UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ELYSIUM HEALTH, INC.,
Petitioner

v.

TRUSTEES OF DARTMOUTH COLLEGE,
Patent Owner

Case IPR2017-01795

Patent 8,383,086

PRELIMINARY RESPONSE TO PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,383,086

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The Trustees of Dartmouth College ("Patent Owner") respectfully submit this Preliminary Response to the Petition seeking *inter partes* review of U.S. Patent No. 8,383,086 (Ex. 1001, "the '086 patent") filed by Elysium Health, Inc. ("Petitioner"). This Response is timely under 35 U.S.C. § 313 and 37 C.F.R. § 42.107 because it is within three months of the August 5, 2017 date of the Notice granting the Petition a filing date. Paper No. 3, Notice of Filing Date, at 1.

I. INTRODUCTION

Patent Owner respectfully submits that *inter partes* review of the '086 patent should not be instituted because Petitioner has failed to demonstrate that it has a reasonable likelihood of prevailing with respect to any of the challenged claims of the '086 patent.

First, Petitioner has not provided any evidence that either of its prior art references of the proposed Grounds discloses a pharmaceutical composition as recited in claim 1 and in each of the dependent claims of the '086 patent. Because neither prior art reference of the proposed Grounds discloses a pharmaceutical composition as described and claimed in the '086 patent, Petitioner cannot establish that the references anticipate claim 1 of the '086 patent.

Second, Petitioner has not provided any evidence that either of its prior art references of the proposed Grounds discloses the essential claim element of a pharmaceutical composition comprising nicotinamide riboside formulated "in

admixture with a carrier" as claimed in independent claim 1 of the '086 patent. Because neither asserted prior art reference discloses nicotinamide riboside formulated in admixture with a pharmaceutically acceptable carrier as disclosed in the '086 patent, Petitioner cannot establish that the references anticipate claim 1 of the '086 patent.

Third, Petitioner has not provided any evidence that either of its prior art references of the proposed Grounds discloses compositions comprising nicotinamide riboside that "is isolated from a natural or synthetic source," as required by claim 2 of the '086 patent. Petitioner instead relies on an improper claim construction and questionable expert testimony for its argument that nicotinamide riboside present in milk or buttermilk is "isolated" from a natural source when milk is removed from a cow. Petitioner cannot establish that the references anticipate claim 2 of the '086 patent.

Fourth, Petitioner has not provided any evidence that either of its prior art references of the proposed Grounds discloses a pharmaceutical composition comprising nicotinamide riboside that "increases NAD+ biosynthesis upon oral administration," as required by dependent claim 5 of the '086 patent. Petitioner instead relies on an argument regarding milk that was already considered by the Examiner and overcome during prosecution of the parent application to the '086

patent. Petitioner cannot establish that the references anticipate claim 5 of the ’086 patent.

For at least these reasons, the institution of an *inter partes* review of the ’086 patent should be denied.

II. BACKGROUND

The ’086 patent is directed to pharmaceutical compositions of nicotinamide riboside that are formulated in admixture with a pharmaceutically acceptable carrier for oral administration. *See* ’086 patent, at claim 1. The ’086 patent issued from an application filed as a continuation of U.S. Patent Application No. 11/912,400 (“the ’400 Application”), which later issued as U.S. Patent No. 8,197,807.

As disclosed in the ’086 patent, the claimed pharmaceutical compositions increase NAD+ biosynthesis upon oral administration. *See* ’086 patent, at claim 5. Increasing NAD+ levels can help to treat a range of diseases and conditions, including cancer. *See, e.g., id.* at 7:36-8:67. As disclosed in the ’086 patent, NAD+ was known to be formed through de novo synthesis, nicotinic acid import, and nicotinamide salvage. *See id.* at 2:20-29, Scheme 1. The ’086 patent inventor, however, discovered that nicotinamide riboside is “an NAD+ precursor in a previously unknown but conserved eukaryotic NAD+ biosynthetic pathway,” and

that "supplementation with nicotinamide riboside as [a] third importable NAD+ precursor can be beneficial for certain conditions." *Id.* at 2:62-3:3, 8:39-41.

The '086 patent achieves the desired supplementation with pharmaceutical compositions comprising nicotinamide riboside in admixture with other pharmaceutically acceptable components, including a pharmaceutically acceptable carrier, formulated for oral administration. *See id.* at claim 1. The '086 patent includes only five claims, and each of the dependent claims depends directly from independent claim 1. For example, dependent claim 2 covers pharmaceutical compositions comprising nicotinamide riboside that "is isolated from a natural or synthetic source." *See id.* at claim 2. The '086 patent specification includes examples of such sources, and further describes methods for isolating nicotinamide riboside from a natural source such as cow's milk. *See id.* at 26:64-27:12.

Contrary to Petitioner's assertions, the '086 patent does not claim any composition found in nature, nor does it claim any inherent properties of any naturally occurring composition. Instead, the claimed invention of the '086 patent covers, *inter alia*, pharmaceutical compositions of nicotinamide riboside formulated in admixture with a pharmaceutically acceptable carrier for oral administration.

III. CLAIM CONSTRUCTION

In an *inter partes* review, claim terms are interpreted according to their "broadest reasonable construction in light of the specification of the patent in which it appears." *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2136 (2016); *see also id.* at 2144-45; 37 C.F.R. § 42.100(b); Office Patent Trial Practice Guide, 77 Fed. Reg. 48756, 48764, 66 (Aug. 14, 2012). The broadest reasonable construction of the terms must be consistent with the patent specification. *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1259-60 (Fed. Cir. 2010) ("[C]laims should always be read in light of the specification and teachings in the underlying patent."). As the Federal Circuit has explained:

> The correct inquiry in giving a claim term its broadest reasonable interpretation in light of the specification is not whether the specification proscribes or precludes some broad reading of the claim term adopted by the examiner. And it is not simply an interpretation that is not inconsistent with the specification. It is an interpretation that corresponds with what and how the inventor describes his invention in the specification, *i.e.*, an interpretation that is "consistent with the specification."

