Newsletter for the ChromaDex External Research Program Investigators (CERPI)

CERPI Communiqué

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And the Award for the EU Nutrition Research Project of the Year Goes To… All of our CERPIs in the EU!

The ChromaDex External Research Program (CERP™) is truly unique in the dietary supplement industry. To date, we are unaware of such an extensive program, especially with the focus on a single ingredient. As a trailblazing program, CERP has evolved from an MTA program to a branded entity within ChromaDex, with over 255 agreements at more than 190 institutions in 33 countries. Research from the program has supported approximately 40% of all peer-reviewed published research on nicotinamide riboside (NR), and more than 70% of the NR human research studies registered on clinicaltrials.gov. Our unique approach of promoting investigator-driven, third-party funded research has proven to be trustworthy in both the scientific and consumer communities. On May 4th, ChromaDex won the NutraIngredients EU 2022 Award for Nutrition Research Project of the Year for studies conducted in the EU. This award honors all CERP Investigators in the EU that are advancing the science of NIAGEN®, ChromaDex's patented nicotinamide riboside chloride, and NAD+ overall. THANK YOU.

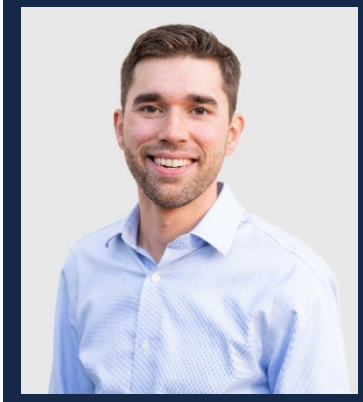
CERP™ is managed by three resolute internal scientists but is supported by nearly every aspect of the business, including Legal, Scientific Affairs, Quality, Supply Chain & Logistics, R&D, Leadership, Sales & Marketing, Regulatory Affairs, Business Development and more. This award validates our vision for sound, trust-worthy science behind our products while creating a community elucidating the benefits of NAD+ boosting. It feels great to have our program and efforts recognized as an industry-leading, international award-winning program. For more information about this award please review our press release and you can watch the virtual awards ceremony here (Nutrition Research Project Awards starts at 28:35). ■

In This Issue

CERP™ is expanding to include other NAD precursors

If you are interested in incorporating novel NAD precursors into your research portfolio? If so, please reach out to us at cerp@chromadex.com. We are expanding the availability of several NAD precursors for basic science and preclinical studies. Adding additional precursors may increase the impact and citations of your research, as well as potentially supporting the development of intellectual property.

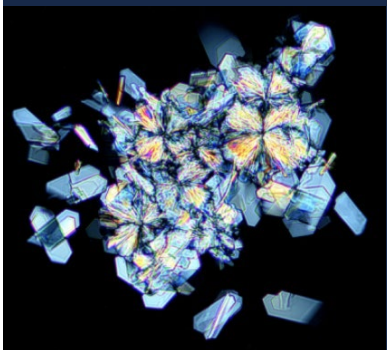
CERPI Highlight



Christopher Martens, PhD
University of Delaware

Want to easily share CERP™ with your colleagues? Have them scan our QR code!

SCAN ME



An Integrative Human Physiologist Seeks to Understand the Effects of NR in the Aging Brain

Dr. Christopher Martens is an Assistant Professor of Kinesiology & Applied Physiology at the University of Delaware and Director of the Neurovascular Aging Laboratory. He completed postdoctoral training at the University of Colorado Boulder where he was among the first to demonstrate that chronic nicotinamide riboside (NR) supplementation raises blood-cellular NAD+ concentrations in humans. Dr. Martens has shifted his attention toward the area of neurovascular aging, focusing on clarifying the mechanisms of cognitive impairment. He is currently leading an ongoing clinical trial where he is evaluating the use of Niagen® supplementation on cognitive health and function.

How did you learn about ChromaDex and (CERP™)?
I have been involved in NAD+ research since early 2014 when I was working as a postdoctoral fellow with Doug Seals at the University of Colorado Boulder. We had been studying the effects of NAD+ precursors for ameliorating vascular aging in mice and were looking to see if our findings translated into humans. At the time, there were few people working on NAD+ precursors in humans and no clinical trials had been completed yet, so we were really on the cutting edge of clinical translation. We were one of the first labs to receive an MTA from ChromaDex for a small pilot clinical trial of NR supplementation in middle-aged and older adults. Because no other trials had been conducted in humans at the time, our pilot study was intentionally small and primarily intended to guide larger efficacy trials. Our primary goals were to assess the safety and tolerability of chronic NR supplementation in humans and to determine whether NR effectively raises the bioavailability of NAD+ in circulating cells. We also sought to gain initial insight into the efficacy of NR for improving physiological function.

