

Paper No. _____
Filed: April 30, 2021

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

THORNE RESEARCH, INC.,
Petitioner,

v.

TRUSTEES OF DARTMOUTH COLLEGE,
Patent Owner.

Case No. IPR2021-00268
Patent No. 8,383,086

**PETITIONER'S REPLY TO
PATENT OWNER'S PRELIMINARY RESPONSE**

TABLE OF CONTENTS

	<u>Page</u>
I. Introduction.....	1
II. Argument	1
A. The declarations of Dr. Bieganowski and Dr. Brenner amount to nothing more than uncorroborated “naked assertions”	3
i. Incomplete understanding	4
ii. Unreliable and interested testimony	5
B. The relied-upon portions of the references are not the “inventive work” of Dr. Brenner.....	8

I. INTRODUCTION

During a conference call held on March 26, 2021, Petitioner Thorne was authorized to file this Reply limited to addressing Patent Owner's "by another" arguments presented in its Preliminary Response. EX1024, 23:11-24:24.

II. ARGUMENT

Five grounds of unpatentability were applied to claim 2 of the '086 patent based on three references: Stamler (EX1006) (Grounds 1 and 2), Bieganowski (EX1008) (Grounds 3 and 4), and Brenner (EX1007) (Ground 5). Pet., 34-35. For the latter two references, the Petition explained how Bieganowski (hereinafter "the *Cell* article") and Brenner (hereinafter, "the '337 PCT") qualified as prior art under §§102(b) and 102(a)/(e), respectively, based on the earliest filing date to which the '086 patent was entitled.¹ See Pet., 6-7, 30 n.6, 32 n.7. In its Preliminary Response, Patent Owner asserted that the references did not qualify as prior art because "Dr. Brenner is the sole inventor of the relied-upon subject matter in the *Cell* article and '337 PCT Publication."² POPR, 11 (capitalization omitted). In support, Patent Owner submitted two scant declarations from Dr. Bieganowski and Dr. Brenner,

¹ Stamler is §102(b) prior art to claim 2 regardless of filing date. Pet., 29 n.5.

² Patent Owner's arguments that the *Cell* article does not qualify as prior art are premised on the assumption that the '086 patent can claim an earlier filing date.

the two authors named on the *Cell* article and the two inventors named on the '337 PCT. See EX2002, EX2003.

At institution stage, Petitioner need only show a “reasonable likelihood” that the claims are unpatentable; that is, a reasonable likelihood that the relied-upon references are “by another,” which is met here as the *Cell* article and the '337 PCT have different inventive entities than the challenged '086 patent. The burden of production thus shifts to Patent Owner to demonstrate that the references are not “by another.” *Nelson Prods., Inc. v. Bal Seal Eng'g, Inc.*, IPR2014-00572, Paper 55, 8 (Sept. 24, 2014). While, in some cases, a declaration may suffice to show that a cited portion of a reference naming a different inventive entity is the inventor’s own work, a declaration that provides no more than a “naked assertion” that the portions of the reference now relied upon as prior art were not “by another,” concerns long-past events, and provides no “context, explanation, or evidence to lend credence to” the declarant’s assertion is insufficient to meet that burden. *EmeraChem Holdings, LLC v. Volkswagen Grp. of Am., Inc.*, 859 F.3d 1341, 1345-47 (Fed. Cir. 2017) (noting concerns regarding “uncorroborated testimony from an alleged inventor...particularly arise when uncorroborated testimony comes from an interested person recalling long-past events”). Here, both declarations contain nothing but bare-bone assertions that provide no meaningful context or corroborating evidence to show how the cited portions relating to work that

occurred eighteen years ago are Dr. Brenner's "inventive work" alone. The lack of corroboration is significant here. Dr. Bieganowski's cross-examination revealed an incomplete understanding of his testimony including what it means to be an inventor, a reliance on discussions with counsel based on memory alone, and a common interest with Dr. Brenner. Moreover, Dr. Bieganowski's account of the work actually performed shows that what Dr. Brenner is trying to claim as his *inventive* work is actually work that had already been part of the public domain. Thus, the conclusory declarations of Dr. Bieganowski and Dr. Brenner fail to meet Patent Owner's burden of production as to the prior art not being "by another" and thus a reasonable likelihood exists that the relevant portions of the '337 PCT and the *Cell* article qualify as prior art. Institution should be granted.

