Project 9.2. Linking abnormal Ca2+ signaling and the unfolded protein response with Huntington's disease pathology in both YAC128 mouse model and iPSC-derived neurons from HD patients.

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WWW: https://www.iimcb.gov.pl/en/research/laboratories/2-laboratory-of-neurodegeneration-kuznicki-laboratory

Background:
Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by the aggregation of mutant huntingtin and degeneration of medium spiny neurons (MSNs) in the striatum. Abnormal Ca2+ signaling is considered as an early event in HD pathology since disturbances in Ca2+ homeostasis were found in HD models and postmortem samples from HD patients. One of the pathways for Ca2+ signaling is store-operated calcium entry (SOCE). The activation of inositol-(1,4,5)triphosphate receptor 1 (IP3R1) results in Ca2+ release, which decreases ER Ca2+ content and activates Ca2+ influx through SOC channels. Elevated SOCE and increased IP3R1 activity was previously reported in MSNs from the transgenic model of HD, YAC128. The project is based on the hypothesis that neurodegeneration in HD is induced by disturbances in Ca2+ signaling in neurons. Previously we found that huntingtin-associated protein 1 (HAP1) that is overexpressed in striatal neurons and binds to mutant huntingtin causes dysregulation of Ca2+ signaling by increased activation of both SOCE and IP3R1 receptors. We intend to examine the link between dysregulated Ca2+ signals and neuronal cell death in HD. The experiments will be performed in YAC128 MSNs cultures and neurons delivered by the reprogramming of fibroblasts from HD patients with the application on CRISPR/Cas9-based editing strategies and Ca2+ signaling inhibitors.

Aim:
The project aims to investigate whether and how the disturbed Ca2+ homeostasis affects HD pathology. A Ph.D. project related to this issue will be done using different HD models. One position is available in the project. We are looking for a person interested in neurobiology, with experience in working with animal models (mice, zebrafish), cell cultures, and biochemical techniques (immunoprecipitation, western blot). Knowledge/experience in iPSCs cultures is welcome.