In re Smith Int'l, Inc., No. 2016-2303, 2017 WL 4247407, at *5 (Fed. Cir. 2017) (quoting *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997)).

The specification should also be considered in light of the express language of the claims themselves. *See Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062

(Fed. Cir. 2016) ("Construing individual words of a claim without considering the context in which those words appear is simply not 'reasonable.'").

In the absence of a reasonable claim construction, a petitioner cannot show a reasonable likelihood of success on its grounds for unpatentability. *See Microsoft Corp. v. Proxyconn, Inc.*, IPR2012-00026, Paper 17 at p. 24 (PTAB Dec. 21, 2012) (explaining that "[a]s this argument is premised on Petitioner's erroneous claim construction we are not persuaded of a reasonable likelihood of prevailing"). Because Petitioner has not offered a reasonable claim construction of the limitation "is isolated from a natural or synthetic source" as claimed in dependent claim 2 of the '086 patent, Petitioner has not demonstrated a reasonable likelihood that it will prevail at least on its assertion that claim 2 is unpatentable.

A. "carrier" (Claim 1)

In addition to the "is isolated" phrase proposed by Petitioner and discussed in more detail below, Patent Owner requests that the Board construe the term "carrier" and adopt Patent Owner's proposed construction below:

Claim Term	Proposed Construction
"carrier"	pharmaceutically acceptable carrier

1. Patent Owner's Proposed Construction Is Consistent With The Claims

All of the '086 patent claims are directed to a "pharmaceutical composition," so the construction for any term in the claims should be construed in the context of those pharmaceutical compositions. *See ACTV, Inc. v. Walt Disney Co.*, 346 F.3d 1082, 1088 (Fed. Cir. 2003) ("While certain terms may be at the center of the claim construction debate, the context of the surrounding words of the claim also must be considered in determining the ordinary and customary meaning of those terms."). The use of the "pharmaceutical composition" phrase in the preamble of claim 1 provides the necessary context for construing the other terms. *See* MPEP § 2111.02 (citing *Poly-Am. LP v. GSE Lining Tech. Inc.*, 383 F.3d 1303, 1310 (Fed. Cir. 2004) ("[A] '[r]eview of the entirety of the '047 patent reveals that the preamble language relating to 'blown-film' does not state a purpose or an intended use of the invention, but rather discloses a fundamental characteristic of the claimed invention that is properly construed as a limitation of the claim.'")). Moreover, the preamble phrase "pharmaceutical composition" in claim 1 is the antecedent basis for the other four recitations of "[t]he pharmaceutical composition of claim 1" in the dependent claims. *See Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1339 (Fed. Cir. 2003) ("When limitations in the body of the claim rely upon and derive antecedent basis from the preamble, then the preamble may act as a necessary component of the claimed invention.").

Claim 1 is specifically directed to "[a] pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier, wherein said composition is formulated for oral administration." '086 patent, at claim 1. Given the context of this claim, a person of ordinary skill in the art would understand that the claimed carrier must be one that is appropriate for use in a pharmaceutical composition. Moreover, the recitation of "admixture" in the claim confirms that the nicotinamide riboside is deliberately mixed together with the type of carrier that will lead to a formulation appropriate for oral administration. In other words, a person of ordinary skill in the art would understand the claimed "carrier" to be a pharmaceutically acceptable carrier.

2. Patent Owner's Proposed Construction Is Consistent With The Specification

The patent specification supports Patent Owner's proposed construction of the claimed "carrier" as a "pharmaceutically acceptable carrier." The specification describes the claimed compositions, including the pharmaceutically acceptable carriers as follows:

> Polypeptides, nucleic acids, vectors, dietary supplements (i.e. nicotinamide riboside), and nicotinamide riboside-related prodrugs produced or identified in accordance with the methods of the invention can be conveniently used or administered in a composition containing the active agent in combination with a ***pharmaceutically-acceptable carrier***. Such compositions can be prepared by methods

> and contain carriers which are well-known in the art. A generally recognized compendium of such methods and ingredients is Remington: The Science and Practice of Pharmacy, Alfonso R. Gennaro, editor, 20th ed. Lippingcott Williams & Wilkins: Philadelphia, Pa., 2000.

'086 patent, at 28:49-60 (emphasis added). A person of ordinary skill in the art would readily understand that the claimed nicotinamide riboside compositions must include a "pharmaceutically acceptable carrier," particularly in light of the patent's description of common formulation methods and citation to the compendium for pharmacy practice. As reflected in the claims, those common formulation methods include the deliberate step of mixing the nicotinamide riboside with a pharmaceutically acceptable carrier to create the claimed formulation comprising nicotinamide riboside "in admixture with a carrier." '086 patent, at claim 1.

The specification also describes the function of such pharmaceutically acceptable carriers, including that they are "involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body." *Id.* at 28:62-64. The specification further emphasizes that the claimed carriers must be "acceptable in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient." *Id.* at 28:65-67; *see also id.* at 29:15-6 (describing example carriers as "non-toxic compatible

substances employed in formulations"). These descriptions are consistent with the way a person of ordinary skill in the art would understand a pharmaceutically acceptable carrier.

Petitioner's proffered expert Dr. Baur uses some of these same concepts in his own discussion of the term "carrier," and so would presumably agree with Patent Owner's proposed construction. Specifically, although Petitioner fails to address whether the prior art actually contained a pharmaceutically acceptable carrier, Petitioner's expert equates carriers with "components that will bind and stabilize the compound." *See* Pet. at 13; Ex. 1002 at 17, ¶32.

