Report of the project "Targeting Cav2.1 to recover firing defects and degeneration of Purkinje neurons in ARSACS". (1st year)

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This project aimed to identify potential therapeutic molecules to address calcium dysregulation in ARSACS, for which currently no disease-modifying therapies are available.
Our previous work (Del Bondio et al., 2023) demonstrated that correcting altered calcium homeostasis can halt Purkinje cell degeneration and improve motor symptoms in a mouse model of the disease, providing strong proof of concept that calcium signaling pathways represent a promising therapeutic target in ARSACS.
Building on these findings, and on our more recent evidence that sacsin plays an important role in regulating calcium channels in Purkinje neurons, this project is exploring complementary pharmacological strategies aimed at restoring calcium homeostasis in disease models. In particular, we investigated the potential of clinically approved compounds known to modulate calcium-related pathways as candidates for drug repurposing in ARSACS.
In parallel, we established a collaboration with a specialized contract research organization to perform a large-scale screening campaign aimed at identifying novel compounds with similar or complementary mechanisms of action. This effort combined advanced computational approaches, virtual screening, and experimental validation to prioritize candidate molecules for further development.
By integrating targeted drug repurposing with broader compound discovery efforts, this project generated important tools, preliminary proof-of-concept data, and a portfolio of promising candidate molecules that we are exploring in the frame of the second year of funding.
Overall, these results provide a strong foundation for the future development of therapeutic strategies aimed at slowing or preventing Purkinje cell dysfunction and degeneration in ARSACS.