IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CHROMADEX, INC. and TRUSTEES OF DARTMOUTH COLLEGE, Plaintiffs, v. ELYSIUM HEALTH, INC., Defendant.	Civil Action No. 18-1434-CFC [redacted]

PLAINTIFFS' RESPONSE TO ELYSIUM'S *DAUBERT* MOTION (NO. 1) TO EXCLUDE OPINIONS OF ROBERT W. SOBOL AND ROBERT D. LARSEN (D.I. 220)

Dated: May 14, 2021

OF COUNSEL:
Christopher N. Sipes
R. Jason Fowler
Ashley Winkler
Emily Mondry
Evan S. Krygowski
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street NW
Washington, DC 20001
(202) 662-6000
csipes@cov.com
jfowler@cov.com
awinkler@cov.com
emondry@cov.com
ekrygowski@cov.com

YOUNG CONAWAY STARGATT & TAYLOR, LLP

Adam W. Poff (No. 3990)
Pilar G. Kraman (No. 5199)
Rodney Square
1000 North King Street
Wilmington, DE 19801
(302) 571-6600
apoff@ycst.com
pkraman@ycst.com

Counsel for Plaintiffs ChromaDex, Inc. and Trustees of Dartmouth College

Patrick Flynn
COVINGTON & BURLING LLP
3000 El Camino Real
5 Palo Alto Square, 10th Floor
Palo Alto, CA 94306
(650) 632-4732
pflynn@cov.com

James F. Haley, Jr.
HALEY GUILIANO LLP
75 Broad Street, Suite 1000
New York, NY 10004
(646) 973-2500
james.haley@hglaw.com

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

TABLE OF ABBREVIATIONS

Abbreviation	Description
The Dartmouth Patents	U.S. Patent Nos. 8,383,086 and 8,197,807
The '807 Patent	U.S. Patent No. 8,197,807
The '086 Patent	U.S. Patent No. 8,383,086
The Asserted Claims	Claims 1–3 of the '807 Patent and Claim 2 of the '086 Patent
ChromaDex	Plaintiff ChromaDex, Inc.
Dartmouth	Plaintiff Trustees of Dartmouth College
Plaintiffs	collectively, Plaintiffs ChromaDex, Inc. and Trustees of Dartmouth College
Elysium	Defendant Elysium Health, Inc.
NR	nicotinamide riboside
isolated NR	isolated nicotinamide riboside
POSA	person of ordinary skill in the art
PTAB	Patent Trial and Appeal Board
D.I. 220	Opening Brief in Support of Elysium's *Daubert* Motion (No. 1) to Exclude Opinions of Robert W. Sobol and Robert D. Larsen
Ex.	Exhibit to Declaration of Adam W. Poff in Support of Plaintiffs' Response to Elysium's *Daubert* Motion (No. 1) to Exclude Opinions of Robert W. Sobol and Robert D. Larsen

Plaintiffs' experts, Drs. Sobol and Larsen, applied the Court's constructions in forming and expressing their opinions. For every opinion Elysium challenges in its *Daubert* motion no. 1, Drs. Sobol and Larsen are clear that they understood and relied on the proper constructions. "That [Elysium] disagrees with [Plaintiffs'] experts' ***application*** of the claim construction goes to the weight to be given to the testimony, not its admissibility." *Vehicle IP, LLC v. AT&T Mobility LLC*, 227 F. Supp. 3d 319, 326 (D. Del. 2016) (emphasis added); *see also Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 763 F. Supp. 2d 671, 695 (D. Del. 2010) ("The implications of the Court's construction are matters on which the parties' experts may opine, and may disagree.").

I. The Court should not exclude Dr. Sobol's opinion that the Asserted Claims are directed to patentable subject matter.

Elysium seeks to exclude all of Dr. Sobol's opinions about the patentability under § 101 because Dr. Sobol allegedly imposes a "quantity requirement on the amount of NR in the claimed compositions." D.I. 220, 2-3. Elysium also alleges that Dr. Sobol's analysis improperly required that the isolated NR, not the claimed compositions, increases NAD^+ biosynthesis. *Id.*, 3.

