CCDS Scientific + Patient

SYMPOSIUM

2024 SALT LAKE CITY

PROGRAM AGENDA & ABSTRACTS

JUNE 29 & 30

ACD

ASSOCIATION FOR CREATINE DEFICIENCIES

SPECIAL SESSION

Perspectives on CCDS: Caregivers & Clinicians

5:00 PM - 6:00 PM MDT

Amanda Atkins
GAMT Caregiver

Jacob Britz
GAMT Caregiver

Erik Cota
CTD Caregiver

Nicola Longo, PhD, MD
Clinician, Researcher

Judith Miller, PhD
Clinical Psychologist

Kimberly Morris
CTD Caregiver

Ashlea Pfannenstiel
CTD Caregiver

ACD ASSOCIATION FOR CREATINE DEFICIENCIES

OPENING SESSION

Opening remarks and session overview

8:45 AM - 9:00 AM MDT

Heidi Wallis
Association for Creatine Deficiencies

BIO

Heidi is the Executive Director of the Association for Creatine Deficiencies and parent of four children, two of which have GAMT Deficiency, a rare cerebral creatine deficiency syndrome with severe neurological impacts if not diagnosed and treated from birth. Heidi and team recently completed a two year project to establish, through patient and expert consensus, a Core Outcome Set (COS) for GAMT and CTD clinical trials. Her team is preparing to begin a second project this fall to establish “Considerations for CTD & GAMT Outcome Measurement Tools (OMTs)” as a companion to the COS. Prior to working for ACD she was a grant analyst and project manager in the Utah Public Health Lab Newborn Screening program. Heidi is a voting member of the Utah Newborn Screening Advisory Committee and collaborated in the nomination and eventual adoption of GAMT on the RUSP. Heidi's vision is that one day all creatine deficiencies will be diagnosed at birth, through routine newborn screening, and will be treated with an effective and appropriate treatment before the onset of symptoms.

SESSION I: NEWBORN SCREENING

The family experience of a GAMT NBS diagnosis and 3 year retrospective

9:00 AM - 9:15 AM MDT

Becky & Stew Tribe
Caregivers (GAMT)

BIO

Becky and Stew Tribe are parents of two children, Linden and Woody. Becky is a public school teacher and Stew works in advertising. Originally from Lindon, Utah, Becky and Stew moved to Los Angeles until their most recent move in 2021 back to Pleasant Grove, Utah.

ABSTRACT

The Tribes’ young son, Woody, was the first infant diagnosed with GAMT deficiency by newborn screening in 2020. They will share the unexpected diagnosis, its impact on their family, accessing patient support, and how Woody is doing today with his GAMT diagnosis and treatment.

SESSION I: NEWBORN SCREENING

Cerebral creatine deficiency syndromes: from screening to diagnosis

9:15 AM - 9:45 AM MDT

Marzia Pasquali, PhD, FACMG
University of Utah and ARUP Laboratories
Authors: Marzia Pasquali; Nicola Longo

BIO

Dr. Pasquali is a professor of Pathology, the Program Director of the ACGME accredited Fellowship program in Clinical Biochemical Genetics at the University of Utah School of Medicine, and the Section Chief and Medical Director of Biochemical Genetics at ARUP Laboratories. Dr. Pasquali earned her degrees of doctor in pharmaceutical chemistry and technology and pharmacy doctor at the University of Parma School of Pharmacy in Italy. She trained in clinical biochemical genetics at Emory University, in Atlanta, Georgia where later served as the co-director of the Biochemical Genetics Laboratory. Dr. Pasquali is board certified in Clinical Biochemical Genetics. She is a member of the Society for Inherited Metabolic Disorders, the American College of Medical Genetics and Genomics, and several other professional societies. Her research interests are newborn screening, disorders of carnitine and creatine metabolism and transport, and lysosomal storage disorders.

ABSTRACT

Cerebral creatine deficiency syndromes (CCDS) are characterized by lack of creatine in the brain. They are caused by defects in creatine synthesis or transport, and can result in intellectual disability, autistic-like behavior, seizures, speech and cognitive delays.

Therapy is effective if initiated early for L-arginine:glycine amidino transferase (AGAT) deficiency and guanidinoacetate methyltransferase (GAMT) deficiency. There is still no therapy for creatine transporter deficiency (CTD), even though some patients respond to creatine supplementation. Early identification is key to prevent irreversible brain damage.

The effectiveness of newborn screening (NBS) for GAMT deficiency has been recognized and GAMT deficiency is now included in the NBS Recommended Uniform Screening Panel (RUSP). Measurement of guanidinoacetate and creatine in dried blood spots (DBS) allows to identify GAMT deficiency with an extremely low false positive rate. Biochemical confirmation is obtained with measurement of plasma guanidinoacetate, which is elevated, and creatine followed by genetic testing. In patients with AGAT deficiency, guanidinoacetate is very low; however, there are no data about NBS yet. The diagnosis of CTD is usually established by an increased creatine/creatinine ratio in urine. Currently, there are no informative biomarkers for identifying CTD in blood spots. We have observed a significant difference in creatine, creatinine, and creatine/creatinine ratio in a small number of NBS residual DBS of patients with CTD. If these preliminary data are confirmed, it will be possible to identify infants with CTD at birth. Early identification will allow early intervention and, perhaps, improve outcome even though currently a specific therapy is not available.

SESSION I: NEWBORN SCREENING

Newborn screening, confirmatory testing and long-term care of patients with guanidinoacetate methyltrasferase (GAMT) deficiency

9:45 AM - 10:15 AM MDT

Nicola Longo, PhD, MD
University of Utah
Authors: Nicola Longo; Marzia Pasquali

BIO

Dr. Nicola Longo received his M.D. and Ph.D. in molecular biology and pathology from the University of Parma, School of Medicine in Italy. He then trained in Pediatrics, Medical and Biochemical Genetics at Emory University in Atlanta, Georgia, USA. Dr. Longo has been a Professor of Pediatrics and Chief of the Division of Medical Genetics in the Department of Pediatrics at the University of Utah from 2001 to 2024. He has also served as Medical co-Director of the Biochemical Genetics and newborn screening Lab at ARUP Laboratories in Salt Lake City. Since June 2024, he is a Professor and the Chief of Medical Genetics at UCLA. His research concerns the molecular bases of metabolic disorders, their identification through newborn screening, their natural history, and the development of novel therapies.

He has a long-standing interest in membrane transporters for which he has worked on amino acid, glucose, carnitine and creatine transporters. He follows several patients with brain creatine deficiency and has an active interest in developing new methods to facilitate their detection by newborn screening, improving existing therapies and developing new ones for these conditions.

ABSTRACT

Guanidinoacetate methyltransferase (GAMT) deficiency impairs creatine synthesis and causes accumulation of guanidinoacetate (GAA) and other guanidino-compounds, which can be neurotoxic. GAMT deficiency can result in intellectual disability and seizures, which can be prevented by early detection by neonatal screening and appropriate therapy. GAMT deficiency is part of the recommended uniform newborn screening panel in the USA with a few States already screening for it and others planning to start soon. Guanidinoacetate is elevated in blood spots collected typically, at 1-2 days of age and remains consistently elevated with time. Creatine levels are not decreased in blood spots of infants with GAMT deficiency collected at 1-2 days of age, reflecting placental transfer of creatine from the mother to the fetus, but start declining after 7-14 days of life. Arginase deficiency, a urea cycle disorder, can also cause elevated guanidinoacetate with normal creatine levels in newborns. Diagnostic confirmation requires measurement of guanidinoacetate and creatine in plasma, with false negative results reported in urine, in addition to plasma amino acids to exclude arginase deficiency. Diagnosis can be further confirmed by genetic testing and detection of a low creatine peak by brain MRS. Therapy consists in the administration of supplements of creatine and ornithine in conjunction with a protein-restricted diet to reduce arginine formation. Sodium benzoate (100-200 mg/kg/day) is used in some centers to reduce glycine levels and guanidinoacetate. Outcome is strongly dependent on the time at which therapy is initiated with completely normal development to date in children identified by newborn screening.

SESSION I: NEWBORN SCREENING

Identification of creatine transporter deficiency using plasma creatine and creatinine: following up an initial finding

10:15 AM - 10:45 PM MDT

Patricia Hall
Mayo Clinic
Authors: Karen Sanders; Dawn Peck; Gisele Pino; April Studinski Jones; Amy White; Dimitar Gavrilov; Dietrich Matern; Devin Oglesbee; Matthew Schultz; Silvia Tortorelli; Patricia L. Hall

BIO

I completed my undergraduate and graduate training at the University of Regina in Canada, prior to joining the Biochemical Genetics Laboratory at Mayo Clinic for my ABMGG fellowship in Clinical Biochemical Genetics. After completing my fellowship in 2013, I successfully passed by board examination and started a position at Emory Genetics Laboratory, later EGL Genetics. During this time, I served as a member of the Georgia Newborn Screening Advisory Committee, and later served as co-chair. In 2021, I started as Newborn Screening Laboratory Director with the Georgia Department of Public Health, overseeing implementation of screening for three lysosomal storage disorders. In 2022, I returned to Mayo Clinic as co-Director of the Biochemical Genetics Laboratory. My interests include newborn screening, quality improvement, post-analytical tools and screening improvement.

ABSTRACT

We recently published an initial report of the identification of creatine transporter deficiency (CRTRD) in plasma specimens with an abnormal creatine / creatinine ratio driven primarily by decreased creatinine values, rather than the markedly increased creatine values observed in urine specimens. This early report was based on the observation of 8 hemizygous individuals. To follow-up on this finding, further work is needed to determine if this finding is similarly diagnostic to the urine profile, and the applicability of this finding to heterozygous individuals.

In addition to further delineating the plasma findings in affected individuals, the identification of a blood abnormality raises the possibility of detection by newborn screening programs, if treatment options evolve to meet current criteria. Creatine and creatinine can be added to most amino acid and acylcarnitine analyses already performed, and in many cases have been added to improve the performance of screening for guanidinoacetate methyltransferase deficiency. Evaluation of reference ranges for creatinine, with particular attention paid to the lower end in dried blood spots can be an early step. Retrospective data review from states that have a history of screening using both markers may also be beneficial. Retrieval of stored specimens may also be helpful, but a review of storage conditions and marker stability should be thoroughly examined prior to such analyses.

SESSION I: NEWBORN SCREENING

Newborn screening panel discussion

11:00 AM - 11:45 AM MDT

Patricia Hall

Mayo Clinic
Minnesota NBS

Heidi Wallis

Association for Creatine Deficiencies

Barb Lesko, MPH
Allison Forkner, MLS

Indiana NBS

Sarah Young, PhD

Duke University

Kim Hart, MS

Utah NBS

SESSION 2: BIOLOGY OF CEREBRAL CREATINE DEFICIENCIES

Creatine transporter knockout mice enter their teenage years: what do we know and where are we going from here?

1:00 PM - 1:30 PM MDT

Matthew R. Skelton, PhD
Cincinnati Children's Hospital Medical Center
Authors: Mathew R. Skelton

BIO

Dr. Matthew Skelton is an Assistant Professor of Neurology at Cincinnati Children's Hospital Medical Center. Dr. Skelton developed the first Slc6a8 knockout mouse, published in 2011. Since then he has published 20 manuscripts related to the role of creatine in the brain. He is a member of the ACD's Scientific and Medical Advisory Board and is proud to have been awarded the first ACD grant.

He has a long-standing interest in membrane transporters for which he has worked on amino acid, glucose, carnitine and creatine transporters. He follows several patients with brain creatine deficiency and has an active interest in developing new methods to facilitate their detection by newborn screening, improving existing therapies and developing new ones for these conditions.

ABSTRACT

Very little was known about the role of creatine in brain function prior to the discovery of creatine deficiency syndromes (CDS) near the turn of the century. For the most part, creatine was viewed as an essential component in muscle function and a sports supplement. The surprising neurological phenotype of these disorders showed that creatine was important in brain function. The discovery of CDSs created a need for high-fidelity preclinical models to test treatments and discover mechanisms that underlie these disorders. Our lab published the first mouse model of creatine transporter deficiency (CTD), the most prevalent cause of CDSs, in 2011. Since then, 2 additional mouse models and one rat model have been developed. These rodent models recapitulate many of the known features of CTD. This provides an excellent avenue for testing treatments for CTD. While these models have provided a significant advancement in our understanding of CTD, many challenges remain. The challenge of treating CTD has proved to be quite daunting, highlighting the need for further work. The purpose of this presentation is to discuss how these models have advanced our understanding of Cr in the brain and how these models have been used to test treatments for CTD.

