August 18, 2023

Caregiver Session

Noon - 12:15 PM PDT | 21:00 - 21:15 CET

Heidi Wallis

Association for Creatine Deficiencies

Bio

Heidi holds a Bachelor of Science degree in Business Management. Prior to working for ACD Heidi worked as a grant analyst and project manager in the Utah Newborn Screening Informatics program. She serves as a member of the Utah Newborn Screening Advisory Committee, Mountain States Regional Genetics Network Utah team, ClinGen DAPC Working Group, and ClinGen CCDS Variant Curation Expert Panel. Heidi's vision for the future is that all creatine deficiencies will be screened for at birth and that each disorder will have a safe and effective treatment. Heidi lives in Salt Lake City, Utah with her husband, Trey, and their four children. Samantha (20) was diagnosed with GAMT deficiency at 5-1/2 years of age and Louis (11) was diagnosed with GAMT deficiency and began treatment shortly after birth.

Updates & Overview of Caregiver Session

12:15 - 1:00 PM PDT | 21:15 - 22:00 CET

Jenny Goldstein, PhD

University of North Carolina at Chapel Hill

Bio

Jenny Goldstein is an assistant professor of Genetics at University of North Carolina at Chapel Hill. Originally from Scotland, Jenny started her career in human genetics at the University of Aberdeen where she received her PhD in molecular genetics. She moved to the University of California, Berkeley, to carry out post-doctoral studies in Cell Biology, and went on to complete a Master's program in Genetic Counseling at Virginia Commonwealth University. Jenny worked as a pediatric genetic counselor and clinical research coordinator at Duke University Medical Center for 15 years. While at Duke, Jenny worked as a genetic counselor with families with GAMT deficiency and CTD, and also coordinated research on a newborn screening study on GAMT deficiency. Now at UNC, Jenny works with the Clinical Genome Resource (ClinGen), a NIH-funded effort to create a publicly available resource on gene-disease clinical validity and the pathogenicity of genetic variants.

Abstract

"The Genetics of Cerebral Creatine deficiency Syndromes (CCDS): Genetic variants, genetic testing, and inheritance explained"

Learning that a family member or loved one has a CCDS can come with a deluge of information that raises many questions. This can be a lot to consider at the same time as adjusting to a new diagnosis. In this session, we will discuss one area that caregivers may have questions about – the genetics of CCDS. We will begin by reviewing basic information on genes and proteins, how variants in genes can affect how well proteins work, and how this relates to the different types of CCDS; AGAT deficiency, GAMT deficiency, and creatine transporter deficiency. This will lead into a review of different types of genetic tests, and the information that is typically provided on a genetic testing report, including definitions for various scientific terms that are commonly encountered. Finally, we will discuss how the different forms of CCDS are passed on from one generation to the next. The session will include polling questions to help participants think about the different concepts that are presented.

August 18, 2023

Caregiver Session

1:00 - 1:45 PM PDT | 22:00 - 22:45 CET

Jessica Kruger

Sibling Support Project

Bio

Jess Kruger was born and raised in Long Island, New York. As a sibling to two Autistic brothers, Jess has been passionate about disability acceptance and inclusion since the earliest days of her life. Jess earned her bachelor's degree in International Studies and Spanish from Eckerd College in 2014. Since graduation, Jess has worked with several community based organizations and even spent time as a Youth Development volunteer in the Peace Corps. Jess' experiences fueled a passion for the field of Social Work, and she is now currently pursuing her Masters in Social Work at the Silberman School of Social Work in NYC. A combination of Jess' lived experiences and professional development have inspired her entrance into the world of sibling support for "sibs" or siblings of brothers and sisters with disabilities, special needs, and/or complex medical, mental health needs. Jess has been Sibling Support Project Sibshops Facilitator Certified since 2021. Sibshops is a recreational peer support program for young siblings of brothers and sisters with disabilities. In addition to her studies, Jess currently works as a Sibshops Facilitator for a local NYC non-profit, running in-person Sibshops and community sibling mentoring experiences. Jess also facilitates online Sibshops for several national associations. She is passionate about working with people, activism, and striving to make the world a kinder place for everyone.

Abstract

"Sibling Support & Sibshops"

The sibling relationship is often the most long lasting one a person has in their lifetime. When a disability is present, siblings may fill unique roles for their brothers/sisters, such as advocate, supporter, and caregiver. Sibs often become the next generation of primary caregivers. This presentation will provide insight into the sibling experience and give resources for family support and the importance of building connections with other sibs through programs like Sibshops.

1:45 - 2:30 PM PDT | 22:45 - 23:30 CET

Deborah Bilder, MD

University of North Carolina at Chapel Hill

Bio

Debbie Bilder, MD is a Professor in the Department of Psychiatry in the Division of Child & Adolescent Psychiatry at the University of Utah Huntsman Mental Health Institute. She hold adjunct appointments in the departments of Pediatrics and Educational Psychology. She completed the triple board residency program (Pediatrics, General Psychiatry, Child & Adolescent Psychiatry) at the University of Utah and maintains board certification in all three specialties. She is the Principal Investigator for the Utah Registry of Autism and Developmental Disabilities and co-Principal Investigator for the Centers of Disease Control and Prevention's Autism and Developmental Disabilities Monitoring Network Utah site. Her clinical expertise is in psychiatric assessment and treatment for individuals across the lifespan with severe neurodevelopmental disabilities. Dr. Bilder joined the CCDS Expert Panel this past fall and has enjoyed learning from parents and experts about the medical and mental health experiences of children with CCDS.

Abstract

"Psychiatric Approach to Emotional and Behavioral Crises in Children with Cerebral Creatine Deficiency Syndrome"

This talk will discuss common underlying mental and physical health concerns that lead to emotional and behavioral crises in children with developmental disorders, with a focus on CCDS. The Sources of Distress will also be introduced. This is a publically available web-based tool for parents of children with developmental disorders who experience significant emotional and behavioral concerns. This tool gives parents an opportunity to describe what they know about their child in a manner that translates into the presence of specific treatable conditions that frequently contribute to irritability and agitation. I will discuss my assessment and treatment approach to common concerns raised by CCDS parents based on what I have learned through my participation on the expert panel.

August 18, 2023

Caregiver Session

2:30 - 3:15 PM PDT | 23:30 - 00:15 CET

Association for Creatine Deficiencies Board of Directors

Interactive Q&A

3:15 - 3:30 PM PDT | 00:15 - 00:30 CET

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.

Overview of next week's scientific sessions & Conclusion

August 25, 2023

General Session Day 1

OPENING SESSION 8:00 - 8:30 AM PDT | 17:00 - 17:30 CET

Sangeetha Iyer, PhD

Association for Creatine Deficiencies

Opening Remarks

OPENING SESSION 8:30 - 9:15 AM PDT | 17:30 - 18:15 CET

Julia Vitarello

Mila's Miracle Foundation

Bio

Julia Vitarello is Founder & CEO of Mila's Miracle Foundation. Her life has taken her from Washington, DC, where she grew up, to Amherst College, where she pursued a liberal arts degree, and then to Italy, where she lived and worked for many years. She finally settled in Boulder, Colorado, where she headed a small company and started a family. Travel, language, outdoor sports, and playing with her kids were her passions. But Julia's life took a drastic turn in December 2016 when her then six-year-old daughter Mila was diagnosed with a rare and fatal genetic condition - Batten Disease.

Upon learning that Mila's disease had no cure and no child had ever survived it, Julia started Mila's Miracle Foundation (MMF) to initiate and fund novel treatments. She raised nearly $5M in grass-roots efforts from over 6000 supporters, while at the same time being a mom and caregiver. In an unprecedented race against time to save her daughter, Julia collaborated alongside Dr. Timothy Yu and his team at Boston Children's Hospital (BCH) to develop the first-ever drug tailored to just one person, affectionately named milasen. After showing great promise in the first year of treatment, Mila's disease slowly continued to progress. In February 2021, Mila's big spirit left her little body. What began as a race to save Mila's life, has since turned into an opportunity to pave an entirely new treatment path for children with fatal genetic diseases.

