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 IPR2017-01796

Patent 8,197,807

PRELIMINARY RESPONSE TO PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,197,807

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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. 8,197,807 (Ex. 1001, "the '807 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 '807 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 '807 patent.

First, Petitioner has not provided any evidence that either of its prior art references of the proposed Grounds discloses the essential claim element of "isolated nicotinamide riboside" as claimed in independent claim 1 of the '807 patent. Petitioner instead relies on an improper claim construction and expert testimony for the inapposite conclusion that nicotinamide riboside present in milk or buttermilk is "isolated" when milk is removed from a cow. Because neither prior art reference of the proposed Grounds discloses isolated nicotinamide riboside like that claimed in the '807 patent, Petitioner cannot establish that the references anticipate the claims of the '807 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 composition of isolated nicotinamide riboside that "increases NAD+ biosynthesis upon oral administration," as required by independent claim 1 of the '807 patent. Petitioner instead relies on an argument regarding milk that was already considered by the Examiner and overcome during prosecution, which is a sufficient basis for the Board to exercise its discretion under 35 U.S.C. § 325(d) and deny institution.

Third, Petitioner has not provided any evidence that either of its prior art references of the proposed Grounds discloses the essential claim element of the isolated nicotinamide riboside "in admixture with a carrier" as claimed in independent claim 1 of the '807 patent. Because neither prior art reference of the proposed Grounds discloses nicotinamide riboside in admixture with a carrier like that claimed in the '807 patent, Petitioner cannot establish that the references anticipate the claims of the '807 patent.

Fourth, 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 '807 patent. Petitioner again 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. Because neither prior art reference discloses nicotinamide riboside isolated from a natural or synthetic source as in claim 2 of the ’807 patent, Petitioner cannot establish that the references anticipate claim 2 of the ’807 patent.

For at least these reasons, the institution of an *inter partes* review of the ’807 patent should be denied.

II. BACKGROUND

The ’807 patent is directed to compositions of isolated nicotinamide riboside formulated in admixture with a carrier that increase NAD+ biosynthesis upon oral administration. *See* ’807 patent, at claim 1. Increasing NAD+ levels can help to treat a range of diseases and conditions, including cancer. *See, e.g.*, *id.* at 7:54-9:20. As disclosed in the ’807 patent, NAD+ was known to be formed through de novo synthesis, nicotinic acid import, and nicotinamide salvage. *See id.* at 2:25-35, Scheme 1. The ’807 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 3:3-11, 8:58-60.

The ’807 patent achieves the desired supplementation by isolating nicotinamide riboside, whether through chemical synthesis or extraction from a

natural or synthetic source, and formulating the isolated product in admixture with a carrier for oral administration. As covered by claim 1, these compositions of isolated nicotinamide riboside "increase[] NAD+ biosynthesis upon oral administration." *See* '807 patent, at claim 1.

The '807 patent includes only three claims, and both dependent claims depend directly from independent claim 1. Specifically, dependent claim 2 covers the compositions of claim 1 wherein the nicotinamide riboside "is isolated from a natural or synthetic source." *See* '807 patent, at claim 2. The '807 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 27:39-54. Finally, dependent claim 3 covers specific types of oral formulations of the claim 1 compositions, including "a tablet, troche, capsule, elixir, suspension, syrup, wafer, chewing gum, or food." *See id.* at claim 3.

Contrary to Petitioner's assertions, the '807 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 '807 patent covers specific compositions of an isolated molecule (i.e., nicotinamide riboside) that can increase NAD+ biosynthesis when formulated in admixture with a carrier.

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.'").

The patent prosecution history is also relevant for determining the correct construction of a disputed term in an *inter partes* review. *See D'Agostino v. Mastercard Int'l Inc.*, 844 F.3d 945, 948 (Fed. Cir. 2016) (quoting *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015) (stating that "the Board 'should also consult the patent's prosecution history in proceedings in which the patent has been brought back to the agency for a second review'").

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 "isolated nicotinamide riboside" limitation of independent claim 1 of the '807 patent, Petitioner has not demonstrated a reasonable likelihood that it will prevail on its assertion that the claims are unpatentable.

