October 19-20, 2023

The Neuro, 3801 University Street | Jeanne Timmins Amphitheatre

Program Booklet

Ataxia Charlevoix-Saguenay Foundation
Research that heals

neuro
Institut-Hôpital neurologique de Montréal
Montreal Neurological Institute-Hospital

Université Laval | Centre de recherche | CHU de Québec Université Laval | McGill | Faculty of Medicine and Health Sciences | Faculté de médecine et des sciences de la santé

Table of Contents

7th INTERNATIONAL SYMPOSIUM ON ARSACS

The 7th International Symposium on Autosomal Spastic Recessive Ataxia of Charlevoix-Saguenay (ARSACS) is a great opportunity to learn about the latest advancements in ARSACS research and to exchange with participants to further advance knowledge that could lead to treatments. ARSACS is a rare neurological disorder found not only in the province of Quebec, but several cases have been reported in several countries.

The symposium is a free scientific and collaborative event open to anyone who is interested in rare neurological diseases. The main objectives of the symposium are to bring together all research stakeholders, neurologists, clinicians, students, patients and their families as well as the public and to provide a unique opportunity for discovery and discussion.

PROGRAM

Thursday, October 19, 2023

2:30 – 3:00	Registration & Arrival
3:00	**Opening Remarks** *Sonia Gobeil, Ataxia Charlevoix- Saguenay Foundation* Master of Ceremonies: *Francois Gros-Louis, CHU de Québec, Université Laval*
3:10	**Session 1: From Biomarkers to Treatment in ARSACS** *Chair: Anne McKinney, PhD, McGill University*
	Magnetic Resonance Imaging Biomarkers in ARSACS *Sirio Cocozza, MD, PhD, University of Naples, Italy* **Mitochondria & Cytoskeletal Dysfunction in ARSACS** *Mohan Babu, PhD, University of Regina, Canada* **Exploring the Role of Genetic and Epigenetic Modifiers in ARSACS** *Daniele Galatolo, PhD, University of Pisa, Italy* **Charting the Molecular and Cellular Progression of ARSACS** *Justin Wolter, PhD, University of Wisconsin-Madison, USA* **Question Period**
4:25	Refreshment Pause
4:35	**Keynote: SCA2: Preclinical Models and ASO Therapy Development** *Stefan M Pulst, MD, PhD, University of Utah, USA*
5:35 – 7:00	Cocktail & Poster Session

Friday, October 20, 2023

7:30 – 8:00	Registration & Arrival
8:00	**Opening Remarks** *Nicolas Dupré, MD, PhD, CHU de Québec-Laval University, Canada*
8:15	**Session 2: Cellular Dysfunction in ARSACS** *Mohan Babu, PhD, University of Regina, Canada*
	Does ARSACS Degeneration Proceed Through a SARM1-Dependent Pathway? *Thomas Schwarz, PhD, Harvard University, USA*
	Restoring Calcium Homeostasis in Purkinje Cells Arrests Neurodegeneration and Neuroinflammation in the ARSACS Mouse Model *Francesca Maltecca, PhD, San Raffaele Scientific Institute, Italy*
	The Role of Sacsin on Glial Cells *Federico Herrera, PhD, University of Lisbon, Portugal*
	Metabolic Rewiring in Cellular Models of ARSACS *Paul Chapple, PhD, Queen Mary University of London, UK*
	Question Period
9:15	Refreshment Pause
9:25	**Session 3: Improvements in Treatment for ARSACS Patients** *Chair: Nicolas Dupré, CHU de Québec-Laval University, Canada*
	How Natural History Studies Contribute to the Development and Assessment of Interventions *Cynthia Gagnon, PhD, Sherbrooke University, Canada*
	Development and Evaluation of the Efficacy of a Home Rehabilitation Program Aiming to Increase Motor Control, Balance, Mobility, Falls and Activity of Daily Living in People with ARSACS *Élise Duchesne, PHT, PhD, University of Quebec at Chicoutimi, Canada*
	Talk tbc *Josée Larochelle, MD, Paediatric Physiatrist, CHU de Ste Justine, Canada*
	New Developments in the Treatment of Communication Difficulties in Progressive Ataxias

	Anja Lowit, PhD, Strathclyde University, Glasgow (Virtual)
	Question Period
10:10	Refreshment Pause
10:30	**Session 4: Question Period with ARSACS Patients, their Carers, and Partners** *Chair: Cynthia Gagnon, PhD, Sherbrooke University, Canada*
	Betsy Trainor, ARSACS Foundation Board of Directors, Attorney, Parent, Virginia, USA
	Olivier Jérôme, CATALIS Québec, Canada
	Claudia Maltais, ARSACS, Canada (Virtual)
	Kymberly Hoffman, ARSACS, USA
11:30	**Keynote: Cerebellar Modelling using Human IPSCs** *Esther Becker, PhD, MSc, University of Oxford, UK*
12:30	Lunch Pause
1:30	**Session 5: The Biochemistry of Sacsin** *Chair: Francesca Maltecca, PhD, San Raffaele Scientific Institute, Italy*
	Towards Determining the Structure of Sacsin
	Walid Houry, PhD, University of Toronto, Canada
	Leveraging Proteomics to Understand Sacsin Biology
	Nevan Krogan, PhD, University of California at San Francisco, USA (Virtual)
	Understanding the Role of Metals in ARSACS
	Graham George, BSc, DPhil, University of Saskatchewan, Canada
	Question Period
2:15	**Session 6: From Animal Models to Clinical Translation** *Chair: Justin Wolter, PhD, University of Wisconsin-Madison, USA*
	Exploring and Treating Cognitive Dysmetria in a Mouse Model of ARSACS
	Stefan Strack, PhD, University of Iowa, USA
	Novel Therapeutic Approaches for ARSACS
	Alanna Watt, PhD, McGill University, Canada
	Sacsin: from Domains' Functions to Biomarkers and Therapy

