Filed on behalf of Elysium Health, Inc.

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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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ELYSIUM HEALTH, INC.
Petitioner,

v.

TRUSTEES OF DARTMOUTH COLLEGE,
Patent Owner.

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Case: IPR2017-01795
U.S. Patent No. 8,383,086 B2

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# PETITION
# for *Inter Partes* Review

**TABLE OF CONTENTS**

# TABLE OF AUTHORITIES

## Cases



## Statutory Authorities



## Rules and Regulations

## PETITIONER'S LIST OF EXHIBITS

| Exhibit No. | Description |
|---|---|
| **1001** | U.S. Patent No. 8,383,086 B2 |
| **1002** | Declaration of Joseph A. Baur, Ph.D. |
| **1003** | Excerpts from Prosecution History of Serial No. 11/912,400 |
| **1004** | Prosecution History of Serial No. 13/445,289 |
| **1005** | Joseph Goldberger et al., "A Study of the Blacktongue-Preventative Action of 16 Foodstuffs, with Special Reference to the Identity of Blacktongue of Dogs and Pellagra of Man," *Public Health Reports*, 43(23):1385-1454 (1928) ("Goldberger et al.") |
| **1006** | Joseph Goldberger and W.F. Tanner, "A Study of the Treatment and Prevention of Pellagra," *Public Health Reports*, 39(3):87-107 (1924) ("Goldberger and Tanner") |
| **1007** | Samuel A.J. Trammell et al., "Nicotinamide Riboside is a Major NAD+ Precursor Vitamin in Cow Milk," *J. of Nutrition*, 146(5):965-963 (2016) ("Trammell I") |
| **1008** | Samuel A.J. Trammell et al., "Nicotinamide Riboside is Uniquely and Orally Bioavailable in Mice and Humans," *Nature Communications*, Vol. 7, Art. No. 12948 (2016) ("Trammell II") |
| **1009** | Joseph Goldberger et al., "A Further Study of Experimental Blacktongue with Special Reference to the Blacktongue Preventative in Yeast," *Public Health Reports*, 43(12):657-694 (1928) |
| **1010** | Laurent Mouchiroud et al., "$NAD^+$ Metabolism, a Therapeutic Target for Age-Related Metabolic Disease," *Crit. Rev. Biochem. Mol. Biol*., 48(4):397-408 (2013) ("Mouchiroud et al.") |
| **1011** | Texas Agricultural Extension Service, "Good Milk for Good Meals," *Texas Agricultural Experiment Station*, Bulletin No. 807 (1956) ("Good Milk") |
| **1012** | William Douglas McFarlane and Hugh Lehman Fulmer, "The Colorimetric Determination of the Tyrosine and |

| | |
|---|---|
| | Tryptophan Content of Various Crude Protein Concentrates," *Biochemical Journal*, 24(6):1601-1610 (1930) |
| **1013** | Library of Congress copy of Joseph Goldberger et al., "A Further Study of Experimental Blacktongue with Special Reference to the Blacktongue Preventative in Yeast," *Public Health Reports*, 43(12):657-694 (1928) |
| **1014** | Library of Congress copy of Joseph Goldberger and W.F. Tanner, "A Study of the Treatment and Prevention of Pellagra," *Public Health Reports*, 39(3):87-107 (Jan. 18, 1924) |
| **1015** | Library of Congress copy of Joseph Goldberger et al., "A Study of the Blacktongue-Preventative Action of 16 Foodstuffs, with Special Reference to the Identity of Blacktongue of Dogs and Pellagra of Man," *Public Health Reports*, 43(23):1385-1454 (1928) |
| **1016** | Texas A&M University Library catalogue webpage showing Good Milk's publication details and call number at the library of Texas A&M University obtained from https://libcat.tamu.edu/vwebv/holdingsInfo?searchId=73&recCount=50&recPointer=2&bibId=1216980 as of July 13, 2017 |
| **1017** | Krishna S. Tummala, et al., "Inhibition of De Novo NAD+ Synthesis by Oncogenic URI Causes Liver Tumorigenesis through DNA Damage," *Cancer Cell*, 26:826-839 (2014) ("Tummala") |
| **1018** | Carles Cantó et al., "The NAD+ Precursor Nicotinamide Riboside Enhances Oxidative Metabolism and Protects against High-Fat Diet-Induced Obesity," *Cell Metabolism*, 15:838-847 (2012) ("Cantó") |
| **1019** | Bing Gong et al., "Nicotinamide riboside restores cognition through an upregulation of proliferator-activated receptor-y coactivator 1α regulated β-secretase 1 degradation and mitochondrial gene expression in Alzheimer's mouse models," *Neurobiol. Aging*, 34:1581-1588 (2013) ("Gong") |
| **1020** | Joseph Goldberger et al., "The Prevention of Pellagra: A Test of Diet Among Institutional Inmates," *Public Health Reports*, 30(43):3117-3131 (1915) ("The Prevention of Pellagra") |

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|---|---|
| **1021** | Joseph Goldberger et al., "A Study of the Relation of Diet to Pellagra Incidence in Seven Textile-Mill Communities of South Carolina in 1916," *Public Health Report*, 35(12):648-713 (1920) ("Relation of Diet to Pellagra Incidence") |
| **1022** | Declaration of Brendan T. Jones |

# I. INTRODUCTION

Elysium Health, Inc. petitions for *inter partes* review of claims 1–5 of U.S. Patent No. 8,383,086 B2 (Ex. 1001) (the "'086 patent"). For the reasons set forth below, there is a reasonable likelihood that the claims are unpatentable as anticipated under 35 U.S.C. § 102 in view of the references submitted by Petitioner.

