Understanding the Role of Disease-Associated Microglia in ARSACS Progression

Autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS) is a rare inherited neurological disorder that begins in childhood and causes progressive problems with balance, coordination, and muscle control. ARSACS is caused by mutations in the *SACS* gene, which produces a protein called sacsin. Sacsin is particularly important in the cerebellum, the brain region responsible for motor control. In ARSACS, Purkinje cells (PCs) in the cerebellum are among the first to be damaged, and their loss significantly contributes to disease symptoms.

Our previous research has shown that ARSACS disrupts the cytoskeleton of these neurons, impairing the transport of essential components such as mitochondria. These defects lead to cellular stress and, ultimately, degeneration of Purkinje cells.
We have also discovered that ARSACS triggers a strong immune response in the cerebellum. Microglia, the resident immune cells of the central nervous system, shift from a homeostatic resting state to a highly activated form known as disease-associated microglia (DAM). This type of microglia is known to play a role in other neurological diseases, but its contribution in ARSACS remains unclear.

The goal of this project is to determine whether this immune response contributes to Purkinje cell damage or, conversely, plays a protective role.
Objective 1: Identify the localization of activated microglia in the ARSACS cerebellum and determine whether they are concentrated in areas where Purkinje cells begin to degenerate.
Objective 2: Experimentally modulate microglial activity in a murine model of ARSACS to assess whether increasing or reducing their activation affects neuronal survival.

Understanding how neuroinflammation influences ARSACS progression may reveal new therapeutic targets and contribute to the development of effective treatments for this currently incurable childhood disease.

Beyond Neurons: Analysis of Sacsin-Mediated Mechanisms Underlying Oligodendrocyte Dysfunction in ARSACS

Autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS) is a rare inherited disorder that affects the brain, causing muscle stiffness, impaired coordination, and progressive loss of motor control. The disease is caused by mutations in a gene that produces a protein called sacsin, which is essential for the health of brain cells.

So far, research has mainly focused on neurons damaged by the disease. However, recent findings have shown that another type of brain cell, called oligodendrocytes, also produces sacsin. These cells wrap nerve fibers with a protective sheath called myelin, which is crucial for the transmission of nerve signals and proper brain function.

Our project will use advanced technologies to investigate how the loss of sacsin affects these support cells and their ability to form myelin. We will use genetically modified human oligodendrocyte models that do not express sacsin to better understand the role of this protein in myelin formation and cellular function.

This knowledge could lead to new strategies to protect both neurons and support cells in ARSACS and to develop improved treatments for people living with this severe disease.

From Damage to Renewal: Inducing Mitophagy to Correct Mitochondrial Defects in Autosomal Recessive Spastic Ataxia of Charlevoix–Saguenay (ARSACS)

Autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS) is a rare inherited neurodegenerative disorder that usually begins in childhood and leads to a progressive loss of balance, coordination, and motor abilities. The disease is caused by mutations in the SACS gene, which is responsible for producing a protein called Sacsin. The precise function of this protein is not yet fully understood, but when Sacsin is absent or does not function properly, neurons—particularly those in the brain region that controls movement—progressively die. Currently, there are no treatments capable of slowing or halting disease progression.

Recent research has shown that one of the main problems in ARSACS involves mitochondrial dysfunction. Mitochondria, the “powerhouses” of the cell, are normally removed and replaced when damaged through a process called mitophagy. In ARSACS, this mechanism is impaired, leading to the accumulation of defective mitochondria and increased oxidative stress, which contributes to neuronal death.

Our project aims to understand why mitophagy does not function properly in the absence of Sacsin and to test a new strategy to reactivate this essential mitochondrial quality control mechanism.

The target of this study is the protein USP14, whose inhibition stimulates mitophagy and improves mitochondrial health in neurons. By analyzing neurons derived from human stem cells, we will assess whether inhibition of USP14 using specific inhibitors promotes mitophagy, restores energy balance, and protects neurons from degeneration.

This study will help clarify the mechanisms underlying impaired mitochondrial quality control in ARSACS and evaluate a novel therapeutic target that may offer new perspectives for patients affected by ARSACS.