Physiological characterization of functional deficits and potential therapeutic targets in ARSACS mice.

Progress report- August 2016
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Autosomal recessive spastic ataxia of Charlevoix Saguenay (ARSACS) is a neurological disease with a childhood onset. A knockout mouse model of ARSACS has recently been successfully made ($Sacs^{-/-}$) which exhibits changes in the cerebellum, an area of the brain essential for the performance of smooth and accurate goal-directed movement, postural adjustments to maintain balance and learning new motor skills, similar to what was observed in ARSACS patients. Previous studies on this mouse have identified cellular and behavioural alterations such as ataxia, loss of cerbellular Purkinje cells and impairment of neurofilament and mitochondria. However the functional alterations of Purkinje cells in ARSACS have as yet to be characterised. The McKinney and Watt labs have joined forces to investigate what leads to the functional deficits of the neurons and find potential novel targets for preventing or rescuing the functional deficits observed in ARSACS.

In the last year with support from the ARSACS Foundation we have established and maintained a $Sacs^{-/-}$ mouse colony in the Goodman Cancer Centre building that are used by the Watt and McKinney labs. Using these mice we have conducted research to determine what functional changes underlie the behavioural deficits and are currently drafting a manuscript for publication. In addition, we have successfully recruited Dr. Brenda Toscano-Marquez to Dr Watts's lab. We are currently finalizing the recruitment of a second postdoc to be in Dr McKinney's lab.

To date, we have already obtained very interesting data showing changes in both synaptic inputs onto cerebellar Purkinje cells and the firing output of Purkinje cells in ARSACS mice prior to the time of the first detectable motor deficits. This is accompanied with changes in the connectivity of Purkinje cells to their targets neurons in the deep cerebellar nuclei (DCN). We are currently investigating if these alterations are predominately expressed in a specific subset of Purkinje cells since this could help lead to a more targeted therapeutic strategy.

We recently began testing several drugs that have been shown previously to have successfully reduced ataxic symptoms in other animal models of ataxia. Based on functional similarities between ARSACS mice and these other ataxias we will screen a number of potential therapeutic molecules, including 4-aminopyridine (4-AP), which has been found to improve firing deficits in spinocerebellar ataxia type 1 (SCA1; which has similar Purkinje cell firing and synaptic changes as ARSACS mice), SCA6, and episodic ataxia type 2 (EA2); Flufenamic acid which has been shown to restore membrane potential in SCA1; and EBIO, which has been shown to improve firing regularity and frequency in EA2. Our preliminary findings suggest that in contrast to what has been observed in SCA1 and other forms of ataxia, 4-AP does not significantly affect the firing rates of Purkinje cells in $Sacs^{-/-}$ mice, although we have only tested a relatively low concentration at present, and are currently testing higher concentrations.