A. The declarations of Dr. Bieganowski and Dr. Brenner amount to nothing more than uncorroborated "naked assertions"

The conclusory and deficient nature of Dr. Bieganowski's and Dr. Brenner's declarations is facially apparent. Of the eight paragraphs provided in Dr. Bieganowski's declaration, two vaguely allude to a supposed "research project relating to nicotinamide riboside." EX2003, ¶¶6-7. While the paragraphs broadly mention Dr. Bieganowski's work in performing "the experiments and assays" that were used to "identify[] yeast and human genes that have nicotinamide riboside kinase activity," (*id.*, ¶6), no discussion is provided concerning Dr. Bieganowski's or Dr. Brenner's work as it relates to the subject matter for which the references

were actually relied upon—*i.e.*, teaching a composition containing isolated NR. Instead, Dr. Bieganowski simply states “[a]ny portions of the ’337 PCT or the *Cell* article that could be said to disclose the inventions of the ’086 patent are the inventive work of Dr. Brenner alone.” *Id.*, ¶7. Dr. Brenner’s declaration presents similar statements that lack any real context of his “inventive work” as it relates to the subject matter of claim 2 and the relevant portions of the references. *See* EX2002, ¶¶13 (stating only he “was responsible for all aspects of the NR research project related to therapeutic uses and compositions of nicotinamide riboside”), 15-19 (listing citations of EX1007 and EX1008 and merely stating “the relied-upon portions...represent my invention alone”). The cross-examination of Dr. Bieganowski, however, shows that the context missing from these declarations is significant and the naked assertions provided by Dr. Bieganowski and Dr. Brenner should be entitled to little or no weight.

i. Incomplete understanding

In declaring that “[a]ny portions of the ’337 PCT or the *Cell* article that could be said to disclose the inventions of the ’086 patent are the inventive work of Dr. Brenner alone” (EX2003, ¶7), Dr. Bieganowski failed to apprise himself of the factual and legal basis to make this statement. For example, in preparing his declaration, Dr. Bieganowski readily admitted that he did not review the ’337 PCT or the *Cell* article (EX1025, 12:3-20), and thus, did not actually assess the extent to

which the relied-upon portions of the references represent his contribution alone, Dr. Brenner's contribution alone, or both. *E.g., Duncan Parking Techs., Inc. v. IPS Grp., Inc.*, 914 F.3d 1347, 1358 (Fed. Cir. 2019) (noting analysis requires a determination of "what portions of the reference patent were relied on as prior art," and an evaluation of "the degree to which those portions were conceived 'by another'"); *Watson Labs., Inc. v. United Therapeutics, Corp.*, IPR2017-01621, Paper 33, 11-12 (instituting trial where declarants "d[id] not testify as to their contribution to [the prior-art reference] or otherwise describe the work they did in connection with the 17 patient study"). Dr. Bieganowski also acknowledged that he had no understanding of the term "inventor" nor was he provided such an understanding by counsel. EX1025, 26:24-27:10; *see also id.*, 32:17-33:15 (Dr. Bieganowski acknowledging he was also not informed that claim 1 of the '086 patent was not subject matter invented by Dr. Brenner). Thus, Dr. Bieganowski lacked the fundamental understanding that would have been necessary to conclude that the "portions of the '337 PCT or the *Cell* article that could be said to disclose the inventions of the '086 patent" was "the inventive work of Dr. Brenner alone."

ii. Unreliable and interested testimony

The time period between Dr. Bieganowski's and Dr. Brenner's declarations and the work described in the references, along with the interest of the declarants, illustrate the insufficiency of the declarations alone in establishing that the relevant

portions of the '337 PCT and the *Cell* article are not “by another.” See *EmeraChem*, 859 F.3d at 1346-47 (“[C]orroborating an inventor’s testimony is a well-established principle in our case law” and “[a] number of factors may guide the corroboration assessment, including the time period between the event and trial and the interest of the corroborating witness in the subject matter in suit”).

