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 8,383,086

PATENT OWNER RESPONSE

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Pursuant to 35 U.S.C. § 316(a)(8) and 37 C.F.R. § 42.120, Trustees of Dartmouth College ("Patent Owner") respectfully submit this Response to the Petition filed by Thorne Research, Inc. ("Petitioner") regarding U.S. Patent No. 8,383,086 (Ex. 1001, "the '086 patent").

I. INTRODUCTION

Petitioner bears "the burden of proving a proposition of unpatentability by a preponderance of the evidence." 35 U.S.C. § 316(e). Petitioner has failed to meet that burden here.

First, the two references asserted in Grounds 3-5 are not prior art. The relied-upon portions of the '337 PCT Publication[1] and *Cell* article[2] regarding claim

[1] International Publication No. WO 2005/077091 A2 ("the '337 PCT Publication") (Ex. 1007).

[2] Bieganowski & Brenner, "Discoveries of Nicotinamide Riboside as a Nutrient and Conserved *NRK* Genes Establish a Preiss-Handler Independent Route to NAD^+ in Fungi and Humans," 117 *Cell* 495 (May 14, 2004) ("the *Cell* article") (Ex. 1008).

2 of the ’086 patent are not “by another,” and thus these two references are not prior art under either pre-AIA § 102(a) or § 102(e).[3]

Moreover, Petitioner’s priority argument is based entirely on an unsupported theory that the ’086 patent priority claim is defective under the Paris Convention treaty. Tellingly, Petitioner cites no U.S. law or statute in support of its theory. The ’086 patent makes a proper priority claim to the ’701 Application under 35 U.S.C. § 120, the controlling U.S. statute, and Petitioner does not even argue otherwise. Thus, as the Board correctly found in its Institution Decision, the *Cell* article is not prior art under pre-AIA § 102(b).

Second, Grounds 1-2 based on Stamler fail to establish anticipation or obviousness. These Grounds are premised on an unsupported and improper application of collateral estoppel. Also, Stamler fails to disclose or suggest (1) “[a] pharmaceutical composition comprising nicotinamide riboside,” (2) the nicotinamide riboside “in admixture with a carrier,” or (3) that the nicotinamide riboside “is isolated from a natural or synthetic source.”

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[3] The Petition refers to the ’337 PCT Publication and *Cell* article as “Brenner” (Ex. 1007) and “Bieganowski” (Ex. 1008), respectively. *See* Pet. at 30-33, 54. Patent Owner refers to the asserted references as the ’337 PCT Publication (Ex. 1007) and *Cell* article (Ex. 1008) to avoid confusion with eponymous declarations in this IPR.

Indeed, the Petition's anticipation analysis fails because Petitioner concedes that these limitations are not explicitly disclosed by Stamler and does not argue inherency. The Petition's obviousness analysis likewise fails due to Petitioner's reliance on unsupported assertions and failure to address either all legal requirements for obviousness or all claim elements.

For at least the reasons set forth herein, Petitioner has failed to meet its burden to establish that claim 2 of the '086 patent is unpatentable.

II. BACKGROUND OF DR. BRENNER'S INVENTION

Charles M. Brenner, Ph.D. ("Dr. Brenner") is the sole inventor of the '086 patent. Ex. 2002 ¶¶ 5, 10-14; '086 patent at (75). The claimed invention stemmed from a nicotinamide riboside ("NR") research project ("NR research project") that Dr. Brenner led in late 2003 and early 2004 at Dartmouth Medical School. *See id.* ¶¶ 10-14; Ex. 2015 ¶¶ 6-14.

For decades prior to Dr. Brenner's invention, scientists knew about the importance of nicotinamide adenine dinucleotide ("NAD+") to human health, *see* Ex. 2017 at 83 (explaining that NAD+ is of "immeasurable importance in cellular metabolism"), and that increasing NAD+ levels could aid in treating numerous diseases, *see* Ex. 2018 (filed 1988) at Abstract; Ex. 2019 (filed 1999) at 1:14-18. While scientists were aware that compounds such as nicotinic acid and nicotinamide were capable of increasing NAD+ levels, *see* Ex. 2018 at 2:33-43,

prior to the invention of Dr. Brenner, the role of NR in increasing NAD+ levels was not understood. Ex. 2015 ¶ 8.

Dr. Brenner realized that there were unsolved problems in NAD+ metabolism and a potential opportunity for gene and pathway discovery related to NAD+, which led him to focus on NR. *Id.* ¶ 8. As part of the NR research project, Dr. Brenner established that NR is an NAD+ precursor in a previously-unknown pathway. *Id.* ¶ 9. Dr. Brenner's research project also led to the identification of "yeast nicotinamide riboside kinase, Nrk1, and both human Nrk enzymes and [the demonstration of] their specific functions in NAD+ metabolism biochemically and genetically." *Id.* ¶ 10; Ex. 1008 at 495. Dr. Brenner's research led him to conclude that NR is a useful compound for elevation of NAD+ and that supplementation with NR may be beneficial. Ex. 2015 ¶ 10. It was Dr. Brenner alone who conceived of the invention of claim 2 of the '086 patent. *Id.* ¶¶ 5, 10, 12-13; Ex. 2002 ¶ 13.

Dr. Brenner's laboratory research team included a postdoctoral fellow named Pawel Bieganowski Ph.D. ("Dr. Bieganowski"), who performed, at Dr. Brenner's direction, experiments and assays for identifying yeast and human genes that have Nrk activity. Ex. 2002 ¶ 12; Ex. 2003 ¶ 6; Ex. 2015 ¶ 11. Dr. Bieganowski did not have an inventive role in any aspect of Dr. Brenner's

inventions regarding therapeutic uses or compositions of NR. Ex. 2002 ¶ 13; Ex. 2003 ¶ 7; Ex. 2015 ¶ 12.

As a result of the NR research project, Dartmouth filed U.S. Provisional Patent Application No. 60/543,347 ("the '347 Provisional") on February 10, 2004, and International Application No. PCT/US2005/004337 ("the '337 PCT Application") on February 9, 2005, which claimed priority to the '347 Provisional. *See* Ex. 1005; Ex. 1007; Ex. 2002 ¶¶ 6-7, 14; Ex. 2015 ¶ 13. On August 25, 2005, the '337 PCT Application was published as the '337 PCT Publication, which Petitioner asserts in Ground 5 as the "Brenner" reference. *See* Pet. at 32, 35; Ex. 1007; Ex. 2002 ¶ 7. The '347 Provisional and '337 PCT Publication both name Dr. Brenner and Dr. Bieganowski as co-inventors, but the portions of the '337 PCT Publication relied upon by the Petition are solely the invention of Dr. Brenner. *See* Ex. 1005 at 3; Ex. 1007 at (75); Pet. at 32-33, 48-50; Ex. 2002 ¶¶ 6-7, 15-16; Ex. 2003 ¶¶ 5, 7; Ex. 2015 ¶¶ 14-26.

Certain aspects of the NR research project were also included in the *Cell* article, which was published on May 14, 2004, and which Petitioner asserts in Grounds 3-4 of this IPR as the "Bieganowski" reference. *See* Pet. at 30, 35; Ex. 1008; Ex. 2002 ¶ 8; Ex. 2015 ¶ 13. The *Cell* article names Dr. Brenner and Dr. Bieganowski as co-authors, but the portions of the *Cell* article relied upon by the

Petition are solely the invention of Dr. Brenner. *See* Ex. 1008 at 495; Pet. at 42-48; Ex. 2002 ¶¶ 8, 17-19; Ex. 2003 ¶¶ 5, 7; Ex. 2015 ¶¶ 14-15, 27-30.

The '086 patent is directed to pharmaceutical compositions of NR formulated in admixture with a carrier for oral administration, wherein the NR is isolated from a natural or synthetic source. *See* '086 patent at claims 1-2. The '086 patent issued from a continuation application of U.S. Patent Application No. 11/912,400 ("the '400 Application"), which later issued as U.S. Patent No. 8,197,807 ("the '807 patent"). The '400 Application is a national stage entry of International Application No. PCT/US2006/015495 ("the '495 PCT"), which claims priority to U.S. Patent Application No. 11/113,701 ("the '701 Application"). The '086 patent thus claims priority to the '701 Application. *See id.* at 1:7-13.

III. PETITIONER HAS NOT MET ITS BURDEN OF SHOWING THAT EITHER THE *CELL* ARTICLE (GROUNDS 3-4) OR THE '337 PCT PUBLICATION (GROUND 5) IS PRIOR ART

Petitioner asserts Grounds 3-4 based on the *Cell* article and Ground 5 based on the '337 PCT Publication, but neither of these references is prior art. First, the portions of the *Cell* article and '337 PCT Publication that Petitioner relies upon for the invention of claim 2 were conceived by the named inventor of the '086 patent (Dr. Brenner), not "by another" (Dr. Bieganowski), meaning that the *Cell* article and '337 PCT Publication are not prior art under 35 U.S.C. § 102(a) or § 102(e). Second, as the Board correctly found in its Institution Decision, Petitioner's unsupported and inapplicable Paris Convention argument regarding the '086 patent's priority fails to establish the *Cell* article as prior art under 35 U.S.C. § 102(b).

A. The Asserted *Cell* Article and '337 PCT Publication Are Not "By Another" and Thus Not Prior Art Under 35 U.S.C. § 102(a) or § 102(e)

Grounds 3-5 of the Petition are based on the *Cell* article and '337 PCT Publication. *See* Pet. at 35, 42-50. To qualify as § 102(a) or § 102(e) prior art, these references must be "by another," *i.e.*, the relied-upon subject matter thereof must have been invented by someone other than the inventor of the challenged '086 patent (Dr. Brenner). The relied-upon subject matter, however, was invented

solely by Dr. Brenner, as confirmed by declaration testimony from Dr. Brenner,[4] corroborating disclaimer declaration and deposition testimony from Dr. Bieganowski, the superior-subordinate relationship between Drs. Brenner and Bieganowski, and Dr. Brenner's review of documentation. The *Cell* article and the '337 PCT Publication are therefore not "by another" and not prior art under § 102(a) or § 102(e).

1. To Qualify as Prior Art Under § 102(a) or § 102(e), Relied-Upon Subject Matter in the Reference Must Be Invented "By Another," *i.e.*, by Dr. Bieganowski

Under Pre-AIA § 102, an inventor's own work is prior art *only if* it constitutes a statutory bar under § 102(b). *See In re Katz*, 687 F.2d 450, 454 (C.C.P.A. 1982). An inventor's own work is thus not prior art under § 102(a) or § 102(e). *See id.*; § 102(e).

A patentee may "overcome a prior art reference under section 102(e)" by "establish[ing] that the relevant disclosure describes their own invention." *In re Costello*, 717 F.2d 1346, 1351 (Fed. Cir. 1983). For this, "the relevant question is

[4] A first declaration of Dr. Brenner was submitted in connection with Patent Owner's Preliminary Response. Ex. 2002. Patent Owner also submits a second declaration of Dr. Brenner in connection with this Patent Owner Response. Ex. 2015.