Ana Buj Bel, PhD, Genethon, France

Benoit Gentil, PhD, McGill University, Canada

Question Period

3:00	Round Table – Summary & Next Steps

Discussion Leaders:

Nicolas Dupré, MD, PhD, CHU de Québec-Laval University, Canada

Federico Herrera, PhD, University of Lisbon, Portugal

Anne McKinney, PhD, McGill University, Canada

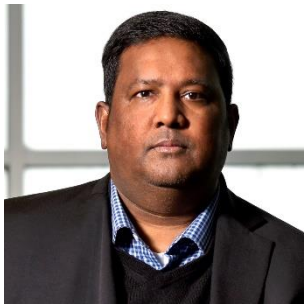
Betsy Trainor, ARSACS Foundation Board of Directors, Attorney, parent, Virginia, USA

Justin Wolter, PhD, University of Wisconsin-Madison, USA

3:30	Closing Remarks

Alanna Watt, PhD, McGill University, Canada

SPEAKER, HOST, AND CHAIR BIOGRAPHIES



Mohan Babu

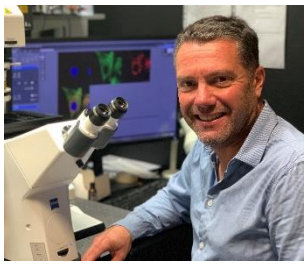
Dr. Babu is an Associate Professor in the Department of Biochemistry at the University of Regina. He is an internationally recognized leader in network biology, and a pioneer for mapping epistatic relationships and membrane-associated protein complexes in prokaryotes and eukaryotes. His research excellence has been acknowledged with a CIHR-IG Maud Menten new investigator award. He is an advisory board member of the international mitochondrial (mt) human proteome initiative and a team leader of the mitoNET Canada. Building on years of groundwork using large-scale proteomics and quantitative genetics, his research work aims to address how mt protein dysfunction contributes to the pathogenesis of neurodegenerative disorders (e.g. Alzheimer's, Parkinson's, ALS), and how these disease associated mt proteins organize and function in cellular pathways and macromolecular assemblies in human neurons. By focusing on these gaps, he aims to uncover causal mechanisms and mt protein-specific pathway targets to treat the underlying mt disorders.

Esther Becker

Esther Becker is Professor of Translational Neuroscience in the Nuffield Department of Clinical Neurosciences at the University of Oxford. After receiving her MSc in Medical Biology from the University of Amsterdam in the Netherlands, Esther completed her PhD under the supervision of Azad Bonni at Harvard University. She then moved to the University of Oxford, UK for her post-doctoral studies on the Moonwalker mouse, a novel mouse model of cerebellar ataxia. Subsequently, she was awarded a Royal Society Research Fellowship to establish her own research program. The Becker group is interested in the genetic and molecular underpinnings of cerebellar ataxia and related cerebellar disorders. In an effort to develop improved human and disease-relevant models to study cerebellar disorders and develop treatments, the Becker group has developed a method to generate cerebellar neurons and organoids from human induced pluripotent stem cells.Esther is a member of the Executive Committee of the Society for Research on the Cerebellum and Ataxias and sits on the Research Advisory Committee for Action for A-T.

Ana Buj Bello

Ana Buj-Bello graduated from the Faculty of Medicine, University of Lleida, Spain in 1994, and gained her PhD on developmental neurobiology at the School of Biological and Medical Sciences, University of St. Andrews, Scotland. She is now INSERM researcher and group leader at Genethon, in Evry, France. Ana Buj-Bello has worked on myotubular myopathy for several years and generated two mouse models of the disease. Studies using these mice showed that skeletal muscle is indeed the primary tissue involved in the pathogenesis of X-linked MTM and that myotubularin is essential for muscle growth and proper distribution of organelles in myofibres. In 2009, Ana Buj Bello was awarded a two year grant by the Myotubular Trust to develop a variety of therapeutic 'rescue' approaches, such as gene therapy and drug administration.



Paul Chapple

Paul Chapple is a cell biologist in the Faculty of Medicine & Dentistry at Queen Mary University of London. His research concentrates on understanding the role of cell stress and molecular chaperones in health and disease, with a focus on neurodegeneration. He became interested in sacsin, the protein that is mutated in ARSACS, because it contains regions of homology to known molecular chaperones. PC's ARSACS research has focused on sacsin's role and what goes wrong at the cellular level when its function is lost. Most recently, in collaboration with Dr Justin Wolter, his group have performed comprehensive multi-omic and cellular profiling of sacsin knockout cell lines. This revealed that sacsi loss impacts microtubule trafficking and cell adhesions, leading to the discovery that sacsin is required for normal localisation of synaptic adhesion proteins.