How would you define your research interests and areas of expertise?
I am an integrative human physiologist with a background studying cardiovascular health in normal aging and chronic disease. Since starting my tenure-track position at the University of Delaware, my laboratory has focused on studying the impact of vascular aging on risk for mild cognitive impairment (MCI) and Alzheimer's disease (AD). Despite over a century of prior research, there remain no clear disease-modifying therapies for AD, prompting an urgent need for innovative treatment and preventive strategies. My earlier work on promoting vascular health with NAD+ precursors has naturally led to new studies of NR supplementation for improving brain health in older adults which I am very excited to be involved with.

What are your most significant discoveries as it relates to NAD+ and supplementing with NR?
We published the main results of our pilot trial in early 2018 (Martens et al., 2018. Nature Communications). Our study was successful in meeting its primary objectives regarding safety, tolerability, and blood bioavailability. The main "signal" we observed with regards to efficacy was a reduction systolic blood pressure after NR supplementation that seemed most pronounced in those with elevated blood pressure at baseline. It's important to point out that this was only a secondary goal of the study, and our participants were quite healthy at the start. The study also had a small sample size so there is more work to be done to replicate our initial observations. Nevertheless, our pilot study has helped advance the field which has since experienced tremendous growth in the number of ongoing clinical trials across a wide range of clinical indications.

In your opinion, what are some important gaps in NAD+ and NR research?
I think there are a lot of unknowns in this field, which makes it an exciting time to be working on NAD+ boosting compounds. It has been interesting to join a field that, until recently, has been dominated by basic scientists. There are so many challenges associated with translational research and the pace of clinical trials is much slower than most people realize. Compared to

what we know about the effects of NAD+ boosting compounds in animal models, our knowledge in humans is extremely limited. Now that some of the early work on safety and tolerability has been completed, we can begin to conduct larger studies in clinical populations where reductions in NAD+ bioavailability may be more pronounced. Some of this work is already starting to take place, including in my own lab. Another important knowledge gap that remains is how effective oral NAD+ boosters are at reaching target organs. Until recently, we've been limited by blood-based measures of bioavailability; however, new imaging techniques and other novel biomarkers are emerging that make it easier for us to assess target engagement. These studies will be critical for advancing clinical translation in this field. Fortunately, the NIH has taken an interest and recently hosted a public workshop to identify knowledge gaps and advance the next generation of clinical trials of NAD+ boosting compounds.

What are your future NR research plans? How are you funding this research?
I was fortunate to receive a Career Development Award (K01) from the National Institute on Aging when I started my faculty position in 2017. This grant has supported an ongoing clinical trial in my laboratory of NR supplementation for improving memory and cerebrovascular function in older adults with MCI, an early form of AD. Our study was briefly halted due to the COVID-19 pandemic, but we are back up and running and about halfway through enrollment. I've also remained actively involved as a co-Investigator or consultant on four other clinical trials of NR supplementation, including a NIH-funded trial with Dr. Doug Seals in older adults with hypertension. Our goal is to replicate and confirm the initial finding of reduced systolic blood pressure that we observed in our 2018 pilot study. As I said earlier, the pace of clinical research can be slow, and it takes many years to translate initial observations into larger trials that guide clinical practice. I've been very fortunate to be on the forefront of this translation for almost a decade and I'm really excited to see where things go from here. ■

Best Practices for CERP Investigators

The CERP team is excited to finally announce the completion of two documents that outline best practices for investigators studying nicotinamide riboside (NR). Separate versions for preclinical and clinical investigators are available. These guidance documents are intended to arm NR investigators with the fundamental knowledge to design and conduct high-quality studies that are informative and reproducible. Topics that are covered include general recommendations for experimental design, considerations for solution/media preparation, NAD+ metabolomics protocols, and optimum procedures for material storage and handling.

We are encouraging all CERP investigators to incorporate NAD+ analysis into your studies. Though many CERP studies are using kits to compare NAD+/NADH ratios, the gold standard for NAD+ analysis is liquid chromatography, mass spectrometry (LC-MS)-based quantitative metabolomics. LC-MS methods can also be employed to quantitatively evaluate NAD+ associated metabolites, also known as the NADome. The NADome may provide additional insight related to NAD+ metabolism and utilization, especially in highly energy intensive tissues, such as the muscle. References for published methods for sample collection and LC-MS analysis are included in the Best Practices.

