2022-1116

United States Court of Appeals for the Federal Circuit

CHROMADEX, INC., TRUSTEES OF DARTMOUTH COLLEGE,

Plaintiffs-Appellants,

– v. –

ELYSIUM HEALTH, INC.,

Defendant-Appellee.

On Appeal from the United States District Court for the District of Delaware in No. 1:18-cv-01434-CFC-JLH, Chief Judge Colm F. Connolly

PETITION OF PLAINTIFFS-APPELLANTS CHROMADEX, INC. AND TRUSTEES OF DARTMOUTH COLLEGE FOR PANEL REHEARING AND REHEARING EN BANC

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MARCH 15, 2023

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 2022-1116

Short Case Caption ChromaDex, Inc. v. Elysium Health, Inc.

Filing Party/Entity ChromaDex, Inc.

Instructions:

1. Complete each section of the form and select none or N/A if appropriate.
2. Please enter only one item per box; attach additional pages as needed, and check the box to indicate such pages are attached.
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I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 03/15/2023

Signature: /s/ William L. Mentlik

Name: William L. Mentlik

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☐ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☐ None/Not Applicable
ChromaDex, Inc.	N/A	ChromaDex, Inc. is a wholly owned subsidiary of ChromaDex Corporation.
Trustees of Dartmouth College	N/A	N/A

☐ Additional pages attached

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☐ Additional pages attached

Emily Mondry (Covington & Burling LLP)	Evan Krygowski (Covington & Burling) (no longer with firm)	James F. Haley, Jr. (Haley Guiliano LLP)
Patrick Flynn (Covington & Burling LLP)	Adam Poff (Young, Conaway, Stargatt & Taylor LLP)	
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5. Related Cases. Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

☑ Yes (file separate notice; see below) ☐ No ☐ N/A (amicus/movant)

If yes, concurrently file a separate Notice of Related Case Information that complies with Fed. Cir. R. 47.5(b). **Please do not duplicate information.** This separate Notice must only be filed with the first Certificate of Interest or, subsequently, if information changes during the pendency of the appeal. Fed. Cir. R. 47.5(b).

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

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I. STATEMENT UNDER FEDERAL CIRCUIT RULE 35(b)

Based on my professional judgment, I believe that the panel decision is contrary to the following decisions of the Supreme Court of the United States or the precedents of this Court:

- *Berkheimer v. HP Inc.*, 881 F.3d 1360 (Fed. Cir. 2018) (although patent eligibility is an issue of law, genuine issues of material fact underlying patent eligibility determination preclude summary judgment);
- *Diamond v. Chakrabarty*, 447 U.S. 303, 309-10 (1980) (naturally occurring substance or composition of matter that is altered to have markedly different properties is patent eligible);
- *Natural Alternatives Int'l, Inc. v. Creative Compounds, LLC*, 918 F.3d 1338 (Fed. Cir. 2019) (applying *Alice/Mayo* two-step framework to patent eligibility of claims directed to "natural products," and holding that treatment composition containing natural substance was patent eligible because it had functional capabilities lacking in substance as it appears in nature);
- *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 573 U.S. 208 (2014) (holding that two-step framework for analyzing patent eligibility applies to claims directed to "natural phenomena"); and

- *Rapid Litig. Mgmt. v. CellzDirect, Inc.*, 827 F.3d 1042 (Fed. Cir. 2016) (claim incorporating natural law patent eligible under *Alice/Mayo* step two if application in the claims was not routine or conventional).

Based on my professional judgment, I believe this appeal requires an answer to the following precedent-setting questions of exceptional importance:

- May a claim that includes an isolated natural substance in a treatment formulation be denied patent eligibility on summary judgment when there are disputed fact issues as to whether the isolated substance and formulation have markedly different properties from the naturally occurring form of the substance and the potential for significant utility?

- May a court evaluating patent eligibility for a claim directed to a purported "natural product" bypass *Alice/Mayo* step two, even though *Alice* states that the two-step framework applies to claims directed to "natural phenomena"?

By: /s/ William L. Mentlik
William L. Mentlik
Attorney for Plaintiffs-Appellants ChromaDex, Inc. and Trustees of Dartmouth College

II. PRIOR PROCEEDINGS

The ’807 Patent claims a treatment formulation that increases NAD+ biosynthesis and thus improves human health and treats disease, using an isolated form of nicotinamide riboside (“NR”) that is combined with another NAD+ precursor and formulated for oral administration. (Appx2539.) A panel of this Court affirmed the district court’s grant of summary judgment of patent ineligibility, concluding that the claims are directed to a product of nature and do not include any additional inventive concept. (Op. 9-10.)

III. POINTS OF LAW OR FACT OVERLOOKED BY THE COURT

ChromaDex respectfully submits that the panel’s decision overlooked material facts with respect to both steps of the *Alice/Mayo* framework.