In her quest to open up the field of individualized medicines which Mila pioneered, Julia has engaged academics, biotechs, government and foundations in this space and created a global following of Mila's story. In addition to running MMF, Julia co-founded the N=1 Collaborative which serves as the global scientific hub for medicines like milasen, as well as a biotech aiming to prove a viable business model to make individualized medicines sustainable. Julia regularly presents at scientific meetings and conferences across the country. In collaboration with fellow rare disease foundations, she initiated the work toward an ongoing novel gene replacement therapy trial targeting Mila's variant of Batten (CLN7) and a Neurodegenerative Disease Clinic at Children's Hospital Colorado. Through MMF, Julia co-runs the first-ever single cell atlas of pediatric disease with BCH, funds basic science research in the US and Europe, and hosts meetings with industry experts and patient advocates alike. Driven by a sense of and responsibility to help other families like her own, Julia is dedicated to turning Mila's story into a new treatment path for children across rare diseases in hopes of moving from "Mila to Millions" and making individualized medicines routine worldwide.

Abstract

August 25, 2023

General Session Day 1

SESSION 1 9:30 - 9:45 AM PDT | 18:30 - 18:45 CET

Judith Miller, PhD, MS

Center for Autism Research, The Children's Hospital of Philadelphia, Philadelphia, PA, US

Bio

Judith S. Miller, PhD, MS, is a psychologist in the Department of Child and Adolescent Psychiatry and Behavioral Sciences and a senior scientist and training director in the Center for Autism Research at Children's hospital of Philadelphia. Her areas of expertise include autism spectrum, neurodevelopmental conditions, and quality improvement. Her research focused on diagnostic and outcome issues, including differentiating autism from other genetic and psychiatric conditions, diagnostic and outcome studies across the lifespan, early identification and screening, and improving systems of care. She received her MS in Psychology and her PhD in Clinical Child and Family Psychology from the University of Utah, and she completed her postdoctoral fellowship at Emory University School of Medicine, Atlanta, GA.

Abstract

"Clinical Characteristics of Creatine Transporter Deficiency (CTD): Final Results of the Vigilan Observational Study"

Introduction: Little is known about the natural history of CTD, an X-linked disorder of disrupted creatine transport into cells. Methods: This study (NCT02931682) used parent questionnaires and clinical assessments to characterize clinical features of males with confirmed CTD (SLC6A8 pathogenic variant) for up to 4 years. Results: Fifty patients (mean baseline age, 8.8 years; range, 1.5-24.4 years) were enrolled. Mean age at first symptom was 9.0 months, mean time from initial evaluation to diagnosis was 3.2 years, and mean CTD diagnosis age was 4.9 years. In addition to global developmental delay, medical history included seizures (68%), hypotonia (decreased muscle tone; 50%), aggressive behavior (46%), self-injurious behavior (40%), autism spectrum disorder features (32%), attention deficit disorder (32%), anxiety disorder (20%), and cardiac arrhythmia (8%). Baseline language levels were single words (42%), sentences (33%), babbling (15%), no speech (4%), and unknown (4%). Behaviorally, based on the ABC-2 questionnaire, patients with CTD often exhibited irritability and hyperactivity. Baseline gastrointestinal symptoms included constipation (44%), choking/gagging (32%), vomiting (16%), and gastroesophageal reflux disease (12%). Across measures, little change or improvement was seen over time. Conclusions: In patients with CTD, symptoms occurred early in life, with a prolonged delay before CTD diagnosis. Further, patients with CTD experienced a range of neurologic, cardiac, and gastrointestinal symptoms and had meaningful and persistent delays and impairments in language and cognitive ability, with very limited skill development over the four-year study. Significant and persistent impairments suggest therapeutic intervention would be needed at a young age to improve outcomes.

SESSION 1 9:45 - 10:00 AM PDT | 18:45 - 19:00 CET

Seth Berger, PhD, MD

Children's National Hospital

Bio

Seth Berger, M.D., Ph.D. is a Physician Scientist board certified in pediatric, medical genetics, and biochemical genetics working at Children's National Hospital and Research Institute in Washington, DC. His research focuses on bioinformatic approaches to improve molecular diagnostic testing for rare diseases.

Abstract

"Evidence For Cardiac Arrythmia Risk in Creatine Transport Disorder"

Creatine transport deficiency (CTD), caused by variants in the SLC6A8 gene, has been classically characterized by its neurodevelopmental features including developmental delay, seizures, and autism spectrum disorder. In addition to its role in the brain, creatine is an important energy source in the heart. Emerging evidence suggests that individuals with CTD may be at increased risk of cardiomyopathy or cardiac rhythm abnormalities such as prolonged QTc, which can predispose to dangerous arrhythmias triggered by electrolyte disturbances or certain medications. We present our center's experience with cardiac evaluations in two patients with molecularly and biochemically confirmed CTD. The first is a 10 year old boy who developed drug-induced torsades de pointes after receiving Haldol in a PICU during his recovery from a severe intercurrent illness. Subsequent cardiac evaluations showed persistent QTc prolongation requiring ICD implantation. The second patient is a 4-year-old boy with no known cardiac history. He was seen by cardiology for screening given the emerging evidence for arrhythmia risk in CTD where EKG showed a prolonged QTc. He was started on Nadolol and recommended to avoid QT prolonging medications. Based on these cases, we believe baseline electrocardiographic screening is important for individuals with CTD and avoidance of known QT prolonging medications should be considered.

August 25, 2023

General Session Day 1

SESSION 1 10:00 - 10:15 AM PDT | 19:00 - 19:15 CET

Samar Rahhal, MD
NICHD

Bio

Dr. Samar Rahhal is a pediatric endocrinologist. She graduated medical school from the American University of Beirut medical center in 2001 and subsequently did her residency training in pediatrics at the Cleveland Clinic Foundation, followed by pediatric endocrinology specialization at Riley children's hospital at Indiana University in Indianapolis, IN. She is currently a staff clinician at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) at the National institutes of health (NIH) where she was the principal investigator (PI) on the Creatine transporter deficiency natural history study.

Abstract

"Elevated amyloid beta peptides and total tau in cerebrospinal fluid in individuals with Creatine Transporter Deficiency"

Background: Creatine transporter deficiency (CTD) is a rare X-linked disorder of creatine transport caused by pathogenic variants in SLC6A8 (Xq28). The disorder is marked by developmental delay, especially speech delay. The biomarkers Aβ40, Aβ42 and total tau are elevated in Alzheimer disease (AD), a common neurodegenerative disorder pathologically characterized by Aβ peptide containing amyloid plaques and tau neurofibrillary tangles. Although CTD results in neuronal energy deficiency, the pathological processes underlying the CTD phenotype are not fully characterized. Methods: Cerebral spinal fluid (CSF) was collected as an optional part of a natural history study of CTD (NCT02931682). Aβ40, Aβ42 and total tau levels were quantified in CSF from individuals with CTD and from age-appropriate comparison samples. Neuro3-Plex enzyme-linked immunoassay was performed on a Quanterix SR-X instrument. The Vineland Adaptive Behavior Scale, 3rd Edition was used to determine an overall Adaptive Behavior Composite (ABC) standard score. Results: CSF from 12 individuals with CTD and 23 age appropriate non-CTD comparison samples were analyzed. We found that levels of total tau [t(32)=4.05, p=.0003], Aβ40 [t(31)=6.11, p<.0001], and Aβ42 [t(32)=3.20, p=.003] were elevated in the participants with CTD relative to the comparison group. Additionally, except for one individual that we considered an outlier, all three biomarkers correlated inversely with the adaptive behavior score (total tau: ρ = -0.60 [-0.88, 0.005]; Aβ40: ρ = -0.67 [-0.91, - 0.12]; Aβ42: ρ = -0.62 [-0.89, -0.02]). Conclusion: We describe here the novel finding of elevated protein biomarkers in the CSF of individuals with CTD. Aβ40, Aβ42 and total tau are markedly elevated in individuals with CTD compared to comparison samples, and increased levels of these biomarkers inversely correlated with ABC scores. These findings need to be confirmed in a larger CTD cohort. We hypothesize that elevated CSF levels of Aβ40 and Aβ42 are due to cellular energy deficiency. Elevated CSF total tau levels may indicate ongoing neuronal damage. The observation of increased Aβ40, Aβ42 and total tau levels in CSF from individuals with CTD may provide insight into pathological mechanisms contributing to the CTD phenotype and may be useful as a potential biomarker for therapeutic trials in the future.