For example, the events at issue occurred nearly eighteen years ago. In addition to failing to review the underlying references being asserted as prior art, Dr. Bieganowski also failed to review “any other lab notebooks or other documents from [his] time at Dr. Brenner’s laboratory,” instead admitting that his statements were “based solely on [his] memory...of what [he] remember[ed] after 18 years” during discussions with counsel in preparation of this IPR. EX1025, 9:14-23, 11:22-12:2, 12:21-24; *see also* EX2002, ¶9 (Dr. Brenner similarly making no assertions to having reviewed contemporaneous laboratory documents). The fallibility of Dr. Bieganowski’s reliance on memory alone is illustrated when Dr. Bieganowski was asked about the accuracy of the content disclosed in the '086 patent. In response, Dr. Bieganowski initially would not give an answer because “[t]he whole document was written after I left Dartmouth and it doesn’t refer...directly to my work in any way.” EX1025, 10:21-25. Yet the '086 patent contains verbatim description found in both the '337 PCT and the *Cell* article, including description of the experiments he performed. *See, e.g., Pet.*, 32-33

(noting the '337 PCT “has essentially the same disclosure as the challenged '086 patent”); EX1008, 500 (detailing experimental procedures); EX1007, 63:1-67:2 (detailing same); EX1001, 31:50-34:35 (detailing same). In failing to recognize his own work in a document he said to have reviewed (EX2003, ¶7), Dr. Bieganowski’s assertions regarding his contributions (or lack thereof) to work performed long ago should be met with significant skepticism.

Moreover, both declarants have an interest at stake. Dr. Brenner, for instance, is the named inventor of the '086 patent and the Chief Scientific Advisor for Chromadex, Inc., a licensee of the '086 patent and a named plaintiff in litigation asserting the '086 patent. *See Leadership, Charles Brenner, Ph.D. Biography*, Chromadex, <https://www.chromadex.com/bios/charles-brenner/> (last visited April 29, 2021); Paper 5, 2-3. In addition, although implying that his working relationship with Dr. Brenner began in mid-2003 and ended in 2006 (EX2003, ¶6; *see also* EX2002, ¶12), Dr. Bieganowski acknowledged that he began work as a postdoctoral fellow in Dr. Brenner’s laboratory as early as 1998. EX1025, 13:2-25. More importantly, Dr. Bieganowski also admitted to having a paid consulting agreement with Chromadex in connection with his work with Dr. Brenner. *See* EX1025, 6:18-7:5. Thus, aside from raising the question as to why Dr. Bieganowski would have a consulting agreement with a licensee of the '086 patent for work that, according to him, simply encompassed running experiments

designed and directed by Dr. Brenner, his financial relationship with Chromadex raises the substantial possibility of bias and further highlights the need for contemporaneous corroborating evidence. *See EmeraChem*, 859 F.3d at 1346 (stating need for corroboration “when uncorroborated testimony comes from an interested person recalling long-past events”).