As to step one, the panel found that “the asserted claims … claim a product of nature” (Op. 9), but the composition of the claims is most assuredly *not* found in nature. “Isolated NR” is a requirement of all claims, and is different from naturally occurring NR found in milk. (Op. 6.) How different it is, and whether the differences are “marked,” is a deeply factual inquiry. The panel decision, however, did not fully consider the facts underlying that inquiry, and—without any expert testimony or other sufficient evidentiary basis—simply concluded that the claims effectively cover milk, and any differences between isolated NR and natural NR found in milk are insignificant. (*Id.* 8.)

When ChromaDex accepted the district court's proposed construction of "isolated NR," which differed from that proposed by either party, ChromaDex did so with the district court's assurances that, at an eventual trial, the court would hear competing expert testimony on the factual question of whether NR in a given embodiment was sufficiently purified to constitute "isolated NR." (Appx2880.) The panel's decision deprives ChromaDex of that opportunity. It concludes, without evidentiary support, that embodiments in which NR is not purified even to a level where it would be bioavailable nonetheless contain "isolated NR." (Op. 8.) It also concludes that milk is "formulated" and includes an "admixture" of ingredients, when there is no record support for those propositions. These conclusions were contrary to *Berkheimer*, 881 F.3d at 1370, and Rule 56, which preclude summary judgment in these circumstances.

The panel further stated that it was unnecessary to address *Alice/Mayo* step two (Op. 9), but that conclusion overlooked authoritative guidance in *Alice*, 573 U.S. at 217, stating that the two-step framework developed in *Mayo* applies to claims directed to *all* patent ineligible concepts, including "natural phenomena." The panel ultimately addressed step two briefly, but overlooked significant evidence showing that Dr. Brenner's inventive activities in developing an oral formulation of isolated NR were anything but "well-understood, routine and conventional." Contrary to what the district court found (Appx41), Elysium in fact conceded that NR in nature

is biologically inactive. It had no known therapeutic effect, and no one had devised a way to change it to produce such an effect through oral administration. Isolated NR, in contrast, changed NR and allowed its therapeutic benefits to be realized. These critical facts should have precluded summary judgment against ChromaDex.

IV. ARGUMENT

A. The Panel Erred By Resolving Disputed Factual Issues Regarding *Alice/Mayo* Step One Against Non-Movant ChromaDex On Summary Judgment, In Violation Of *Berkheimer* And Rule 56

1. *Berkheimer* And Rule 56 Preclude Summary Judgment Regarding Patent Eligibility When There Are Genuine Issues Of Material Fact As To Underlying Issues

As this Court explained in *Berkheimer*, the patent eligibility inquiry may include underlying issues of fact. 881 F.3d at 1365, 1368. If there are genuine disputes of material fact on such issues, summary judgment is inappropriate. *Id.* at 1370; Fed. R. Civ. P. 56(a). This Court reviews the grant of summary judgment under the law of the regional circuit. In the Third Circuit, a reviewing court views the facts on summary judgment in the light most favorable to the non-moving party. *Accenture Global Servs. v. Guidewire Software, Inc.*, 728 F.3d 1336, 1340 (Fed. Cir. 2013) citing *A.W. v. Jersey City Pub. Schs.*, 486 F.3d 791, 794 (3d Cir. 2007).

In *Berkheimer*, this Court reversed a summary judgment of patent ineligibility because there were genuine issues of material fact as to whether the claims performed activities that were well-understood, routine and conventional under *Alice/Mayo* step two. *Berkheimer*, 881 F.3d at 1370. The Court, however, did not

limit to that context its holding that patent eligibility may depend on underlying facts. Disputed material facts regarding *Alice/Mayo* step one likewise preclude summary judgment. *Id.*

2. Determining Which Compositions Are Sufficiently Purified To Constitute "Isolated NR" Is A Factual Matter For Expert Witnesses

A linchpin of the panel's determination that the claims lack "markedly different characteristics" from milk was its finding that the district court's construction of "isolated NR" "does not require that the NR be separated from the lactalbumin whey protein, but only from 'some of the other components associated with the source of [NR].' The claims, therefore, do not necessarily require that the isolated NR be bioavailable." (Op. 9, citing Appx22.) In so finding, the panel did not rely on or cite any evidence concerning particular NR embodiments or the purity of such embodiments. Rather, the panel resolved disputed facts against non-movant ChromaDex, contravening the summary judgment standard.

When the district court secured ChromaDex's consent to the agreed-upon construction of "isolated NR" at the *Markman* hearing, it did so with assurances to ChromaDex, and ChromaDex's clear understanding, that the parties would litigate at a jury trial, *as an issue of fact*, the question of which compositions contained isolated NR. As the district court stated: "***we're going to have experts telling me whether something is substantially free or not …. They're going to basically be,***

what's the level of the impurity essentially." (Appx2880 (emphasis supplied).) Indeed, the district court stated that this seemed to be "the right thing to do." (*Id.*) ChromaDex took the district court at its word and agreed. (*Id.*) Accordingly, the extent to which components must be removed from a natural source of NR to create "isolated NR" was a fact issue for the jury, not an issue that could be resolved on summary judgment.[1]