# II. BACKGROUND

## A. The '086 Patent

The '086 patent is directed to pharmaceutical compositions comprising nicotinamide riboside. Nicotinamide riboside is a form of vitamin B3 that is found in nature (*e.g.*, in milk). (Ex. 1002, Declaration of Joseph A. Baur, Ph.D. ("Baur Decl.") ¶11.) Nicotinamide riboside is a precursor of nicotinamide adenine dinucleotide (NAD+), a coenzyme associated with a variety of biological activities. (*Id*. ¶10.) Other NAD+ precursors include nicotinic acid and tryptophan. (*Id*.) NAD+ deficiency can cause pellagra, a disease whose symptoms in humans include dermatitis, diarrhea, and dementia, and death if untreated. (*Id*. ¶15.)

The '086 patent purports to disclose the discovery of a biosynthetic pathway that is naturally present in eukaryotic cells and converts nicotinamide riboside to NAD+. (Ex. 1001, '086 patent at 2:62-3:3.) Based

on the discovery of this natural phenomenon, the ’086 patent claims pharmaceutical compositions—a term the patent uses to cover tablets, capsules, elixirs, food, and more—comprising nicotinamide riboside. (Ex. 1001, ’086 patent at 53:38-54:42.)

Independent claim 1 is indicative of the broad subject matter claimed and is reproduced below.

> 1. A pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier, wherein said composition is formulated for oral administration.

Dependent claim 2 confirms that the nicotinamide riboside of claim 1 may be naturally occurring:

> 2. The pharmaceutical composition of claim 1, wherein the nicotinamide riboside is isolated from a natural or synthetic source.

### B. **Prosecution History of the ’086 Patent**

The ’086 patent issued from a continuation application of Serial No. 11/912,400 (the “’400 application), which issued as U.S. Patent No. 8,197,807.

In the ’400 application, the applicant initially sought an independent claim drawn to a composition comprising isolated nicotinamide riboside in

admixture with a carrier (then pending as claim 30), and dependent claims specifying that the nicotinamide riboside is isolated from a natural or synthetic source (claim 31) and that the composition is formulated for oral administration (claim 32). (Exhibit 1003, Excerpts from Prosecution History of Serial No. 11/912,400, at 3.)

All three claims were rejected as anticipated by two references by Saunders et al. which, the Examiner found, disclose the preparation of a composition comprising isolated nicotinamide riboside in water. (*Id*. at 16.) All three claims were also rejected as anticipated by Tanimori, which, the Examiner found, teaches the production of a syrup and solid form comprising nicotinamide riboside. (*Id*. at 17-18.) In explaining why these disclosures anticipate claim 32—the dependent claim requiring that the composition is formulated for oral administration—the Examiner noted that the claim does not specify the dose or application of the claimed formulation. (*Id*.) As explained below, the applicant never amended the claims to specify the does or application of the claimed formulation and instead overcame the Examiner's rejections by adding other limitations.

In response to the Examiner's initial rejection of all three claims, the applicant amended the independent claim by specifying that the carrier

comprises several common carriers (*e.g.*, sugar, starch, cellulose) but not including water, which is the carrier the Examiner found was disclosed in the Saunders et al. references. (*Id*. at 34.) The Applicant also added a new dependent claim (claim 33) specifying that "the formulation comprises a tablet, troche, capsule, elixir, suspension, syrup, wafer, chewing gum, or food." (*Id*.)

The Examiner rejected the amended claims under 35 U.S.C. § 103(a). (*Id*. at 46-50.) To overcome this rejection, the applicant amended the independent claim again, this time to require that the nicotinamide riboside is "in combination with one or more of tryptophan, nicotinic acid, or nicotinamide." (*Id*. at 79.) The Examiner concluded that the claims were obvious even with this additional limitation. (*Id*. at 90-94; *see also id*. at 113-117.)

In response, the applicant amended the independent claim to require that the claimed composition "is formulated for oral administration," and relied upon a Declaration from the sole named inventor, Charles Brenner, to argue that nicotinamide riboside was orally bioavailable in unexpectedly high levels. (*Id*. at 121-24, 132-35.) The Examiner found that this amendment did not overcome the obviousness rejection and noted that one

of ordinary skill in the art would have been motivated to provide an oral formulation because nicotinamide riboside is present in milk. (*Id*. at 138-39.) The applicant then amended the independent claim to require that the composition "increases NAD+ biosynthesis upon oral administration." (*Id*. at 142-47.) The Examiner thereafter allowed the claims as claims 1-3 of the '807 patent. (*Id*. at 159-61.) Although the Examiner acknowledged that nicotinamide riboside is present in milk, the Examiner did not recognize that the administration of milk in the prior art therefore inherently anticipates the claims.

The continuation application that led to the '086 patent, Serial No. 13/445,289, was rejected on double patenting grounds only. (Exhibit 1004, Prosecution History of Serial No. 13/445,289, at 125-29.) The Applicant filed a terminal disclaimer to overcome that rejection, and the claims were allowed. (*Id*. at 140-43, 150, 153.)