B. The relied-upon portions of the references are not the “inventive work” of Dr. Brenner

The bare assertions provided in the declarations are insufficient to meet Patent Owner’s burden of production on the issue of “by another.” Nevertheless, Dr. Bieganowski’s account of the work he performed in connection with the ’337 PCT and the *Cell* article demonstrate that the relied-upon portions of the references are not the “inventive work” of Dr. Brenner, but rather the work of others. As an initial matter, in its Preliminary Response, Patent Owner suggests that for the references to qualify as “by another,” it must be shown that “the relied-upon portions of the *Cell* article and ’337 PCT Publication were invented by Dr. Bieganowski rather than Dr. Brenner.” POPR, 10. However, Dr. Bieganowski can also be a *co-inventor* to the subject matter, thus making that subject matter “by another.” *See Duncan*, 914 F.3d at 1358 (“[T]he law requires only that a co-inventor make a contribution to the conception of the subject matter of the claim.”). In addition, and more significantly, the relied-upon portions of the ’337 PCT and the *Cell* article may still be applied as prior art to the ’086 patent if those

portions do not represent the *inventive* work of Dr. Brenner, but instead represent the work of those in the prior art. See *In re Facius*, 408 F.2d 1396, 1407 (CCPA 1969) (“The real question is whether...appellant has also clearly established the fact that he invented the relevant subject matter disclosed in the patent. If he merely brought the prior art to the attention of the patentee, then the disclosure in the patent is available against appellant even though appellant was, in a fashion, responsible for that particular disclosure...”). That is the case here.

As Dr. Bieganowski explained, he “performed every experiment that is described in the Cell paper.” EX1025, 19:11-12. This involved running “the GROg[] assays to show that NAD mutants could grow on...medium supplemented with Nicotinamide Riboside” and “measur[ing] kinase activity of Nicotinamide Riboside kinase in humans and yeasts.” *Id.*, 19:20-23; see also *id.*, 16:18-17:18, 18:3-15 (stating “there was no Nicotinamide Riboside project,” with initial work involving supplementing NAD mutants with NAD). It also involved obtaining the NR used in the experiments, which included sourcing NR and making his own preparations. *Id.*, 20:2-7. Dr. Bieganowski further admitted that the processes he used were conventional “laboratory protocols existing previously” that were “described in the handbooks, and there was nothing unusual about them,” and NR and its isolation was already known. *Id.*, 22:4-23:5 (stating his experiments involved “nothing inventive” and were “completely routine techniques”), 20:2-

21:21 (purchasing isolated NR from “a company named Sigma-Aldrich”), 29:18-25, 30:17-31:1 (acknowledging neither he nor Dr. Brenner was the first person to obtain NR from a natural or synthetic source); EX1001, 26:64-27:4, 28:16-21 (confirming known isolation of NR).

As noted in the Petition, the Board previously found that Dr. Brenner was not an inventor of the subject matter recited in claim 1 of the '086 patent. *See* Pet., 14-17. Claim 2 further recites “the nicotinamide riboside is isolated from a natural or synthetic source.” As acknowledged by Dr. Bieganowski, he performed all the experiments detailed in the *Cell* article, including the NR preparations described in the *Cell* article (and reproduced in the '337 PCT). *See* EX1008, 500 (*Cell* article describing enzymatic preparation of NR and whey vitamin fraction preparation); EX1007, 64:29-65:9 ('337 PCT Example 2 describing same). As explained in the Petition, these preparations represent a composition comprising isolated NR as recited in claim 2. Pet., 43-45, 49-50; *see also* EX1017, 17-18 (Patent Owner citing Example 2 as example embodiment of isolated NR compositions) (citing EX1001, 32:54-33:2). Because Dr. Bieganowski alone made these compositions using techniques already known in the art, it cannot be said that this subject matter—the same subject matter recited in claim 2 of the '086 patent—is Dr. Brenner’s *inventive* work. Dr. Brenner’s claiming of work that he himself did not invent cannot disqualify the relied-upon portions of the references as prior art.