… whether the portions of the reference relied on as prior art, and the subject matter of the claims in question, represent the work of a common inventive entity." *EmeraChem Holdings, LLC v. Volkswagen Grp. of Am., Inc.*, 859 F.3d 1341, 1345 (Fed. Cir. 2017) (internal quotation omitted). A patentee may overcome a prior art reference under § 102(a) the same way, *i.e.*, by establishing that the relied-upon portions of the reference describe their own invention. *See Katz*, 687 F.2d at 455.

The Federal Circuit set forth the following test "to decide whether a reference … is 'by another'":

> [T]he Board must (1) determine what portions of the reference … were relied on as prior art to anticipate the claim limitations at issue, (2) evaluate the degree to which those portions were conceived "by another," and (3) decide whether that other person's contribution is significant enough, when measured against the full anticipating disclosure, to render him a joint inventor of the applied portions of the reference … .

Duncan Parking Techs., Inc. v. IPS Grp., Inc., 914 F.3d 1347, 1358 (Fed. Cir. 2019); *see, e.g.*, *Ethicon LLC v. Intuitive Surgical, Inc.*, 847 F. App'x 901, 908-09 (Fed. Cir. 2021) (applying the *Duncan Parking* test and reversing the Board).

Moreover, the burden of production and the ultimate burden of persuasion are on Petitioner to establish that the *Cell* article and '337 PCT Publication are "by another" and therefore prior art. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015); 35 U.S.C. § 316(e); *Varian Med. Sys.*

v. William Beaumont Hospital, IPR2016-00160, Paper 82, 21-22 (P.T.A.B. May 4, 2017).

Under the *Duncan Parking* test, for the *Cell* article or the '337 PCT Publication to be prior art to claim 2, someone other than Dr. Brenner, the sole inventor of the '086 patent, must have "conceived" some "significant" contribution to the relied-upon portions of the reference and thus be a "joint inventor" of the relied-upon portions. Dr. Bieganowski is the only potential "other person[]," as he is the only other individual named in the *Cell* article and '337 PCT Publication besides Dr. Brenner. *See* Ex. 1007 at (75); Ex. 1008 at 495. Therefore, Petitioner has the burden of establishing that Dr. Bieganowski conceived of—and thus invented—some significant contribution to the relied-upon portions of those two references.

Petitioner's Reply to Patent Owner's Preliminary Response argues that a reference may alternatively be "by another" if the "[relied-upon] portions do not represent the *inventive* work of Dr. Brenner, but instead represent the work of those in the prior art." Paper 15 at 8-10 (emphasis in original). That is, Petitioner argues that the references are "by another" because certain relied-upon portions were allegedly in the prior art and thus not invented by either Dr. Brenner or Dr. Bieganowski. But Petitioner is wrong on multiple levels.

Foundationally, if the relied-upon portions were already in the prior art, then Petitioner could just assert the underlying prior art reference. But instead, Petitioner attempts to obfuscate and back-door a way around the proper "by another" analysis. The law discussed above makes clear that the "by another" analysis asks who *invented* the relied-upon portions and does not, as Petitioner argues, ask whether the relied-upon portions constitute an invention in the first place as opposed to merely "the work of those in the prior art."

Indeed, the "by another" test in *Duncan Parking* presumes that the relied-upon portions are inventive by asking whether those applied portions were "conceived" and "joint[ly] invent[ed]" by some other person. 914 F.3d at 1358; *see also CSL Behring LLC v. Bioverativ Therapeutics Inc.*, IPR2018-01313, Paper 10, 11 (P.T.A.B. Jan. 9, 2019) ("As to what inquiry is relevant, in *Katz* the Federal Circuit determined that a reference by an inventor co-authored with non-inventors was not § 102(a) prior art on the basis that the co-authors contribution fails to rise to joint inventorship … ." (citing 687 F.2d at 455-56)). Moreover, the *Duncan Parking* test requires an identifiable "other person[]" in order for a reference to be "by another," and does not contemplate, as Petitioner suggests, that relied-upon portions of a reference can be contributed generally by "those in the prior art." *Compare* 914 F.3d at 1358 *with* Paper 15 at 8-10.

2. The Invention of the '086 Patent and Relied-Upon Subject Matter in the *Cell* Article and '337 PCT Publication

Dr. Brenner worked from 2003 to 2009 as a professor and researcher at Dartmouth Medical School, where he was the project leader and principal investigator of the NR research project. Ex. 2002 ¶ 10. As a part of that project, in late 2003, Dr. Brenner directed experiments and assays related to NR, and as a result, Dr. Brenner discovered that NR is an NAD+ precursor in a previously-unknown pathway, identified and named an Nrk gene and discovered sequences of the Nrk1 and Nrk2 genes in humans, and ultimately conceived of therapeutic uses and compositions of NR. *Id.* ¶ 11; Ex. 2015 ¶¶ 9-10, 12. One member of Dr. Brenner's research team was Dr. Bieganowski, a postdoctoral fellow in molecular biology who performed, at Dr. Brenner's direction, experiments and assays for identifying yeast and human genes that have Nrk activity. Ex. 2002 ¶ 12; Ex. 2003 ¶ 6; Ex. 2015 ¶¶ 11-12.

Certain aspects of the NR research project were disclosed in the '347 Provisional, which Dartmouth filed on February 20, 2004. Ex. 2002 ¶ 14; *see* Ex. 1005 at 2. Dartmouth later claimed priority to the '347 Provisional in the '337 PCT Application, which was published as the '337 PCT Publication. *See* Ex. 1007; Pet. at 32; Ex. 2002 ¶¶ 6-7, 15; Ex. 2003 ¶¶ 5, 7. Certain results from the NR research project were also published in the *Cell* article. *See* Ex. 1008; Pet. at 30; Ex. 2002 ¶¶ 8, 14, 17-18; Ex. 2003 ¶¶ 5, 7.

The ’347 Provisional and the ’337 PCT Publication name both Dr. Brenner and Dr. Bieganowski as co-inventors. *See* Ex. 1005 at 3; Ex. 1007 at (75); Ex. 2002 ¶¶ 6-7; Ex. 2003 ¶ 5. Likewise, the *Cell* article names both Dr. Brenner and Dr. Bieganowski as co-authors. *See* Ex. 1008 at 495; Ex. 2002 ¶ 8; Ex. 2003 ¶ 5. Petitioner’s initial assertion of these references as prior art under § 102(a) and § 102(e) is based merely on the fact that these references name both Dr. Brenner and Dr. Bieganowski. Pet. at 32 n.7.

However, under *Duncan Parking*, to determine whether these two references are actually “by another,” the Board must determine specifically “what portions of the reference … [are] relied on as prior art to [invalidate] the claim limitations at issue.” 914 F.3d at 1358; *see Ethicon*, 847 F. App’x at 908-09 (reversing the Board because it “did not correctly identify the portions of [the reference] relied on”).

Here, the invention that is recited in claim 2 of the ’086 patent is a composition for therapeutic use of NR, which is isolated from a natural or synthetic source. Thus, while some relied-upon portions of the *Cell* article and ’337 PCT Publication mention isolation techniques and other routine or previously-known methods and technologies as background, all are specifically applied to, and relied upon in the context of, therapeutic uses and compositions of NR. Ex. 2015 ¶¶ 15-30; *see* Ex. 2016 at 83:3-13, 84:23-86:8, 87:1-7, 87:23-88:25

(acknowledging that cited portions of the *Cell* article and '337 PCT Publication are being relied upon for a "pharmaceutical composition").

3. The Relied-Upon Subject Matter in the *Cell* Article and '337 PCT Publication Was Invented Only by Dr. Brenner And Not Dr. Bieganowski

Dr. Brenner is the sole named inventor of the challenged '086 patent. '086 patent at (75); Ex. 2002 ¶¶ 1-5. Dr. Brenner is also the sole inventor of the subject matter of the *Cell* article and '337 PCT Publication upon which Petitioner relies for Grounds 3-5, and therefore neither of those references is "by another."

All relied-upon portions of the *Cell* article and '337 PCT Publication are relied upon by Petitioner in relation to the therapeutic use of NR in an oral pharmaceutical composition with a carrier, which is the subject of challenged claim 2. And Dr. Brenner was solely responsible for all aspects of the NR research project related to therapeutic uses and compositions of NR and all inventions regarding the same. Ex. 2002 ¶ 13; Ex. 2015 ¶¶ 12, 15-30; *see also* Ex. 2003 ¶ 7. Dr. Bieganowski did not contribute to or conceive of any aspect of the NR research project regarding therapeutic uses or compositions of NR, much less make a contribution "significant enough, when measured against the full anticipating disclosure, to render him a joint inventor" under *Duncan Parking*. 914 F.3d at 1358; Ex. 2002 ¶ 13; Ex. 2003 ¶ 7; Ex. 2015 ¶¶ 4, 11-12.

a. Dr. Brenner Invented the Relied-Upon Subject Matter in the Cell Article

The relied-upon portions of the *Cell* article represent the invention of Dr. Brenner alone, as Dr. Bieganowski did not invent any subject matter in these relied-upon portions of the *Cell* article. *See* Pet. at 42-48; Ex. 2002 ¶¶ 17-19; Ex. 2003 ¶ 7; Ex. 2015 ¶¶ 15, 27-30. In his declarations, Dr. Brenner identifies each portion of the *Cell* article cited by Petitioner, identifies specifically the subject matter that Petitioner relies upon in each of these cited portions, and then explains how the relied-upon subject matter of each individual cited portion constitutes his invention alone. Ex. 2002 ¶¶ 17-19; Ex. 2015 ¶¶ 15, 27-30. More specifically, Dr. Brenner's second declaration (Ex. 2015) explains that the relied-upon portions of the '337 PCT Publication relate to aspects of his invention of a pharmaceutical composition of NR such as discovery that NR is an NAD+ precursor in a previously-unknown pathway (¶ 28), identification of sources of NR for use in therapeutic compositions (¶¶ 28-29), and use of NR as a therapeutic (¶¶ 28-30). Dr. Brenner also explains that he alone designed the experiments and assays described in the *Cell* article and that Dr. Bieganowski's role was to perform the assays and experiments at his direction. *Id.* ¶¶ 28-29.

b. Dr. Brenner Invented the Relied-Upon Subject Matter in the'337 PCT Publication

The relied-upon portions of the '337 PCT Publication represent the invention of Dr. Brenner alone, as Dr. Bieganowski did not invent any subject matter in these relied-upon portions of the '337 PCT Publication. *See* Pet. at 32-33, 48-50; Ex. 2002 ¶¶ 15-16; Ex. 2003 ¶ 7; Ex. 2015 ¶¶ 15-26. In his declarations, Dr. Brenner identifies each portion of the '337 PCT Publication cited by Petitioner, identifies specifically the subject matter that Petitioner relies upon in each of these cited portions, and then explains how the relied-upon subject matter of each individual cited portion constitutes his invention alone. Ex. 2002 ¶¶ 15-16; Ex. 2015 ¶¶ 15-26. More specifically, Dr. Brenner's second declaration (Ex. 2015) explains that the relied-upon portions of the '337 PCT Publication relate to aspects of his invention of a pharmaceutical composition of NR such as discovery that NR is an NAD+ precursor in a previously-unknown pathway (¶ 18), identification of sources of NR for use in therapeutics (¶¶ 19, 23-24, 26), use of NR as a therapeutic (¶¶ 20-22), and carriers and forms of administration for a pharmaceutical composition of NR (¶ 25). Again, Dr. Brenner also explains that he alone designed the experiments and assays described in the '337 PCT Publication and that Dr. Bieganowski's role was to perform the assays and experiments at his direction. *Id.* ¶¶ 17, 23-24, 26.

c. Dr. Bieganowski Disclaimed Any Inventive Contribution to the Relied-Upon Subject Matter

Dr. Bieganowski, in his sworn declaration, disclaims any inventive contribution to the relied-upon portions of the *Cell* article and '337 PCT Publication. Ex. 2003 ¶ 7. He also confirms that Dr. Brenner designed the experiments related to the NR research project, and that his role was to perform the experiments at Dr. Brenner's direction. *Id.* ¶ 6.