The panel, however, without any expert testimony from either party, inventor testimony or citations to the patent specification, resolved this factual issue and found that "isolated NR" reads on embodiments with such minimal purification that none of the lactalbumin whey protein is removed, and embodiments that have so little pure NR that the NR lacks biological activity. (Op. 9.) Finding that the claims "encompass ... at least one embodiment that covers milk, ***except*** that the NR element is 'isolated'" (*id.* 8 (emphasis supplied)), the panel then effectively ignored the

[1] In Elysium's IPR challenging the '807 Patent, the PTAB construed "isolated NR" to include the 25% minimum purity requirement that ChromaDex subsequently advanced in the litigation. The PTAB held that "isolated" requires that the NR be "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." *Elysium Health, Inc. v. Trustees of Dartmouth College,* IPR2017-01796, Institution Decision (Paper No. 9), at 8 (Jan. 18, 2018). On that basis, the PTAB determined that neither milk, skim milk nor buttermilk anticipated the claims. (*Id.* 8-11.) When agreeing to the district court's construction of "isolated NR" here, ChromaDex did not relinquish its argument that a minimum purity threshold (*e.g.*, 25%) must be satisfied for an embodiment to include "isolated NR" within the meaning of the claimed invention. ChromaDex simply deferred that argument for resolution at trial. (Appx2880.)

significance of that exception, concluding simply that the claims "encompass a product of nature." (*Id.*) Thus, despite the explicit guidance of the district court as to how the scope of "isolated NR" would be litigated, ChromaDex was denied the opportunity to submit expert testimony or other evidence to prove "whether something is substantially free or not," "what's the level of impurity" and whether the level of NR purity is consistent with characterizing a substance as "isolated NR." (Appx2880.)

The patent specification does not support expanding "isolated NR" to cover a natural source of NR from which so little has been removed that it has no therapeutic value. Indeed, the very purpose of the invention is to prevent or treat a disease or condition by administering an isolated NR composition.[2] (*E.g.*, Appx2514, 4:26-31, Appx2526, 28:41-57.) Thus, the patent discusses using NR to increase NAD+ synthesis, which does not occur if the NR is bound to lactalbumin whey protein. (Appx2426, 28:35-29:23; Appx10205, 20:2-8.) There is no written description disclosure of skim milk as an isolated NR composition, for example, or any other purportedly isolated NR that lacks biological activity. On the other hand, there is clear written description support for removing whey protein from NR by isolating NR from "deproteinized whey fraction of cow's milk." (Appx2526, 27:7-8.)

[2] The patent also notes that NR can be used with NAD+ precursors such as tryptophan, but only to optimize and supplement the efficacy of NR in treating particular conditions, not to substitute for NR. (Appx2527, 29:19-23.)

Other evidence demonstrates that there is at least an issue of fact as to whether "isolated NR" includes embodiments in which only small amounts of contaminants, or components unrelated to NR's activity (such as milk fat), have been removed. Dr. Brenner's deposition testimony reinforces the view that such modifications would not create "isolated NR," and NR in products like skim milk or buttermilk "is certainly not isolated," as he explained. (Appx10175, ¶ 154.) As ChromaDex's expert, Dr. Sobel, explained, isolated NR is bioavailable and boosts NAD+ (Appx10192, ¶ 954), whereas naturally occurring NR in milk does not have these attributes. (Appx10205, 20:2-8, Appx10166, ¶ 88, Appx10204 (Elysium admitting that "one can't eat enough of anything to boost NAD+ levels"); *see also* Appx10100, Appx9687.)

While claim construction is decided by a court, the district court here explicitly reserved to ChromaDex the right to offer testimony on whether a given NR constitutes "isolated NR" within the meaning of the agreed-upon construction. That approach was consistent with well-settled law that whether a claim covers a given embodiment, for purposes of infringement or validity, is a question of fact. *Amgen, Inc. v. Hoechst Marion Roussel,* 314 F.3d 1313, 1339 (Fed. Cir. 2003) (infringement); *In re Antor Media Corp.*, 689 F.3d 1282, 1287 (Fed. Cir. 2012) (anticipation).

Based on what is now an acknowledged error, the district court found that "NR in milk … enhances NAD+ biosynthesis." (Appx37; Op. 9 n.4.) That finding, in turn, led the district court to reject ChromaDex's argument that characteristics of isolated NR that allow it to enhance NAD+ biosynthesis, such as bioavailability, make isolated NR markedly different from NR in milk. (*Id.*) The district court's error was, accordingly, anything but harmless. It practically guaranteed that the district court would not examine facts that ChromaDex might offer regarding the unique characteristics of isolated NR.

If ChromaDex were given the opportunity to present facts on the differences between the claimed embodiments and naturally occurring products, and succeeded in establishing that the "isolated NR" of the claims must include sufficiently pure NR to boost NAD+ biosynthesis, that alone would distinguish the claims from naturally occurring NR and make them markedly different. As Elysium's expert admitted, NR in milk is not biologically available because lactalbumin whey protein binds to the NR in milk and renders it inactive. (Appx10205, 20:2-8.) Thus, the bioavailability of isolated NR is in stark contrast to the biological inactivity of NR in milk, and makes claims requiring isolated NR for oral administration to increase NAD+ biosynthesis markedly different from any "product of nature."