Sirio Cocozza

Sirio Cocozza obtained his Medical Degree at the University of Naples "Federico II", Italy, in 2012, where he also completed his Residency in Radiology in 2018 and obtained a PhD in 2021, defending a thesis on the application of advanced MRI techniques for the study of the cerebellum. His research interests include the application of different advanced MRI techniques to investigate neuroinflammatory and rare neurodegenerative disorders. Author of more than 120 scientific publications on indexed Journals, Sirio Cocozza is the Principal Investigator (PI) of the University of Naples "Federico II" site for the ENIGMA-Ataxia working group and co-leads the Ataxia Global Initiative MRI Working Group (with Ian Harding, PhD, Pierre-Gilles Henry, PhD and Gulin Oz, PhD). He is PI of a funded project by the Telethon Foundation on ARSACS, and co-PI (with Filippo Maria Santorelli, MD, PhD) of the MRI Working Group of a European Joint Programme on Rare Diseases funded project on spastic ataxias (PROSPAX).

Elise Duchesne

Dr. Duchesne graduated from Laval University's physiotherapy program in 2006. She completed a master's degree and a Ph.D. from 2006 to 2012. Her thesis focused on skeletal muscle injuries, more specifically on the contribution of inflammation to the repair process. In January 2012, Dr. Duchesne was hired as a professor/researcher in the Université du Québec à Chicoutimi's physiotherapy program. As an independent researcher, her works focus namely on developing rehabilitation interventions. She carried out original and innovative experimental designs based on her knowledge of muscle physiology and her access to the large cohorts of NMD patients found in the Saguenay–Lac-St-Jean region such as people with Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS). Her contributions to the field of neuromuscular diseases include the clinical and fundamental study of rehabilitation interventions on skeletal muscle impairments, the support of clinical trial readiness by reaching international consensus on outcome measures, the documentation of metrological properties, the documentation natural history of the disease and the establishment of a phenotypic data and biological material biobank.

Nicolas Dupré

Dr. Nicolas Dupré, MD MSc FRCP FAAN, is a neurologist with expertise in neuromuscular and neurogenetic diseases. So far, he has published more than 175 peer-reviewed articles and six book chapters (H-index 43), including the presentation of a new clinical classification of recessive ataxias. He is the founder and director of the ALS Clinic of the CHU de Quebec - Université Laval. He is also co-director of the Quebec Parkinson Network. In addition, he is member of the executive of the ARSACS Foundation and of Capture ALS, a national and international research initiative in development to accelerate the development of therapeutics for amyotrophic lateral sclerosis (ALS).

Cynthia Gagnon

Cynthia is a senior career-award researcher specializing in adult genetic neuromuscular disorders. She holds a professorial appointment at the School of Rehabilitation at the University of Sherbrooke. She is the scientific director of the Groupe de recherche interdisciplinaire sur les maladies neuromusculaires (GRIMN) and is a researcher at the Centre de recherche Charles-Le Moyne-Saguenay-Lac-St-Jean sur les innovations en santé. Cynthia trained as an occupational therapist at McGill University. She has a doctoral degree in experimental medicine from Laval University and pursued a postdoctoral fellowship in program evaluation at Montreal University. Her work aims at improving clinical care and speeding up trial readiness in the most prevalent neuromuscular diseases in Canada. Her main interest is to document the natural history of the disease through an interdisciplinary perspective to be able to document the progression of the disease and to identify significant predictor and explanatory factors related to participation in daily activities and social roles of patients such as work and autonomous living. Her other interest is to define the best outcome measures to assess potential

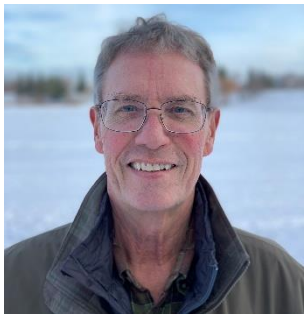
therapeutic targets such as muscle strength, fatigue or cognitive functions. She also works on developing knowledge translation strategies related to rare diseases to ensure effective and just-in-time knowledge translation to the interdisciplinary team through different strategies including wiki, articles, clinical practice guidelines to improve clinical care for patients and their families. She is involved in several international projects in relation to myotonic dystrophy type 1 (DM1), oculopharyngeal muscular dystrophy (OPMD) and autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS).

Daniele Galatolo

Daniele Galatolo's research is focused on understanding the genetic causes and molecular mechanisms underlying hereditary ataxias and spastic paraplegias. Currently, the aims of Daniele Galatolo's projects are to explore the role of genetic and epigenetic modifiers in ARSACS, and to uncover the molecular mechanisms of ARSACS-related retinal defects using the retinal pigment epithelium (RPE) cell system. Daniele Galatolo is also collaborating on ongoing projects concerning the generation and characterization of in vitro and in vivo models of other forms of hereditary ataxias and spastic paraplegias, including CYP2U1, SPG7, and HPDL related disorders.

Benoit Gentil

Dr. Gentil is an Assistant Professor at McGill University in the Department of Kinesiology and Physical Education and the Sylvan Adams Sport Science Institute, specializing in the genetics and epigenetics of motor development and performance. He received his Ph.D. from Grenoble University and has dedicated the last two decades to the identification of pathogenic mechanisms and therapeutic opportunities for rare neurological diseases, like autosomal Recessive Ataxia of Charlevoix-Saguenay, Charcot-Marie-Tooth disease, and others. Dr. Gentil is also a strong advocate of the rare disease community and pursues his commitment as a member of the medical and scientific advisory board of Muscular Dystrophy Canada.