Despite having the opportunity to depose Dr. Bieganowski on this issue, Petitioner obtained ***zero*** evidence that Dr. Bieganowski conceived any aspect of the relied-upon portions. *See generally* Paper 15 (failing to even argue, much less cite deposition evidence, that Dr. Bieganowski conceived or invented any aspect of the relied-upon subject matter). Instead, Dr. Bieganowski's deposition testimony confirmed that he did not invent any aspect of the relied-upon portions. Ex. 1025 at 26:14-23, 10:10-20 (disowning any inventive contribution related to the "use of NR as a drug or supplement"); *see also* Ex. 1025 at 19:10-14, 21:22-22:14 (testifying that Dr. Brenner designed the experiments reflected in the *Cell* paper and that Dr. Bieganowski performed those experiments at Dr. Brenner's direction using routine techniques).

4. Patent Owner's Evidence For the "By Another" Issue Is Corroborated and Sufficient

Patent Owner presents unequivocal declarations regarding who invented the relied-upon subject matter of the *Cell* article and '337 PCT Publication, including two declarations from the only inventor of the '086 patent, Dr. Brenner (Ex. 2002, Ex. 2015), and a corroborating disclaimer declaration from an uninterested person, Dr. Bieganowski (Ex. 2003), who is the only other individual named in the references. Dr. Brenner's declarations and Dr. Bieganowski's corroborating declaration are all further corroborated by Dr. Bieganowski's deposition testimony that he did not invent the relied-upon portions (Ex. 1025). Moreover, the declaration testimony is further corroborated by the professor-subordinate relationship between Drs. Brenner and Bieganowski, the declarants' respective roles in the NR research project, and Dr. Brenner's review of contemporaneous documentation in the form of the first public description (Ex. 1008) and early patent filings (Ex. 1005, Ex. 1007) describing the NR research project. This evidence is more than sufficient to corroborate Dr. Brenner's testimony and to establish that the relied-upon portions of the two references are "by another."

Where an inventor of a challenged patent is one of two co-authors or co-inventors of an earlier reference, either a declaration by the inventor of the challenged patent that he conceived the relied-upon portions or a disclaimer declaration by the other named co-author or co-inventor of the reference can be

sufficient to establish that the reference is not "by another" and is thus not prior art. *See, e.g.*, *Katz*, 687 F.2d at 455-56 (finding inventor declaration sufficient for § 102(a) reference); *In re DeBaun*, 687 F.2d 459, 463 (C.C.P.A. 1982) (finding inventor declaration sufficient for § 102(e) reference); *Ex Parte Hirschler*, 1952 Pat. App. LEXIS 55, at *7-10 (B.P.A.I. Jan. 31, 1952) (finding disclaimer affidavit sufficient for § 102(a) reference); *In re Mathews*, 408 F.2d 1393, 1396 (C.C.P.A. 1969) (finding disclaimer declaration sufficient for § 102(e) reference). Although either an inventor declaration or a disclaimer declaration can suffice, here, Patent Owner provides both and thus leaves no doubt. *See* Ex. 2002; Ex. 2003; Ex. 2015.

Also, Dr. Brenner's declaration testimony is not a "naked assertion" as Petitioner alleges. *See* Paper 15 at 2-4 (citing *EmeraChem*, 859 F.3d at 1345-47). *EmeraChem* found that a "declaration amounts to a naked assertion by an inventor" when "[n]othing in the declaration itself, or in addition to the declaration, provides any context, explanation, or evidence to lend credence to the inventor's bare assertion." 859 F.3d at 1345. Here, however, Dr. Brenner's declarations provide background and context for the laboratory work and inventions that led to and are reflected in the at-issue references, including the respective roles of Drs. Brenner and Bieganowski. *See* Ex. 2002 ¶¶ 10-14; Ex. 2015 ¶¶ 6-14. Dr. Brenner also individually discusses each relied-upon portion of the at-issue references and

explains how the relied-upon subject matter in each portion relates to his work and constitutes his invention alone. *See* Ex. 2015 ¶¶ 15-30.

Additionally, Dr. Brenner's declarations are corroborated by Dr. Bieganowski's uninterested disclaimer declaration, which confirms that he did not contribute to "therapeutic uses or compositions of [NR]" and instead simply performed, at Dr. Brenner's direction, "the experiments and assays [Dr. Brenner] had designed for identifying yeast and human genes that have [NR] kinase activity." Ex. 2003 ¶¶ 6-7; *see Varian*, IPR2016-00160, Paper 82, 21-22; *Sandt Tech., Ltd. v. Resco Metal & Plastics Corp.*, 264 F.3d 1344, 1351 (Fed. Cir. 2001) ("[T]estimony of someone other than the alleged inventor may corroborate an inventor's testimony." (citation omitted)). Dr. Brenner's declarations, as well as Dr. Bieganowski's own declaration, are further corroborated by Dr. Bieganowski's deposition, where he again confirmed that he is not an inventor of the subject matter at issue. *See* Ex. 1025 at 10:10-20, 21:22-22:14. Dr. Bieganowski's deposition testimony also confirmed the context of the NR research project, including that Dr. Brenner designed all of the experiments reflected in the *Cell* article and that Dr. Bieganowski performed those experiments at Dr. Brenner's direction using routine techniques. *Id.* at 16:18-17:16, 19:10-14, 21:22-22:14.

Additionally, Dr. Brenner's testimony is corroborated by the superior-subordinate relationship between him and Dr. Bieganowski in relation to the NR

research project that resulted in the *Cell* article and '337 PCT Publication. For example, when an inventor declaration provides "explanation that [the inventor's] co-authors [for an asserted reference] were students under his direction and supervision," then it contains "more than a naked assertion." *EmeraChem*, 859 F.3d at 1347-48. That is true here, as Dr. Brenner's declarations, as well as the corroborating declaration and deposition testimony by Dr. Bieganowski, explain that Dr. Brenner designed the relevant experiments and that Dr. Bieganowski, as a postdoctoral fellow in Dr. Brenner's laboratory, performed experiments under Dr. Brenner's direction and supervision. *See* Ex. 2002 ¶¶ 10-12; Ex. 2015 ¶¶ 11-12; Ex. 2003 ¶ 6; Ex. 1025 at 16:18-17:16, 19:10-14, 21:22-22:14. The *Cell* article itself further corroborates this relationship by listing Dr. Brenner as the senior author and only providing correspondence information for Dr. Brenner. Ex. 1008 at 495.

Additionally, while an inventor is not required to rely upon contemporaneous documentary evidence, *see EmeraChem*, 859 F.3d at 1347, Dr. Brenner's testimony is supported by his review of contemporaneous documentation of his NR research project. This documentation includes the *Cell* article itself, as the first, contemporaneous, public description of Dr. Brenner's work on the subject matter at issue, as well as the '347 Provisional, as an early, contemporaneous patent filing regarding the same. Ex. 2015 ¶¶ 3, 13; Ex. 2002 ¶

9. Dr. Brenner also bases his declaration testimony on his review of an intervening declaration regarding therapeutic NR formulations that he submitted to the USPTO in 2012 as an inventor of the related '400 Application. *Id.* ¶ 14, Exhibit A. This documentation confirmed Dr. Brenner's memory that he conceived the inventions in the relied-upon portions of the at-issue references. *Id.* ¶¶ 13-14.

Additionally, the claims and inventorship of the '086 patent and '807 patent versus the '337 PCT support the declarants' testimony that therapeutic compositions of NR were conceived by only Dr. Brenner because the '086 patent and '807 patent, which name only Dr. Brenner as an inventor, only include claims directed to pharmaceutical compositions of NR, whereas the '337 PCT, which also names Dr. Bieganowski as an inventor, includes claims not limited to therapeutic compositions of NR. *See* '086 patent at claims 1-5; Ex. 2004 at claims 1-3; Ex. 1007 at 68-72.

In sum, the totality of the evidence is consistent and makes clear that the relied-upon subject matter in both the *Cell* article and '337 PCT Publication asserted in Grounds 3-5 is Dr. Brenner's own invention and not the invention of Dr. Bieganowski.

5. The Board's Institution Decision in IPR2021-00491

The Board's Institution Decision in *Thorne Research, Inc. v. Trustees of Dartmouth College*, IPR2021-00491 ("the '491 IPR") is also relevant to the "by

another" issue here. In the '491 IPR, Petitioner asserts the *Cell* article and '337 PCT Publication as purported prior art against claims of the'807 patent, a related parent of the '086 patent, and at the preliminary stage of the '491 IPR, Patent Owner sought to establish that those references are not "by another" by submitting evidence that is substantially similar to Dr. Brenner's first declaration and Dr. Bieganowski's declaration and deposition testimony in the present IPR. *Compare* Ex. 2002, Ex, 2003, Ex. 1025 *with* IPR2021-00491, Ex. 2002, Ex. 2003, Ex. 2004. However, the "by another" analysis in the Board's Institution Decision in the '491 IPR did not consider the layers of corroboration and the full scope of all pertinent evidence here.

