OCTOBER 2023

CITRIN FOUNDATION QUARTERLY NEWSLETTER

CITRIN FOUNDATION GLOBAL SYMPOSIUM 2023

We recently held our second in-person Symposium, 18th to 20th Sep 2023, hosted at Magdalene College, University of Cambridge, UK. It was attended by over 50 researchers, clinicians, and biotech representatives from all over the world. The event was a resounding success and demonstrated the new, global and holistic approach the Foundation has adopted to act as a nexus and bring together professionals with multidisciplinary backgrounds to work collaboratively.

The event included a two-day scientific program and a half-day patient-oriented session. The scientific program kicked off with an Overview Session featuring speakers from the Scientific Supervisory Board of the Foundation. This session aimed to share the current understanding of the basic science and clinical presentations of CD, highlighting knowledge gaps in the field that would need to be addressed.

Our Co-founders Barbara Yu and Yen How Tai opened the session detailing the strategic roadmap for the Foundation. They also announced a major new initiative, the establishment of a UCD Translational Research Center at the University Children's Hospital at Zürich, which is soon to be finalized. The Center will be headed by Johannes Häberle who is a global expert in UCD and will aim to solve UCD holistically by merging the understanding of basic science and clinical developments, using citrin deficiency (CD) as a model disease. The Foundation will put significant resources into ensuring its success with a 10-year commitment plan.

John Walker, Nobel Laureate and Chair of the Foundation's Scientific Supervisory Board then delivered the keynote speech: "Citrin Deficiency, the Questions and the Paths to Answers", followed by a presentation by Johannes Häberle on "The Linkage of Biochemistry and Pathophysiology of Citrin Deficiency to Clinical Presentations, Current Research Landscape and Unanswered Questions". Finally, Hannele Yki-Järvinen presented "Citrin Deficiency Associated Liver Disease (CDALD) in Adults, Pathophysiology and Potential Therapeutic Implications."

The advancement of the basic scientific understanding of CD underpins our efforts in developing therapies and tackling the condition. The next session was the “Developments in the Basic Scientific Understanding of Citrin Deficiency”. Sotiria Tavoulari from the University of Cambridge spoke about her group’s research on the development of cellular models to elucidate the pathogenic mechanisms in citrin deficiency and their findings so far. Diana Stojanovski from the University of Melbourne presented on the molecular mechanisms of citrin biogenesis and how it is trafficked to the inner mitochondrial membrane. This was then followed by Georgios Makris from the University Children’s Hospital Zürich, who presented on the biochemical, cellular, and functional methods used for the study of CD.

Our Novel Therapies Session was a major highlight of the scientific program as it detailed all the exciting potential new therapies that the Foundation has invested in or is exploring. This included: the potential of gene editing on CD by Gerald Schwank from the University of Zürich, the development of nanoparticles to improve oral bioavailability of amino acids by Yukio Nagasaki from the University of Tsukuba, small molecules focused on modulating NAD+ availability by Joseph Baur from the University of Pennsylvania, and the evaluation of aralar as a replacement for citrin by Laura Contreras from the Autonomous University of Madrid. Marc Prenkti from the University of Montreal discussed the possibility of targeting liver glycerol-3-phosphate phosphatase and the glycerol shunt for citrin deficiency.

One of the primary areas of therapy development at the Foundation is to advance mRNA therapy for CD. The Foundation invited Paolo Martini, Chief Scientific Officer at Moderna, our partner in the development of mRNA therapy, to share his insights about mRNA therapy for the treatment of rare genetic disorders. Julien Baruteau from Great Ormond Street Institute of Child Health, University College London, also gave a presentation on mRNA therapy for liver inherited metabolic diseases.

We anticipate significant strides in the development of therapeutic interventions for CD in the coming years, allowing us to offer personalized treatments to our patients. However, before that can be achieved, it is crucial to first establish effective diagnostic tools and reliable biomarkers to accurately measure disease progression and test the effectiveness of any potential therapies. Additionally, a comprehensive clinical strategy will be essential for identifying more patient cohorts and for successfully bringing these therapies to clinics. To this end, we dedicated a session to “Novel Diagnostic Tools & Center Initiatives” to demonstrate our relevant ongoing efforts.