SESSION 2: BIOLOGY OF CEREBRAL CREATINE DEFICIENCIES

Optimization of a stable isotope-labelled substrate assay for measuring AGAT activity

1:30 PM - 2:00 PM MDT

Alex Lee
University of Toronto
Authors: Alex Lee; Lucas Anderson; Momin Kashif; Ilona Tkachyova; Andreas Schulze

BIO

Alex is currently a PhD student in the Department of Biochemistry at the University of Toronto. He works in the lab of Dr. Andreas Schulze at the Hospital for Sick Children where his research focuses primarily on investigating how AGAT expression is controlled and regulated by creatine. Alex was also a previous recipient of the ACD fellowship.

ABSTRACT

Creatine is a molecule that facilitates the regeneration and distribution of ATP and buffers imbalances in ATP levels to maintain its homeostasis. Pathogenic variants in GATM, GAMT, or SLC6A8 cause the development of creatine deficiency syndromes (CDS). These diseases are characterized by a severe reduction of creatine within the brain and results in developmental delays and seizures.

Our goal is to develop an assay that can accurately measure AGAT enzyme activity in various cells and tissues which would allow for the determination of baseline AGAT levels in healthy controls and allow for comparisons between suspected patients. To measure AGAT activity, we adapted the stable-isotope method from Verhoeven et al. In this assay, we used stable-isotope labeled substrates to produce 13C215N3 guanidinoacetate which can be quantified by LC-MS/MS to determine specific AGAT activity.

For this assay, we chose to measure AGAT activity in lymphocytes, lymphoblasts, and fibroblasts as these cell types would be readily obtainable from blood and skin, respectively. AGAT activity was measurable in lymphocytes and lymphoblasts, but not fibroblasts. Furthermore, we also performed assays to determine AGAT activity in various mouse tissues such as kidney, liver, brain, muscle, and heart. We were able to quantify AGAT activity in all tissues with the exception of liver. Measuring AGAT levels in the liver required the addition of Nor-NOHA to inhibit the activity of arginase which interfered with the enzymatic assay.

Moving forward, we aim to measure AGAT from additional human samples to establish a comprehensive baseline of AGAT activity.

SESSION 2: BIOLOGY OF CEREBRAL CREATINE DEFICIENCIES

Gene delivery of AGAT and GAMT boosts creatine levels in creatine transporter deficiency patient fibroblasts

2:00 PM - 2:30 PM MDT

Steve Baker, PhD, MD
University of Utah
Authors: Chloe Wells; Jon Sorgenfrei; Sadie L. Johnson; Devin Albertson; Jared Rutter; Steven Andrew Baker

BIO

Dr. Steven Baker is a clinical pathologist specializing in transfusion medicine and hemostasis. Dr. Baker obtained a B.S. in Biological Sciences from Cornell University in 2005. He completed his MD and PhD training in the combined MSTP at Baylor College of Medicine in 2014. He then performed a residency in clinical pathology at Stanford University, before an instructorship in coagulation and fellowship training in transfusion medicine, also at Stanford. He joined the faculty of the University of Utah Department of Pathology as an Assistant Professor in 2021 where he currently serves as the Associate Medical Director of Transfusion Medicine. His scientific interests span a wide variety of topics, from pediatric neuroscience to age-related disease. The work he will be presented was funded by a grant from the ACD to investigate a potential gene therapy for patients with Creatine Transporter Deficiency. He is also developing computational tools to study vertebrate lifespan variation.

ABSTRACT

Genetic defects in endogenous creatine synthesis, or its transport across cellular membranes, lead to a common set of phenotypes referred to as Cerebral Creatine Deficiency Syndrome (CCDS). CCDS type1 accounts for ~70% of cases and owes to loss-of-function mutations in the X-linked gene SLC6A8. Affected individuals suffer from intellectual disability, autistic-like behaviors, and epilepsy. There are currently no effective therapies for this disorder, but gene therapy has emerged as a potential approach. The two enzymes which comprise the endogenous creatine synthetic pathway (AGAT and GAMT) are expressed throughout the body, but rely on the protein product of SLC6A8, creatine transporter 1 (CT1), to transport creatine into target cell types. We hypothesized that gene delivery of AGAT and GAMT into patient cells would bypass the need for CT1 and allow for internal synthesis of creatine in end-user cells. We tested this strategy in two human cell types: HEK293T cells and primary fibroblasts. Co-delivery of AGAT and GAMT increased internal creatine concentrations by 7.6-fold in HEK293T cells ($P < 0.05$) and 12.3-fold in healthy control fibroblasts ($P < 0.05$). We then employed this approach to primary fibroblasts from patients with CCDS type1. This resulted in up to an 11.6-fold increase in intracellular creatine concentrations ($P < 0.05$), far exceeding the intracellular concentration of creatine in healthy control fibroblasts (10.4 vs 1.6 nmoles/mg protein, respectively). Importantly, overexpression of AGAT and GAMT resulted in proper targeting of these enzymes to their natural cellular compartment and improved the growth of patient fibroblasts ($P < 0.05$).

SESSION 3: ADVANCES IN THERAPEUTIC DEVELOPMENT FOR CCDS

Drug screening for GAMT deficiency targeting AGAT expression

2:45 PM - 3:15 PM MDT

Andreas Schulze, PhD
University of The Hospital for Sick Children and University of Toronto, Toronto, ON, Canada
Authors: Ilona Tkachyova; Michael Tropak; Alex Lee; Alessandro Datti; Shinya Ito; Andreas Schulze

BIO

Dr. Andreas Schulze is a metabolic pediatrician and professor in the Departments of Paediatrics and Biochemistry at University of Toronto. He is the Medical Director of the Newborn Screening Program at The Hospital for Sick Children (SickKids) Toronto and Senior Associate Scientist at the SickKids Research Institute.

Schulze receive a medical diploma and a doctorate in medicine from the Faculty of Medicine at Leipzig University in 1987. After completing graduate training and PhD in Physiological Biochemistry under the supervision of Dr. Hans-Joachim Boehme and Dr. Eberhard Hoffmann (1987-1992), Schulze pursued postgraduate clinical training in Pediatrics at the University Children's Hospital in Heidelberg under Dr. Hans-Juergen Bremer and Dr. Georg F. Hoffmann (1992-1999). Schulze defended a Professorial Thesis (Habilitation) and received the Venia Legendi from the Ruprecht-Karls University Heidelberg in 2004. He is board certified in Physiological Biochemistry (1993) and in Pediatrics (1999).

Since 2007, Schulze works as clinician scientist at The Hospital for Sick Children in Toronto. As a clinician he takes care of children with inborn errors of metabolism and oversees the SickKids Newborn Screening Program. As a scientist, he established a research group and a research laboratory at the SickKids Research Institute. Dr. Schulze's research is centered around creatine deficiency syndromes and regulation of creatine homeostasis. His research encompasses the metabolism of arginine, ornithine, and guanidino compounds, and includes small molecule drug discovery.

ABSTRACT

We have identified AGAT as druggable target for the treatment of GAMT deficiency with drug repurposing for AGAT gene repression as a potential strategy.

HeLa cells stably expressing a construct consisting of an AGAT promoter and a firefly luciferase reporter were used for high-content screening and secondary screening of drugs reducing the expression of AGAT. Further assessment included human cell lines resembling GAMT deficiency and an Nanoluc luciferase (NLuc) reporter integrated into the AGAT gene in HAP1 cell lines.

To validate our screening platform, we treated cells with creatine and ornithine. As expected, AGAT promoter reporter activity was reduced with creatine but not ornithine. Screening of six drug libraries (ca. 6K molecules) identified 43 high score drug candidates (activity ≤ -3SD, viability ≥ -2SD). Dose-response experiments extracted 6 candidates for which IC50 could be established. Candidates were further analyzed for rate of AGAT synthesizing guanidinoacetate in HepRG cells. Only one candidate showed some efficacy. In parallel, we tested all drug candidates that were efficient in the promoter-reporter cells in HAP1 cells that had the NLuc reporter integrated in the AGAT gene. None of the candidates could be confirmed with any significant inhibitory efficacy.

In summary, we learned that AGAT promoter firefly luciferase reporter approach, although relatively easy, may not lead to relevant findings. Instead, when investigating for gene repressors one would have to apply a screening platform that has the reporter integrated in the native gene to maintain the full circuit of factors involved in the regulation of gene expression.

SESSION 3: ADVANCES IN THERAPEUTIC DEVELOPMENT FOR CCDS

CBT101, an innovative compound that delivers creatine to neurons

3:15 PM - 3:45 PM MDT

Thomas Joudinaud, PhD, MD
Ceres Brain Therapeutics
Authors: Thomas Joudinaud

BIO

Dr. Thomas Joudinaud, is the CEO and co-founder of Ceres Brain Therapeutics. He is a former cardiovascular and thoracic surgeon (MD) holding a PhD in pharmacology from the University of Montana. Over the past 15 years, he has served as a Pharma Strategy consultant, contributing to market assessments and development plans for products in rare diseases. Thomas has excelled in portfolio reviews, resource allocation for leading pharmaceutical companies, and the evaluation of business plans, price potential, and sales forecasts for products in development. His collaborative ventures include prestigious pharma consulting firms like The Boston Consulting Group and AEC Partners.

ABSTRACT

Ceres Brain Therapeutics, a spin-off from the leading academic French center, the CEA, was created in 2019 by the CEA, Dr Aloïse Mabondzo, PhD, Dr Henri Bénech, PharmD, PhD and Dr Thomas Joudinaud, MD, PhD.

Ceres is developing CBT101, a prodrug of creatine, that is administered in the nose. In the nasal cavity, CBT101 enter the olfactory and trigeminal neurons, migrates along them to reach their origins, the olfactory bulb and the trigeminal cores and then diffuses from one neuron to the other toward all areas of the brain. Ceres' Creatine-to-NeuronsTM efficacy has been proven extensively in SLC6A8 KO mice, WT mice and cynomolgus monkeys, demonstrating creatine delivery and biological, metabolic and cognitive improvement.

In 2023-2024, Ceres has conducted the IMPD/IND enabling studies to reach the clinical phase:

- Demonstrating a plateau of efficacy within a range of dosages in knockout (KO) mice.
- Developing a robust manufacturing process that enables scale up and ensures compliance with regulatory rules.
- Demonstrating good tolerance to chronic short-term administration in the frame of two short-term regulatory toxicological studies.

Depending on funding, Ceres plans to conduct in the next months a Phase 1 clinical trial pending authorization by regulatory authorities, as well as a 9-month toxicology study to meet the regulatory requirements before setting-up a Phase 2 clinical trial in patients with CTD.

SESSION 3: ADVANCES IN THERAPEUTIC DEVELOPMENT FOR CCDS

Towards the discovery of small molecules that restore the expression and function of CTD variants

3:45 PM - 4:15 PM MDT

Charles Kuntz, PhD
Purdue University
Authors: Charles P. Kuntz; Jacklyn M. Gallagher; Haritha Manoharan; Jonathan P. Schlebach

BIO

Charles received a BS in Biochemistry from Indiana University in Bloomington, Indiana and a PhD in medicinal chemistry and molecular pharmacology at Purdue University in the laboratory of Prof. Eric Barker. At Purdue he studied the pharmacology and structural biology of the serotonin transporter using methods from computational chemistry and computational biology, such as protein structure prediction, molecular docking, and binding free energy calculations using molecular dynamics simulation. In 2018 he joined Prof. Jonathan Schlebach's laboratory at Indiana University where he uses computational biology approaches to understand the mutational sequence constraints of membrane proteins and how this contributes to disease. The Class A GPCR rhodopsin has primarily been utilized in these studies as a model system and as an important object in itself as rhodopsin mutations can lead to retinitis pigmentosa, a form of congenital night blindness. Charles joined the Schlebach lab at Purdue University as a Research Scholar in 2023. As the previous recipient of ACD fellowship in 2022, Charles is still engaged in studies searching for possible small molecule therapies for creatine deficiencies using virtual screening, molecular docking, and protein structure prediction and modeling. He has been a Visiting Scholar in the laboratory of Prof. Jens Meiler at Vanderbilt University, contributing to an ongoing collaboration between the Schlebach Lab and Meiler Lab to use machine learning methods to predict the effects of mutation on membrane protein trafficking. Charles is hoping to broaden the scope of his expertise into GPCR pharmacology with new work on a systems-level study of GPCR expression and homeostasis.