That tryptophan may also produce minor increases in NAD+ biosynthesis does not eradicate the differences between isolated and natural NR. And treating a

patient using isolated NR to increase NAD+ biosynthesis is markedly different from anything that milk can do, and creates the potential for significant utility that milk does not have. *Natural Alternatives*, 918 F.3d at 1348-49 (treatment composition containing beta alanine was patent eligible because it had functional capabilities lacking in naturally occurring beta alanine).

As the Supreme Court explained in *Funk Brothers*, a relevant inquiry for claims that combine naturally occurring ingredients is whether the "combination of species ... produces … enlargement of the range of their utility." *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 131 (1948). Here, the combination of isolated NR with tryptophan enlarges the range of utility in boosting NAD+ biosynthesis over the combination of naturally occurring NR and tryptophan in milk, supporting patent eligibility. *Id.*

As in *Chakrabarty*, 447 U.S. at 305, 309-10, and unlike *Myriad,* 569 U.S. at 590-91, Dr. Brenner changed a naturally occurring substance, NR, to give it new properties (the ability to improve human health by increasing NAD+ biosynthesis) that naturally occurring NR did not have. "Isolated NR" is fundamentally different from "a new mineral discovered in the earth or a new plant found in the wild," which are not patentable subject matter. *Chakrabarty*, 447 U.S. at 309. The fact that the claims add further components (such as, optionally, tryptophan) to create a treatment formulation does not make them *less* patent eligible.

3. Additional Claim Elements Raise Further Questions Of Fact Not Amenable To Resolution On Summary Judgment

In finding that the claims "read on milk" (except that milk does not include isolated NR), the panel made additional factual inferences that are not compelled, or even supported, by the record. For example, the panel found that milk is an "admixture" of NR and one of tryptophan, nicotinic acid and nicotinamide with a sugar (Op. 5), without any evidence that any components are added together or mixed in forming milk. Milk is simply a naturally occurring product; nothing is "admixed" to create it, unlike chocolate milk, which is an admixture of milk and chocolate syrup. Likewise, the panel found that milk is "formulated" for oral administration (*id.*), but milk is not "formulated" at all. Water or orange juice also can be consumed orally, but that does not mean they are "formulated" for oral administration. Indeed, the panel's only support for these propositions was ChromaDex's admission that milk contains lactose and can be consumed orally. (Op. 5-6, citing Appx10096.) That does not prove that milk is an "admixture" or "formulated." And because a Section 101 analysis must consider the claims as a whole, *Diamond v. Diehr*, 450 U.S. 175, 188 (1981), the panel erred in resolving against ChromaDex factual questions regarding these additional claim elements that raised at least disputed issues of fact.

B. The Panel Erred By Foregoing A Full Examination Under *Alice/Mayo* Step Two, And Ignoring Significant Evidence Of An Inventive Concept By Dr. Brenner

1. The *Alice/Mayo* Two-Step Framework Applies In All Cases Involving Patent Ineligible Concepts, Including Those Involving Natural Phenomena

The Supreme Court has described *Alice/Mayo* step two as the search for an "inventive concept." *Alice*, 573 U.S. at 217-218, citing *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 72 (2012). The panel stated that it was not necessary to reach step two because the Supreme Court in *Myriad* applied *Chakrabarty's* "markedly different characteristics" test for claims directed to "natural phenomena," without applying step two. (Op. 9.) *Alice*, however, compels a contrary conclusion.

In *Alice*, decided after *Myriad*, the Supreme Court reaffirmed the two-step test set forth in *Mayo*. In describing the two-step framework, the Court explained that it applied to "patents that claim laws of nature, ***natural phenomena***, and abstract ideas …." *Alice*, 573 U.S. at 217 (emphasis supplied). The present case involves a claim to a purported "product of nature," which falls within the category of natural phenomena. Nowhere did the Court in *Alice* exempt such cases from the two-step framework. Rather, the Court held that it applies to claims involving all patent-ineligible concepts. *Id.*

Alice cited and discussed *Myriad*, without suggesting that *Myriad* involved a wholly different analytical framework, and without stating that natural product cases should be treated differently than computer cases such as *Alice*. *Alice*, 573 U.S. at 216, 224. *Myriad* likewise did not say that it was departing from *Mayo*. To the contrary, the Supreme Court's analysis included consideration of whether Myriad's claims included an inventive concept. As the Court explained: "Myriad did not create anything. To be sure, it found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention." *Myriad*, 569 U.S. at 591. Thus, the Court evaluated whether an inventive concept could preserve patent eligibility, consistent with *Mayo* step two.

This Court has also endorsed the two-step framework for natural products cases. In *Natural Alternatives* this Court relied on *Chakrabarty* to assist with the determination of whether the claims were directed to a natural product in step one, but then also analyzed step two for all claims. *Natural Alternatives*, 918 F.3d at 1347, 1349.