SESSION 2 10:45 - 11:00 AM PDT | 19:45 - 20:00 CET

Evandro Ferrada, PhD

CeMM - Center for Molecular Medicine of the Austrian Academy of Sciences

Bio

Evandro Ferrada is a computational biologist originally trained in biochemistry and evolutionary biology. He obtained his PhD at the University of Zurich, working on molecular evolution. He carried out postdoctoral work at the Santa Fe Institute in New Mexico, and at the Department of Genome Sciences of the University of Washington, Seattle, USA. In June 2021 he joined the REsolution Consortium where he is contributing to the analysis of human genetic variation and to the functional characterization of solute carriers using large-scale mutagenesis data.

Abstract

"Experimental and computational interpretation of the SLC6A8 creatine transporter variome"

Creatine is an essential metabolite for the storage and rapid supply of energy in muscle and nerve cells. In humans, impaired metabolism, transport, and distribution of creatine throughout tissues can cause varying forms of mental disability, also known as creatine deficiency syndrome (CDS). So far, 80 mutations in the creatine transporter (SLC6A8) have been associated to CDS. To better understand the effect of human genetic variants on the physiology of SLC6A8 and their possible impact on CDS, we studied 30 missense variants including 15 variants of unknown significance (VUS), two of which are reported here for the first time. We expressed these variants in HEK293 cells and explored their subcellular localization and transport activity. We also applied computational methods to predict variant effect and estimate site-specific changes in thermodynamic stability. To explore variants that might have a differential effect on the transporter's conformers along the transport cycle, we constructed homology models of the inward facing, and outward facing conformations. In addition, we used mass-spectrometry to study proteins that interact with wild type SLC6A8 in HEK293 cells. In silico models of the protein complexes revealed how two variants impact the interaction interface of SLC6A8 with other proteins. Overall, our analyses reveal diverse mechanisms of pathogenicity, and disambiguate the pathogenicity of 15 VUS, including two previously unreported variants obtained from CDS patients.

August 25, 2023

General Session Day 1

SESSION 2 11:00 - 11:15 AM PDT | 20:00 - 20:15 CET

Jacklyn Gallagher
Purdue University

Bio

I am a rising third year PhD student in the Schlebach Lab at Purdue University. Our lab investigates the physiochemical reactions that impact proteostasis – the homeostasis of integral membrane proteins. Proteostasis disruptions often lead to a vast array of diseases and 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 hybrid techniques to identify small molecule therapeutic leads that are suitable for optimization as pharmacochaperone targets for misfolded conformations of SLC6A8. My previous undergraduate and graduate (MS) 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 small molecule library against the IF conformation of CT1 for compound leads, which we obtained (53) whereby 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

"Towards the Discovery of Small Molecules that Restore the Expression and Function of CTD Variants"

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 hypothesize that small molecules that selectively bind to the IF conformation of CT1 will enhance the expression and activity of misfolded CT1 variants. To test this hypothesis, 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 appear to enhance total WT CT1 levels including one that enhances expression 4-fold. We are currently working to determine how these molecules impact the cellular trafficking and function of CT1 as well as how this may vary among pathogenic CT1 variants. These compounds hold great promise for the development of novel pharmacological chaperones for the treatment of CTD.

SESSION 2 11:15 - 11:30 AM PDT | 20:15- 20:30 CET

Nicola Longo, PhD, MD
University of Utah

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 He is a Professor of Pediatrics and Adjunct Professor of Pathology, Nutrition and Integrative Physiology at the University of Utah in Salt Lake City, UT. He is also the Chief of the Division of Medical Genetics, Director of the Metabolic Service, Director of the Training Program in Medical Biochemical Genetics and Medical Director of the Biochemical Genetics Lab at ARUP Laboratories in Salt Lake City. His clinical 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.

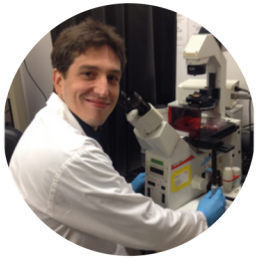
August 25, 2023

General Session Day 1

Abstract

"Inhibitors of arginine glycine aminidinotransferase as a therapy for GAMT deficiency"

Guanidinoacetate methyltransferase (GAMT) deficiency results in the accumulation of guanidinoacetate (GAA) that is toxic for the brain. Current therapies can restore creatine levels and can reduce, but not normalize levels of guanidinoacetate. Inhibition of arginine: glycine amidinotransferase (AGAT) should suppress the synthesis of guanidinoacetate and could normalize levels of guanidinoacetate in serum and in the brain, improving the outcome of patients with GAMT deficiency. Atomwise performed a virtual screen using a library composed of ~3M compounds against the crystal structure of AGAT (PDB 4JDW). Based on the predicted binding affinity and computed drug-like properties, 96 compounds were evaluated for their abilities to inhibit the synthesis of GAA by recombinant human AGAT enzyme. Eight compounds inhibited more than 75% of control AGAT activity in vitro, with 3 of them inhibiting more than 92%, which is close to the efficacy of 1 mM ornithine that is used clinically to reduce GAA production. The chemical structures of the strongest inhibitors have a backbone based on arginine, the natural substrate of the enzyme. Dose-response experiments indicated that half-maximal inhibition was achieved at 20-60 M, a concentration still too high to utilize these compounds clinically. A new company is generating new chemicals based on our initial hits and we will continue to screen new compounds as they are generated. This will be followed by testing in cellular and animal models of GAMT deficiency to confirm potency and safety of these AGAT inhibitors.



SESSION 2 11:30 - 11:45 AM PDT | 20:30 - 20:45 CET

Peter Axerio-Cilies

BC Children's Hospital

Bio

PAC received a BS in Chemistry from the University of British Columbia after which he began his graduate studies in Pharmaceutical Sciences and his PhD in Neurology/Experimental Medicine. He is now a postdoctoral fellow at the University of British Columbia from the Department of Medicine and Psychiatry at the Djavad Mowafaghian Centre for Brain Health (UBC). His research in the last 12 years has been focused on various brain transporters and how they can be modulated by drugs and consequently used as treatments for epilepsy, Schizophrenia, Alzheimer's disease and other rare genetic diseases. He has recently engaged in the development of new treatments for creatine transporter (SLC6A8) deficiency. He has 16 years experience in generating lead drug prototypes for various protein targets associated with neurological disorders and rare genetic diseases (including solute carrier transporters), which have led to numerous successful patents, publications and clinical trials.

Abstract

"Restoring function to defective SLC6A8 creatine transporter variants using small molecules and drug repurposing"

Cerebral creatine transporter deficiency (CCTD) causes X-linked intellectual disability, with de-novo mutations of the transporter (SLC6A8) occurring in up to 30% of cases. Given a large variety of SLC6A8 mutations reported in the clinic coupled with a spectrum of surface expression profiles, for many drugs, effective response will likely be limited to particular types of mutations. Thus, the development of new methods for high-throughput screening of transporter function and expression in response to new therapeutic molecules will help to customize therapies according to individuals' genotype and improve treatment outcomes. We are using an in-house developed drug-repurposing pipeline to identify FDA-approved drugs and natural products that can restore functional activity of dysfunctional SLC6A8 transporters caused by de-novo genetic mutations. This pipeline harnesses computer-aided drug design and functional assays to efficiently and quickly screen drugs that rescue SLC6A8 transporter dysfunction and/or surface expression of SLC6A8. In total, we have identified 11 'hit' functional correctors and a potential expression corrector that can partially restore SLC6A8 function in-vitro. Building on our screening results, we will be transitioning to testing cells that come directly from patients (e.g., human skin fibroblasts) who have been diagnosed with a dysfunctional variant of SLC6A8. We have set up a robust mass spectrometry-based assay using these human which will quantify the creatine uptake with high accuracy and monitor other key biomarkers. This research could help to pave the way for new therapeutic options for CCTD patients based on their unique variant profile.

August 25, 2023

General Session Day 1

SESSION 3 12:00 - 12:15 PM PDT | 21:00 - 21:15 CET

Jenny Goldstein, PhD

University of North Carolina at Chapel Hill

Bio

Jenny Goldstein is an assistant professor of Genetics at University of North Carolina at Chapel Hill. Originally from Scotland, Jenny started her career in human genetics at the University of Aberdeen where she received her PhD in molecular genetics. She moved to the University of California, Berkeley, to carry out post-doctoral studies in Cell Biology, and went on to complete a Master's program in Genetic Counseling at Virginia Commonwealth University. Jenny worked as a pediatric genetic counselor and clinical research coordinator at Duke University Medical Center for 15 years. While at Duke, Jenny worked as a genetic counselor with families with GAMT deficiency and CTD, and also coordinated research on a newborn screening study on GAMT deficiency. Now at UNC, Jenny works with the Clinical Genome Resource (ClinGen), a NIH-funded effort to create a publicly available resource on gene-disease clinical validity and the pathogenicity of genetic variants.