## III. SUMMARY OF CHALLENGES AND RELIEF REQUESTED

Petitioner asserts the following challenges, supported by expert testimony of Joseph A. Baur, Ph.D., a professor and researcher at the University of Pennsylvania School of Medicine (Ex. 1002):

| Ground | Reference | Basis | Claims Challenged |
|---|---|---|---|
| I | Goldberger et al. | § 102 | 1-5 |
| II | Goldberger and Tanner | § 102 | 1-5 |

Petitioner requests that the Board cancel claims 1-5 of the '086 patent because they are unpatentable under 35 U.S.C. § 102.

## IV. PERSON OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the relevant timeframe (*i.e.*, the mid-2000s) would have had a Ph.D. in biology, biochemistry, or a similar field. (Ex. 1002, Baur Decl., ¶24.)

## V. CLAIM CONSTRUCTION

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144 (2016).

Independent claim 1 is drawn to a "pharmaceutical composition . . . formulated for oral administration." Dependent claim 3 specifies that the claimed formulation comprises "a tablet, troche, capsule, elixir, suspension, syrup, wafer, chewing gum, or food." Accordingly, the broadest reasonable interpretation of the term "pharmaceutical composition" should be

understood to include at least a tablet, troche, capsule, elixir, suspension, syrup, wafer, chewing gum, or food. *See Alcon Research, LTD. v. Apotex Inc.*, 687 F.3d 1362, 1367-1368 (Fed. Cir. 2012) (explaining that "a dependent claim cannot be broader than the claim from which it depends" and holding that independent claim must cover at least the range covered by dependent claim).

Dependent claim 2 requires that the nicotinamide riboside "is isolated" from a natural or synthetic source. The specification states:

> As used herein, an isolated molecule . . . means a molecule separated or substantially free from at least some of the other components of the naturally occurring organism, such as for example, the cell structural components or other polypeptides or nucleic acids commonly found associated with the molecule.

(Ex. 1001, '086 patent at 9:3-9:10.) Accordingly, "is isolated" in claim 2 should be understood to mean "is separated or substantially free from at least some of the other components of the naturally occurring organism."

All other terms in the challenged claims are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

## VI. SPECIFIC GROUNDS FOR PETITION

### A. Ground I: Goldberger et al. Anticipates Claims 1-5

Claims 1-5 are unpatentable under 35 U.S.C. § 102(b) as anticipated by Joseph Goldberger et al., "A Study of the Blacktongue-Preventative Action of 16 Foodstuffs, with Special Reference to the Identity of Blacktongue of Dogs and Pellagra of Man," *Public Health Reports*, 43(23):1385-1454 (1928) ("Goldberger et al.") (Ex. 1006)[1], as evidenced by Samuel A.J. Trammell et al., "Nicotinamide Riboside is a Major NAD+ Precursor Vitamin in Cow Milk," *J. of Nutrition*, 146(5):965-963 (2016) ("Trammell I") (Ex. 1007) and Samuel A.J. Trammell et al., "Nicotinamide Riboside is Uniquely and Orally Bioavailable in Mice and Humans," *Nature Communications*, Vol. 7, Art. No. 12948 (2016) ("Trammell II") (Ex. 1008).

Goldberger et al. qualifies as prior art under 35 U.S.C. § 102(b) because it was published in 1928, more than one year before the earliest possible priority date. Goldberger et al. was not cited during prosecution of the '086 patent.

[1] A copy of Goldberger et al. from the Library of Congress's collection is submitted as Exhibit 1015.

Cow milk has been consumed throughout history. One example of milk consumption in the prior art is Goldberger et al., a 1928 article examining a variety of different foods, including skim milk, administered to dogs to prevent the onset of what Goldberger et al. refers to as "blacktongue." (Ex. 1005, Goldberger et al. at 1385-86; Ex. 1002, Baur Decl., ¶¶20-21.) Blacktongue, which is also known as black tongue disease and various other names, is a canine disease caused by NAD+ deficiency and is identical to pellagra in humans. (Ex. 1005, Goldberger et al. at 1385-86, 1446-47; Laurent Mouchiroud et al., "$NAD^+$ Metabolism, a Therapeutic Target for Age-Related Metabolic Disease," *Crit. Rev. Biochem. Mol. Biol.*, 48(4):397-408 (2013) ("Mouchiroud et al.") (Ex. 1010) at 2; Ex. 1002, Baur Decl., ¶¶15, 20, 36.)

Goldberger et al. discloses an experiment in which five dogs were fed a base diet, designated "Diet No. 123," which was known to induce blacktongue.[2] (Ex. 1005, Goldberger et al. at 1403; Ex. 1002, Baur Decl.,

[2] In "A Further Study of Experimental Blacktongue with Special Reference to the Blacktongue Preventative in Yeast," *Public Health Reports*, 43(12):657-694 (1928) (Ex. 1009), Goldberger and his co-authors report that

¶¶20-21.) This base diet was supplemented with a daily dose of skim milk administered "by drench" (*i.e.*, orally). (Ex. 1005, Goldberger et al. at 1402-1403; Ex. 1002, Baur Decl., ¶20.) Three of the five dogs showed no evidence of blacktongue over the course of the study; one developed slight transient evidence of an attack after one year; and one developed a "well marked attack" after a period of 37 days. (Ex. 1005, Goldberger et al. at 1403-1404; Ex. 1002, Baur Decl., ¶21.) Goldberger noted that the diet fed to the dogs, when not supplemented by milk, "has regularly resulted in an attack of blacktongue within a period only exceptionally longer than about two months." (*Id*.) Based on these results, Goldberger et al. concluded that milk "contains the blacktongue preventative." (*Id*.)

