

## **"High-throughput strategy to identify large domains of Sacsin" – Dr Kalle Gehring**

Summary of project progress under the 2015-2016 funding

The loss of the Sacsin protein has serious physiological consequences and leads to the neurodegenerative disease ARSACS. In our lab, we are using the tools of structural biology to visualize the 3D structure of the protein. Sacsin is an extremely large protein and difficult to visualize in its entirety. To speed structural studies, we have been pursuing two approaches. The first is to test Sacsin proteins from a wide variety of species in the expectation that some will be more suitable for study. The second is a divide-and-conquer strategy in which we are examining the structure of smaller fragments. Recent work has focused on three repeated segments within the Sacsin, termed SIRPTs. We have focused on the first repeat and are engineering sequences from divergent biological sources (from mammals to plants) that are optimal for bacterial expression, stability, and structural studies. Three protein fragments have yielded encouraging results and are being prepared for structural studies. In the parallel, we are carrying out high-throughput screens of shorter fragments and constructs with potentially beneficial mutations. Visualizing the 3D structure of Sacsin is an important step in understanding its function in neuronal health. Through our studies, we hope to design therapies to compensate for the absence of Sacsin in patients.