Abstract

"The ClinGen Variant Curation Expert Panel for Cerebral Creatine Deficiency Disorders: Classifying the clinical significance of variants in GATM, GAMT, and SLC6A8."

The NIH-funded ClinGen Cerebral Creatine Deficiency Syndromes (CCDS) Variant Curation Expert Panel (VCEP) has developed guidelines to classify the clinical significance of variants in GATM, GAMT, and SLC6A8 by adapting the 2015 American College of Medical Genetics/Association of Molecular Pathology variant interpretation guidelines for these genes. To date, the CCDS VCEP has classified 43 variants in GATM, 55 variants in GAMT, and 44 variants in SLC6A8 and the group has submitted these classifications to ClinVar, a public variant database supported by the National Center for Biotechnology Information. The availability of these guidelines and variant classifications can 1) help genetic testing laboratories to provide accurate information to health care providers, 2) inform studies on the prevalence of these disorders, such as the Broad Institute's Rare Genomes study, and 3) contribute to the overall understanding of the genetic causes of the CCDS. However, a significant number of variants in these genes are classified as "uncertain clinical significance" or have conflicting classifications from different submitters in ClinVar. Additional data from patients with these variants as well as the availability of robust functional studies may help to resolve their classifications. Therefore, the VCEP is partnering with the Association for Creatine Deficiencies (ACD) and ClinGen's GenomeConnect to use anonymized registry data to further inform the variant classification process. We will provide an update on the work of the CCDS VCEP to date, as well as our future plans.

SESSION 3 12:15 - 12:30 PM PDT | 21:15 - 21:30 CET

Filippo Ingoglia, PhD

University of Utah / ARUP Laboratories

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

"Functional studies in creatine transporter deficiency"

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.

August 25, 2023

General Session Day 1

SESSION 3 12:30 - 12:45 PM PDT | 21:30 - 21:45 CET

Samantha Baxter, MS

Broad Institute of MIT and Harvard

Bio

Samantha Baxter is the associate director of genetic and genomic data sharing, and a genetic counselor in the Program in Medical and Population Genetics Translational Genomics Group (TGG) at the Broad Institute of MIT and Harvard. She is the operations manager and council member for gnomAD, she co-chairs the policy working group for the GREGoR Consortium, and she leads the TGG's variant curation team. As part of Baxter's ongoing research, in partnership with Chan Zuckerberg's Rare As One network, she uses various curation and gnomAD allele frequencies to estimate the prevalence of rare disease in the global population. Her work has a strong focus on data modeling, scaling processes for data sharing, and most importantly partnering with patient advocacy groups to improve genomic research.

Abstract

"Understanding CCDS Prevalence"

Knowledge of a disease's true prevalence is critical to advancing the care of affected individuals, including for determining the goals and allocating resources for research studies and therapeutic development and building patient advocacy networks. Yet, for the vast majority of rare diseases, prevalence is unknown. Traditional methods, such as counting cases of known affected individuals in medical records or newborn screening, can yield biased and inaccurate estimates of a disease's true prevalence, both globally and within different ethnic sub-populations. Genetic prevalence, the estimated proportion of a population that has a causal genotype for a genetic disorder, can help address this challenge and estimate the prevalence of rare disorders. Here, we present a process for estimating the genetic prevalence of GAMT-related ACD, including where the data is pulled from, how estimates are calculated, the latest results and limitations. We will also discuss the importance of data sharing, variant curation and the impact of a ClinGen Variant Curation Expert Panel (VCEP) partnering with a disease community and the disease community.

SESSION 4 1:15 - 1:30 PM PDT | 22:15 - 22:30 CET

Sylvia Stockler, PhD, MD

Department of Pediatrics, UBC; Division of Biochemical Genetics, BC Children's Hospital

Bio

Sylvia Stockler-Ipsiroglu, MD PhD FRCPC, is a Professor of Pediatrics in the Department of Pediatrics, UBC and a distinguished clinical biochemical geneticist in the Division of Biochemical Genetics at BC Children's Hospital in Vancouver, BC, Canada. With her background in biochemical genetics and pediatric neurology, her main interest resides in finding treatments for children with neurometabolic conditions and rare diseases, including cerebral creatine deficiency syndromes (CCDS). With a passion for improving the lives of young patients and their families, Dr. Stockler has devoted her career to advancing our understanding of rare metabolic disorders. She uses an integrated approach based on clinical, biochemical, molecular genetic, magnetic resonance spectroscopy (MRS), and imaging analyses. Her insights have shed light on the important biochemical pathways that underlie these conditions. She is the PI of several investigator initiated and industry sponsored clinical trials for rare disease treatments and is especially interested in practice and observation-informed evidence in rare diseases. She also serves on the Association for Creatine Deficiencies (ACD) Scientific Medical Advisory Board.

Abstract

"Creating a Core Outcome Set (COS): A collaboration between CTD & GAMT deficiency parents and physicians"

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. Additionally, the road to clinical trials has historically overlooked the patient and caregiver perspective, thus limiting the extent to which their experiences are incorporated into the selection of endpoints used. To address these issues, researchers partner with patient groups to identify a small set of disease-specific outcomes deemed important by stakeholders that must be reported in research studies and clinical trials; this list of outcomes is called a core outcome set (COS). We have partnered with the ACD to develop a COS of 8-10 outcomes for creatine transporter deficiency (CTD) and guanidinoacetate methyltransferase (GAMT) deficiency to ensure consistent evaluation of therapies, using clinically significant outcomes for patients and caregivers. We will discuss our multifaceted approach, which includes (1) conducting evidence reviews (i.e., focus groups, literature reviews, patient registry data), (2) developing three Delphi surveys for input from patients, caregivers, and experts, and (3) hosting a consensus meeting with key stakeholders to finalize the COS. In doing so, a COS for CTD and GAMT deficiency will (1) increase community engagement, (2) facilitate patient/caregiver empowerment, (3) ensure a patient-centered approach for accelerating drug development, (4) minimize bias, and (5) promote a more efficient use of resources.

ACD
ASSOCIATION FOR CREATINE DEFICIENCIES

August 25, 2023

General Session Day 1

SESSION 4 1:30 - 1:45 PM PDT | 22:30 - 22:45 CET

Emily Reinhardt, MS

Association for Creatine Deficiency Syndromes

Bio

Emily Reinhardt has almost 15 years of research experience, with particular emphasis in pre-clinical and translational neuroscience research. Through her love of science, she is passionate about using data to improve the lives of people within her community. Emily is a graduate of Kansas State University, earning both her BS and MS in Psychological Sciences with a focus in Behavioral Neuroscience. Emily currently serves as ACD's Patient Registry Coordinator, which allows her to put science into action by collaborating directly with patients, caregivers, and researchers.

Abstract

"CreatineInfo Patient Registry: Data in Action"

The CreatineInfo Patient Registry & Natural History Study was launched in 2021 and is dedicated to the three cerebral creatine deficiency syndromes (CCDS). The registry is hosted on the NORD IamRare platform and the data is owned and directed by the ACD. CreatineInfo consists of nearly 200 participants from all three CCDSs in six different continents. The CreatineInfo Patient Registry (1) has established itself as an invaluable resource for new and existing CCDS investigators, (2) provides a path for action and contribution among patients and caregivers, and (3) is opening new research possibilities to advance CCDS research. We will provide updates on the data currently in the registry, including updated data from the Patient Meaningful Outcomes (PMO) survey and most recently the Oral Medication survey, which was developed with an industry partner. The genetic reports submitted via the Diagnosis and Medical Notes surveys support classification of genetic variants through the ClinGen CCDS Variant Curation Expert Panel. Through future surveys, the registry will provide opportunities to understand impacts of CCDS such as epilepsy, growth, communication, and other areas. With its further growth, our registry will be significantly benefited via translation of our registry and surveys into languages other than English (e.g., French, Spanish), thereby permitting better statistical estimates through increased power and precision. Ultimately, the goal of the CreatineInfo Patient Registry is to better understand how individuals all over the world are affected by CCDS, and our presentation will provide the necessary updates and plans to ensure this goal is achieved.