Accordingly, there is no basis to limit cases involving natural products or other natural phenomena to a one-step analysis under *Chakrabarty* and *Myriad*.

2. Dr. Brenner's Claims Reflect An Inventive Concept That Was Not Well-Understood, Routine Or Conventional

At *Alice/Mayo* step two, if the claim limitations "involve more than performance of 'well-understood, routine, [and] conventional activities previously

known to the industry,'" the claims satisfy the second step and are patent eligible. *Berkheimer*, 881 F.3d at 1367, citing *Content Extraction & Transmission LLC v. Wells Fargo Bank, Nat'l Ass'n*, 776 F.3d 1343, 1347-48 (Fed. Cir. 2014), quoting *Alice*, 573 U.S. at 225. Whether a combination of claim elements is well-understood, routine and conventional to a skilled artisan is a question of fact. *Berkheimer*, 881 F.3d at 1368, 1370 (reversing summary judgment of patent ineligibility because of fact questions concerning whether claims perform well-understood, routine and conventional activities).

Having decided that consideration of step two was not required, the panel conducted only a brief discussion of step two that failed to consider material evidence bearing on the critical question of whether the claims, taken as a whole, represented well-understood, routine and conventional activities. The record evidence showed that they did not.

As an initial matter, the panel's conclusion (Op. 9-10) that Dr. Brenner did no more than discover and then claim a natural principle — *i.e.*, something that already existed in nature — was incorrect. According to the panel, "recognizing the utility of NR is nothing more than recognizing a natural phenomenon, which is not inventive." (*Id.* 10.) But NR in nature did ***not*** have utility. The NR in milk is inactive, as discussed above. It is also present in minute quantities that would be ineffective no matter what. (Appx10162-63, Appx10166, Appx10174-10175,

Appx10245.) Thus, NR in milk does not increase NAD+ biosynthesis upon oral administration, nor does it improve health or treat disease by means of elevating NAD+ levels. (Appx10166, Appx10205, 20:2-8.)

In contrast, it is undisputed that isolated NR, which Dr. Brenner invented, was ***not*** available in nature. Under any view of the claims as construed, isolated NR must be separated from impurities, which necessarily has not occurred in the natural source of NR. And, as explained above, isolated NR increases NAD+ biosynthesis when administered orally because it contains at least some pure NR, which is bioactive. Thus, the notion that Dr. Brenner simply appreciated a property or functional capability that already occurred in nature, and drafted a claim to the patent ineligible concept itself — which was the basis for the panel's determination that the claims would fail at step two (Op. 9-10) — was incorrect.

These circumstances distinguish this case in critical respects from decisions like *Myriad*. In *Myriad*, the isolated product — a strand of DNA — was identical functionally to the DNA that occurs in nature. It had the same nucleotide sequence and was capable of producing the same amino acid sequence as natural DNA. Nothing was different about the natural DNA corresponding to the claimed sequences, except that it had not been isolated. *Myriad*, 569 U.S. at 584, 590. Not so here. The natural NR in milk would not work, whereas the isolated NR would work to increase NAD+ biosynthesis.

Furthermore, Dr. Brenner's claimed invention was neither well-understood, routine, nor conventional. Before Dr. Brenner' work, persons of skill in the art were not even aware that NR could be isolated and then used as an orally available vitamin. (Appx41, citing Appx10180, ¶ 164.) Far from being well-understood, ways of making NR orally bioavailable were not known at all. Because naturally occurring NR did not work to increase NAD+ biosynthesis and was not known to have utility in treating disease or improving human health, isolating and formulating NR for oral administration to achieve those results flew in the face of conventional wisdom. Dr. Brenner's claims, which incorporate the requirements of isolating NR and formulating it for oral administration in a composition to increase NAD+ biosynthesis, were the opposite of routine. (*Id.*)

In *Mayo*, the claims failed step two because the steps of administering the drug, measuring metabolite levels, and adjusting dosage, were already being performed by those in the field. *Mayo*, 566 U.S. at 72-73. Likewise, in *Ariosa*, the steps of preparing, amplifying, and detecting genetic sequences were already being done. *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1377-78 (Fed. Cir. 2015). Here, no one was using any form of NR (isolated or not) to provide therapeutic benefits through formulation and oral administration.

In *CellzDirect*, 827 F.3d at 1042, the patentee incorporated the natural law that hepatocytes can survive multiple freeze-thaw cycles into a claimed method for

freezing and thawing hepatocytes at least two times. Even though the individual steps of freezing and thawing were well known, *id.* at 1051, the claims were patent eligible under step two because the prior art had only disclosed a single freeze-thaw cycle. *Id.* Just as freezing and thawing twice went against prevailing wisdom in *CellzDirect*, *id.*, here, preparing an oral formulation of NR that increases NAD+ biosynthesis defied conventional wisdom. As *CellzDirect* explains, incorporating features that were simply not known in the art "can hardly be considered routine or conventional … even though it was the inventor's discovery of something natural that led them to do so." *Id.*

Elysium submitted no contrary facts to ChromaDex's evidence that the claimed invention was not well-understood, routine or conventional. It merely noted that the claims do not recite any inventive isolation techniques, which is beside the point. At the very least, the facts advanced by ChromaDex create a genuine issue of material fact on *Alice/Mayo* step two that precludes the grant of summary judgment.

