Filed on behalf of: Thorne Research, Inc.
By: Michael T. Rosato (mrosato@wsgr.com)
Lora M. Green (lgreen@wsgr.com)
Tasha M. Thomas (tthomas@wsgr.com)
WILSON SONSINI GOODRICH & ROSATI
701 Fifth Avenue, Suite 5100
Seattle, WA 98104-7036

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

THORNE RESEARCH, INC.,
Petitioner,

v.

TRUSTEES OF DARTMOUTH COLLEGE,
Patent Owner.

Case No. IPR2021-00491
Patent No. 8,197,807

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 8,197,807

TABLE OF CONTENTS

Page

I. INTRODUCTION

Thorne Research, Inc., ("Thorne" or "Petitioner") hereby requests review of U.S. Patent No. 8,197,807 to Charles M. Brenner ("the '807 patent," EX1001), which is currently assigned to the Trustees of Dartmouth College ("Dartmouth").

This is the second *inter partes* review filed against the '807 patent. The first IPR, IPR2017-01796 ("the '1796 IPR"), was filed by Elysium Health, Inc. ("Elysium"). Elysium challenged the claims of the '807 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* EX1025, 7-11, 18-21. In its Institution Decision ("DI"), the Board declined to institute on the grounds presented in the petition because 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. *See* EX1027, 5-8, 10-11.

This petition demonstrates that 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 '807 patent, which admits that NR was freely available. The '807 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, 27:39-42. 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.*, 27:45-46, 28:59-61. The '807 patent also acknowledges that supplements, such a NR, "can be prepared by methods and contain carriers that are well-known in the art." *Id.*, 29:29-31.

Moreover, because Patent Owner failed to meet the requirements of Article 4 of the Paris Convention, which governs priority claims made in applications filed under the Patent Cooperation Treaty ("PCT"), April 20, 2006, is the earliest priority date to which Patent Owner is entitled. Accordingly, Patent Owner's published PCT application, WO 2005/077091 (EX1007, "Brenner") published August 25, 2005, which has a different inventive entity and essentially the same disclosure of the '807 patent, is prior art to the '807 patent and anticipates the challenged claims.

This petition thus demonstrates a reasonable likelihood that claims 1-3 are unpatentable, and Thorne respectfully requests institution of this proceeding.

A. Brief Overview of the '807 Patent

The '807 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 '807 patent relate to compositions of isolated NR formulated for oral administration, wherein the isolated NR is in combination with

one or more of tryptophan, nicotinic acid, or nicotinamide in admixture with a carrier. *See* EX1002, ¶¶17-18, 34-36.

One known pathway of biosynthetic synthesis of nicotinamide adenine dinucleotide ("NAD+") uses tryptophan, and supplementation with niacins (*i.e.*, nicotinic acid and nicotinamide) prevents pellagra in populations with tryptophan-poor diets. EX1001, 1:23-30. The '807 patent explains that nicotinic acid and nicotinamide are known vitamin forms of NAD+. *Id.*, 1:23-25. That is, as acknowledged by the '807 patent, "[i]t is well-established that nicotinic acid is phosphoribosylated to nicotinic acid mononucleotide (NaMN), which is then adenylated to form nicotinic acid adenine dinucleotide (NaAD), which in turn is amidated to form NAD+." *Id.*, 1:30-35 (citations omitted). The '807 patent also discloses yeast and human nicotinamide riboside kinase enzymes ("Nrk"), which have specific functions in NAD+ metabolism. *Id.*, 3:11-13; EX1002, ¶¶19-20.

The '807 patent also discloses "a dietary supplement composition containing nicotinamide riboside identified in accordance with the methods of the present invention and a carrier." EX1001, 4:21-23; EX1002, ¶21. The '807 patent generally states that the NR may be "administered in combination with tryptophan, nicotinic acid or nicotinamide." EX1001, 4:34-36. The '807 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, 3:3-5, 3:10-11;

EX1002, ¶20. The ’807 patent describes a method for identifying natural sources of NR using a mutant strain of yeast, where the yeast is only able to grow normally when supplied with a source containing NR. EX1001, 7:66-8:10. The ’807 patent also discloses that “milk is a source of nicotinamide riboside.” *Id.*, 3:19-20; *see also id.*, 7:66-8:1 (noting NR was identified in an acid whey preparation from cow’s milk); EX1002, ¶27. As demonstrated by the ’807 patent, NR found in the whey fraction of milk was sufficient to support the growth of a yeast strain that requires NR for growth. EX1001, 7:66-8:10, 27:7-9; EX1002, ¶27.

As acknowledged by the ’807 patent, NR can be obtained commercially, isolated from natural sources using standard methods, or synthesized using established methods. EX1001, 27:39-42, 27:45-46, 28:58-61; EX1002, ¶23. For example, the ’807 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, Monsanto/Searle, Eli Lilly and Pharmacia.” EX1001, 27:39-42; EX1002, ¶¶24-26. A wide variety of carriers are also disclosed by the ’807 patent, which notes that the compositions “can be prepared by methods and contain carriers which are well-known in the art.” EX1001, 29:43-58, 29:27-35; EX1002, ¶¶29-30.

The ’807 patent further discloses methods for preventing or treating a disease or condition associated with the NR pathway of NAD+ biosynthesis. EX1001, 4:24-26; EX1002, ¶22. The ’807 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, 28:35-41; EX1002, ¶28.

As for a therapeutically effective amount, the ’807 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, 29:11-14. 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.*, 29:14-18; EX1002, ¶31.

The ’807 patent provides five examples, only one of which is relevant to the claimed composition. EX1002, ¶¶32-33. Specifically, Example 2 teaches preparation of a vitamin fraction from whey, as well as synthesis of NR from NMN. EX1001, 33:30-45; EX1002, ¶32.