SESSION 4 1:45 - 2:00 PM PDT | 22:45 - 23:00 CET

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

"Clinical Trial Neurodevelopmental Outcome Measurement: Lessons Learned"

Creatine Deficiency disorders have in common with many other neurometabolic disorders that neurodevelopmental is affected early on, and parents and caregivers are interested in improving neurodevelopmental outcomes when treatments are considered. However, these conditions affect broad areas of developmental, with little known about the natural history of the conditions and a lot of heterogeneity in phenotypes presumed from published data. Therefore, measurement of neurodevelopmental phenotypes is important, and this measurement needs to be able to measure change over time for usefulness in clinical trials. However, there are significant limitations in existing measures both in measuring significant impairment (which a portion of these populations may be affected by) and measurement of change in developmental domains, especially when significant impairment is present at baseline. These issues are exacerbated when considering young children, who will likely be the focus of novel treatment efforts to come. This talk will discuss some of the lessons learned from engagement in studies and caregiver focused efforts to improve measurement and reporting of neurodevelopmental outcomes.

August 25, 2023

General Session Day 1

2:15 - 2:30 PM PDT | 23:15 - 23:30 CET

Sangeetha Iyer, PhD

Association for Creatine Deficiencies

ACD Closing Remarks – Day 1

August 26, 2023

General Session Day 2

SESSION 5 8:00 - 8:15 AM PDT | 17:00 - 17:15 CET

Dan Coller

Association for Creatine Deficiencies

Bio

Dan has experience from the private sector, managing companies in the building technology industry for the past 15 years. Working with clients in biotech, pharmaceutical and technology sectors provided knowledge in research grants and clinical trials. Coller also has significant experience with financial control and oversight with heavily regulated contracts with the US Navy, State of California, U.S. Department of Veterans Affairs, and dozens of federal and state programs. Coller obtained his bachelor's degree from the University of Southern California, and lives in San Diego, Calif., with his wife Erin Coller, their eight-year-old son Cadman who was diagnosed with Creatine Transporter Deficiency in 2017, and their five-year-old daughter Emma.

ACD Opening Remarks – Day 2

SESSION 5 8:15 - 8:30 AM PDT | 17:15 - 17:30 CET

Aloïse Mabondzo

Paris Saclay University, CEA, Neurovascular Unit Research and Therapeutic Innovation Laboratory

Bio

Dr. Aloïse Mabondzo joined the CEA, the Life Science Division, in May of 1998 as the leader of a Neurovascular Unit Research and Therapeutic Innovation 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 67 articles in peer reviewed journals, 8patents. He has directed 20 PhD students, and 9 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. Very recently, its first medicine candidate was validated by the FDA and obtained the Orphan Drug Designation by the EMA.

Abstract

"Deciphering the Neuropathophysiology Mechanism in Cerebral Organoids from Creatine Transporter Deficiency Patient iPSCs"

Creatine transporter deficiency (CTD) is a rare genetic and metabolic disorder in which a mutation in the Slc6a8 gene on the X chromosome leads to loss of functionality of the creatine transporter (CrT). CTD patients present with intellectual disability, language delay and behavioral disorders. At present, no effective therapy is available. To identify new therapeutic targets, it is important to develop new, relevant human CTD models. We focus on the development and characterization of brain organoids from CTD patients. We shed light on the mechanisms underlying creatine-mediated proteomic changes in the brain.The molecular methods involved the application of shotgun proteomics, integrative bioinformatics, statistical modeling and molecular biology. Our findings show that brain organoids mimic the forebrain and express markers of neural progenitor, intermediate progenitors, immature and mature neurons and astrocytes. CTD brain organoids did not show an increase in Cr concentration when incubated in Cr supplemented media, highlighting a deficient CrT. CTD brain organoids show a significant reduction of neural progenitor cell markers, suggesting a neurogenesis deficit in CTD. Shotgun proteomics analyses of 4,219 proteins identified proteins dysregulated in CTD brain organoids. Integrative bioinformatics and statistical modeling highlighted key proteins altered in CTD and associated with intellectual disability, epilepsy and autism. Among these proteins, GSK3β, a key regulator of neurogenesis, was upregulated and more activated in CTD as indicated by reduced Ser9 phosphorylation. These new observations open new avenues for designing better therapeutic strategies for the treatment of CTD.

August 26, 2023

General Session Day 2

SESSION 5 8:30 - 8:45 AM PDT | 17:30 - 17:45 CET

Ludovica Iovino, PhD

Institute of Neuroscience, Italian National Research Council (CNR), Pisa, Italy/ IRCCS Stella Maris Foundation, Pisa, Italy

Bio

Dr. Ludovica Iovino graduated in Biology at the University of Florence in 2015 and trained in the PhD program in Biomedical Sciences, curriculum Neurophysiology, at the University of Florence from 2015 to 2018. Her PhD research activity was aim at understanding the basic neural mechanisms underlying the respiratory rhythm generation. In 2019, following a short period as visiting researcher at the University of Florence, she was awarded a three-year post-doctoral fellowship at the Department of Biology of the University of Padova, where she studied how aberrant glutamate handling by glial cells contributes to different brain pathophysiological conditions. Since November 2022, she joined Dr. Laura Baroncelli's Lab at the Neuroscience Institute of CNR in Pisa for a second postdoctoral project granted by the Telethon Foundation. Her research activity is currently dedicated to the study of preclinical efficacy of gene therapy in the treatment of Creatine Transporter Deficiency. Her scientific led to the publication of 12 original research papers and 2 Scientific Reviews in international peer-reviewed journals.

Abstract

"Gene replacement therapy for the cure of Creatine Transporter Deficiency Syndrome"

Creatine Transporter Deficiency (CTD) is an X-linked incurable disorder originating from mutations of the solute carrier family 6-member 8 (SLC6A8) gene encoding for the cellular creatine (Cr) transporter (CRT). Brain Cr depletion causes a predominantly neurological clinical picture including intellectual disability, psycho-motor impairment, autistic-like behavior and seizures. To understand whether gene therapy might be a potential disease-modifying treatment for CTD, we developed an adeno-associated viral vector (AAV9) carrying a functional copy of the human SLC6A8 gene driven by a small synthetic promoter (AAV-SLC6A8). We found that a single intraventricular infusion of AAV-SLC6A8 in newborn wild-type and Slc6a8 mutant mice induced a widespread distribution of the transgene in the brain, accompanied by significant increase in cerebral Cr levels, rescue of functional brain hypoconnectivity and improvement of autistic-like stereotyped behavior. In contrast, this strategy did not ameliorate cognitive function in mutant animals and induced a deterioration of mnemonic performance in treated wild-type mice. These results prompted us to devise a second-generation gene therapy cassette aiming at maximizing the beneficial effects of treatment and mitigate potential safety issues. As an alternative to the use of non-native promoters for expressing SLC6A8, we are testing a portion of its endogenous regulatory sequence. Using in vitro models, we found that this strategy reduces transgene expression, potentially better mimicking physiological CRT levels. In summary, our results provide proof-of-concept evidence that gene therapy has potential applications for treating CTD and suggest that further steps of vector engineering to finely tune CRT expression are crucial for optimising efficacy

SESSION 5 8:45 - 9:00 AM PDT | 17:45 - 18:00 CET

Laura Baroncelli, PhD

Institute of Neuroscience, Italian National Research Council (CNR), Pisa, Italy/ IRCCS Stella Maris Foundation, Pisa, Italy

Bio

Laura Baroncelli graduated in Biology from the University of Pisa in 2005 and received her doctorate degree in Neurobiology from the Scuola Normale Superiore in 2009. Following a fellowship at Scuola Normale Superiore, in 2010, she was awarded a two-year post-doctoral fellowship at the Accademia Nazionale dei Lincei in Italy. Since 2011, she has been researcher at the Neuroscience Institute (IN) of CNR in Pisa. She has published over 58 original research papers in international peer-reviewed journals. She was awarded funding by Fondazione Roma, LUMOS Pharma, Italian Ministry of Health, Lejeune Foundation, Telethon, European Joint Program on Rare Diseases for the study of creatine-related disorders. She is also an Academic Editor of Neural Plasticity and Scientific Report, and reviewer for various international journals and national agencies.