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

Petitioner proposes a construction for "is isolated" in dependent claim 2 that is inconsistent with the claim language and patent specification. As discussed in more detail below, the "is isolated" term is part of a phrase in dependent claim 2 that provides context for understanding the claimed nicotinamide riboside. *See Trivascular*, 812 F.3d at 1062 ("Construing individual words of a claim without considering the context in which those words appear is simply not 'reasonable.'"). Accordingly, Patent Owner requests that the Board construe the full phrase as shown below:

Claim Term	Proposed Construction
"is isolated from a natural or synthetic source"	fractionated from other cellular components

1. Patent Owner's Proposed Construction Is Consistent With The Specification

The specification is replete with discussions of the term "isolated," including almost fifty instances of the term in the specification, eleven of which appear in the Background of the Invention. Many instances of the individual term appear in descriptions of the process of isolating molecules from natural or synthetic sources, and all of these instances support Patent Owner's construction of the "is isolated from a natural or synthetic source" phrase.

The specification explains that the source of nicotinamide riboside "can be from a natural or synthetic source identified by the method of the instant invention, or can be chemically synthesized using established methods (Tanimori (2002) *Bioorg. Med. Chem. Lett.* 12:1135-1137; Franchetti (2004) *Bioorg. Med. Chem. Lett.* 14:4655-4658)." '086 patent, at 28:16-21. As an initial matter, this teaching confirms that the claimed nicotinamide riboside can be (1) chemically synthesized, (2) isolated from a natural source, or (3) isolated from a synthetic source. While the specification points to the cited "established methods" for chemical synthesis

of nicotinamide riboside, the specification provides several details on isolating the compound from a natural or synthetic source.

First, the specification describes a method for identifying natural or synthetic sources of nicotinamide riboside:

> Thus, the present invention also encompasses [] a method for identifying such natural or synthetic sources. As a first step of the method, a first cell lacking a functional glutamine-dependent NAD+ synthetase is contacted with an isolated extract from a natural or synthetic source. . . .
>
> As a second step of the method, a second cell lacking a functional glutamine-dependent NAD+ synthetase and a functional nicotinamide riboside kinase is contacted with the same isolated extract from the natural or synthetic source of the prior step. . . .
>
> As a subsequent step of the method, the growth of the first cell and second cell are compared. If the isolated extract contains a nicotinamide riboside, the first cell will grow and the second cell will not.

'086 patent, at 26:37-63. Although the claims do not recite these identification steps, they provide background and context for how a person of ordinary skill in the art would obtain nicotinamide riboside that is not chemically synthesized.

Second, the specification identifies various synthetic and natural sources from which nicotinamide riboside can be isolated:

> Synthetic sources of nicotinamide riboside can include any library of chemicals commercially available from most large chemical companies. . . .
>
> Natural sources which can be tested for the presence of [] nicotinamide riboside include, but are not limited to, cow's milk, serum, meats, eggs, fruit and cereals.

'086 patent, at 26:64-27:3.

Finally, the specification includes a description of standard methods for isolating extracts from natural sources:

> Isolated extracts of the natural sources can be prepared using standard methods. For example, the natural source can be ground or homogenized in a buffered solution, centrifuged to remove cellular debris, and fractionated to remove salts, carbohydrates, polypeptides, nucleic acids, fats and the like before being tested on the mutant[] strains of the invention. Any source of nicotinamide riboside that scores positively in the assay of the invention can be further fractionated and confirmed by standard methods of HPLC and mass spectrometry.

'086 patent, at 27:3-12; *see also id.* at Example 2, 32:54-33:2 (describing "Nicotinamide Riboside and Whey Preparations"); 19:5-28 (describing common purification techniques, including fractionation, in the context of Nrk polypeptides).

These teachings for identification and isolation of nicotinamide riboside for use in the claimed pharmaceutical compositions are consistent with the way a person of ordinary skill in the art would understand the claimed phrase "is isolated from a natural or synthetic source." Contrary to Petitioner's arguments, the claims do not cover natural sources of nicotinamide riboside. Instead, the '086 patent specification identifies various natural and synthetic sources for the compound and then teaches a person of ordinary skill in the art how to isolate nicotinamide riboside from those sources, including from cow's milk. *See* '086 patent, at 26:64-27:3. Specifically, the specification teaches the use of fractionation techniques to remove the other cellular components of cow's milk so that the nicotinamide riboside can be isolated suitably for use in the claimed compositions. *See id.* at 27:3-12, 32:54-33:2. Accordingly, the specification supports Patent Owner's proposed construction of the phrase "is isolated from a natural or synthetic source" as "fractionated from other cellular components."

2. Patent Owner's Proposed Construction Is Consistent With The Claim Language

In light of the teachings in the specification, the '086 patent claim language also supports Patent Owner's claim construction proposal for the "is isolated from a natural or synthetic source" phrase, including that the Board should construe the broader phrase in which the "is isolated" phrase proposed by Petitioner appears.

The context in which the proposed phrase appears is critical for defining it in the manner dictated by the specification.

Claim 2 covers "[t]he pharmaceutical composition of claim 1, wherein the nicotinamide riboside is isolated from a natural or synthetic source." '086 patent, at 53:41-43. As disclosed in the specification and confirmed by the words of the claim itself, "isolated" in claim 2 refers to the process of isolating the nicotinamide riboside for use in the claimed compositions. Claim 2 is narrower than claim 1 because it further specifies that the nicotinamide riboside "is isolated from a natural or synthetic source," to the exclusion of the third option of chemically synthesizing the compound. *See* '086 patent, at 28:16-21. The correct definition of the phrase in which "isolated" appears in claim 2 will therefore be the one that is consistent with the scope of the claim itself. Specifically, the construction should be consistent with the disclosure of standard methods for isolating extracts from natural sources, such as fractionating nicotinamide riboside from other cellular components. *See* '086 patent, at 27:3-12.

