Paper No. ___
Filed: December 21, 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 IPR2021-00268
Patent No. 8,383,086

PETITIONER'S REPLY TO PATENT OWNER RESPONSE

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I. INTRODUCTION

PO fails to: (1) establish that claim 2 is entitled to a filing date prior to April 20, 2006; (2) offer sufficient evidence that Bieganowski and Brenner are not the work of "another"; and (3) refute that the preponderance of the evidence supports that claim 2 is unpatentable over Stamler.

II. THE EARLIEST EFFECTIVE FILING DATE OF CLAIM 2 IS APRIL 20, 2006

The earliest filing date claim 2 is entitled under Article 4 of the Paris Convention is April 20, 2006. Pet., 6-14. PO responds that its priority claim is proper, as all requirements of §120 are met. POR, 27. PO fails to address its own prosecution history, consistent with the filing date claim 2 is entitled to under Article 4, in which the USPTO only accorded benefit back to April 20, 2006.

The '086 patent is a continuation of U.S. Application No. 11/912,400 ("the '400 application"), which issued as U.S. Patent No. 8,197,807 ("the '807 patent"), the subject of IPR2021-00491 ("the '491 IPR"). The '400 application is the national stage application of International Patent Application No. PCT/US2006/015495 ("the '495 PCT"), which was filed on April 26, 2006. EX1001, (63). The cover pages of the '086 and '807 patents only recite priority back to the '495 PCT, which is consistent with the data on USPTO's PAIR database. Both the '086 and '807 patents state that the '495 PCT claims priority back to U.S. Application No. 11/113,701 ("the '701 application"), filed April 25,

2005. EX1001, 1:1:9-12; EX2004, 1:11-13. The '807 patent further claims priority to PCT/US2005/00437 and US Provisional Application 60/543,347 ("the '347 provisional"). EX2004, 1:14-18.

During prosecution of the '086 patent, PO asked for a corrected filing receipt claiming benefit back to the '701 application (EX1004, 131-136), which was rejected (*id.*, 130). PO failed to file an additional request. Similarly, during prosecution of the '807 patent, the USPTO mailed out a corrected filing receipt granting priority to the '495 PCT (EX1020, 42), as reflected on the cover page, while the original filing receipt acknowledged the priority chain back to the '347 provisional (*id.*, 225). Again, there is nothing in the '807 patent's file history reflecting that PO tried to correct the corrected filing receipt only granting priority back to the '495 PCT.

The priority grants by the USPTO for both the '086 and '807 patents are consistent with Article 4 of the Paris Convention. PO was put on notice through the corrected filing receipts issued by the USPTO and has failed to take any corrective action. IPR2015-00414, Paper 34, 15 (noting, in denying priority, PO could have sought certificate of correction or reissue, but failed to do so); *Braun v. Becton, Dickinson and Co.*, 1:16-cv-411-RGA, 7 (D. Del. June 9, 2017) (citing IPR2015-00414 for same proposition). PO's arguments otherwise should be rejected.

III. BIEGANOWSKI AND BRENNER ARE BY ANOTHER

PO does not contest that Bieganowski (EX1008; alternatively, "the *Cell* article") and Brenner (EX1007; alternatively, "the '337 PCT") anticipate and/or render obvious claim 2. PO only contends the references do not qualify as prior art because the relied-upon portions of the references are not "by another." POR, 7-28. PO has failed to produce sufficient evidence corroborating Dr. Brenner's bare assertions that he is "the sole inventor" of the relied-upon subject matter. As such, the references are prior art and render claim 2 unpatentable.

A. PO Continues to Provide Only "Naked Assertions" Regarding Inventorship

"It is well established…that when a party seeks to prove conception through an inventor's testimony the party must proffer evidence, in addition to the inventor's own statements and documents, corroborating the inventor's testimony." *Apator Miitors APS v. Kamstrup A/S*, 887 F.3d 1293, 1296 (Fed. Cir. 2018). Corroborating evidence must be "independent of information received from the inventor," *Hahn v. Wong*, 892 F.2d 1028, 1032 (Fed. Cir. 1989), and "[t]he sufficiency of the proffered corroboration is determined by a 'rule of reason' analysis in which all pertinent evidence is examined," *Apator*, 887 F.3d at 1295.

Evidence that corroborates PO's contentions that Dr. Brenner alone conceived of the subject matter discussed in the applied prior-art references is non-existent. In its preliminary response, PO submitted two scant declarations, each

from Dr. Bieganowski and Dr. Brenner. *See* EX2002, EX2003. As noted in Petitioner's pre-institution reply, both declarations contain only 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. Paper 15, 2-3. The Board agreed, finding the declarations conclusory and unable to support the conclusion that the references, which on their face attribute the work to both Drs. Bieganowski and Brenner, are not the work of another. *See* '491 IPR, Paper 18 ("'491 ID"), 18-20.