Graham George

Dr. Graham George is a Professor and Tier 1 Canada Research Chair in X-ray Absorption Spectroscopy at the University of Saskatchewan. Dr. George has been a user of synchrotron radiation since 1982 and since then has built career-long expertise in the use and development of synchrotron radiation techniques. Dr. George has more than 300 publications in the primary peer-reviewed scientific literature. His h-index (Google Scholar) is 78 and he has more than 22,000 citations. He is a Fellow of the Royal Society of Canada, and a Fellow of the Royal Society of Chemistry (U.K).

Federico Herrera

Dr. Herrera is interested in two main research areas: 1) the molecular mechanisms underlying CNS damage and repair; and 2) the development of new molecular tools and cell models of neurodegenerative disorders to test innovative therapeutic strategies. His expertise in cell signalling and cell models of disease allows him to collaborate actively with physicists, chemists, biologists and computational biologists in a wide diversity of fields beyond neurodegeneration.Dr. Herrera obtained his PhD degree at the University of Oviedo (Spain) and carried out postdoctoral research at The Salk Institute (La Jolla, CA, USA) and the Instituto de Medicina Molecular (Lisbon, Portugal). He started his own laboratory at the Instituto de Tecnologia Quimica e Biologica (ITQB NOVA, Oeiras, Portugal) in 2014, and in 2019 he moved to his current position as an Auxiliary Professor at the Faculty of Sciences (Univ. of Lisbon). Dr. Herrera has published >50 articles, H index >23, >3500 citations.

Kymberly Hoffman

Kymberly Hoffman is a multiple business owner with previous clinical experience as a child life specialist and a certified infant massage educator. She boasts 13 years of clinical expertise gained from working in various children's hospitals. Prior to her clinical career, she served as a research assistant at CU Health Science Center within the autism research group. Kymberly is also a dedicated foster/adopt mom to twin boys, having previously fostered four other children and two more after adopting her boys. Although born in Colorado, she currently resides in South Carolina with her husband and two boys. Kymberly currently maintains a very part-time remote work arrangement. She faced a misdiagnosis of Charcot Marie Tooth at the age of 24 and later, at 44, received a diagnosis of ARSACS.

Walid A. Houry

Dr. Walid A. Houry is a Professor in the Department of Biochemistry and Department of Chemistry at the University of Toronto. Dr. Houry obtained his Ph.D. from Cornell University and then did his postdoctoral training at the Sloan-Kettering Institute in New York City and at the Max-Planck-Institute for Biochemistry in Munich, Germany. He is interested in the general area cellular stress responses and the role of molecular chaperones and proteases in these responses. His group is also interested in the development of novel anticancers, antibiotics, and antivirals by identifying compounds that target these chaperones and proteases and result in the dysregulation of protein homeostasis in the cell. He has been recognized with national and international awards including awards from the Tokyo Biochemical Research Foundation (2011), the National Research Foundation of South Africa (2015), the Sigma Xi Scientific Research Honor Society (2021), and OIC-COMSTECH Distinguished Scholar Program, Islamabad, Pakistan (2022).

Olivier Jérôme

With 15 years' professional experience in the general and operational management of healthcare organizations, Olivier has led a variety of missions, all centred on patients, caregivers and clinicians. A seasoned manager in organizational development and operationalization of healthcare programs, Olivier has actively participated in the creation, reorganization and growth of the clinical units, laboratories and patient organizations under his direction in the fields of reproductive medicine, obstetrics, oncology and rare diseases. Olivier also has a strong knowledge of the political environment and government affairs in healthcare at both federal and provincial levels, expertise which he will use to the benefit of patients in order to facilitate and accelerate access to innovative treatments. With a passion for research and access to healthcare innovation, Olivier leads CATALIS's clinical research engagement programs and services for patients, caregivers and healthcare professionals.

Nevan Krogan

Dr. Krogan was born and raised in Regina, Saskatchewan, Canada, obtained his undergraduate degree from the University of Regina and his PhD from the University of Toronto. Dr. Krogan's lab at UCSF focuses on developing and applying quantitative, systematic proteomic and genetic approaches to study complex biological and biomedical problems. At present time, the Krogan group is focused on studying cancer, infectious disease and psychiatric disorders.

Anja Lowit

Anja Lowit is a Professor of Speech and Language Therapy at Strathclyde University in Glasgow, Scotland. She has a track record of exploring the nature of communication problems caused by progressive neurological diseases and developing new treatment methods for these.

Josée Larochelle

Dr. Josée (Jo) Larochelle is a physiatrist specialized in paediatrics, who did her fellowship in Sydney, Australia at the Sydney Childrens' Hospital Network affiliated to the University of Sydney. She works with multidisciplinary teams at Marie-Enfant rehabilitation centre (CHU Sainte-Justine) and Lucie-Bruneau rehabilitation centre for children and young adults with various neuromuscular diseases (NMD), including ARSACS. Dr. Larochelle is also responsible for neuromuscular disease training of Physical Medicine and Rehabilitation residents at Université de Montréal.