ABSTRACT

Over 100 loss-of-function (LOF) mutations within the SLC6A8 creatine transporter (CT1) are known to cause creatine transporter deficiency (CTD) syndrome. Most of these mutations enhance CT1 misfolding and degradation, and the resulting loss of the transporter protein ultimately compromises creatine uptake within the brain and other organs. Creatine uptake could therefore be restored by small molecule "correctors" that rescue the expression of misfolded variants, the development of which has recently revolutionized the treatment of several other genetic diseases of membrane protein misfolding. Cumulative observations concerning the mechanistic effects of drugs targeting related SLC6 transporters such as the serotonin (SERT) and dopamine (DAT) transporters suggest compounds that selectively bind to their inward-facing (IF) conformation generally enhance their expression and maturation. Based on these considerations, we set out to identify small molecules that selectively bind to the IF conformation of CT1 in order to restore the expression and activity of misfolded CT1 variants. Towards this goal, we developed a virtual screening approach to identify small molecules that selectively bind to the IF conformation of CT1, then profiled their effects on CT1 expression. Of our top 53 candidates, we identify several that alter the expression profile of WT CT1 and a few that enhance its expression at the plasma membrane. We are currently working to determine how these molecules impact CT1 function and how they impact pathogenic CT1 variants. Additionally, based on the structures of our top hits, we are currently searching for second-generation compounds with increased potency. These results represent an important step toward the development of novel pharmacological chaperones for the treatment of CTD.

SPECIAL INTEREST SESSION

CREAT_criteria: What have we learned regarding CTD patient epilepsy? A prospective study in creatine transporter deficiency (SLC6A8) patients to determine the most relevant outcome measures

4:15 PM - 4:45 PM MDT

Aurore Curie, PhD, MD

French National Reference Center for Rare Diseases with Intellectual Disability, Department of Child Neurology, Woman Mother and Child Hospital, Lyon University Hospital, Bron, France; Lyon Neuroscience Research Center, CNRS UMR5292, Inserm U1028, Lyon, France ; Claude Bernard Lyon 1 University, Lyon, France

Authors: Aurore Curie; Lisa Ouss; Fahra Gheurbi; Michaël Pommier; Nathalie Touil; Emma Geay; Tiphaine Courtalon; Amandine Brun; Léa Saverat; Florian Ducret; Axelle Poulain; Marion Buchy; Solène Roudet; Oriane Susini; David Cheillan; Ganaëlle Remerand; Christine Barnerias; Anaïs Brassier; Alice Goldenberg; Anne-Laure Avice-Denizet; Agathe Roubertie; Laurence Lion-François; Stéphanie Marignier; Pascale De Lonlay; Fanny Mochel; Vincent Navarro; James Lespinasse; Didier Lacombe; Renaud Touraine; Sylvain Rheims; Nathalie Bedoin; Matthildi Papathanasiou; Eleni Panagiotakaki; Jean-Baptiste Van der Henst; Laure Pisella; Eric Chabanat; Hélène Ratiney; Anne Cheylus; Yves Rossetti; Yves Paulignan; François Cotton; Vincent des Portes

BIO

Aurore Curie is a child neurologist (MD, PhD) at the Child Neurology Department of Lyon University Hospital (Assistant Professor) and the Reference Center for Intellectual Disability (ID) from rare causes (Co-Head). She is affiliated to the Lyon Neuroscience Research Center (CNRS UMR5292, Inserm U1028, Lyon, France) and also part of the DéfiScience national network for rare diseases of brain development and ID. She coordinates a French Inter University Diploma (DIU) on Neurodevelopmental Disorders. She has a strong expertise in genetics (especially in X-linked ID) and in neuroscience. She developed new outcome measure adapted to ID patients (HCL/CNRS patent). She contributed to the development of the research plateform “Cognitoscope”. Her clinical and research expertise is dedicated to X-Linked ID and other ID from rare causes. She described cognitive profiles of neurodevelopmental disorders (including ARX, PQBP1, Rab-GDI, SLC6A8 mutated patients) using eye-tracking and neuroimaging analysis, and contributed to several multisite clinical trials for Fragile X syndrome. She also furthered our knowledge on placebo effect in ID patients, and the different trial plans that can be used in ID patients to test for an effect (Randomized controlled double blind Clinical Trials (RCT) but also n-of-1 trials, also called Single-Case Experimental Designs or SCEDs).

ABSTRACT

Creatine Transporter Deficiency (CTD) is a rare genetic disorder related to SLC6A8 pathogenic variants, leading to moderate-to-severe Intellectual Disability. As new therapeutic avenues are emerging, it is necessary to identify objective, reliable and sensitive outcome measures.

To determine these relevant endpoints and describe clinical/cognitive profile in CTD, using both existing neuropsychological tests, and new outcome measures specifically developed for CTD, we performed a prospective study on 24 French Male CTD patients. We precisely described CTD developmental trajectory, neurological/morphological examination, actimetry, cognitive assessment (Leiter, Simple reasoning tasks on tablet with 4 increasing difficulty levels), language (PPVT-5, EVT-3), motor assessment (kinematic task, Purdue-Pegboard), Social assessment (ADOS, eye-tracking analysis of social visual scenes), as well as parental questionnaires (Vineland, ABC, PDD-MRS, CBI). Moreover, neuroimaging analysis was performed including spectroscopy with precise quantification of the creatine peak.

We present here preliminary results on the first 23 CTD patients included in the study (mean age 16.7 years, [6.7 to 26.9]). Mean non verbal IQ was 55.5 [30-75]. 96% of the CTD patients could perform the first level of simple reasoning tasks (match-to-sample), 83% the second level (categorization), 70% the SimpleMatrices task, and 65% could perform the implicit rules learning task. Tasks on tablets could be easily performed at home under remote supervision through visioconference. All patients were able to perform eye-tracking analysis. The mean average steps per day was 12265.

This study will contribute to define the outcome measures that could be used in future clinical trials in CTD patients despite their cognitive deficit.

SPECIAL INTEREST SESSION

Getting ready for clinical studies / advocating for girls

4:45 PM - 5:00 PM MDT

Carole Chehowah
Xtraordinaire

BIO

I am the mother of a 34 years old CTD girl. After spending 28 years in the finance industry, and being involved for CTD children, I am now the VP of Xtraordinaire and head of the CTD commission, I am advocating for all rare X linked neurodevelopment disorders.

ABSTRACT

A quick presentation on how to get families and patients ready for clinical trials:

- expectations
- fears
- education
- how we can help the physicians and industry

Follow up on girls, and how we can better advocate for them.

Unraveling SLC6A8 creatine deficiency: Insights into Neurodevelopment through Organoid Research

Aleksander Bogoniewski
University of California, Los Angeles
Authors: Aleksander Bogoniewski; Taryn Diep; Leo Cigarroa; Gerald Lipshutz

BIO

Aleks is a rising third-year PhD student in the Lipshutz lab at the University of California, Los Angeles, dedicated to gene therapy strategies targeting mutations in the SLC6A8 creatine transporter and GAMT associated with Creatine Transporter Deficiency (CTD). Building on his undergraduate research experience, where he received the UCLA-CIRM Pathways to Stem Cell Science Fellowship focusing on cerebral organoids for Autism Spectrum Disorder, Aleks now applies his expertise to develop cerebral organoid models for both SLC6A8 and GAMT mutations. His multifaceted approach includes conducting sophisticated analyses such as electrophysiology, 2-photon calcium imaging, transcriptomic analyses, and RNA sequencing. Additionally, Aleks is actively engaged in exploring the potential of adeno-associated vectors for genetic corrections targeting both SLC6A8 mutations and GAMT deficiency. Through his research endeavors, Aleks aims to narrow the therapeutic gap and propel forward treatment options for individuals impacted by SLC6A8 creatine transporter deficiency and GAMT mutations.

ABSTRACT

The discovery of the first mutation in the SLC6A8 creatine transporter gene marked a significant advancement in understanding the pathophysiology of X-linked neuronal impairments with an unknown etiology. The absence of functional SLC6A8 creatine transporters results in inadequate uptake of the high-energy metabolite creatine into the brain, causing a spectrum of neurodevelopmental delays including intellectual disability, epilepsy, and behavioral disorders. Conventional therapeutic approaches, such as oral creatine supplementation, are ineffective due to the inability of patients with SLC6A8 mutation to facilitate cerebral creatine transport, leaving a significant therapeutic void and lack of symptom relief. Furthermore, there is a significant lack of knowledge regarding the cerebral development of individuals afflicted with SLC6A8 creatine transporter deficiency.

Our research aims to address this gap by examining the developmental processes underlying SLC6A8 mutations using cerebral organoids and evaluating a range of adeno-associated virus (AAV)-mediated therapeutic interventions aimed at increasing cerebral creatine levels. Preliminary findings from our laboratory reveal a notable acceleration in the growth rate of cerebral organoids from individuals with SLC6A8 mutations compared to CRISPR-corrected isogenic controls. Subsequent investigations into AAV vectors will extend these observations to murine models and continue to explore organoid models through comprehensive transcriptome analyses, RNA sequencing, and advanced electrophysiological assessments.

Through our multidisciplinary approach encompassing stem cell biology, gene therapy, and neurodevelopmental research, we aim to bridge the therapeutic gap and advance treatment paradigms for individuals affected by SLC6A8 creatine transporter deficiency.

CREAT_criteria Study: what have we learned regarding the cardiac phenotype of patients with creatine transporter deficiency (SLC6A8)?

Aurore Curie, PhD, MD

French National Reference Center for Rare Diseases with Intellectual Disability, Department of Child Neurology, Woman Mother and Child Hospital, Lyon University Hospital, Bron, France; Lyon Neuroscience Research Center, CNRS UMR5292, Inserm U1028, Lyon, France ; Claude Bernard Lyon 1 University, Lyon, France

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BIO

Aurore Curie is a child neurologist (MD, PhD) at the Child Neurology Department of Lyon University Hospital (Assistant Professor) and the Reference Center for Intellectual Disability (ID) from rare causes (Co-Head). She is affiliated to the Lyon Neuroscience Research Center (CNRS UMR5292, Inserm U1028, Lyon, France) and also part of the DéfiScience national network for rare diseases of brain development and ID. She coordinates a French Inter University Diploma (DIU) on Neurodevelopmental Disorders. She has a strong expertise in genetics (especially in X-linked ID) and in neuroscience. She developed new outcome measure adapted to ID patients (HCL/CNRS patent). She contributed to the development of the research plateform “Cognitoscope”. Her clinical and research expertise is dedicated to X-Linked ID and other ID from rare causes. She described cognitive profiles of neurodevelopmental disorders (including ARX, PQBP1, Rab-GDI, SLC6A8 mutated patients) using eye-tracking and neuroimaging analysis, and contributed to several multisite clinical trials for Fragile X syndrome. She also furthered our knowledge on placebo effect in ID patients, and the different trial plans that can be used in ID patients to test for an effect (Randomized controlled double blind Clinical Trials (RCT) but also n-of-1 trials, also called Single-Case Experimental Designs or SCEDs).

ABSTRACT

Creatine Transporter Deficiency (CTD) is a rare genetic disorder related to SLC6A8 pathogenic variants, leading to moderate to severe intellectual disability. Little is known about the cardiac consequences of the disease. A model of CTD in mice suggested a risk of sudden cardiac death. Long QTc interval, frequent premature ventricular contractions (PVCs) and left ventricular dilatation (LVD) were reported in some CTD patients.

In order to determine the cardiac CTD patient phenotype, we performed a prospective study on 24 French male CTD patient including resting 12-lead ECG, 24-hour ambulatory ECG and transthoracic echocardiography (TTE).

We present here preliminary results on the first 17 CTD patients included (mean age 17.5 ± 4.2 years). 24-hour ambulatory ECG was impossible in 2 patients. No patient had syncope. No patient had LVD, or LV systolic dysfunction. LV posterior wall thinning was observed in only one patient. On resting 12-lead ECG, prominent U-waves were common (80%) and the QTc was of normal duration in all patients when U-waves were excluded (429.5 ± 21.5 ms). 24-hour ambulatory ECG revealed an abnormal intermittent ECG pattern, associating paroxysmal prominent U-waves (100%) and paroxysmal biphasic T-waves (93.3 %). PVCs were rare (30.1 ± 79.2 per 24h).

Contrary to what was suggested in the literature, we did not find any long QTc interval (after exclusion of U-waves) or LVD. We documented abnormal ventricular repolarization pattern with prominent U-waves and biphasic T-waves. Cardiac follow-up is needed.