Put on notice of this evidentiary insufficiency, PO responds only with a second Brenner declaration that purportedly "explains how the relied upon subject matter" from the references "constitutes his invention alone." *See* POR, 15. This second declaration adds nothing more to the conclusory testimony already of record, again amounting to only naked assertions that Dr. Brenner alone invented the subject matter described in the references. As explained below, the totality of the evidence fails to support a conclusion that these references are not the work "of another." *See EmeraChem Holdings, LLC v. Volkswagen Group of America, Inc.*, 859 F.3d 1341, 1347 (Fed. Cir. 2017).

B. Dr. Brenner's Claims Are Insufficiently Corroborated

The only additional evidence PO has submitted to support its claims is a second declaration from Dr. Brenner. The claims made by Dr. Brenner are facially

inconsistent with the record and are insufficiently corroborated.

1. Dr. Brenner's testimony is not credible

In his second declaration, Dr. Brenner purports to rely on "contemporaneous" documentation that allegedly "confirm[s] [his] memory of how [he] came up with the ideas that are claimed in the '086 patent." EX2015, ¶¶13-14; *see also* POR, 21-22. This documentation consists of only four items: the *Cell* article, the '347 provisional, the '337 PCT, and a Rule 132 declaration submitted to the Patent Office during prosecution of the '400 application. *See* EX2015, ¶¶3, 13-14, Attachment A; EX1030, 14:11-15:23 (confirming limited review). As an initial matter, only the last document is new (*cf.* EX2002, ¶9) and is a far cry from constituting "contemporaneous" evidence. As acknowledged by Dr. Brenner, the Rule 132 declaration was "prepared in 2012" using data generated in 2012—eight years after the work first described in the *Cell* article. EX1030, 42:2-15; Attachment A (January 2012 signature date). Thus, Dr. Brenner's contention that a document produced in 2012 somehow reflects "contemporaneous" evidence that "confirms [his] memory that [he] came up with the ideas reflected" in documents produced in 2004 strains credibility. *See* EX2015, ¶14.

Further, Dr. Brenner's assertions that the *Cell* article, the '347 provisional, and the '337 PCT "confirm [his] memory" that he alone conceived of the relied-

upon portions of the references also lack credence.[1] In his second declaration, Dr. Brenner appears to claim the entirety of the work described in the *Cell* article and the '337 PCT as his own, reducing Dr. Bieganowski's role to a mere technician. Dr. Brenner claims that he alone: was "the one that discovered NR as a precursor in a previously unknown eukaryotic NAD+ biosynthetic pathway" (EX2015, ¶¶18, 28); "came up with the plan for locating and identifying the nicotinamide riboside kinase gene" (*id.*, ¶11); had the "idea to locate sources of NR" using yeast mutants and "designed the experiments" and "developed the assay for locating sources of NR" (*id.*, ¶¶19, 23-24, 26, 29); and conceived of the idea to "use NR as a therapeutic" (*id.*, ¶¶20-22, 25, 30). These claims, however, represent the ***entirety*** of the work described in the *Cell* article and the '337 PCT. *See id.*, ¶¶7-12 (describing *Cell* work and claiming "all of the ideas to conduct th[e described] experiments were mine alone"); ¶28 (claiming *Cell* Abstract as his work alone); EX1030, 11:7-13:12 (referring to '337 PCT as "legal documentation of the same discovery" described in *Cell*).

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[1] To the extent these documents represent "contemporaneous" evidence, they support Petitioner's position that the work described is "by another" because these documents listed both Drs. Brenner and Bieganowski as contributors at creation.

Despite Dr. Brenner's claims to this work, Dr. Bieganowski was nevertheless first author on the *Cell* article. Although PO contends that Dr. Brenner's inclusion as corresponding author substantiates his claims (POR, 21), it was Dr. Brenner, as corresponding author, who was "responsible for ensuring that all appropriate contributors are listed as authors." EX1035. And it was Dr. Bieganowski—to the exclusion of "others" Dr. Brenner directed in his lab (EX2015, ¶¶11, 17, 19, 28)—that was listed as an author, even though Dr. Brenner now claims it was ***he*** who wrote the *Cell* article.[2] EX1030, 12:18-13:12 (referencing *Cell* article as "the text that I wrote").

More significantly, Dr. Bieganowski was also included as an inventor on the '347 provisional and the '337 PCT. Dr. Brenner confirmed that, during preparation and filing of these applications, he created and submitted invention disclosure forms to Dartmouth's technology transfer office, yet none of this contemporaneous evidence was reviewed or submitted to substantiate his claims. *See* EX1030, 26:6-28:4. Dr. Brenner also testified that he conferred with the

[2] This is also inconsistent with Dr. Bieganowski's testimony. *Infra*, section III.B.3.

technology transfer office and the attorney who filed both the patent applications[3] and confirmed he would not let an attorney "file a document on [his] behalf without reviewing that document for accuracy." *See id.*, 14:7-10, 19:10-23:12, 24:21-25:16; EX1005, 3; EX1029, 1-2. And following these communications and submitted paperwork, Dr. Bieganowski remained an inventor on the '347 provisional and the '337 PCT. EX1005, 3; EX1029, 5, 7, 10, 13. Indeed, Dr. Bieganowski continued to be a named inventor when the '337 PCT entered its national stage. *See* EX1034, 1 (Australian patent application naming Dr. Bieganowski).

