IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CHROMADEX, INC. and TRUSTEES OF DARTMOUTH COLLEGE,	)	**REDACTED PUBLIC VERSION**
Plaintiffs,	)	C.A. No. 18-1434-CFC
v.	)	
ELYSIUM HEALTH, INC.,	)	
Defendant.	)	

ELYSIUM'S OPENING BRIEF IN SUPPORT OF MOTION FOR SUMMARY JUDGMENT (NO. 1) OF INVALIDITY UNDER 35 U.S.C. § 101

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I. Summary of Argument

All four asserted claims—claims 1-3 of U.S. Patent No. 8,197,807 ("'807 patent") and claim 2 of U.S. Patent No. 8,383,086 ("'086 patent")—are invalid under 35 U.S.C. §101 because they claim unpatentable products of nature.

II. Background[1]

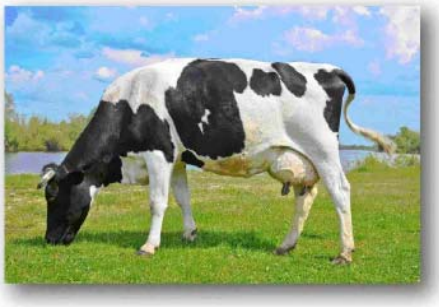
The asserted claims are directed to compositions comprising isolated nicotinamide riboside ("NR"). NR is a naturally-occurring vitamin present in cow milk. SF1-01. Animal cells naturally convert NR into NAD+. Ex. C at 53, 74. NAD+ is a coenzyme associated with various biological activities. Ex. F at ¶¶ 35-36. A deficiency in NAD+ causes the diseases pellagra (in humans) and blacktongue (in dogs). SF1-07.

Not only is the natural occurrence of NR in milk undisputed, it is used by ChromaDex to promote the sale of its NR ingredient product (Niagen®) and the NR supplement product TruNiagen® as natural products. On its website, ChromaDex describes NR as "an example of a naturally-occurring nutrient" and characterizes Niagen as a "nature-identical" form of NR. Ex. M. In slide decks ChromaDex states that "TruNiagen is… found Naturally in Milk". Ex. N at -CDXDE_000057025.

[1] For the facts material to this motion, see the accompanying First Statement of Facts ("SF1"). Citations to exhibits ("Ex.") refer to the exhibits attached thereto.

ChromaDex

TruNiagen is GRAS, Found Naturally in Milk



Metabolome, μmol/L	Total (n = 18)	*S. aureus* negative (n = 12)	*S. aureus* positive (n = 6)
Nicotinamide	7.3 ± 1.5[2]	7.7 ± 1.2	6.4 ± 1.7
NR	4.3 ± 2.6	5.1 ± 2.6	2.7 ± 1.9
NA	<1.0	<1.0	<1.0
NMN	<0.4	<0.4	<0.4
NAD^+	<0.08	<0.08	<0.08
NAR	<0.04	<0.04	<0.04
$NAD(P)^+$	<0.02	<0.02	<0.02
NAAD	<0.01	<0.01	<0.01

[1] NA, nicotinic acid; NAAD, nicotinic acid adenine dinucleotide; NAR, nicotinic acid riboside; NMN, nicotinamide mononucleotide; NR, nicotinamide riboside.
[2] Mean ± SD (all such values).

Trammell *et al* 2016 J Nutrition

	Organic					Conventional				
	Brand A	Brand B	Brand C	Brand D	All	Brand A	Brand B	Brand C	Brand D	All
Nicotinamide, μmol/L	2.4	7.1	5.0	7.9	5.6 ± 2.5	5.6	0.67	8.9	5.4	5.2 ± 3.4
NR, μmol/L	3.1	0.84	2.2	1.4	1.9 ± 1.0	2.5	1.7	5.4	2.7	3.1 ± 1.6

[1] Values are expressed as means ± SDs, n = 4. NR, nicotinamide riboside.

NR is Also Present in Human Breast Milk (Unpublished Data)

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These are just some of the many documents in which ChromaDex or the inventor, Charles Brenner, emphasize that NR is a natural product. *E.g.*, Ex. O (NR is "a natural product that we have found in bovine milk"); *id.* ("If you have handled milk, you have handled nicotinamide riboside"); Ex. P (NR "is derived from milk… the thing that moms get to their kids.").