Accordingly, the claim language of dependent claim 2 confirms that the Board should construe the phrase "is isolated from a natural or synthetic source." Because claim 1 must necessarily be broader than claim 2, and in light of the teachings of the specification, nicotinamide riboside that "is isolated from a natural or synthetic source" must be distinguished from nicotinamide riboside that is

chemically synthesized. In other words, nicotinamide riboside that "is isolated from a natural or synthetic source" is nicotinamide riboside that is fractionated from other cellular components.

3. Petitioner's Proposed Construction Should Not Be Adopted

a. Petitioner's Proposed Construction Is Inconsistent With The Specification and Claims

Petitioner's proposed construction for "is isolated" ignores the teachings of the specification in favor of a single, incomplete, phrase pulled out of context. Although Petitioner quotes the majority of the passage discussing "isolated" nucleic acids, Petitioner concludes that any molecule in the patent "is isolated" if it "is separated or substantially free from at least some of the other components of the naturally occurring organism." Pet. at 7. Although Petitioner claims its proposed construction is pulled from the specification, Petitioner's proposal is incomplete because it ignores the language of the claims themselves and the teachings in the specification regarding nicotinamide riboside.

Petitioner fails to even disclose that the passage to which it cites discusses nucleic acids rather than the claimed nicotinamide riboside. Moreover, Petitioner fails to account for the portion of its cited passage that explains that "isolated" nucleic acids must be substantially free from at least some of "the cell structural components or other polypeptides or nucleic acids commonly found associated with the molecule." *See* '086 patent, at 9:3-10. As a result, Petitioner's proposed

construction is incomplete with respect to both nicotinamide riboside and the very compound discussed in the portion of the specification from which Petitioner extracted the construction.

In addition to the disclosure regarding nucleic acids, the specification includes disclosures regarding, *inter alia*, expression vectors, polypeptides, prodrugs, and cultured cells. The claims themselves are directed only to nicotinamide riboside compounds, so the construction of the "is isolated" phrase should be informed by the patent disclosures regarding nicotinamide riboside. The specification includes numerous teachings regarding the methods for isolating nicotinamide riboside that Petitioner never mentions.

Moreover, Petitioner's proposed construction is improper at least because it attempts to "constru[e] individual words of a claim without considering the context in which those words appear." *Trivascular*, 812 F.3d at 1062; *see also ACTV*, 346 F.3d at 1088 ("While certain terms may be at the center of the claim construction debate, the context of the surrounding words of the claim also must be considered in determining the ordinary and customary meaning of those terms."). For example, if Petitioner's proposed construction were inserted into the language of claim 2, the claim would become nonsensical because it would read as "[t]he pharmaceutical composition of claim 1, wherein the nicotinamide riboside [is

separated or substantially free from at least some of the other components of the naturally occurring organism] from a natural or synthetic source." *See* Pet. at 7.

Because claim 2 recites nicotinamide riboside that "is isolated from a natural or synthetic source" and the specification includes detailed explanations of methods for isolating nicotinamide riboside from the claimed sources, it is more appropriate to construe the broader phrase consistently with those teachings. *See Trivascular*, 812 F.3d at 1062 (criticizing constructions that "interpret the words in a claim without regard for the full claim language and the written description"). Specifically, and as discussed above, the specification describes common purification and fractionation techniques that are consistent with Patent Owner's proposed construction. On the other hand, Petitioner ignores those teachings, even while its expert purports to understand "purified precursors [of NAD+]," including purified nicotinamide. *See* Ex. 1002 at 10, ¶15 (discussing precursor molecules, including nicotinamide riboside, that can be used to synthesize NAD+, and stating that modern cases of pellagra in humans "would be treated with purified precursors"). Accordingly, Petitioner's proposed construction for the "is isolated" phrase should be rejected and the broader phrase "is isolated from a natural or synthetic source" should be construed consistent with Patent Owner's proposal above.

b. Petitioner's Proposed Construction Is Unreasonably Broad

Petitioner's proposed construction is unreasonably broad because it would read on milk that has been removed from a cow. Petitioner asserts that "[t]he nicotinamide riboside naturally present in the skim milk Goldberger et al. administered to dogs is isolated … from a natural source: the cow." Pet. at 14-15. In other words, under Petitioner's proposed construction, the nicotinamide riboside in milk is "isolated" only after it is evacuated from a cow, but not before. Such a result defies common sense. Moreover, Petitioner's unreasonably broad construction makes no sense in light of the specification, which teaches that cow's milk is a natural source from which nicotinamide riboside may be isolated, not a source of isolated nicotinamide riboside. *See In re Smith Int'l*, 2017 WL 4247407, at *5 (concluding that giving a disputed term "such a strained breadth in the face of the otherwise different description in the specification was unreasonable").

For example, the specification discloses "a method for identifying a natural or synthetic source for nicotinamide riboside" and further specifies that "[i]n one embodiment, the natural source is cow's milk." '086 patent, at 4:8-20. The specification further discloses that "nicotinamide riboside [was] isolated from deproteinized whey fraction of cow's milk" and further explains those procedures in Example 2. *See id.* at 26:32-34, 32:54-33:2. Finally, the specification identifies cow's milk as a source of nicotinamide riboside and explains that the nicotinamide

riboside can be isolated from the cow's milk using standard methods, such as centrifugation and fractionation. *See id.* at 26:67-27:12. The Federal Circuit has made clear that the broadest reasonable construction does not include those that are "unreasonable under general claim construction principles." *In Re Smith*, 2017 WL 4247407, at *5. Unreasonable constructions include those that are divorced from the specification and record evidence." *Id.* Petitioner's unreasonably broad construction covering milk is divorced from the patent specification and makes no sense in the context of the inventions described therein.