While PO tries to explain this discrepancy by arguing that the claims of the '337 PCT are "not limited to therapeutic compositions of NR" (POR, 22), PO's contentions are undermined by what Dr. Brenner claims is his own work. Specifically, in addition to including claims directed to uses of NR compositions (EX1007, claims 16-17), the '337 PCT also includes claims relating to the

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[3] Dr. Brenner could not recall specifically whether he discussed the applications with the attorney (EX1030, 21:20-24:18), which casts doubt on Dr. Brenner's ability to "confirm [his] memory" concerning long-past events based only on documents that he himself is now claiming as his own.

sequenced Nrk gene (*id.*, claims 1-13, 21-25), methods for identifying sources of NR (*id.*, claims 14-15), and treatment methods associated with the Nrk pathway (*id.*, claims 18-20). Dr. Brenner contends that all of these aspects represent his ideas alone, and thus, according to Dr. Brenner, only he is an inventor of these claims. This, however, is facially contradicted by the '337 PCT—a document reviewed for accuracy by Dr. Brenner and filed by an attorney working for Dartmouth's technology transfer office—which also lists Dr. Bieganowski as an inventor of the claims.

Lastly, while Dr. Brenner asserts he "was the one that discovered NR as a precursor in a previously unknown eukaryotic NAD+ biosynthetic pathway" (EX2015, ¶18), outside the context of litigation, Dr. Brenner readily attributes the discovery to both him and Dr. Bieganowski. *See* EX1028, 4:18-22 (stating "***Pawel Bieganowski and I, in 2004, discovered*** the vitamin activity of NR"); EX1030, 16:25-18:1 (confirming pathway is vitamin activity of NR), 32:21-34:8 (authenticating interview). As Dr. Brenner admitted, it was already known to use a vitamin to supplement the diet. EX1030, 16:3-16; *see also* Paper 15, 8-10 (noting Dr. Bieganowski prepared isolated NR compositions using conventional methods); EX1033, 10-11 (district court finding isolated NR compositions not an inventive concept under *Alice*). Thus, even if one were to assume that it was Dr. Brenner's idea alone to use NR therapeutically, Dr. Bieganowski's role in the discovery of

the pathway represents a contribution significant enough to render him a joint inventor of the relied-upon subject matter. *See Duncan Parking Techs., Inc. v. IPS Grp., Inc.*, 914 F.3d 1347, 1358-59 (Fed. Cir. 2019). Moreover, Dr. Brenner's statements, made in absence of the self-interest that underlies his testimony here, are consistent with the authors and inventors named on the *Cell* article and '337 PCT, confirming that Dr. Brenner's declaration testimony is not credible.

2. Dr. Brenner's bias

Dr. Brenner's testimony is further undermined by his substantial bias. Although not disclosed in his declarations, Dr. Brenner is the Chief Scientific Advisor to Chromadex, a licensee of the '086 patent and a named plaintiff in litigation. *See* EX1028, 2:8-21; EX1030, 34:19-35:5 (role is paid position), 37:4-12; EX1032 (listing'086 patent for NR supplement, Tru Niagen); Paper 5, 2-3. Dr. Brenner also receives a monthly retainer, owns stock and options in Chromadex, owned a company purchased by Chromadex, and receives royalties for Tru Niagen sales. EX1030, 35:21-37:3, 38:14-22 (reporting about half-a-million dollars in royalties). Moreover, although Dr. Brenner claims not to be involved in marketing, his picture is on the Chromadex website for Tru Niagen, which he promotes. *See* EX1030, 35:13-17; EX1031; EX1028, 56:14-21, 61:24-62:4. Thus, Dr. Brenner's interest in the outcome of this proceeding is substantial, underscoring the need for actual evidence corroborating his testimony.

3. Dr. Bieganowski's testimony fails to corroborate Dr. Brenner's assertions

PO asserts that Dr. Bieganowski's "disclaimer declaration" is sufficient to corroborate Dr. Brenner's assertions. *See* POR, 17-18. As an initial matter, PO relies on the same declaration and deposition testimony that the Board found insufficient to support a finding that the relied-upon portions represent the work of Dr. Brenner alone. *See* '491 ID, 20. In response, PO argues "[t]he Board's analysis…appears to evaluate Dr. Bieganowski's declaration as that of an interested inventor requiring corroboration." POR, 24. The Board, however, found that Dr. Bieganowski's testimony was itself insufficient to corroborate Dr. Brenner's assertions because Dr. Bieganowski provided only conclusory testimony, "relied exclusively on his memory" of long-past events, and "did not review either the Brenner or Bieganowski references." '491 ID, 19; *EmeraChem*, 859 F.3d at 1347-48 (leaving it to fact-finder to determine degree of corroboration needed in each case). These concerns remain unaddressed by PO.

