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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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THORNE RESEARCH, INC.,
Petitioner,

v.

TRUSTEES OF DARTMOUTH COLLEGE,
Patent Owner.

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

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# PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 8,383,086

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## I. INTRODUCTION

Thorne Research, Inc., ("Thorne" or "Petitioner") hereby requests review of U.S. Patent No. 8,383,086 to Charles M. Brenner ("the '086 patent," EX1001), which is currently assigned to the Trustees of Dartmouth College ("Dartmouth").

This is the second *inter partes* review filed against the '086 patent. The first IPR, IPR2017-01795 ("the '1795 IPR"), was filed by Elysium Health, Inc. ("Elysium"). Elysium challenged the claims of the '086 patent in that proceeding on the basis of art that taught the use of milk, skim milk, or buttermilk for the treatment of black-tongue in dogs and pellagra in human subjects. *See* EX1015, 8-12, 18-22; EX1018, 15-16, 31-32. In its Final Written Decision ("FWD"), the Board determined that all of the claims of the '086 patent were shown to be unpatentable over those references, except for claim 2. EX1018, 42. As to claim 2, the Board found that Elysium had not demonstrated that the active agent required by the claims, nicotinamide riboside ("NR"), was isolated as that term had been construed. *Id.*, 26-27, 37-38.

This petition demonstrates that pharmaceutical compositions of "isolated" NR were known, or would have been obvious, in view of the understanding of the art at the time of invention. And that is not surprising from a reading of the '086 patent, which admits that NR was freely available. The '086 patent specifically acknowledges that "[s]ynthetic sources of nicotinamide riboside can include any

library of chemicals commercially available from most large chemical companies including Merck, Glaxo, Bristol Meyers Squibb, Monsanto/Searle, Eli Lilly and Pharmacia." EX1001, 26:64-67. The patent acknowledges further that "[i]solated extracts of the natural sources can be prepared using standard methods," or that NR "can be chemically synthesized using established methods." *Id.*, 27:3-4, 28:16-21. The '086 patent also acknowledges that supplements, such a NR, "can be prepared by methods and contain carriers that are well-known in the art." *Id.*, 28:54-56. Finally, Stamler, as discussed below, disclosed a pharmaceutical composition comprising NR. EX1006, 4.

Finally, Dartmouth is collaterally estopped from relying on the limitations of claim 1 to support the patentability of claim 2 based on the Board's determination of unpatentability of claim 1 in the '1795 IPR. *See MaxLinear, Inc. v. CF CRESPE LLC*, 880 F.3d 1373, 1377 (Fed. Cir. 2018) (citing *Blonder-Tongue Labs., Inc. v. Univ. of Illinois Found.*, 402 U.S. 313 (1971)). That is especially true given that Dartmouth dropped its appeal of the Board's holding of the unpatentability of claims 1 and 3-5 in the '1795 IPR. *See* EX1021; EX1022.

This petition thus demonstrates a reasonable likelihood that claim 2 is unpatentable, and Thorne respectfully requests institution of this proceeding.

### A. Brief Overview of the ’086 Patent

The ’086 patent is entitled “Nicotinamide Riboside Kinase Compositions and Methods for Using the Same,” with Charles M. Brenner being the sole named inventor. The claims of the ’086 patent relate to pharmaceutical compositions of nicotinamide riboside formulated for oral administration. *See* EX1002, ¶¶17-18.

One known pathway of biosynthetic synthesis of nicotinamide adenine dinucleotide (“NAD+”) uses tryptophan, and supplementation with niacins prevents pellagra in populations with tryptophan-poor diets. EX1001, 1:23-27. The ’086 patent teaches that nicotinic acid and nicotinamide (collectively, niacins) are the vitamin forms of NAD+. *Id.*, 1:20-23. The ’086 patent thus discloses yeast and human nicotinamide riboside kinase enzymes (“Nrk”), which have specific functions in NAD+ metabolism. *Id.*, 3:2-6; EX1002, ¶¶19-20.

The ’086 patent also discloses “a dietary supplement composition comprising nicotinamide riboside identified in accordance with the methods of the present invention and a carrier.” EX1001, 4:14-16; EX1002, ¶21. The ’086 patent notes that NR was known to be a precursor for NAD+ in bacteria, but it was found that it is also a precursor to NAD+ in a eukaryotic biosynthetic pathway. EX1001, 2:62-64, 3:1-3; EX1002, ¶20. According to the ’086 patent, NR can be obtained commercially, isolated from natural sources using standard methods, or synthesized using established methods. EX1001, 26:64-67; 27:3-4; 28:16-21;

EX1002, ¶23. The ’086 patent describes a method for identifying natural sources of NR using a mutant strain of yeast, where the yeast exhibits normal growth so long as it is supplied with a source containing NR. EX1001, 7:49-60. The ’086 patent also discloses that “milk is a source of nicotinamide riboside.” *Id.* 3:11-12; *see also id.*, 7:49-61 (noting NR was identified in an acid whey preparation from cow’s milk); EX1002, ¶27. As demonstrated by the ’086 patent, NR isolated from the whey fraction of milk was sufficient to support the growth of a yeast strain that requires NR for growth. EX1001, 7:49-51, 26:32-34.

As acknowledged by the ’086 patent, NR can be obtained commercially, isolated from natural sources using standard methods, or synthesized using established methods. *Id.*, 26:64-67, 27:3-4, 28:16-21; EX1002, ¶¶23-26. For example, the ’086 patent discloses that “[s]ynthetic sources of nicotinamide riboside can include any library of chemicals commercially available from most large chemical companies including Merck, Glaxo, Bristol Myers Squibb, Mosanto/Searle, Eli Lilly and Pharmacia.” EX1001, 26:64-67; EX1002, ¶24. A wide variety of carriers are also disclosed by the ’086 patent, which notes that the compositions may be prepared using carriers and methods that are well known in the art. EX1001, 28:52-60; EX1002, ¶¶29-30.

The ’086 patent further discloses methods for preventing or treating a disease or condition associated with the NR pathway of NAD+ biosynthesis. EX1001, 4:17-19; EX1002, ¶22. The ’086 patent teaches:

> [A]gents (e.g., nicotinamide riboside) that work through the discovered nicotinamide riboside kinase pathway of NAD+ biosynthesis could have therapeutic value in improving plasma lipid profiles, preventing stroke, providing neuroprotection with chemotherapy treatment, treating fungal infections, preventing or reducing neurodegeneration, or in prolonging health and well-being.

EX1001, 27:60-66; EX1002, ¶28.

As for a therapeutically effective amount, the ’086 patent teaches that it is the amount of NR that “prevents, reduces, alleviates or eliminates the signs or symptoms of the disease or condition being prevented or treated.” EX1001, 28:36-39. The patent further states that the effective amount will vary with the disease or condition being addressed, and that the skilled clinician can evaluate the disease or condition after treatment and adjust the amount of NR as needed. *Id.*, 28:40-43; EX1002, ¶31.

The ’086 patent provides five examples, only one of which is relevant to the claimed pharmaceutical composition. EX1002, ¶32. Specifically, Example 2 teaches preparation of a vitamin fraction from whey. EX1001, 32:55-33:2; EX1002, ¶¶32-33.

Claim 1 of the ’086 patent (previously cancelled as being anticipated by the prior art) recites:

A pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier, wherein said composition is formulated for oral administration.

Claim 2 is dependent from claim 1, and recites:

The pharmaceutical composition of claim 1, wherein the nicotinamide riboside is isolated from a natural or synthetic source.

*See* EX1002, ¶¶34-36.