August 26, 2023

General Session Day 2

Abstract

"Optical imaging as a prognostic tool for monitoring brain function in Creatine Transporter Deficiency Syndrome"

The efficacy study of potential treatments for Creatine Transporter Deficiency (CTD) is hindered by the scarcity of unbiased, quantitative, non-invasive biomarkers for monitoring brain function. Growing evidence points to visual impairments across multiple neurodevelopmental disorders and the use of evoked responses as functional biomarker for the study of the severity and progression of such disorders. We examined cortical responses to visual stimulation using intrinsic optical signal imaging in a mouse model of CTD. We demonstrated the enhancement in the amplitude of responses driven by contralateral eye stimulation in 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. We developed an innovative visual stimulation protocol with high entertaining value, demonstrating that this paradigm is able to elicit a significant activation of visual cortex both in typically developing and ASD children. Preliminary results suggest that evoked hemodynamic responses (HR) are higher in CTD patients compared to healthy controls. Our goal is to improve the pipeline of therapeutic development more in general in Creatine Deficiency Syndromes and neurodevelopmental disorders, demonstrating the importance to implement HR measures in clinical trials.

SESSION 6 9:00 - 9:15 AM PDT | 17:30 - 17:45 CET

Romain Bernasconi

Laboratory of Systems Biology, Department of Cybernetics, Tallinn University of Technology, Estonia

Bio

I'm a second-year PhD student in the Laboratory of Systems Biology at Tallinn University of Technology (Tallinn, Estonia). I'm originally from the sports science field, which brought me a wide knowledge about skeletal muscle function. Today, I'm studying the consequences of creatine deficiency on muscle function through 2 mice models: AGAT KO and GAMT KO. The purpose of my research is to unravel and understand how creatine deficiency affects the energetic state and triggers the modification of the muscle phenotype.

Abstract

"Creatine-deficiency in AGAT KO but not GAMT KO causes a muscle-specific shift in the myosin heavy chain composition."

Skeletal muscles represent 50 % of the human body weight and can be categorized into two types: locomotor and postural. Skeletal muscles express different types of fibers. Some fibers are more endurant, use aerobic metabolism, and generate less force (Type 1 and 2a), while others are more explosive, use anaerobic metabolism, and generate a lot of force (Type 2X and 2B). The muscle fiber composition is determined by its function and can be influenced by training, diseases, diet, age, etc. Among these factors, the energy status of the muscle cell, which is mainly maintained by the creatine kinase system, plays a major role in the fiber transition and the maintenance of muscle mass. Previous studies on creatine-deficient AGAT KO mice following a creatine-free diet showed that their locomotor skeletal muscles are greatly affected. They exhibit severe atrophy and change their metabolism toward aerobic. Here, we show that creatine deficiency in AGAT KO mice affects the muscle mass and fiber composition toward an oxidative phenotype in the locomotor muscles exclusively. However, we also show that GAMT KO skeletal muscles do not suffer from the lack of creatine. We propose mechanisms at the cellular level to explain the differences between AGAT KO muscle types and between AGAT KO and GAMT KO mouse models.

August 26, 2023

General Session Day 2

SESSION 6 9:30 - 9:45 AM PDT | 17:30 - 17:45 CET

Gerald Lipshutz, MD, MS

UCLA School of Medicine

Bio

Gerald 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. Dr. Lipshutz is a Professor within 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 where he investigates the underlying brain dysfunction in certain metabolic disorders including GAMT deficiency where he is also studying a gene therapy approach to treat the disorder.

Abstract

"Toxic Effects of Guanidinoacetic Acid (GAA): Implications for Brain Pathology in GAMT Deficiency"

In GAMT deficiency, developmental delay and intellectual disability are typical while muscular hypotonia, involuntary movements, ataxia and autistic or self-aggressive behavior are common. Extrapyramidal movements and seizures occur, often refractory to antiepileptics. Severe expressive language delay is also common with most having no speech or language and if present, is limited. On imaging, delayed myelination is a finding detected in some. Plasma analysis demonstrates increased levels of guanidinoacetate (GAA); in the brains of affected mice, not only is GAA elevated, but B-guanidinopropionic acid (GPA) and g-guanidinobutyric acid (GBA) are also abnormally high. How these biochemical abnormalities result in these myriad of functional brain abnormalities has not been completely understood. Utilizing the Gamt deficient mouse, we explored the effect that GAA, GPA, and GBA have on brain cells to in part elucidate the mechanism. We show that GAA and other related compounds including GBA share structural similarities with GABA, evoke GABAA receptor (GABAAR) mediated currents in cerebellar granule cells in the brain, and displace the high-affinity GABA-site radioligand [3H]muscimol in total brain homogenate GABAARs. As a GABA agonist, GAA is particularly potent in both activating GABAARs (EC50 ~6 μM) and displacing the GABAAR ligand [3H]muscimol (IC50 ~3 μM) at pathophysiologically relevant concentrations. In other studies, we isolated oligodendrocyte progenitor cells from mice. We found that both GPA and GBA are toxic at certain concentrations affecting their maturation. Together these findings help explain in part the mechanisms of toxicity to the brain in GAMT deficiency.

SESSION 6 9:45 - 10:00 AM PDT | 17:45 - 18:00 CET

Robyn Binsfeld

Queen's University, Centre for Neuroscience Studies

Bio

Robyn Binsfeld is a PhD student at Queen's University in Kingston, Ontario Canada working under the supervision of Dr. Jagdeep Walia. Her research centres on developing gene therapies to treat inherited neurological disorders, with a special focus on GAMT creatine deficiency. She holds a BSc honours degree from Queen's University and is a recipient of the MITACS accelerate grant award.

Abstract

"Expression and function of guanidinoacetate methyltransferase (GAMT) is restored in cellular and murine models of GAMT creatine deficiency following treatment with scAAV9.hGAMT"

Creatine deficiency disorders such as guanidinoacetate methyltransferase deficiency (GAMT-D) are inborn errors of metabolism resulting in several neurological manifestations including developmental delay, intellectual disability, and epilepsy, emphasizing the role of creatine in the brain. Current treatments, while partially successful do not fully restore creatine levels or reduce accumulation of the toxic guanidinoacetate (GAA) intermediate in the brain. We present a proof-of concept study testing an AAV9-based gene therapy for treatment of GAMT-D. A construct containing the codon-optimized coding sequence for human GAMT was designed to be packaged in a self-complementary AAV9 vector. Plasmid DNA was delivered to knockout cells via lipid-mediated transfection and scAAV9.hGAMT via intrathecal lumbar puncture to GAMT-D mice. GAMT expression was assessed by western blot and qPCR, while tissues, and serum were analysed using mass spectrometry to detect creatine and GAA levels. Protein and mRNA expression of GAMT were restored resulting in increased intracellular creatine content and reduced GAA accumulation in cellular models of GAMT-D following treatment. In a murine model of GAMT-D, intrathecal delivery of scAAV9.hGAMT, significantly increased creatine content and decreased GAA accumulation throughout the body, including the brain. These same results were observed over time in the serum of treated animals compared to untreated controls. This study represents proof-of-principle results for effective restoration of GAA and creatine levels in the brain and periphery using an AAV9 based gene therapy. scAAV9.hGAMT is being further investigated to determine an appropriate therapeutic window for efficacy and safety with the goal of future translation to treat human patients.

August 26, 2023

General Session Day 2

SESSION 7 10:30 - 10:45 AM PDT | 18:30 - 18:45 CET

Olivier Braissant, PhD

Service of Clinical Chemistry, Lausanne University Hospital, Switzerland

Bio

Working since 1997 in the Service of Clinical Chemistry of the Lausanne University Hospital (Switzerland), my research line deals, since more than 20 years, with the understanding of creatine synthesis, metabolism and transport within central nervous system, and with Cerebral Creatine Deficincy Syndroms (CCDS). In particular, I am developing in vitro and in vivo models of CCDS in order to better understand them, and to develop innovative treatment strategies. We have recently established a rat model of CTD, the Slc6a8Y389C rat, by introducing, in the rat Slc6a8 gene, one of the missense mutations identified in human CTD. We have shown that this Slc6a8Y389C rat presents most of the phenotypes observed in human CTD (brain creatine deficiency, biochemical markers, behavioral and locomotor defects, ...). We are now advancing on the development of a gene therapy protocol, using AAV vectors, to correct CTD in our Slc6a8Y389C rat model.