Further, there remain inconsistencies between Dr. Bieganowski's testimony and Dr. Brenner's assertions. For example, as discussed above, Dr. Brenner claims that he alone discovered the vitamin pathway of NR. *Supra*, section III.B.1. Yet, Dr. Bieganowski testified that the content described in the *Cell* article was the discovery of this pathway and it was unnecessary for him to review the article because he "did this work" and he "know[s] what's in this paper," indicating a

substantial contribution by Dr. Bieganowski to the *Cell* article. EX1025, 12:13-20, 25:7-24; *cf.*, EX1030, 12:18-13:12 (Dr. Brenner referring to the *Cell* article as "the text that I wrote").

In addition, Dr. Bieganowski's vague "disclaimer" testimony relates only to "the experiments and assays" Dr. Brenner allegedly designed for identifying yeast and human genes having Nrk activity and "therapeutic uses or compositions of" NR. EX2003, ¶¶6-7. With regard to the former, it remains unclear what exactly Dr. Brenner designed when Dr. Bieganowski testified that the experiments he performed were simply the product of routine techniques. *See* EX1025, 22:4-23:3; EX1030, 41:11-42:1. With regard to the latter, even if one were to assume that Dr. Brenner alone conceived of using NR therapeutically, Dr. Bieganowski's role in the discovery of the vitamin pathway would be sufficient to make him a joint inventor of the relied-upon subject matter. *Supra*, section III.B.1; *see also* EX1025, 27:3-10 (Dr. Bieganowski confirming he had no understanding of inventorship).

Finally, PO contends that Dr. Brenner's assertions are "corroborated by the superior-subordinate relationship between him and Dr. Bieganowski," arguing that an inventor declaration is sufficient when it explains that co-authors "were students under [the inventor's] direction and supervision." POR, 20-21. This case, however, goes well beyond a factual scenario that simply involves student co-

authors. Dr. Bieganowski was a postdoctoral fellow who worked in Dr. Brenner's laboratory for five years prior to the *Cell* work. EX1025, 13:23-25; *see also* EX1030, 18:23-19:4 (Dr. Bieganowski "an exceptional scientist"). He was the first-named author on the *Cell* article and a named inventor on two patent applications filed in relation to that work. He was also contacted by Chromadex regarding his work and entered into a paid consulting agreement with the company. EX1025, 6:18-7:1. This evidence suggests a relationship more substantial than just "superior-subordinate"—one that itself raises questions of bias and undermines the credibility of Dr. Bieganowski's "disclaimer" testimony.

While a patent challenger has the burden of producing evidence to support a conclusion of unpatentability, a patent owner bears the burden of producing evidence to support a claim that an asserted reference is not by another. *Cf. Apator*, 887 F.3d at 1297 (noting, under §102(g), patent owner must prove conception occurred prior to effective date, not that challenger must prove it did not). Petitioner met its burden of production by producing the *Cell* article and the '337 PCT, both of which list a different inventive entity. PO's response is only conclusory testimony that is uncorroborated and inconsistent with the totality of the evidence. The record fails to support PO's contentions that the relied-upon portions of Brenner and Bieganowski are not "by another."

IV. CLAIM 2 IS ANTICIPATED BY AND/OR OBVIOUS OVER STAMLER

The preponderance of evidence of record demonstrates that claim 2 is unpatentable over Stamler.

A. "is isolated from a natural or synthetic source"

PO advances a product-by-process construction for claim 2, arguing the NR must have been made in a certain way: it must be "isolated from" some distinct "natural or synthetic source" that is itself not part of the claimed product. *See, e.g.*, POR, 32-33, 43-44 (arguing Stamler does not disclose "a natural or synthetic source" from which NR is "isolated from"), 45-46 (arguing Franchetti does not disclose "a separate isolation process"), 46. PO's expert confirmed this interpretation. EX1027, 55:1-21 ("Q.…So in essence, your view of 'isolated' requires the process step of isolating from a source; is that correct? …. A. That's what I'm saying…."), 51:13-21.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself." *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985). "If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *Id.* Under the Board's construction, the resulting product of the claimed composition—*i.e.*, the "isolated" NR—simply requires NR that is at least 25%

pure. EX1023, 8-9; EX1018, 12.

It is undisputed that NR of at least 25% purity is the same regardless of the process used to produce that NR. *Infra*, section IV.C.3. Thus, for unpatentability, it is sufficient to show that the prior art disclosed or suggested NR of that purity. Further, PO's attempts to distinguish chemically-synthesized NR from the process limitations of claim 2 are unavailing.