IV. PETITIONER HAS NOT DEMONSTRATED "A REASONABLE LIKELIHOOD OF PREVAILING" AGAINST AT LEAST ONE CLAIM OF THE '086 PATENT UNDER 35 U.S.C. § 314(a)

Under 35 U.S.C. § 314(a), an *inter partes* review may only be instituted where "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least one of the claims challenged in the petition." *See also* 37 C.F.R. § 42.108(c). The burden of showing that this statutory threshold has been met belongs to Petitioner. *See, e.g.*, Office Patent Trial Practice Guide, 77 Fed. Reg. 48756, 48756 (Aug. 14, 2012) ("The Board . . . may institute a trial where the petitioner establishes that the standards for instituting the requested trial are met . . . .").

Petitioner asserts two anticipation grounds in its challenge of the ’086 patent. However, Petitioner has not shown that either of its prior art references of the proposed Grounds disclose the essential “carrier” element required by independent claim 1 of the ’086 patent. Because the other two challenged claims depend directly from claim 1, Petitioner has failed to establish that the prior art references of the proposed Grounds anticipate any of the challenged claims. Moreover, Petitioner fails to establish that the prior art references of the proposed Grounds disclose elements required by the dependent claims, including (1) nicotinamide riboside that “is isolated from a natural or synthetic source” as required by claim 2, and (2) a pharmaceutical composition that “increases NAD+ biosynthesis upon oral administration” as required by claim 5.

Accordingly, Petitioner has failed to meet its burden of showing that there is a reasonable likelihood that it would prevail with respect to any of the challenged claims, and Petitioner’s request for *inter partes* review should be denied.

A. Ground 1: Petitioner Has Not Demonstrated A "Reasonable Likelihood Of Prevailing" As To Claims 1-5 Over Goldberger et al.

1. Goldberger et al. Does Not Disclose "A pharmaceutical composition comprising"

Petitioner offers no analysis of whether Goldberger et al. discloses "a pharmaceutical composition" and instead questions whether this preamble phrase is limiting in the context of the '086 patent. *See* Pet. at 12. As discussed above, "a pharmaceutical composition" is a limiting phrase and provides the necessary context for construing the terms of and analyzing the scope of the claims.

Petitioner concludes only that "Goldberger et al. discloses the administration of skim milk to dogs as a dietary supplement to prevent blacktongue." Pet. at 12. Petitioner also concludes that the milk disclosed in Goldberger et al. falls within the scope of the claimed "pharmaceutical composition" without providing any analysis or support for its conclusion. *See id.*

Accordingly, Petitioner has failed to establish that Goldberger et al. discloses the necessary element of "a pharmaceutical composition comprising" required by independent claim 1. Because the other challenged claims depend from claim 1, and further recite the same "pharmaceutical composition," Petitioner has failed to show a reasonable likelihood that it will prevail in demonstrating that Goldberger et al. anticipates claims 1-5 of the '086 patent.

2. Goldberger et al. Does Not Disclose Nicotinamide Riboside "in admixture with a carrier"

Claim 1 covers compositions that include a "carrier," which a person of ordinary skill in the art would understand to be a "pharmaceutically acceptable carrier," particularly in light of the preamble's requirement that the carrier is part of "a pharmaceutical composition." The claim further requires that nicotinamide riboside is "in admixture" with the claimed carrier. Despite these requirements, Petitioner offers only a single sentence regarding this limitation, and does not even point to any disclosure within Goldberger et al. *See* Pet. at 13. Instead, Petitioner relies on its expert, who concludes that the nicotinamide riboside in the milk disclosed in Goldberger et al. "is in admixture with other components of the milk, including components that are demonstrated in Trammell I to bind and stabilize the compound." Ex. 1002 at 17, ¶ 32. No support for the statement is provided with respect to either why the Expert believes there is a disclosure of an admixture or a carrier as required by the claims.

First, the reference Dr. Baur relies on for his conclusion, Trammell I, does not identify any of the components that allegedly bind and stabilize the nicotinamide riboside. Instead, Trammell I reports generally that nicotinamide riboside "is a bound metabolite in cow milk" and that it "is more stable in milk than in water, suggesting that the metabolite might be complexed to a protective factor." Ex. 1007 at 5. With respect to the identity of that protective factor,

Trammell I concludes that "[f]urther research is needed . . . to identify the molecular basis of [nicotinamide riboside] binding to milk." *Id.* at 6.

Second, Petitioner's conclusion that Goldberger et al. discloses nicotinamide riboside that "is in a mixture with other components of the milk" does not establish that the combination of nicotinamide riboside and other components is an "admixture" as required by the claim. *See* Pet. at 13 (emphasis added). Petitioner's reliance on Dr. Baur's statement about skim milk is insufficient to establish that Goldberger et al. discloses a pharmaceutically acceptable carrier, let alone a carrier that is in admixture with any other components. Dr. Baur does not draw any connection between his conclusory statement and any disclosure in Goldberger et al. This is not surprising because there is no discussion of admixtures, carriers, pharmaceuticals, or pharmaceutically acceptable carriers in Goldberger et al. A person of ordinary skill in the art would understand how to prepare the claimed compositions using the teachings of the '086 patent, including selection of a pharmaceutically acceptable carrier. *See* '086 patent, at 28:49-60. A person of ordinary skill in the art would also readily understand that the milk disclosed in Goldberger et al. was not prepared as an admixture of nicotinamide riboside and a carrier.

Accordingly, Petitioner has failed to establish that Goldberger et al. discloses the necessary element of nicotinamide riboside "in admixture with a

carrier" as required by independent claim 1. Because the other challenged claims depend from claim 1, Petitioner has failed to show a reasonable likelihood that it will prevail in demonstrating that Goldberger et al. anticipates claims 1-5 of the '086 patent.