Claim 1 of the ’807 patent recites:

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 comprising a sugar, starch, cellulose, powdered tragacanth, malt, gelatin, talc, cocoa butter, suppository wax, oil, glycol, polyol, ester, agar, buffering agent, alginic acid, isotonic saline, Ringer’s solution, ethyl alcohol, polyester, polycarbonate, or polyanhydride, wherein said composition is formulated for oral administration and increases NAD+ biosynthesis upon oral administration.

Claim 2 is dependent from claim 1, and recites:

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

Claim 3 is also dependent from claim 1, and recites:

The composition of claim 1, wherein the formulation comprises a tablet, troche, capsule, elixir, suspension, syrup, wafer, chewing gum, or food.

See EX1002, ¶¶34-36.

B. Brief Overview of the Prosecution History

i. Summary of the claims’ prosecution

The ’807 patent arose from U.S. Application No. 11/912,400 (“the ’400 application”), filed on November 20, 2007. The original claims of the ’400

application were subject to a restriction requirement. *See* EX1004, 209-16. In response, applicant submitted a new set of claims directed to "[a] composition comprising isolated nicotinamide riboside in admixture with a carrier." *Id.*, 198-204.

The examiner rejected the claims as anticipated by either Saunders (EX1028 (Saunders 1), EX1029 (Saunders 2)) or Tanimori (EX1024). *See* EX1004, 182-84. Saunders prepared NR by enzymatic degradation of NAD+ or NMN, while Tanimori synthesized NR from nicotinamide and β-D-ribofuranose 1,2,3,5-tetraacetate. *Id*. The examiner additionally cited Tanimori for teaching "that nicotinamide riboside is a precursor of nicotinamide mononucleotide (β-NMN) which is a component used for chemical or enzymatic preparation of NAD+." *Id.* at 184. Applicant amended the claims to further recite specific options for the carrier and that the isolated NR was in combination with one or more of tryptophan, nicotinic acid, or nicotinamide. *Id.*, 128. The examiner applied the same references, rejecting the claims as obvious. *See id.*, 115-18 (further applying Cuny (EX1016) as disclosing well-known carrier materials). Applicant again amended the claims to additionally recite that the composition is formulated for oral administration and increases NAD+ biosynthesis upon oral administration. *See* 1004, 57, 75. With regard to the former limitation, the examiner considered the claims obvious over the same references, but allowed the claims in view of the

latter limitation. *See id.*, 50-51, 71-72. During prosecution, applicant pointed to Bieganowski (EX1008) as evidence establishing that NR was an NAD+ precursor in humans. *Id.*, 103-04.

ii. The earliest effective filing date of the claims is April 20, 2006

On its face, the '807 patent purports to be the national-stage entry of International Patent Application No. PCT/US2006/015495 ("the '495 PCT application") filed on April 20, 2006. EX1001, (22), (86). The '807 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, which, in turn, is a continuation-in-part of International Patent Application No. PCT/US2005/004337 ("the '337 PCT application," published as WO 2005/077091), filed February 9, 2005. EX1001, 1:11-15. The '337 PCT application claims the benefit of priority to U.S. Provisional Application 60/534,347 ("the '347 provisional"). EX1001, 1:15-19. As explained below, per the rules governing priority claims under the Paris Convention for the Protection of Industrial Property ("the Paris Convention"), the '807 patent is, at best, only

entitled to the filing date of the '495 PCT application, which is April 20, 2006, and not the filing dates of any of its earlier-claimed applications.[1]

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***

---

[1] 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, Dartmouth is unable to remove Bieganowski as a prior-art reference.

> ***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 the claims of the challenged '807 patent. This is demonstrated by the table below, which compares the limitations of claims 1-3 to the disclosure of the '347 provisional.

Claim 1	**The '347 provisional (EX1005)[2]**
[1.Preamble] A composition comprising isolated	"Another aspect of the present invention is a dietary supplement composition containing

[2] As cited in the Table, the disclosure presented herein also appears in the '807 patent's specification.

nicotinamide riboside	nicotinamide riboside identified in accordance with the methods of the present invention and a carrier." EX1005, 6:27-30; *cf.* EX1001, 4:21-23. "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.* EX1001, 4:23-31. "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, 27:7-12. "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, 27:39-46, 33:30-45. "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 or other polypeptides or nucleic acids commonly found 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)." EX1005, 16:13-24; *cf.*, EX1001, 9:23-33.
[1.1] in combination with one or more of tryptophan,	"The method involves administering to a patient having a disease or condition associated with the nicotinamide riboside kinase pathway of NAD+

nicotinic acid, or nicotinamide,	biosynthesis an effective amount of a nicotinamide riboside composition so that the signs or symptoms of the disease or condition are prevented or reduced…. In another embodiment, the nicotinamide riboside is further administered in combination with tryptophan, nicotinic acid or nicotinamide." EX1005, 7:1-10; *cf.* EX1001, 4:23-36.
[1.2] wherein said combination is in admixture with a carrier comprising a sugar, starch, cellulose, powdered tragacanth, malt, gelatin, talc, cocoa butter, suppository wax, oil, glycol, polyol, ester, agar, buffering agent, alginic acid, isotonic saline, Ringer's solution, ethyl alcohol, polyester, polycarbonate, or polyanhydride,	"Another aspect of the present invention is a dietary supplement composition containing nicotinamide riboside…and a carrier." EX1005, 6:27-30; *cf.* EX1001, 4:21-23. "Polypeptides, nucleic acids, vectors, dietary supplements (*i.e.* nicotinamide riboside), and nicotinamide riboside-related prodrugs…can be 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, 29:24-62.
[1.3] wherein said composition is formulated for oral administration and	"Polypeptides, nucleic acids, vectors, dietary supplements, and nicotinamide riboside-related prodrugs…can be administered via any route

increases NAD+ biosynthesis upon oral administration.	includ[ing], but not limited to, oral…." EX1005, 57:25-58:9; *cf.* EX1001, 29:63-30:12. "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, 30:19-56. "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, 3:3-11, 4:21-33, 9:9-14. "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, 28:41-45.
Claim 2	**The '347 provisional (EX1005)**
The composition of claim 1, 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, 4:8-9. "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, 4:21-23. "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, 27:7-12. "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, 27:39-46, 33:30-45.
Claim 3	**The '347 provisional (EX1005)**
The composition of claim 1, wherein the formulation comprises a tablet, troche, capsule, elixir, suspension, syrup, wafer, chewing gum, or food.	"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; *cf.* EX1001, 30:19-23.