V. CONCLUSION

If the panel's decision stands, its impact will extend far beyond this case, creating uncertainty in the industry and for lower courts. And the creative efforts of researchers who would seek to develop new therapeutic formulations from naturally occurring substances, by modifying those substances to exhibit characteristics and

properties not present in the substances as they exist in nature, will be chilled, as they will be denied their day in court to establish that their inventions are patentable.

ChromaDex thus respectfully requests rehearing by the panel or by the Court *en banc*, and reversal of the holding of invalidity under 35 U.S.C. § 101.

Respectfully submitted,

LERNER, DAVID, LITTENBERG, KRUMHOLZ & MENTLIK, LLP

Attorneys for Plaintiffs-Appellants ChromaDex, Inc. and Trustees of Dartmouth College

Dated: March 15, 2023

By: /s/ William L. Mentlik
William L. Mentlik

ADDENDUM

United States Court of Appeals for the Federal Circuit

CHROMADEX, INC., TRUSTEES OF DARTMOUTH COLLEGE,
Plaintiffs-Appellants

v.

ELYSIUM HEALTH, INC.,
Defendant-Appellee

2022-1116

Appeal from the United States District Court for the District of Delaware in No. 1:18-cv-01434-CFC-JLH, Chief Judge Colm F. Connolly.

Decided: February 13, 2023

WILLIAM L. MENTLIK, Lerner, David, Littenberg, Krumholz & Mentlik, LLP, Cranford, NJ, argued for plaintiffs-appellants. Also represented by RUSSELL W. FAEGENBURG, STEPHEN F. ROTH; ROBERT JASON FOWLER, CHRISTOPHER NEIL SIPES, ASHLEY MARIE WINKLER, Covington & Burling LLP, Washington, DC.

JEREMY YOUNKIN, Foley Hoag LLP, Boston, MA, argued for defendant-appellee. Also represented by DONALD ROSS WARE.

Before PROST, CHEN, and STOLL, *Circuit Judges*.

PROST, *Circuit Judge*.

ChromaDex, Inc. ("ChromaDex") and the Trustees of Dartmouth College ("Dartmouth") (collectively, "Appellants") appeal the decision of the U.S. District Court for the District of Delaware granting Elysium Health, Inc.'s ("Elysium") motion for summary judgment that the asserted claims of U.S. Patent No. 8,197,807 ("the '807 patent") are directed to unpatentable subject matter under 35 U.S.C. § 101.[1] We affirm.

BACKGROUND

I

The '807 patent is directed to dietary supplements containing isolated nicotinamide riboside ("NR"), a form of vitamin B3 naturally present—in non-isolated form—in cow's milk and other products.[2] *See* '807 patent col. 27 ll. 42–45. Animal cells convert ingested NR into the coenzyme nicotinamide adenine dinucleotide, or NAD+. NAD+ deficiencies can cause diseases in both animals and humans.

The asserted claims are claims 1–3 of the '807 patent. Representative claim 1 recites:

> 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

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[1] Appellants also sought review of the district court's invalidation of claim 2 of U.S. Patent No. 8,383,086. The voluntary dismissal of a related appeal mooted that part of the case.

[2] For the sake of brevity, we use the word "milk" in the rest of this opinion to describe natural cow's milk.

> 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 increased NAD+ biosynthesis upon oral administration.

II

ChromaDex sells, among other products, dietary supplements in the form of pharmaceutical compositions of NR embodying the '807 patent. It licenses the patent from Dartmouth. Appellants sued Elysium, a former ChromaDex customer, for patent infringement in September 2018. The district court construed several claim terms; relevant here, the court construed "isolated [NR]" to mean "[NR] that is separated or substantially free from at least some other components associated with the source of [NR]." J.A. 22.

Elysium moved for summary judgment, arguing that the asserted claims were invalid under 35 U.S.C. § 101, and the district court granted the motion. *See ChromaDex, Inc. v. Elysium Health, Inc.*, 561 F. Supp. 3d 460 (D. Del. 2021). The district court concluded that the claims were directed to a natural phenomenon, namely, "compositions comprising isolated [NR], a naturally occurring vitamin present in cow milk." *Id.* at 464 (cleaned up). It rejected ChromaDex's argument that the characteristics of isolated NR purportedly different from naturally occurring NR—stability, bioavailability, sufficient purity, and therapeutic efficacy—render the claims patent-eligible, observing that none of those characteristics were part of the claims. *Id.* at 465. It concluded that "the decision to create an oral formulation of NR after discovering that NR is orally bioavailable is simply applying a patent-ineligible law of nature." *Id.* at 467.