**B. Brief Overview of the Prosecution History**

The ’086 patent arose from U.S. Application No. 13/445,289, filed on April 12, 2012. During prosecution, the claims of the ’086 patent were rejected only on obviousness-type double-patenting grounds. EX1004, 176-78. After filing a terminal disclaimer, the claims were allowed and issued as claims 1-5 of the ’086 patent. EX1004, 151, 161-62, 170.

i. <u>The earliest effective filing date of claim 2 is April 20, 2006</u>

On its face, the ’086 patent purports to be a continuation of U.S. Application No. 11/912,400 (“the ’400 application”), which issued as U.S. Patent No. 8,197,807 (“the ’807 patent”) and is the national-stage entry of International Patent Application No. PCT/US2006/015495 (“the ’495 PCT application”) filed on April

20, 2006. EX1001, (63). The ’086 patent further states that the ’495 PCT application claims the benefit of priority to U.S. Application No. 11/113,701 (“the ’701 application”), filed April 25, 2005. *Id.*, 1:7-13. As explained below, claim 2 of the ’086 patent is, at best, only entitled to the filing date of the ’495 PCT application, which is April 20, 2006, and not the filing date of the ’701 application. Thorne notes, however, that the references relied upon in this petition to challenge claim 2 are prior art to the ’086 patent regardless of whether the 2006 or the 2005 priority date is adopted. But because Bieganowski (EX1008) was published more than one year before the April 20, 2006 priority date Dartmouth is only able to claim under the Paris Convention for the Protection of Industrial Property (“Paris Convention”), Dartmouth is unable to remove Bieganowski as a prior-art reference.

Although not specifically referenced by the ’086 patent, the ’701 application itself claims to be a continuation-in-part of International Patent Application PCT/US2005/04337 (“the ’337 PCT application,” published as WO 2005/077091 (EX1007, “Brenner”)), which claims the benefit of priority to U.S. Provisional Application 60/534,347 (“the ’347 provisional”). EX1019, 11.

Article 4 of the Paris Convention governs priority claims made in applications filed under the Patent Cooperation Treaty (PCT). *See* PCT, Art. 8, sec. 2(a) (“[T]he conditions for, and the effect of, any priority claim…shall be as

provided in Article 4…of the Paris Convention….”). Sections (C)(1)-(2) and C(4) of Article 4 state:

> (C)(1) The periods of priority…shall be ***twelve months*** for patents and utility models, and six months for industrial designs and trademarks.
> (C)(2) These periods ***shall start from the date of filing of the first application***; the day of filing shall not be included in the period.
>
> ***
>
> (C)(4) ***A subsequent application concerning the same subject as a previous first application*** within the meaning of paragraph (2), above, filed in the same country of the Union, ***shall be considered as the first application***, of which the filing date shall be the starting point of the period of priority, ***if, at the time of filing the subsequent application, the said previous application has been withdrawn, abandoned, or refused, without having been laid open to public inspection and without leaving any rights outstanding, and if it has not yet served as a basis for claiming a right of priority***. The previous application may not thereafter serve as a basis for claiming a right of priority.

Emphasis added.

Thus, under Paris Convention rules, to make a proper claim of priority for subject matter contained in a PCT application, the PCT application must have been filed within twelve months of the filing of the ***first*** application containing that subject matter. A subsequently-filed application containing the same subject matter may qualify as a “first” application only if the previous application has been

withdrawn, abandoned, or refused and has not yet served as a basis for claiming a right of priority at the time of the subsequently-filed application's filing.

The '347 provisional, filed on February 10, 2004, was the first application filed containing the subject matter of claim 2. This is demonstrated by the table below, which compares the limitations of claim 2 to the disclosure of the '347 provisional.

| **Claim 2** | **The '347 provisional (EX1005)[1]** |
|---|---|
| [Preamble] A pharmaceutical composition comprising | "Another aspect of the present invention is a dietary supplement composition containing nicotinamide riboside identified in accordance with the methods of the present invention and a carrier." EX1005, 6:27-30; *cf.* EX1001, 4:14-16.<br>"A still further aspect of the present invention is a method for preventing or treating a disease or condition associated with the nicotinamide riboside kinase pathway of NAD+ biosynthesis. The method involves administering to a patient…an effective amount of a nicotinamide riboside composition…." EX1005, 6:31-7:6; *cf.* |

[1] As cited in the Table, the disclosure presented herein also appears in the '086 patent's specification.

| | |
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| | EX1001, 4:16-23. |
| [a] nicotinamide riboside | "It has now been shown that nicotinamide riboside, which was known to be an NAD+ precursor in bacteria such as *Haemophilus influenza*…is an NAD+ precursor in a previously unknown but conserved eukaryotic NAD+ biosynthetic pathway." EX1005, 4:2-10; *see also id.*, 6:27-7:6, 15:32-16:5 ("nicotinamide riboside supplementation could be one route to improve lipid profiles in humans" and "could be an important supplement for acute conditions such as stroke"); *cf.* EX1001, 2:62-3:3, 4:14-23, 8:57-62.<br><br>"Thus, another aspect of the present invention is a method for preventing or treating a disease or condition…by administering an effective amount of a nicotinamide riboside composition." EX1005, 55:20-56:10; *cf.* EX1001, 27:66-28:15. |
| [b] in admixture with a carrier | "Another aspect of the present invention is a dietary supplement composition containing nicotinamide riboside…and a carrier." EX1005, 6:27-30; *cf.* EX1001, 4:14-16.<br><br>"Polypeptides, nucleic acids, vectors, dietary supplements (*i.e.* nicotinamide riboside), and nicotinamide riboside-related prodrugs…can be |

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| | conveniently used or administered in a composition containing the active agent in combination with a carrier. Such compositions can be prepared by methods and contain carriers which are well-known in the art." EX1005, 56:16-57:2; *see also id.*, 57:3-24 (listing exemplary carriers); *cf.* EX1001, 28:49-29:20. |
| [c] wherein said composition is formulated for oral administration | "Polypeptides, nucleic acids, vectors, dietary supplements, and nicotinamide riboside-related prodrugs…can be administered via any route includ[ing], but not limited to, oral…." EX1005, 57:25-58:9; *cf.* EX1001, 29:21-37.<br>"For oral therapeutic administration, the compound can be combined with one or more carriers and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums, foods and the like." EX1005, 58:15-19; *see also id.*, 58:26-59:20 (describing various means for oral administration); *cf.* EX1001, 29:43-30:12. |
| [d] wherein the nicotinamide riboside is isolated from a natural or synthetic source. | "A still further aspect of the present invention is a method for identifying a natural or synthetic source for nicotinamide riboside." EX1005, 6:13-15; *cf.* EX1001, 4:1-2. |

| | |
|---|---|
| | "Another aspect of the present invention is a dietary supplement composition containing nicotinamide riboside identified in accordance with the present invention and a carrier." EX1005, 6:27-30; *cf.* EX1001, 4:14-16.<br><br>"As described herein, nicotinamide riboside isolated from deproteinized whey fraction of cow's milk was sufficient to support *NRK1*-dependent growth in a *qns1* mutant. Accordingly, mutant strains generated herein will be useful in identifying other natural or synthetic sources for nicotinamide riboside for use in dietary supplements." EX1005, 53:17-24; *cf.* EX1001, 26:32-39.<br><br>"Synthetic sources of nicotinamide riboside can include any library of chemicals commercially available from most large chemical companies including Merck, Glaxo, Bristol Meyers Squibb, Monsanto/Searle, Eli Lilly and Pharmacia. Natural sources which can be tested for the presence of a nicotinamide riboside include, but are not limited to, cow's milk, serum, meats, eggs, fruit and cereals. Isolated extracts of the natural sources can be prepared using standard methods." EX1005, 54:19-55:2; *see also id.*, 64:29-65:9 (Example 2 describing preparation of |

| | |
|---|---|
| | isolated NR with a whey vitamin fraction); *cf.* EX1001, 26:64-27:4, 32:54-33:2. |

As noted above, the '495 PCT application was filed on April 20, 2006, more than twelve months after the filing of the '347 provisional. EX1001, (63). Therefore, the '495 PCT application ***cannot*** claim priority back to the '347 provisional with respect to the subject matter of claim 2.[2] Moreover, because the Paris Convention rules have not been followed, any earlier claim of priority to subsequently-filed applications (*i.e.*, the '701 application, filed April 25, 2005) containing the same subject matter as the '347 provisional is defective and has been lost.[3] As a result, the earliest possible priority date for claim 2 is April 20,

[2] Nor can the '495 PCT application claim priority to the '337 PCT application, which was filed on February 9, 2005. EX1007, (22).