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, (87). Therefore, the '495 PCT application ***cannot*** claim priority back to the '347 provisional with respect to the subject matter of claims 1-3, nor can it claim priority to the subsequently-filed '337 PCT application, which was filed February

9, 2005. 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 claims 1-3 of the '807 patent is April 20, 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 the claims (*i.e.*, the '347 provisional).[4]

---

[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, 241. 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.

[4] The '807 patent also cannot directly claim priority to the '701 application because the '701 application had been abandoned before the filing date of the '807 patent (November 20, 2007). *See* EX1019, 1-4 (notice of abandonment mailed December 28, 2006).

This understanding is consistent with the Office's Corrected Filing Receipt issued for the '807 patent, which corrected the patent's priority claim to include only the benefit of the '495 PCT application's filing date. *Compare* EX1004, 42 (corrected filing receipt) *with id.*, 225 (original filing receipt).

C. Brief Overview of Prior and Related IPR Proceedings

As noted above, the '807 patent was the subject of a prior IPR proceeding, the '1796 IPR, initiated by Petitioner Elysium on July 17, 2017, but denied institution by the Board on January 18, 2018. Also relevant, a child patent to the '807 patent, U.S. Patent No. 8,383,086 ("the '086 patent"), was the subject of another IPR proceeding, IPR2017-01795 ("the '1795 IPR"), brought by Petitioner Elysium. The '1795 IPR was instituted and received a Final Written Decision ("FWD") determining all claims, except a dependent claim directed to a pharmaceutical composition containing isolated NR, were unpatentable.[5]

i. The '807 patent's prior IPR proceeding

The Elysium petition requested review of claims 1-3 of the '807 patent and advanced two grounds: (1) claims 1-3 as anticipated under 35 U.S.C. § 102(b) by Goldberger et al., *A Study of the Blacktongue-Preventive Action of 16 Foodstuffs,*

[5] The current Petitioner, Thorne, is not an entity related to Elysium, nor was Thorne involved in the Elysium IPRs.

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 1-3 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* EX1025, 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 id.*, 8-10, 18-19. Although not known to the researchers at the time, later research had established that NR, in addition to tryptophan and nicotinamide, was naturally present in milk, and thus, the milk orally administered in the references necessarily contained NR in combination with tryptophan and nicotinamide. *See id*., 11-13, 20, 24-25. Later research also established that NR prevented the diseases studied in the references and was more orally bioavailable than nicotinamide, making it a more potent booster of NAD+ biosynthesis. *See id*., 10-11, 15, 21, 26.

In its petition, Elysium advanced a construction for the term "isolated" recited in the claims 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." EX1025, 6-7 (citing EX1001, 9:23-30). With this construction, Elysium argued that the claims were 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." EX1025, 14-16. 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.*, 23.

In its DI, 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." EX1027, 7-8 (citing EX1001, 9:21-33, 53:59-60). The Board then concluded that, under this interpretation, while Elysium had offered evidence that the NR had "been separated from fat," Elysium had offered no evidence to show that the "nicotinamide riboside constitute[d] at least 25% by weight of the remaining composition." EX1027, 10. In other words, the Board found that Elysium had failed to adequately substantiate the inherency

theory advanced in its petition materials as to the term "isolated," and thus institution was denied.

ii. The '086 patent's prior IPR proceeding

Elysium also petitioned for IPR of claims 1-5 of the '086 patent based on the same two references and inherency theory applied in the '1796 IPR. In contrast to the claims challenged in the '1796 IPR, only dependent claim 2 required "isolated" NR. EX1024, claims 1-5. In the Board's FWD, all claims, except claim 2, were found unpatentable. EX1018, 16, 32, 42. Independent claim 1, which recited an orally-administered pharmaceutical composition comprising NR in admixture with a carrier, was found anticipated by the oral consumption of the milk products taught in Goldberger and Goldberger and Tanner because "not only is NR a constituent of milk, but…it is active in the production of NAD+" and milk includes a carrier in the form of lactose. *Id.*, 21, 24 (noting the "Specification teaches that materials that can be used as carriers 'include sugars, such as lactose'"); *see also id.*, 14-15 (construing "carrier").

The Board also found claim 3, which recites the composition includes "a tablet, troche, capsule, elixir, suspension, syrup, wafer chewing gum or food,"[6] was anticipated by Goldberger and Goldberger and Tanner because milk is a food. *Id.*,

[6] Claim 3 of the '807 patent recites the same limitation.

27-28. For claim 4, which recites the composition comprises "one or more of tryptophan, nicotinic acid, and nicotinamide,"[7] the Board found that the milk used in the references "contains nicotinamide and tryptophan" and thus anticipated the claim. *Id.*, 28. Finally, for claim 5, which recites the composition "increases NAD+ biosynthesis upon oral administration,"[8] the Board found that "the consumption of milk increases NAD+ biosynthesis" and that "the NR in milk is used to produce NAD+ *in vivo*." *Id.*, 30-31.

Because claim 2 required the NR to be "isolated," the Board found that Elysium had not sufficiently shown that the milk products administered in Goldberger and Goldberger and Tanner contained "isolated" NR for the same reasons given in the '1796 IPR's DI.

The Board's decision as to Elysium's appeal of claim 2 was summarily affirmed by the Federal Circuit. EX1020, 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, making the Board's findings with respect to claims 1 and 3-5 of the '086 patent final. *See* EX1021; EX1022.