In addition to requiring that NR be present in the composition, the '807 claims specify that the NR must be "in combination with one or more of tryptophan, nicotinic acid, or nicotinamide." Like NR, these three compounds are NAD+ precursors and also occur in nature. Ex. C at 55, 82-84, 92-93; Ex. E at ¶ 29. Two of them—tryptophan and nicotinamide—naturally occur in combination with NR in milk. SF1-01, SF1-02; SF1-03. The '807 claims also require that the composition increase NAD+ biosynthesis; similarly, the "pharmaceutical

composition" of claim 2 of the '086 patent, as construed by the Court, must be capable of improving or prolonging the health or well-being of animals. Milk meets both of these requirements: it can be used to prevent or treat NAD+ deficiency diseases and, therefore, is capable of increasing NAD+ biosynthesis to improve the health of animals. SF1-07, SF1-08.

III. Argument

A patent claim is invalid if it is directed to unpatentable subject matter. *See* 35 U.S.C. § 101. "Laws of nature, natural phenomena, and abstract ideas are not patentable." *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 589 (2013). The Supreme Court has set forth a two-step framework to determine whether claims are directed to unpatentable subject matter. *Mayo Collaborative Servs. v. Prometheus Labs, Inc.*, 566 U.S. 66, 77-78 (2012); *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 573 U.S. 208, 217-18 (2014). First, a court determines whether the claims are directed to one of the patent-ineligible concepts. *See Alice*, 573 U.S. at 217-18. Second, it determines whether additional elements of the claim "transform the nature of the claim into a patent-eligible application." *Id.*

A. Step One: The Claimed Compositions Comprising "Isolated" NR are Directed to Unpatentable Products of Nature

1. The Asserted Claims are Directed to Natural Products

The claims of the '807 patent are "directed to" compositions containing NR in combination with tryptophan, nicotinic acid, and/or nicotinamide, where the compositions increase NAD+ biosynthesis upon oral administration.[2] Such compositions are found in nature. It is undisputed that milk naturally contains NR. SF1-01. The "in combination with" element, as construed by the Court, requires only that tryptophan, nicotinic acid, and/or nicotinamide be "found in" the composition. D.I. 152. Both tryptophan and nicotinamide are found in milk. SF1-02; SF1-03. It is undisputed that milk prevents or treats pellagra and blacktongue, NAD+ deficiency diseases in humans and dogs, respectively. SF1-07; SF1-08.

[2] Claim 1 of the '807 patent is reproduced below:

> 1. 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 [or a list of other carriers], wherein said composition is formulated for oral administration and increases NAD+ biosynthesis upon oral administration.

Ex. A at 53:59-54:58.

Thus, milk increases NAD+ biosynthesis upon oral administration.[3] *Id.*; *see also* SF1-09; SF1-10.

As for the dependent claims, Claim 2 adds a source limitation that allows the NR to be isolated from a "natural" source. This element underscores that the claimed invention is directed to a natural product. Claim 3 states that the composition can be a food. Milk is a food. SF1-06.

Claim 2 of the '086 patent is also directed to a natural product. The "pharmaceutical composition" of the '086 claims (under the Court's claim construction) must be capable of "improv[ing] or prolong[ing] the health or well-being of" animals. D.I. 152. As demonstrated by its anti-pellagra and anti-blacktongue properties, milk can be used to improve health. SF1-07; SF1-08; *see also* Ex. C at 233. Dependent claim 2's specification that the NR can be isolated from a "natural" source again emphasizes that the claim is directed to natural products.

a. Under Supreme Court Precedent, the "Isolated" Limitation Does Not Make the Natural Product Patentable

In response to Elysium's arguments, Plaintiffs misrepresent what the claims, as construed by the Court, actually cover. Many of Plaintiffs' improper claim

[3] The other elements of claim 1 of the '807 patent also are found in milk. Milk is a food that naturally contains the carrier lactose, a sugar, and is formulated for oral administration. SF1-04; SF1-05; SF1-06.

interpretations are rooted in the claim term "isolated." However, this Court's construction of "isolated" requires only that the NR be "separated or substantially free from at least ***some of the other components associated with the source***." D.I. 152 (emphasis added). The "isolated" limitation does not make the claims patent eligible. On the contrary, under the Supreme Court's holding in *Myriad*, "isolating" a natural substance by separating, purifying, substantially freeing it, or otherwise isolating it from components of its source does not transform an unpatentable natural product into patentable subject matter.

In *Myriad*, the composition claims at issue recited "isolated" DNA sequences, such as "[a]n ***isolated*** DNA coding for a BRCA1 polypeptide." *Myriad*, 569 U.S. at 584 (emphasis added). The Federal Circuit had held that the "isolated" limitation made the claims patent eligible. *Id.* at 587. But the Supreme Court reversed, holding that claims to "isolated DNA" were directed to unpatentable products of nature. *Id.* at 595.