Claudia Maltais

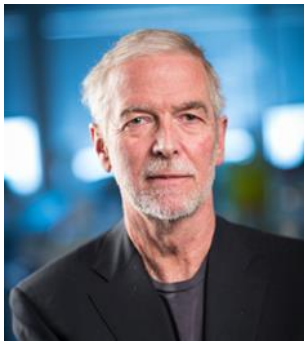
Claudia Maltais received a bachelor's degree in anthropology from the Université de Montréal in 2007. Claudia is passionate about science and animals (her dream was to be a primatologist). She loves traveling and completed an internship in Mali and worked as a French second language monitor in New-Brunswick and Nunavut. Claudia lives with Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS).

Francesca Maltecca

Francesca Maltecca is the head of the Mitochondrial Dysfunctions in Neurodegeneration Unit at Ospedale San Raffaele, Milan, Italy. She has a background in human genetics, with specific training and competence in inherited cerebellar ataxias. Her past and present research work focuses on the dissection of molecular mechanisms of inherited cerebellar ataxias with primary or secondary mitochondrial origin (SCA28, SPAX5, ARSACS). She is a member of the Ataxia Global Initiative, where she co-coordinates the working group dedicated to preclinical trials in mouse models of ataxia. She is also part of an international research consortium studying drug development in recessive ataxias (Treat-ARCA), funded by the European Joint Program for Rare Diseases. She has been awarded twice with the Young Investigator Award for the SCAs Research, from National Ataxia Foundation, US.

Anne McKinney

Professor Anne McKinney is an accomplished international scientific researcher focusing on deciphering the molecular basis of neuronal synaptic stability and neuronal circuitry with the aim of developing therapies for ataxia, neurodevelopmental disorders, epilepsy, and neurodegenerative diseases. She is a Full Professor at McGill University, Canada, in the Department of Pharmacology and Therapeutics. She has served as the Associate Vice Principal of Research in Health Affairs and Associate Dean in Medicine and Health Sciences at McGill University. She has published over 162 abstracts, 1 book chapter and 62 peer-reviewed publications in journals such as Nature Medicine, Nature Neuroscience, J. Physiology, Neurobiology of Disease. She has received prizes for her research, including the prestigious International Pfizer Research Prize in Basic Sciences in Neurobiology. Dr. McKinney is frequently invited to present the lab's research at international and national meetings and serves on many International Advisory Boards, including Neurocure a Cluster of Excellence in the Neurosciences at the Charitie Univeritatsmedizin Berlin.



Stefan Pulst

Stefan-M. Pulst, MD, Dr. Med is a Professor and Chair of the Department of Neurology and the Dale L. Rindlisbacher Endowed Chair in Neurodegeneration Research at the University of Utah. His clinical and research interests focus on inherited diseases of the nervous system with an emphasis on spinocerebellar ataxias and Parkinson´s disease. He received his medical school training at Medizinische Hochschule, Hannover (Germany) and at Harvard Medical School, Boston. After beginning neurology residency in Hannover, he moved to Boston and was senior and chief resident in the Harvard Longwood Neurology Program. He then moved to San Francisco and did basic research on brain tumors at the UCSF brain tumor research center and in neurobiology in the Department of Physiology. Prior to joining the faculty at the University of Utah, he was a Professor of Medicine, Neurology, and Neurobiology at the UCLA School of Medicine in Los Angeles. His laboratory group has contributed to the identification of several ataxia and ALS genes and pioneered the use of ASOs targeting ATXN2 and STAU1.

Thomas Schwarz

The Schwarz Lab works at the intersection of neuroscience and cell biology. In the last decade, the mechanisms of axonal transport and the dynamics of mitochondria have become primary areas of interest and combine fundamental cell biology with insight into the etiology and treatment of neurodegenerative disorders. Our approach has been to use whatever system is most pertinent to the scientific question, from Drosophila genetics to rodent neurons, to patient-derived iPSCs. We combine advanced imaging methods, molecular biology, genetics, and pharmacology to reach our goal of a mechanistic understanding. One current focus is on neurodegenerative mechanisms and, in particular, how defects in mitochondrial transport and clearance contribute to neuropathology in Parkinson's Disease and ALS. These studies complement our other projects on synapse formation and the cell biological processes that allow a growth cone to transform into a functional synaptic bouton.

Stefan Strack

Dr. Strack is a Professor and Vice Chair in the Department of Neuroscience and Pharmacology at the University of Iowa. Born and raised in Germany, he received his MSc and PhD degrees at the State University of New York at Albany. He completed postdoctoral training at Vanderbilt University before joining the faculty at the University of Iowa in 2000. Dr. Strack has authored over 80 publications and has been awarded continuous NIH support since 2002. Dr. Strack's research over the last two decades has focused on the structure, function, and regulation of protein phosphatases (in particular PP2A and PP2B) and PKA/AKAP signaling complexes as they pertain to normal brain function and various neurological and neurodevelopmental disorders. A second area of interest is the regulation of mitochondrial dynamics by protein kinases and phosphatases, in particular regulation of the mitochondrial fission enzyme dynamin-related protein 1 (Drp1). Their work on Drp1 sparked their interest in ARSACS, in which earlier work suggested inhibition of mitochondrial fission in Purkinje neurons as a pathogenic mechanism

Betsy Trainor

Betsy Trainor is a corporate attorney for a northern Virginia defense contractor specializing in laser systems for customers such as the Department of Defense and NASA. She is a mother of four and an avid animal lover. She currently sits on the Board of Directors for the ARSACS Foundation and spends a large portion of her free time fundraising and networking for the rare disease community. Betsy is also an amateur nature photographer and enjoys visiting and hiking in America's National Parks.