[7] This same limitation appears in claim 1 of the '807 patent.

[8] This same limitation appears in claim 1 of the '807 patent.

D. The Board Should Not Exercise Its Discretion under Section 325(d) to Deny Institution[9]

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 new arguments and art not before the Office, either during prosecution of the '807 patent or during the '1796 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

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

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 the '807 patent's prosecution and the '1796 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 two grounds. Ground 1 relies on obviousness 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") and U.S. Patent Application Publication No. 2003/0185918 (EX1015, "Rosenbloom"). Ground 2 relies on anticipation over Brenner (EX1007), the WO publication of the '337 PCT application.

As detailed more below, 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. *See infra*, sections I.F.i, VI.A. Brenner has essentially the same disclosure as the '807 patent, and, for the reasons discussed above in section I.B.ii, is prior art to the '807 patent. *See infra*, sections I.F.iii, VI.B. These references are materially different from the art asserted in the '1796 proceeding, which investigated the general preventative effect of milk consumption for black-tongue in dogs and pellagra in human subjects.

The art is also materially different than that applied during prosecution of the '807 patent. The examiner applied an effective filing date based on an assumed-intact priority chain through to the filing date of the '347 provisional. *See* EX1004, 181 (acknowledging priority claim), 225 (original filing receipt). The examiner, however, did not substantively examine whether the '807 patent was in fact entitled to a priority date that extends beyond the '495 PCT application's filing date. As explained above in section I.B.ii, because the '495 PCT application improperly claims priority to an application that was not the first application describing the subject matter of the claims, the earliest effective filing date for the '807 patent is the filing date of the '495 PCT application, April 20, 2006. The art presented in this petition is materially different than that applied during

prosecution because the art qualifies as prior art based on the '807 patent's correct priority date, which was not analyzed by the examiner. The art presented in this petition also 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 '807 patent.

ii. The asserted art is not cumulative

The references are also not cumulative. With respect to the '1796 IPR, Elysium relied upon art teaching the oral administration of a natural food source (*i.e.*, milk) that inherently contained NR. With respect to prosecution, as noted above, the examiner did not consider art qualifying as prior art based on the April 20, 2006 priority date. The asserted art in this petition also goes further: it establishes that, prior to the effective filing date of the '807 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 compositions claimed by the '807 patent.

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

None of Bieganowski, Rosenbloom, or Brenner formed the basis of a rejection during prosecution of the '807 patent. Moreover, these references were not asserted in any of the grounds of the '1796 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 the claims of the '807 patent.

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 claims 1-3 of the '807 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.

i. Factors 1 and 2

Thorne was not a petitioner, nor a real party-in-interest, to the first petition filed against the '807 patent. Thus, the first two factors weigh heavily in favor of institution.

ii. Factors 3-5

Although the DI of the '1796 IPR issued in 2018, as discussed above, because 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 the priority date of the '807 patent and 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 claims 1-3 stand in contrast to the grounds presented in the '1796 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. The '807 patent includes only one independent claim and two dependent claims. The petition also provides an efficient, meritorious analysis of these claims, presenting only two grounds based on three references (one two-reference obviousness ground and one anticipation ground). 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 claims 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 composition of claims 1-3.

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 one of the nutrients 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 '807 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 preparing a whey vitamin fraction from cow's milk. 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 '807 patent, methods of isolating or synthesizing NR were known to the ordinary artisan. EX1001, 27:45-46, 28:58-63; 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 claims 1-3 of the '807 patent is described briefly below. *See* EX1002, ¶¶47-55.

i. Bieganowski[10]

Bieganowski discloses a new biosynthetic pathway for the production of NAD+ in eukaryotes using NR as a precursor. EX1008, Abstract; EX1002, ¶48.

[10] Bieganowski published on May 14, 2004, making it prior art under pre-AIA § 102(b). Charles Brenner, the inventor of the '807 patent, is also a named author on this paper. Although listed on the face of the patent, Bieganowski was not applied during prosecution of the '807 patent or before the Board in the '1796 IPR.

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, ¶49; *cf.* EX1001, 27:45-51 (stating known isolation methods include fractionation "to remove salts, carbohydrates, polypeptides, nucleic acids, fats and the like"); EX1017, 17-19 (Patent Owner arguing that the term "isolated" means "fractionated from other cellular components" as consistent with the specification). Bieganowski also discloses synthesis of NR by treating NMN with alkaline phosphatase. EX1008, 500; EX1002, ¶50.

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, ¶51. 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, ¶52. According to Bieganowski, although nicotinic 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, ¶52.

ii. Rosenbloom[11]

Rosenbloom is drawn to a nutritional supplement. EX1015, ¶2. According to Rosenbloom, the supplement may be "formulated in any orally acceptable dosage form including, but not limited to, capsules, tablets, lozenges, troches, hard candies, powders, sprays, gels, elixirs, syrups, and suspensions or solutions." EX1015, ¶94. Rosenbloom further teaches a variety of pharmaceutically acceptable carriers, including sugar, starch, microcrystalline cellulose, and talc among others. *Id.*, ¶¶95-96; EX1002, ¶53.

iii. Brenner[12]

Brenner, the WO publication of the '337 PCT application, has essentially the same disclosure as the challenged '807 patent. EX1002, ¶54. *See*, *e.g.*, *supra*,

[11] Rosenbloom published October 2, 2003, making it prior art under pre-AIA §102(b).

[12] 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

section I.A (discussing the '807 patent). Thus, Brenner teaches that an "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." EX1007, 6:23-26; EX1002, ¶54. Brenner discloses further that "[i]n another embodiment, the nicotinamide riboside is further administered in combination with tryptophan, nicotinic acid or nicotinamide." EX1007, 7:3-6; EX1002, ¶55.