[3] At the time of the '701 application's filing, the '347 provisional had not been "withdrawn, abandoned, or refused" as the '701 application itself claimed a benefit of priority to the '347 provisional. *See* EX1019, 11. The '347 provisional also served as a basis for priority in the '337 PCT application. *See* EX1007, (30). Thus, the '701 application as a subsequent application to the same subject matter cannot qualify as a "first" application under Paris Convention rules.

2006, the filing date of the ’495 PCT application, because the ’495 PCT application does not meet the requirements of Section 4 of the Paris Convention as it was filed more than twelve months after the filing of the first application containing the subject matter of claim 2 (*i.e.*, the ’347 provisional).

### C. Brief Overview of the Prior IPR Proceeding

As noted above, the ’086 patent was the subject of a prior IPR proceeding, the ’1795 IPR, initiated by Petitioner Elysium on July 17, 2017. The current Petitioner, Thorne, is not an entity related to Elysium, nor was Thorne involved in the Elysium IPR.

The Elysium petition requested review of original claims 1-5 of the ’086 patent and advanced two grounds: (1) claims 1-5 as anticipated under 35 U.S.C. § 102(b) by Goldberger et al., *A Study of the Blacktongue-Preventive Action of 16 Foodstuffs, with Special Reference to the Identity of Blacktongue of Dogs and Pellagra of Man*, 43 Pub. Health Reports 1385 (1928) (EX1011, “Goldberger”); and (2) claims 1-5 as anticipated under § 102(b) by Goldberger and Tanner, *A Study of the Treatment and Prevention of Pellagra*, 39 Pub. Health Reports 87 (1924) (EX1012, “Goldberger and Tanner”). *See* EX1018, 5.

The grounds advanced by Elysium relied in large part on inherency. The primary references described studies on the oral consumption of cow skim milk and buttermilk to prevent the onset of “black-tongue” in dogs and pellagra in

human subjects, respectively. *See* EX1018, 15-16, 31-32. Although not known to the researchers at the time, later research had established that NR was naturally present in milk, and thus, the milk orally administered in the references necessarily contained NR. *See id*., 16, 19-21. Later research also established that NR was the preventative cause of the diseases studied in the references. *See id*.

In its petition, Elysium advanced a construction for the term "isolated" recited in claim 2 as meaning "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." EX1015, 7 (citing EX1001, 9:3-10). With this construction, Elysium argued that claim 2 was anticipated by Goldberger because "[s]kim milk is the product that remains when almost all of the cream is removed from whole milk," making the NR naturally present in the skim milk "isolated during the process of converting whole milk to skim milk because, during that process, the non-fat elements of whole milk (including nicotinamide riboside present in skim milk) are separated from the fat." *Id.*, 14-15. Elysium advanced similar arguments in its second ground, reasoning the buttermilk orally administered in Goldberger and Tanner also contained "isolated" NR due to the process of converting whole milk or cream to buttermilk. *Id.*, 25.

The Board instituted on all claims, except claim 2, under the first ground, and declined to institute on the second ground as cumulative. EX1023, 18-19. With respect to claim 2, the Board construed the term "isolated" to mean "the nicotinamide riboside is separated or substantially free from at least some of the other components associated with the source of the molecule such that it constitutes at least 25% (w/w) of the composition." *Id.*, 7-9 (citing EX1001, 9:3-12, 9:23-26, 9:31-33, 53:59-60). The Board then concluded that, under this interpretation, while Elysium had offered evidence that the NR had "been separated from at least some of the other components associated with nicotinamide riboside, e.g., fat," Elysium had offered no evidence to show that the "nicotinamide riboside constitute[d] at least 25% by weight of the remaining composition." *Id.*, 13-14. In other words, the Board found that Elysium had failed to adequately substantiate the inherency theory advanced in its petition materials as to claim 2.

After institution, pursuant to the Supreme Court's decision in *SAS Institute, Inc. v. Iancu*, 138 S. Ct. 1348 (2018), the Board modified its institution decision to institute on all challenged claims and all grounds presented in the petition. EX1016, 2; EX1018, 2-3. In its FWD, the Board maintained its construction of the term "isolated" and determined that Elysium had provided no persuasive evidence in the record to show that NR had constituted at least 25% (w/w) of the skim milk and buttermilk administered in the references. EX1018, 12-14, 26, 38. The Board

further found that, regardless of any minimum percentage by weight of NR, the NR present in the skim milk or buttermilk was not "isolated" because "significant amounts of other components remain after the fat is removed." *Id.*, 27, 38. For claims 1 and 3-5, the Board agreed that Elysium had established by a preponderance of the evidence that Goldberger and Goldberger and Tanner anticipated those claims. *Id.*, 42. The Board's decision as to Elysium's appeal of claim 2 was summarily affirmed by the Federal Circuit. EX1004, 1-2. Dartmouth, although cross-appealing the Board's decision as to claims 1 and 3-5, moved to dismiss its appeal before briefing, which was granted by the court. *See* EX1021; EX1022. As such, all appeals have been exhausted, and judgement that claims 1 and 3-5 of the '086 patent are unpatentable is now final.

### D. The Board Should Not Exercise Its Discretion under Section 325(d) to Deny Institution[4]

Dartmouth may urge the Board to deny institution because "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). As described below, however, this petition presents

[4] The Board's precedential decision in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (Mar. 20, 2020), does not apply. While Chromadex has threatened litigation, there currently is no co-pending district court litigation between Thorne and Dartmouth, or its licensee, Chromadex.

new arguments and art not before the Office, either during prosecution of the '086 patent or during the '1795 IPR.

In determining whether to exercise its discretion to deny institution under § 325(d), the Board applies a two-part framework. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 (Feb. 13, 2020) (precedential). The first part assesses "whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office." *Id.*, 8. "[I]f either condition of [the] first part of the framework is satisfied," the second part assesses "whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of [the] challenged claims." *Id.* Three factors help inform whether the first part of the framework is satisfied: (1) the similarities and material differences between the asserted art and the prior art involved during examination; (2) the cumulative nature of the asserted art and the prior art evaluated during examination; and (3) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art. *Id.*, 9-10; *see also Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (Dec. 15, 2017) (precedential).

As discussed below, this petition presents art and arguments that are materially different than those presented to the Office during prosecution of the

’086 patent, its parent application (the ’400 application), and the ’1795 IPR. Thus, the first part of the Board’s two-part framework is not satisfied, and the second part need not be reached. The Board should decline to exercise its discretion under § 325(d).

i. The asserted art is materially different

The petition presents five single-reference grounds. Grounds 1 and 2 rely on anticipation and obviousness, respectively, in view of International Patent Application No. WO2002/055018 (EX1006, “Stamler”). Grounds 3 and 4 rely on anticipation and obviousness, respectively, in view of P. Bieganowski & C. Brenner, *Discoveries of Nicotinamide Riboside as a Nutrient and Conserved* NRK *Genes Establish a Preiss-Handler Independent Route to NAD$^+$ in Fungi and Humans*, 117 Cell 495 (2004) (EX1008, “Bieganowski”). Ground 5 relies on anticipation over Brenner (EX1007), the publication of the ’337 PCT application.

As detailed more below, Stamler generally relates to therapeutic methods of modulating nitric oxide bioactivity by inhibiting the enzyme glutathione-dependent formaldehyde dehydrogenase. *See infra*, section I.F.i. One inhibitor specifically taught by Stamler is NR. Stamler further teaches that one method for administrating the inhibitor is oral administration. Bieganowski identifies a new biosynthetic pathway for the production of NAD+ in eukaryotes using NR as a precursor. The reference contemplates NR as an appropriate supplementation for

generating NAD+, which is useful in treating certain medical conditions. Brenner has essentially the same disclosure as the ’086 patent, and, for the reasons discussed above in section I.B.i, is prior art to the ’086 patent. *See infra*, section I.F.iii. These references are materially different from the art asserted in the ’1795 proceeding, which investigated the general preventative effect of milk consumption for black-tongue in dogs and pellagra in human subjects.

