Newsletter for the ChromaDex External Research Program Investigators (CERPI)

CERPI Communiqué

Volume 3, Issue 1, March 2022

In This Issue

Setting the Standard for Excellence in Academic & Dietary Supplement Industry Relationships

- 249 MTAs
- 181 Institutions
- 33 Countries
- 12+ Funded Studies
- 103 Peer-Reviewed Publications
- 17 Clinical Publications
- Average Journal Impact Factor: 7.4

Publications Demonstrating Potential Clinical Benefits of Nicotinamide Riboside

The nicotinamide adenine dinucleotide (NAD+) precursor, nicotinamide riboside (NR) has demonstrated numerous potential benefits in cell culture and animal models. Initial clinical studies of NR were designed to evaluate human safety and bioavailability at various doses and dosing regimens. However, some of the early studies, including Martens et al. 2018 and Elhassan et al. 2019, not only demonstrated that NR supplementation safely increased NAD+ or NAD+ flux (as evidenced by elevations in NAD+ metabolites, also known as the NADome), they also indicated potential cardiac and inflammation benefits, respectively.

Translation of preclinical findings beyond NR bioavailability and safety have been challenging, with several clinical trials resulting in null findings. Challenges in translation have included identifying the optimal dose, timing, and treatment duration. In most rodent studies, NR was provided *ad libitum*, in either water or food, thus continual dosing may at least partially explain the more potent health-modifying effects that were observed in these experimental models. Finally, demonstrating a benefit of NR monotherapy in acute/intermediate duration clinical studies employing relatively healthy persons might be difficult, particularly in the absence of a stressor that elicits metabolic perturbations (e.g., overnutrition, rigorous exercise program, alcohol ingestion). However, three recent pilot studies have started to turn the table, showing potential clinical benefits of NR in various study populations.

Benefits in children and adults with Ataxia Telangiectasia. In an open label study led by Dr. Michèl A.A.P. Willemsen of the Radboud University Medical Center, 24 patients with ataxia telangiectasia (A-T) were supplemented with NR (25 mg/kg bodyweight per day) for four months. A-T is a neurodegenerative disorder, caused by variants of the A-T mutated (ATM) gene, which contributes to multiple cellular processes (e.g., energy metabolism, DNA repair, and stress response) and clinically manifests as immunodeficiency and cancer predisposition. Treatment with NR in this group was safe and well-tolerated, with no adverse events reported. Ataxia scores improved in the study participants during supplementation; interestingly however, the benefits were reversed over the two-month of treatment-free follow-up. Serum immunoglobulin profiles also improved, and metabolomic analysis revealed increases in NAD+ metabolites and purine nucleosides. The findings of this study are highly encouraging and will hopefully support the development of a larger, placebo-controlled clinical trial involving A-T patients.

NR study in young healthy patients, followed by ex vivo analysis in healthy and lupus patients demonstrates inflammation-modulating properties of NR. Dr. Michael Sack led a team from the National Institutes of Health, National Heart, Lung and Blood Institute through a multidimensional study including a double blinded, placebo-controlled study of 35 healthy patients given 1,000 mg of NR daily for 1 week, and separate studies involving ex vivo analysis of isolated monocytes from healthy volunteers and patients with systemic lupus

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erythematosus (SLE). Analysis of genes in monocytes between the placebo and NR groups "revealed enrichment in lysosome-, vacuole-, or secretory granule–related processes and autophagy." In primary cells pretreated with NR followed by lipopolysaccharide stimulation, NR blunted Type-I interferon signaling by restoring cellular NAD+ levels, impacting inosine signaling and attenuating autophagy in monocytic cells. This work will hopefully support the development of a clinical study in individuals with SLE.