The Board's analysis found that Dr. Brenner's testimony was "conclusory," that he did not use any contemporaneous documentation to confirm his memory, and that his testimony was not supported by any corroborating evidence. IPR2021-00491, Paper 18, 17-20. At the outset, a second declaration from Dr. Brenner that individually addresses each relied-upon portion of the at-issue references, as discussed above in Section III.A.3, is submitted herewith, and this declaration was not previously submitted in the '491 IPR. Second, the Board did not consider that the *Cell* article and '347 Provisional constitute contemporaneous documentation that Dr. Brenner reviewed to affirm his memory, as discussed above in Section III.A.4. For example, the Board, without explanation, did not consider Dr.

Brenner's consideration of the *Cell* article because it is an asserted reference. But the *Cell* article is documentary evidence of the experiments and work Drs. Brenner and Bieganowski were undertaking at that time. Moreover, in the present IPR, Dr. Brenner relied upon an intervening 2012 declaration to affirm his memory. Ex. 2015 ¶ 14, Exhibit A. Additionally, the Board did not recognize that Dr. Brenner's testimony is corroborated by both Dr. Bieganowski's uninterested disclaimer declaration and deposition testimony, as well as the superior-subordinate relationship between Drs. Brenner and Bieganowski, as discussed above in Sections III.A.3-4.

The Board's analysis also found Dr. Bieganowski's declaration to be uncorroborated and conclusory. IPR2021-00491, Paper 18, 18-20. This finding appears to evaluate Dr. Bieganowski's declaration as that of an interested inventor requiring corroboration. But Dr. Bieganowski submitted a *disclaimer* declaration, was deposed by the Petitioner, and his involvement "does not rise to the level of self-interest required to justify triggering application of the corroboration rule." *See Thomson, S.A. v. Quixote Corp.*, 166 F.3d 1172, 1176 (Fed. Cir. 1999). Dr. Bieganowski's disclaimer declaration is one form of corroborating evidence for Dr. Brenner's inventor declaration. The Board points to no authority requiring or explaining why corroborating testimony, like Dr. Bieganowski's, also needs to be separately corroborated by even more evidence. Additionally, Dr. Bieganowski's

testimony is also reliable and credible because it was under oath and subject to cross-examination. *See Trans Ova Genetics, LC v. XY, LLC*, No. IPR2018-00250, Paper 35, 10 n.9 (P.T.A.B. June 26, 2019).

The Board's analysis also found that Dr. Brenner claimed to have invented the work of another. IPR2021-00491, Paper 18, 19-20. However, Dr. Brenner's second declaration submitted herewith clarifies that the portion of the '337 PCT Publication at issue (at 3:31-4:6) is relied upon by Petitioner for its teaching that NR is an NAD+ precursor in a previously-unknown pathway, which Dr. Brenner discovered, and not for its disclosure of others' work regarding NR being a NAD+ precursor in bacteria. Ex. 2015 ¶ 18. The Board's analysis also focused on the wrong subject matter regarding the *Cell* article, as Petitioner does not rely upon the *Cell* article for just teaching NR isolation techniques but instead for allegedly teaching the therapeutic use of isolated NR in a pharmaceutical composition, as discussed in Section III.A.2. *See also* Ex. 2015 ¶¶ 27-30.

B. The Asserted *Cell* Article Is Not Prior Art Under 35 U.S.C. § 102(b)

Grounds 3-4 of the Petition are based on the *Cell* article, which Petitioner asserts is prior art under pre-AIA § 102(b). *See* Pet. at 30 n.6, 35, 42-48. However, as Patent Owner explained in its Preliminary Response, and as the Board correctly found in its Institution Decision, the *Cell* article does not qualify as prior art under § 102(b). Paper 10 at 14-25; Paper 21 at 15-17. This is because the '086

patent claims priority to the '701 Application filed April 25, 2005 (*see* '086 patent at 1:7-13), and the *Cell* article—which was not purportedly published until May 14, 2004 (*see* Pet. at 30 n.6; Ex. 1008 at 495)—therefore was not published "more than one year prior to" the '086 patent's priority date as required by § 102(b).

Petitioner's challenge to the '086 patent's priority claim is unsupported and inapplicable. Petitioner's challenge is premised entirely the Paris Convention (Article 4(C)(1)-(2), (4)) and the PCT (Article 8(2)(a)). *See* Pet. at 7-14. However, these treaties are not self-executing and are only given effect if implemented by U.S. statute. *See In re Rath*, 402 F.3d 1207, 1209-10 (Fed. Cir. 2005); *Yasuko Kawai v. Metlestics*, 480 F.2d 880, 884 (C.C.P.A. 1973); *Actelion Pharm., Ltd. v. Matal*, 881 F.3d 1339, 1341 (Fed. Cir. 2018). Petitioner's priority argument thus fails because it relies entirely on non-binding treaties and cites no U.S. statute or case law for support. *See* Pet. at 6-14.

Additionally, the relied-upon portions of the Paris Convention and PCT are enacted in 35 U.S.C. § 119. *See Scimed Life Sys. v. Medtronic Vascular, Inc.*, 468 F. Supp. 2d 60, 67 n.6 (D.D.C. 2006) (citing *Vogel v. Jones*, 486 F.2d 1068, 1072 (C.C.P.A. 1973)). Section 119, however, relates to claims of ***foreign*** priority. *See* § 119(a), (c); *Return Mail, Inc. v. U.S. Postal Serv.*, 139 S. Ct. 1853, 1864 n.5 (2019); *In re Gosteli*, 872 F.2d 1008, 1010-11 (Fed. Cir. 1989); *see also* Paris Convention Art. 4(A)(1). Here, the '086 patent's priority claim instead involves

only ***domestic*** priority, via U.S. patent applications and a PCT application designating the United States. *See* '086 patent at 1:7-13. This domestic priority claim is governed by § 120, and § 119 is inapplicable. *See* §§ 120, 363, 365(c); *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1324 n.5 (Fed. Cir. 2008).

Moreover, even if the Paris Convention and PCT were self-executing and applied by the Board, Petitioner's argument fails because PCT Article 8(2)(b) includes a relevant exception under which the '495 PCT's priority claim to the '701 Application is exempted from the rule that Petitioner relies upon in Paris Convention Article 4.

Under the proper governing statute, the '086 patent's priority claim to the '701 Application is proper because it satisfies each of the requirements of § 120, as do the priority claims of the intermediate '400 Application and '495 PCT. *See* '086 patent at 1:7-13; *In re NTP, Inc.*, 654 F.3d 1268, 1277 (Fed. Cir. 2011). Indeed, the Petition fails to argue otherwise. *See* Pet. at 6-14. First, each application in the priority chain satisfies the requirements of § 112 regarding claim 2 of the '086 patent, as the specifications of the '086 patent, '400 Application, '495 PCT, and '701 Application are all the same with respect to disclosure of the claim 2 invention. For example, the Petition asserts that the subject matter of claim 2 of the '086 patent is supported by the following disclosures in the '086 patent: 2:62-3:3, 4:1-2, 4:14-23, 8:57-62, 26:32-39, 26:64-27:4, 27:66-28:15, 28:49-29:37,

29:43-30:12, 32:54-33:2. *See* Pet. at 9-13. And those same exact disclosures are contained in the ’400 Application, ’495 PCT, and ’701 Application. Second, all applications in the priority chain name the same common inventor: Dr. Brenner. *See* ’086 patent at (75); Ex. 2004 at (75); Ex. 2005 at (75); Ex. 2006 at 1. Third, there was co-pendency among applications in the priority chain because each link in the chain was co-pending with the preceding application in the chain. For example, the ’086 patent was filed on April 12, 2012, before the issuance of the ’400 Application as the ’807 patent on June 12, 2012. *See* ’086 patent at (22); Ex. 2004 at (45). Fourth, all applications in the chain specifically identify the earlier-filed applications to which priority is claimed. For example, the ’086 patent contains a reference to the ’701 Application and to the earlier-filed ’400 Application and ’495 PCT in the chain. *See* ’086 Patent at 1:7-13.

IV. PETITIONER HAS NOT MET ITS BURDEN OF SHOWING UNPATENTABILITY OVER EITHER GROUND 1 OR 2 BECAUSE STAMLER DOES NOT DISCLOSE OR SUGGEST ALL LIMITATIONS OF CLAIM 2

Petitioner asserts Grounds 1-2 based on Stamler but fails to establish that Stamler discloses or suggests all limitations of claim 2 of the ’086 patent. First, Petitioner asserts a collateral estoppel argument in an attempt to dodge the requirement of showing that Stamler discloses or suggests the limitations incorporated into claim 2 via its dependency on claim 1, but this argument is unsupported and contrary to law. Next, Petitioner’s anticipation analysis fails

because, as Petitioner concedes, Stamler does not disclose several claim limitations and Petitioner does not argue that Stamler inherently discloses any of the missing limitations. Further, Petitioner's obviousness analysis likewise fails because the Petition relies on unsupported conclusory statements, does not address several obviousness requirements, and does not address or show all limitations of claim 2.

A. Claim Construction

In an IPR, claim terms "shall be construed using the same claim construction standard that would be used to construe the claim in a civil action …, including construing the claim in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." 37 C.F.R. § 42.100(b); *see Immunex Corp. v. Sanofi-Aventis U.S. LLC*, 977 F.3d 1212, 1216 (Fed. Cir. 2020).[5] For purposes of claim construction, the Board may consider claim construction determinations from related IPRs and civil proceedings. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and

[5] Patent Owner contends that a person of ordinary skill in the art with respect to the '086 patent would be someone with a Ph.D. in biochemistry or similar field in the pharmaceutical sciences, with familiarity and experience with pharmacokinetics. Ex. 2014 ¶¶ 18-21. Petitioner applies the same level of ordinary skill. Pet. at 33.

Appeal Board, 83 Fed. Reg. 51,340, 51,344, 51,349 (Oct. 11, 2018); 37 C.F.R. § 42.100(b).

Certain claim terms of the '086 patent have already been construed in a previous IPR—*Elysium Health Inc. v. Trustees of Dartmouth College*, IPR2017-01795 ("the '1795 IPR"), *see* Ex. 1018—and in a co-pending civil action in the District Court for the District of Delaware ("District Court")—*ChromaDex, Inc., et al. v. Elysium Health, Inc.*, Case No. 18-cv-01434 (D. Del.), *see* Ex. 2007; Ex. 2011 ¶ 4.

1. "pharmaceutical composition comprising nicotinamide riboside" (Claim 1)

The Board previously construed "pharmaceutical composition comprising nicotinamide riboside" as shown below.

Claim Term	Construction by the Board in the '1795 IPR
"pharmaceutical composition comprising nicotinamide riboside"	"a composition, including a food composition, which contains NR as an active agent in an amount effective for the treatment or prevention of a disease or condition associated with the nicotinamide riboside kinase pathway of NAD+ biosynthesis" *See* Ex. 1018 at 10-11.