As noted above, the examiner did not apply a prior-art rejection during prosecution of the ’086 patent. During prosecution of its parent, the ’400 application, applicant submitted claims directed to a “composition comprising isolated nicotinamide riboside in admixture with a carrier.” *See* EX1020, 200 (also submitting dependent claims further reciting that the NR “is isolated from a natural or synthetic source” and “the composition is formulated for oral administration”). The examiner applied two anticipatory references to the claims: one teaching the preparation of isolated NR in water and another teaching the chemical synthesis of NR into a colorless syrup or white solid form. *See id.*, 182-84. Ultimately, applicant amended the claims substantially to overcome the prior art and obtained allowance with a final amendment reciting that the composition “increases NAD+ biosynthesis upon oral administration”—a feature found by the Board in the ’1795 IPR to be inherent to compositions containing NR as an active agent. *See* EX1020, 57; EX1018, 29-30. The art presented in this petition differs materially because it

specifically discloses or suggests oral administration of isolated NR, and specifically addresses the limitation found to be lacking during prosecution of the '400 application. Thus, this factor does not support discretionary denial of the petition. *Cf. Alphatec Holdings, Inc. v. Nuvasive, Inc.*, IPR2019-00361, Paper 59, 23-27 (July 8, 2020) (discussing issue preclusion as to the limitations of a previously canceled claim).

ii. The asserted art is not cumulative

The references are also not cumulative. With respect to the '1795 IPR, Elysium relied upon art teaching the oral administration of a natural food source (*i.e.*, milk) that inherently contained NR. The asserted art in this petition goes further: it establishes that, prior to the effective filing date of claim 2 of the '086 patent, NR and its isolation were known, its use was known to be beneficial for treating certain disorders, and its administration may be done orally. Thus, the art applied in this petition explicitly discloses and at least suggests the pharmaceutical composition of challenged claim 2.

iii. The asserted art was not materially evaluated during examination or during the previous IPR

None of Stamler, Bieganowski, or Brenner formed the basis of a rejection during prosecution of the '086 patent or its parent, the '400 application. Moreover, these references were not asserted in any of the grounds of the '1795 IPR nor were they submitted as exhibits for the Board's consideration of the record. Thus, the

asserted art has not been materially evaluated by the Office in the context of claim 2 of the ’086 patent.

As explained above, Elysium advanced an unsubstantiated inherency theory as to claim 2 in the ’1795 IPR; that is, that the claim was anticipated by the administration of milk to dogs and human subjects for the prevention and treatment of black-tongue and pellagra. EX1018, 12-14, 26, 38. The Board rejected that argument on the basis that it was not sufficiently shown that the NR present in milk was inherently “isolated” as had been construed. *Id*. Nevertheless, the Board did hold that claim 1, from which claim 2 depends, was unpatentable over the prior art. Dartmouth is thus now precluded from relying on the limitations of claim 1 as imparting patentability to challenged claim 2. The collateral estoppel faced by Dartmouth thus also underscores the unpatentability of claim 2 in a manner not previously presented to the Office. *See MaxLinear, Inc. v. CF CRESPE LLC*, 880 F.3d 1373, 1377 (Fed. Cir. 2018) (noting a patentee is estopped from asserting the validity of a patent that has been declared invalid in a prior suit against a different defendant, unless patentee demonstrates that he did not have full and fair opportunity, procedurally, substantively, and evidentially, to litigate the validity of his patent in the prior suit) (citing *Blonder-Tongue Labs., Inc. v. Univ. of Illinois Found.*, 402 U.S. 313 (1971)); *see also Alphatec Holdings, Inc. v. Nuvasive, Inc.*, IPR2019-00361, Paper 59, 23 (July 8, 2020).

### E. The Board Should Not Exercise Its Discretion under Section 314(a) to Deny Institution

Dartmouth may also urge the Board to exercise its discretion under § 314(a) to deny institution because this is the second petition filed requesting IPR of claim 2 of the '086 patent. When evaluating whether to deny institution of a "follow-on" petition, the Board generally looks to seven factors: (1) whether the same petitioner previously filed a petition directed to the same claims of the same patent; (2) whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it; (3) whether at the time of filing of the second petition the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition; (4) the length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition; (5) whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent; (6) the finite resources of the Board; and (7) the requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than one year after the date on which the Director notices institution of review. *Gen. Plastic Indus. Co., Ltd. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19, 9-10 (Sept. 6, 2017) (precedential). As explained

below, the *General Plastic* factors weigh heavily in favor of institution of the petition.

Moreover, Dartmouth is collaterally estopped from relying on the limitations of claim 1 to support the patentability of claim 2 based on the Board's determination of unpatentability of claim 1 in the '1795 IPR. *See MaxLinear, Inc.*, 880 F.3d at 1377; *supra*, section I.D.iii. This underscores the fact that *General Plastic* is inapposite.

i. Factors 1 and 2

Thorne was not a petitioner, nor a real party-in-interest, to the first petition filed against the '086 patent. Thus, the first two factors weigh heavily in favor of institution.

ii. Factors 3-5

Although the FWD of the '1795 IPR issued in 2018, as discussed above, as Thorne was not a party to the first IPR, it had no say in the timing of the first IPR. Moreover, as explained above in section I.D, the grounds presented in this petition do not substantially overlap with those presented in the first petition. Rather, the grounds presented are based on references and evidence not previously before the Board, particularly as they relate to establishing the known isolation of NR from natural and synthetic sources—evidence found lacking in the previous IPR. Thus, the nature of the grounds and the rationale supporting the unpatentability of claim

2 stand in contrast to the grounds presented in the '1795 IPR, which relied on the inherent "isolation" of NR in milk products. This supports the conclusion that the previous proceeding was not used as a roadmap for the present petition. Thus, these factors also weigh in favor of institution.

iii. Factors 6 and 7

The present petition will not require the Board to expend large resources to review nor will it unduly prevent the Board from meeting its statutory one-year deadline to issue a final written decision upon institution. Only one dependent claim is challenged in this petition; a claim that depends from one that has already been found unpatentable by the Board and affirmed by the Federal Circuit. The petition also provides an efficient analysis of claim 2, presenting five grounds based on three references (three anticipation grounds and two single-reference obviousness grounds), with the analysis particularly establishing how the limitations of dependent claim 2 fail to confer any novel or nonobvious concept to an already-unpatentable pharmaceutical composition. As a result, the present petition comports with the Board's guiding principle of maintaining the efficient administration of the Office and its ability to complete IPR proceedings in a timely manner. Thus, these factors also weigh in favor of institution.

Accordingly, the Board should decline any invitation to exercise its discretion under § 314(a) to deny the petition.

### F. Brief Overview of the Scope and Content of the Prior Art

As explained in detail in the corresponding Declaration of Dr. Samie Jaffrey (EX1002; *see id.*, ¶¶1-5 (detailing qualifications)) and addressed in further detail below (Section VI), the involved claim would not have been considered new or non-obvious to a person of ordinary skill in the art at the relevant time. Specifically, the prior art discloses and/or renders obvious the NR pharmaceutical composition of claim 2.

NAD+ is essential for life of all organisms. EX1002, ¶37. It serves as a coenzyme for oxidoreductases, as well as a source for ADPribosyl groups used in various reactions, including those that retard aging in experimental systems. EX1008, Abstract; EX1002, ¶37.

In 1924, Goldberger and Tanner demonstrated a treatment and prevention of pellegra, caused by a deficiency in NAD+ (EX1013, 2) in humans, in which 29 subjects were provided a diet that included 1,200 grams of buttermilk a day for up to a year. EX1012, 93; EX1002, ¶38. In 1928, Goldberger demonstrated that skim milk exercised a preventative action against black-tongue (EX1011, 1402-05), which is also caused by a deficiency of NAD+ (EX1013, 2). EX1002, ¶39.