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they fed diet No. 123 to 14 dogs and observed "all 14 of the test animals developed blacktongue, the first distinctive signs of which appeared within not to exceed 53 days after beginning the test diet." *Id*. at 661. The authors also note that blacktongue was "[a]llowed to take its course without therapeutic interference in two of the dogs, and it ended in the death of both animals." *Id*. A copy of this article from the Library of Congress's collection is submitted as Exhibit 1013.

Later research explains the biological processes underlying the results reported in Goldberger et al. (Ex. 1002, Baur Decl., ¶¶10-14, 316-36.) As the ’086 patent states, nicotinamide riboside is an NAD+ precursor in a eukaryotic NAD+ biosynthetic pathway. (Ex. 1001, ’086 patent, 2:62-3:3; Ex. 1002, Baur Decl., ¶10.) The Trammell I co-authors, including Charles Brenner, the named inventor of the ’086 patent, demonstrate that nicotinamide riboside in high concentration is naturally present in cow milk. Trammell I examined the NAD+ precursor vitamin concentration in raw cow milk and in skim cow milk and found that ~40% is present as nicotinamide riboside, with the remaining ~60% present as nicotinamide. (Ex. 1007, Trammell I at 3 (Table 1), 5 (Table 3), and 6; Ex. 1002, Baur Decl., ¶13.)

Recent scientific studies also confirm that the oral bioavailability of nicotinamide riboside is as great or greater than that of nicotinamide. For example, Trammell II (also co-authored by the ’086 patent inventor) reports that nicotinamide riboside is a more potent booster of NAD+ than nicotinamide or nicotinic acid. (Ex. 1008, Trammell II at 6-7, 11; Ex. 1002, Baur Decl., ¶14.) During prosecution of the parent application, Brenner submitted a sworn Declaration in response to an obviousness rejection affirming that nicotinamide riboside is more orally available than

nicotinamide to produce NAD+. (Ex. 1003, Excerpts from Prosecution History of Serial No. 11/912,400, at 132-35; Ex. 1002, Baur Decl., ¶14.) The two Trammell references (which were not available to the examiners during prosecution of the '086 patent) make clear that Goldberger et al.'s skim milk supplement prevented blacktongue because the naturally occurring NAD+ precursors in milk, which include nicotinamide riboside, increased NAD+ biosynthesis. (Ex. 1002, Baur Decl., ¶5.)

**1. Independent Claim 1**

Claim 1 is anticipated by Goldberger et al.

**a. "A pharmaceutical composition comprising"**

To the extent this preamble is limiting, Goldberger et al. discloses the administration of skim milk to dogs as a dietary supplement to prevent blacktongue. (Ex. 1005, Goldberger et al. at 1402-1403; Ex. 1002, Baur Decl., ¶31.) As explained above in Section V, the claim term "pharmaceutical composition" includes food, such as milk.

**b. "nicotinamide riboside"**

Trammell I's analysis of the NAD+ precursors in milk shows that a significant concentration of nicotinamide riboside is naturally present in skim milk. (Ex. 1007, Trammell I at 3 (Table 1), 5 (Table 3), and 6; Ex. 1002, Baur Decl., ¶¶11, 31.) Accordingly, the skim milk disclosed in

Goldberger et al. necessarily contained nicotinamide riboside.[3] (Ex. 1002, Baur Decl., ¶¶11, 31.)

**c. "in admixture with a carrier"**

In skim milk, nicotinamide riboside is "in admixture" (*i.e.*, in a mixture with) with "a carrier," because the nicotinamide riboside is in a mixture with other components of the milk, including components that will bind and stabilize the compound. (Ex. 1002, Baur Decl., ¶32.)

**d. "wherein said composition is formulated for oral administration"**

[3] "Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." *Brassica Protection Prods. LLC v. Sunrise Farms (In re Cruciferous Sprout Litig.)*, 301 F.3d 1343, 1349 (Fed. Cir. 2002) (internal quotation omitted). Whether the prior art recognized that nicotinamide riboside is inherent in milk is irrelevant to the anticipation analysis. *See, e.g., SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005) ("[I]nherent anticipation does not require a person of ordinary skill in the art to recognize the inherent disclosure in the prior art at the time the art is created.").

Finally, the skim milk in Goldberger et al. was administered orally. (Ex. 1002, Baur Decl., ¶32.)

Thus, the skim milk disclosed in Goldberger et al. in 1928 was a pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier, wherein said composition is formulated for oral administration. (Ex. 1002, Baur Decl., ¶32.)

**2. Dependent Claim 2**

Claim 2 depends from claim 1, and the analysis for claim 1 in Section VI.A.1 is incorporated by reference. Further, Goldberger et al. discloses "wherein the nicotinamide riboside is isolated from a natural or synthetic source." (Ex. 1002, Baur Decl., ¶33.) Skim milk is the product that remains when almost all of the cream is removed from whole milk. (Texas Agricultural Extension Service, "Good Milk for Good Meals," *Texas Agricultural Experiment Station*, Bulletin No. 807 (1956) ("Good Milk") (Ex. 1011) at 6; Ex. 1002, Baur Decl., ¶33.[4])

The nicotinamide riboside naturally present in the skim milk Goldberger et al. administered to dogs is isolated (*i.e.*, separated or

[4] The Texas A&M University Library catalogue webpage showing Good Milk's publication details and call number is provided as Exhibit 1016.

substantially free from at least some of the other components of the naturally occurring organism) from a natural source: the cow. The nicotinamide riboside in skim milk is further 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. (Ex. 1002, Baur Decl., ¶33.)