In addition to the Board's construction in the '1795 IPR, the District Court construed the shorter phrase "pharmaceutical composition" to mean "a composition that can be used to improve or prolong the health or well-being of humans or other animals." *See* Ex. 2007 at 3. While Petitioner's arguments fail under either construction, Patent Owner applies the Board's prior construction from the '1795 IPR for purposes of this Patent Owner Response.

2. "carrier" (Claim 1)

The Board previously construed the claim term "carrier" as shown below.

Claim Term	Construction by the Board in the '1795 IPR
"carrier"	"[A] liquid or solid filler, diluent, excipient, or solvent encapsulating material, [that] is involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be acceptable in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient." *See* Ex. 1018 at 14-15.

Patent Owner applies this construction for purposes of this Patent Owner Response.

3. "is isolated from a natural or synthetic source" (Claim 2)

The Board previously construed part of this claim phrase in claim 2—specifically, the term "is isolated"—as shown below.

Claim Term	Construction by the Board in the '1795 IPR
"is isolated"	"the nicotinamide riboside is separated or substantially free from at least some of the other components associated with the source of the molecule such that it constitutes at least 25% (w/w) of the composition" *See* Ex. 1018 at 14.

While the Board previously construed the specific term "is isolated," the Board did not construe the entire claim phrase of "is isolated from a natural or synthetic source." *See* Ex. 1018 at 5-15.[6]

For purposes of Patent Owner's Preliminary Response, Patent Owner applied the Board's prior construction of the limited term "is isolated" but did not

[6] In related litigation, the District Court construed the entire claim phrase to mean "the nicotinamide riboside is isolated from a natural source or synthetic source and is not chemically synthesized." *See* Ex. 2007 at 2. Plaintiffs disagreed with the District Court's construction because it adopted an improper waiver analysis. *See* Ex. 2008 at 41-52, 63-67; Ex. 2011 ¶ 5.

propose a construction for the entire claim phrase. *See* Paper 10 at 30-31.[7] For purposes of this Response, Patent Owner proposes the plain and ordinary meaning of the entire claim phrase, which requires the following, per the express language of the claim: (A) "a natural or synthetic source" of NR and (B) that the NR of the claimed pharmaceutical composition "is isolated from" that source. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) (en banc); '086 patent at claims 1-2; Ex. 2014 ¶¶ 38-39.

This plain and ordinary meaning is consistent with the specification. For example, the '086 patent specification discloses sources of NR (28:16-21), methods for identifying natural or synthetic sources (26:37-63), specific natural or synthetic sources from which NR can be isolated, such as commercially available synthetic sources (26:64-27:3), and methods for isolating extracts, for example, from natural sources (27:3-12, 32:54-33:2, 19:5-28). Moreover, this plain and

[7] In the POPR, Patent Owner expressly stated that it was applying the Board's prior construction of the term "is isolated" specifically "for purposes of [the] Preliminary Response." Paper 10 at 30-31. Patent Owner's application of the Board's prior construction of the specific term "is isolated" does not preclude Patent Owner from proposing a construction for the entire claim phrase in which that specific term is recited.

ordinary meaning's requirement that NR be "isolated from" the claimed source is consistent with the specification, which distinguishes between NR that is "isolated from" a natural or synthetic source and the source itself. *See* '086 patent at 26:64-27:12, 28:16-21, 53:41-43; Ex. 2007 at 2; *see also* Ex. 2014 ¶ 40.

The Petition only addressed the construction of the specific term "is isolated," to which Petitioner applied the Board's prior construction of this limited term. *See* Pet. at 35-38. Petitioner failed to espouse or apply any construction for the entire claim phrase of "is isolated from a natural or synthetic source." *See id.*; Ex. 2016 at 79:12-81:13 (admitting that for his analysis, Dr. Jaffrey adopted a construction for only the term "isolated" and not for the entire claim phrase). The Board's Institution Decision also only addressed the construction of the specific term "is isolated" and not the claim phrase as a whole. *See* Paper 21 at 18-19. As explained below, consideration of the plain and ordinary meaning of this claim phrase illustrates that claim 2 is not invalid over Stamler because Stamler does not disclose or suggest both (A) "a natural or synthetic source" of NR and (B) NR that "is isolated from" that source.

B. Petitioner's Collateral Estoppel Argument Is Unsupported

Petitioner, based on a conclusory misapplication of the law, attempts to avoid its burden to establish unpatentability. Petitioner argues throughout the Petition that Patent Owner is collaterally estopped from relying on the limitations

of claim 1 to support the patentability of claim 2 allegedly due to the Board's prior determination in the '1795 IPR that claim 1 was unpatentable over Goldberger et al. and Goldberger and Tanner. *See* Pet. at 2, 22, 24, 39, 43, 49. The only support that Petitioner provides for its collateral estoppel argument are citations to two decisions: (1) *MaxLinear, Inc. v. CF CRESPE LLC*, 880 F.3d 1373, 1377 (Fed. Cir. 2018) and (2) *Alphatec Holdings, Inc. v. Nuvasive, Inc.*, IPR2019-00361, Paper 59, 23-27 (P.T.A.B. July 8, 2020). *Id.* As a threshold matter, Petitioner's argument fails because Petitioner does not make the requisite showing for collateral estoppel. Regardless, because the references in this IPR are *different* than the references in the prior '1795 IPR, Patent Owner is not estopped from arguing that the references in this IPR fail to teach the limitations of claim 1 from which challenged claim 2 depends. As explained herein, the Board's preliminary decision to the contrary in its Institution Decision is not consistent with the principles of collateral estoppel.

First, Petitioner fails to make the requisite showing for collateral estoppel. "A party seeking to apply the doctrine of collateral estoppel based on a prior action must show that (1) the previous determination was necessary to the decision; (2) the identical issue was previously litigated; (3) the issue was actually decided in a decision that was final, valid, and on the merits; and (4) the party being precluded from relitigating the issue was adequately represented in the previous action. *United Access Techs., LLC v. CenturyTel Broadband Servs. LLC*, 778 F.3d 1327,

1331 (Fed. Cir. 2015) (citations omitted). Petitioner's conclusory collateral estoppel argument does not address these *United Access* factors and thus fails for that reason alone. *See* Pet. at 2, 22, 24, 39, 43, 49.

Second, because different prior art is asserted in this IPR compared to the previous '1795 IPR, the "identical issue" was not previously litigated and thus *United Access* factor (2) is not met and collateral estoppel does not apply. *See TicketNetwork, Inc. et al. v. Ceats, Inc.*, IPR2018-00245, Paper 50, 9 (P.T.A.B. May 31, 2019) ("***Different art*** makes different grounds, which makes for ***different issues***. Collateral estoppel is ***not appropriate*** where the issues are different." (emphasis added) (citing *In re Freeman*, 30 F.3d 1459, 1465 (Fed. Cir. 1994)). Indeed, in *Alphatec*, the Board's decision to apply collateral estoppel was predicated on the fact that the later IPR involved the ***same prior art*** as the earlier IPR. *See Alphatec*, Paper 59, 26 (finding that [i] "the prior action determined that Frey and Michelson teach or suggest all the limitations of … claim 1" and [ii] "Petitioner presents the same issue," *i.e.*, whether Frey and Michelson teach those same limitations, and therefore holding that "the identical issue" was previously litigated).

Certainly the fact that claim 1 was invalidated in the previous '1795 IPR over Goldberger et al. and Goldberger and Tanner does not absolve Petitioner of its burden to establish that the completely different references here in this IPR

disclose each and every limitation of the presumptively valid claim 2, including the limitations of claim 1 incorporated therein. *See, e.g.*, 35 U.S.C. § 282 ("Each claim of a patent … shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim."); *K-Swiss Inc. v. Glide'n Lock GmbH*, 567 F. App'x 906, 911 (Fed. Cir. 2014) ("[I]n order to determine whether [the reference] anticipates dependent claims 3-5, which incorporate the limitations of claim 1, we must first determine whether [the reference] also anticipates independent claim 1).

Third, the Board's preliminary finding for *United Access* factor (2), that "the same issue is present in the instant case" as in the previous '1795 IPR, is not consistent with the aforementioned principles of collateral estoppel. Paper 21 at 12. The Board's reasoning was based on *MaxLinear*, which involved a remand for the Board to consider a dependent claim where the independent claims had been previously found unpatentable over different prior art in another IPR. 880 F.3d at 1374-75. Per the remand instructions, "[i]f the differences between the [dependent] claims and [independent] claims do not materially alter the question of invalidity, collateral estoppel applies," but on the other hand, if "the [dependent] claims present materially different issues that alter the question of patentability, making them patentably distinct from [the independent claims]," then collateral

estoppel does not apply and "the dependent claims … survive the unpatentability of [the independent claims]." *Id.* at 1377-78 (internal quotation marks and citations omitted). The "materially different issue" test in the *MaxLinear* remand instructions is thus for determining whether to apply collateral estoppel to claim 2 in the first place, not for limiting the Board's review to the "materially different issue" as the Board did in the Institution Decision. *See* Paper 21 at 13. Here, there is a "materially different issue" of patentability between claims 1 and 2, as acknowledged by the Board's Institution Decision in this IPR (Paper 21 at 13) and the Board's Final Written Decision in the previous '1795 IPR, which found claim 2 patentable but not claim 1 (Ex. 1018 at 3). Therefore, *MaxLinear* does not support the application of collateral estoppel as proposed by Petitioner.

Moreover, on remand from *MaxLinear*, the Board declined to perform the collateral estoppel analysis as to the dependent claims because the remanded IPR involved different prior art than the IPR in which the independent claims were found unpatentable. *See MaxLinear, Inc. v. Cresta Tech. Corp.*, IPR2015-00592, Paper 87, 36-37 (P.T.A.B. Apr. 17, 2019).

MaxLinear thus does not prevent Patent Owner from arguing that Stamler, which was not asserted in the previous '1795 IPR, fails to invalidate dependent claim 2 in this IPR based on Stamler's failure to teach limitations incorporated into claim 2 from independent claim 1.

C. Ground 1: Stamler Does Not Anticipate Claim 2

Petitioner fails to show that Stamler either explicitly or inherently discloses every limitation of claim 2 of the '086 patent, as required for anticipation. Specifically, Stamler does not disclose "[a] pharmaceutical composition comprising nicotinamide riboside," that the NR is "in admixture with a carrier," or that the NR "is isolated from a natural or synthetic source." '086 patent at claims 1-2. Petitioner concedes that Stamler does not explicitly disclose these limitations, *see* Pet. at 41-42, and Petitioner does not argue that Stamler discloses these limitations inherently.

1. Stamler Does Not Disclose "A pharmaceutical composition comprising nicotinamide riboside"

Claim 2 requires a "pharmaceutical composition comprising nicotinamide riboside," as recited in and incorporated from claim 1. '086 patent at claims 1-2. Petitioner fails to show that Stamler either explicitly or inherently discloses this limitation. Ex. 2014 ¶¶ 41-43, 48.