The district court entered judgment of invalidity, and this appeal followed.[3] We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

I

We review the district court's grant of summary judgment under the law of the regional circuit, here the Third Circuit, which reviews such issues de novo. *Junker v. Med. Components, Inc.*, 25 F.4th 1027, 1032 (Fed. Cir. 2022) (citing *Gonzalez v. Sec'y of Dep't of Homeland Sec.*, 678 F.3d 254, 257 (3d Cir. 2012)). Summary judgment is appropriate when, drawing all reasonable inferences in the nonmoving party's favor, "there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a); *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986). Eligibility under § 101 may involve questions of fact but is, ultimately, a question of law that we review de novo. *Nat. Alts. Int'l, Inc. v. Creative Compounds, LLC*, 918 F.3d 1338, 1342 (Fed. Cir. 2019); *Interval Licensing LLC v. AOL, Inc.*, 896 F.3d 1335, 1342 (Fed. Cir. 2018).

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a

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[3] Appellants also challenge the district court's orders granting-in-part Elysium's motion to dismiss for lack of standing and denying its motion for leave to amend, as well as one of its claim constructions. The district court's standing order only dismissed claims of infringement based on activities alleged to have occurred on or after March 13, 2017, *see* J.A. 16–17, so the eligibility issue remained live. Because we affirm the district court's invalidity judgment, we do not reach either the standing or the claim construction issues.

patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. "Laws of nature, natural phenomena, and abstract ideas," in contrast, "are not patentable." *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 589 (2013).

II

The parties agree that NR is naturally present in milk. It is undisputed that milk is a naturally occurring product that is not patent eligible. The parties also acknowledge that milk contains tryptophan and lactose, a sugar. And no one disputes that the tryptophan in milk treats NAD+ deficiencies. The claims are very broad and read on milk with only one difference as shown:

Element	**Milk**
[1p] "A composition comprising"	Milk is a composition.
[1a] "isolated [NR]"	Milk contains NR, but the NR is not isolated. J.A. 10095.
[1b] "in combination with one or more of tryptophan, nicotinic acid, or nicotinamide"	Milk contains tryptophan and nicotinamide. J.A. 10095.
[1c] "wherein said combination is an 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	Milk is an admixture containing a sugar (lactose). J.A. 10096

saline, Ringer's solution, ethyl alcohol, polyester, polycarbonate, or polyanhydride"	
[1d] "wherein said composition is formulated for oral administration"	Milk is formulated for oral administration. *See* J.A. 10096.
[1e] "and increases NAD+ biosynthesis upon oral administration."	Milk (through tryptophan) increases NAD+ biosynthesis upon consumption. *See* J.A. 10096.

So the only difference between at least one embodiment within the scope of the claims and natural milk is that the NR in the former is isolated.

The Supreme Court's decisions in *Myriad* and *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980), apply here. In *Chakrabarty*, the Court found eligible claims to a genetically engineered bacterium "capable of breaking down multiple components of crude oil." 447 U.S. at 305, 318. No naturally occurring bacteria possessed the same property. *Id.* Accordingly, in the Court's view, the "claim [was] not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity having a distinctive name, character and use." *Id.* at 309–10 (cleaned up). Because "the patentee ha[d] produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility," the Court upheld the claims. *Id.* at 310.

As in *Myriad*, under the circumstances presented here, the act of isolating the NR compared to how NR naturally exists in milk is not sufficient, on its own, to confer patent eligibility. *See Myriad*, 569 U.S. at 590–93. The claimed compositions remain indistinguishable from natural milk

because, other than separation from some other components, the isolated NR is no different structurally or functionally from its natural counterpart in milk. *Chakrabarty* defines the inquiry: to be patentable, the claimed composition must "ha[ve] markedly different characteristics and have the potential for significant utility." 447 U.S. at 310. Milk, like the claimed compositions, undisputedly "increase[s] NAD+ biosynthesis" upon oral administration. The claimed compositions do not exhibit markedly different characteristics from natural milk and are, therefore, invalid for claiming a patent-ineligible product of nature. *Cf. Myriad*, 569 U.S. at 579 (concluding "that a naturally occurring DNA segment is *a product of nature* and not patent eligible merely because it has been isolated" (emphasis added)).

Our *Natural Alternatives* decision is particularly instructive. There, we upheld, at the motion-to-dismiss stage, claims directed to dietary supplements containing beta-alanine. *See* 918 F.3d at 1341. We concluded that the patents there claimed "specific treatment formulations that incorporate[d] natural products" and that those formulations "ha[d] different characteristics and c[ould] be used in a manner that beta-alanine as it appears in nature cannot." *Id.* at 1348. Specifically, the "natural products ha[d] been isolated and then incorporated into a dosage form"—"between about 0.4 grams to 16 grams"—"with particular characteristics"—namely, to "effectively increase[] athletic performance." *Id.* at 1348–49. Those markedly different characteristics distinguished the claimed supplements from natural beta-alanine and preserved the claims' validity. *Id.* at 1349.

