**“Charting the neurodevelopmental stage of ARSACS (NeurodevARSACS): A cross-species longitudinal characterization of the early molecular changes in the brain, CSF and blood”**

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The project aims to define the early molecular and cellular changes in ARSACS, hypothesizing a neurodevelopmental disease phase preceding neurodegeneration. Using a cross-species approach, the study characterizes cerebellar deficits in an ARSACS mouse model alongside fluid biomarkers in both mice and human patients, establishing a mechanistic link between early brain pathology and accessible biomarkers. This work aims to provide critical insights for developing preemptive therapeutic strategies and identifying biomarkers that can serve as clinical trial endpoints, thereby accelerating future interventions for ARSACS.

Over the past two years this team has successfully generated single-nucleus RNA-seq data from the ARSACS mouse at four key time points along disease progression (n=60 animals, ~200k cells). These experiments revealed age dependent alterations in specific cell types, reflecting a cascade of cellular events that define distinct stages. We were able to molecularly dissect Purkinje neuron subtypes, revealing the pathways that distinguish susceptible and resilient neurons. Future studies aim to leverage this information to define pathways which could be targeted to promote Purkinje survival. We also found stage specific involvement of non-neuronal cell types, highlighting the complex interplay of neuronal dysfunction, systemic responses, and time.

To connect this molecular data to patient data, this project collected cerebrospinal fluid and plasma from ARSACS mice and human patients, and analyzed the protein biomarker landscape with both label free mass-spectrometry and targeted assays of promising biomarker candidates. Again, this data highlighted stage dependent proteomic signatures, which reflect both underlying disease mechanisms and systemic response to neuronal dysfunction. Importantly, the Synofzik lab also identified and validated candidate biomarkers that clearly distinguish cases from controls.

The team aims to submit this data for publication in 2025, alongside the public release of these comprehensive dataset to be used by the broader ARSACS research community.