In 1935, Booher looked at a "vitamin G" concentrate, containing vitamin G as well as other unknown vitamins, as a preventative for black-tongue. EX1009, 429, 435; EX1002, ¶40. The vitamin concentrate was prepared by a preliminary

extraction of low-lactose whey powder, followed by concentration and drying. EX1009, 429, 435. The concentrate was then reextracted, and again concentrated and dried. *Id.*, 429-430. Dogs were given black-tongue producing diets, and subsequently developed symptoms of black-tongue, such as lesions and gastro-intestinal symptoms. *Id.*, 430-431. Dogs that received the vitamin concentrate recovered. *Id.*, 431-432 (noting "dog was in buoyant spirits and in excellent physical condition at the end of the test"). Booher concluded that the "vitamin G concentrate obtained from low-lactose whey powder which carries, in addition to vitamin G (lactoflavin), at least one other heat-stable vitamin necessary for rat-growth, ha[d] been found effective for the prevention or cure of black-tongue." *Id.*, 435; EX1002, ¶40.

NR is now recognized to be the nutrient found in milk that can lead to increases in NAD+. *See* EX1002, ¶¶41-42. NR is not produced by the body but is obtained as part of the diet. *See id.*, ¶42. In a 2004 paper, Bieganowski and Brenner (the inventor of the '086 patent) demonstrated that NR is a NAD+ precursor, and thus is a useful compound for elevating NAD+ levels in humans. EX1008, 495; EX1002, ¶41. Bieganowski specifically teaches a method of isolating NR from whey powder. EX1008, 500. Accordingly, the ordinary artisan would have understood that the normal route of administration of NR is orally. EX1002, ¶42.

Moreover, as acknowledged by the ’086 patent, methods of isolating or synthesizing NR were known to the ordinary artisan. EX1001, 27:3-4; EX1002, ¶43. For example, Tanimori discloses a simple and efficient method of synthesizing NR. EX1014, Abstract; EX1002, ¶44. According to Tanimori, NR is a precursor of nicotinamide mononucleotide, which is a component of both chemical and enzymatic preparation of NAD+. EX1014, 1135. Franchetti discloses a stereoselective synthesis of NR. EX1010, Abstract; EX1002, ¶45. Franchetti notes that NR is an intermediate in a biosynthetic pathway in which nicotinamide is converted to NAD+. EX1010, 4655. In addition, Franchetti notes that “NAD is a co-factor in numerous enzyme-catalyzed redox reactions in all living organisms and plays a fundamental role in cellular metabolic processes,” and it is “crucial … that proper levels of NAD are regulated and maintained for cellular survival.” *Id.*

Additionally, in 2002, Stamler disclosed a pharmaceutical composition of NR for the treatment of a variety of conditions. EX1006, 4, 13-14; EX1002, ¶46.

The prior art applied to claim 2 of the ’086 patent is described briefly below. *See* EX1002, ¶¶47-56.

i. Stamler[5]

Stamler is drawn to methods of modulating nitric oxide (NO) bioactivity to obtain a therapeutic effect. EX1006, 1; EX1002, ¶48. According to Stamler, inhibiting the enzyme glutathione-dependent formaldehyde dehydrogenase mediates NO donor therapy and nitrosative stress and NO bioactivity *in vivo*. EX1006, 2. Inhibition of the enzyme inhibits the proliferation of pathologically proliferating cells and increases NO bioactivity in diseases where beneficial. EX1002, ¶48.

Stamler teaches that patients afflicted with disorders in which an inhibitor of glutathione-dependent formaldehyde dehydrogenase would benefit include breathing disorders (*e.g.*, asthma, cystic fibrosis, and ARDS), heart disease, hypertension, ischemic coronary syndromes, atherosclerosis, glaucoma, diseases characterized by angiogenesis (*e.g.*, coronary artery disease), disorders where there is a risk of thrombosis or restenosis occurring, chronic inflammatory diseases (*e.g.*, AIDS, dementia, and psoriasis), diseases where there is risk of apoptosis occurring (*e.g.*, heart failure, atherosclerosis, degenerative neurologic disorders, arthritis and

[5] Stamler published on July 18, 2002, making it prior art under pre-AIA § 102(b). Stamler is not listed on the face of the '086 patent nor was it addressed during prosecution or during the '1795 IPR.

liver injury (ischemic or alcoholic)), impotence, obesity caused by eating in response to craving for food, stroke, reperfusion injury (e.g., traumatic muscle injury in heart or lung or crush injury), and disorders where preconditioning of heart or brain for NO protection against subsequent ischemic events is beneficial. EX1006, 13-14; EX1002, ¶49.

Stamler notes that one class of compounds that may be used in its methods as inhibitors of glutathione-dependent formaldehyde dehydrogenase includes NR. EX1006, 3-4; EX1002, ¶52. A therapeutically effective amount provides for amelioration or protects against a risk associated with the disorder, and therapeutically effective amounts include ranges from 1 μg to 10 g/kg and often ranges from 10 μg to 1 g/kg, or 10 μg to 100 mg/kg body weight of the patient. EX1006, 15; EX1002, ¶50. Stamler teaches further that oral administration is preferred. EX1006, 15; EX1002, ¶51.

ii. Bieganowski[6]

Bieganowski discloses a new biosynthetic pathway for the production of NAD+ in eukaryotes using NR as a precursor. EX1008, Abstract; EX1002, ¶53.

[6] Bieganowski published on May 14, 2004, making it prior art under pre-AIA § 102(b). Charles Brenner, the inventor of the '086 patent, is also a named author on this paper. Although listed on the face of the patent, Bieganowski was not

As taught by Bieganowski and noted above, "NAD+ is essential for life in all organisms." EX1008, Abstract. Bieganowski notes that NR is found in natural sources, such as milk, and it specifically teaches that a vitamin fraction of whey contains NR. *Id.*, Abstract, 499; EX1002, ¶54; *cf.* EX1001, 26:64-27:12 (stating known isolation methods include fractionation "to remove salts, carbohydrates, polypeptides, nucleic acids, fats and the like"); EX1017, 17-19 (arguing term "isolated" means "fractionated from other cellular components" as consistent with the specification).

According to Bieganowski, "[t]he persistence of 'niacin' as a mixture of nicotinamide and nicotinic acid may attest to the utility of utilizing multiple pathways to generate NAD+ and suggests that supplementation with nicotinamide riboside as third importable NAD+ precursor may be beneficial for certain conditions." EX1008, 499; EX1002, ¶55. In particular, Bieganowski notes that high doses of nicotinic acid are effective at reducing levels of cholesterol, and are also effective in controlling low-density lipoprotein cholesterol, increasing high-density lipoprotein cholesterol, and reducing triglyceride and lipoprotein levels. EX1008, 499-500; EX1002, ¶56. According to Bieganowski, although nicotinic

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addressed during prosecution of the '086 patent or before the Board in the '1795 IPR.

acid effects all of the key lipids in a desirable direction, as well as decreasing mortality in target populations, its use is limited because of "flushing," a side effect of heat and redness. EX1008, 500. Thus, Bieganowski states that NR may be a preferred route of improving lipid profiles in humans. *Id.*; EX1002, ¶56.

iii. Brenner[7]

Brenner, the WO publication of the '337 PCT application, has essentially the same disclosure as the challenged '086 patent. *See*, *e.g.*, Section I.A (discussing the teaching of the '086 patent). Thus, Brenner teaches that an "aspect of the present invention is a dietary supplement composition containing nicotinamide

[7] Brenner published on August 25, 2005, making it prior art under pre-AIA § 102(a). Brenner is also prior art under § 102(e), as it was filed on February 9, 2005, and claims priority to the '347 provisional, filed February 10, 2004. Brenner and the '347 provisional contain substantially the same specification and identical claims. In addition, Brenner also lists Pawel Bieganowski as an inventor, whereas the '086 patent only lists Charles Brenner as an inventor, and thus Brenner qualifies as an application "by another." Although Thorne bears the ultimate burden of persuasion, Dartmouth has the burden of production of demonstrating whether Brenner is "by another." *Nelson Prods., Inc. v. Bal Seal Eng'g, Inc.*, IPR2014-00572, Paper 55, 8 (Sept. 24, 2014).

riboside identified in accordance with the methods of the present invention and a carrier." EX1007, 6:23-26; EX1002, ¶57.