This session was opened by Kimitoshi Nakamura, who presented on the efforts that he and his team have undertaken at the CD Center of Excellence at Kumamoto University such as: uncovering more CD patients, devising a novel NBS method, launching of a patient registry and expanding the natural history study of patients in Japan for long-term follow-up. Nicola Longo from the University of Utah shared the same view on the importance of an effective NBS method by discussing his experience of NBS of CD patients in the US.

Johannes Häberle discussed the Foundation’s landmark global omics study which aims to identify novel circulating biomarkers of CD. He also presented on the ureagenesis test, which he and his team developed as a significant improvement over previous methods for accurately measuring ureagenesis functions in CD patients. Both studies will be conducted on a large number of CD patients via multiple centers globally, demonstrating the impact of the Foundation acting as a nexus to bring together different pieces to enable such studies to be conducted.

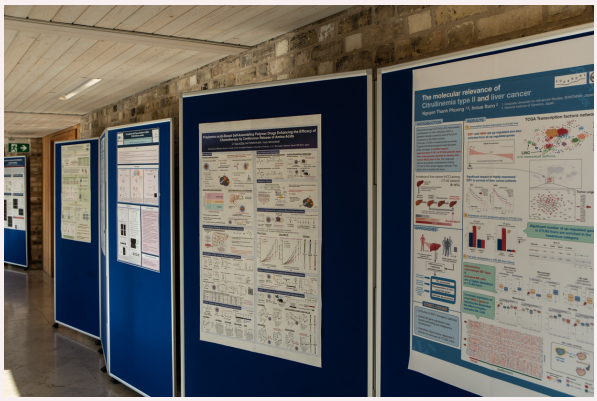
Lastly, we would like to specially thank Marc Hellerstein from the University of California Berkeley, who joined us online from his hospital bed to deliver a talk on the application of metabolic flux studies in animal models and CD patients to better understand the metabolic consequences of CD.

CD is a pan-ethnic condition with diverse clinical presentations. One of the keys to finding a cure lies in broadening our understanding of how it impacts patients worldwide. The “Emerging Clinical Evidence on CD”, and “Global Insights on CD and Other Relevant IEMs” sessions were dedicated for such purposes.

Ituro Inoue from the National Institute of Genetics, Japan, initiated the session with a talk on recent findings utilizing transcriptomics analysis on liver tissues of CTLN2 patients. Masahide Yazaki from Shinshu University detailed his therapeutic experience with LOLA (L-ornithine L-aspartate) in CTLN2 patients. Kimihiko Oishi from the Jikei University School of Medicine described some emerging clinical and biochemical characteristics of CD patients in Japan. Shirou Matsumoto from Kumamoto University presented his findings from a single-center clinical trial which explored the use of L-carnitine, MCT oil and branched-chain amino acids as treatments for citrin deficiency. Saikat Santra from Birmingham Women’s and Children’s Hospital presented on the variation in the FTTDCD phase of CD, with a focus on two ethnic populations in the UK. Robin Lachmann from University College London Hospital gave a talk on CD and other UCDs in adult patients. Finally, Ljubica Caldovic from the Children’s National Hospital in the USA presented a datamining approach on the transcriptional regulation of the citrin gene.

The scientific sessions also included a poster session. We would like to congratulate Alice Sowton from the University of Cambridge and Nguyen Thi Mai Huong from the National Children’s Hospital Hanoi, who were awarded best poster presentation prizes for the scientific and clinical categories respectively.

The scientific portion of the event ended with closing remarks by John Walker and a gala dinner at the college’s historic dining hall.



The next half-day was dedicated to our patients which was both memorable and heart-warming. Over 150 patients and family members joined us in person and online from Japan, Korea, Bulgaria, the United States, the United Kingdom, Germany, Indonesia, Malaysia, India, Pakistan, Austria, Vietnam, Greece and Taiwan.

