"Elucidating mechanisms underlying motor coordination rescue in a mouse model of ARSACS"

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Since cerebellar dysfunction is thought to underlie ARSACS pathology, work from the Watt and McKinney labs focuses on identifying novel disease-causing mechanisms in a mouse model of ARSACS, as well as implementing new therapeutic approaches to ameliorate cerebellar function and motor deficits. We have had a productive year since our last progress report in 2022, and want to take this opportunity to thank the Foundation for their support.

Of particular note, in 2023, we had a manuscript accepted for publication, Toscano Marquez *et al., A mitochondrial-targeted antioxidant (MitoQ) improves motor coordination and reduces Purkinje cell death in a mouse model of ARSACS* in Neurobiology of Disease (Impact factor 7.05). This manuscript shows that chronic oral administration of MitoQ prevents motor coordination decline associated with disease progression in a mouse model of ARSACS, and shows our expertise in performing pre-clinical interrogation of drugs. As a result of this successful publication, we have recently signed an agreement with Minoryx to test their drug leriglitazone in ARSACS mice, which will commence in 2024.

We have also identified promising new dysregulated gene products using RNA-Seq and bioinformatics and are pursuing these experimentally. We are also following up on previous work that identified changes in non-neuronal cells in the cerebellum of ARSACS mice. Thus, we have multiple avenues of research that we are pursuing in 2024 and expect to submit an invited manuscript to a special issue of the journal Cerebellum that highlights research on ARSACS.

We have disseminated our work widely, with Prof. McKinney presenting at Berlin Neuroscience 2023, posters at ICAR 2022 and CAN 2023. Prof. Watt has also been a member of the planning committee for the International ARSACS Symposium in 2023.

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