A. "isolated" Terms (Claims 1, 2)

Petitioner proposes constructions for "isolated" in independent claim 1 and "is isolated" in dependent claim 2 that are inconsistent with the claim language and

patent specification. Petitioner offers essentially the same construction for both terms based on a single phrase in the specification, but the proposed constructions ignore the language of the claims and the teachings of the specification. The "isolated" terms are more properly read in the context of the claims in which they appear because they are part of broader phrases that provide critical context for the meaning of each "isolated" term. *See Trivascular, Inc.*, 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 phrases as shown below:

Claim Term	Proposed Construction
"isolated nicotinamide riboside"	nicotinamide riboside that is substantially free from other molecules
"is isolated from a natural or synthetic source"	fractionated from other cellular components

1. Patent Owner's Proposed Constructions Are 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. All of the descriptions of isolated molecules and the process of isolating molecules from natural or synthetic sources support Patent Owner's constructions of the "isolated" terms.

The first appearance of the word "isolated" in the Detailed Description is in a discussion of isolated nucleic acids and polypeptides:

> The present invention is an isolated nucleic acid containing a eukaryotic nucleotide sequence encoding a nicotinamide riboside kinase polypeptide. As used herein, ***an isolated molecule*** (e.g., an isolated nucleic acid such as genomic DNA, RNA or cDNA or an isolated polypeptide) means a molecule separated or substantially free from at least some of the other components of the naturally occurring organism, such as for example, the cell structural components or other polypeptides or nucleic acids commonly found associated with the molecule. When ***the isolated molecule*** is a polypeptide, said polypeptide is at least about 25%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or more pure (w/w).

'807 patent at 9:21-33 (emphasis added). Although this passage does not refer to "isolated nicotinamide riboside," it does confirm that the patent uses "isolated" in the way a person of ordinary skill in the art would understand the term. Specifically, "isolated" molecules are those that are purified or otherwise separated to be substantially free from other molecules. Accordingly, the claimed "isolated nicotinamide riboside" is nicotinamide riboside that is substantially free from other

molecules. The teachings in the specification regarding identification and isolation of nicotinamide riboside also support this construction.

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)." '807 patent, at 28:58-63. 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.

'807 patent, at 27:7-38. Although the claims do not recite any of these identification steps, they provide background and context for how a person of ordinary skill in the art would obtain isolated 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.

'807 patent, at 27:39-45.

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.

'807 patent, at 27:45-54; *see also id.* at Example 2, 33:30-45 (describing "Nicotinamide Riboside and Whey Preparations"); 19:44-67 (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 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 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* '807 patent, at 27:39-45. 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* '807 patent, at 27:45-54, 33:30-45. 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 Constructions Are Consistent With The Claims

In light of the teachings in the specification, the '807 patent claim language also supports Patent Owner's claim construction proposals for the "isolated" terms, including that the Board should construe the broader phrases in which the "isolated" terms appear. Although the word "isolated" appears in both independent claim 1 and dependent claim 2, the context in which the terms appear is critical for defining the terms in the manner dictated by the specification.

The phrase "isolated nicotinamide riboside" appears in claim 1, the only independent claim. Claim 1 specifically claims compositions of the isolated nicotinamide riboside in combination with other components, the specific type of formulation, and the effect of those compositions:

> A composition comprising ***isolated nicotinamide riboside*** in combination with one or more of tryptophan, nicotinic acid, or nicotinamide, wherein said combination is in admixture with a carrier . . . wherein said composition is formulated for oral

> administration and increases NAD+ biosynthesis upon oral administration.

’807 patent, at 53:59-54:58 (emphasis added). As supported by the specification, the “isolated nicotinamide riboside” recited in claim 1 refers to the nicotinamide riboside molecule itself. In other words, as used in claim 1, “isolated nicotinamide riboside” is nicotinamide riboside that is substantially free from other molecules.

In contrast, claim 2 recites that “the nicotinamide riboside is isolated from a natural or synthetic source.” ’807 patent, at 54:60-61. 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 chemically synthesizing the compound. *See* ’807 patent, at 28:58-63. 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* ’807 patent, at 27:45-54.

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 Constructions Should Not Be Adopted

a. Petitioner's Proposed Constructions Are Inconsistent With the Specification and Claims

Petitioner's proposed constructions ignore 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 "separate or substantially free from at least some of the other components of the naturally occurring organism." Pet. at 6. Although Petitioner claims its proposed constructions for the "isolated" terms are pulled from the specification, Petitioner's proposals are incomplete because they ignore 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* '807 patent, at 9:23-30. 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 both "isolated" terms should be informed by the patent disclosures regarding nicotinamide riboside. The specification includes numerous teachings regarding the meaning of "isolated" in the context of nicotinamide riboside that Petitioner never mentions. As discussed above, those teachings support Patent Owner's proposal to construe the broader phrase of "isolated nicotinamide riboside" in claim 1 and are consistent with the way a person of ordinary skill in the art would understand the "isolated nicotinamide riboside" phrase.