Small molecule therapeutic approach for creatine transporter deficiency: creatine prodrug delivery targeting fatty acid amide hydrolase

Alex Edwin
Stanford School of Medicine
Authors: Alex Edwin; Albert Garofalo; Jing Zhao; Marcus Schonemann; Thomas Montine

BIO

Alex received his bachelor's degree in neuroscience from Santa Clara University. He also minored in Spanish and biology. During his time there, he studied fMRI data to identify patterns of resting-state functional brain connectivity in individuals with Autism Spectrum Disorder. Currently, he utilizes hippocampal slice cultures, cell cultures, and biochemical assays to screen small molecule drug compounds. His research is conducted with hopes to identify novel therapeutics for X-linked creatine deficiency, Alzheimer's disease, and Parkinson's disease.

ABSTRACT

Effective delivery of creatine or a creatine mimetic has been the goal of numerous therapeutic approaches for the treatment of Creatine Transporter Deficiency. To date, the most advanced approaches utilize ester and amide prodrug linkages for delivery of creatine across the blood brain barrier and neuronal membranes. As a result of this work, fatty acid amide hydrolase (FAAH) has been identified as a potential enzymatic target for the controlled release of creatine within neurons. FAAH is highly expressed in brain tissue and has a broad specificity for various fatty acid amide compounds. However, prodrugs that currently target FAAH tend to suffer from poor metabolic stability and low solubility, reducing their bioavailability. To address these issues, our research focuses on refining current prodrug delivery methods. We have developed two assays for the measurement of creatine release from prodrugs in human HAP1 CrT KO cell cultures and mouse CrT KO hippocampal slice cultures. With these assays, our ongoing research seeks to identify a novel orally administered creatine therapeutic which has enhanced solubility and bioavailability within the CNS.

Towards the discovery of small molecules that restore the expression and function of CTD variants

Jacklyn M. Gallagher
Purdue University
Authors: Jacklyn M. Gallagher; Charles P. Kuntz; & Jonathan P. Schlebach

BIO

I am a rising 4th year graduate student in the Schlebach lab at Purdue University. Our lab investigates the physiochemical reactions that impact proteostasis, where disruptions often lead to a vast array of diseases. These disruptions can arise from mechanisms such as alterations during protein synthesis and/ or protein misfolding. Broadly, my research focuses on uncovering structural insights into the native and non-native conformation(s) of SLC6A8, the creatine transporter (CT1). More specifically, our lab is applying a hybrid technique to identify small molecule therapeutic leads that are suitable for optimization as pharmacochaperone targets for native and misfolded conformations of SLC6A8 to enhance plasma membrane expression and function.

My previous academic research was conducted in a laboratory that focuses on medicinal chemistry and drug discovery (small molecules) from natural products. Charles Kuntz, a computational chemist and staff scientist in our lab, previously focused on modeling the serotonin transporter for his PhD research; a SLC6 family member that has the same conformational transport mechanism as CT1 and was just shown to be stabilized in the inward-facing (IF) conformation by small molecules. Our combined understanding and foundations in proteins and small molecules compliments a hybrid approach, where he screened a commercially available library against the IF conformation of CT1 for compound leads. We obtained 53 compounds and I am now utilizing various methods to investigate the impact of each small molecule on the expression and function of CT1, in hopes to also gain structural insights into the native and non-native conformations of CT1.

ABSTRACT

Over 100 loss-of-function (LOF) mutations within the SLC6A8 creatine transporter (CT1) are known to cause creatine transporter deficiency (CTD) syndrome. Most of these mutations enhance CT1 misfolding and degradation, and the resulting loss of the transporter protein ultimately compromises creatine uptake within the brain and other organs. Creatine uptake could therefore be restored by small molecule “correctors” that rescue the expression of misfolded variants, the development of which has recently revolutionized the treatment of several other genetic diseases of membrane protein misfolding. Cumulative observations concerning the mechanistic effects of drugs targeting related SLC6 transporters such as the serotonin (SERT) and dopamine (DAT) transporters suggest compounds that selectively bind to their inward-facing (IF) conformation generally enhance their expression and maturation. Based on these considerations, we set out to identify small molecules that selectively bind to the IF conformation of CT1 in order to restore the expression and activity of misfolded CT1 variants. Towards this goal, we developed a virtual screening approach to identify small molecules that selectively bind to the IF conformation of CT1, then profiled their effects on CT1 expression. Of our top 53 candidates, we identify several that alter the expression profile of WT CT1 and a few that enhance its expression at the plasma membrane. We are currently working to determine how these molecules impact CT1 function and how they impact pathogenic CT1 variants. Additionally, based on the structures of our top hits, we are currently searching for second-generation compounds with increased potency. These results represent an important step toward the development of novel pharmacological chaperones for the treatment of CTD.

2023 Cerebral Creatine Deficiency Syndromes Externally-Led Patient Focused Drug Development Voice of the Patient Report

Celeste Graham, MEd
Association for Creatine Deficiencies
Authors: Celeste Graham; Emily Reinhardt; Heidi Wallis; Chrystal Palaty

BIO

Celeste received her Bachelor of Arts Degree in Child and Family Development (Birth-Kindergarten Licensure) from the University of North Carolina at Charlotte in 2006 and her Master of Arts Degree in Special Education: General Curriculum (K-12 Licensure) from Western Carolina University in 2011.

Professionally, Celeste is currently an Integrated Care Navigator for a patient and caregiver advocacy nonprofit agency, which has been the perfect combination of her education, experience, and life with Levi. Prior to her current position, she was a special education teacher in various capacities within a local North Carolina public school system for 15 years. Her entire career has been focused on working with children with special needs and their families.

Personally, Celeste is a wife to Phil and a mom to four kiddos--Paisley, Levi, Blaine, and Gabriel. Levi is affected by Creatine Transporter Deficiency (CTD).

Celeste has been involved with the Association for Creatine Deficiencies (ACD) since 2018, serving as a volunteer, a board ambassador, and currently as a board member.

ABSTRACT

Externally-Led Patient Focused Drug Development (ELPFDD) meetings are a methodical way to make sure that patient and caregiver perspectives related to living with a disease are considered throughout the drug development process. In addition to patients and caregivers, these meetings are attended by regulatory agencies, industry, researchers, and clinicians. Following the ELPFDD, an extensive Voice of the Patient (VOP) report is compiled, capturing all of the data and a summary of the information shared throughout the meeting. This report is submitted to the FDA, to be used as a reference point when drugs or therapies are reviewed.

The Association for Creatine Deficiencies (ACD) hosted a virtual ELPFDD meeting in January 2023 on Cerebral Creatine Deficiency Syndromes (CCDS). Following a brief introduction with remarks from the FDA and a clinical overview of CCDS, the meeting was divided into two main sessions - one focusing on living with CCDS and the other focusing on current and future approaches to treatment for CCDS. The CCDS VOP is a comprehensive summary from the meeting. It includes key insights, a wealth of data, and impactful quotes from patients and caregivers throughout. This poster aims to provide a visual summary of the CCDS VOP.

Functional studies in creatine transporter deficiency

Filippo Ingoglia, PhD
University of Utah
Authors: Filippo Ingoglia; Sheelu Kumari; Marzia Pasquali; Nicola Longo

BIO

Dr. Filippo Ingoglia, PhD, is a biochemical geneticist, assistant professor in the Department of Pathology at the University of Utah, and medical director at the ARUP Laboratories. Dr. Ingoglia was born and raised in Italy, where he completed all his higher education, receiving BA, MA, and PhD degrees from the University of Parma. During his PhD training, he spent four months at the University of Utah as a visiting fellow, and the lab's research was focused on rare inherited metabolic disorders. That experience piqued his interest in biochemical genetics, and to apply to the Clinical Biochemical Genetics Fellowship with the Department of Pathology two years later. In 2021 he graduated and obtained the American Board of Medical Genetics and Genomics (ABMGG) certification in Clinical Biochemical Genetics. Since he stepped into the biochemical genetics field, he has focused on creatine metabolism in patients with urea cycle disorders and, ultimately, on the development of methods to determine the effectiveness of potential therapeutic agents for the treatment of guanidinoacetate methyltransferase (GAMT) deficiency. In 2023 Dr. Ingoglia joined the Creatine Deficiency Research Center, Funded by ACD and launched at the University of Utah. He will contribute with his expertise in cellular transport studies by developing a functional test to confirm the diagnosis of creatine transporter deficiency (CTD), to determine whether there is residual creatine transport activity in CTD patients, and to define the function of variants of uncertain significance.

ABSTRACT

Creatine transporter deficiency (CTD) is an X-linked disorder caused by variants in the creatine transporter gene (SLC6A8) and characterized by intellectual disability, failure to thrive, speech delay, autistic-like behavior, and seizures. Affected patients have increased urine creatine/creatinine ratio and pathogenic variants in the SLC6A8 gene. Genetic testing can miss variants outside the coding region of the gene or detect missense variants of uncertain significance (VUSs). In such cases, a functional assay can be used to confirm the diagnosis. We are developing a new assay to measure creatine transport in fibroblasts using a stable isotope rather than radioactive creatine. Uptake in cells from patients with suspected creatine transporter deficiency will be compared to those of normal cells and cells with known pathogenic variants in the SLC6A8 gene. In addition, we will immortalize fibroblasts hemizygous for a null allele and express in them the normal SLC6A8 minigene and one in which VUS have been recreated. This assay will confirm the diagnosis of creatine transporter deficiency, determine whether there is residual creatine transport activity, and define the function of VUS without the need for a skin biopsy in each patient.

Effect of creatine supplementation on AGAT expression and metabolic intermediates in GAMT-deficient mice

Alex Lee
University of Toronto
Authors: Ilona Tkachyova; Madeleine Hall; Josh Atienza; Haneen Ali; Jens Feugmann; Nico Guischard; Dahai Wang; Alex Lee; Michael Tropak; Andreas Schulze

BIO

Alex is currently a PhD student in the Department of Biochemistry at the University of Toronto. He works in the lab of Dr. Andreas Schulze at the Hospital for Sick Children where his research focuses primarily on investigating how AGAT expression is controlled and regulated by creatine. Alex was also a previous recipient of the ACD fellowship.

ABSTRACT

We carried a multidimensional study to examine the effect of creatine supplementation on arginine-derived guanidino compounds, AGAT expression and AGAT activity in creatine-deficient mouse model. Adult wildtype, heterozygous and GAMT-deficient mice were kept either on creatine-free, 2% or 4% creatine supplemented mouse chow for 10 weeks. Mouse urine and blood were collected at the beginning and the end of the trial; mouse tissues were harvested at the end of the study. An appropriate age matching non-treatment mouse group was used as a control for tissue analysis.

In urine, plasma and selected tissues LCMSMS analysis demonstrated varied effect of creatine supplementation on creatine and guanidino acetate (GAA) levels. Wildtype mice showed increase of creatine in urine, plasma, kidneys and liver and there was no change in brain, heart and muscle. Mutant mice on the other hand showed increase of creatine in urine, plasma and all organs. Further, creatine supplementation led to decrease of GAA in urine, plasma and all organs of wildtype mice. Mutant mice also showed reduction of GAA in their organs, except liver. Western blot analysis revealed marked decrease in AGAT gene expression in kidneys, brain and liver following creatine supplementation. Since the creatine effect on AGAT mRNA in liver was inconclusive, we measured AGAT enzyme activity and could confirm reduced AGAT activity.

In conclusion, we can demonstrate the efficacy of creatine on reduction of GAA in mice. The mechanism by which creatine reduces GAA is the noticeable inhibitory effect of creatine on AGAT expression.

Ribosome-stalling reporters suggest the N-terminus of AGAT acting as a creatine-dependent translation-arrest peptide

Alex Lee
University of Toronto
Authors: Michael B. Tropak; Alex Lee; Ilona Tkachyova; Dahai Wang; Andreas Schulze

BIO

Alex is currently a PhD student in the Department of Biochemistry at the University of Toronto. He works in the lab of Dr. Andreas Schulze at the Hospital for Sick Children where his research focuses primarily on investigating how AGAT expression is controlled and regulated by creatine. Alex was also a previous recipient of the ACD fellowship.

ABSTRACT

Arginine:glycine amidinotransferase (AGAT) is the rate-limiting enzyme in the two-step biosynthetic pathway of creatine (CT).

Increasing intracellular levels of CT results in decreased AGAT mRNA, protein expression, and enzyme activity. In previously described experiments, we have used genome editing to produce a HAP1 cell line that expresses a C-terminal tagged AGAT-NanoLuc Luciferase (AGAT-NLuc) reporter to monitor the decrease in AGAT expression with increasing intracellular CT. Co-treatment with CT and a transcriptional inhibitor, Actinomycin D, or a translation inhibitor, cycloheximide, suggested the involvement of a post-transcriptional mechanism controlling in AGAT expression. We have identified a 23 amino acid long sequence on the N-terminus of AGAT ('AGAT peptide') that enables the CT responsiveness. Fusing this sequence in-frame or as an upstream open reading frame to Firefly Luciferase and expression in cells results in a dose-dependent decrease in luminescence with increasing CT.

