“Structural Determination and Super Resolution Imaging of Sacsin”

Dr. Walid A. Houry, Department of Biochemistry

Temerty Faculty of Medicine, University of Toronto

GENERAL AIMS OF THE PROJECT

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a juvenile progressive movement disorder caused by mutations in a gene called *SACS*, which produces a protein with the same name (SACS or sacsin). The disease is characterized by very early onset, where the afflicted individual shows signs of neuropathy. Knowledge of the protein structure is crucial for providing clues to its biological activity and to identify or design drugs that can bind to and correct the protein properties and function. Unfortunately, the sacsin protein is among the largest in human cells (4579 amino acid residues), which hindered determination of its structure and made basic biochemical experiments problematic. In the previous funding period, we made good progress towards purifying the full-length native protein and obtaining initial electron microscopy (EM) images of it. This was only possible by the previous funding support provided by the Ataxia Charlevoix-Saguenay Foundation. Here, through the continued support of the Foundation, we propose to scale up our protein purification efforts to obtain a high-resolution structure of sacsin using cryoEM.

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