Abstract

"Rescue of myocytes and locomotor activity through intracisternal AAV9 gene therapy in a rat model of creatine transporter deficiency"

Cerebral Creatine deficiency syndromes (CCDS) are inherited metabolic disorders caused by mutations in GATM, GAMT and SLC6A8 genes, which mainly affect central nervous system. CCDS are characterized by brain Cr deficiency, intellectual disability with severe speech delay, behavioral troubles, epilepsy and motor dysfunction. AGAT- and GAMT-deficient patients can be treated by oral supplementation of high creatine doses, leading to partial replenishment of brain creatine and neurological improvement. In contrast, no satisfactory treatment has been found so far for Cr transporter deficiency (SLC6A8 deficiency or CTD), in particular for male patients (the SLC6A8 gene being located on the X chromosome), and the development of innovative therapies is needed. We have developed an adeno-associated virus 9 (AAV9) gene therapy approach to transduce the functional Slc6a8 creatine transporter within the brain of our in vivo CTD model, the Slc6a8Y389C rat. We show here that intracisternal injection of the AAV9-Slc6a8-Flag vector, at post-natal day 11, efficiently transduced the functional Slc6a8 Cr transporter in neurons of cerebellum, medulla oblongata and spinal cord of Slc6a8Y389C/y rat males, up to at least 16 weeks post-injection. This AAV9-Slc6a8-Flag transduction led to a partial recovery of creatine within the transduced cerebral regions, as well as to the rescue of the myocyte alterations and locomotor defaults observed in control non-injected Slc6a8Y389C/y rat males.

SESSION 7 10:45 - 11:00 AM PDT | 18:45 - 19:00 CET

Troy Webster

Queen's University, Centre for Neuroscience Studies

Bio

Troy Webster is a PhD Candidate in the lab of Dr. Jagdeep Walia at Queen's University in Kingston Ontario. The Walia lab specializes in the treatment of rare genetic neurological disorders using gene therapy where Troy has been designing and testing a gene therapy for creatine transporter disorder.

Abstract

"ICV Delivery of SLC6A8 by scAAV9 Rescues Biochemical and Behavioral Phenotypes in a Mouse Model of SLC6A8 Deficiency"

Objectives: 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. Here we propose a novel gene therapy as a potential treatment for SLC6A8 deficiency. Design and Methods: We quantify the efficiency of creatine restoration both in vitro and in vivo following delivery of SLC6A8 in a deficient model. In vitro we measure the intracellular creatine uptake following transfection of a codon optimized SLC6A8 plasmid in patient fibroblasts. Next, we test the efficacy of a self complimentary AAV9 carrying a codon optimized SLC6A8 6-months post intracerebroventricular (ICV) injection to restore both behavioral and biochemical phenotypes in SLC6A8 KO mice.

August 26, 2023

General Session Day 2

SESSION 7 11:00 - 11:15 AM PDT | 19:00 - 19:15 CET

Steven Baker, PhD, MD

University of Utah

Bio

Dr. Baker is a physician-scientist who currently serves as an Associate Director of Transfusion Medicine with University of Utah Health. His scientific interests span a wide variety of topics, from pediatric neuroscience to age-related disease. He is currently funded by an award from the Association for Creatine Deficiencies (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

"Partnering with ACD to Form a Creatine Deficiency Research Center for Gene Therapy"

The University of Utah and the Association for Creatine Deficiencies (ACD) have teamed up to develop newborn screening techniques, novel diagnostics, and a strategy for gene therapy for these disorders. Together we have created the Creatine Deficiency Research Center (CDRC) housed at the University of Utah and ARUP. Within the CDRC, our laboratory is investigating a novel gene therapy strategy for Creatine Transporter Deficiency (CTD). This disorder accounts for ~1-2% of all X-linked intellectual disability, making it the second most common non-chromosomal genetic cause in this large group of patients. Therapeutic options are currently not available for patients with complete loss-of-function of the gene, SLC6A8, encoding the body's principal transporter, CT1. Complete loss-of-function mutations of this gene are found in the vast majority of children with CTD. Amongst patients with disorders of creatine metabolism, CTD accounts for 72% of cases and therefore developing a treatment for these individuals would meet a significant clinical need. Neurons are postulated to be a major end-user of creatine in the brain. These cells exhibit Gamt expression, but very low to undetectable levels of Agat. We propose to express AGAT in neurons as a potential means of bypassing the loss of CT1 activity in patients with CTD. To this end, we are first studying patient fibroblasts with disease causing SLC6A8 mutations for creatine uptake and endogenous synthesis with and without AGAT gene delivery. Longer term, we will culture neurons from Slc6a8 KO mice and assess their ability to synthesize creatine internally upon AGAT expression.

SESSION 8 11:30 - 11:45 AM PDT | 19:30 - 19:45 CET

Maurizio Balestrino

Department of Neurosciences (DINOGMI), University of Genoa and IRCCS Policlinic Hospital, Genoa, Italy

Bio

Maurizio Balestrino was born in Genova, Italy, the same city where Christopher Columbus was born. He received the Degree in Medicine and Surgery, with honors, in 1980 and the Diploma of Specialist in Neurology in 1984. From 1983 through 1986 he was a Research Associate in the Department of Physiology at Duke University, where he learnt experimental methods in electrophysiology and started a keen interest in anoxic brain damage and in neuroprotection. Still at that time, he became interested in creatine as a neuroprotectant. Back in Italy he continued to have clinical responsibilities as a neurologist and to carry out experimental research in brain anoxia or ischemia. His interest in creatine as a neuroprotectant drove him to experimental studies of creatine deficiency conditions, especially creatine transporter deficiency. At present, he is Associate Professor in the Department of Neuroscience, Ophthalmology and Genetics of the University of Genova. He is also Director of the Laboratory of Experimental Neurophysiology in the same Department. He has been Coordinator of several research projects investigating research on creatine or creatine-derived compounds for clinical conditions. His research interests include creatine as a medicinal compound and creatine-derived compounds with possible therapeutical effects.

Abstract

"Selective alteration of the left arcuate fasciculus in creatine transporter deficiency"

In hereditary creatine transporter deficiency (CTD) brain creatine is missing and language impairment is a prominent symptom (1). In two patients (28 and 18 y.o.), T1 and T2 MRI imaging was unremarkable, but the left arcuate fasciculus (connecting Wernicke's and Broca's language areas) showed marked decrease in mean fractional anisotropy (FA) compared to healthy controls. By contrast, FA values in the corticospinal tract were within the 95% confidence interval of healthy controls' values. Although white matter atrophy was reported in CTD (2), this is the first report a selective abnormality of the language-relevant arcuate fasciculus, suggesting a possible regional-specific impact of creatine deficiency.

August 26, 2023

General Session Day 2

SESSION 8 11:45 - 12:00 PM PDT | 19:45 - 20:00 CET

Saadet Mercimek-Andrews, PhD

Department of Medical Genetics, University of Alberta

Bio

Dr. Andrews has clinical research in creatine deficiency disorders for 20 years. She published estimated carrier frequency of GAMT, AGAT and creatine transporter deficiencies in the general population using functional characterization of missense variants. She is the co-chair of CCDS variant curation expert panel and has been working with this expert panel over 5 years. She also has several clinical case studies to report treatment outcomes of GAMT and creatine transporter deficiencies as international outcome studies using REDCap questionnaire. Dr. Andrews is one of the scientific board members for ACD. She has been working with ACD to develop seizure survey in creatine deficiency disorders to increase knowledge, identify best seizure treatments to help patients with creatine deficiency disorders for their seizure management. She is also part of expert panel webinars organized by ACD.

