr. [Del Priore’s] Declaration — until [Petitioner] file[s] its Motion to Exclude.” *Hunter’s Manufacturing Company, Inc. v. Ravin Crossbows, LLC*, IPR2023-00407, Paper 53, 40-41 (citing *B/E Aerospace, Inc. v. MAG Aerospace Indus., LLC*, IPR2014-01511, Paper 104, 8 (PTAB March 18, 2016)).

Accordingly, Dr. Del Priore’s opinions on “enzyme kinetics” in the context of the visual cycle should not be excluded.

VI. Conclusion

Patent Owner respectfully requests that Petitioner’s Motion be denied.

Respectfully submitted,

Dated: March 11, 2025

/Mark J. Feldstein/

Mark J. Feldstein, Reg. No. 46,693

Counsel for Patent Owner

The Trustees of Columbia University in the
City of New York

CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing PATENT OWNER'S
OPPOSITION TO PETITIONER'S MOTION TO EXCLUDE was served
electronically via email on March 11, 2025, in its entirety on the following:

Jad A. Mills
Michael T. Rosato
Wilson, Sonsini, Goodrich & Rosati
701 Fifth Avenue, Suite 5100
Seattle, WA 98104-7036
jmills@wsgr.com
mrosato@wsgr.com

Matthew Bresnahan
Wilson, Sonsini, Goodrich & Rosati
12235 El Camino Real
San Diego, CA 82130-3002
mbresnahan@wsgr.com

Petitioner has consented to service by electronic mail.

Dated: March 11, 2025

/William Esper/
William Esper
Legal Assistant and PTAB Coordinator
Finnegan, Henderson, Farabow,
Garrett & Dunner, LLP