B. Collateral Estoppel

PO attempts to bypass collateral estoppel because this IPR involves different art. *See* POR, 35-36. Yet, collateral estoppel "centers around whether an issue of law or fact has been previously litigated." *In re Freeman*, 30 F.3d 1459, 1465 (Fed. Cir. 1994). Thus, merely because different art is involved here, PO is estopped from arguing ***issues***, including issues of fact, that were previously decided by the Board. As discussed below, PO's arguments that Stamler does not disclose or suggest limitations specific to claim 1 contradict previously-decided factual findings, which PO is estopped from re-litigating. *Infra*, section IV.E.

C. Stamler Anticipates Claim 2

1. "A pharmaceutical composition comprising" NR

PO argues Stamler does not disclose the claimed "pharmaceutical composition" because it does not expressly use the word "composition" or describe a particular NR formulation. POR, 39-40. Yet PO and its expert agree that Stamler teaches "methods of treatment with certain classes of compounds,"

including NR. POR, 40; EX1027, 36:8-11; *see also id.*, 36:16-19, 37:8-22 (acknowledging Stamler discloses oral administration and using a therapeutically effective amount). PO's expert also agreed that treatment with a drug typically involves administering a composition comprising the drug. EX1027, 35:23-36:1. As Dr. Jaffrey explained, Stamler discloses the critical ingredient (NR) and the route of administration (oral), which a POSA would have understood as disclosing the use of standard formulations. EX2016, 26:4-27:8 ("when you don't state exactly the exact ingredients, it means generic…, use a standard form"), 28:15-23, 29:24-30:25, 31:19-32:5, 34:22-35:5; *see also* Pet., 38-39 (citing EX1002, ¶¶70-73). Indeed, Stamler itself evidences this straightforward point by disclosing working examples of treating patients using an active ingredient in admixture with, e.g., saline—*i.e.*, a "pharmaceutical composition" as broadly defined and claimed by the '086 patent. *See, e.g.*, EX1006, 29 (Examples I and II); EX1027, 40:12-41:12 (Dr. Amiji agreeing Examples I and II describe "compositions"); EX1001, 29:1-20 (disclosing "saline" as a carrier).

2. NR "in admixture with a carrier"

PO similarly argues that Stamler does not disclose NR "in admixture with a carrier" because Stamler does not recite explicit carriers to be used with NR. POR, 41-42. As the petition noted, however, "[g]iven the different dosage amounts, as well as Stamler's teaching that oral administration is preferred," the POSA would

have understood that Stamler discloses NR "in admixture with a carrier to provide for oral administration." Pet., 39 (citing EX1002, ¶73).

Like the term "pharmaceutical composition," the '086 patent describes the term "carrier" broadly, identifying examples such as "oils" and "saline." EX1001, 29:1-20; *see also* EX1018, 23-24 (finding claimed "carrier" encompasses milk). There is no dispute that carriers, their uses, and how they could be formulated were well-known to POSAs. EX1001, 28:54-60; EX1027, 21:10-22:24 (agreeing '086 patent lists commonly-used carriers), 20:16-21:9 (testifying Remington provides sufficient guidance for formulation); EX1033, 10-11 (claimed composition lacks inventive concept). As Dr. Jaffrey testified, POSAs knew to "look at the chemical structure of NR" and would "know how to prepare the formulations and what's compatible" based on that structure. EX2016, 46:4-23 (POSA would understand NR was not "chemically reactive" and was "very soluble," and POSA would "know right from that all your options instantaneously"); *see also id.*, 40:7-16, 42:20-43:1. Thus, by disclosing the critical ingredient (NR) and the route of administration (oral), Stamler provides sufficient guidance to the POSA to form a pharmaceutical composition comprising NR in admixture with a carrier as broadly recited in claim 2. *In re Arkley*, 455 F.2d 586, 589 (CCPA 1972) (disclosure of sufficient "blaze marks" anticipates).

3. NR "is isolated from a natural or synthetic source"

As discussed above, PO advances a product-by-process construction for the claimed "isolated" NR. *Supra*, section IV.A. PO uses this construction to argue that Stamler does not disclose "isolated" NR because it does not disclose an additional isolation step to the NR that Stamler discloses as being commercially available or obtained from known synthetic methods. *See* POR, 43-44. As noted in the petition, POSAs would have understood that synthetic and commercially-obtained NR described in Stamler would have been purified to at least 25% (w/w) as required by the Board's construction, which PO does not dispute. Pet., 40 (citing EX1002, ¶¶75-76; EX1010, 4656 (showing synthetic yield for NR of 45%, which was then further purified)). PO's expert admitted there is no difference between NR compositions of the same purity even if the NR was obtained using different processes. EX1027, 52:10-15 ("Q. So if I gave you a sample that was 99 percent NR, would you be able to determine the source of that NR? A. No. I wouldn't be able to tell you where it came from…."), 56:12-17 ("Q.…Would that final [NR] molecule differ if you synthesized it as opposed to isolating it from a natural source? A. No, it wouldn't…."); *see also id.*, 51:22-52:9, 52:16-21, 54:1-12. Thus, because Stamler discloses using commercially-available or synthesized NR, which would have been understood to have the required purity, Stamler discloses the product of claim 2 irrespective of the process used to make the NR.