### G. Brief Overview of the Level of Skill in the Art

In the '1795 IPR, Patent Owner Dartmouth defined the person of ordinary skill as "someone with a Ph.D. in biochemistry or similar field in the pharmaceutical sciences, with familiarity and experience with pharmacokinetics." EX1017, 6. This Petition applies Dartmouth's definition. *See also* EX1002, ¶¶58-59.

## II. GROUNDS FOR STANDING

Thorne certifies that, under 37 C.F.R. § 42.104(a), the '086 patent is available for *inter partes* review, and Thorne is not barred or estopped from requesting *inter partes* review of the '086 patent on the grounds identified.

## III. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

Real Party-in-Interest (37 C.F.R. § 42.8(b)(1)): Thorne Research, Inc. is the real party-in-interest.

Related Matters (37 C.F.R. § 42.8(b)(2)): This is the second *inter partes* review filed against the '086 patent. The '1795 IPR, was filed by Elysium Health, Inc., and the Board found all claims, except claim 2 challenged here, unpatentable. *Elysium Health, Inc. v. Trustees of Dartmouth College*, IPR2017-01795, Paper 39, 42 (Jan. 16, 2019).

Elysium also challenged the related '807 patent in IPR2017-01796, in which the Board denied institution. *Elysium Health, Inc. v. Trustees of Dartmouth College*, IPR2017-01796, Paper 9 (Jan. 18, 2018).

Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))

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Service Information – 37 C.F.R. § 42.8(b)(4). Thorne hereby consents to electronic service. Please direct all correspondence to lead and back-up counsel at the contact information below. A power of attorney accompanies this petition.

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## IV. STATEMENT OF THE PRECISE RELIEF REQUESTED

Thorne requests review of claim 2 of the '086 patent under 35 U.S.C. § 311 and AIA § 6 under the grounds as follows:

| Ground | Claim | Description |
|---|---|---|
| 1 | 2 | Anticipated under 35 U.S.C. § 102(b) by Stamler |
| 2 | 2 | Obvious under 35 U.S.C. § 103(a) over Stamler |

| | | |
|---|---|---|
| 3 | 2 | Anticipated under 35 U.S.C. § 102(b) by Bieganowski |
| 4 | 2 | Obvious under 35 U.S.C. § 103(a) over Bieganowski |
| 5 | 2 | Anticipated under 35 U.S.C. § 102(a) or (e) by Brenner |

## V. CLAIM CONSTRUCTION

The claim terms should be given their ordinary and customary meaning consistent with the specification, as a person of ordinary skill in the art ("POSA") would have understood them. 37 C.F.R. § 42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc*).

As relevant to challenged claim 2, the Board in the '1795 IPR construed the terms discussed below. Although the claims were construed under the broadest reasonable construction standard, the constructions adopted by the Board in that proceeding are consistent with the disclosure of the '086 patent, as well as how a POSA would have understood those terms. The following constructions, previously adopted by the Board and underlying the final judgement of the unpatentability of claims of the challenged patent, were observed in the unpatentability analysis presented in this Petition. *See also* EX1002, ¶¶60-67.

### A. "pharmaceutical composition comprising nicotinamide riboside"

The Board in the '1795 IPR construed "pharmaceutical composition comprising nicotinamide riboside" as a "composition where NR is the active agent" as being consistent with the specification of the '086 patent, as well as the

wording of the claim itself. EX1018, 9. The Board noted further that the use of the transition phrase "comprising" did not exclude the presence of additional active agents. *Id.*; EX1002, ¶63.

**B. "carrier"**

The Board construed carrier broadly in the '1795 IPR. Specifically, it construed "carrier" to mean:

> a liquid or solid filler, diluent, excipient, or solvent encapsulating material, [that] is involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be acceptable in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient.

*Id.*, 14-15 (quoting EX1023, 6-7); *see also* EX1001, 28:61-67; EX1002, ¶64.

**C. "isolated"**

The Board in the '1795 IPR construed "isolated" as inclusive of "the nicotinamide riboside … [being] separated or substantially free from at least some of the other components associated with the source of the molecule such that it constitutes at least 25% (w/w) of the composition." EX1018, 12. In so doing, the Board acknowledged that this level of purity was discussed in the specification only in the context of proteins, but "determined that one skilled in the art would have understood that this level of purity extends to other types of 'isolated' molecules referenced in the Specification, including NR." *Id.*; EX1002, ¶65.

In this regard, the specification does explicitly discuss "isolated"[8] NR. EX1002, ¶66. Specifically, the disclosure of the '086 patent references "nicotinamide riboside isolated from deproteinized whey fraction of cow's milk

[8] In its Patent Owner Preliminary Response in the '1795 IPR, Patent Owner Dartmouth argued that "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." '1795 IPR, Paper 8, 15; *see also* EX1017, 17-18. The only time the '086 patent mentions isolation from a "synthetic source" is when it states "[s]ynthetic sources of nicotinamide riboside can include any library of chemicals commercially available from most large chemical companies," without discussing how the NR is "isolated" from those sources. EX1001, 26:64-66. In addition, claim 2 is drawn to a composition and not a method. Patent Owner failed to explain how isolating from a synthetic source imparted any structural change compared to chemically synthesizing or isolating the NR from a natural source. *See In re Thorne*, 777 F.2d 695, 697 (Fed. Cir. 1985) (noting "determination of patentability is based on the product itself"), *Amgen Inc. v. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1369-70 ("In determining the validity of a product-by-process claim, the focus is on the product and the process of making it.").

was sufficient to support NRK1-dependent growth" in a yeast mutant dependent on NR for growth. EX1001, 26:32-34; *see also id.*, 32:54-33:2 (Example 2 exemplifying isolation of NR from whey and noting that it was used at 50% by volume); EX1017, 18 (Patent Owner Dartmouth citing Example 2 as support for specification disclosing "cow's milk as a source from which nicotinamide riboside can be isolated, and standard methods for isolating nicotinamide riboside from that cow's milk").

## VI. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

### A. [Ground 1] Claim 2 Is Anticipated by Stamler (EX1006)

Claim 1, from which claim 2 depends, recites a pharmaceutical composition comprising NR in admixture with a carrier, wherein the composition is formulated for oral administration. Claim 2 of the '086 patent merely adds the limitation that the NR is isolated from a natural or synthetic source. *See* EX1002, ¶¶68-69.

#### i. "pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier, wherein the composition is formulated for oral administration"

Stamler discloses methods of treating a patient by administering a therapeutically effective amount of an inhibitor of glutathione-dependent formaldehyde dehydrogenase, where the patient is afflicted with a disorder ameliorated by NO donor therapy or afflicted with pathologically proliferating cells. EX1006, 2; *see also id.* at 13-17; EX1002, ¶70. Such disorders include a

"degenerative neurologic disorder." EX1006, 13; EX1002, ¶70. According to Stamler, one class of compounds that may be used as inhibitors of glutathione-dependent formaldehyde dehydrogenase are competitors for NAD+ binding, such as NR. EX1006, 3-4; EX1002, ¶70. Thus, Stamler teaches a pharmaceutical composition comprising NR. EX1002, ¶71.

Stamler discloses further that the preferred method of administration is oral administration. EX1006, 15; EX1002, ¶72. Stamler teaches that, in general, "the dosage, i.e., the therapeutically effective amount, ranges from 1 μg to 10 g/kg and often ranges from 10 μg to 1 g/kg or 10 μg to 100 mg/kg body weight of the patient, per day." EX1006, 15; EX1002, ¶72. Given the different dosage amounts, as well as Stamler's teaching that oral administration is preferred, the ordinary artisan would have understood that Stamler discloses nicotinamide riboside in admixture with a carrier to provide for oral administration to a patient. EX1002, ¶73.