As Elysium admits, however, Dr. Sobol stated that the claimed compositions "don't speak to a threshold amount [of isolated NR]," D.I. 220, 3 (quoting Sobol Dep. (Ex. 3), 199), and that his analysis does not require the isolated NR to increase NAD^+ biosynthesis, *id.*, 4 (citing Ex. 3, 204-05). Simply put, Dr. Sobol applied the

correct constructions. *See, e.g.*, Ex. 3, 209:4-16 (no quantity requirement); *id.*, 203:3-4 ("the composition is what is increasing NAD biosynthesis").[1]

Despite clear evidence that Dr. Sobol did not impose additional claim requirements, Elysium misconstrues a single paragraph from Dr. Sobol's report to argue that "improper constructions infect the entirety of [Dr. Sobol's] opinions." D.I. 220, 2 (quoting Ex. 4, ¶ 142). Elysium is wrong. Dr. Sobol does not apply improper constructions in ¶ 142, but instead merely identifies ways in which the claimed compositions have "different characteristics and the potential for significant utility" beyond NR as it appears in milk. *See Natural Alternatives Int'l, Inc. v. Creative Compounds, LLC*, 918 F.3d 1338, 1348 (Fed. Cir. 2019).

This is a disputed issue. Elysium assumes without evidence that milk delivers NR upon oral administration. Dr. Sobol explains that it does not, and that to achieve the benefits of the claimed compositions the NR must instead be isolated and formulated for oral administration. Ex. 4, ¶ 143; *see also id.*, ¶¶ 329-334. Strikingly, even Dr. Adams: (1) acknowledges that he found no flaw in Dr. Sobol's calculation of the trace amount of NR in milk, Ex. 6, 129:5-7; (2) agrees that much of the NR in milk is not bioavailable, and thus not active, because it is bound to whey protein, *id.*,

[1] Elysium also fails to acknowledge that the only NAD^+ precursor recited in claim 2 of the '086 Patent is NR. Thus, whether isolated NR increases NAD^+ biosynthesis, and thus improves or prolongs the health or well-being of the recipient, is clearly relevant to the pharmaceutical composition of claim 2 of the '086 Patent.

119:22-120:12; and (3) admits that any NR in the water fraction of milk will be subject to hydrolytic degradation, *id.*, 122:22-124:9. Elysium itself represents to consumers that while NR "can be found in trace amounts in various foods, though, one can't eat enough of anything to boost NAD+ levels," Ex. 7, CDXDE_000165405, and has even filed patent applications claiming the use of compositions of NR to treat health disorders that cannot be treated by simply drinking milk, *see* Ex. 4, ¶¶ 66-72, 179-80.

Elysium's disagreement with Dr. Sobol's analysis of the differences between the claimed compositions and milk is not a claim-construction issue. Dr. Sobol instead disputes Dr. Adams' assumption that milk and the claimed compositions have the same characteristics and potential utility. This is entirely proper in the context of a patentability determination. *Nat. Alternatives*, 918 F.3d at 1348.

II. The Court should not exclude Dr. Sobol's opinion that skim milk and buttermilk do not contain "isolated NR."

The Court construed "isolated nicotinamide riboside" as "nicotinamide riboside that is separated or substantially free from at least some of the other components associated with the source of the nicotinamide riboside." The Court clarified during the *Markman* hearing: "[W]e're going to have experts telling me whether something is substantially free or not. … [W]hat's the level of impurity essentially. … [T]hat seems to me to probably be the right thing to do." Ex. 8, 29:14-22; *see also id.*, 30:12-14 ("You're going to argue over what substantially free is and

[the jury is] going to look at the two competing experts and decide who is more credible."). This is precisely what Dr. Sobol's opinions go to.

Specifically, Dr. Sobol calculated that the concentration of NR in skim milk is 0.000059% w/w, or 0.59 ppm, and concluded that this exceedingly low concentration of NR is not "isolated NR" within the meaning of the claims because it is not separated or substantially free of other components. *See, e.g.*, Ex. 4, ¶¶ 279, 280, 312. Dr. Sobol never adds an amount or purity requirement to the claims, as Elysium alleges (D.I. 220, 5), and expressly states that his analysis does not rely on any minimum level of NR from the claims. Ex. 4, ¶¶ 280, 313.

Dr. Sobol shows that skim milk does not contain "isolated NR" by demonstrating that skim milk has a lower concentration of NR (0.000059% w/w) than whole milk (0.000107% w/w), thus demonstrating that skimming milk does not separate NR from other components or otherwise concentrate it. *Id.*, ¶ 282. Dr. Sobol also shows that the trace amount of NR in skim milk is approximately 420,000 times less than the minimum concentration of an isolated polypeptide identified in the specification (*id.*, ¶ 280), and about 1,500 times less than the 0.1% that the specification teaches should be contained in an NR composition for oral administration (*id.*, ¶ 293).

Dr. Adams assumes, without evidentiary support, that the amount of NR in buttermilk is the same as the amount of NR in whole milk. Ex. 9, ¶ 255. Although

Dr. Sobol disagreed with Dr. Adams' assumption (Ex. 4, ¶¶ 347, 355), Dr. Sobol rebutted the assumption at face value and again concluded that the exceedingly low concentration of NR (0.000107% w/w) is not "isolated NR" within the meaning of the claims. *Id.*, ¶ 345. As with skim milk, Dr. Sobol did not impose an amount or purity requirement. *E.g.*, *id.*, ¶¶ 344-45.

