Report 2021-2022: The group headed by F. Maltecca at Ospedale San Raffaele, Milan, Italy has conducted a series of immunoprecipitation experiments of sacsin in the mouse cerebellum followed by label free quantitative mass spectrometry. They discovered the specific interaction of sacsin with proteins regulating calcium homeostasis in Purkinje cells and validated these interactors by co-immunoprecipitation experiments. They also performed functional evaluation of these interactions by multi-OMICS, imaging and electrophysiological approaches in Sacs<sup>-/-</sup> cerebellum.

The absence of sacsin impacts on these proteins finally leading to early alteration of calcium homeostasis, that could represent the trigger of the ataxic phenotype in the Sacs<sup>-/-</sup> mouse. These findings are in line with the positive results previously obtained with Ceftriaxone treatment in Sacs<sup>-/-</sup> mice. Further studies are ongoing in the second year of funding to establish whether the identified sacsin interactors could represent direct target for therapy.