It is our hope that you find these documents to be helpful resources to support your ongoing and future studies, whether you are a veteran NAD+ researcher or new to the field. Of course, in keeping with our dedication to continual improvement, these documents will regularly undergo refinement as the science of NR advances and our understanding of its effects expands.

All incoming CERPIs will receive the appropriate Best Practices document along with their series of onboarding papers upon Material Transfer Agreement (MTA) execution. All existing CERPIs may request the Best Practices documents by emailing cerp@chromadex.com. ■

Reminder

Do not forget to submit your progress report every six (6) months, or as stipulated in your MTA. An updated progress report is required when requesting additional material or submitting an MTA amendment. We will provide you with a progress report form to simplify the process.

Request forms at cerp@chromadex.com for:

- **Abstract, manuscript, poster, or presentation slides submissions**
- **Bulk or clinical material requests**
- **Requesting an amendment**

Image source: superfoodly.com

When researching natural products, botanicals, or new materials, do you confirm the identity of the material through an analytical method? If not, how confident are you when reporting your results? ChromaDex Standards offers over 3000 high quality reference standards for various botanicals and natural products. Click link below to find out more.

ChromaDex Standards

Recent CERP™ Publications:

Kim, M.-B., et al. (2022). Nicotinamide riboside supplementation exerts an anti-obesity effect and prevents inflammation and fibrosis in white adipose tissue of female diet-induced obesity mice. J Nutritional Biochem, 109058. doi: 10.1016/j.jnutbio.2022.109058.

Freeberg, K. A., et al. (2022). Nicotinamide Riboside Supplementation for Treating Elevated Systolic Blood Pressure and Arterial Stiffness in Midlife and Older Adults. Frontiers Cardiovasc Medicine 9, 881703. doi: 10.3389/fcvm.2022.881703.

ChromaDex, empowered by:

Thank you to our content contributors, editors, and reviewers:

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How We Support the CERPI Community

Among the primary goals of the ChromaDex External Research Program (CERP™) is to build community and lend our support to external investigators. That is why, in addition to issuing the aforementioned documents that outline best practices in NR research for clinical and preclinical investigators, the CERP™ team works internally and cross-functionally to assist our CERP investigators in various avenues.

The following are some other services that we offer for CERPIs:

- **Letters of support**: More than 95% of the work done through our program is investigator initiated and third party funded, nevertheless, we are more than happy to contribute to the grant application process by supplying letters of support.
- **Support US FDA Investigational New Drug (IND) filings**: When ChromaDex materials are utilized to study treatment or prevention of a disease or study a sensitive population, Institutional Review Boards (IRBs, or equivalent) may require CERPIs to prepare IND filings for clinical trials.
    - To support these filings, once both the material transfer and non-disclosure agreements are executed, CERP™ will provide technical support documents for the development of an investigator's brochure.
    - With permission from all parties involved, we have successfully connected new IND filers with other CERP™ clinical researchers with a history of favorable IND filings to provide letters of authorization.
    - Coming Soon: Our team is working to complete a Foundational Investigator's Brochure (FIB) for Niagen®, which once completed, will provide clinical investigators with background information and detailed safety/toxicology data derived from published and unpublished studies. Many investigators may find the FIB to be particularly helpful for developing their Investigator's Brochure for IRB applications, IND filings, and for FDA and NIH progress reporting.
- **Intellectual property 'first look'**: We help investigators identify potential intellectual property opportunities so they can commercialize their technical inventions.
- **Recommendations on study design and manuscripts to improve likelihood of success**: We strongly value the scientific independence of our CERPIs. Because we possess an intimate understanding of the published and unpublished literature supporting our materials, we may occasionally suggest prospective CERPIs to modify or expand the experimental methods and/or scope (prior to study initiation) to help elucidate current gaps in the literature. Likewise, our team provides an early peer-review of completed manuscript drafts to identify potential areas of improvement, including references, which strengthen chances of acceptance into academic journals.

Furthermore, we have been internally evaluating CERP™ efficiency and employing strategies to improve the efficiency and effectiveness of our program, including shortening the time it takes to execute an MTA. It is our sincere hope and expectation that these efforts will translate to greater CERPI satisfaction and success. If you have any questions or comments regarding these services provided by the CERP™ team, please contact cerp@chromadex.com. ■

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ChromaDex External Research Program

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