The Court explained that the location and order of the claimed DNA sequences "existed in nature before Myriad found them," just as NR existed in nature before Dartmouth filed its patent applications. *Id*. at 590. The Court rejected Myriad's argument that the "isolated" limitation made the claimed subject matter patentable: "Nor are Myriad's claims saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a nonnaturally

occurring molecule." *Id*. at 593. The Court recognized that Myriad "found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention." *Id*. at 591, 595. Separating NR from its source material likewise is not an act of invention.

The Federal Circuit has since applied *Myriad* to find other isolated natural products unpatentable. In *In re Bhagat*, the Federal Circuit affirmed the USPTO's rejection of claims directed to fatty acid mixtures that occurred naturally in walnut oil and olive oil. 726 Fed. Appx. 772, 778-79 (Fed. Cir. Mar. 16, 2018). The court rejected arguments that extracts from naturally occurring plants "are not natural products because the extraction processes required to obtain edible oils from olives and walnuts transform the claimed lipids from natural products." *Id.* Similarly, in *BRCA1 & BRCA2-Based Hereditary Cancer Test Patent Litig. v. Ambry Genetics Corp*., 774 F.3d 755, 759 (Fed. Cir. 2014), the Court analyzed a claim to "[a] pair of single-stranded DNA primers." As the court explained, primers are "short, synthetic, single-stranded DNA molecules" that are "structurally identical to the ends of DNA fragments found in nature." *Id*. at 758, 760. The Court rejected arguments that the claimed primers were patentable because, unlike naturally occurring double-stranded DNA, "single-stranded DNA cannot be found in the human body." *Id*. at 760. The Court explained that separating out a portion of

DNA from its natural environment does not make the separated DNA patentable. *Id*. The same is true of the "isolated" NR claimed here.

b. The Claimed Compositions are not Markedly Different from Natural Milk

In *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980), the Supreme Court explained that, to be patentable, a composition must have "markedly different characteristics from any found in nature." *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980); *see also, e.g.*, *In re Roslin Inst.*, 750 F.3d 1333, 1336 (Fed. Cir. 2014) ("[D]iscoveries that possess markedly different characteristics from any found in nature are eligible for patent protection."). Here, as discussed above, the only structural difference between natural milk and the claimed composition—that the composition contain "isolated" NR—is insufficient as a matter of law under *Myriad*. Dartmouth cannot obtain a patent monopoly on compositions comprising a natural combination of NAD+ precursors simply by requiring that the NR component be "isolated."

Moreover, the claims as construed do not require the composition to have any non-natural functional properties that give the composition "markedly different characteristics from any found in nature". The claims' only functional requirements are that the composition "increase NAD+ biosynthesis upon oral administration" ('807 patent) or be a "pharmaceutical composition" ('086 patent). The Court construed the former limitation to require increasing NAD+

biosynthesis relative to the level "if the composition were not administered to an animal." D.I. 152. The Court construed "pharmaceutical composition" to require a capability to improve the health/well-being of an animal. *Id.*

Naturally-occurring milk has those properties. When milk is orally administered to humans and dogs, it prevents or treats the NAD+ deficiency diseases pellagra and blacktongue. SF1-07; SF1-08.[4] Thus natural milk increased those animal's NAD+ biosynthesis relative to the disease-inducing levels they suffered prior to ingesting the milk. *Id.*; *see also* SF1-09; SF1-10. In doing so, it improved their health. SF1-08; *see also* Ex. C at 233. In short, the functional requirements of the claimed inventions are the ***same as***, not "markedly different from," a natural product. *See Sensormatic Elecs., LLC v. Wyze Labs, Inc.*, 484 F. Supp.3d 161, 166 (D. Del. 2020) (Connolly, J.) (functions that are "features or results of the claimed abstract concepts… do not take the asserted patents beyond those concepts").

[4] Plaintiffs' expert Dr. Sobol argues that it is the tryptophan in milk, not the NR, that is responsible for its anti-pellagra and anti-blacktongue properties. This is irrelevant. The '807 patent claims do not require that the ***isolated NR*** increase NAD+ biosynthesis. Rather, they require that the ***composition*** (which can be NR in combination with tryptophan) increase NAD+ biosynthesis. Plaintiffs acknowledged this in their claim construction briefing: "Claim 1 recites that the claimed 'composition'—not any one of its particular components—'increases NAD+ biosynthesis upon oral administration.'" D.I. 99 at 93. Dr. Sobol also admitted that in the asserted claims it is the composition, not the NR, that must increase NAD+ biosynthesis. Ex. C at 204-205.