Respectfully submitted,

Dated: April 30, 2021

/ Michael T. Rosato /

Michael T. Rosato, Lead Counsel

Reg. No. 52,182

LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 8,383,086 to Brenner
1002	Declaration of Dr. Samie Jafferey, M.D., Ph.D.
1003	<i>Curriculum Vitae</i> of Dr. Samie Jafferey, M.D., Ph.D.
1004	File History of United States Patent Application No. 13/445,289
1005	United States Provisional Patent Application No. 60/543,347
1006	International Publication No. WO 02/055018 A2 to Stamler et al.
1007	International Publication No. WO 2005/077091 A2 to Brenner et al.
1008	Bieganowski et al., “Discoveries of Nicotinamide Riboside as a Nutrient and Conserved <i>NRK</i> Genes Establish a Preiss-Handler Independent Route to NAD in Fungi and Humans,” <i>Cell</i> 117 (May 14, 2004)
1009	Booher et al., “Vitamin G Concentrates as Preventives Against Black-Tongue,” <i>American Journal of Physiology</i> 114 (1935)
1010	Franchetti et al., “Stereoselective synthesis of nicotinamide β -ribose and nucleoside analogs,” <i>Bioorganic & Medicinal Chemistry Letters</i> 14 (2004)
1011	Goldberger et al., “A Study of the Blacktongue-Preventive Action of 16 Foodstuffs, with Special Reference to the Identity of Blacktongue of Dogs and Pellagra of Man,” <i>Public Health Reports</i> 43 (June 8, 1928)
1012	Goldberger et al., “A Study of the Treatment and Prevention of Pellagra. Experiments Showing the Value of Fresh Meat and of Milk, the Therapeutic Failure of Gelatin, and the Preventive Failure of Butter and Cod-Liver Oil,” <i>Public Health Reports</i> 39 (January 18, 1924)
1013	Mouchiroud et al., “NAD ⁺ metabolism, a therapeutic target for age-related metabolic disease,” <i>Crit. Rev. Biochem. Mol. Biol.</i> 48 (2013)
1014	Tanimori et al., “An Efficient Chemical Synthesis of Nicotinamide Riboside (NAR) and Analogues,” <i>Bioorganic & Medicinal Chemistry Letter</i> 12 (2002)
1015	Petition for <i>Inter Partes</i> Review, <i>Elysium Health Inc. v. Trustees of Dartmouth College</i> , Case No. IPR2017-01795 (July 17, 2017)

1016	Order: Conduct of the Proceeding, <i>Elysium Health Inc. v. Trustees of Dartmouth College</i> , Case No. IPR2017-01795 (April 27, 2018)
1017	Patent Owner Response, <i>Elysium Health Inc. v. Trustees of Dartmouth College</i> , Case No. IPR2017-01795 (June 4, 2018)
1018	Final Written Decision, <i>Elysium Health Inc. v. Trustees of Dartmouth College</i> , Case No. IPR2017-01795 (January 16, 2019)
1019	Excerpts from File History of United States Patent Application No. 11/113,701
1020	File History of United States Patent Application No. 11/912,400
1021	Order Granting Motion to Voluntarily Dismiss Appeal No. 19-1682, <i>Elysium Health, Inc. v. Trustees of Dartmouth College</i> , Case No. 19-1630 et al. (August 19, 2019)
1022	Patent Owner's Notice of Cross-Appeal, <i>Elysium Health Inc. v. Trustees of Dartmouth College</i> , Case No. IPR2017-01795 (March 20, 2019)
1023	Decision: Institution of <i>Inter Partes</i> Review, <i>Elysium Health Inc. v. Trustees of Dartmouth College</i> , Case No. IPR2017-01795 (January 29, 2018)
1024	Transcript of March 26, 2021 Conference Call
1025	Transcript of April 16, 2021 Deposition of Pawel Bieganski, Ph.D.

CERTIFICATE OF SERVICE

I certify that the foregoing Petitioner's Reply to Patent Owner's Preliminary Response and Exhibit 1025 were served on April 30, 2021, on the Patent Owner at the electronic service addresses of the Patent Owner as follows:

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Respectfully submitted,

Date: April 30, 2021

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