Dr. Sobol observed that the NR in milk products has not been shown to increase NAD^+ biosynthesis upon oral administration. *E.g.*, *id.*, ¶¶ 328, 360. Notably, the literature cited by Dr. Adams for the presence of NR in skim milk, Trammell I, teaches that the NR is bound to whey protein, and thus not biologically available upon oral administration. *See, e.g.*, Ex. 6, 120:2-8; Ex. 4, ¶¶ 332, 350. These observations do not modify the Court's construction to require "isolated NR" to increase NAD^+ biosynthesis, as Elysium alleges. D.I. 220, 7. Rather, they further support Dr. Sobol's opinion that the trace amount of NR in milk is not isolated.

It is Elysium's expert that flouts the Court's claim construction. For example, Dr. Adams found no flaw in Dr. Sobol's calculations of the trace amounts of NR in skim milk, but nevertheless concluded that it contains "isolated NR" because skimming milk removes some amount of fat from whole milk, even where the overall concentration of the NR in skim milk is reduced or unchanged from whole

milk. Ex. 10, ¶¶ 61-62, 65; *see also id.*, ¶ 109 (similar conclusion and reasoning for buttermilk). This is the opposite of isolation.

Thus, the experts now dispute whether the NR in skim milk and buttermilk is "separated or substantially free from at least some of the other components associated with the source of the nicotinamide riboside"—a factual dispute this Court predicted during the *Markman* hearing. Dr. Sobol's § 102 opinions about "isolated NR" should not be excluded, and the jury should "look at the two competing experts and decide who is more credible." Ex. 8, 30:12-14.

III. The Court should not exclude the opinions of Drs. Sobol and Larsen that "derivatives" of NR are salts and esters of NR like those described in the patents that deliver the NR moiety following administration

The Court construed "nicotinamide riboside" as "nicotinamide riboside or a derivative (e.g., L-valine or L-phenylalanine esters) of nicotinamide riboside." The experts dispute application of this claim construction, with Elysium's expert ignoring the exemplary derivatives expressly set forth in the construction, as well as the specification's description of their function. Regardless, these factual disputes are not grounds to exclude testimony from Plaintiffs' experts, but instead are fodder for cross-examination. *Vehicle IP*, 227 F. Supp. 3d at 326.

Drs. Sobol and Larsen opined that a POSA reading the patent specification would understand a "derivative (e.g., L-valine or L-phenylalanine esters)" to have shared characteristics, such as being a salt or ester of similar structure. *E.g.*, Ex. 5,

¶ 26; Ex. 4, ¶¶ 1002-03. Notably, Dr. Adams took a similar approach during claim construction, representing to the Court that "[t]wo common ways of derivatizing a compound for oral administration as of 2004 were creating salts and ester forms of the compound" and that "[a] person of ordinary skill in the art, reading the claims in view of the specification, would understand the 'nicotinamide riboside' in the claims would include nicotinamide riboside … as well as derivatives of nicotinamide riboside (including at least both salts and esters)." Ex. 11, ¶¶ 13, 18. Dr. Adams did not suggest, during claim construction, that the claims encompass "derivatives" of NR beyond salts and esters like the L-valine and L-phenylalanine ones. *See* Ex. 6, 256:19-259:22 (conceding specification describes certain salt and ester derivatives having common structural and functional properties); '807 patent, 29:4-8. Drs. Sobol and Larsen's opinions concerning the compounds constituting a "derivative (e.g., L-valine or L-phenylalanine esters)" of NR are fully consistent with the claim construction record.

By contrast, it is Elysium and Dr. Adams that now abandon the Court's claim construction and the existing record. Dr. Adams simply ignores the portion of the claim construction referring to the L-valine or L-phenylalanine esters and makes no effort to apply a POSA's understanding of the patent specification's description of the NR derivatives. *See* Ex. 6, 259:14-260:3, 261:11-262:4, 265:21-266:2. He maintains that a "derivative" is any compound that contains the NR structure

substituted with any "arbitrary substituent" at any position, which leads to his conclusion that there are billions of them. *See, e.g.*, Ex. 9, ¶ 784; Ex. 10, ¶ 279.