Petitioner concedes that Stamler does not explicitly disclose a pharmaceutical composition comprising NR. *See* Pet. at 41 (admitting that "Stamler does not provide a specific example of a pharmaceutical composition comprising NR"); Ex. 1002 ¶ 81 (same). Indeed, Petitioner fails to identify even a single composition in Stamler (*see* Pet. at 38-39), and the only mention of ***any*** "composition" in Stamler is the inapplicable disclosure of a "topical composition"

of ribavirin (*see* Stamler at 15). Ex. 2014 ¶ 44. Dr. Jaffrey likewise admitted that Stamler fails to expressly disclose a pharmaceutical composition comprising NR. Ex. 2016 at 28:25-29:21. This is because there is no disclosure in Stamler of a "pharmaceutical composition comprising nicotinamide riboside." Ex. 2014 ¶ 45.

Stamler's teachings are instead directed and limited to ***methods of treatment*** with certain classes of compounds. *See* Stamler at 2-3 (disclosing that all three of Stamler's embodiments are "directed to a method of treating a patient"); Petition at 38 (acknowledging that "Stamler discloses methods of treating a patient," not pharmaceutical compositions); Ex. 2016 at 31:1-14, 32:11-33:14, 57:8-12, 58:17-22 (admitting that "Stamler is directed towards methods of treatment" or "therapeutic use of compounds"); Ex. 2014 ¶ 46. Petitioner does not establish that these methods disclose, much less enable, "[a] pharmaceutical composition comprising nicotinamide riboside" as required by claim 2. Ex. 2014 ¶ 47. At most, Dr. Jaffrey testified that these methods merely "describe ***part of*** [a] composition." Ex. 2016 at 31:1-32:5 (emphasis added).

Moreover, Petitioner does not argue that Stamler *inherently* discloses this limitation. *See* Pet. at 38-39; *see also* Pet. at 21 (alleging that the references in this IPR disclose the composition of claim 2 "explicitly," in contrast to the references asserted in the previous '1795 IPR, which relied upon inherency); Ex. 2014 ¶ 43.

2. Stamler Does Not Disclose Nicotinamide Riboside "in admixture with a carrier"

Claim 2 requires that the claimed "pharmaceutical composition" comprises NR "in admixture with a carrier," as recited in and incorporated from claim 1. '086 patent at claims 1-2. Petitioner fails to show that Stamler either explicitly or inherently discloses this limitation. Ex. 2014 ¶¶ 41, 49-50, 53.

Petitioner concedes that Stamler does not explicitly disclose the claimed "carrier." *See* Pet. at 41 (admitting that "Stamler does not expressly identify a carrier for oral administration"). Indeed, Petitioner fails to identify a single carrier in Stamler. *See id.* at 38-39. Dr. Jaffrey likewise admitted that Stamler fails to explicitly disclose any carrier or excipients. Ex. 2016 at 34:16-20, 40:18-41:2, 53:1-11. This is because there is no disclosure in Stamler of a "carrier," "filler," "diluent," "excipient," or "solvent." *See* Ex. 1018 at 14-15; Ex. 2014 ¶ 51. Stamler does not disclose a pharmaceutical composition of NR, as discussed above, much less a carrier for inclusion in such a composition.

Moreover, Petitioner does not argue that Stamler *inherently* discloses this limitation. *See* Pet. at 38-39; *see also* Pet. at 21 (alleging that the references in this IPR disclose the composition of claim 2 "explicitly," in contrast to the references asserted in the previous '1795 IPR, which relied upon inherency); Ex. 2014 ¶ 50.

Rather than argue that Stamler either explicitly or inherently discloses NR "in admixture with a carrier," as required for anticipation, Petitioner instead relies

on what "an ordinary artisan would have understood" and cites only a paragraph in Dr. Jaffrey's declaration, which in turn cites only the '086 patent itself. *See* Pet. at 39 (citing Ex. 1002 ¶ 73). But this argument is insufficient for anticipation. *Cf. In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997) (holding that anticipation requires an explicit or inherent disclosure). Moreover, Petitioner attempts to cover up Stamler's deficiency by improperly conflating this claim limitation with the separate claim 1 limitation of "formulated for oral administration." *See* Ex. 1002 ¶ 78 (claim chart combines the limitation of "in admixture with a carrier" with the limitation of "formulated for oral administration" but only cites Stamler's disclosure of oral administration); Ex. 2014 ¶ 52.

3. Stamler Does Not Disclose Both (A) "a natural or synthetic source" of Nicotinamide Riboside and (B) Nicotinamide Riboside that "is isolated from" that Source

Claim 2 requires that the claimed "pharmaceutical composition" comprises NR that "is isolated from a natural or synthetic source." '086 patent at claim 2. As explained above in Section IV.A.3, based on the express claim language and the specification, the plain and ordinary meaning of this claim phrase requires both (A) "a natural or synthetic source" of NR and (B) that the NR of the claimed pharmaceutical composition "is isolated from" that source. Under this plain and ordinary meaning, Petitioner fails to show that Stamler either explicitly or inherently discloses this limitation. Ex. 2014 ¶¶ 41, 54-55, 67.

For this limitation, Petitioner relies solely on Stamler's disclosure of NR and Stamler's statement that "[t]he compounds specifically described above are [i] available commercially or [ii] their synthesis is described in or obvious from the literature." *See* Pet. at 39-40 (citing Ex. 1006 at 4, 13); Ex. 1002 at 24; Ex. 2016 at 58:23-59:21. But neither Stamler's [i] commercially available NR nor its [ii] synthesized NR constitutes disclosure of both (A) "a natural or synthetic source" of NR and (B) NR that "is isolated from" that source. Ex. 2014 ¶ 56. Indeed, Petitioner fails to even identify what disclosure of Stamler it alleges to be the claimed "natural or synthetic source," and regardless, Petitioner concedes that "Stamler … does not explicitly state that the NR is isolated." Pet. at 40, 42; Ex. 2014 ¶ 57.

On one hand, Stamler's [i] commercially available NR fails to disclose this limitation. Petitioner does not identify whether Stamler's [i] commercially available NR purportedly constitutes either (A) the claimed "natural or synthetic source" of NR or (B) the claimed NR that "is isolated from" the source. *See* Pet. at 40; Ex. 2014 ¶ 57. If Stamler's [i] commercially available NR only constitutes (A) the "natural or synthetic source," then Stamler fails to teach (B) NR "isolated from" that source, because Dr. Jaffrey admitted that Stamler does not teach that NR is *isolated from* the [i] commercially available NR. Ex. 2016 at 62:17-63:5; Ex. 2014 ¶ 58. And there is no evidence that Stamler's [i] commercially available

NR constitutes (B) NR that "is isolated from" some source because, as Dr. Jaffrey admitted, Stamler does not disclose that its [i] commercially available NR is "isolated from" any source. Ex. 2016 at 66:1-67:3; Ex. 2014 ¶ 60-61.

On the other hand, Stamler's [ii] synthesized NR also fails to disclose this limitation. Petitioner again does not identify whether Stamler's [ii] synthesized NR purportedly constitutes either (A) the claimed "natural or synthetic source" of NR or (B) the claimed NR that "is isolated from" the source. *See* Pet. at 40; Ex. 2014 ¶ 57. If Stamler's [ii] synthesized NR constitutes only (A) the "natural or synthetic source," then Stamler fails to teach (B) NR "isolated from" that source, because Dr. Jaffrey admitted that Stamler does not teach that NR is *isolated from* the [ii] synthesized NR. Ex. 2016 at 65:14-25; Ex. 2014 ¶ 59. And there is no evidence that Stamler's [ii] synthesized NR constitutes (B) NR that "is isolated from" some source because Stamler does not disclose that its [ii] synthesized NR is "isolated from" any source. Ex. 2014 ¶ 60-61. This is demonstrated by Dr. Jaffrey's testimony because he testified that Stamler's [ii] synthesized NR is isolated from an alleged "synthetic preparation," but Dr. Jaffrey admitted that this alleged "synthetic preparation" source is not disclosed in Stamler. Ex. 2016 at 71:24-74:1. And there is no mention in the Petition of this alleged "synthetic preparation" source. *See* Pet. at 40.

Petitioner's failure to establish that Stamler discloses NR that "is isolated from a natural or synthetic source" is not surprising because there is no such disclosure in Stamler. Ex. 2014 ¶ 62. Instead, Petitioner resorts to an entirely different reference not included in Ground 1, *i.e.*, Ex. 1010 ("Franchetti"), in an apparent attempt to address this limitation. *See* Pet. at 40. Indeed, Franchetti is Petitioner's only purported evidence with respect to something being "isolated." *See id.* But Petitioner's reliance on this separate reference is improper and fails to establish that Stamler discloses each and every limitation of claim 2, as required for anticipation. *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999) ("To anticipate, a single reference must teach every limitation of the claimed invention.").

Franchetti nonetheless fails to resolve the deficiency in Stamler. Petitioner relies upon Franchetti's disclosure of a synthesis step in which NR is "purified by chromatography on activated charcoal and isolated as a white solid." Pet. at 40 (citing Ex. 1010 at 4656). But Franchetti is wholly directed to a method for chemically synthesizing NR, as recognized by the '086 patent, the Petition, and Dr. Jaffrey. *See* Ex. 1010 at title ("Stereoselective synthesis of nicotinamide β-riboside and nucleoside analogs"); '086 patent at 28:16-21; Pet. at 28, 40; Ex. 2016 at 76:10-12; Ex. 2014 ¶¶ 63-64. Thus, the alleged isolation step included in Franchetti is ***part of Franchetti's synthesis process***, not a separate isolation

process performed subsequent to Franchetti's synthesis process. *See* Ex. 2016 at 78:1-23; Ex. 2014 ¶¶ 64-65. Indeed, Dr. Jaffrey testified at length that every synthesis involves an isolation step. *See, e.g.*, Ex. 2016 at 21:14-19, 67:4-15, 68:25-69:18. And therefore, when considering Stamler's disclosure of [ii] synthesized NR, *i.e.*, a "synthetic source," a person of ordinary skill in the art would have understood the alleged isolation step in Franchetti to merely be part of the synthesis process that results in that "synthetic source," not a separate subsequent step by which NR "is isolated from" the "synthetic source." *See* Ex. 2016 at 78:1-23; Ex. 2014 ¶ 65.

As previously noted, the plain meaning of the claim language distinguishes between NR that "is isolated from a … synthetic source" and the source itself. While the synthesized NR disclosed in Stamler could qualify as a synthetic source of NR, an isolation step during the synthesis process (*i.e.*, the process for making the synthetic source) cannot qualify as the "isolation" step of claim 2 because the claim requires that the NR be isolated ***from*** the source. Thus, claim 2 requires more than a mere isolation step in a chemical synthesis, as taught by Franchetti. *See* '086 patent at 26:64-67, 28:16-21 (citing Franchetti as an "established

method[]" from which NR "can be chemically synthesized" to obtain "[t]he source of nicotinamide riboside"); Ex. 2014 ¶ 66.[8]

Moreover, Petitioner does not argue that Stamler *inherently* discloses this limitation. *See* Pet. at 40; *see also* Pet. at 21 (alleging that the references in this IPR disclose the composition of claim 2 "explicitly," in contrast to the references asserted in the previous '1795 IPR, which relied upon inherency); Ex. 2014 ¶ 55.