For the "is isolated" phrase in claim 2, Petitioner proposes only that the word "is" be added to its "isolated" construction. *See* Pet. at 7. Petitioner's proposed construction is improper at least because it attempts to "construe 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 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 6-7. Even if the claim could be understood using Petitioner's proposed construction, the virtual identity between Petitioner's proposed constructions for the two "isolated" terms would improperly render claim 2 redundant to claim 1.

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 constructions for the "isolated" terms should be rejected.

b. Petitioner's Proposed Constructions Are Unreasonably Broad

Petitioner's proposed constructions are unreasonably broad because they 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 the cow." Pet. at 12. 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, Inc.*, No. 2016-2303, 2017 WL 4247407, at *5 (Fed. Cir. 2017) (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." '807 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 27:7-9, 33:30-45. 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 27:42-54. 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 constructions covering milk are divorced from the patent specification, and make 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 '807 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 '807 patent. However, Petitioner has not shown that either of its prior art references of the proposed Grounds disclose elements required by independent claim 1 of the '807 patent. Specifically, Petitioner fails to establish that the prior art references of the proposed Grounds disclose (1) a composition comprising nicotinamide riboside that is substantially free from other molecules, and (2) isolated nicotinamide riboside in admixture with a carrier. Petitioner also fails to establish that the references of the proposed Grounds disclose a composition that "increases NAD+ biosynthesis upon oral administration," as required by claim 1. Petitioner's

arguments on this essential limitation are the same as arguments raised and overcome during prosecution, so the petition can be denied on this basis alone under 35 U.S.C. § 325(d). *See Prism Pharma Co. v. Choongwae Pharma Corp.*, IPR2014-00315, Paper No. 14, at 12-13 (exercising discretion to deny institution under 35 U.S.C. § 325(d) because "substantially the same arguments were presented to the Office previously").

Because the other two challenged claims depend directly from claim 1, Petitioner has failed to establish that the asserted prior art references anticipate any of the challenged claims. Moreover, Petitioner fails to establish that the asserted references disclose compositions comprising nicotinamide riboside that is fractionated from other cellular components, as required by dependent claim 2 of the '807 patent.

A. Ground 1: Petitioner Has Not Demonstrated A "Reasonable Likelihood Of Prevailing" As To Claims 1-3 Over Goldberger et al.

1. Goldberger et al. Does Not Disclose "isolated nicotinamide riboside"

Independent claim 1 covers compositions comprising "isolated nicotinamide riboside," and the proper construction of that phrase requires the compositions to be formulated using nicotinamide riboside that is substantially free from other molecules. *See* '807 patent, at claim 1. However, Petitioner does not offer any evidence that the skim milk disclosed in Goldberger et al. was formulated using

"isolated nicotinamide riboside." Instead, Petitioner relies on two later-published articles from 2016 to conclude only that the milk disclosed in Goldberger et al. "necessarily contained nicotinamide riboside." Pet. at 12. With respect to "isolated," Petitioner asserts that the nicotinamide riboside in the skim milk used in Goldberger et al. is isolated because it was extracted from a cow (i.e., the naturally occurring organism). *See id.* Petitioner's cow argument strains credulity because nicotinamide riboside in milk taken from a cow is not free from other molecules just because the milk is no longer inside the cow.

Petitioner's reliance on Goldberger et al. directly contradicts the teachings of the '807 patent, which explains that cow's milk is a source from which nicotinamide riboside can be extracted. There is no dispute that cow's milk contains nicotinamide riboside. The '807 patent specification discloses as much and further describes methods for extracting nicotinamide riboside from milk so that it is "isolated" for formulation with other components as required by the claims. *See* '807 patent, at 27:7-9, 27:42-54, 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 4:19-20. Once a source 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 42-54.

In contrast, Petitioner does not, because it cannot, cite to any disclosure in Goldberger et al. that identifies individual components of skim milk or the source or purity of those components. 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" term. *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 "isolated nicotinamide riboside."