Alanna Watt

Alanna Watt has worked in the cerebellar field for over 15 years, authoring >30 articles and book chapters. She is an editor for three journals, is a member of the College of Reviewers for CIHR, and is a member of the scientific review panel for Ataxia Canada. She has organized meetings, including the Cerebellum Satellite at the recent Canadian Association for Neuroscience meeting, as well as symposia at the Federation of European Neuroscience Societies (FENS) and Society for Neuroscience (SfN) meetings. She is Vice-Chair of the 2023 Gordon Conference on the Cerebellum and will Chair the meeting in 2025. She has given invited seminars at Universities, Research Institutes, and conferences. She has served as Interim Chair of Biology at McGill, and is a member of the McGill Senate.

Justin Wolter

Dr. Wolter completed his Ph.D. in the lab of Dr. Marco Mangone at Arizona State University, studying principles of microRNA evolution. During his post-doc and the University of North Carolina, he worked in the labs of Mark Zylka, adapting CRISPR to treat Angelman Syndrome, and Jason Stein using libraries of genetically diverse human brain cells to identify genetic modifiers of disease outcomes. Justin is currently an assistant professor in the School of Medicine and Public Health at the University of Wisconsin Madison. His lab studies how genetic variation – common and rare – affects risk and resilience to neurodevelopmental disorders.

SPEAKER ABSTRACTS

Thursday, October 19, 2023

Magnetic Resonance Imaging Biomarkers in ARSACS

Sirio Cocozza, MD, PhD, University of Naples, Italy

Magnetic Resonance Imaging (MRI) plays an unquestionable role in the work-up of patients with hereditary ataxias, including ARSACS. Indeed, it allows for an accurate in-vivo evaluation of brain anatomy, useful in identifying possible peculiar patterns of involvement that can aid neurologists in the differential diagnosis process. Nevertheless, brain MRI is not only a useful diagnostic tool, beingalso a technique able to provide accurate and reproducible information about the underlying pathophysiology of damage development. This can be achieved via the application of advanced imaging techniques, such as brain volumetry or diffusion MRI. The talk will therefore cover these two main different aspects of brain MRI in ARSACS: the conventional and the advanced imaging, presenting for both the current knowledge and the future perspectives.

Mitochondria & Cytoskeletal Dysfunction in ARSACS

Mohan Babu, PhD, University of Regina, Canada

Abstract coming soon.

Exploring the Role of Genetic and Epigenetic Modifiers in ARSACS

Daniele Galatolo, PhD, University of Pisa, Italy

The wide spectrum of ARSACS clinical pictures made us suppose that factors others than the specific mutations could contribute further to the disease. To test our hypothesis, in two experimental groups of ARSACS patients, one characterized by early (years<6) and the other by later onset (years>35), we applied Whole Genome Sequencing (WGS) and Whole Genome Bisulfite Sequencing (WGBS) to assess the co-occurrence of deleterious variants and the existence of epigenetic implications, respectively. WGS analysis showed a set of rare and deleterious variants in genes that might contribute as modifier; several of them are associated with disorders where spasticity or ataxia occur as symptoms, or to other neurological conditions. However, preliminary analyses suggest that most genes are private. On the other hand, WGBS showed differences in the methylation levels among groups. Non-CG methylation, that is uncommon in mammals compared to methylation on CG sites, also seemed to have a role. Furthermore, mitophagy and autophagy were found to be strongly involved in differentially methylated regions. Other known pathways were confirmed to be implicated in the disease such as synaptic function, focal adhesions, and oxidative phosphorylation. Moreover, other pathways novel to ARSACS resulted to be involved, including cell signalling pathways, axon guidance, and regulation of actin cytoskeleton. Our study confirms the presence of genetic and epigenetic modifiers in ARSACS and indicate epigenetics as a novel field in ARSACS worth of further investigations.

Charting the Molecular and Cellular Progression of ARSACS

Justin Wolter, PhD, University of Wisconsin-Madison, USA

Abstract coming soon.

Keynote: SCA2: Preclinical Models and ASO Therapy Development

Stefan M Pulst, MD, PhD, University of Utah, USA

Spinocerebellar Ataxia type 2 (SCA2) is a polyglutamine disease affecting several neuronal systems in addition to the cerebellum. We will discuss the development of mouse models replicating salient features of the human disease and their use for preclinical therapy evaluation. We will focus on the development of rigorous methods for preclinical evaluation as they apply to ATXN2 ASO development and recent research on other targets in the ATXN2 protein complex.

Friday October 20, 2023

Does ARSACS Degeneration Proceed Through a SARM1-Dependent Pathway?

Thomas Schwarz, PhD, Harvard University, USA

Abstract coming soon.