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

Patent Owner Dartmouth did not proffer a definition for the level of ordinary skill in the '1796 IPR, but it did set forth a definition in the related '1795 IPR, defining 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

---

and the '347 provisional contain substantially the same specification and identical claims. In addition, Brenner also lists Pawel Bieganowski as an inventor, whereas the '807 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).

pharmacokinetics." EX1017, 6. This petition applies Dartmouth's definition. *See also* EX1002, ¶¶56-57.

II. GROUNDS FOR STANDING

Thorne certifies that, under 37 C.F.R. § 42.104(a), the '807 patent is available for *inter partes* review, and Thorne is not barred or estopped from requesting *inter partes* review of the '807 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 '807 patent. The '1796 IPR, was filed by Elysium Health, Inc., and the Board declined institution. *Elysium Health, Inc. v. Trustees of Dartmouth College*, IPR2017-01796, Paper 9 (Jan. 18, 2018) (EX1027).

Elysium also challenged the related '086 patent in IPR2017-01795, in which the Board found all claims, except claim 2, unpatentable. *Elysium Health, Inc. v. Trustees of Dartmouth College*, IPR2017-01795, Paper 39, 42 (Jan. 16, 2019) (EX1018). Petitioner here, Thorne, filed a petition challenging claim 2 of the related '086 patent, IPR2021-00268, on December 1, 2020.

In addition, the '807 patent, along with the '086 patent, are being asserted by Patent Owner, Trustees of Dartmouth College, and its licensee, Chromadex,

against Elysium Health Inc. *Chromadex, Inc. v. Elysium Health, Inc.*, Case No. 18-cv-01435 (D. Del.) ("Elysium litigation").[13]

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

Lead Counsel: Michael T. Rosato (Reg. No. 52,182)

Back-Up Counsel: Lora M. Green (Reg. No. 43,541)

Tasha M. Thomas (Reg. No. 73,207)

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.

Email: mrosato@wsgr.com; lgreen@wsgr.com; tthomas@wsgr.com

Post: WILSON SONSINI GOODRICH & ROSATI, 701 Fifth Avenue, Suite 5100, Seattle, WA 98104-7036

Tel.: 206-883-2529 Fax: 206-883-2699

IV. STATEMENT OF THE PRECISE RELIEF REQUESTED

Thorne requests review of claim 1-3 of the '807 patent under 35 U.S.C.

[13] Petitioner here, Thorne, is not a party to that district court proceeding, and as previously discussed, is not related in any way to the defendant in that litigation, Elysium. Thorne notes, however, that Patent Owner has recently separately threatened it with litigation over both the '807 and the '086 patents.

§ 311 and AIA § 6 under the grounds as follows:

Ground	Claims	Description
1	1-3	Obvious under 35 U.S.C. § 103(a) over Bieganowski and Rosenbloom
2	1-3	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*). In addition, "unless otherwise compelled...the same claim term in the same patent or related patents carries the same construed meaning." *Omega Eng'g, Inc. v. Raytek Corp.,* 334 F.3d 1314, 1334 (Fed. Cir.2003).

As relevant to the challenged claims of the '807 patent, the Board in the '1795 IPR and the '1796 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 '807 patent, as well as how a POSA would have understood those

terms. The following constructions, previously adopted by the Board, were observed in the unpatentability analysis presented in this Petition. *See also* EX1002, ¶¶58-61, 65.

A. "carrier"

Relevant to this petition, the Board construed carrier in the related '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.

EX1018, 14-15 (quoting EX1023, 6-7); *see also* EX1001, 29:35-42; EX1002, ¶62.

B. "isolated"

The Board in both the '1795 IPR and the '1796 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; EX1027, 7-8. 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, ¶63.

In this regard, the specification does explicitly discuss "isolated" NR. EX1002, ¶64. Specifically, the disclosure of the '807 patent references "nicotinamide riboside isolated from deproteinized whey fraction of cow's milk was sufficient to support NRK1-dependent growth" in a yeast mutant dependent on NR for growth. EX1001, 27:7-9; *see also id.*, 33:30-45 (Example 2 exemplifying isolation of NR with a milk whey fraction and noting that it was used at 50% by volume); *see also* EX1026, 11-12 (Patent Owner Dartmouth citing Example 2 as support for specification disclosing "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"); EX1031, 2 (the district court in the Elysium litigation construing "isolated nicotinamide riboside" as "nicotinamide riboside that is separated or substantially free from at least some of the other components associated with the source of the nicotinamide riboside").

VI. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. [Ground 1] Claims 1-3 Are Obvious over Bieganowski (EX1008) and Rosenbloom (EX1015)

Bieganowski notes 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.*, 495. 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.*, Abstract; EX1002, ¶66.

Bieganowski also discloses 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, 499-500, Abstract; EX1002, ¶67. 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, ¶68. Bieganowski discloses also that "eukaryotes also synthesize NAD+ de novo via the kynurenine pathway from tryptophan." EX1008, 495; EX1002, ¶68.

Specifically, Bieganowski discloses the same methods for isolating and synthesizing NR as taught by Example 2 of the '807 patent. *Compare* EX1008, 500 *with* EX1001, 33:30-45; *see* EX1002, ¶69. Bieganowski discloses treating

NMN with alkaline phosphatase in 20mM Tris (which reads on a "carrier" comprising "a buffering agent" as recited in challenged claim 1) to produce NR. EX1008, 500. Bieganowski also discloses preparing a whey vitamin fraction from commercially obtained nonfat cow's milk by adjusting the pH, removing the denatured casein, followed by passage through a filter. *Id.* The NR synthesized from NMN was used at 10μM and the whey fraction was used at 50% by volume. *Id.*

To the extent that Bieganowski fails to teach further isolation of NR as required by the Board's construction and its formulation with additional conventional pharmaceutical carriers used in oral formulations, it would have been obvious to do so, because, as discussed above, synthetic methods for making NR, as well as methods for isolating NR were known in the art, as were methods of making oral formulations of vitamins and supplements. *See, e.g.*, EX1001, 27:45-46 ("Isolated extracts of the natural sources can be prepared using standard methods."), 28:58-63 ("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 standard methods." (citing Tanimori (EX1014) and Franchetti (EX1010)); EX1002, ¶70. Specifically, Rosenbloom is relied upon for teaching conventional carriers and dosage forms for an oral supplement formulation. EX1015, ¶¶94-96; EX1002, ¶71. The POSA would have had reason

to do so because Bieganowski discloses that supplementation with NR as an NAD+ precursor may be beneficial for certain conditions. *See* EX1008, Abstract, 499-500; EX1002, ¶70. The POSA also would have had reason to include tryptophan and/or nicotinamide as those compounds are also NR precursors, and thus their inclusion with NR in an oral formulation would also be expected to lead to increased levels of NAD+. *E.g.*, EX1008, Abstract, 495; EX1002, ¶70.