NR supplementation increased brain NAD+ in patients with Parkinson's Disease. Dr. Charalampos Tzoulis's team at Haukeland University Hospital and various collaborators published the first placebo controlled, NR-only, phase I clinical trial in Parkinson's disease (PD) patients. Study participants with newly diagnosed PD were given NR (1,000 mg/day) or placebo for 30 days, which was shown to be safe in the study population, with no serious adverse events reported. In most patients supplemented with NR, there was an increase in cerebral NAD+, resulting in altered brain metabolism and clinical improvement in those patients. NR also decreased inflammatory cytokines in cerebrospinal fluid and serum. This research group is now conducting a double blind, randomized control study for a full year in patients with PD. ■

CERP™ Milestone: 100 Peer-Reviewed Publications

On January 31st, 2022, ChromaDex announced and celebrated the 100th peer-reviewed publication from ChromaDex External Research Program (CERP™). Formerly the MTA Program, CERP™ was established in 2013 by ChromaDex Co-Founder and Executive Chairman Frank Jaksch, to support scientists and catapult the research behind ChromaDex's materials. The unique program provides material, in kind, while also supporting the technical needs of its external investigators. To date, the program has produced more than 45% of all peer-reviewed NR-focused publications, and 70% of the peer-reviewed clinical NR publications. Over 90% of CERP™ agreements are investigator-initiated and third-party funded, representing over $85 million in estimated total research value. This approach results in greater trust in the research, as skepticism of industry-funded research has been a challenge in the dietary supplement industry.

The 100th milestone publication was first authored by Dr. Marta Hamity, with Dr. Donna Hammond as the senior author. The paper titled, "Nicotinamide Riboside Alleviates Corneal and Somatic Hypersensitivity Induced by Paclitaxel in Male Rats," was published in *Investigative Ophthalmology & Visual Science*. This is the third peer-reviewed CERP™ paper from this research team at the University of Iowa.

The first publication from CERP™ was Fang et al. 2014 from Dr. Vilhelm A. Bohr's lab, while he was with the National Institutes of Health, National Institute of Aging.

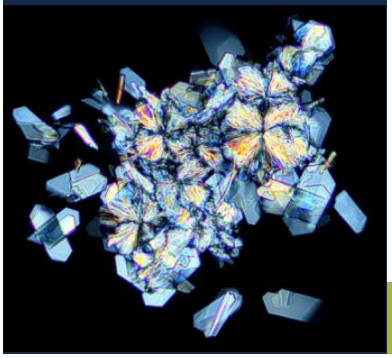
ChromaDex has primarily provided Niagen® (nicotinamide riboside chloride) for research, but has also supplied other ChromaDex materials including Immulina®, pterostilbene, other NAD+ precursors, and labelled compounds for published studies. This has resulted in 103 publications, of which 17 were developed from clinical research; CERP publications have an average journal impact factor of 7.412. We are looking forward to the publications under review and development from all CERPIs, as this work continues to advance science in an impactful way. ■

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**



2022 Conferences

After a year of attending numerous online conferences in 2021, the ChromaDex CERP™ Science team is once again looking forward to leaving our mark in meetings and conferences scheduled across the country in 2022. To start off the conference season, several ChromaDex team members attended the Natural Products Expo West, in Anaheim, California earlier this month. Our own CERP™ Director, Yasmeen Nkrumah-Elie sat on a panel discussing diversity, equity, and inclusion during the session, "The State of Supplements: Supply (Chain) & Demand." This is just the beginning with peak conference attendance scheduled for the month of June.

To kick things off, ChromaDex will have a major presence at Nutrition 2022, the annual flagship event hosted by the American Society for Nutrition (ASN), which will be held virtually this year. As a Sustaining Partner of the ASN, ChromaDex will sponsor a satellite symposium in which members of the scientific community will deliver research on NAD+/NR to a multidisciplinary audience. ChromaDex-sponsored satellite symposiums in previous years have resulted in significant audience engagement, totaling more than 4,700 views in 2020. In addition, CERP™ team members Rebecca Idoine, Jun Kwon, and Yasmeen Nkrumah-Elie will each present an abstract.

Also in June, ChromaDex team members will attend the Annual Conference and Expo of the International Society of Sports Nutrition in Fort Lauderdale, Florida, United States. ChromaDex Director of Scientific Affairs, Mona Rosene, will highlight the current state of research on the relationship between NAD, muscle, and physical performance, and conclude by drawing attention toward future research needs. Finally, the month of conferences will conclude with the FASEB NAD+ Metabolism and Signaling Conference, which will feature NR expert and ChromaDex Chief Scientific Advisor, Dr. Charles Brenner as a speaker, as well as several other CERPIs. This conference is to be held in-person in Steamboat, Colorado, United States, and we highly encourage attendance and participation from our CERPI community.