Abstract

"Autosomal dominant Fanconi syndrome due to a heterozygous pathogenic variant in GATM and review of the literature"

Objective: To report a patient with autosomal dominant Fanconi syndrome due to a heterozygous pathogenic variant in GATM. Design and Methods: We reviewed patient chart for clinical, biochemical, and molecular genetic investigation results. We reviewed the literature. Results: This sixty-six-year-old female was born to non-consanguine parents. She finished university and worked as a teacher. She was diagnosed with adult onset hereditary Fanconi syndrome and renal tubular acidosis at age 30 years which progressed to kidney insufficiency. She has been on peritoneal dialysis and in the wait list for kidney transplantation. She was referred to medical genetics clinic for underlying genetic causes of Fanconi syndrome at age 65 years. Her targeted next generation sequencing panel identified a heterozygous known pathogenic variant in GATM (c.1022C>T; p.Pro341Leu). Her family history was positive for Fanconi syndrome in her father, paternal aunt, and brother who died. Brain magnetic resonance spectroscopy (MRS) revealed a partially decreased creatine peak. Plasma guanidinoacetate was low (0.7 micromol/L; reference range 1.1-3.3). Plasma creatine was low-normal (11.8 micromol/L; reference range 7.1-96.5). There were 28 individuals from 5 families with Fanconi syndrome with four different heterozygous pathogenic variants in GATM. One patient had normal creatine peak on MRS. None of the patients had guanidinoacetate or creatine measurements. Conclusion: We report a new patient with Fanconi syndrome who has heterozygous pathogenic variant in GATM. We report for the first time, low guanidinoacetate and low-normal creatine in plasma. Trial of creatine supplementation would be interesting if they are diagnosed early to prevent kidney insufficiency.

SESSION 8 12:00 - 12:15 PM PDT | 20:00 - 20:15 CET

Heidi Wallis

Association for Creatine Deficiencies

Bio

Heidi holds a Bachelor of Science degree in Business Management. Prior to working for ACD Heidi worked as a grant analyst and project manager in the Utah Newborn Screening Informatics program. She serves as a member of the Utah Newborn Screening Advisory Committee, Mountain States Regional Genetics Network Utah team, ClinGen DAPC Working Group, and ClinGen CCDS Variant Curation Expert Panel. Heidi's vision for the future is that all creatine deficiencies will be screened for at birth and that each disorder will have a safe and effective treatment. Heidi lives in Salt Lake City, Utah with her husband, Trey, and their four children. Samantha (20) was diagnosed with GAMT deficiency at 5-1/2 years of age and Louis (11) was diagnosed with GAMT deficiency and began treatment shortly after birth.

Abstract

"PaReNts Project: Development of a CCDS Expert Panel"

Cerebral Creatine Deficiency Syndromes (CCDS) are rare and complex disorders necessitating a collaborative partnership between caregivers and medical practitioners to both understand the needs of CCDS patients and formulate optimal care approaches. For this purpose, the Patients Advancing Research Networks (PaReNts) initiative, led by ACD, launched the CCDS Expert Panel series in late 2022. Through this online initiative experts in the field of CCDS, allied clinicians, and caregivers trained in research engagement bring together their knowledge and experiences to highlight and address the issues of greatest concern to the health and well being of CCDS patients.

August 26, 2023

General Session Day 2

CLOSING SESSION 12:45 - 1:00 PM PDT | 20:45 - 21:00 CET

Thomas Joudinaud, PhD, MD

Ceres BRAIN Therapeutics

Bio

Thomas Joudinaud, MD, PHD is CEO of Ceres Brain Therapeutics. Thomas graduated MD from Paris medical School in 2006 as a cardio-thoracic and vascular surgeon. After a few years as a surgeon, he joined the Paris office of the Boston Consulting Group, a strategy consulting firm in 2009, where he conducted numerous assignments for pharma companies. In 2016, he joined AEC Partners a a Partner, a strategy consulting boutique specialized in Healthcare. In 2019, he founded Ceres Brain Therapeutics with Henri Bénech, Aloise Mabondzo, Sophie Sussini, Anne-Cécile Guyot and the CEA.

Abstract

"Ceres Brain Therapeutics – French team developing an innovative drug to deliver creatine to neurons"

Ceres Brain Therapeutics, a spin-off from the leading academic French center, the CEA, was created in 2019 by the CEA, Dr Aloise Mabondzo, PhD, Dr Henri Bénech, PharmD, PhD and Dr Thomas Joudinaud, MD, PhD. Ceres aims at tackling the challenges of Creatine Transporter Deficiency (CTD) by developing a drug with the ability to deliver creatine into the neurons despite the lack of creatine transporter SLC6A8 at Blood Brain Barrier and neuron membrane levels. Indeed, to be efficient, creatine, even at low dose, needs to be delivered inside the brain neurons. Based on CEA's previous work, Ceres developed CBT101, a drug candidate, that combines all necessary features to deliver creatine into brain neurons. CBT101 will be administrated in the nasal cavity to directly enter the brain neurons leveraging the nose to brain pathway. This is the Ceres' creatine-to-neurons™ solution. CBT101 has completed a full proof of its distribution and efficacy through multiple experiments in the last years, from patient cell ex-vivo penetration to biological, metabolism, and cognition improvement in two different published KO mice models and in non-human primates. Ceres is now preparing the IMPD/IND to reach the clinical phase, by scaling up the manufacturing process and performing toxicological studies. Preliminary studies show good tolerance to chronic short-term administration. Ceres looks forward to starting the clinical trials after the completion of the IMPD/IND enabling studies and the authorization or the regulatory authorities.

CLOSING SESSION 1:00 - 1:15 PM PDT | 21:00 - 21:15 CET

Sebastian Leon

University of Central Florida

Bio

I was born in Bogota, Colombia, and raised in South Florida and Orlando. At the University of Central Florida, I pursued my undergraduate degree in Biomedical Sciences with a minor in Mathematics, where my fascination with neuroscience, biochemistry, and the education thereof flourished. Later, I earned my Master's in Nanotechnology under the guidance of Dr. Swadeshmukul Santra. During this time, I delved into nanotechnologies, exploring their applications in agriculture and biomedicine. Throughout my academic journey, I balanced my studies with part-time roles as a teaching assistant and personal trainer. These experiences deepened my passion for medicine and neuroscience, and they also repeatedly exposed me to the potential of creatine as both a sports and cognitive supplement. My exploration of the power of nanotechnology and creatine culminated in my graduate thesis. I focused on the development of creatine-loaded nanoparticles, aiming to address neuroinflammatory conditions like Multiple Sclerosis and Traumatic Brain injury. Additionally, I discovered that the efficient loading of creatine in these nanoparticles could offer a promising therapy for conditions such as Creatine Transporter Deficiency. Presently, I am working as a medical assistant and graduate researcher while applying to medical school. My goal is to pursue a combined M.D./Ph.D. degree where I can continue my research at the intersection of nanotechnology and neuroscience while treating those afflicted with these debilitating conditions.

Abstract

"Advancing Therapeutic Strategies for Creatine Deficiency Syndromes: Novel Creatine-Loaded Nanoparticles for Targeted Cell Delivery"

Creatine deficiency syndromes (CDS) encompass a group of rare genetic disorders affecting creatine metabolism and transport, consisting of creatine biosynthesis defects guanidinoacetate methyltransferase (GAMT) deficiency, L-arginine:glycine amidinotransferase (AGAT) deficiency, and creatine transporter (CRTR) deficiency. While creatine monohydrate supplementation has shown some efficacy in improving the quality of life for affected individuals, there currently exist no standardized clinical practice guidelines for CDS management. Moreover, individuals with CRTR deficiency do not respond to creatine supplementation due to the lack of the necessary creatine transporter. To address these challenges, innovative therapeutic approaches must be developed to facilitate the direct delivery of creatine into brain cells via endocytosis or other cell-mediated mechanisms that do not necessitate the creatine transporter. Nanotechnology offers potential solutions via enhanced penetration through biological barriers compared to their traditional drug counterparts. Similarly, particles can be designed to have multifunctionality and tuned to specific cell types. In this study, creatine-loaded nano polymer matrices were synthesized and characterized, revealing an average size of 204 nm, a surface charge of -40 mV, and a polydispersity index of 0.17. Furthermore, the loading efficiency of creatine exceeded 90% and demonstrated surface tunability with the addition of polyethylene glycol (PEG). These findings lay the groundwork for the development of targeted and effective creatine delivery methods, offering new avenues for managing creatine deficiency disorders.

August 26, 2023

General Session Day 2

CLOSING SESSION 1:15 - 2:00 PM PDT | 21:15 - 22:00 CET

Interactive Panel

Therapeutic Developments for CCDS
Gerald Lipshutz, Laura Baroncelli, Sylvia Stockler, and Jagdeep Walia




CLOSING SESSION 2:00 - 2:15 PM PDT | 22:00 - 21:15 CET

Sangeetha Iyer, PhD

Association for Creatine Deficiencies

ACD Closing Remarks – Day 2