D. Ground 2: Stamler Does Not Render Obvious Claim 2

Petitioner fails to show that Stamler discloses or suggests every limitation of claim 2 of the '086 patent, as required for obviousness. *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (holding that "obviousness requires a suggestion of all limitations in a claim" (citation omitted)). Specifically, Stamler does not disclose or suggest "[a] pharmaceutical composition comprising nicotinamide riboside," that the NR is "in admixture with a carrier," or that the NR "is isolated from a natural or synthetic source." '086 patent at claims 1-2; Ex. 2014 ¶ 68. Petitioner's obviousness arguments for these limitations fail because

[8] Stamler would also not anticipate claim 2 of the '086 patent if the Board were to adopt the District Court's construction of the claim phrase "is isolated from a natural or synthetic source," as it also requires the NR to be isolated ***from*** a natural source or synthetic source. *See* Ex. 2007 at 2.

they are conclusory, do not establish a motivation to modify Stamler, do not establish a reasonable expectation of success, and do not address every element of the claim.

1. Stamler Does Not Teach or Suggest (i) "A pharmaceutical composition comprising nicotinamide riboside" or (ii) Nicotinamide Riboside "in admixture with a carrier"

Petitioner concedes that Stamler does not disclose a pharmaceutical composition comprising NR. *See* Pet. at 41 (admitting that "Stamler does not provide a specific example of a pharmaceutical composition comprising NR"); Ex. 1002 ¶ 81 (same); Ex. 2016 at 28:25-29:21 (same). Petitioner also concedes that Stamler does not disclose the claimed "carrier." *See* Pet. at 41 (admitting that "Stamler does not expressly identify a carrier for oral administration"); Ex. 2016 at 34:16-20, 40:18-41:2, 53:1-11 (same). Petitioner argues instead that these limitations are allegedly obvious "given Stamler's express suggestion of orally administering an inhibitor of glutathione-dependent formaldehyde dehydrogenase, such as NR," and "to facilitate administration of the NR to a patient." Pet. at 41. Petitioner argues that "formulating nicotinamide riboside for oral administration would have been well within the level of skill of the ordinary artisan." *Id.* at 41-42. This is the entirety of the Petition's obviousness argument for these two limitations. *See id.*

a. Petitioner's Obviousness Argument Is Conclusory

Petitioner's obviousness argument fails because it is conclusory. "Rejections on obviousness grounds, in particular, cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *TQ Delta, LLC v. Cisco Sys.*, 942 F.3d 1352, 1359 (Fed. Cir. 2019) (internal quotation marks and citation omitted). In *TQ Delta*, the Federal Circuit reversed the finding of obviousness where the Board relied only on two paragraphs in the petition, which were in turn based on only the asserted reference (which did not expressly disclose a limitation) and two conclusory paragraphs of an expert declaration that, in turn, was based only on the asserted reference. *See id.* at 1361-63.

Here, Petitioner's obviousness argument for the "pharmaceutical composition" and "carrier" limitations is substantially similar to that in *TQ Delta* because the argument comes from a single paragraph of the Petition and cites only Stamler, the challenged '086 patent itself, and four conclusory paragraphs of Dr. Jaffrey's declaration that, in turn, only cite Stamler and the '086 patent. *See* Pet. at 41-42 (citing Ex. 1006, Ex. 1001, Ex. 1002 ¶¶ 80-83); Ex. 1002 ¶¶ 80-83 (citing Ex. 1006, Ex. 1001); Ex. 2016 at 48:9-49:16. And just as in *TQ Delta*, Stamler "provides no express discussion" of the claimed pharmaceutical composition or carrier, and Dr. Jaffrey "fails to identify any other evidence" besides Stamler and

"instead offers only unsupported and conclusory statements." 942 F.3d at 1362. For example, Dr. Jaffrey offers conclusory statements that "a person of ordinary skill in the art would have found it obvious to provide [the claimed] composition," that there was "well-known use of carriers to facilitate administration of pharmaceutical compositions containing an active agent, such as nicotinamide riboside, to a patient," and that "formulating nicotinamide riboside for oral administration would have been well within the level of skill of the ordinary artisan at the time of invention." Ex. 1002 ¶¶ 81-83. As in *TQ Delta*, however, these statements by Dr. Jaffrey "[are] unsupported by any evidence other than the disclosure of the invention in the [challenged patent]." 942 F.3d at 1362. Petitioner's obviousness argument thus fails because the Federal Circuit has "repeatedly recognized that conclusory expert testimony is inadequate to support an obviousness determination." *Id.* at 1359.

b. Petitioner's Obviousness Argument Fails to Establish a Motivation to Modify

Petitioner's obviousness argument for these two limitations is also deficient because the Petition completely fails to state any motivation to modify Stamler. Obviousness based on only a single reference nonetheless requires a showing of motivation to modify the reference to meet the limitations of the claim. *See Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1361 (Fed. Cir. 2016). The Petition, however, does not mention a single motivation for modifying Stamler. *See* Pet. at

41-42. And although the Petition relies on Dr. Jaffrey's declaration, *see id.* (citing Ex. 1002 ¶¶ 80-83), Dr. Jaffrey's conclusory testimony is insufficient to show a motivation to modify Stamler. *TQ Delta*, 942 F.3d at 1362-63. Indeed, Dr. Jaffrey testified that he "did not discuss single reference obviousness" in his declaration and does not even understand the concept of modifying a reference for obviousness, much less understand that single-reference obviousness still requires a motivation to modify the reference. Ex. 2016 at 49:17-51:22.[9]

c. Petitioner's Obviousness Argument Fails to Establish a Reasonable Expectation of Success

Petitioner's obviousness argument for these two limitations is also deficient because the Petition completely fails to address whether a person of ordinary skill in the art would have had a reasonable expectation of success of creating, based on Stamler, "[a] pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier" as required by claim 2. *See* Pet. at 41-42; *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) (holding that the "consistent criterion" for obviousness is "a reasonable likelihood of success, viewed in the

[9] Dr. Jaffrey gave this testimony despite the fact that his own declaration uses single-reference obviousness for Grounds 2 and 4 (¶¶ 79-86, 98-105), includes a discussion of the legal standard for single-reference obviousness (¶ 16), and includes discussion of a motivation to modify for Ground 4 (¶¶ 101-102).

light of the prior art."). Also, the Petition and Dr. Jaffrey's declaration rely on disclosures in the challenged '086 patent itself to argue obviousness, but "the expectation of success must be founded in the prior art, not in the applicant's disclosure." *Dow Chem.*, 837 F.2d at 473; *see* Pet. at 41-42; Ex. 1002 ¶ 82.

Regardless, there is no expectation of success based on Stamler because Stamler does not provide ***any*** guidance for how to formulate a "pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier," as claimed. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365 (Fed. Cir. 2007); *Grunenthal GMBH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1344-45 (Fed. Cir. 2019); Ex. 2014 ¶ 70.

As discussed above, Stamler does not disclose any "pharmaceutical composition" comprising NR or any "carrier." *See* Pet. at 41; Ex. 2016 at 28:25-29:21, 34:16-20, 40:18-41:2, 53:1-11. At most, Stamler merely indicates the active component (NR) and the route of administration (oral). *See* Pet. at 41. But there are many parameters for formulating a pharmaceutical composition and many options for each parameter. Ex. 2014 ¶ 71. Such parameters include the oral delivery form and aspects thereof, carrier and amount thereof, other excipients and amounts thereof, processes for making the composition, and the compatibility of these various parameters with each other and with the active component. *Id.* ¶ 72. Stamler fails to indicate which parameters are critical or to provide any direction as

to which of the many possible choices is likely to be successful for any parameter. *Id.* ¶ 73; Ex. 2016 at 52:11-24.

Indeed, as Dr. Jaffrey acknowledged, a pharmaceutical composition of NR may not be effective if, for example, it includes a noncompatible carrier, includes a noncompatible amount of an otherwise compatible carrier, includes some other noncompatible ingredient, or is made using a process that is not compatible with NR. Ex. 2016 at 37:12-17, 38:1-9, 43:23-44:7, 46:24-47:12, 39:16-40:6; Ex. 2014 ¶ 74. And, as Dr. Jaffrey conceded, Stamler fails to disclose: any oral delivery form, much less which oral delivery form is compatible with NR; any carriers or excipients, much less which carriers are compatible with NR; any amounts of any ingredients other than NR, much less what amounts of carriers are compatible with NR; or what formulation processes to use for making a pharmaceutical composition of NR. Ex. 2016 at 40:18-41:25, 28:10-23, 34:1-20, 52:11-54:9; Ex. 2014 ¶ 75. For example, without such information, there is no reasonable expectation of success for selecting a "carrier" because per the Board's prior construction, "[e]ach carrier must be acceptable in the sense of being compatible with the other ingredients of the formulation." Ex. 1018 at 14-15; Ex. 2014 ¶ 76. Moreover, no other evidence besides Stamler (or the '086 patent itself) is cited by the Petition or Dr. Jaffrey's declaration to establish obviousness of these limitations. *See* Pet. at 41-42; Ex. 1002 ¶¶ 80-83.

Petitioner's failure to establish a reasonable likelihood of success based on Stamler is especially true here because claim 2 of the '086 patent is directed to a "pharmaceutical composition," and as the Federal Circuit has recognized, chemical arts such as formulation science are unpredictable. *See Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008); *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013); Ex. 2014 ¶¶ 77-78.