3. Goldberger et al. Does Not Disclose A Pharmaceutical Composition Wherein The Nicotinamide Riboside "is isolated from a natural or synthetic source"

Claim 2 covers the pharmaceutical compositions of claim 1 "wherein the nicotinamide riboside is isolated from a natural or synthetic source." '086 patent, at claim 2. As discussed above, Petitioner has failed to establish that Goldberger et al. anticipates claim 1 of the '086 patent, from which claim 2 depends, so Petitioner cannot establish that Goldberger et al. anticipates claim 2.

With respect to "is isolated from a natural or synthetic source," Petitioner does not offer any evidence that the prior art contains nicotinamide riboside that is "fractionated from other cellular components." Petitioner asserts that the nicotinamide riboside in the skim milk used in Goldberger et al. is isolated from a natural source because it was extracted from a cow. *See* Pet. at 14-15. Petitioner's cow argument fails because removing milk from a cow is not the same as fractionating the nicotinamide riboside contained in that milk from the other cellular components. Similarly, separating out fat from non-fat elements in milk

does not fractionate the nicotinamide riboside from other cellular components. *See* Pet. at 15.

Petitioner's cow argument contradicts the '086 patent teachings, which explain that cow's milk is a source from which nicotinamide riboside can be extracted. *See* '086 patent, at 26:32-34, 26:67-27:12, Example 2. As stated in the specification, "[i]n one embodiment, the natural source [of the claimed nicotinamide riboside] is cow's milk." *Id.* at 4:12-13. Once a source such as cow's milk is identified, the specification explains that "[i]solated extracts of the natural sources can be prepared using standard methods," including homogenization in a buffered solution, centrifugation, and fractionation. *Id.* at 26:67-27:12.

In contrast, Petitioner does not, because it cannot, cite to any disclosure in Goldberger et al. that identifies how an individual component such as nicotinamide riboside is extracted from the skim milk, or any other natural or synthetic source. The only conclusion drawn in Goldberger et al. is that "[i]t thus appears that milk contains the preventive for both blacktongue and pellagra, but, considered in relation to effective quantity, contains it in relatively small amount." Ex. 1005 at 22. Petitioner's anticipation argument fails because it is based on an unreasonably broad claim construction of the "is isolated" phrase. *See In re Smith*, 2017 WL 4247407, at *6 (reversing the Board's anticipation findings for lack of substantial

evidence because they were based on an unreasonably broad claim construction). Goldberger et al. simply does not disclose any separation or extraction of individual components from the milk, so it does not disclose the claimed nicotinamide riboside "that is isolated from a natural or synthetic source."

4. Goldberger et al. Does Not Disclose A Pharmaceutical Composition That "increases NAD+ biosynthesis upon oral administration"

Claim 5 of the '086 patent covers pharmaceutical compositions that "increase NAD+ biosynthesis upon oral administration." *See* '086 patent, at claim 5. Petitioner concludes that Goldberger et al. inherently discloses this limitation because skim milk was administered to the test subject dogs. *See* Pet. at 17. However, this same argument was made during prosecution of the '400 Application, of which the '086 patent is a continuation. After the applicant successfully overcame this milk argument, the '400 Application issued as U.S. Patent No. 8,197,807.

Specifically, during prosecution of the '400 Application, the Examiner rejected the claims on the grounds that "nicotinamide riboside is known to be present in milk." Ex. 1003 at 139. The patent applicant overcame the Examiner's rejection by amending what later issued as claim 1 of the '807 patent to add "and increases NAD+ biosynthesis upon oral formulation" and confirming that "[t]he mere fact that nicotinamide riboside is present in milk is in no way suggestive or

predictive of an oral formulation of nicotinamide riboside being bioavailable and increasing biosynthesis of NAD+ upon oral administration…" *Id.* at 142, 144. The Examiner found the applicant's arguments regarding NAD+ biosynthesis persuasive and allowed the claim. *See id.* at 160.

Accordingly, Petitioner's challenge should be rejected because "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d); *see also Prism Pharma Co. v. Choongwae Pharma Corp.*, IPR2014-00315, Paper No. 14, at 12-13 (denying institution because "substantially the same arguments were presented to the Office previously"); *Edwards Lifesciences Corp. v. Boston Sci. Scimed, Inc.*, IPR2017-00072, Paper No. 8, at 11 (denying institution because Petitioner presented arguments the Board found "to be the same or substantially the same as information considered during prosecution in the context of other references").

Petitioner has failed to establish that Goldberger et al. discloses a pharmaceutical composition that "increase[s] NAD+ biosynthesis upon oral administration" as required by dependent claim 5.

Institution of Ground 1 should be denied.

B. Ground 2: Petitioner Has Not Demonstrated A "Reasonable Likelihood Of Prevailing" As To Claims 1-5 Over Goldberger and Tanner

1. Goldberger and Tanner Does Not Disclose "A pharmaceutical composition comprising"

Petitioner offers no analysis of whether Goldberger and Tanner discloses "a pharmaceutical composition" and instead questions whether this preamble phrase is limiting in the context of the '086 patent. *See* Pet. at 22. As discussed above, "a pharmaceutical composition" is a limiting phrase and provides the necessary context for construing the terms of and analyzing the scope of the claims.

Petitioner concludes only that "Goldberger and Tanner discloses the successful administration of buttermilk to prevent the onset of pellagra – a disease caused by NAD+ deficiency." Pet. at 22. Petitioner also concludes that the buttermilk disclosed in Goldberger and Tanner falls within the scope of the claimed "pharmaceutical composition" without providing any analysis or support for its conclusion. *See id.* at 23.