**3. Dependent Claim 3**

Claim 3 depends from claim 1, and the analysis for claim 1 in Section VI.A.1 is incorporated by reference. Further, Goldberger et al. discloses "wherein the formulation comprises a tablet, troche, capsule, elixir, suspension, syrup, wafer, chewing gum, or food." (Ex. 1002, Baur Decl., ¶3.) The milk disclosed in Goldberger et al. is a food. (Ex. 1002, Baur Decl., ¶3.)

**4. Dependent Claim 4**

Claim 4 depends from claim 1, and the analysis for claim 1 in Section VI.A.1 is incorporated by reference. Further, Goldberger et al. discloses "further comprising one or more of tryptophan, nicotinic acid, or nicotinamide." The milk disclosed in Goldberger et al. inherently comprises, in addition to nicotinamide riboside, tryptophan and nicotinamide. (Ex. 1002, Baur Decl., ¶¶11, 35.) Trammell I explains that

"[i]t has long been known that the NAD+ precursors in milk include nicotinamide and tryptophan." (Ex. 1007, Trammell I at 1, 3; Ex. 1002, Baur Decl., ¶35.) Trammell I also presents data establishing that nicotinamide is present in skim milk. (Ex. 1007, Trammell I at 5 (Table 3); Ex. 1002, Baur Decl., ¶35.)

**5. Dependent Claim 5**

Claim 5 depends from claim 1, and the analysis for claim 1 in Section VI.A.1 is incorporated by reference. Further, Goldberger et al. discloses "which increases NAD+ biosynthesis upon oral administration." (Ex. 1002, Baur Decl., ¶36.) The skim milk disclosed in Goldberger et al. increases NAD+ biosynthesis to test subjects upon oral administration. (Ex. 1002, Baur Decl., ¶36.) As the '086 patent acknowledges, nicotinamide riboside is an NAD+ precursor in a eukaryotic NAD+ biosynthetic pathway. (Ex. 1001, '086 patent, 2:62-3:3; Ex. 1002, Baur Decl., ¶10.)

Trammell I shows that approximately 40% of the NAD+ precursor vitamin concentration in milk is present as nicotinamide riboside. (Ex. 1007, Trammell I at 6; Ex. 1002, Baur Decl., ¶¶4, 36.) Trammell II and the Brenner Declaration submitted during prosecution of the parent '400 application show that orally consumed nicotinamide riboside is a potent booster of NAD+. (Ex. 1008, Trammell II, at 6-7, 11; Ex. 1003, Ex. 1003,

Excerpts from Prosecution History of Serial No. 11/912,400, at 132-35; Ex. 1002, Baur Decl., ¶¶14, 36.) Accordingly, the consumption of skim milk inherently increases NAD+ biosynthesis. (Ex. 1002, Baur Decl., ¶36.) *See, e.g., SmithKline Beecham Corp. v. Apotex Corp*., 403 F.3d 1331, 1343 (Fed. Cir. 2005) (prior art reference inherently anticipates where reference is "sufficient to show that the natural result flowing from the operation as taught in the prior art would result in the claimed product") (internal quotation and citation omitted).

In addition, Goldberger et al. discloses that most of the dogs whose blacktongue-inducing diets were supplemented with skim milk did not experience blacktongue. (Ex. 1005, Goldberger et al. at 1403-1404; Ex. 1002, Baur Decl., ¶¶20-21, 36.) As noted above, blacktongue is caused by deficiency of NAD+. (Ex. 1010, Mouchiroud at 2; Ex. 1002, Baur Decl., ¶15.) Accordingly, Goldberger et al.'s results are direct evidence that NAD+ biosynthesis in the dogs increased upon oral administration of skim milk. (Ex. 1002, Baur Decl., ¶36.)

**6. Conclusion**

Goldberger et al. discloses, either expressly or inherently, each element of claims 1-5 of the '086 patent. The inventors of the '086 patent cannot patent the milk disclosed in Goldberger et al. based on the alleged

discovery of properties inherent in milk. *See, e.g., Brassica Protection Prods. LLC v. Sunrise Farms (In re Cruciferous Sprout Litig.)*, 301 F.3d 1343, 1351-52 (Fed. Cir. 1002).

In *Brassica*, the Federal Circuit held that claims directed to a method of preparing a food product rich in glucosinolates, and a method of preparing a human food product from sprouts, among other claims, were inherently anticipated by the prior cultivation and consumption of sprouts. The Court noted that the patent owner "has done nothing more than recognize properties inherent in certain prior art sprouts." *Id*. at 1350. For the same reason, the prior administration of milk, as disclosed in Goldberger et al., inherently anticipates claims 1-5 of the '086 patent. *See also, e.g., Upsher-Smith Labs v. Pamlab, L.L.C.*, 412 F.3d 1319, 1323 (Fed. Cir. 2005) (inventor's discovery of the scientific principles explaining why prior art vitamin compositions are more effective than other compositions "does not entitle him to remove the prior art from the public domain by patenting those compositions").