Because Stamler provides no guidance for how to formulate an effective pharmaceutical composition and carrier for NR, coupled with the unpredictable nature of formulation science and the lack of any other cited evidence, Petitioner has failed to established a reasonable expectation of success for formulating a "pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier" based on Stamler.

d. Testimony by Petitioner's Expert, Dr. Jaffrey, Should Be Given Little Weight Compared to Patent Owner's Expert, Dr. Amiji

Petitioner's obviousness argument regarding the claim limitations of "a pharmaceutical composition" and "carrier" is entirely premised on Dr. Jaffrey's declaration because it is the only evidence Petitioner cites other than the '086 patent itself and Stamler, which fails to disclose these limitations. *See* Pet. at 41-42 (citing Ex. 1006, Ex. 1001, Ex. 1002 ¶¶ 80-83). Aside from the conclusory nature of the declaration, the Board should additionally afford little weight to the

testimony of Dr. Jaffrey because he is relatively inexperienced in formulation of pharmaceutical compositions. Dr. Jaffrey's experience is with mechanisms and therapeutic effects of pharmaceutical compounds, which was the subject of his undergraduate and graduate research. *See* Ex. 2016 at 8:3-23; Ex. 1003 at 1. Notably, Dr. Jaffrey has never formulated a pharmaceutical composition for human therapeutic use, and his only formulation experience is for purposes of his academic research, usually for animal administration. Ex. 2016 at 13:15-17, 12:5-24. Indeed, Dr. Jaffrey does not even satisfy Petitioner's definition for the person of ordinary skill in the art because Dr. Jaffrey has an M.D. and a Ph.D. in Neuroscience, not a "Ph.D. in biochemistry or similar field in the pharmaceutical sciences." *See* Pet. at 33; Ex. 1003 at 1; Ex. 2016 at 8:24-9:10. Dr. Jaffrey even testified that he was "not aware of … an example" where a carrier's safety can depend on a pharmaceutical composition's other ingredients, which directly conflicts with the construction of the term "carrier." Ex. 2016 at 43:3-8; Ex. 1018 at 14-15.

In contrast, Patent Owner's expert, Dr. Amiji, has credentials and experience specific to formulating pharmaceutical compositions. *See* Ex. 2014 ¶¶ 5-16. Therefore, Dr. Jaffrey's testimony regarding the obviousness of the claimed "pharmaceutical composition" and "carrier" for NR should be given little weight.

2. Stamler Does Not Teach or Suggest Both (A) "a natural or synthetic source" of Nicotinamide Riboside and (B) Nicotinamide Riboside that "is isolated from" that Source

Claim 2 requires that the claimed "pharmaceutical composition" comprises NR that "is isolated from a natural or synthetic source," and as explained above in Section IV.A.3, the plain and ordinary meaning of this claim phrase requires both (A) "a natural or synthetic source" of NR and (B) that the NR of the claimed pharmaceutical composition "is isolated from" that source.

As explained above in Section IV.C.3, for this limitation, Petitioner relies solely on Stamler's disclosure of [i] commercially available NR or [ii] synthesized NR. *See* Pet. at 39-40 (citing Ex. 1006 at 4, 13); Ex. 1002 at 24; Ex. 2016 at 58:23-59:21. As also explained above in Section IV.C.3, each of these two disclosures in Stamler fails to disclose both (A) "a natural or synthetic source" of NR and (B) NR that "is isolated from" that source. Ex. 2014 ¶ 79-80. Indeed, Petitioner concedes that "Stamler … does not explicitly state that the NR is isolated." Pet. at 42. Petitioner argues instead that this limitation is obvious based on a single paragraph in the Petition, which alleges only that "synthesis of isolated NR was known in the art"; "NR can be obtained commercially, isolated from natural sources using standard methods, or synthesized using established methods"; and "it would have been well within the level of skill of the POSA to

determine the level of isolation and purity for oral administration." *Id.* This is the entirety of Petitioner's obviousness argument for this limitation. *See id.*

Petitioner makes no attempt with any of its conclusory arguments to show how the disclosure of Stamler teaches or suggests the limitation of "is isolated from a natural or synthetic source." Indeed, the portions of the Petition and Dr. Jaffrey's declaration that relate to this limitation for Ground 2 do not contain even a single citation to Stamler or single mention of Stamler's disclosures, much less discuss how the disclosures of Stamler are alleged to teach or suggest the elements of this limitation. *See* Pet. at 42 (failing to cite or discuss Ex. 1006); Ex. 1002 ¶¶ 84-86 (same).

Petitioner's obviousness argument regarding this limitation also fails because it does not address every element of the limitation. To prove obviousness, Petitioner must demonstrate how each and every claim feature is shown or suggested by Stamler. *CFMT*, 349 F.3d at 1342 (holding that "obviousness requires a suggestion of all limitations in a claim" (citation omitted)). The Petition, however, does not even argue that Stamler discloses or suggests (A) "a natural or synthetic source" as required by the plain and ordinary meaning of claim 2, much less that Stamler discloses or suggests (B) that NR "is isolated from" that source. *See* Pet. at 42; Ex. 2014 ¶ 81. For completeness, however, below is a more

particular explanation as to the Petition's deficiencies and why Stamler does not disclose or suggest both (A) and (B). Ex. 2014 ¶¶ 85, 89

As explained above in Section IV.C.3, if Stamler's [i] commercially available NR or [ii] synthesized NR is considered to be only (A) "a natural or synthetic source" of NR, then Stamler does not disclose (B) NR that is further "isolated from" either [i] or [ii]. *See* Ex. 2016 at 62:17-63:5, 65:14-25; Ex. 2014 ¶ 82. For Ground 2, Petitioner fails to even argue, much less establish, that based on Stamler, it would have been obvious to person of ordinary skill in the art for NR to be further "isolated from" either Stamler's [i] commercially available NR or [ii] synthesized NR. *See* Pet. at 42. Indeed, based on Stamler, a person of ordinary skill would have considered the NR disclosed in Stamler to be sufficient and would not have had any motivation to use NR "isolated from" either of those sources. Ex. 2014 ¶ 82.

As also explained above in Section IV.C.3, Stamler does not disclose that Stamler's [i] commercially available NR itself is (B) "isolated from" some (A) "natural or synthetic source." *See* Ex. 2016 at 66:1-67:3; Ex. 2014 ¶ 83. For Ground 2, Petitioner fails to even argue, much less establish, that it would have been obvious based on Stamler for a person of ordinary skill in the art to use [i] commercially available NR that is "isolated from" a "natural or synthetic source." *See* Pet. at 42. Indeed, Petitioner does not even argue or provide evidence that

there existed [i] commercially available NR that was "isolated" as opposed to synthesized. Ex. 2014 ¶ 83. Rather, based on Stamler's disclosure of synthesized NR, a person of ordinary skill would have understood [i] commercially available NR to be synthesized and would not have had any motivation to instead use [i] commercially available NR that was "isolated from" a "natural or synthetic source." *Id.*

As also explained above in Section IV.C.3, Stamler does not disclose that Stamler's [ii] synthesized NR itself is (B) "isolated from" some (A) "natural or synthetic source." *See, e.g.*, Ex. 2016 at 71:24-74:1; Ex. 2014 ¶ 84. For Ground 2, Petitioner does not argue that it would have been obvious based on Stamler for a person of ordinary skill in the art to use [ii] synthesized NR that is "isolated from" a "natural or synthetic source." *See* Pet. at 42. Indeed, that argument would fail because the plain and ordinary meaning of this limitation distinguishes between NR and the source from which the NR is isolated. Ex. 2014 ¶ 84. Moreover, based on Stamler, a person of ordinary skill would have known and just used chemically synthesized NR and would not have had any motivation to use NR that is instead "isolated from" a "natural or synthetic source." *Id.*

Just as Petitioner did for Ground 1, Petitioner appears to resort to an entirely different reference not included in Ground 2—*i.e.*, Franchetti—in an attempt to address this limitation. *See* Pet. at 42 (citing Franchetti for purported "synthesis of

isolated NR"). However, because Franchetti is not an asserted reference in Ground 2, Petitioner's reliance thereon for the teaching of this limitation is improper.

Regardless, Franchetti fails to resolve the deficiency in Stamler because, as explained above in Section IV.C.3, the alleged isolation step in Franchetti that Petitioner relies upon is ***part of Franchetti's synthesis process***. *See* Ex. 1010 at 4656; '086 patent at 28:16-21; Ex. 2016 at 76:10-12, 78:1-23; Ex. 2014 ¶ 86. And therefore, when considering Stamler's disclosure of [ii] synthesized NR, *i.e.*, a "synthetic source," a person of ordinary skill in the art would have understood the alleged isolation step in Franchetti to merely be part of the synthesis process that results in that "synthetic source," not a separate subsequent step by which NR "is isolated from" the "synthetic source." *See* Ex. 2016 at 78:1-23; '086 patent at 28:16-21 (citing Franchetti as an "established method[]" from which NR "can be chemically synthesized" to obtain "[t]he source of nicotinamide riboside"); Ex. 2014 ¶¶ 87-88.

Moreover, Petitioner's obviousness argument regarding this limitation also fails for similar reasons as discussed above for the limitations of "[a] pharmaceutical composition comprising nicotinamide riboside" and NR "in admixture with a carrier." That is, Petitioner's obviousness argument for the limitation of "is isolated from a natural or synthetic source" fails because, as in *TQ Delta*, the argument (one paragraph) and related portion of Dr. Jaffrey's

declaration (three paragraphs) are conclusory and rely only upon Stamler (which Petitioner admits does not disclose the limitation), the '086 patent itself, and a reference discussed in the '086 patent (*i.e.*, Franchetti). *See* 942 F.3d at 1359, 1361-63; Pet. at 42 (citing Ex. 1002 ¶¶ 84-86; Ex. 1001; Ex. 1010); Ex. 1002 ¶¶ 84-86 (citing Ex. 1001; Ex. 1010); Ex. 2016 at 74:11-75:16.

Petitioner's obviousness argument for this limitation is also deficient because the Petition fails completely to state any motivation to modify Stamler or address any reasonable expectation of success. *See* Pet. at 42; *Arendi*, 832 F.3d at 1361 (holding that a motivation to modify is nonetheless required for single-reference obviousness); *Dow Chem.*, 837 F.2d at 473 (holding that "a reasonable expectation of success" is a "consistent criterion" for obviousness). Indeed, Dr. Jaffrey testified that he does not even understand the concept of modifying a reference for obviousness. Ex. 2016 at 49:17-51:22.

Additionally, as explained above in Section IV.D.1.d, Dr. Jaffrey's testimony regarding obviousness should be given little weight compared to the testimony of Dr. Amiji because Dr. Amiji specializes in the development and formulation of pharmaceutical compositions, such as the pharmaceutical composition of claim 2, whereas Dr. Jaffrey's experience is primarily directed to the mechanisms and therapeutic effects of pharmaceutical compounds. *See, e.g.*, Ex. 2014 ¶¶ 6-16; Ex. 2016 at 8:3-15.

V. CONCLUSION

For the foregoing reasons, the Board should reject all grounds in the Petition and find that claim 2 of the '086 patent is patentable.

Respectfully submitted,

Date: September 21, 2021

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CERTIFICATION UNDER 37 C.F.R. § 42.24

Under the provisions of 37 C.F.R. § 42.24, the undersigned hereby certifies that the foregoing document contains 13,997 words, and thus complies with the word-count limits of 37 C.F.R. § 42.24.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), the undersigned hereby certifies that a copy of the foregoing PATENT OWNER RESPONSE was served on September 21, 2021 by filing this document through the Patent Trial and Appeal Board End to End as well as by delivering a copy via the delivery method indicated to the attorneys of record for the Petitioner as follows:

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