

Summary of Progress made by McKinney & Watt team on ARSACS project Dec 2017

Purkinje cell Synaptic and Intrinsic Changes

Recap: Synaptic and intrinsic changes found in Sacs KO mice are very similar to those seen in other forms of ataxia.

- Paper on synaptic and intrinsic changes in Sacs KO mice. We plan to submit the paper by the end of 2017
- Electrophysiological analysis of Sacs KI mice (in collaboration with Brais lab), with similar (but milder) changes observed as in KO mice.
- Working to establish drug-screening validation pipeline. This will likely involve cultured Purkinje cells allowing us to test synaptic and intrinsic changes in Purkinje cells rapidly to test drugs identified from Brais and Schwartz lab. Discussing next steps to get optimize the testing.
- Continuing progress on understanding mechanisms underlying these changes, with several potential mechanisms, based on other ataxia models, tested.

Therapeutic Interventions

Recap: MitoQ is currently in clinical tests for MS, and has shown promising results in mouse models of several neurodegenerative diseases, including (in 2016) another form of ataxia, SCA1.

- Progress made on MitoQ project, with robust, significant behavioural improvements on Rotarod and elevated beam assays after chronic oral administration of MitoQ.
- Progress is underway in understanding the mechanistic underpinnings of MitoQ action.
- This promising avenue of research that will be published as soon as possible, anticipated by the end of 2018.

Research Resource Development

Recap: New technological directions to drive our ARSACS research forward.

- Crossed Sacs KO mice with L7-tau-GFP mice so that we have Purkinje cells expressing GFP in Sacs KO mice. These mice will be a useful tool for imaging studies as now have Purkinje cells labeled in situ (e.g. soon will be used in MitoQ study) as well as sorting Purkinje cells, etc. These mice will be shared with other ARSACS researchers.
- Alanna is currently on sabbatical working in Hedlund lab at the Karolinska Institute to learn transcriptomic from single cells. With this technique we will be able to examine different gene expression in anterior (susceptible) and posterior (resistant) Purkinje cells from both control and Sacs KO mice.

Funding Updates

Recap: Utilize all opportunities for funding in order to move ARSACS research forward.

- Alanna and Anne submitted Letter of Intent for Healthy Brains Healthy Lives Innovative Ideas Program together with Brais lab. If selected, full grant will be submitted in January 2018. We should hear in the next 2 weeks if we can proceed to full application.
- Plans to submit CIHR grant, likely together with Brais lab in Spring 2018.