Accordingly, Petitioner has failed to establish that Goldberger and Tanner discloses the necessary element of "a pharmaceutical composition comprising" required by independent claim 1. Because the other challenged claims depend from claim 1, and further recite the same "pharmaceutical composition," Petitioner has failed to show a reasonable likelihood that it will prevail in demonstrating that Goldberger and Tanner anticipates claims 1-5 of the '086 patent.

2. Goldberger and Tanner Does Not Disclose Nicotinamide Riboside "in admixture with a carrier"

Claim 1 covers compositions that include a "carrier," which a person of ordinary skill in the art would understand to be a "pharmaceutically acceptable carrier." The claim further requires that nicotinamide riboside is "in admixture" with the claimed carrier. Like in Ground 1, however, Petitioner offers only a single sentence regarding this limitation, and does not even point to any disclosure within Goldberger and Tanner. Pet. at 24. Instead, Petitioner relies on its expert, who similarly offers no citation or analysis in support of his conclusion that the nicotinamide riboside in the buttermilk disclosed in Goldberger and Tanner "is in admixture with other soluble components of the milk, including components that are demonstrated in Trammell I to bind and stabilize the compound." Ex. 1002 at 19-20, ¶ 37. No support for the statement is provided with respect to either why the Expert believes there is a disclosure of an admixture or a carrier as required by the claims.

First, the reference Dr. Baur relies on for his conclusion, Trammell I, does not identify any of the components that allegedly bind and stabilize the nicotinamide riboside. Instead, Trammell I reports generally that nicotinamide riboside "is a bound metabolite in cow milk" and that it "is more stable in milk than in water, suggesting that the metabolite might be complexed to a protective factor." Ex. 1007 at 5. With respect to the identity of that protective factor,

Trammell I concludes that "[f]urther research is needed … to identify the molecular basis of [nicotinamide riboside] binding to milk." *Id.* at 6.

Second, Petitioner's conclusion that Goldberger and Tanner discloses nicotinamide riboside that "is in a mixture with other soluble components of milk" does not establish that the combination of nicotinamide riboside and other components is an "admixture" as required by the claim. *See* Pet. at 24 (emphasis added). Petitioner's reliance on Dr. Baur's statement about buttermilk is insufficient to establish that Goldberger and Tanner discloses a pharmaceutically acceptable carrier, let alone a carrier that is in admixture with any other components. Moreover, Dr. Baur does not draw any connection between his conclusory statement and any disclosure in Goldberger and Tanner. This is not surprising because there is no discussion of admixtures, carriers, pharmaceuticals, or pharmaceutically acceptable carriers in Goldberger and Tanner. A person of ordinary skill in the art would understand how to prepare the claimed compositions using the teachings of the '086 patent, including selection of a pharmaceutically acceptable carrier. *See* '086 patent, at 28:49-60. A person of ordinary skill in the art would also readily understand that the buttermilk disclosed in Goldberger and Tanner was not prepared as an admixture of nicotinamide riboside and a carrier.

Accordingly, Petitioner has failed to establish that Goldberger and Tanner discloses the necessary element of nicotinamide riboside "in admixture with a

carrier" as required by independent claim 1. Because the other challenged claims depend from claim 1, Petitioner has failed to show a reasonable likelihood that it will prevail in demonstrating that Goldberger and Tanner anticipates claims 1-5 of the '086 patent.

3. Goldberger and Tanner Does Not Disclose A Pharmaceutical Composition Wherein The Nicotinamide Riboside "is isolated from a natural or synthetic source"

Claim 2 covers the pharmaceutical compositions of claim 1 "wherein the nicotinamide riboside is isolated from a natural or synthetic source." '086 patent, at claim 2. As discussed above, Petitioner has failed to establish that Goldberger and Tanner anticipates claim 1 of the '086 patent, from which claim 2 depends, so Petitioner cannot establish that Goldberger and Tanner anticipates claim 2.

With respect to "is isolated from a natural or synthetic source," Petitioner does not offer any evidence that the prior art contains nicotinamide riboside that is "fractionated from other cellular components." Petitioner asserts that the nicotinamide riboside in the buttermilk used in Goldberger and Tanner is isolated from a natural source because it was extracted from a cow. *See* Pet. at 25. Petitioner's cow argument fails because removing milk from a cow is not the same as fractionating the nicotinamide riboside contained in that milk from the other cellular components. Similarly, converting whole milk or cream to buttermilk ("the liquid left behind after milk or cream is churned into butter…is separated

from the portion of the milk or cream that is churned into butter") does not fractionate the nicotinamide riboside from other cellular components. *See* Pet. at 25, Ex. 1002 at 20, ¶ 38.

As discussed above, Petitioner's cow argument is directly contradictory to the '086 patent teachings because the patent teaches methods for extracting nicotinamide riboside from cow's milk. *See* '086 patent, at 26:32-34, 26:67-27:12, Example 2. As stated in the specification, "[i]n one embodiment, the natural source [of the claimed nicotinamide riboside] is cow's milk." *Id.* at 4:12-13. Once a source such as cow's milk is identified, the specification explains that "[i]solated extracts of the natural sources can be prepared using standard methods," including homogenization in a buffered solution, centrifugation, and fractionation. *Id.* at 26:67-27:12.

In contrast, Petitioner does not, because it cannot, cite to any disclosure in Goldberger and Tanner that identifies how an individual component such as nicotinamide riboside is extracted from buttermilk, or any other natural or synthetic source. The only conclusion drawn in Goldberger and Tanner is that "[f]resh meat and milk contain the essential pellagra-preventive factor or factors." Ex. 1006 at 14. Petitioner's anticipation argument fails because it is based on an unreasonably broad claim construction of the "is isolated" phrase. *See In re Smith*, 2017 WL 4247407, at *6 (reversing the Board's anticipation findings for lack of

substantial evidence because they were based on an unreasonably broad claim construction). Goldberger and Tanner simply does not disclose any separation or extraction of individual components from the buttermilk, so it does not disclose the claimed nicotinamide riboside "that is isolated from a natural or synthetic source."