Here, in contrast, the asserted claims do not have characteristics markedly different from milk. Both the claimed compositions and milk "increase[] NAD+ biosynthesis upon oral administration." Appellants argue that the claimed compositions are advantageous over milk because the isolation of NR allows for significantly more NAD+

biosynthesis than is found in milk and that the large quantity of NR itself *can alone* increase NAD+ biosynthesis. But the asserted claims do not require any minimum quantity of isolated NR. Nor do these claims attribute the claimed increase in NAD+ biosynthesis to the isolated NR, requiring only that the *composition* increase NAD+ production. Because milk increases NAD+ biosynthesis, the claimed compositions do not possess characteristics markedly different from those found in nature. To be sure, the claims cover several different composition embodiments, some of which are structurally different from milk. However, as noted above, the claims also encompass—as both parties agree—at least one embodiment that covers milk, except that the NR element is "isolated." Because the claims are broad enough to encompass a product of nature, it is invalid under § 101.

Appellants nonetheless argue that the claims, in fact, possess markedly different characteristics that render them patent-eligible. *See* Appellants' Br. 28–31. They base this argument on two main points: (1) "NR is found in milk in only trace amounts," *i.e.*, one part per million; and (2) "what little NR is found in milk is not bioavailable" because it is bound to the lactalbumin whey protein. *Id.* at 29.[4] The problem for Appellants is two-fold. First, as

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[4] Appellants also identify a factual error in the district court's opinion. The court stated that it was "undisputed that NR in milk . . . enhances NAD+ biosynthesis." *ChromaDex*, 561 F. Supp. 3d at 465. Appellants correctly point out that the NR in milk does not enhance NAD+ biosynthesis, that it argued as much to the district court, and that Elysium conceded the point. *See, e.g.*, J.A. 10245 (Elysium admitting that "one can't eat enough of anything [containing trace amounts of NR] to boost NAD+ levels"). That error was harmless, however, because the claims do not require that the NR, specifically, increase NAD+

discussed above, milk increases NAD+ biosynthesis (albeit because it contains tryptophan rather than because of the trace amounts of NR), and that is the only therapeutic effect that the claims require. Second, the claims simply do not reflect the distinctions Appellants rely on: they do not require any specific quantity of isolated NR, and the district court's construction for "isolated [NR]," which Appellants do not challenge on appeal, does not require that the NR be separated from the lactalbumin whey protein but only from "*some* of the other components associated with the source of [NR]." J.A. 22 (emphasis added). The claims, therefore, do not necessarily require that the isolated NR be bioavailable, meaning that the claimed compositions do not necessarily possess markedly different characteristics from milk, as they must to be patent-eligible.

We conclude that the asserted claims lack markedly different characteristics from milk. They claim a product of nature and are not patent eligible.

III

The inquiry could end here—the Supreme Court in *Myriad* relied on *Chakrabarty*'s "markedly different characteristics" framework for analyzing whether the claimed compositions there were directed to a natural phenomenon; the Court never applied the *Alice*/*Mayo* two-step framework despite deciding the case after *Mayo*. *See Myriad*, 569 U.S. at 593–95; *see also Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 573 U.S. 208, 217 (2014); *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 77–80 (2012). But if resort to *Alice*/*Mayo* is necessary, then at step one we conclude the asserted claims are directed to a product of nature for the reasons stated above, and at step two the claims lack an inventive step because they are directed to

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biosynthesis; it is enough if the claimed composition accomplishes that objective, and milk does so.

nothing more than compositions that increase NAD+ biosynthesis, which is the very natural principle that renders the claims patent-ineligible.[5]

Appellants identify only two possible inventive steps: "[1] recognizing the utility of NR for enhancing health and well-being and [2] the wisdom of *isolating* the NR to provide concentrations higher than what occur naturally." Appellants' Br. 31 (emphasis original). But recognizing the utility of NR is nothing more than recognizing a natural phenomenon, which is not inventive. *See Myriad*, 569 U.S. at 591. And the act of isolating the NR by itself, no matter how difficult or brilliant it may have been (although the specification makes clear that it was conventional), similarly does not turn an otherwise patent-ineligible product of nature into a patentable invention. *See id.* So the claims would likewise fail at step two.

CONCLUSION

We have considered Appellants' remaining arguments and find them unpersuasive. As Appellants conceded at oral argument, our resolution of the patent-eligibility issue moots the standing question. For the reasons set forth

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[5] In *Natural Alternatives*, we purported to analyze the patent-eligibility of the claimed compositions under *Alice*/*Mayo*'s two-step framework. *See Nat. Alts.*, 918 F.3d at 1342, 1348–49. But because we concluded that factual allegations relating to the claimed compositions' markedly different characteristics from natural beta-alanine precluded judgment on the pleadings, the analysis functionally examined only the *Chakrabarty* question. *See id.* at 1348. Indeed, in one prior case, we analyzed composition-of-matter claims under *Myriad* and *Chakrabarty* but analyzed method claims under *Mayo*. *Compare In re BRCA1- and BRCA2*, 774 F.3d 755, 759–61 (Fed. Cir. 2014), *with id.* at 761–765.

above, we affirm the district court's judgment that the asserted claims of the '807 patent are invalid under 35 U.S.C. § 101.

AFFIRMED

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

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