We hypothesize that the mechanism by which CT controls AGAT expression involves ribosomal stalling. During translation, CT could interact with the nascent AGAT peptide arresting further AGAT translation and reducing AGAT mRNA stability. We have generated a series translation-arrest reporters consisting of a N-terminal Nanoluc Luciferase and C-terminal Firefly luciferase with InterVening Sequences consisting of Internal Ribosome Entry Sites and/or P2A Translation Re-initiation Sequences along with the wild type or mutated AGAT peptide.

Our results are highly suggestive of the AGAT nascent N-terminal amino acid sequence acting as a translation arrest peptide.

Novel creatine-loaded nanoparticles: A potential therapeutic avenue for creatine transporter deficiency

Sebastian Leon
University of Central Florida
Authors: Sebastian Leon; Jorge Pereira; Xiufang Guo; Swadeshmukul Santra

BIO

I am a Colombian-American scientist interested in investigating the intersection between medicine and nanotechnology. While I have always been fascinated by the nervous system, I wasn't introduced to nanotech until my third year as an undergraduate. From there I would complete a Master's in Nanotechnology at the University of Central Florida under Dr. Swadeshmukul Santra.

My Master's thesis focused on the development of creatine-loaded nanoparticles as a potential therapeutic intervention for head trauma. This research not only provided me with invaluable hands-on experience within the realm of chemistry and material characterization.

Subsequently, my research focus shifted towards addressing Cerebral Creatine Deficiency Syndromes (CCDS), with a specific focus on Creatine Transporter Deficiency (CTD). My current project aims to devise a particle-based solution capable of delivering creatine directly to brain tissue. By circumventing the limitations of oral supplementation, this innovative approach holds promise as a potential treatment option for individuals affected by CCDS, particularly those with CTD.

I will begin training as a physician-scientist at the Donald and Barbara Zucker School of Medicine this August and strive to make the world a better place one person at a time through the development of nanoscale tools and therapies.

ABSTRACT

Creatine Transporter Deficiency (CTD) is an X-linked disorder characterized by a dysfunctional Creatine Transporter (CrT), leading to impaired creatine uptake and disrupted cerebral energy metabolism. Despite the critical role of creatine in cellular energy balance, effective treatments for CTD are currently lacking. Novel therapeutic approaches, such as gene therapy or nanoscale delivery systems, hold promise for addressing this unmet medical need.

In this study, we report the synthesis and characterization of novel creatine-loaded, polyphenol-based particles. Our particles exhibit an impressive loading capacity exceeding 50% and demonstrate no discernible toxicity towards mature hiPSC cortical neurons. Comprehensive characterization employing LC-MS, FTIR, UV-visible spectroscopy, fluorescence spectrophotometry, and Dynamic Light Scattering highlights the distinctive properties of this innovative formulation, laying a solid foundation for its further advancement.

FTIR spectroscopy analysis reveals no alterations to creatine, suggesting its loading mechanism relies on Van der Waals forces rather than permanent chemical conjugation. Additionally, fluorescence spectrophotometry indicates a close interaction between creatine and the phenolic compound utilized in the synthesis. Importantly, the synthesized particles are composed of Generally Regarded as Safe (GRAS) materials, ensuring their safety for biomedical applications, and have an average hydrodynamic radius of 318 nm, a zeta-potential of -18 mV, and a polydispersity index of 0.22.

Establishing a Core Outcome Set (COS) for CTD & GAMT deficiency through caregiver and health professional collaboration

Zahra Nasseri Moghaddam
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Authors: Zahra Nasseri Moghaddam; Emily Reinhardt; Audrey Thurm; Heidi Wallis; Sylvia Stöckler-Ipsiroglu

BIO

Zahra Nasseri Moghaddam is a genetics research assistant at Dr. Sylvia Stockler's lab within the Department of Pediatrics at UBC. Located in the Division of Biochemical Genetics at BC Children's Hospital in Vancouver, BC, Canada, her research interests reside in rare genetic disorders and the impact of genetic testing on clinical patient management. She is also involved in the development of core outcome sets for several rare disorders, including creatine transporter deficiency (CTD) and GAMT deficiency. Her passion lies in supporting families of children with various metabolic disorders, and she is dedicated to expanding her knowledge and expertise in this area through clinical research and international collaboration with researchers, clinicians, and families. With plans to begin her master's in genetic counseling this upcoming fall, she is driven to support individuals in their diagnostic odysseys.

ABSTRACT

Clinical trials aim to determine the safety and effectiveness of interventions by evaluating their impact on diverse endpoints. However, inconsistencies in defining and measuring these endpoints have posed challenges in applying and comparing trial results. A list of important outcomes, called a core outcome set (COS), is developed to identify a small set of disease-specific outcomes deemed important by stakeholders, and should be reported in every research study and clinical trial. Unfortunately, patient and caregiver perspectives have historically been overlooked in the COS development process, thus limiting their input into the outcome selection. ACD collaborated with caregivers and health professionals to develop a COS of eight outcomes for creatine transporter deficiency (CTD) and guanidinoacetate methyltransferase (GAMT) deficiency. Caregivers were partners throughout the COS development process, increasing community engagement and facilitating caregiver empowerment. Here, we provide an overview of our entire COS development project. Our multifaceted approach included (1) conducting evidence reviews (i.e., focus groups, literature reviews, patient registry data), (2) developing three Delphi surveys for input from the CCDS community at large, and (3) hosting a consensus workshop with caregivers and health professionals to finalize the COS. We expect that this project will (1) ensure a patient-centered approach for accelerating drug development, (2) minimize bias, and (3) promote a more efficient use of resources.

Evaluating cardiovascular health among CCDS patients enrolled in the CreatineInfo Patient Registry

Emily Reinhardt
Association for Creatine Deficiencies
Authors: Enaika Kishnani; Emily Reinhardt; Mark Levin, MD; Heidi Wallis

BIO

Emily currently serves as ACD's Patient Registry Coordinator, which affords her the privilege of collaborating directly with CCDS patients, caregivers, researchers, and other rare disease partners. Emily is a graduate of Kansas State University, earning both her BS and MS in Psychology with a focus in Behavioral Neuroscience. She has over 15 years of research experience, with particular emphasis in pre-clinical and translational neuroscience. Through her love of science, Emily is passionate about using data to improve the lives of people in her community.

ABSTRACT

Prior research has demonstrated that patients with creatine transporter deficiency (CTD) are at greater risk for developing a cardiovascular condition called prolonged QTc, which is an irregular heart rhythm. Although prior research has been conducted to understand the relationship between CTD and cardiovascular health, little research has been conducted to determine whether or not there is a relationship between arginine:glycine amidinotransferase (AGAT) or guanidinoacetate methyltransferase (GAMT) deficiencies and cardiovascular health. Therefore, the goal of this project was to better understand the relationship between all three cerebral creatine deficiency syndromes (CCDS) and cardiovascular health using patient- and caregiver-reported data. We developed a cardiovascular health survey which was launched via the CreatineInfo Patient Registry. Survey questions included topics such as the CCDS patient's cardiovascular health history, cardiovascular testing, exercise habits, and family cardiovascular history. This survey was the first to capture cardiovascular health data within our CreatineInfo patient registry. Our preliminary findings show that CTD patients report experiencing cardiovascular conditions, unlike GAMT and AGAT deficiency patients. Additional research is needed to fully understand the long-term impacts on cardiovascular health among CCDS patients.

Lifecycle and promotion of a custom patient registry survey with an industry partner

Emily Reinhardt
Association for Creatine Deficiencies
Authors: Emily Reinhardt; Heidi Wallis; Krista Viau; Sangeetha Iyer

BIO

Emily currently serves as ACD's Patient Registry Coordinator, which affords her the privilege of collaborating directly with CCDS patients, caregivers, researchers, and other rare disease partners. Emily is a graduate of Kansas State University, earning both her BS and MS in Psychology with a focus in Behavioral Neuroscience. She has over 15 years of research experience, with particular emphasis in pre-clinical and translational neuroscience. Through her love of science, Emily is passionate about using data to improve the lives of people in her community.

ABSTRACT

Background: An Association for Creatine Deficiency (ACD) industry partner developing a possible treatment for creatine transporter deficiency (CTD) approached ACD to develop a custom patient registry survey to learn about oral medication preferences to inform the development of their therapeutic.

Methods:

1. Created a data sharing agreement to establish protections for both ACD and the industry partner, and define project services, deadlines, deliverables, and payment schedule
2. Drafted a survey in collaboration with the industry partner
3. Consulted with a metabolic dietician to provide guidance on the proposed questions
4. Gathered feedback from ACD's Family Advisory Board (FAB). Feedback from the FAB ensured patient and caregiver perspectives were represented in the survey questions and the language was participant-friendly.
5. Developed a recruitment campaign to promote community engagement with the survey

Results:

1. An industry and non-profit data sharing agreement appropriate for future use
2. A custom oral medication survey
3. A successful recruitment campaign with high participant engagement surpassing our target goal, with 37 CTD participants completing the survey in the first six weeks
4. A final data report containing aggregate, de-identified results from the survey
5. Insights into patient oral medication preferences appropriate for sharing with stakeholders in future drug development efforts
6. Industry partner support of registry costs resulting in a self-sustaining registry

Conclusions: Development of a custom registry survey can mutually benefit patient advocacy groups and industry partners. ACD observed that survey participants were incentivized to complete the survey by simply knowing that their data had meaningful implications, setting the foundation for future successful survey recruitment strategies.

An ongoing collaboration: The Association for Creatine Deficiencies and the Clinical Genome resource work together to facilitate variant classification

Amanda Thomas-Wilson, PhD, FACMG
Clinical Genome Resource (ClinGen), Cerebral Creatine Deficiencies Variant Curation Expert Panel
Authors: Jennifer L. Goldstein; Heidi Wallis; Emily Reinhardt; Juliann M. Savatt; Erin Rooney Riggs; Amanda Thomas-Wilson; Emily Groopman; Vimla Aggarwal; Simona Bianconi; Raquel Fernandez; Kim Hart; Emily Kyle; Nicole Liang; Nicola Longo; Christine Preston; Daniel Reich; Meredith Weaver; Sarah Young; Saadet Mercimek-Andrews

BIO

Amanda Thomas-Wilson, PhD, FACMG is a current member of the Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel (CCDS VCEP) of the Clinical Genome Resource (ClinGen). She has been an active member of the panel since its inception, and she is presenting a poster on behalf of the CCDS VCEP to highlight the collaboration with the Association for Creatine Deficiencies and give an update on CCDS VCEP activities in the past year.

ABSTRACT

Background/Objectives: Understanding the clinical significance of variants within the genes causing cerebral creatine deficiency syndromes (CCDS) is important to ensure timely diagnosis and initiation of treatment for these neurological disorders. The Association for Creatine Deficiencies (ACD), a patient advocacy organization, collaborates with the NIH-funded Clinical Genome resource (ClinGen) to share data and assist in robust variant classification.

Methods: Via collaboration with ClinGen's GenomeConnect, ACD registry participants provide their genetic testing reports for submission to the public variant database, ClinVar. Data is also shared with the ClinGen CCDS Variant Curation Expert Panel (VCEP), which has developed guidelines for classification of variants in the genes causing CCDS (GAMT, GATM, SLC6A8) and submits those classifications to ClinVar as part of an FDA-approved process.

Results: Using published data, the ClinGen CCDS VCEP has classified 43 variants from ACD registry participants; 15 were classified by the VCEP as pathogenic (8 SLC6A8, 7 GAMT), 7 likely pathogenic (LP) (5 SLC6A8, 2 GAMT), 2 benign (1 SLC6A8, 1 GAMT), and 19 were variants of uncertain significance (VUS) (15 SLC6A8, 4 GAMT). 12 VUS were identified as tending towards LP by the VCEP based on the strength of evidence already available; ACD participants with these variants were recontacted to request additional case-level data (biochemical testing, magnetic resonance spectroscopy, family history, genetic testing of parents) with the goal of reclassifying these variants as LP or pathogenic.

Conclusions: Collaboration between the ACD and ClinGen increases understanding of the clinical significance of variants in the gene causing CCDS and may serve as a model for collaboration between other ClinGen VCEPs and patient advocacy organizations.