Restoring Calcium Homeostasis in Purkinje Cells Arrests Neurodegeneration and Neuroinflammation in the ARSACS Mouse Model

Francesca Maltecca, PhD, San Raffaele Scientific Institute, Italy

ARSACS is caused by mutations in SACS gene encoding sacsin, a huge protein highly expressed in cerebellar Purkinje cells (PCs). ARSACS patients, as well as mouse models, display early degeneration of PCs, but the underlying mechanisms remain largely unexplored, with no available treatments. In our recent work, we demonstrated aberrant calcium (Ca2+) homeostasis and its impact on PC degeneration in ARSACS. Mechanistically, we found pathological elevation in Ca2+-evoked responses in Sacs-/- PCs, as the result of defective mitochondria and ER trafficking to distal dendrites and strong downregulation of key Ca2+ buffer-proteins. Alteration of cytoskeletal linkers, that we identified as specific sacsin interactors, likely account for faulty organellar trafficking in Sacs-/- cerebellum. Based on this pathogenetic cascade, we treated Sacs-/- mice with Ceftriaxone, a repurposed drug which exerts neuroprotection by limiting neuronal glutamatergic stimulation, and thus Ca2+ fluxes into PCs. Ceftriaxone treatment significantly improved motor performances of Sacs-/- mice, at both pre- and post-symptomatic stages. We correlated this effect to restored Ca2+ homeostasis, which arrests PC degeneration and attenuates secondary neuroinflammation. In the talk, newly produced data further linking sacsin to Ca2+ deregulation in PCs will be presented. Altogether, our findings disclose new key steps in ARSACS pathogenesis and support further optimization of Ceftriaxone in pre-clinical and clinical settings for the treatment of ARSACS patients.

The Role of Sacsin on Glial Cells

Federico Herrera, PhD, University of Lisbon, Portugal

Research on sacsin dysfunction is largely focused on neuronal cells, just as it happened historically for more common neurodegenerative disorders, such as Huntington's, Parkinson's, and Alzheimer's diseases. However, glial cells play key roles in developmental and neurodegenerative disorders, including some with similarities with ARSACS, such as Alexander disease and Giant Axonal Neuropathy. Public databases and our own results indicate that medium-high sacsin levels can be found in mouse and human astrocytes, Müller glia, microglia, and macrophages. Furthermore, mouse sacsin mRNA expression is as high in astrocytes as in neurons, displaying the highest levels in younger animals (postnatal day 7) and decreasing with age. Human fetal astrocytes express the same mRNA expression levels as neurons, also decreasing as astrocytes mature. However, the role of sacsin in glial phenotype and function remains unexplored. We are generating glial cell models of ARSACS. Sacsin knockout in C6 rat glioblastoma cells leads to disruption of glial intermediate filament networks (GFAP, Vimentin, Nestin) and alterations in the response of cells to stress and inflammatory cues, as well as organelle disorganization and disruption of developmental signaling pathways. Current funding from the ARSACS foundation allowed us to advance further in these issues, and we will present some of our latest data.

Metabolic Rewiring in Cellular Models of ARSACS

Paul Chapple, PhD, Queen Mary University of London, UK

Impaired mitochondrial health is implicated in the pathogenesis of ARSACS. Evidence for this includes cellular models of ARSACS exhibit disruption of mitochondrial transport and network organisation, as well as reduced oxidative phosphorylation and increased levels of superoxide in sacsin knockdown cells and ARSACS patient fibroblasts. The metabolic functions of mitochondria reach far beyond bioenergetics. Thus, to better understand the mitochondrial deficit in ARSACS, and its metabolic consequences, we performed mass spectrometry-based tracer analysis, with both glucose and glutamine traced carbon, comparing the metabolite profiles between wild-type and sacsin knockout cell lines. Data from this analysis and other recent work will be presented.

How Natural History Studies Contribute to the Development and Assessment of Interventions

Cynthia Gagnon, PhD, Sherbrooke University, Canada

Abstract coming soon.

Development and Evaluation of the Efficacy of a Home Rehabilitation Program Aiming to Increase Motor Control, Balance, Mobility, Falls and Activities of Daily Living in People with ARSACS

Élise Duchesne, PHT, PhD. University of Quebec at Chicoutimi, Canada

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is characterized by the presence of neuropathic, pyramidal, and cerebellar deficiencies, which clinically manifest by ataxia, incoordination and motor control, strength, and balance impairments. A few studies have shown that participation in a rehabilitation program improves functional abilities, mobility, coordination, and symptomatology in

ARSACS or comparable populations. However, mobility issues limit the ability of people with ARSACS to participate in such programs. Our research team recently developed the PACE-ARSACS tool, a home exercise program specifically adapted to this population. After an initial standardized assessment by a physiotherapist, where a decision tree is used to assign a program with the appropriate difficulty level according to each participant's ability, the program is carried out at home independently. Objective. The aim of this study was to determine whether this adapted exercise program can improve the physical capacity of adults with ARSACS. Methods. Twenty participants (10 men and 10 women) were recruited to complete a control phase (usual activities) followed by an experimental phase (exercise program to be carried out 3 times a week), lasting twelve weeks each. Physical assessments were performed at three measurement times (T0: beginning of control phase, T1: end of control phase/start of intervention, and T2: end of intervention) where balance, mobility, social participation, and ataxia severity were assessed. Results. Fourteen participants completed the study. As expected, no disease progression was measured between T0 and T1. Our results showed a significant improvement in social participation and disease severity between T1 and T2. However, the walking speed was significantly decreased following the training program. Also, the results show a median cohort performance greater than the standard error of measurement for standing and sitting balance, step descent at maximal and comfortable speed, participation, and ataxia severity. This study provides encouraging results regarding the effects of a home exercise program for the ARSCS population. However, more research is needed to establish a standardized exercise program for this population and to make it accessible to non-expert clinicians of the disease.

A physiatrist guide to ARSACS.

Josée Larochelle, MD, paediatric physiatrist, CHU Ste Justine, Canada

Abstract coming soon.