We are incredibly grateful to siblings Carson and Akemi Kawabata who gave live presentations about their experiences growing up with CD. **We also debuted our patient video, which told the diverse stories of our membership. The video is now available for viewing on our YouTube channel.**

We let our patients understand what we do by showing them a video comprised of the researchers and clinicians we work with, having presentations by Barbara Yu, John Walker, Johannes Häberle and Kimitoshi Nakamura, who specifically talked about current CD management and guidelines. Sami Qadri also presented on the Adult Metabolic Study; a planned clinical study slated to begin next year. Finally, our Patient Engagement and Clinical Program Manager, Shaima Alterkawi, spoke about what we have accomplished over the last year as well as the future of our support initiatives. The session ended with a Q and A session with our Global Expert Panel, offering those in attendance an opportunity to voice their concerns and have their questions answered.

Following the end of the official program, the Foundation invited attendees to partake in an afternoon of social networking activities and a farewell dinner.

We hope that this Symposium has succeeded in providing an excellent opportunity for all participants to present their latest research findings, discuss and brainstorm new ideas, deepen our understanding of CD and highlight areas that need to be focused on.

As we move forward, we are committed to carry with us the spirit of collaboration, the sense of unity and the determination that this symposium has instilled in us, leaving us inspired and confident in our ability to one day solve CD holistically.

Thank you once again to all who attended and contributed to this remarkable event. We look forward to what lies ahead. Please visit our YouTube channel to view our symposium highlights reel.

RESEARCH UPDATES

Publications:

We are glad to announce that research supported by the Foundation under the CD Center of Excellence at Kumamoto University in Japan has recently been accepted for publication in the Journal of Inherited Metabolic Disease. The first author of the paper is Jun Kido and the last author is Kimitoshi Nakamura, with Johannes Häberle as a contributing author. Below is a brief summary of the key findings and significance of their publication:

Improved sensitivity and specificity for citrin deficiency using selected amino acids and acylcarnitines in the newborn screening. Kido et al. JIMD, 2023.

This study explores the use of a new method of NBS to improve the detection of newborn CD patients by combining the evaluation of arginine (Arg), citrulline (Cit), isoleucine+leucine (Ile + Leu), tyrosine (Tyr), and free carnitine (C0)/glutarylcarnitine (C5-DC) ratios. A retrospective re-analysis of NBS results from 96 NICCD patients using this new method showed that it was significantly more sensitive and specific than existing NBS methods to diagnose CD, including pre-symptomatic newborns who were later diagnosed with the condition. The authors propose that the following method could be implemented to existing NBS programs at no additional cost to enhance the accuracy of diagnosis.

CONFERENCE UPDATES

64th Annual Meeting of the Japanese Society for Inherited Metabolic Diseases (JSIMD) – Oct 2023, Osaka, Japan

Earlier this month, the Foundation sponsored a Citrin Deficiency (CD) symposium at the 64th JSIMD Annual Meeting in Osaka. The CD symposium was co-chaired by Johannes Häberle and Kimitoshi Nakamura. Our Co-founder, Barbara Yu, delivered a presentation that highlighted the new CD research initiatives and progress made by the Foundation. Johannes Häberle discussed the pre-clinical requirements for improving the management of CD. Kimitoshi Nakamura presented on the role of the CD Center of Excellence. Finally, Ituro Inoue closed the session with a presentation about the dysregulation of gene expression in liver samples from CTLN2 patients. Additionally, the Foundation co-hosted a CD luncheon with Kimitoshi Nakamura, where many prominent regional clinicians with an interest in CD attended, further advancing our goals.

PATIENT INITIATIVES

Patient committee volunteering

We are excited to invite passionate adult patients and parents of patients from our global community to join our Citrin Deficiency Patient Committee. As part of this committee, members will serve as regional patient representatives, contributing their unique insights and experiences to a global board. If you know any patients or family members who may be interested in learning more about this initiative, please email patients@citrinfoundation.org.

Thank you for being a part of the Foundation's journey to finding a cure for citrin deficiency. We welcome suggestions on how we can improve our resources as well as ideas for new projects to explore.

If you would like to get in touch, please email us at info@citrinfoundation.org for general inquiries or grants@citrinfoundation.org for grant inquiries.

You can look forward to the next edition of our newsletter in January

https://citrinfoundation.org/