Accordingly, Petitioner has failed to establish that Goldberger et al. discloses the necessary element of "isolated nicotinamide riboside" 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 1-3 of the '807 patent.

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

Claim 1 covers compositions of isolated nicotinamide riboside that are "in admixture with a carrier." Petitioner offers only a single sentence regarding this

limitation, and does not even point to any disclosure within Goldberger et al. Pet. at 13. Instead, Petitioner relies on its expert, who similarly offers no citation or analysis in support of his conclusion that "[t]he combination of [nicotinamide riboside] and nicotinamide in skim milk is in admixture with other components of the milk, including a sugar (i.e., lactose)." Ex. 1002 at 17, ¶ 32. In particular, the Expert does not explain why he believes there is a disclosure of an admixture or a carrier as required by the claims.

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 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 et al. This is not surprising because there is no discussion of admixtures or carriers in Goldberger et al. A person of ordinary skill in the art would understand that a composition comprising isolated nicotinamide riboside "in admixture with a carrier" is something that is deliberately prepared (as opposed to something naturally occurring in a cow's udder, for example) and would further understand how to prepare the claimed

compositions using the teachings of the ’807 patent. *See* ’807 patent, at 29:24-35. 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 isolated 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 1-3 of the ’807 patent.

3. Goldberger et al. Does Not Disclose A Composition That “increases NAD+ biosynthesis upon oral administration”

Claim 1 of the ’807 patent covers compositions comprising isolated nicotinamide riboside that “increase[] NAD+ biosynthesis upon oral administration.” *See* ’807 patent, at claim 1. Petitioner concludes that Goldberger et al. inherently discloses this limitation because skim milk was administered to the test subject dogs. *See* Pet. at 14. However, the ’807 patent applicant overcame this same argument regarding milk during prosecution.

In the January 27, 2012 Advisory Action, 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

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 the necessary element of a composition that “increases NAD+ biosynthesis upon oral administration” 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 1-3 of the ’807 patent.

4. Goldberger et al. Does Not Disclose Nicotinamide Riboside “isolated from a natural or synthetic source”

Claim 2 covers the compositions of claim 1 “wherein the nicotinamide riboside is isolated from a natural or synthetic source.” ’807 patent, at claim 2. As discussed above, Petitioner has failed to establish that Goldberger et al. anticipates claim 1 of the ’807 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 16. 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 16.

As discussed above, Petitioner’s cow argument is directly contradictory to the ’807 patent teachings because the patent teaches methods for extracting

nicotinamide riboside from cow's milk. *See* '807 patent, at 27:7-9, 27:42-54, 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 4:19-20. 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 27:42-54.

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" term. *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."

Institution of Ground 1 should be denied.

B. Ground 2: Petitioner Has Not Demonstrated A "Reasonable Likelihood Of Prevailing" As To Claims 1-3 Over Goldberger and Tanner

1. Goldberger and Tanner Does Not Disclose "isolated nicotinamide riboside"

Independent claim 1 covers compositions comprising "isolated nicotinamide riboside," and the proper construction of that phrase requires the compositions to be formulated using nicotinamide riboside that is substantially free from other molecules. *See* '807 patent, at claim 1. However, Petitioner does not offer any evidence that the buttermilk disclosed in Goldberger and Tanner was formulated using "isolated nicotinamide riboside." Like its arguments in Ground 1, Petitioner relies on two later-published articles from 2016 to conclude only that "nicotinamide riboside is inherently present in buttermilk too." Pet. at 22. With respect to "isolated," Petitioner relies on its expert's conclusion that "the [nicotinamide riboside] in buttermilk is isolated, first, from the cow, and later from the whole milk or cream, when the fat elements that are churned into butter are separated from the water-soluble elements, including [nicotinamide riboside]." Pet. at 23; Ex. 1002 at 19, ¶ 38.

Just as in Ground 1, Petitioner's cow argument fails because nicotinamide riboside in milk taken from a cow is not free from other molecules just because the milk is no longer inside the cow. Similarly, Dr. Baur's description of the

conversion process to buttermilk confirms that the nicotinamide remains with all other components of "the water-soluble elements" of whole milk or cream, which is directly contradictory to the teachings of the '807 patent regarding isolated nicotinamide riboside. *See* Ex. 1002 at 19, ¶ 38; *see also* Pet. at 23. Petitioner's arguments are also insufficient to establish anticipation of the '807 patent.