New Developments in the Treatment of Communication Difficulties in Progressive Ataxias

Anja Lowit, PhD, Strathclyde University, Glasgow (Virtual)

The treatment of communication disorders in ataxia has seen a lot of development over the last 5 years, with a number of exploratory studies published, including one that specifically involved people with ARSACS. This presentation will briefly cover the type of communication problems people might experience and present the various treatment options that are now available to address these. Whilst we do not have definitive evidence for the effectiveness of these treatments yet they present new avenues to explore for clinicians to support people with ARSACS with their communication difficulties.

Keynote: Cerebellar Modelling using Human IPSCs

Esther Becker, PhD, MSc, University of Oxford, UK

The cerebellum is a fascinating brain structure that has a long-established role in motor learning and coordination but is also increasingly implicated in higher cognitive and affective processes. Its protracted development makes the cerebellum particularly vulnerable to genetic and physical insults, resulting in many different disorders ranging from ataxia to autism spectrum disorder. While much has been learned about the cerebellum from animal models, it is increasingly recognized that the biology of the human cerebellum is different from other species. As such, the use of human-specific models for cerebellar

diseases and drug development is highly desirable. The advent of iPSC technology has revolutionized pre-clinical research and allowed the development of in vitro human disease models for a wide range of disorders. Here, I will discuss methods to generate cerebellar models from human iPSC and how these can be utilized for the modelling of diseases of the cerebellum.

Towards Determining the Structure of Sacsin

Walid Houry, PhD, University of Toronto, Canada

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a juvenile progressive movement disorder caused by mutations in a gene called SACS, which produces a protein with the same name (SACS or sacsin). The disease is characterized by very early onset, where the afflicted individual shows signs of neuropathy. Knowledge of the protein structure is crucial for providing clues to its biological activity and to identify or design drugs that can bind to and correct the protein properties and function. Unfortunately, the sacsin protein is among the largest in human cells (4579 amino acid residues), which hindered determination of its structure and made basic biochemical experiments problematic. Supported by funding from The Ataxia Charlevoix-Saguenay Foundation, my group has undertaken a research program aimed at determining the structure of the full-length protein. We have now established protocols that enabled us to purify the full length protein, and we are in the process of determining the structure of the protein using electron microscopy approaches. Our efforts in this regard will be discussed at the meeting.

Leveraging Proteomics to Understand Sacsin Biology

Nevan Krogan, PhD, University of California at San Fransisco, USA (Virtual)

Abstract coming soon.

Understanding the Role of Metals in ARSACS

Graham George, BSc, DPhil, University of Saskatchewan, Canada

ARSACS is one of ~40 known human diseases that involve protein misfolding, and is the only member of this group of diseases for which a role for dysregulation of metals, such as copper or zinc, has never been demonstrated. Our research seeks to establish whether metal dysregulation is or is not involved in ARSACS. Our driving hypothesis is that the metallome, defined as the inventory of metal species present in tissues, is perturbed in ARSACS and that this perturbation is pathologically relevant. We have addressed this using synchrotron X-ray fluorescence imaging employing the facilities at the Canadian Light Source and the Advanced Photon Source for two distinct sample types: an ARSACS mouse model and cultured fibroblasts. In the mouse model we compared brain sections from wild-type (control) (WT) and Sacs knock-out (KO) mice. Notably, increased copper was observed in KO relative to WT in the cortex, and in the cerebellum, “hot-spots” of zinc accumulation were observed. Studies of human fibroblasts compared controls and fibroblasts from two patients. Here differences were subtle at best; with one patient no significant differences were observed, but with the other slightly altered zinc levels were observed. These results will be discussed together with their implications.

Exploring and Treating Cognitive Dysmetria in a Mouse Model of ARSACS

Stefan Strack, PhD, University of Iowa, USA

Cognitive and mood changes are a common comorbidity of cerebellar disorders and lesions, but underlying mechanisms are poorly understood. Mapping the developmental timeline of motor and non-motor symptoms of a progressive cerebellar ataxia model, the Sacs KO mouse, is one of the objectives of our work. Indeed, preliminary studies revesl that cognitve preceeds motor dysfunction in both heterozygous and homozygous Sacs KO mice. Leveraging our expertise in preclinical work with mouse models of neurodevelopmental disorders, we are aiming to improve working memory in ARSACS mice with drugs that are nearing or are already in the pipeline for FDA approval. Therefore, our work will not only advance our mechanistic understanding of the role of the cerebellum in cognition but may also fast-track treatments for ARSACS and other cerebellar disorders.

Novel Therapeutic Approaches for ARSACS

Alanna Watt, PhD, McGill University, Canada

Abstract coming soon.

Sacsin: from Domains' Functions to Biomarkers and Therapy

Ana Buj Bell, PhD, Genethon, France

Benoit Gentil, PhD, McGill University, Canada

Abstract coming soon.

ORGANIZING COMMITTEE

Mathieu Blais

Nicolas Dupré

Chantal Gobeil

Sonia Gobeil

François Gros-Louis

Massimo Pandolfo

Deborah Rashcovsky

Alanna Watt

OUR SPONSORS

neuro
Institut-Hôpital
neurologique de Montréal
Montreal Neurological
Institute-Hospital

UNIVERSITÉ LAVAL CENTRE DE RECHERCHE CHU de Québec Université Laval McGill Faculty of Medicine and Health Sciences Faculté de médecine et des sciences de la santé