Though not typically attended by many in the academic community, ChromaDex is a proud and active member of the Council for Responsible Nutrition (CRN), one of the main trade organizations for the dietary supplement industry. This year's CRN Science in Session (formerly Day of Science) is being chaired by Dr. Nkrumah-Elie, and she is considering tapping the shoulders of CERPIs to present at the meeting.

ChromaDex is also planning to send representatives to conferences hosted by the American Chemical Society, Association of Official Analytical Chemists International, and American Society for Mass Spectrometry. Attendance at these meetings re-affirm ChromaDex's commitment to provide reference standards to the highest level of quality for our consumers, and our involvement in the analytical community.

Finally, though we may not attend this year, we would like the CERPI community to consider attendance and participation at the American Aging Association 50th Annual Meeting, Mitochondrial Medicine Symposium, Academy of Nutrition & Dietetics Food & Nutrition Conference & Expo, and Metabesity 2022.

As always, please ensure that our team has read and reviewed your abstracts and presentation slides/poster prior to submission to any conference, as described in your MTA. We have forms for each type of submission to make the process easier. Our team will do our best to review your abstracts and presentations quickly and inform you of any potential intellectual property that you may want to consider. If you have any questions or would like to request forms, please send an email to cerp@chromadex.com. ■

Were your research studies delayed due to COVID-19 closures and replated impacts of the pandemic?

If you need to extend your MTA or alter your scope of work, please request the MTA Amendment Form and we will get right on it. As a friendly reminder, per the agreement, you are only allowed to use ChromaDex's material for the activities specified in the agreement and during the duration of the agreement.

Do you need reference standards for your research? Did you know that ChromaDex offers over 3000 high quality reference standards for various botanicals and natural products? For more information, go to ChromaDex Standards

Did we miss your publication?

Please be sure to send your manuscripts to cerp@chromadex.com prior to submission and keep us updated as you move through the publication process.

Empowered By:

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

Rebecca Idoine, Jun Kwon, Yasmeen Nkrumah-Elie, Jason Brody, Aron Erickson, Andrew Shao, & Heather Van Blarcom

Reminder of Upcoming Capsule Vendor Change

Previously, we announced we are moving to a different capsule vendor to nearly replicate the two-toned capsule colors provided by the previous vendor. They also use similar materials to produce the capsules. Initially, we were planning to only use the new capsule vendor temporarily, as we did not want to interrupt ongoing studies with the introduction of a new capsule. However, we will need to use this vendor for our future manufacturing runs as well.

Our CERP™ science team, R&D, QA & QC, logistics, legal, and supply chain teams work tirelessly to ensure the protection of our CERPIs and the integrity of our research and commercial material. We acknowledge that this change in vendors has the potential to create challenges for our clinical investigators. We are committed to continually providing high quality material. We will be sending a notice to all CERPI studies that will be potentially affected and will include the certificate of analysis for the new capsules. We can provide additional information, upon request, to support notification and address concerns of Institutional Review Boards, and funding and regulatory agencies.

We sincerely apologize for this inconvenience, and we are here to work with you, answer your questions, and hopefully prevent any significant impact to your research. Feel free to reach out to CERP@chromadex.com with your questions and requests. ■

New CERP™ Publications

Brakedal, B., et al. (2022). The NADPARK study: A randomized phase I trial of nicotinamide riboside supplementation in Parkinson's disease. Cell Metab 34, 396-407.e6. doi:10.1016/j.cmet.2022.02.001.

Lozada-Fernández, V. V., et al. (2022). Nicotinamide Riboside-Conditioned Microbiota Deflects High-Fat Diet-Induced Weight Gain in Mice. Msystems 7, e00230-21. doi:10.1128/msystems.00230-21.

Wu, J., et al. (2022). Boosting NAD+ blunts toll-like receptor-4 induced type-I interferon in control and systemic lupus erythematosus monocytes. J Clin Invest. doi:10.1172/jci139828.

Hamity, M. V., et al. (2022). Nicotinamide Riboside Alleviates Corneal and Somatic Hypersensitivity Induced by Paclitaxel in Male Rats. Invest Ophth Vis Sci 63, 38. doi:10.1167/iovs.63.1.38.

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