Bieganowski thus renders the claimed NR pharmaceutical composition formulated for oral administration obvious. EX1002, ¶72. As Dr. Jaffrey testifies, formulating vitamins and supplements for oral administration was well known and routine, which is also consistent with the teachings of the '807 patent. *Id*. at ¶71. 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 administering NAD+ precursors, including NR, orally to achieve increased levels of NAD+. EX1002, ¶72. The ordinary artisan would have had reason to provide such a composition in order to modulate lipid levels and reduce mortality in target populations as taught by Bieganowski. *Id.*, ¶73. 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*. Bieganowski provides further motivation by teaching that

NR is a nutrient found in milk, and by specifically suggesting supplementation with NR. EX1008, Abstract, 499-500; EX1002, ¶73.

i. Claim 1

a. Element 1.Preamble: A composition comprising isolated nicotinamide riboside

Bieganowski discloses that NR "was discovered as a nutrient in milk." EX1008, Abstract; EX1002, ¶74. Bieganowski also discloses NR isolated as a whey fraction from commercial skim milk, 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, which are the same methods provided in Example 2 of the '807 patent. *Compare* EX1008, 500 *with* EX1001, 33:30-45 (Example 2); EX1002, ¶74; *see also* EX1008, 499-500 (suggesting NR supplementation for NAD+ biosynthesis); EX1026, 11-12 (citing Example 2 as suitable methods for isolating NR); EX1017, 17-18 (same). 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 for the successful treatment of black-tongue); EX1002, ¶75. Accordingly, Bieganowski discloses a composition comprising isolated NR.

Moreover, as noted above, Bieganowski discloses an isolated whey fraction containing NR, and also discloses a method of synthesizing NR. EX1008, 500;

EX1002, ¶74. And as discussed above, additional methods for synthesis of isolated NR were known in the art. *E.g.*, EX1010, 4656; EX1001, 28:58-63 (citing Franchetti as an established method for synthesizing NR); EX1002, ¶76. Furthermore, as the '807 patent acknowledges, NR can be obtained commercially, isolated from natural sources using standard methods, or synthesized using established methods. EX1001, 27:39-46, 27:45-46, 28:58-63; EX1002, ¶76. It would have been well within the level of skill of the POSA to determine the level of isolation and purity desired for oral administration, including achieving a formulation that is at least 25% NR as construed by the Board. *E.g.*, EX1001, 29:25-35 (demonstrating the level of skill of a POSA by noting that compositions may be prepared and contain carriers that are well known in the art), 27:45-46 (isolated NR extracts can be prepared using standard methods), 28:58-63 (NR can be obtained chemically synthesized using established methods); EX1002, ¶77; *see also* EX1010, 4656 (Franchetti 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, 28:58-63 (citing Franchetti as an established method for synthesizing NR).

b. Element 1.1: in combination with one or more of tryptophan, nicotinic acid, or nicotinamide

In view of the disclosure of Bieganowski, it would have been obvious to add one or more of tryptophan, nicotinic acid, or nicotinamide to the NR composition

of Bieganowski. EX1002, ¶78. As the Board recognized in the '1795 IPR, milk contains NR, nicotinamide, and tryptophan. EX1023, 14-15 (citing EX1030, 1). Moreover, Bieganowski discloses that both tryptophan and nicotinamide are precursors for NAD+. EX1008, 495; EX1002, ¶78. It would have thus been obvious to the POSA to include tryptophan and/or nicotinamide in a composition containing isolated NR formulated for oral administration as all three compounds are precursors for NAD+. *See In re Kerkhoven,* 626 F.2d 846, 850 (CCPA 1980) ("It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art."); EX1002, ¶79. The ordinary artisan would have had a reasonable expectation of success of combining NR with tryptophan and/or nicotinamide given that NR, tryptophan, and nicotinamide are all found together in milk and were all known precursors for NAD+. EX1002, ¶¶78-79.

c. Element 1.2: wherein said combination is in admixture with a carrier comprising a sugar, starch, cellulose, powdered tragacanth, malt, gelatin, talc, cocoa butter, suppository wax, oil, glycol, polyol, ester, agar, buffering agent, alginic acid, isotonic saline, Ringer's solution, ethyl alcohol, polyester, polycarbonate, or polyanhydride,

As discussed above, Bieganowski suggests and provides a reason as well as a reasonable expectation of success for administering NR plus tryptophan and/or

nicotinamide. Although Bieganowski synthesizes NR in a Tris buffering agent, which reads on a "carrier" as recited in claim 1 (*see* EX1008, 500), Bieganowski fails to explicitly disclose the use of a carrier (such as the buffering agent Tris) that may be used in a composition comprising isolated NR as well as tryptophan and/or nicotinamide. EX1002, ¶80.

Rosenbloom discloses a supplement formulated for oral administration using conventional carriers, such as carbohydrates, including lactose (a sugar), talc, and gelatin. EX1015, ¶¶95-98; EX1002, ¶81.

