7th International ARSACS Symposium
October 19-20, 2023
Summary of the event

Prepared by:

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On October 19-20, 2023, the ARSACS Foundation hosted the 7th International Symposium on ARSACS at the Neuro, on the campus of McGill University in Montreal, Québec. A central goal of the ARSACS Foundation is to promote communication and collaboration between the many individuals whose lives are touched by ARSACS, including people with ARSACS, family members, advocates, clinicians, and scientists. The biannual Symposium is the centerpiece of these efforts, and creates opportunities for formal and informal interactions, which motivate and focus research efforts around the world.

There were many highlights of this year's symposium, including patient centered clinical studies, molecular and cellular biomarkers, insight into the basic function and structure of sacsin, and, excitingly, disease modifying therapeutic strategies in the ARSACS mouse model. As descriptions of each of these talks will be summarized in a subsequent publication, here we discuss the broader context of the Symposium, and highlight some especially notable moments.

For the first time, this year's Symposium included a panel of people whose lives are personally touched by ARSACS. The panel was led by Dr. Cynthia Gagnon, a leader in clinical ARSACS care and natural history, and included Claudia Maltais and Kymberly Hoffman, who live with ARSACS, and Betsy Trainor, whose daughter Ally was recently diagnosed with ARSACS. For members of the audience who do not have the privilege of regularly interacting with people living with ARSACS, hearing their stories is not an experience we are likely to forget. Publicly speaking about your personal life takes tremendous courage. The stories of how ARSACS touches their daily lives were eloquent and personal, and the emotional weight of their journeys rippled through the audience. But the difficult moments were punctuated by stories of humor and joy, moments that are just as important and can see us through the toughest challenges. Dr. Gagnon eloquently stated that as clinicians and scientists we are all personally passionate about our work, but it is for Claudia, Kym, and Ally that we do what we do.

A common thread that ran through each story was the struggle of the diagnostic journey, which often lasts decades, and can include many misdiagnoses along the way. Betsy's metaphor of being hung over a cliff perfectly describes the uncertainty which shapes patients and families lives prior to a diagnosis. All the panelists acknowledged the shock of receiving an ARSACS diagnosis, but also found some relief at discovering a community of people who are working together to improve their lives. A quick poll of the audience by Dr. Gagnon revealed that of all the clinicians and scientists in the room,

only one researcher worked on ARSACS prior to the existence of the ARSACS Foundation; the legacy of the Foundation is in the strength of the community that it has grown around patients. As clinical and personal genetic testing becomes more commonplace (the *SACS* delT mutation common in Québec is now included the 23andMe Health panel), and clinical and scientific knowledge of ARSACS becomes more widespread, the Foundation stands as the pillar of support and guidance for the ARSACS community.

The Symposium featured two scientific keynote speakers, Dr. Stefan Pulst, Professor and Chair of Neurology at the University of Utah, and Dr. Esther Becker, Professor of Translational Neuroscience at Oxford University. Bringing expertise from other cerebellar diseases, their work addresses important areas of opportunity for the ARSACS research community: the design of hypothesis based therapeutic strategies, and disease modeling in the human cerebellum.

There are few disease modifying therapies for any neurodegenerative disease. This is due in large part to the complicated underlying biology, and slow progressive nature of these diseases. The first keynote lecture by Dr. Pulst spanned three decades of work in spinocerebellar ataxia 2 (SCA2), an autosomal dominant ataxia caused by a trinucleotide repeat expansion in the *ATXN2* gene. Dr. Pulst's therapeutic strategy centers on reducing the expression of the toxic form of ATXN2. The strength of this approach is that it directly targets the causal molecular deficit in SCA2. Dr. Pulst described several strategies to target ATXN2, including drug screens, disrupting ATXN2 interacting proteins, and antisense oligonucleotides targeting ATXN2, which are currently in clinical trials. For the community of ARSACS researchers, Dr. Pulst's work emphasizes that a wide range of strategies are essential in the quest for an effective therapy. Importantly, strategies that may not directly lead to the clinic often reveal crucial information which lead to more refined therapies, and better clinical trial design. Rigorous experiments which clarify underlying biological mechanisms are critical for the development of disease modifying therapies.

"Mice are not men or women." These words were uttered repeatedly during the symposium. Preclinical researchers rely heavily on mice, as they are an accessible mammalian model that allows therapeutic testing in the brain of a living organism. However, the need for more relevant models is clear given the poor track record of translating successful therapies in mice into human patients. The second keynote speaker, Dr. Esther Becker, has developed complex cellular models of the human cerebellum from induced pluripotent stem cells (iPSCs). Recent advances in iPSC technology allow researchers to generate three-dimensional aggregates of neural cells, called organoids, which can self-organize into structures that resemble those in the human brain. Dr. Becker's lab is among the first to develop cerebellar organoids, which contain most of the major cerebellar cell types including Purkinje neurons, which are especially vulnerable in ARSACS. Currently, these organoids most closely resemble the third trimester human cerebellum, and Dr. Becker described two examples of how organoids can be used to study neurodevelopmental diseases. As it is increasingly clear that ARSACS has a neurodevelopmental component which precedes neurodegeneration, cerebellar organoids will be indispensable in understanding how the loss of sacsin affects human cerebellar development. Looking forward, Dr. Becker alluded to efforts by her lab to develop organoids which resemble the mature cerebellum, which will be a powerful tool to study the mechanisms of neurodegeneration in the human context.

The Symposium concluded with a panel led by Dr. Anne McKinney, Full Professor at McGill University, and included speakers with patient, clinical, and scientific perspectives. Each shared their views on how best to focus the research community moving forward.

Dr. Nicolas Dupré, neurologist and Full Professor at Québec-Laval University, discussed clinical trial preparedness. Specifically, we need a better understand the ARSACS phenotypes from longitudinal studies, including imaging, natural history, factors affecting age of onset, and the distinct rates at which patients lose motor, peripheral, and cerebellar neurons. Importantly, Dr. Dupré suggested that prioritizing therapies where the risks and toxicities are well known will minimize the risk of clinical trial failure.

For scientific perspectives the panel included Dr. Justin Wolter, Assistant Professor at the University of Wisconsin Madison, and Dr. Federico Herrera, Professor at NOVA University Lisbon. Both Drs. Wolter and Herrera agree that a major gap in knowledge is in the early stages of ARSACS, prior to the onset of the neurodegeneration. By understanding the earliest events in ARSACS we can distinguish the primary molecular deficiencies in ARSACS from the secondary molecular cascades which follow. Finding similarities with other neurodegenerative diseases may also reveal critical information that can inform therapeutic strategies and clinical trials in ARSACS. Dr. Wolter also emphasized the necessity of communication and collaboration between scientists in order to minimize redundancy and focus efforts. This necessarily requires data sharing, transparency, and no hesitation to reach out to colleagues.

And to conclude the symposium, Betsy Trainor offered a new definition of ARSACS to help guide our efforts in the coming years:

Action: Get involved! Join the patient registry, read the research, stay informed, consider fundraising. People working together in small groups can move mountains.
Research: Critical to finding answers, a focal point of the ARSACS community
Science: Understanding that science is the key, and giving the scientific process time to unfold requires patience and persistence.
Awareness: Spread it! Scientists should be talking about ARSACS to their colleagues and institutions, clinicians should be raising awareness about ARSACS with other clinicians.
Collaboration: Only together will our aims be achieved.
Saving Lives: The ultimate goal!

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