Improved outcomes in early treated GAMT deficiency – a sibling study

Heidi Wallis
Association for Creatine Deficiencies
Authors: Liora Caspi; Robin Hayeems; Andreas Schulze

BIO

Heidi is the Executive Director of the Association for Creatine Deficiencies and parent of four children, two of which have GAMT Deficiency, a rare cerebral creatine deficiency syndrome with severe neurological impacts if not diagnosed and treated from birth. Heidi and team recently completed a two year project to establish, through patient and expert consensus, a Core Outcome Set (COS) for GAMT and CTD clinical trials. Her team is preparing to begin a second project this fall to establish "Considerations for CTD & GAMT Outcome Measurement Tools (OMTs)" as a companion to the COS. Prior to working for ACD she was a grant analyst and project manager in the Utah Public Health Lab Newborn Screening program. Heidi is a voting member of the Utah Newborn Screening Advisory Committee and collaborated in the nomination and eventual adoption of GAMT on the RUSP. Heidi's vision is that one day all creatine deficiencies will be diagnosed at birth, through routine newborn screening, and will be treated with an effective and appropriate treatment before the onset of symptoms.

ABSTRACT

Background: Singular observations in GAMT deficiency, an ultra-rare, severe neurodevelopmental disorder, imply the benefit of early, presymptomatic treatment.

Methods: Four GAMT- and 8 age-matched control sibling pairs were enrolled. Based on structured interviews with 4 GAMT families a Redcap questionnaire was constructed. For example, parents were asked to indicate whether and when their child achieved specific milestones, achieved them with support, or did not achieve them. Questions included developmental milestones, fine motor-, cognitive-, self-care-, and social skills, behavior, coordination, and therapy/support.

Results: GAMT sibling pairs were diagnosed at 0.0/5.6, 0.0/0.8, 1.1/5.8, and 3.8/8.8 y (younger/older), with current age of 11. 4/16.8 y (9.0-13.6/14.0-18.7) (mean (range), younger/older). The healthy controls were 9.9/13.5 y (4.9-12.0/8.8-16.0).

In interviews, the parents identified intellectual level, communication, and self-care skills as the major difference between their two children with GAMT.

Using the questionnaire responses, we compared the older child with its younger sibling in each pair. In GAMT, the comparison revealed consistent and distinct differences in every tested domain with the younger sibling performing better than its older sibling. There was no such difference in control sibling pairs.

We further assessed GAMT outcome of early treatment (initiated <13 months, n=4) vs late treatment (initiated >3 years, n=4). There was normal to almost normal outcome in the early treatment group, while all children with late treatment demonstrated mostly large deficits in all investigated domains.

Conclusion: This study convincingly confirms the notion that early initiation of treatment results in much improved outcomes in children with GAMT deficiency. Early identification of affected individuals required for timely treatment, ideally in the presymptomatic phase of the disease, makes universal newborn screening for GAMT mandatory.

A drug repurposing pipeline to find treatments for SLC6A8/CRT-1 (creatine transporter) deficiency

Rhonwyn Waterson
BC Children's Hospital Research Institute, University of British Columbia, Vancouver, Canada
Authors: Rhonwyn Waterson; Aamina Shah; Roger Dyer; Peter Axerio-Cilies; Sylvia Stockler-Ipsiroglu

BIO

Rhonwyn is a medical student studying at the University College Dublin in Ireland. Raised in Vancouver, Canada she is excited to be working in Dr Sylvia Stockler's lab at the BC Children's Hospital Research Institute as a Summer Student. Together with Dr Axerio-Cilies (a former ACD fellowship award recipient), Aamina Shah (lab technician) and Roger Dyer (manager mass spectrometry facility) Rhonwyn is currently working on experiments with SLC6A8 variant fibroblasts that have deficient creatine transport to characterize creatine uptake in these cells, with the goal of identifying a drug that can rescue the transporter function. She hopes to continue being involved in creatine deficiency research in the future and is considering specializing in paediatrics upon completing medical school.

ABSTRACT

Rational:
There is currently no treatment for SLC6A8/CRT-1 related intellectual disability. We have established a 3-tier pipeline to find repurpose-able drugs for this condition.

Methods:

- Tier 1: In silico drug screening using a library of FDA approved drugs to identify drugs that would bind to the high-resolution 3D structure of SLC6A8/CRT-1 protein.
- Tier 2: In vitro testing of candidate drugs for their ability to rescue mutant SLC6A8/CRT-1 activity using electrophysiological patch clamp technique and measuring changes in transmembrane sodium gradient in SLC6A8 variant transfected HEK293 cells.
- Tier 3: To further validate tier 2 results, creatine uptake studies are performed in SLC6A8 deficient human fibroblasts measuring cellular uptake of D3 labelled creatine (D3-creatine) and its intracellular conversion to phosphocreatine (D3-PCr). Guanidino-propionate (GPA), a competitive inhibitor of SLC6A8-mediated creatine uptake is used to confirm SLC6A8 specificity of the measured uptake rates.

Results:
Using Tier 1 and 2 we have identified 12 candidate drugs / compounds which partially rescue deficient SLC6A8 activity in transfected HEK293 cells. 6/12 compounds can potentially be used for off label prescription in n-of-1 studies. 5/6 are effective in variant Phe408del and Asn336del. One compound (4PBA) showed efficacy in several SLC6A8/CRT-1 missense mutations.

We have created data for time and dose dependent D3-creatine uptake in wild type and Phe408del fibroblasts informing experimental protocols for further drug testing.

Work in progress:
To test D3-creatine uptake in Phe408del fibroblasts (purchased from the Coriell Biobank) and in Asn336del fibroblasts (once available) in response to 5 repurpose-able drugs identified in tier 2.

Acknowledgement: Our research is generously supported by the ACD.

DAY 2 OPENING SESSION

Opening remarks and session overview

8:45 AM - 9:00 AM MDT

Sangeetha Iyer, PhD
Association for Creatine Deficiencies

BIO

Dr. Sangeetha Iyer received her PhD in Molecular Pharmacology from the University of Pittsburgh and went on to complete her postdoctoral research at the University of Texas at Austin. She has over ten years of experience in model/assay development and drug screening for human disorders. Dr. Iyer is currently employed at Denali Therapeutics Inc, where she and her team develop assays for early as well as late stage therapeutic programs headed to the clinic. She works across multiple therapeutic modalities such as gene therapy, large molecules as well as small molecule drug candidates. Prior to Denali Therapeutics, Dr. Iyer was employed at Perlara PBC, a drug discovery company in San Francisco committed to finding therapeutics for rare genetic diseases. During her time there, she specialized in all aspects of the therapeutic discovery process- creating tools to study a specific disease, conducting drug discovery screens and identifying biomarkers for a successful transition to clinic. In her role, she also interacted with parents and foundations and laid the foundation for PerlQuests- a patient-driven personalized drug discovery program. With the assistance of clinical KOL's and parent advocates, she was involved in generating a roadmap for an n=1 trial for phosphomannomutase 2 deficiency that is currently underway. Since 2020, Dr. Iyer has been working with the Association of Creatine Deficiencies as their scientific consultant to refine their scientific research roadmap. She brings her expertise in working with rare disease patient groups, clinical KOL's and scientific discovery processes to her role with the ACD.

SPECIAL INTEREST SESSION

Roots to wings: Building a solid foundation for connection & communication

9:00 AM - 10:00 AM MDT

Tannalynn Neufeld, MS, CCC-SLP
www.aaccessible.org

BIO

Tanna is a speech-language pathologist (speech therapist) with nearly 20 years of experience supporting children who struggle to develop speech and language due to neurodevelopmental differences. In addition to her core training in speech and language development and disorders, she has obtained interdisciplinary knowledge and skills which she carries into a developmental, whose-child and family approach to education and therapeutic care. Tanna has experience in augmentative and alternative communication (AAC) strategies to support communication development for non-speaking individuals across the lifespan. She currently works as a parent coach and is pursuing a doctoral degree in infant and early childhood development, focusing specifically on developmental disabilities and infant/early childhood mental health. When not learning or providing direct care to children and families, Tanna presents at national and international conferences, including online webinars and workshops.

ABSTRACT

As the origins of symbolic development, emotions and relationships play a prominent role in language acquisition and expression. This caregiver-focused session explores the symbiotic relationship between social-emotional development and relational connection ('roots') and language development ('wings'). Utilizing the Functional Emotional Developmental Model, participants will explore the importance of supporting social-emotional, pre-language capacities alongside language development for children with complex communication needs who use a variety of expressive modalities, including speech, sign language, and augmentative and alternative communication (AAC) tools. Participants will be encouraged to consider how weak social-emotional, and pre-language foundations contribute to language learning barriers, scattered skills, and challenging behavior. From this perspective, participants will learn how to support language developmental through interaction strategies rooted in the power of the caregiver-child relationship and underscored by a consideration of the individual differences and unique developmental trajectories of each child.

SESSION 4: BIOMARKERS & ENDPOINTS

Clinical characteristics of creatine transporter deficiency (CTD): Final results of the Vigilan observational study

10:00 AM - 10:30 AM MDT

Judith Miller, PhD
Children's Hospital of Philadelphia

Authors: Aurore Curie, Matthildi Papathanasiou, Fahra Gheurbi, Michaël Pommier, Tiphaine Courtalon, Amandine Brun, Léa Saverat, Florian Ducret, Axelle Poulain, Marion Buchy, Solène Roudet, Oriane Susini, David Cheillan, Ganaëlle Remerand, Christine Barnerias, Anaïs Brassier, Alice Goldenberg, Anne-Laure Avice-Denizet, Agathe Roubertie, Laurence Lion-François, Stéphanie Marignier, Pascale De Lonlay, Fanny Mochel, Vincent Navarro, James Lespinasse, Didier Lacombe, Renaud Touraine, Sylvain Rheims, Nathalie Bedoin, Jean-Baptiste Van der Henst, Laure Pisella, Eric Chabanat, Anne Cheylus, Yves Rossetti, Yves Paulignan, Eleni Panagiotakaki, Vincent des Portes

BIO

Judith Miller, PhD, is a clinical psychologist with 25 years' experience in developmental disorders. She has a joint appointment as Associate Professor in both the Psychiatry and Pediatrics departments at the Children's Hospital of Philadelphia (CHOP), which is affiliated with the Perelman School of Medicine at the University of Pennsylvania. She is also the Clinical Training Director at the Center for Autism Research, and the Associate Director for the Leadership in Education in Neurodevelopmental Disorders (LEND) program at CHOP. Her research focuses on screening, diagnosis, and outcomes across the lifespan for individuals with neurodevelopmental disorders.

ABSTRACT

Introduction: Results from the Vigilan Observational Study of Creatine Transporter Deficiency (CTD) can help us learn the developmental trajectories in this population.

Methods: This study (NCT02931682) used parent questionnaires, clinical assessments, and direct testing to characterize clinical features of males with confirmed CTD (SLC6A8 pathogenic variant) for up to 4 years.

Results: Fifty patients (mean baseline age, 7.6 years; range, 1.5-24.4 years) were enrolled. The most common first symptoms parents recognized (with hindsight) were developmental delays or difficulty feeding/gastrointestinal symptoms/failure to thrive before 12 months, or developmental delays between 12-36 months. Without a known family history, the median age of first symptom in hindsight was 6 months, median age of first evaluation was 15 months, and median age of diagnosis of CTD was 43 months. From parent history and prospective data collection during the study, we tracked whether and at what age participants reached four notable functional milestones (ages of walking, first words, first sentences, toileting skills) or experienced the onset of a seizure disorder. We will also present medication usage, non-pharmacological interventions, and developmental trajectories from standardized developmental testing across the study period. For standardized testing, we also modeled the trajectories seen in our CTD sample in contrast to trajectories expected for children in the general population.

Conclusions: The summary interpretation of observations made provides an important means of evaluating trajectories of developmental disruption associated with CTD, which may improve clinical care as well as research into the impact of possible interventions.

SESSION 4: BIOMARKERS & ENDPOINTS

An ongoing collaboration: The Association for Creatine Deficiencies and the Clinical Genome resource work together to facilitate variant classification

10:30 AM - 11:00 AM MDT

Amanda Thomas-Wilson, PhD, FACMG
Clinical Genome Resource (ClinGen), Cerebral Creatine Deficiencies Variant Curation Expert Panel

Authors: Amanda Thomas-Wilson; Jennifer L. Goldstein; Heidi Wallis; Emily Reinhardt; Juliann M. Savatt; Erin Rooney Riggs; Emily Groopman; Vimla Aggarwal; Simona Bianconi; Raquel Fernandez; Kim Hart; Emily Kyle; Nicole Liang; Nicola Longo; Christine Preston; Daniel Reich; Meredith Weaver; Sarah Young; Saadet Mercimek-Andrews

BIO

Amanda Thomas-Wilson, PhD, FACMG is a current member of the Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel (CCDS VCEP) of the Clinical Genome Resource (ClinGen). She has been an active member of the panel since its inception, and she is presenting a poster on behalf of the CCDS VCEP to highlight the collaboration with the Association for Creatine Deficiencies and give an update on CCDS VCEP activities in the past year.