### B. **Ground II: Goldberger and Tanner Anticipates Claims 1-5**

Claims 1-5 are unpatentable under 35 U.S.C. § 102(b) as anticipated by Joseph Goldberger and W.F. Tanner, "A Study of the Treatment and Prevention of Pellagra," *Public Health Reports*, 39(3):87-107 (Jan. 18, 1924)

("Goldberger and Tanner") (Ex. 1006)[5], as explained by Trammell I and Trammell II.

Goldberger and Tanner qualifies as prior art under 35 U.S.C. § 102(b) because it was published in 1924, more than one year before the earliest possible priority date. Goldberger and Tanner was not cited during prosecution of the '086 patent.

In the early 1920s, Goldberger and Tanner studied whether a variety of different foods could treat and prevent pellagra, a vitamin deficiency disease that was prevalent in the American South at the time. (Ex. 1002, Baur Decl., ¶¶15-21.) Goldberger and Tanner explains that in 1922, the researchers conducted experiments at the Georgia State Sanitarium to determine whether milk prevents pellagra. (Ex. 1006, Goldberger and Tanner at 92-93; Ex. 1002, Baur Decl., ¶¶17-19.) A daily allowance of approximately 40 ounces of buttermilk was offered to each of the 29 patients as a beverage. (Ex. 1006, Goldberger and Tanner at 93; Ex. 1002, Baur Decl., ¶17.) Buttermilk is the product that remains when butter is removed

[5] A copy of Goldberger and Tanner from the Library of Congress's collection is submitted as Exhibit 1014.

from milk or cream in the process of churning. (Ex. 1006, Goldberger and Tanner, at 93; Ex. 1011, Good Milk, at 6; Ex. 1002, Baur Decl., ¶¶6-17.[6])

None of the 29 subjects developed any evidence of pellagra. Goldberger and Tanner explained that without the buttermilk, 40%-50% of the test subjects would have developed pellagra during the observation period. (Ex. 1006, Goldberger and Tanner at 93; Ex. 1002, Baur Decl., ¶18.) The test results, Goldberger and Tanner report, are "conclusive evidence of the preventive action of the buttermilk." (Ex. 1006, Goldberger and Tanner at 93; Ex. 1002, Baur Decl., ¶18; *see also, e.g.*, Ex. 1007, Trammell I at 1 ("One of the earliest treatments for pellagra was consumption of 1.5-2 pints of cow milk.")).

As with the results reported in Goldberger et al. discussed above, later research explains the biological processes underlying the results reported in

[6] Goldberger and Tanner note that "[i]n the rural areas of the South, milk is most commonly consumed as buttermilk." (Ex. 1006, Goldberger and Tanner, at 93.) In Relation of Diet to Pellagra Incidence, Goldberger explains that "home-churned buttermilk was the predominating form in which milk was used" by the South Carolina households participating in that study. (Ex. 1021, Relation of Diet to Pellagra Incidence, at 681.)

Goldberger and Tanner. (Ex. 1002, Baur Decl., ¶¶10-14.) As the '086 patent states, nicotinamide riboside is an NAD+ precursor in a eukaryotic NAD+ biosynthetic pathway. (Ex. 1001, '086 patent, 2:62-3:3; Ex. 1002, Baur Decl., ¶10.) As discussed above, Trammell I shows that a substantial concentration of NAD+ precursor vitamins in raw cow milk and in skim cow milk is present as nicotinamide riboside. (Ex. 1007, Trammell I at 3 (Table 1), 5 (Table 3), and 6; Ex. 1002, Baur Decl., ¶11.) As explained below, nicotinamide riboside is present in buttermilk too. (Ex. 1002, Baur Decl., ¶12.)

Nicotinamide riboside is a water soluble molecule that is stable in milk. (*Id.*) Accordingly, most of the nicotinamide riboside originally present in whole milk or cream remains in the aqueous buttermilk after the whole milk or cream is churned to make butter. (*Id.*) The removal of butter from whole milk or cream to make buttermilk therefore increases the concentration of the nicotinamide riboside originally present in the whole milk or cream. (Ex. 1002, Baur Decl., ¶12.) Moreover, Goldberger and Tanner found that the pellagra-preventing activity of buttermilk is

significantly higher than that of butter. (Ex. 1006, Goldberger and Tanner at 93, 95; Ex. 1002, Baur Decl., ¶12.[7])

Trammell II and the Brenner Declaration show that orally consumed nicotinamide riboside increases NAD+. (Ex. 1008, Trammell II at 6-7, 11; Ex. 1003, Excerpts from Prosecution History of Serial No. 11/912,400, at 132-35; Ex. 1002, Baur Decl., ¶¶13-14, 37.) Goldberger and Tanner's buttermilk treatment prevented pellagra because the naturally occurring NAD+ precursors in buttermilk increased NAD+ biosynthesis. (Ex. 1002, Baur Decl., ¶43.)

**1. Independent Claim 1**

Claim 1 is anticipated by Goldberger and Tanner.

**a. "A pharmaceutical composition comprising"**

To the extent this preamble is limiting, Goldberger and Tanner discloses the successful administration of buttermilk to prevent the onset of pellagra—a disease caused by NAD+ deficiency. (Ex. 1006, Goldberger

[7] Consistent with this result, Goldberger et al. found that the "preventative potency of . . . butter would seem to have been of a rather feeble order" and concluded that "while not devoid of it, butter is a relatively very poor source of the blacktongue preventative." (Ex. 1005, Goldberger et al., at 1420.)

and Tanner at 93; Ex. 1002, Baur Decl., ¶¶15, 37.) As explained above in Section V, the claim term "pharmaceutical composition" must include food such as buttermilk.