See Thorpe, 777 F.2d at 697.

Moreover, faced with clear evidence that conventional methods for synthesizing NR involve an isolation step, PO argues that such a step "cannot qualify as the 'isolation' step of claim 2". POR, 45-46. PO's arguments are predicated on limiting a "synthetic source" only to synthesized product after it has been isolated. *See id.*, 46. As PO acknowledges, Dr. Jaffrey explained how known methods for the chemical synthesis of NR routinely involved the isolation of NR from the resulting synthesized product (*i.e.*, "a synthetic source"). *See, e.g.*, EX2016, 70:5-7 ("chemical synthesis is a process of isolating…a molecule from precursors"), 70:14-18, 71:3-9 ("[s]ynthesis involves an isolation from a synthetic preparation"), 20:19-21:19; POR, 44.

Indeed, when it was beneficial for infringement purposes, PO argued the same before the district court. In particular, PO argued that "a compound produced by a synthetic reaction, from which NR can be isolated, is, by definition, a 'synthetic source' of NR. The NR that is subsequently *isolated* from the result of that synthetic reaction would be both 'chemically synthesized' and 'isolated from a natural or synthetic source.'" EX2008, 45-46; *see also id.*, 43, 48 (contrasting isolation from "NR that is chemically synthesized without any separation or extraction step (for example, where the NR is used along with the other reaction products)"). PO further pointed to Tanimori (EX1014) and Franchetti (EX1010) as

disclosing processes "in which a broth containing NR is synthesized, and then the NR is isolated from that broth," noting "these papers expressly recognize the distinction between the chemical synthesis of the NR and the isolation of that NR from the broth created by the chemical synthesis." EX2008, 64-65; *see also id.*, 44-45, 50, 63; Pet., 28; EX2016, 74:20-75:13. In arguing Elysium infringed claim 2, PO took the position that "Franchetti expressly recognize[s] that the synthesis of NR is distinct from the isolation of NR from the chemically synthesized broth." EX2008, 66 (citing EX1010, 4656); EX1010, 4656 (showing synthetic preparation in Scheme 1 and separately discussing isolation from preparation); EX2016, 77:2-24. Thus, Stamler discloses "isolated" NR made by the process limitations advanced by PO because conventional methods for chemically synthesizing NR, as evidenced by Franchetti and Tanimori, routinely involved isolating NR from a chemically-synthesized preparation.

D. Stamler Renders Claim 2 Obvious

1. Pharmaceutical composition and carrier

a) Stamler suggests the claimed composition

With respect to claim 1 limitations, PO alleges the petition's evidence of obvious "is conclusory" because it "cites only Stamler, the challenged '086 patent itself, and four conclusory paragraphs of Dr. Jaffrey's declaration" and "fails to state any motivation to modify Stamler." POR, 49-51. PO, however, ignores evidence of the POSA's level of skill, the breadth of its claims, and Dr. Jaffrey's

reasoned explanation as to why Stamler itself suggests the claimed pharmaceutical composition.

Claim 2 is not directed to any particular NR formulation. The '086 patent contemplates a broad range of conventional composition forms encompassed by the claimed "pharmaceutical composition" and "carrier," and acknowledges the POSA's skill in selecting the materials appropriate for administering the desired active ingredient (*e.g.*, NR). *Supra*, sections IV.C.1-2. A patent's admissions of the POSA's knowledge are proper evidence of the level of ordinary skill. *In re Morsa*, 803 F.3d 1374, 1377 (Fed. Cir. 2015). Contrary to PO's claims, Dr. Jaffrey's testimony regarding the knowledge and skill of the POSA are far from conclusory and corroborated by the '086 patent itself. *See also* EX2016, 17:2-22:15 (discussing experience in formulating isolated NR compositions).

Further, the petition identified a sufficient rationale supported by the disclosure of Stamler itself. Pet., 41 (citing EX1002, ¶¶80-83). That is, as discussed above, Stamler discloses treating patients using NR and administering it orally, which would have suggested to a POSA to prepare a composition containing NR with a carrier for administration. *Supra*, sections IV.C.1-2. Indeed, Stamler evidences this point. EX1006, 29.

b) Stamler provides a reasonable expectation of success

PO argues a POSA would not have had a reasonable expectation of success

in formulating a composition comprising NR and a carrier, alleging Stamler does not provide guidance for how to make such a formulation. POR, 52. However, PO's expert readily admitted resources familiar to POSAs, such as Remington, would have "provide[d] guidance on development of formulations and provide[d] the different types of excipients that are used in developing formulations." EX1027, 20:16-21:9, 76. As noted by Dr. Jaffrey, once the chemical structure of the active ingredient (NR) and the form of administration (oral) were known, the POSA would have "instantaneously" known which carriers would be compatible and how to prepare such formulations. EX2016, 46:4-23.