In *Funk Bros. Seed Co. v. Kalo Inoculant Co*., 333 U.S. 127, 131-32 (1948), the Court held that product claims directed to a man-made mixture of naturally-occurring strains of bacteria claimed patent-ineligible subject matter. The Court explained that the inventor's discovery that certain bacterial strains could be mixed together without materially changing their respective properties was not patentable. *Id*. at 132 (noting that the bacteria "serve the ends nature originally provided and act quite independently of any effort of the patentee"). Here, similarly, the claimed inventions to do not materially change the properties of the natural product. Indeed, the grounds for invalidity are even stronger here because the claimed combination (NR with nicotinamide and/or tryptophan) is found in nature, whereas the bacterial combination claimed in *Funk Bros* was not.

2. *Natural Alternatives* Does Not Save the Patents from Invalidity under § 101

In response to Elysium's § 101 arguments, Plaintiffs have relied almost exclusively on the Federal Circuit's decision in *Natural Alternatives Int'l, Inc. v. Creative Compounds, LLC*, 918 F.3d 1338 (Fed. Cir. 2019). *See* Ex. H at 5-6. *Natural Alternatives* does not help Plaintiffs and the differences between the claims upheld in that case and the claims here show why the latter are not patent-eligible.

In *Natural Alternatives*, the Federal Circuit considered three groups of claims related to the amino acid beta-alanine. The first and third groups were

directed to methods of treatment and methods of manufacturing and are not relevant here. The second group—"the Product Claims"—were directed to beta-alanine products that produced a non-natural result, namely they had "different characteristics and can be used in a manner that beta-alanine as it appears in nature cannot." *Id*. at 1348. In particular, the court analyzed patent eligibility based on a construction of the claims requiring that the claimed compositions "***effectively increase athletic performance***," a property that natural compositions containing beta-alanine did not possess. *Id*. (emphasis added). Moreover, some of the claims expressly required "between about 0.4 grams to 16 grams" of beta-alanine, far higher than the amounts in natural sources, in order to obtain the non-natural result. *Id*. at 1349, 1346, n.3. The court accepted, for purposes of analyzing patent eligibility, that the "claimed dosage forms [could] be used to increase athletic performance in a way that naturally occurring beta-alanine cannot." *Id*. at 1349.

In contrast, the asserted claims here do not require any non-natural properties. As discussed, the only functional requirement of the asserted claims is either increasing NAD+ biosynthesis ('807 patent) or improving health ('086 patent). But those are properties that natural milk indisputably possesses, unlike the natural beta-alanine in *Natural Alternatives*, which did not possess the claimed non-natural properties. Nor do the claims here require any supernatural levels of NR in the composition; the claims recite no dosage limitations at all. The NR must

merely be present, in any amount, and need only have been separated or substantially free from at least some of the components of its source.

Natural Alternatives is also distinguishable because the procedural posture was fundamentally different. In *Natural Alternatives*, the Federal Circuit reviewed a district court decision at the Rule 12 stage, before it construed the claims. *Id*. at 1342-43, 1352. Thus, the Federal Circuit was required to apply the patentee's ***proposed*** claim constructions, which specifically distinguished the claims from natural products by importing limitations into the claims. *Id*. at 1343-44; 1352-53. As Judge Reyna explained in his partial dissent, on remand the district court could construe the claims differently and revisit the § 101 issue. *Id*. at 1582. Here, by contrast, this Court has construed the claims and rejected Plaintiffs' attempt to read § 101-inspired limitations into them.

Rather than candidly recognizing the differences between this case and *Natural Alternatives*, Plaintiffs ignore this Court's constructions and attempt to save the claims from § 101 invalidity by imposing claim limitations that do not exist. For example, Plaintiffs' expert, Dr. Sobol, asserts that the claims "are directed to compositions that include isolated NR ***in quantities far beyond that found in nature***, formulated for oral administration to increase NAD+ biosynthesis ***with a surety and in an amount far beyond that which can be achieved from***

naturally occurring NR." Ex. F at ¶ 142 (emphasis added); *see also id*. at ¶¶ 154, 157-159, 161.

These requirements are not in the claims as construed. The claims do not specify a minimum quantity of NR that must be present in the composition, let alone a quantity "far beyond that found in nature." Dr. Sobol was forced to admit in his deposition that "those words are not in the claim construction or claims…. That was my presentation… not in the claims as written." *See* Ex. C at 240-41.