**b. "nicotinamide riboside**

Trammell I's analysis of the NAD+ precursors in milk shows that a significant concentration of nicotinamide riboside is naturally present in raw milk and skim milk. (Ex. 1007, Trammell I at 3 (Table 1), 5 (Table 3), and 6; Ex. 1002, Baur Decl., ¶11.) The disclosure of Goldberger and Tanner, as explained by Trammell I, establishes that nicotinamide riboside is inherently present in buttermilk too.[8] (Ex. 1002, Baur Decl., ¶¶12, 37.)

As noted above, the traditional buttermilk administered to patients in Goldberger and Tanner is the product that remains after butter has been churned from whole milk or cream. (Ex. 1011, Good Milk, at 6; Ex. 1002, Baur Decl., ¶¶12, 37.) Nicotinamide riboside is a water-soluble molecule.

[8] As noted above, a prior art reference that "necessarily functions in accordance with, or includes, the claimed limitations" anticipates regardless of whether the prior art recognized that the claimed limitations were inherently included in the prior art. *See Brassica Protection Prods.*, 301 F.3d at 1349; *SmithKline Beecham Corp.*, 403 F.3d at 1343.

(Ex. 1002, Baur Decl., ¶¶12, 37.) Accordingly, the majority of nicotinamide riboside originally present in the whole milk or cream remains in the aqueous buttermilk when the milk or cream is churned and the butter is removed. (Ex. 1002, Baur Decl., ¶¶12, 37.) The removal of butter from whole milk or cream to make buttermilk therefore necessarily increases the concentration of any nicotinamide riboside originally present in the whole milk or cream from which the buttermilk was made. (Ex. 1002, Baur Decl., ¶¶12, 37.) This is consistent with Goldberger and Tanner's showing that the pellagra-preventing activity of buttermilk is significantly higher than that of butter. (Ex. 1006, Goldberger and Tanner at 93, 95; Ex. 1002, Baur Decl., ¶¶12, 37.)

**c. "in admixture with a carrier"**

In buttermilk, nicotinamide riboside is "in admixture" (*i.e.*, in a mixture with) with "a carrier" because the nicotinamide riboside is in a mixture with other soluble components of milk, including components that bind and stabilize the compound. (Ex. 1002, Baur Decl., ¶37.)

**d. "wherein said composition is formulated for oral administration"**

Finally, the buttermilk in Goldberger and Tanner was administered orally. (Ex. 1002, Baur Decl., ¶37.)

Thus, buttermilk is a pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier, wherein said composition is formulated for oral administration. (Ex. 1002, Baur Decl., ¶37.)

**2. Dependent Claim 2**

Claim 2 depends from claim 1, and the analysis for claim 1 in Section VI.B.1 is incorporated by reference. Further, Goldberger and Tanner discloses "wherein the nicotinamide riboside is isolated from a natural or synthetic source." (Ex. 1002, Baur Decl., ¶38.)

The nicotinamide riboside naturally present in the buttermilk that Goldberger and Tanner administered is isolated (*i.e.*, separated or substantially free from at least some of the other components of the naturally occurring organism) from a natural source: the cow. (Ex. 1002, Baur Decl., ¶38.) Furthermore, the nicotinamide riboside in buttermilk is further isolated during the process of converting whole milk or cream to buttermilk because, during that process, the liquid left behind after milk or cream is churned into butter (including the nicotinamide riboside present in buttermilk) is separated from the portion of the milk or cream that is churned into butter. (Ex. 1002, Baur Decl., ¶38.)

**3. Dependent Claim 3**

Claim 3 depends from claim 1, and the analysis for claim 1 in Section VI.B.1 is incorporated by reference. Further, Goldberger and Tanner discloses "wherein the formulation comprises a tablet, troche, capsule, elixir, suspension, syrup, wafer, chewing gum, or food." (Ex. 1002, Baur Decl., ¶39.) The milk disclosed in Goldberger and Tanner is a food. (*Id*.)

**4. Dependent Claim 4**

Claim 4 depends from claim 1, and the analysis for claim 1 in Section VI.B.1 is incorporated by reference. Further, Goldberger and Tanner discloses "further comprising one or more of tryptophan, nicotinic acid, or nicotinamide." (Ex. 1002, Baur Decl., ¶¶40-42.)

The buttermilk disclosed in Goldberger and Tanner inherently comprises tryptophan and nicotinamide. (*Id*.)

Nicotinamide is necessarily present in buttermilk for the same reasons, given above in connection with Petitioner's analysis of claim 1, that nicotinamide riboside is necessarily present in buttermilk. As explained above, Trammell I establishes that raw milk and skim milk contain nicotinamide. (Ex. 1007, Trammell I, at 1, 3; Ex. 1002, Baur Decl., ¶¶ 35, 40.) Like nicotinamide riboside, nicotinamide is a water-soluble molecule

and will therefore remain in the aqueous buttermilk when the butter is removed. (Ex. 1002, Baur Decl., ¶40.)

