Francesca Maltecca, Progress report

"Investigating the link between impaired mitochondrial trafficking and calcium dysregulation in *Sacs*$^{-/-}$ Purkinje neurons"

This project is based on the hypothesis that a reduced presence of mitochondria in the distal dendritic branches of *Sacs*$^{-/-}$ Purkinje cells (PCs) could result in a dysregulation of calcium homeostasis in these sites and this could contribute to PC degeneration and loss in ARSACS. The disclosure of this phenotype would represent also a strong rationale to test a pharmacological approach on *Sacs*$^{-/-}$ mice aimed at reducing calcium influx in PCs.
In the first year of the project we have started deriving and maintaining cerebellar dissociated primary cultures enriched for PCs from *Sacs*$^{-/-}$ mice and controls. We found that *Sacs*$^{-/-}$ PCs undergo progressive degeneration in vitro, thus making *Sacs*$^{-/-}$ primary PCs a good model to study the pathogenesis of ARSACS. We analyzed mitochondrial distribution in primary PCs and observed that, while in wt and *Sacs*$^{+/-}$ PCs mitochondria entirely fill the dendrites, in *Sacs*$^{-/-}$ PCs they tend to cluster in the cell soma and barely enter the dendritic trees.
To test whether faulty distribution of mitochondria in distal dendrites results in pathological perturbations in calcium homeostasis in these sites and, in turn, in PC degeneration in ARSACS, we are now starting with measurements of cytoplasmic calcium in *Sacs*$^{-/-}$ mice.
In parallel, we are now testing on the ARSACS mouse the efficacy of a pharmacological therapy aimed at reducing calcium influx and oxidative stress in PCs. A cohort of *Sacs*$^{-/-}$ mice and controls has been treated with drug or vehicle at post symptomatic stage (3 months of age). The possible rescue of the ataxic phenotype will be analyzed in the next months through a series of complementary tests (rotarod test for motor performances, histology for PC-degeneration).