Accordingly, Stamler discloses a pharmaceutical composition of NR in admixture with a carrier formulated for oral administration, as required by cancelled claim 1. *See id.* As discussed above, Dartmouth is collaterally estopped from relying on the limitations of claim 1 as imparting patentability to challenged claim 2. *MaxLinear, Inc.*, 880 F.3d at 1377.

ii. "isolated from a natural or synthetic source"

Stamler discloses that the disclosed compounds are available commercially, or their synthesis is described or obvious from the literature, and thus teaches NR isolated from a synthetic or natural source. EX1006, 13; *see also* EX1001, 26:64-67; 27:3-4; 28:16-21; EX1002, ¶74. The POSA would have understood that synthetic and commercially-obtained NR would be "separated or substantially free from at least some of the other components associate with the source of the molecule such that it constitutes at least 25% (w/w) of the composition." *E.g.*, EX1010, 4656 (reporting a synthetic yield for NR of 45% (Scheme 1), which was then purified by chromatography on activated charcoal and isolated as a white solid); EX1001, 28:15-21 (citing Franchetti as an established method for synthesizing NR); EX1002, ¶¶75-76.

Accordingly, Stamler anticipates claim 2. *See also* EX1002, ¶¶77-78 (providing claim chart comparing claim 2 with disclosure of Stamler).

**B. [Ground 2] Claim 2 Is Obvious over Stamler**

The teachings of Stamler as they relate to claim 2 are discussed above as to Ground 1. To the extent that Stamler does not anticipate the composition of claim 1, it renders the claim obvious. *See* EX1002, ¶¶79-86.

i. "pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier, wherein the composition is formulated for oral administration"

Stamler discloses administration of an inhibitor of glutathione-dependent formaldehyde dehydrogenase to a patient, where that inhibitor specifically may be NR. EX1006, 2-4; EX1002, ¶80. Stamler also teaches that the preferred route of administration is oral. EX1006, 15; EX1002, ¶80. Although Stamler does not provide a specific example of a pharmaceutical composition containing NR, it would have been obvious to do so given Stamler's express suggestion of orally administering an inhibitor of glutathione-dependent formaldehyde dehydrogenase, such as NR. EX1006, 3-4, 15; EX1002, ¶81; *cf.* EX1001, 29:21-37 (stating administration of the composition can be "via any route," leaving it to the POSA to determine "[t]he most suitable route in any given case [which] will depend on the nature and severity of the condition being treated and on the nature of the particular compound which is being used"). To the extent that Stamler does not expressly identify a carrier for oral administration, it would have been obvious to do so to facilitate administration of the NR to a patient. EX1002, ¶82; *cf.* EX1001, 28:54-67 (acknowledging "compositions can be prepared by methods and contain carriers which are well-known in the art," and further citing "[a] generally recognized compendium of such methods and ingredients" for formulating such a composition with a carrier). Thus, formulating nicotinamide riboside for oral

administration would have been well within the level of skill of the ordinary artisan. EX1002, ¶83.

ii. "isolated from a natural or synthetic source"

Stamler also does not explicitly state that the NR is isolated. But as discussed above, synthesis of isolated NR was known in the art. *E.g.*, EX1010, 4656; EX1002, ¶84. Moreover, as the '086 patent acknowledges, NR can be obtained commercially, isolated from natural sources using standard methods, or synthesized using established methods. EX1001, 26:64-67; 27:3-4; 28:16-21; EX1002, ¶84 (citing EX1010). It would have been well within the level of skill of the POSA to determine the level of isolation and purity for oral administration. *E.g.*, EX1001, 28:49-60 (demonstrating the level of skill of a POSA by noting that pharmaceutical compositions may be prepared and contain carriers that are well known in the art); EX1002, ¶85.

Accordingly, Stamler renders claim 2 obvious. EX1002, ¶86.

### C. [Ground 3] Claim 2 is Anticipated under 35 U.S.C. § 102 by Bieganowski (EX1008)

As noted above, claim 1, from which claim 2 depends, recites a pharmaceutical composition comprising NR in admixture with a carrier, wherein the composition is formulated for oral administration. Claim 2 of the '086 patent merely adds the limitation that the NR is isolated from a natural or synthetic source. EX1002, ¶¶87-88.

i. "pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier, wherein the composition is formulated for oral administration"

Bieganowski discloses that NR "was discovered as a nutrient in milk." EX1008, Abstract; EX1002, ¶89. Bieganowski also teaches NR isolated as a whey fraction, as well as a synthetic method for NR, in which the NR is provided to yeast at 50% by volume of the whey fraction and at 10μM for the synthetic NR. EX1008, 500; EX1002, ¶89; *see also* EX1008, 499 (suggesting NR supplementation for NAD+ biosynthesis). As evidenced by Booher, the POSA would have understood that both the whey fraction and the synthesized NR would be suitable for oral administration to a mammal, such as a dog. *See, e.g.*, EX1009, 431 (administering a vitamin whey fraction of cow's milk to dogs); EX1002, ¶90.

Accordingly, Bieganowski discloses a pharmaceutical composition of NR in admixture with a carrier formulated for oral administration, as required by cancelled claim 1. EX1002, ¶¶90-91. As discussed above, Dartmouth is collaterally estopped from relying on the limitations of claim 1 as imparting patentability to challenged claim 2. *MaxLinear, Inc.*, 880 F.3d at 1377.

ii. "isolated from a natural or synthetic source"

Bieganowski discloses preparation of a whey fraction of milk, in which "commercial nonfat cow's milk was prepared by adjusting the pH to 4 with HCl, stirring at 55°C for 10 min, removal of denatured casein by centrifugation, and

passage through a 5000 Da filter." EX1008, 500; EX1002, ¶92. The whey vitamin fraction was then added to yeast media at 50% by volume. EX1008, 500. Bieganowski demonstrates that this whey vitamin fraction contains NR. *Id.*, 499. That finding by Bieganowski is consistent with the finding of Booher, discussed above, that a vitamin concentrate obtained from whey from cow's milk added to the diet treated black-tongue in dogs. EX1002, ¶92.

Bieganowski discloses the same method for isolating NR from whey as the '086 patent. EX1002, ¶93. Specifically, according to the '086 patent:

> A whey vitamin fraction of commercial nonfat cow's milk was prepared by adjusting the pH to 4 with HCl, stirring at 55°C for 10 min, removal of denatured casein by centrifugation, and passage through a 5000 Da filter.

*Id.*, 32:54-33:1; *see also* EX1017, 18 (citing same as an exemplary method for isolating NR). As with Bieganowski, the '086 patent also uses the whey in yeast at 50% by volume. *Id.*, 33:1-2; *see also In re Katz Interactive Call Processing Patent Litig.*, 639 F.3d 1303, 1324 (Fed. Cir. 2011) (stating "there is a strong presumption against a claim construction that excludes a disclosed embodiment").

Bieganowski also discloses a synthetic strategy for NR. EX1008, 500; EX1002, ¶94. In the method of Bieganowski, "120µmol NMN (Sigma, concentration corrected by absorption) was treated with 1250 units of calf intestinal alkaline phosphatase (Sigma) for 1 hr at 37°C in 1 ml 100mM NaCl, 20

mM Tris [pH 8.0], 5 mM $MgCL_2$. After hydrolysis of NMN to nicotinamide riboside was verified by HPLC, phosphatase was removed by centrifuging the reaction through a 5000 Da filter (Millipore)." EX1008, 500. The NR was used at 10 μM. EX1002, ¶94.

The POSA would have understood that both the whey fraction and the synthesized NR would meet the "isolated" requirement of claim 2. *E.g.*, EX1001, 32:55, Example 2 (disclosing the same method of providing a vitamin concentrate from whey); EX1002, ¶¶95-96; *cf.*, EX1011, 1403 (testing fresh skim milk for its ability to prevent black-tongue); EX1001, 26:64-27:12 (isolating including fractionation); EX1017, 17-19 (arguing "isolated" means "fractionated from other cellular components").