4. Goldberger and Tanner Does Not Disclose A Pharmaceutical Composition That "increases NAD+ biosynthesis upon oral administration"

Claim 5 of the '086 patent covers pharmaceutical compositions that "increase[] NAD+ biosynthesis upon oral administration." *See* '086 patent, at claim 5. Petitioner concludes that Goldberger and Tanner inherently discloses this limitation because buttermilk was administered to the test subjects. *See* Pet. at 28-9. The only difference between Petitioner's argument here and its arguments for the same element in Ground 1 is that the allegedly invalidating product is buttermilk instead of milk. Petitioner and Dr. Baur treat the buttermilk disclosed in Goldberger and Tanner as effectively the same as milk with respect to nicotinamide riboside. For example, Dr. Baur relies on a later-published article from 2016 for his conclusion that "raw milk and skim milk both contain [nicotinamide riboside]," and then explains:

> Skim milk is the product that remains when almost all of the cream is removed from the whole milk. Traditional buttermilk, such as that which was consumed by the test subjects in Goldberger and Tanner … is the product that remains after butter has been churned from whole

> milk or cream. Because [nicotinamide riboside] is a water-soluble molecule that is stable in milk, the majority of [nicotinamide riboside] originally present in the churned whole milk or cream remains in the aqueous buttermilk when the fat-rich butter is removed.

Ex. 1002 at 8, ¶ 12 (citations omitted). Accordingly, although Petitioner's arguments here are based on buttermilk, they are substantially the same as the arguments the applicant overcame regarding milk during prosecution of the '400 Application, of which the '086 patent is a continuation.

Specifically, during prosecution of the '400 Application, the Examiner rejected the claims on the grounds that "nicotinamide riboside is known to be present in milk." Ex. 1003 at 139. The patent applicant overcame the Examiner's rejection by amending what later issued as claim 1 of the '807 patent to add "and increases NAD+ biosynthesis upon oral formulation" and confirming that "[t]he mere fact that nicotinamide riboside is present in milk is in no way suggestive or predictive of an oral formulation of nicotinamide riboside being bioavailable and increasing biosynthesis of NAD+ upon oral administration…" Ex. 1003 at 142, 144.. The Examiner found the applicant's arguments regarding NAD+ biosynthesis persuasive and allowed the claim. *See* Ex. 1003 at 160.

Accordingly, Petitioner's challenge should be rejected because "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d); *see also Prism Pharma Co. v. Choongwae Pharma*

Corp., IPR2014-00315, Paper No. 14, at 12-13 (denying institution because "substantially the same arguments were presented to the Office previously"); *Edwards Lifesciences Corp. v. Boston Sci. Scimed, Inc.*, IPR2017-00072, Paper No. 8, at 11 (denying institution because Petitioner presented arguments the Board found "to be the same or substantially the same as information considered during prosecution in the context of other references").

Petitioner has failed to establish that Goldberger and Tanner discloses a pharmaceutical composition that "increase[s] NAD+ biosynthesis upon oral administration" as required by dependent claim 5.

Institution of Ground 2 should be denied.

V. CONCLUSION

For the foregoing reasons, there is not a reasonable likelihood of Petitioner prevailing with respect to any challenged claims of the '086 patent. Accordingly, the Petition should be denied under 35 U.S.C. § 314(a).

Respectfully submitted,

Date: November 3, 2017 / John L. Abramic, Reg. No. 51,031/

John L. Abramic, Reg. No. 51,031
James R. Nuttall, Reg. No. 44,978
STEPTOE & JOHNSON LLP
115 South LaSalle Street, Suite 3100
Chicago, IL 60603
Tel: (312) 577-1264
Fax: (312) 577-1370

Harold H. Fox, Reg. No. 41,498
STEPTOE & JOHNSON LLP
1330 Connecticut Avenue, NW
Washington, DC 20036-1795
Tel: (202) 429-6284
Fax: (202) 429-3902

Counsel for Trustees of Dartmouth College

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 7,684 words, and thus complies with the word-count limits of 37 C.F.R. § 42.24.

Date: November 3, 2017

/ John L. Abramic, Reg. No. 51,031/

John L. Abramic, Reg. No. 51,031
James R. Nuttall, Reg. No. 44,978
STEPTOE & JOHNSON LLP
115 South LaSalle Street, Suite 3100
Chicago, IL 60603
Tel: (312) 577-1264
Fax: (312) 577-1370

Harold H. Fox, Reg. No. 41,498
STEPTOE & JOHNSON LLP
1330 Connecticut Avenue, NW
Washington, DC 20036-1795
Tel: (202) 429-6284
Fax: (202) 429-3902

Counsel for Trustees of Dartmouth College

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e), the undersigned hereby certifies that a copy of the foregoing PRELIMINARY RESPONSE TO PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,383,086 was served on November 3, 2017 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:

Via Email:

Brendan Jones
bjones@foleyhoag.com

Donald R. Ware
drw@foleyhoag.com

Jeremy A. Younkin
jyounkin@foleyhoag.com

Via U.S. Mail:
Patent Group
Foley Hoag LLP
155 Seaport Blvd.
Boston, MA 02210

Date: November 3, 2017 By: / John L. Abramic, Reg. No. 51,031/

John L. Abramic, Reg. No. 51,031
STEPTOE & JOHNSON LLP
115 South LaSalle Street, Suite 3100
Chicago, IL 60603
Tel: (312) 577-1264
Fax: (312) 577-1370

Counsel for Trustees of Dartmouth College