ABSTRACT

Background/Objectives: Understanding the clinical significance of variants within the genes causing cerebral creatine deficiency syndromes (CCDS) is important to ensure timely diagnosis and initiation of treatment for these neurological disorders. The Association for Creatine Deficiencies (ACD), a patient advocacy organization, collaborates with the NIH-funded Clinical Genome resource (ClinGen) to share data and assist in robust variant classification.

Methods: Via collaboration with ClinGen's GenomeConnect, ACD registry participants provide their genetic testing reports for submission to the public variant database, ClinVar. Data is also shared with the ClinGen CCDS Variant Curation Expert Panel (VCEP), which has developed guidelines for classification of variants in the genes causing CCDS (GAMT, GATM, SLC6A8) and submits those classifications to ClinVar as part of an FDA-approved process.

Results: Using published data, the ClinGen CCDS VCEP has classified 43 variants from ACD registry participants; 15 were classified by the VCEP as pathogenic (8 SLC6A8, 7 GAMT), 7 likely pathogenic (LP) (5 SLC6A8, 2 GAMT), 2 benign (1 SLC6A8, 1 GAMT), and 19 were variants of uncertain significance (VUS) (15 SLC6A8, 4 GAMT). 12 VUS were identified as tending towards LP by the VCEP based on the strength of evidence already available; ACD participants with these variants were recontacted to request additional case-level data (biochemical testing, magnetic resonance spectroscopy, family history, genetic testing of parents) with the goal of reclassifying these variants as LP or pathogenic.

Conclusions: Collaboration between the ACD and ClinGen increases understanding of the clinical significance of variants in the gene causing CCDS and may serve as a model for collaboration between other ClinGen VCEPs and patient advocacy organizations.

SESSION 4: BIOMARKERS & ENDPOINTS

New biomarkers for dodecyl creatine ester therapeutic efficacy monitoring

11:15 AM - 11:45 AM MDT

Aloïse Mabondzo

Paris-Saclay University, CEA, Department of Medicines and Technologies for Health (MTS), Neurovascular unit and Therapeutic Innovation Laboratory (LENIT), Gif-sur-Yvette cedex 91191, France

Authors: Clémence Disdier; Amélie Soyer; Léa Broca-Brisson; Thomas Joudinaud; Henri Bénech; Matthew R. Skelton; Jean Armengaud; Rifat A. Hamoudi; Nicolas Tournier and Aloïse Mabondzo

BIO

Dr Aloïse Mabondzo, research director is a head of Neurovascular Unit Research & Therapeutic Innivation Laboratory at CEA Saclay in France. He joined the CEA, the Life Science Division, in May of 1998 as the leader of a neurovascular pharmacology Lab with a strong focus on in vitro blood-brain barrier (BBB) modeling and pathophysiology of the brain. His Lab has developed fully characterised in vitro screening tools allowing the optimisation of the molecules under development for brain penetration. His innovative research has made possible the development of research programs in the neuroscience field: Alzheimer's disease, nanotoxicology, ischemic hypoxia encephalopathy, X-linked creatine transporter deficiency disease. Dr Aloïse Mabondzo is author or co-author of 70 articles in peer reviewed journals, nine patents, gave lectures as lecturer and as well as guest speaker, poster presentation in the scientific congress, and he often reviews articles for scientific journals. He has directed twenty PhD students, and seven postdoctoral positions have been part of his team. As a Neuroscientist, Dr Mabondzo aims to bridge the gap between experimental research and clinical therapy for cerebral diseases. He is a cofounder of CERES BRAIN THERAPEUTICS, a spin-off from the French alternative energies and Atomic Energy Commission (CEA), committed to focus its resources to the preclinical development of advance drug over coming years in order to provide CTD patients with a therapeutic solution to deliver creatine in the brain.

ABSTRACT

Creatine transporter deficiency (CTD) is caused by pathogenic variants in SLC6A8, leading to lack of Creatine in the brain. There is no treatment for CTD leaving patients and caregivers have no option but supportive care.

We demonstrated that dodecyl creatine ester (DCE) administered by the nasal route is able to reach the neurons to deliver creatine and that a small dose is sufficient to modulate biomarkers correlating with cognitive functions. However, any cognitive improvement in treated patients will likely take several months to manifest.

To find relevant outcomes measures to monitor DCE efficacy, we investigated the impact of creatine deficiency and DCE treatment in cerebral cells by looking at methylation balance (i) and glucose metabolism (ii). We combine observations in-vivo in SLC6A8-deficient mice and in-vitro in human brain organoids derived from CTD patient cells.

Results:
(i) Our findings reveal hypo-methylation of nucleic acids in both in-vivo and in-vitro CTD models compared to controls leading to alterations of genes and proteins expression by epigenetic mechanisms regulated by DCE treatment in-vivo.
(ii) [18F]FDG PET imaging demonstrated a lower glucose cerebral uptake in SLC6A8-deficient mice compared to controls and a decline of this uptake over a month. Intranasal DCE treatment has a positive impact on this alteration. Mechanistic investigations in vivo and in vitro suggest that intracellular trafficking of glucose transporters may be altered due to inactive AMP-activated protein kinase.

Consistency between observations in the in-vivo and in-vitro models support the value of these new biomarkers to monitor the DCE efficacy.

SESSION 5: GENE THERAPY APPROACHES FOR CCDS

AAV9-based gene therapy results in a durable and dose-dependent correction of the biochemical phenotype in a mouse model of guanidinoacetate methyltransferase (GAMT) creatine deficiency

1:00 PM - 1:30 PM MDT

Jagdeep Walia, MD, FRCPC
Queen's University

Authors: Robyn Binsfeld 1; Troy Webster 1; Ilona Tkachyova 2,3; Emahnee Cover 4; Tesla Peretti 1; Brianna Quinville 1; Melissa Mitchell 5; Andreas Schulze 2,3,6; Jagdeep Walia 1,5,7

BIO

Dr. Jagdeep Walia is a medical geneticist and full-time professor in the Division of Medical Genetics, Department of Pediatrics. He finished his residency in Medical Genetics from University of Manitoba and joined Queen's University in 2012. In his clinical work, Dr. Walia consults across a broad range of genetic issues that affect children and adults, including cancer, prenatal diagnosis, metabolics and general genetics. He teaches genetics at the undergraduate and postgraduate levels.

Dr. Walia launched a clinical and basic genetics research program soon after joining Queen's. His lab focuses on developing novel gene therapy approaches for inherited and acquired neurodegenerative disorders including Creatine deficiency disorders.

ABSTRACT

Objectives: Creatine deficiency disorders such as guanidinoacetate methyltransferase deficiency (GAMT-D) are inborn errors of metabolism resulting in several neurological manifestations including intellectual disability and epilepsy, emphasizing the role of creatine in the brain. Current treatments, while partially successful do not restore creatine levels or reduce accumulation of the toxic guanidinoacetate (GAA) intermediate in the brain. Previously we showed a proof-of concept demonstrating the short-term efficacy of scAAV9.hGAMT for treatment of GAMT-D. Here, we present a dose-response study exploring the durability of the therapy up to 5-months post treatment.

Design and Methods: scAAV9.hGAMT was injected intrathecally to GAMT-D mice at doses ranging from 6.25e10 to 2.5e11 vg/mouse at 6 weeks of age. Mice were sacrificed either 7-weeks or 20-weeks post-treatment. GAMT expression was assessed by western blot and qPCR analysis. Tissues and serum were analyzed using mass spectrometry to detect creatine and GAA.

Results: Intrathecal delivery of scAAV9.hGAMT restored expression of GAMT in the liver and detectable vector copies were found in the brains of treated animals. Creatine was increased while GAA accumulation was decreased in a dose-dependent manner throughout the body including the brain. These same results were observed overtime in the serum with a stabilization of creatine and GAA levels occurring at 6-weeks post injection that was maintained up until the endpoint of 20-weeks post-treatment.

Conclusions: This study adds to the growing findings that support the use of scAAV9.hGAMT as a therapeutic for GAMT-D. scAAV9.hGAMT is being further investigated to determine the safety profile and optimize the dose levels for future translation to clinic.

SESSION 5: GENE THERAPY APPROACHES FOR CCDS

Optimal dosage for IT delivery of SLC6A8 gene therapy

1:30 - 2:00 PM MDT

Troy Webster
Queen's University
Authors: Troy Webster; Chiara Sawilla; Robyn Binsfeld; Ilona Tkachyova; Melissa Mitchell; Steven Gray; Andreas Schulze; Jagdeep Walia

BIO

Troy Webster is a PhD Candidate at Queens University in Kingston Ontario where he has been developing a gene therapy for CTD. Troy was also honoured to be one of the recipients of the 2024 ACD fellowship award.

ABSTRACT

Objective: Solute Carrier Family 6 Member 8 (SLC6A8, creatine transporter) is an X-linked active Na+Cl- dependent transporter responsible for cellular intake of creatine, loss of function mutations result in developmental delay, intellectual disability, motor function impairment, seizures, and hyperactivity. Previously we developed a self-complementary AAV9 vector carrying a codon optimized SLC6A8. This vector showed significant improvement to both biochemical and behavioural phenotypes in a mouse model of SLC6A8 disorder when given via intracerebroventricular injections. However, when delivered through lumbar puncture injections the biochemical improvement was limited. Here we compare the efficacy of 4 different dosages of lumbar puncture given SLC6A8 gene therapy to observe if higher dosages of lumbar puncture gene therapy could improve the effectiveness of the therapy. Efficacy will be assessed through improvements to behavioural phenotypes and the restoration of creatine throughout the central nervous system and muscle tissue.

SESSION 5: GENE THERAPY APPROACHES FOR CCDS

Ubiquitous promoter in AAV9 GAMT gene therapy yields lower levels of guanidinoacetic acid in the brain

2:00 PM - 2:30 PM MDT

Gerald S. Lipshutz, MD, MS
UCLA School of Medicine
Authors: Puja Patel; Ilona Tkachyova; Andreas Schulze; Gerry Lipshutz

BIO

Gerald S. Lipshutz, MD MS received his medical degree from the University of California Los Angeles (UCLA) School of Medicine and completed his postgraduate training at the University of California San Francisco School of Medicine. He is a Professor in the Departments of Surgery and the Department of Molecular and Medical Pharmacology. He is also a member of the Intellectual and Developmental Disabilities Institute at UCLA along with the Broad Center; he presently holds the Goldwyn Chair. His clinical specialty and interests include kidney and pancreas transplantation and gene and cell therapies for single gene metabolic disorders of the liver. Dr. Lipshutz has been an invited participant in multiple National Institutes of Health (NIH) conferences and has served as a grant reviewer for both Wellcome Trust, UK and the US National Institutes of Health where he previously was a standing member of the GDD Study Section. His research focus has been in the development of gene and cell therapies for specific urea cycle disorders and creatine deficiency disorders along with gaining a greater understanding of the underlying neuropathology in some of this disorders. He is dedicated to working to bring such therapies forward to the clinic for such afflicted patients.

ABSTRACT

GAMT deficiency is a disorder of the creatine biosynthesis with elevated levels of guanidinoacetic acid (GAA). We created an array of novel AAV based GAMT vectors and assessed their efficacy in restoring function of the GAMT enzyme and reducing the brain GAA.

Methods: Four AAVs were developed: 1) a single stranded (ss) AAV rh10 with TBG promoter; 2) a ssAAV8 with TBG promoter; 3) a ssAAV9 with CAG promoter/enhancer; and 4) a self-complementary AAV9 with CAG/enhancer promoter. These 4 viruses were injected into Gamt-deficient mice. GAA and creatine levels were analyzed in plasma, brain, and liver after 2 months. In addition, other brain guanidino compounds were determined.

Results: All groups presented with restoration of GAMT function in varying amounts as detected by reduction of GAA/increase of creatine in liver, brain, and plasma. AAV9 with CAG promoter/enhancer proved most effective in lowering brain GAA levels. rh10, AAV8, and AAV9 were equally effective in lowering the plasma GAA and increasing creatine levels.