Not only is Dr. Sobol's distortion of the claims baseless, his opinion relies on arguments that Plaintiffs abandoned. During claim construction, Plaintiffs sought to construe "isolated nicotinamide riboside" as requiring that NR make up at least 25% of the composition. D.I. 99 at 22. When the Court declined to accept this argument, Plaintiffs gave up on it and ***agreed*** to a construction that did not require a threshold amount or concentration of NR, as memorialized in this Court's Claim Construction Order. Ex. G at 29; D.I. 152. Dr. Sobol, when pressed, admitted that the claims "don't speak to a threshold amount, no." Ex. C at 199.

Nor do the claims require that the composition cause a particular amount or degree of NAD+ biosynthesis, let alone "an amount far beyond that which can be achieved from naturally occurring NR," as Plaintiffs now assert. The claims require only that the combination of NAD+ precursors increase NAD+ biosynthesis upon oral administration "relative to the level of NAD+ biosynthesis

if the composition were not administered to an animal." D.I. 152. This construction imposes no requirement on the amount by which NAD+ must be increased, much less that it be "far beyond" what natural compositions, like milk, can accomplish. *See* Ex. C at 239.

Finally, Dr. Sobol's opinions are based on the erroneous assumption that under the asserted claims the ***nicotinamide riboside*** in the composition must increase NAD+ biosynthesis. Ex. F at ¶ 296. Claim 2 of the '086 patent does not even require an increase in NAD+ biosynthesis. As for the '807 patent, as Plaintiffs have recognized (*see* footnote 4 above), the claims of the '807 patent do not require that the ***nicotinamide riboside*** increase NAD+ biosynthesis; they require that the ***composition*** increase NAD+ biosynthesis. *See* D.I. 99 at 93; Ex. C at 204-205.

Plaintiffs' arguments based on *Natural Alternatives* depend on adding claim limitations that do not exist in the claims as construed. Under the controlling case law, the claims clearly are directed to patent-ineligible subject matter.

B. Step 2: The Asserted Claims Lack an Inventive Concept

Step two of the *Mayo* framework is "a search for an 'inventive concept'—*i.e.*, an element or combination of elements that is sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself." *Alice*, 583 U.S. at 217-18. None of the claims here recite

unconventional elements relating to the claimed compositions. The specification acknowledges that NR-containing compositions "can be prepared by methods and contain carriers which are well-known in the art." SF1-11. The only alleged difference between these claims and natural whole milk is that the NR is "isolated". But the patent concedes that isolation from a natural source can be accomplished using well-understood, routine, and conventional activity. It explains that "Isolated extracts of natural sources can be prepared using standard methods." SF1-12; *see Myriad*, 569 U.S. at 582 (scientists can extract DNA using "well known laboratory methods"). Plaintiffs' expert Dr. Sobol acknowledged "[i]t is not the specific techniques of isolation that transform the Asserted Claims beyond a law of nature or natural phenomenon." SF1-13.

Instead, Dr. Sobol asserts:

> [T]he inventive concept is the pioneering decision to create a composition comprising isolated NR formulated for oral administration…. [I]t was not until Dr. Brenner's work in 2004 that the scientific community even became aware of the importance of NR as an orally available vitamin or what it would do in the body.

Ex. F, at ¶ 164. This assertion establishes as a matter of law that the claims fail step 2. As the Federal Circuit has explained, "[t]he inventive concept necessary at step 2 of the *Mayo*/*Alice* analysis cannot be furnished by the unpatentable law of nature (or natural phenomenon or abstract idea) itself." *Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1376 (Fed. Cir. 2016). In other words, "a claim

directed to a newly discovered law of nature (or natural phenomenon or abstract idea) cannot rely on the novelty of that discovery for the inventive concept necessary for patent eligibility." *Id.*; *see Management Sci. Assocs. v. Datavant, Inc.*, 2020 U.S. Dist. LEXIS 244513, at * 23 (D. Del. Dec. 30, 2020) (Connolly, J.) ("The inventive feature, however, cannot be supplied by the abstract idea itself."). Dr. Sobol's opinion does just that: it relies on Dr. Brenner's alleged discovery that NR is an orally available vitamin—a natural phenomenon—as the "inventive concept" of the asserted claim. That argument cannot save the claims. The claims are invalid under Section 101.

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CERTIFICATE OF COMPLIANCE

This brief complies with the type, font and word limitations set forth in this Court's Standing Order Regarding Briefing in All Cases, dated November 6, 2019. This brief contains 3442 words (excluding the title page, table of contents, table of authorities, signature block, and certificate of compliance). This brief has been prepared in 14-point Times New Roman font.

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