Accordingly, Bieganowski anticipates claim 2. *See also* EX1002, ¶97 (providing claim chart).

### D. [Ground 4] Claim 2 Is Obvious over Bieganowski

#### i. "pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier, wherein the composition is formulated for oral administration"

Bieganowski teaches that "NAD+ is essential for life in all organisms, both as a coenzyme for oxidoreductases and as a source of ADPribosyl groups used in various reactions, including those that retard aging in experimental systems." EX1008, Abstract. Bieganowski teaches further that supplementation with NR as a

NAD+ precursor may be beneficial for certain conditions. *Id.* Bieganowski discloses that "[n]icotinamide riboside was discovered as a nutrient in milk, suggesting that nicotinamide is a useful compound for elevation of NAD+ levels in humans." *Id.*, 495, Abstract; EX1002, ¶¶98-99.

Bieganowski also teaches that treatment with nicotinic acid, another NAD+ precursor, has been shown to effect all of the key lipids in a desirable direction and to reduce mortality in target populations, but its use has been limited because of side effects of heat and redness; that is, flushing has limited the use of nicotinic acid. EX1008, 495, Abstract; EX1002, ¶100. NR, a nutrient that is found in natural sources such as cow's milk, may thus be a preferred route of improving lipid profiles in humans. *E.g.*, EX1008, Abstract (noting that NR may be a useful compound for elevation of NAD+ levels in humans as it had been discovered as a nutrient in milk); EX1002, ¶100.

Bieganowski thus renders the claimed NR pharmaceutical composition formulated for oral administration obvious. EX1002, ¶101. As Dr. Jaffrey testifies, formulating vitamin compounds such as NR for oral administration was well known and routine, which is also consistent with the teachings of the '086 patent. *Id.* (citing EX1001, 28:49-60, 29:21-25, 29:43-53). In addition, because Bieganowski teaches that NR is a nutrient found in milk, and is thus ingested orally through diet, the POSA would have had a reasonable expectation of success of

achieving the claimed oral formulation. *Id.* The ordinary artisan would have been motivated to provide such a composition in order modulate lipid levels and reduce mortality in target populations as taught by Bieganowski. *Id.*, ¶102. The ordinary artisan would have had a reasonable expectation of success because Bieganowski teaches that another NAD+ precursor, nicotinic acid, had been shown to effect all of the key lipids in a desirable direction and to reduce mortality in target populations. *Id.*, ¶103. Bieganowski provides further motivation by teaching that NR is a nutrient found in milk, and by specifically suggesting supplementation using NR. EX1008, Abstract, 499; EX1002, ¶¶101-02.

ii. "isolated from a natural or synthetic source"

As discussed above in Ground 3, Bieganowski teaches isolation of NR from whey, as well as a method of synthesizing NR. EX1008, 500; EX1002, ¶104. And as discussed above, additional methods for synthesis of isolated NR were known in the art. *E.g.*, EX1010, 4656; EX1001, 28:15-21 (citing Franchetti as an established method for synthesizing NR). Moreover, as the '086 patent acknowledges, NR can be obtained commercially, isolated from natural sources using standard methods, or synthesized using established methods. EX1001, 26:64-67; 27:3-4; 28:16-21; EX1002, ¶104. It would have been well within the level of skill of the POSA to determine the level of isolation and purity for administration. *E.g.*, EX1001, 28:49-60 (demonstrating the level of skill of a POSA by noting that pharmaceutical

compositions may be prepared and contain carriers that are well known in the art); EX1002, ¶105.

Accordingly, Bieganowski renders claim 2 obvious.

### E. [Ground 5] Claim 2 is Anticipated under 35 U.S.C. § 102 by Brenner (EX1007)

As noted above, claim 1, from which claim 2 depends, recites a pharmaceutical composition comprising NR in admixture with a carrier, wherein the composition is formulated for oral administration. Claim 2 of the '086 patent merely adds the limitation that the NR is isolated from a natural or synthetic source. EX1002, ¶¶106-107.

#### i. "pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier, wherein the composition is formulated for oral administration"

As noted above, the disclosure of Brenner is essentially the same as that of the '086 patent. EX1002, ¶108. Brenner discloses that "[i]t has now been shown that nicotinamide riboside, which was known to be an NAD+ precursor in bacteria such as *Haemophilus influenza*…is an NAD+ precursor in a previously unknown but conserved eukaryotic NAD+ biosynthetic pathway." EX1007, 3:31-4:6; *see also id.*, 15:29-16:2 ("nicotinamide riboside supplementation could be one route to improve lipid profiles in humans" and "could be an important supplement for acute conditions such as stroke"), 55:20-56:10; *cf.* EX1001, 2:62-3:3, 4:14-23, 8:57-62. Brenner thus teaches "a method for preventing or treating a disease or condition

associated with the nicotinamide riboside kinase pathway of NAD+ biosynthesis. The method involves administering to a patient…an effective amount of a nicotinamide riboside composition…." EX1007, 6:27-33; *cf.* EX1001, 4:16-23. Brenner also teaches "a dietary supplement composition containing nicotinamide riboside identified in accordance with the methods of the present invention and a carrier." EX1007, 6:23-26; *see also id.*, 56:16-57:2, 57:3-24; *cf.* EX1001, 4:14-16. "For oral therapeutic administration, the compound can be combined with one or more carriers and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums, foods and the like." EX1007, 58:15-19; *see also id.*, 57:25-58:9, 58:26-59:20 (describing various means for oral administration); EX1002, ¶109; *cf.* EX1001, 29:43-30:12.

Accordingly, Brenner discloses a pharmaceutical composition of NR in admixture with a carrier formulated for oral administration, as required by cancelled claim 1. EX1002, ¶110. As discussed above, Dartmouth is collaterally estopped from relying on the limitations of claim 1 as imparting patentability to challenged claim 2. *MaxLinear, Inc.*, 880 F.3d at 1377.

ii. "isolated from a natural or synthetic source"

Brenner discloses a "method for identifying a natural or synthetic source for nicotinamide riboside" as well as "a dietary supplement composition containing nicotinamide riboside identified in accordance with the present invention and a

carrier." EX1007, 6:9-11, 6:23-26; *cf.* EX1001, 4:1-2, 4:14-16. Brenner describes NR isolated from deproteinized whey fraction of cow's milk. EX1007, 53:17-20; *cf.*, EX1001, 26:32-29. Brenner discloses further:

> Synthetic sources of nicotinamide riboside can include any library of chemicals commercially available from most large chemical companies including Merck, Glaxo, Bristol Meyers Squibb, Monsanto/Searle, Eli Lilly and Pharmacia. Natural sources which can be tested for the presence of a nicotinamide riboside include, but are not limited to, cow's milk, serum, meats, eggs, fruit and cereals. Isolated extracts of the natural sources can be prepared using standard methods.

EX1007, 54:19-55:2; *see also id.*, 64:29-65:9 (Example 2 describing preparation of isolated NR with a whey vitamin fraction); EX1002, ¶111; *cf.* EX1001, 26:64-27:4, 32:54-33:2.

Accordingly. Brenner discloses not only a pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier, wherein the composition is formulated for oral administration, but also discloses that the NR may be isolated from a natural or synthetic source. EX1002, ¶¶112-113. Brenner thus anticipated claim 2.

## VII. CONCLUSION

For the reasons set forth above, claim 2 of the ’086 patent is unpatentable. Thorne therefore requests that an *inter partes* review of this claim be instituted.

Respectfully submitted,

Dated: December 1, 2020

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
Reg. No. 52,182

## VIII. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 10,485 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully submitted,

Dated: December 1, 2020

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
Reg. No. 52,182

## X. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15(A) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 23-2415.

## XI. APPENDIX – LIST OF EXHIBITS

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

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

## CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for Inter Partes Review of U.S. Patent No. 8,383,086 (and accompanying Exhibits 1001-1023) by overnight courier (Federal Express or UPS), on this 1st day of December, 2020, on the Patent Owner at the correspondence address of the Patent Owner as follows:

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Respectfully submitted,

Dated: December 1, 2020

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