Conclusion: The signs/symptoms of GAMT deficiency, caused by both buildup of the neurotoxin GAA and reduced creatine, can be effectively treated in a murine model by AAV gene therapy. While the liver is the main GAA synthesis site, it is important that brain expression also be achieved. AAV-based approaches that utilize a serotype transducing the brain and has a ubiquitous promoter can effectively restore function of GAMT protein in both sites as demonstrated by lower levels of GAA in both the liver and brain, along with restoration of creatine levels.

SESSION 5: GENE THERAPY APPROACHES FOR CCDS

Towards a cure for creatine transporter deficiency: gene therapy and novel functional biomarkers

2:30 PM - 3:00 PM MDT

Laura Baroncelli, PhD
Neuroscience Institute, CNR

Authors: Laura Baroncelli; Federica Di Vetta; Ludovica Iovino; Lorenzo Dadà; Caterina Montani; Alessandro Gozzi; Giulia Sagona; Raffaele Mazziotti; Elena Scaffei; Roberta Battini

BIO

Dr. Baroncelli graduated in Biology at the University of Pisa in 2005 and trained in the PhD program in Neurobiology at the Scuola Normale Superiore from 2006 to 2009. Following a fellowship at Scuola Normale Superiore, she was awarded in 2010 a two-year post-doctoral fellowship at the Accademia Nazionale dei Lincei, in Italy. Since 2011, she is Tenured Researcher at the Neuroscience Institute (IN) of CNR in Pisa. In 2017, she was awarded a six- month travel grant within the program “Post-Doctoral Fellowship- 2017” of Fondazione Umberto Veronesi for a training period with two-photon microscopy at the University Medical Center of Göttingen. Moreover, she is responsible of the group for the research in rare neurodevelopmental disorders and co-responsbile of the fNIRS lab at the Stella Maris Institute. Her scientific production was highly fruitful leading to the publication of 59 original research papers in international peer-reviewed journals (H index Scopus: 27). She was awarded personal fundings by Fondazione Roma, LUMOS Pharma, Italian Ministry of Health, Lejeune Foundation, Telethon Foundation, the European Joint Programme for Rare Diseases, Italian Ministry of Research, and Fondazione Intesa San Paolo for the study of creatine-related disorders and other neurodevelopmental. She is also Academic Editor of Neural Plasticity and Scientific Report, and reviewer for various international journals and national agencies.

ABSTRACT

There is no cure for Creatine Transporter Deficiency (CTD) and the mainstay of care is a palliative approach for managing seizures and behavioral problems. To evaluate gene replacement therapy as a possible disease-modifying treatment, we developed an adeno-associated viral vector carrying a functional copy of the Slc6a8 gene (AAV-Slc6a8). We found that the intracerebroventricular administration of AAV-Slc6a8 to newborn knock-out mice modelling CTD results in the widespread expression of the transgene in the brain, with increased Cr levels. This effects was paralleled by the regression of translationally relevant phenotypes, including a rescue of functional connectivity, the reduction of stereotyped movements and the increase of body weight which persisted into adulthood. Cognitive deficits were instead not prevented by perinatal gene therapy. These results demonstrate that CTD pathology can be partially counteracted by perinatal genetic expression of SLC6A8, thus laying the basis for the development and fine tuning of experimental therapies for this genetic disorder. Furthermore, the efficacy study of potential treatments for CTD is hindered by the scarcity of unbiased, quantitative, non-invasive biomarkers for monitoring brain function. Growing evidence points to the use of evoked responses as functional biomarker for the study of the severity and progression of neurodevelopmental disorders. Using intrinsic optical signal imaging, we demonstrated the enhancement in the amplitude of responses driven by contralateral eye stimulation in CTD mutant mice, most likely reflecting the mitochondrial overactivation in brain circuits. These results support the idea that cerebral oxygen consumption may represent a sensitive readout of functional alterations of neural circuits due to creatine depletion. Functional near-infrared spectroscopy (fNIRS) has been utilized in human subjects as a non-invasive and noiseless technique to monitor cerebral hemodynamics. To assess the translational value of the imaging biomarker, we are evaluating whether visually-evoked fNIRS signals can be used to predict symptom severity in the CTD population. Preliminary results suggest that evoked hemodynamic responses (HR) are higher in CTD patients compared to healthy controls.

SESSION 6: CORE OUTCOMES & CLINICAL READINESS

Establishing a Core Outcome Set (COS) for CTD & GAMT Deficiency

3:15 PM - 3:35 PM MDT

Zahra Nasseri Moghaddam
Department of Pediatrics, UBC; Division of Biochemical Genetics, BC Children's Hospital, Vancouver BC, Canada
Authors: Zahra Nasseri Moghaddam; Emily Reinhardt; Audrey Thurm; Heidi Wallis; Sylvia Stöckler-Ipsiroglu

BIO

Zahra Nasseri Moghaddam is a genetics research assistant at Dr. Sylvia Stockler's lab within the Department of Pediatrics at UBC. Located in the Division of Biochemical Genetics at BC Children's Hospital in Vancouver, BC, Canada, her research interests reside in rare genetic disorders and the impact of genetic testing on clinical patient management. She is also involved in the development of core outcome sets for several rare disorders, including creatine transporter deficiency (CTD) and GAMT deficiency. Her passion lies in supporting families of children with various metabolic disorders, and she is dedicated to expanding her knowledge and expertise in this area through clinical research and international collaboration with researchers, clinicians, and families. With plans to begin her master's in genetic counseling this upcoming fall, she is driven to support individuals in their diagnostic odysseys.

ABSTRACT

Clinical trials aim to determine the safety and effectiveness of interventions by evaluating their impact on diverse endpoints. However, inconsistencies in defining and measuring these endpoints have posed challenges in applying and comparing trial results. A list of important outcomes, called a core outcome set (COS), is developed to identify a small set of disease-specific outcomes deemed important by stakeholders, and should be reported in every research study and clinical trial. Unfortunately, patient and caregiver perspectives have historically been overlooked in the COS development process, thus limiting their input into the outcome selection. ACD collaborated with caregivers and health professionals to develop a COS of eight outcomes for creatine transporter deficiency (CTD) and guanidinoacetate methyltransferase (GAMT) deficiency. Caregivers were partners throughout the COS development process, increasing community engagement and facilitating caregiver empowerment. Here, we will build on previous presentations given at the 2022 and 2023 ACD CCDS Scientific + Patient Symposiums and provide a final update on this COS development project. Specifically, we will share the results from the Delphi Round 3 survey, the in-person Consensus Workshop, and the final COS. We expect that this project will (1) ensure a patient-centered approach for accelerating drug development, (2) minimize bias, and (3) promote a more efficient use of resources.

SESSION 6: CORE OUTCOMES & CLINICAL READINESS

The CreatineInfo Patient Registry: Updates and utilizing the core outcome set (COS) to shape future surveys and prepare for clinical trials

3:35 PM - 4:00 PM MDT

Emily Reinhardt
Association for Creatine Deficiencies
Authors: Emily Reinhardt; Heidi Wallis; Zahra Nasseri Moghaddam; Audrey Thurm; Sylvia Stockler

BIO

Emily currently serves as ACD's Patient Registry Coordinator, which affords her the privilege of collaborating directly with CCDS patients, caregivers, researchers, and other rare disease partners. Emily is a graduate of Kansas State University, earning both her BS and MS in Psychology with a focus in Behavioral Neuroscience. She has over 15 years of research experience, with particular emphasis in pre-clinical and translational neuroscience. Through her love of science, Emily is passionate about using data to improve the lives of people in her community.

ABSTRACT

The CreatineInfo Patient Registry & Natural History Study is a patient- and caregiver-reported registry dedicated to understanding the natural history of the three cerebral creatine deficiency syndromes (CCDS). Over 200 participants around the world with CCDS are currently enrolled in the registry. Since the Association for Creatine Deficiencies (ACD) launched the registry in 2021, it (1) has established itself as an invaluable resource for new and existing CCDS investigators, (2) provides a path for engagement and contribution among CCDS patients and caregivers, and (3) is opening new research possibilities to advance CCDS research. In this presentation, we will provide updates on current data available in the registry and discuss how the registry can provide real-world data (RWD) to support clinical trials and regulatory decision making. In particular, we will discuss how the recently established core outcome set (COS) for creatine transporter deficiency (CTD) and guanidinoacetate methyltransferase (GAMT) deficiency can inform the development of future registry surveys to provide natural history data on these conditions to support the use of the COS in clinical trials.

SESSION 6: CORE OUTCOMES & CLINICAL READINESS

From outcome sets to outcome measures: A focus on measures assessing neurodevelopment

4:00 PM - 4:30 PM MDT

Audrey Thurm, PhD
National Institute Of Mental Health

BIO

Dr. Audrey Thurm, Ph.D. received training at DePaul University and Boston Children's Hospital/Harvard Medical School, and conducted a post-doctoral fellowship at Johns Hopkins School of Medicine. She has been at NIMH since 2002, serving in the extramural program until 2006, as chief of both the Autism and Social Behavior Program, and the Compulsive Repetitive Behaviors Program. In 2006 she moved to the intramural program to help launch the autism research program. She has expertise in longitudinal studies and an interest in markers of the early diagnosis of autism as well as genetic conditions associated with neurodevelopmental disorders.

ABSTRACT

A Core Outcome Set for creatine deficiencies has now been finalized through a partnership with ACD and professionals in the field. This core outcome set includes concepts such as adaptive functioning, cognitive functioning, emotional dysregulation and expressive communications, all constructs assessed in clinical neurodevelopmental evaluations. However, the core outcome set does not specify which measures to be used for such assessments. This talk will focus on what steps could be taken to move from constructs to recommended measures for natural history studies and clinical trials in these populations. Considerations will need to include stakeholder input, feasibility, and importantly, considerations that will make them amenable to showing meaningful change over time that would be necessary to determine if a treatment being studied indeed had clinical benefit in studies. We will also discuss unique aspects of psychometrics underlying standardized measures that may make them amenable to use in such trials with this population.

SESSION 6: CORE OUTCOMES & CLINICAL READINESS

Parents Advancing REsearch NeTworkS 2.0: Expand Community, Tools, & Engagement (PAReNts 2.0: ExCiTE)

4:30 PM - 5:00 PM MDT

Heidi Wallis
Association for Creatine Deficiencies
Authors: Heidi Wallis; Emily Reinhardt; Celeste Graham; Sylvia Stockler; Billy Bennett; Beth Potter; Audrey Thurm

BIO

Heidi is the Executive Director of the Association for Creatine Deficiencies and parent of four children, two of which have GAMT Deficiency, a rare cerebral creatine deficiency syndrome with severe neurological impacts if not diagnosed and treated from birth. Heidi and team recently completed a two year project to establish, through patient and expert consensus, a Core Outcome Set (COS) for GAMT and CTD clinical trials. Her team is preparing to begin a second project this fall to establish “Considerations for CTD & GAMT Outcome Measurement Tools (OMTs)” as a companion to the COS. Prior to working for ACD she was a grant analyst and project manager in the Utah Public Health Lab Newborn Screening program. Heidi is a voting member of the Utah Newborn Screening Advisory Committee and collaborated in the nomination and eventual adoption of GAMT on the RUSP. Heidi's vision is that one day all creatine deficiencies will be diagnosed at birth, through routine newborn screening, and will be treated with an effective and appropriate treatment before the onset of symptoms.

ABSTRACT

ACD will begin work on a second PCORI funded Eugene Washington Engagement Award project in September 2024. The project, “Parents Advancing REsearch NeTworkS 2.0: Expand Community, Tools, & Engagement” (“PAReNts 2.0: ExCiTE”) will build on the work of the first PAReNts project to establish “Considerations for CTD & GAMT Outcome Measurement Tools (OMTs)” as a companion to the “CTD and GAMT Core Outcome Set (COS)”. These considerations will support well-informed clinical trial designs through appropriate measurement tool selection, resulting in accurate and consistent assessment of change in CTD and GAMT patients. Selecting tools to measure changes in this population is challenging because changes can be slow and many tools are not sensitive enough to capture the subtle changes expected from a successful intervention. This is especially true for patients with intellectual and developmental disabilities. Historically, OMTs have been selected without input from patients and caregivers. In the cerebral creatine deficiency syndromes (CCDS) community, caregivers are often best equipped to identify meaningful changes that would improve daily functioning and overall health for patients, so their input is critical. This project will engage and train caregivers throughout the two year project. A diverse stakeholder group of caregivers, clinicians, researchers, scientists, industry, and policymakers will collaborate in three Research Jam sessions, ultimately reaching consensus in 2026 on necessary considerations when selecting appropriate outcome measurement tools for CTD & GAMT clinical trials.