PO goes to great lengths to discount Stamler's disclosure and the POSA's ordinary creativity by invoking an alleged field "unpredictability" and the need for explicit guidance on specific parameters, such as oral delivery form, excipient amounts, and ingredient compatibility. POR, 52-54. If this disclosure was necessary to provide a reasonable expectation of success, then the '086 patent would not be enabling. *In re Paulsen*, 30 F.3d 1465, 1481 n.9 (Fed. Cir. 1994). The '086 patent admits that the compositions generally disclosed "can be prepared by methods and contain carriers which are well-known in the art." EX1001, 28:54-60. The active ingredient contained in these compositions is not limited to NR—it can also be "[p]olypeptides, nucleic acids, vectors…, and nicotinamide riboside-related prodrugs." *Id.*, 28:49-54. The patent goes on to list numerous known

carriers and administration forms, each with their own options for delivery form. *Id.*, 29:1-31:46. The '086 patent does not explain which of the carriers and delivery forms are compatible with which active ingredient, which carriers are compatible with one another, which parameters are critical, or ingredient amounts that should be used. *Id.*; *see also id.*, 28:54-60, 31:28-31 (referencing Remington), 29:61-64 (POSAs "could envision other binders, excipients, sweetening agents and the like" for oral formulation); EX1027, 15:24-16:6, 17:11-18:21, 21:18-22:12, 23:9-24:3, 31:16-32:2 (no disclosure of quality control in '086 patent), 33:23-34:17 (same for dissolution and bioavailability). Instead, the '086 patent relies on the POSA's skill to make those choices, confirming that the field is not as unpredictable as PO alleges and a POSA, relying on conventional knowledge, would reasonably expect success in providing a pharmaceutical composition as broadly recited in claim 2 in view of Stamler's disclosure.

2. Isolated NR

PO advances substantially similar arguments as it does with anticipation. *See* POR, 56-61. As explained above, Stamler discloses using commercially-available NR or NR synthesized through known methods, both of which would have been understood to be at least 25% pure. *Supra*, section IV.C.3; *see also* Pet., 42 (noting POSA's skill in obtaining desired purity); EX1033, 11 ("the physical act of isolating NR is not an inventive concept"). Further, as advanced by PO itself,

known synthetic methods, such as evidenced by Franchetti, routinely involved an isolation step, thus teaching even the process limitations advanced by PO. *Id.* PO's arguments that Stamler does not teach or suggest isolated NR fail for the same reasons discussed above.

E. Dr. Jaffrey Is Credible, While Dr. Amiji Applies An Incorrect Standard

PO argues that Dr. Jaffrey's testimony should be afforded little weight because he is allegedly "inexperienced in formulation of pharmaceutical compositions" and his educational background is in neuroscience. POR, 54-55. While Dr. Jaffrey's degrees may be in neuroscience, PO overlooks that he is "the Greenberg-Star Professor in the Department of Pharmacology at Weill Medical College at Cornell University," where he has been a professor of pharmacology since 2001. EX1002, ¶2; *see also* EX2016, 8:3-10; Pet., 33 (POSA is "someone with a Ph.D. in biochemistry or similar field" and "familiarity with pharmacokinetics"). He also consults with pharmaceutical companies on their drug development programs and regularly makes pharmaceutical compositions during the course of his research. EX2016, 9:11-13:4, 15:4-24. Further, Dr. Jaffrey has worked with NR and formulated pharmaceutical compositions containing isolated NR. *Id.*, 12:5-13:6, 13:18-15:2, 17:14-19:17, 20:19-22:21; EX1002, ¶4. While PO argues that Dr. Jaffrey's experience with isolated NR compositions only concerns "academic research, usually for animal

administration" (POR, 55), his experience is nevertheless commensurate with the scope of the claims. *See* EX1018, 7, 15-18 (administration of milk to dogs anticipates claimed "pharmaceutical composition"). Unlike Dr. Amiji, Dr. Jaffrey's background and testimony is consistent with the '086 patent, the prior art, and the claim as it has been construed.