There is no dispute that cow's milk contains nicotinamide riboside. The '807 patent specification discloses as much and further describes methods for extracting nicotinamide riboside from milk so that it is "isolated" for formulation with other components as required by the claims. *See* '807 patent, at 27:7-9, 27:42-54, 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 4:19-20. Once a source 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 42-54.

In contrast, Petitioner does not, because it cannot, cite to any disclosure in Goldberger and Tanner that identifies individual components of buttermilk or the source or purity of those components. Goldberger and Tanner were unable to identify even the type of molecule responsible for the reported results and concluded only "that the primary etiological dietary factor in pellagra is either a

faulty protein (amino acid) mixture, or a deficiency in some as yet unrecognized complex, or some combination of these." Ex. 1006 at 13. Petitioner's anticipation argument fails because it is based on an unreasonably broad claim construction of the "is isolated" term. *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 buttermilk, so it does not disclose the claimed "isolated nicotinamide riboside."

Accordingly, Petitioner has failed to establish that Goldberger and Tanner discloses the necessary element of "isolated nicotinamide riboside" 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 1-3 of the '807 patent.

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

Claim 1 covers compositions of isolated nicotinamide riboside that are formulated "in admixture with a 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 25. Instead, Petitioner relies

on its expert, who similarly offers no citation or analysis in support of his conclusion that "[t]he combination of [nicotinamide riboside] and nicotinamide in buttermilk is in admixture with other components of the milk, including a sugar (i.e., lactose)." Ex. 1002 at 20, ¶ 41. In particular, the Expert does not explain why he believes there is a disclosure of an admixture or a carrier as required by the claims.

Petitioner's conclusion that Goldberger and Tanner discloses nicotinamide riboside that is "in a mixture with" other components of the buttermilk does not establish that the combination of nicotinamide riboside and other components is an "admixture" as required by the claim. *See* Pet. at 25 (emphasis added). Petitioner's reliance on Dr. Baur's statement about buttermilk is insufficient to establish that Goldberger and Tanner discloses a 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 or carriers in Goldberger and Tanner. A person of ordinary skill in the art would understand that a formulation comprising isolated nicotinamide riboside "in admixture with a carrier" is something that is deliberately prepared (as opposed to something naturally occurring in a cow's udder, for example) and would further understand how to prepare the claimed compositions using the teachings of the

'807 patent. *See* '807 patent, at 29:24-35. 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 isolated nicotinamide riboside and a carrier.

Accordingly, Petitioner has failed to establish that Goldberger and Tanner discloses the necessary element of isolated 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 1-3 of the '807 patent.

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

Claim 1 of the '807 patent covers compositions comprising isolated nicotinamide riboside that "increase[] NAD+ biosynthesis upon oral administration." *See* '807 patent, at claim 1. Petitioner concludes that Goldberger and Tanner inherently discloses this limitation because buttermilk was administered to the test subjects. *See* Pet. at 26. 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 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 7-8, ¶ 12 (citations omitted). Accordingly, although Petitioner's arguments here are based on buttermilk, they are substantially the same as the arguments regarding milk the '807 patent applicant overcame during prosecution.

In the January 27, 2012 Advisory Action, 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 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 and Tanner discloses the necessary element of a composition that "increases NAD+ biosynthesis upon oral administration" 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 1-3 of the '807 patent.

4. Goldberger and Tanner Does Not Disclose Nicotinamide Riboside "isolated from a natural or synthetic source"

Claim 2 covers the compositions of claim 1 "wherein the nicotinamide riboside is isolated from a natural or synthetic source." '807 patent, at claim 2. As

discussed above, Petitioner has failed to establish that Goldberger and Tanner anticipates claim 1 of the ’807 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 28. 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 28, Ex. 1002 at 21, ¶ 45.

As discussed above, Petitioner’s cow argument is directly contradictory to the ’807 patent teachings because the patent teaches methods for extracting nicotinamide riboside from cow’s milk. *See* ’807 patent, at 27:7-9, 27:42-54, 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 4:19-20. 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 42-54.

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" term. *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."

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 of the challenged claims of the ’807 patent. Accordingly, the Petition should be denied under 35 U.S.C. § 314(a).

Respectfully submitted,

Date: November 3, 2017

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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 8,001 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 PRELIMINARY RESPONSE TO PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,197,807 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:

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