It would have been obvious to a POSA to formulate the isolated NR as taught by Bieganowski with tryptophan and/or nicotinamide into an oral dosage form using carriers, such as lactose, talc, and/or gelatin, because the use of such carriers is well known and routine in the art. EX1002, ¶82; *see also* EX1015, ¶¶95-98; EX1001, 29:29-35 (noting the "compositions can be prepared by methods and contain carriers which are well-known in the art").

d. Element 1.3: wherein said composition is formulated for oral administration and increases NAD+ biosynthesis upon oral administration.

As discussed above, it would have been obvious to formulate the composition for oral administration with a reasonable expectation of success. EX1002, ¶83. Bieganowski also specifically discloses that NR is a useful compound for elevating NAD+ levels in humans, and also teaches the biosynthetic

pathway from NR to NAD+. EX1008, Abstract, FIG. 6; EX1004, 103-04; EX1002, ¶¶83-84.

Accordingly, the combination of Bieganowski and Rosenbloom rendered claim 1 obvious. EX1002, ¶85.

ii. Claim 2

Claim 2 depends from claim 1 and recites "wherein the nicotinamide riboside is isolated from a natural or synthetic source." EX1002, ¶86.

As discussed above, Bieganowski discloses that NR "was discovered as a nutrient in milk." EX1008, Abstract; EX1002, ¶87. 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, ¶87; *see also* EX1008, 499-500 (suggesting NR supplementation for NAD+ biosynthesis). As also discussed above in the analysis of claim 1, it would have been well within the level of skill of the POSA to determine the level of isolation and purity desired for oral administration, including achieving a formulation that is at least 25% NR as construed by the Board. *See* EX1002, ¶¶77, 88-89. Thus, Bieganowski teaches isolation of NR from a natural or synthetic source.

Moreover, Patent Owner's argument that "[c]laim 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" is incorrect and technically unsound. *E.g.*, '1795 IPR, Paper 8, 15; *see also* EX1017, 17-18. The only time the '807 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, 27:39-42. In addition, claim 2 is drawn to a composition and not a method. Patent Owner failed to explain (nor does the '807 patent explain) how synthetically producing NR imparts any structural change compared to isolating the NR from a natural or synthetic 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 not on the process of making it.").

Accordingly, the combination Bieganowski and Rosenbloom rendered claim 2 obvious. EX1002, ¶89.

iii. Claim 3

Claim 3 depends from claim 1 and recites "wherein the formulation comprises a tablet, troche, capsule, elixir, suspension, syrup, wafer, chewing gum, or food." EX1002, ¶90.

Rosenblum teaches a supplement for oral administration, wherein "the nutritional supplement of the present invention may be formulated in any orally acceptable dosage form including, but not limited to, capsules, tablets, lozenges, troches, hard candies, powders, sprays, gels, elixirs, syrups, and suspensions or solutions." EX1015, ¶94; EX1002, ¶91.

It would have been obvious to a POSA at the time of invention to formulate the composition of claim 1 into a formulation such as a tablet or capsule as taught by Rosenbloom with a reasonable expectation of success because Rosenbloom teaches that such dosage forms are orally acceptable and conventional. EX1015, ¶94; *see also* EX1001, 29:24-35 (noting that NR "can be conveniently used or administered in a composition containing the active agent in combination with a pharmaceutically acceptable carrier. Such compositions can be prepared by methods and contain carriers which are well-known in the art."), 29:63-67, 30:19-23 (noting that compositions "can be administered via any route includ[ing], but not limited to, oral" and can be "used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums, foods and the like"); EX1002, ¶92.

Accordingly, the combination of Bieganowski and Rosenbloom rendered obvious claim 3 of the '807 patent. EX1002, ¶93.

B. [Ground 2] Claims 1-3 Are Anticipated by Brenner (EX1007)

As discussed above, the disclosure of Brenner is essentially the same as that of the '807 patent. EX1002, ¶94. 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, 3:3-11, 9:3-15. Brenner thus teaches "a method for preventing or treating a disease or condition associated with the nicotinamide riboside kinase pathway of NAD+ biosynthesis." EX1002, ¶95 (quoting EX1007, 55:24-29). "The method involves administering to a patient…an effective amount of a nicotinamide riboside composition…." EX1007, 6:27-33; *cf.* EX1001, 4:24-31. Brenner teaches further that "[i]n another embodiment, the nicotinamide riboside is further administered in combination with tryptophan, nicotinic acid or nicotinamide." EX1007, 7:3-6; EX1002, ¶96; *cf.* EX1001, 4:34-36. 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, 4:21-23. "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, ¶96; *cf.* EX1001, 30:19-29.

i. Claim 1

a. Element 1.Preamble: A composition comprising isolated nicotinamide riboside

Brenner discloses a method for identifying a natural or synthetic source for NR, and a dietary supplement composition containing NR identified in accordance with the methods of the invention. EX1007, 6:9-11, 6:23-26; EX1002, ¶97; *cf.* EX1001, 4:8-9, 4:21-23. Brenner further discloses NR isolated from deproteinized whey protein of cow's milk, as well as synthesis of NR from NMN treated with alkaline phosphatase. EX1007, 53:18-21, 64:29-65:9 (Example 2, describing the same); *see also id.*, 54:25-27 (noting that "[i]solated extracts of the natural sources [of NR] can be prepared using standard methods."), 16:8-21 ("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)."); *cf.* EX1001, 9:31-33, 27:45-46, 33:30-45.

b. Element 1.1: in combination with one or more of tryptophan, nicotinic acid, or nicotinamide,

Brenner specifically teaches that "[i]n another embodiment, the nicotinamide riboside is further administered in combination with tryptophan, nicotinic acid or nicotinamide." EX1007, 7:3-6; EX1002, ¶98; *cf.*, EX1001, 4:34-36.

c. Element 1.2: wherein said combination is in admixture with a carrier comprising a sugar, starch, cellulose, powdered tragacanth, malt, gelatin, talc, cocoa butter, suppository wax, oil, glycol, polyol, ester, agar, buffering agent, alginic acid, isotonic saline, Ringer's solution, ethyl alcohol, polyester, polycarbonate, or polyanhydride,

Brenner teaches that the NR dietary supplement "can be conveniently used or administered in a composition containing the active agent in combination with a carrier," noting that "[s]uch compositions can be prepared by methods and contain carriers which are well-known in the art." EX1007, 56:16-23; EX1002, ¶99; *cf.*, EX1001, 29:24-31. According to Brenner:

> Examples of materials which can serve as carriers include sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum

hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; pH buffered solutions; polyesters, polycarbonates and/or polyanhydrides; and other non-toxic compatible substances employed in formulations.