In contrast to Dr. Jaffrey, Dr. Amiji has no experience working with NR. EX1027, 16:7-9. His testimony is also premised on applying an incorrect reading of the claim scope that fails to account for previously-decided factual issues. For example, Dr. Amiji applied an analysis requiring the claimed "pharmaceutical composition" must be a composition that meets regulatory-agency standards, but this is not required by the claim nor is it supported by the specification. EX1027, 32:3-14 (stating claim requires oral product meeting regulatory quality control tests), 33:13-34:17. Dr. Amiji also rejected the notion that milk and the Example 2 compositions of the '086 patent constitute a "pharmaceutical composition," instead requiring a separate intent to further develop the compositions, which contradicts factual findings made by the Board. EX1027, 24:15-19, 25:9-26:5, 28:22-29:13. *Compare* EX1027, 25:9-23 (stating "cow's milk by itself would not be a pharmaceutical composition"), 28:22-30:2 (stating same for 50% whey fraction and 10 μM NR, requiring further "develop[ment] into a pharmaceutical composition"), *with* EX1018, 18-19 (Board finding skim milk is "a pharmaceutical

composition as that term is used in the challenged claims"), 23-24 (rejecting PO's contention claims "require[] that the ingredients be purposefully mixed"). As explained above, PO is estopped from arguing that limitations recited in claim 1 confer patentability by requiring a stricter reading of the claims already rejected by the Board. Through Dr. Amiji's testimony, PO is attempting to re-litigate these factual disputes.

V. CONCLUSION

For the reasons above, claim 2 is unpatentable.

Respectfully submitted,

Date: December 21, 2021

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
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VI. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Reply complies with the type-volume limitation of 37 C.F.R. §42.24(c). The word count application of the word processing program used to prepare this Petition indicates that the Reply contains 5,600 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(c).

Respectfully submitted,

Date: December 21, 2021

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VII. APPENDIX – 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	*Curriculum Vitae* 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 *NRK* Genes Establish a Preiss-Handler Independent Route to NAD in Fungi and Humans," *Cell 117* (May 14, 2004)
1009	Booher et al., "Vitamin G Concentrates as Preventives Against Black-Tongue," *American Journal of Physiology 114* (1935)
1010	Franchetti et al., "Stereoselective synthesis of nicotinamide β-riboside and nucleoside analogs," *Bioorganic & Medicinal Cehmistry Letters 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," *Public Health Reports 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," *Public Health Reports 39* (January 18, 1924)
1013	Mouchiroud et al., "NAD+ metabolism, a therapeutic target for age-related metabolic disease," *Crit. Rev. Biochem. Mol. Biol. 48* (2013)
1014	Tanimori et al., "An Efficient Chemical Synthesis of Nicotinamide Riboside (NAR) and Analogues," *Bioorganic & Medicinal Chemistry Letter 12* (2002)
1015	Petition for *Inter Partes* Review, *Elysium Health Inc. v. Trustees of Dartmouth* College, Case No. IPR2017-01795 (July 17, 2017)

1016	Order: Conduct of the Proceeding, *Elysium Health Inc. v. Trustees of Dartmouth* College, Case No. IPR2017-01795 (April 27, 2018)
1017	Patent Owner Response, *Elysium Health Inc. v. Trustees of Dartmouth* College, Case No. IPR2017-01795 (June 4, 2018)
1018	Final Written Decision, *Elysium Health Inc. v. Trustees of Dartmouth* College, 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, *Elysium Health, Inc. v. Trustees of Dartmouth College*, Case No. 19-1630 et al. (August 19, 2019)
1022	Patent Owner's Notice of Cross-Appeal, *Elysium Health Inc. v. Trustees of Dartmouth* College, Case No. IPR2017-01795 (March 20, 2019)
1023	Decision: Institution of *Inter Partes* Review, *Elysium Health Inc. v. Trustees of Dartmouth* College, Case No. IPR2017-01795 (January 29, 2018)
1024	Transcript of March 26, 2021 Conference Call
1025	Transcript of April 16, 2021 Deposition of Pawel Bieganowski, Ph.D.
1026	Complaint for Patent Infringement, *Chromadex, Inc. et al. v. Thorne Research, Inc.*, Case No. 1-21-cv-04241 (SDNY) (May 12, 2021)
1027	Transcript of November 12, 2021 Deposition of Mansoor Amiji, Ph.D.
1028	Transcription of Habits & Hustle Podcast Episode 129: Dr. Charles Brenner Discovered Nicotinamide as NAD Precursor, Department Chair at City of Hope (Https://www.youtube.com/watch?v-yla036ebg8g)
1029	File History of Patent Application No. PCT/US2005/004337
1030	Transcript of December 3, 2021 Deposition of Charles Brenner, Ph.D.
1031	Tru Niagen, ChromaDex (https://www.chromadex.com/tru-niagen/)
1032	Ingredients, ChromaDex (https://chromadex.com/patents/)

1033	Memorandum Opinion, *ChromaDex, Inc. et al. v. Elysium Health, Inc.*, Case No. 18-1434-CFC-JLH (D.Del.) (September 21, 2021)
1034	Australian Patent Application No. AU 2005211773 B2 to Bieganowski et al.
1035	Editorial policies, Cell Press (https://www.cell.com/trands/editorial-policies)

CERTIFICATE OF SERVICE

I certify that the foregoing Petitioner's Reply to Patent Owner Response and Exhibits 1027-1035 were served on this 21st day of December, 2021, on the Patent Owner at the correspondence address of the Patent Owner as follows:

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