Moreover, William Douglas McFarlane and Hugh Lehman Fulmer, "The Colorimetric Determination of the Tyrosine and Tryptophan Content of Various Crude Protein Concentrates," *Biochemical Journal*, 24(6):1601-1610 (1930) ("McFarlane and Fulmer") (Ex. 1012) demonstrates that tryptophan is present in dried buttermilk. (Ex. 1012, McFarlane and Fulmer, at, e.g., 1602, 1604, 1608-09; Ex. 1002, Baur Decl., ¶41.) McFarlane and Fulmer tested various protein sources, including dried buttermilk powder, for the presence of tyrosine and tryptophan, and concludes that "[t]he tyrosine and tryptophan content of buttermilk powder has been found to be much higher than that of other crude protein materials investigated." (Ex. 1012, McFarlane and Fulmer at 1609; Ex. 1002, Baur Decl., ¶41.) As buttermilk powder is directly derived from liquid buttermilk, tryptophan must therefore be present in liquid buttermilk as well. (Ex. 1002, Baur Decl., ¶41.)

Accordingly, the buttermilk disclosed in Goldberger and Tanner comprises tryptophan and nicotinamide." (Ex. 1002, Baur Decl., ¶42.)

**5. Dependent Claim 5**

Claim 5 depends from claim 1, and the analysis for claim 1 in Section VI.B.1 is incorporated by reference. Further, Goldberger and Tanner discloses "which increases NAD+ biosynthesis upon oral administration." (Ex. 1002, Baur Decl., ¶43.)

The buttermilk disclosed in Goldberger and Tanner increases NAD+ biosynthesis to test subjects upon oral administration. (Ex. 1002, Baur Decl., ¶43.) As the '086 patent acknowledges, nicotinamide riboside is an NAD+ precursor in a eukaryotic NAD+ biosynthetic pathway. (Ex. 1001, '086 patent, 2:62-3:3; Ex. 1002, Baur Decl., ¶10.) As explained above in connection with Petitioner's discussion of claims 1 and 4, NAD+ precursor vitamins, including nicotinamide riboside, are present in buttermilk. (Ex. 1002, Baur Decl., ¶¶37, 40, 43.) Trammell II and the Brenner Declaration submitted during prosecution of the parent '400 application show that orally consumed nicotinamide riboside is a potent booster of NAD+. (Ex. 1008, Trammell II at 6-7, 11; Ex. 1003, Ex. 1003, Excerpts from Prosecution History of Serial No. 11/912,400, at 132-35; Ex. 1002, Baur Decl., ¶¶14, 36.) Accordingly, the consumption of buttermilk necessarily increases NAD+ biosynthesis. (Ex. 1002, Baur Decl., ¶43.) *See, e.g., SmithKline Beecham Corp.*, 403 F.3d at 1343 (prior art reference inherently anticipates

where reference is "sufficient to show that the natural result flowing from the operation as taught in the prior art would result in the claimed product") (internal quotation and citation omitted).

In addition, Goldberger and Tanner discloses that none of the 29 subjects developed any evidence of pellagra and that, without the buttermilk, 40%-50% of the test subjects would have developed pellagra during the observation period. (Ex. 1006, Goldberger and Tanner at 93; Ex. 1002, Baur Decl., ¶¶18, 43.) Goldberger and Tanner's results are direct evidence that NAD+ biosynthesis increases upon oral administration of buttermilk. (Ex. 1002, Baur Decl., ¶43.)

**6. Conclusion**

Goldberger and Tanner discloses, either expressly or inherently, each element of claims 1-5 of the '086 patent. (Ex. 1002, Baur Decl., ¶¶37-43.) The inventors of the '086 patent cannot patent the buttermilk disclosed in Goldberger and Tanner based on the alleged discovery of properties inherent in buttermilk. *See, e.g.*, *In Brassica Protection Prods.*, 301 F.3d at 1351-52; *Upsher-Smith Labs*, 412 F.3d at 1323.

## VII. CONCLUSION

For the foregoing reasons, there is a reasonable likelihood that claims 1-5 of the ’086 patent are unpatentable as anticipated. Petitioner requests institution of an *inter partes* review to cancel those claims.

## VIII. CERTIFICATION OF GROUND FOR STANDING

Petitioner certifies pursuant to Rule 42.104(a) that the patent for which review is sought is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this Petition.

## IX. MANDATORY NOTICES

### A. Real Party in Interest

The real party in interest is the Petitioner, Elysium Health, Inc.

### B. Related Matters

A counterclaim for misuse of the ’086 patent is asserted in *ChromaDex, Inc. v. Elysium Health, Inc.*, Case No. 16-cv-02277-KES (C.D. Cal.).

The following patent claims the benefit of priority of the filing date of the ’086 patent: U.S. Patent No. 8,197,807 (the ’807 patent). Concurrent with the filing of this Petition, the Petitioner is a second petition for *inter partes review* regarding the ’807 patent.

## C. Lead and Back-up Counsel

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## CERTIFICATE OF COMPLIANCE

This Petition complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i) because, according to the "word count" function of Microsoft Word 2016, the Petition contains 5,591 words, excluding the parts of the Petition exempted from the word count by 37 C.F.R. §42.24(a)(1).

/Brendan T. Jones/
Brendan T. Jones

## CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e)(4) and 42.105, the undersigned certifies that on this date, a true and correct copy of this document (Petition for *Inter Partes* Review), and every Exhibit filed with this document, was served by Federal Express overnight service on the current correspondence address of record for U.S. Patent No. 8,383,086 B2:

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Dated: July 17, 2017

/Brendan T. Jones/
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