EX1007, 57:3-19; EX1002, ¶100; *cf.*, EX1001, 29:43-62.

d. *Element 1.3: wherein said composition is formulated for oral administration and increases NAD+ biosynthesis upon oral administration.*

Brenner teaches that the supplement may be administered via any route, including orally. EX1007, 57:25-30; *cf.* EX1001, 29:63-67. Brenner discloses that NR is a NAD+ precursor in a conserved NAD+ eukaryotic biosynthetic pathway. EX1007, 3:31-4:6, 14:1-13; 15:6-12; EX1002, ¶101; *cf.* EX1001, 3:3-11, 8:11-30, 8:55-60. Thus, increasing NR would increase NAD+ biosynthesis upon oral administration. EX1002, ¶101.

Accordingly, Brenner anticipated claim 1 of the '807 patent. EX1002, ¶102.

ii. Claim 2

Claim 2 depends from claim 1 and recites "wherein the nicotinamide riboside is isolated from a natural or synthetic source." EX1002, ¶103.

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, 4:8-9, 4:21-23; *see also* EX1002,

¶¶104-105. Brenner describes NR "isolated from deproteinized whey fraction of cow's milk." EX1007, 53:17-20; *cf.*, EX1001, 27:7-9. 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 as well as synthesis of NR from NMN); EX1002, ¶106; *cf.* EX1001, 27:39-46, 33:30-45.

Accordingly. Brenner discloses not only a composition comprising isolated 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, ¶107. Brenner thus anticipated claim 2. *Id.*, 108.

iii. Claim 3

Claim 3 depends from claim 1 and recites "wherein the formulation comprises a tablet, troche, capsule, elixir, suspension, syrup, wafer, chewing gum, or food." EX1002, ¶109. Brenner specifically discloses that "[f]or 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, ¶¶110-111; *cf.* EX1001, 29:63-67, 30:19-29.

Accordingly, Brenner anticipated claim 3 of the '807 patent. EX1002, ¶112.

VII. CONCLUSION

For the reasons set forth above, claims 1-3 of the '807 patent are unpatentable. Thorne therefore requests that an *inter partes* review be instituted.

Respectfully submitted,

Dated: February 1, 2021

/ 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 11,435 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully submitted,

Dated: February 1, 2021

/ 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. 8,197,807 to Brenner
1002	Declaration of Dr. Samie Jaffrey, M.D., Ph.D.
1003	*Curriculum Vitae* of Dr. Samie Jaffrey, M.D., Ph.D.
1004	File History of United States Patent Application No. 11/912,400
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	U.S. Patent Publication No. 2003/0185918 to Rosenbloom
1016	U.S. Patent No. 7,491,743 to Cuny et al.
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	File History of United States Patent Application No. 11/113,701
1020	File History of United States Patent Application No. 13/445,289
1021	Order Granting Motion to Voluntarily Dismiss Appeal No. 19-1682, *Elysium Health, Inc. v. Trustees of Dartmouth College*, Case No. 19-1630 et al. (August 19, 2019)
1022	Patent Owner's Notice of Cross-Appeal, *Elysium Health Inc. v. Trustees of Dartmouth* College, Case No. IPR2017-01795 (March 20, 2019)
1023	Decision: Institution of *Inter Partes* Review, *Elysium Health Inc. v. Trustees of Dartmouth* College, Case No. IPR2017-01795 (January 29, 2018)
1024	U.S. Patent No. 8,383,086 to Brenner
1025	Petition for *Inter Partes* Review, *Elysium Health, Inc. v. Trustees of Dartmouth College*, Case no. IPR2017-01796 (July 17, 2017)
1026	Preliminary Response to Petition for *Inter Partes* Review of U.S. Patent No. 8197,807, *Elysium Health, Inc. v. Trustees of Dartmouth College*, Case no. IPR2017-01796 (November 3, 2017)
1027	Decision on Institution, *Elysium Health, Inc. v. Trustees of Dartmouth College*, Case no. IPR2017-01796 (January 18, 2018)
1028	Saunders et al., "Tiazofurin Is Phosphotylated by Three Enzymes from Chinese Hamster Ovary Cells," *Cancer* Research 50 (September 1, 1990)
1029	Saunders et al., "Phosphorylation of 3-Deazaguanosine by Nicotinamide Riboside Kinase in Chinese Hamster Ovary Cells," *Cancer Research* 49 (December 1, 1989)
1030	Trammell et al., "Nicotinamide Riboside Is a Major NAD^+ Precursor Vitamin in Cow Milk[1-3]," *Journal of Nutrition* (April 6, 2016)
1031	Claim Construction Order, *Chromadex, Inc. et al. v. Elysium Health, Inc.*, Case No. 18-1434 (January 5, 2020)

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. 8,197,807 (and accompanying Exhibits 1001-1031) by overnight courier (Federal Express or UPS), on this 1st day of February, 2021, on the Patent Owner at the correspondence address of the Patent Owner as follows:

LICATA & TYRRELL P.C.
66 E. Main Street
Marlton, NJ 08053

TRUSTEES OF DARTMOUTH COLLEGE
11 Rope Ferry RD.
Hanover, NH 03755

Respectfully submitted,

Dated: February 1, 2021

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