Drs. Larsen and Sobol disagreed with Dr. Adams for multiple reasons. For example, Dr. Adams' interpretation treats compounds such as NMN and NAD^+ as "nicotinamide riboside" under the Dartmouth Patents, even though the patents expressly distinguish those compounds from NR. Ex. 4, ¶ 1001 (citing '807 Patent, 8:9-11). Further illustrating his error, Dr. Adams' broad and open-ended view of NR "derivatives" leads him to the impossible and contradictory conclusions that NMN is both (1) a "derivative" of NR within the scope of the claims, Ex. 9, ¶ 313, and also (2) a non-infringing alternative to the claimed compositions comprising isolated NR, Ex. 12, ¶¶ 79, 83. *See* Ex. 7, 184:21-186:21. Moreover, many compounds that Dr. Adams identified as derivatives of NR would not deliver NR upon oral administration, thus contradicting the patent's teachings about the claimed derivatives. Ex. 5, ¶¶ 36-38.

Clearly, there are factual disputes even within Dr. Adams' own testimony on the subject of "derivative (e.g., L-valine or L-phenylalanine esters) of nicotinamide riboside." And Elysium is wrong when it alleges that Drs. Larsen and Sobol "refus[ed] to abide by this Court's construction of 'nicotinamide riboside.'" D.I. 220, 8. Plaintiffs' experts simply disagreed with Elysium's untethered interpretation of

the term "derivative." The opinions of Plaintiffs' experts are proper expert testimony that the jury should be allowed to hear and weigh for itself.

Dated: May 14, 2021

Respectfully submitted,

OF COUNSEL:
Christopher N. Sipes
R. Jason Fowler
Ashley Winkler
Emily Mondry
Evan S. Krygowski
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street NW
Washington, DC 20001
(202) 662-6000
csipes@cov.com
jfowler@cov.com
awinkler@cov.com
emondry@cov.com
ekrygowski@cov.com

Patrick Flynn
COVINGTON & BURLING LLP
3000 El Camino Real
5 Palo Alto Square, 10th Floor
Palo Alto, CA 94306
(650) 632-4732
pflynn@cov.com

James F. Haley, Jr.
HALEY GUILIANO LLP
75 Broad Street, Suite 1000
New York, NY 10004
(646) 973-2500
james.haley@hglaw.com

YOUNG CONAWAY STARGATT & TAYLOR, LLP

/s/ Adam W. Poff
Adam W. Poff (No. 3990)
Pilar G. Kraman (No. 5199)
Rodney Square
1000 North King Street
Wilmington, DE 19801
(302) 571-6600
apoff@ycst.com
pkraman@ycst.com

Counsel for Plaintiffs ChromaDex, Inc. and Trustees of Dartmouth College

WORD COUNT CERTIFICATION

The undersigned counsel hereby certifies that the foregoing contains 2,006 words (exclusive of the title, caption, Table of Contents, Table of Authorities, Table of Abbreviations, and signature block) in Times New Roman 14-point font.

Dated: May 14, 2021

YOUNG CONAWAY STARGATT & TAYLOR, LLP

/s/ Adam W. Poff
Adam W. Poff (No. 3990)
Pilar G. Kraman (No. 5199)
Rodney Square
1000 North King Street
Wilmington, DE 19801
(302) 571-6600
apoff@ycst.com
pkraman@ycst.com

Counsel for Plaintiffs ChromaDex, Inc. and Trustees of Dartmouth College

CERTIFICATE OF SERVICE

I, Adam W. Poff, hereby certify that on May 28, 2021, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

Steven J. Balick
Andrew C. Mayo
ASHBY & GEDDES
500 Delaware Avenue, 8th Floor
Wilmington, DE 19899
sbalick@ashbygeddes.com
amayo@ashbygeddes.com

Donald R. Ware
Peter G. Ellis
Jeremy A. Younkin
Urszula Nowak
Marco J. Quina
Richard Maidman
Joanna McDonough
FOLEY HOAG LLP
155 Seaport Boulevard
Boston, MA 02210
dware@foleyhoag.com
pgellis@foleyhoag.com
jyounkin@foleyhoag.com
unowak@foleyhoag.com
mquina@foleyhoag.com
rmaidman@foleyhoag.com
jmcdonough@foleyhoag.com
elysiumdelaware-dist@foleyhoag.com

Jeffrey I. D. Lewis
Jenny Shum
FOLEY HOAG LLP
1301 Avenue of the Americas
New York, NY 10019
jidlewis@foleyhoag.com
jshum@foleyhoag.com

Attorneys for Defendant

I further certify that on May 28, 2021, I caused the foregoing document to be served via electronic mail upon the above-listed counsel.

Dated: May 28, 2021

YOUNG CONAWAY STARGATT & TAYLOR, LLP

/s/ Adam W. Poff

Adam W. Poff (No. 3990)
Pilar G. Kraman (No. 5199)
Rodney Square
1000 North King Street
Wilmington, Delaware 19801
(302) 571-6600
apoff@ycst.com
pkraman@ycst.com

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