DEMENTIA
RESEARCH
SYNAPSIS FOUNDATION SWITZERLAND

Career Development Award

Project

«Identification of genetic modulators of prion transfer via genome wide CRISPR screens»

Granted amount	CHF 200'000
Starting date	1.2.2023
Duration	24 months

Main applicant

PhD Elena De Cecco
Institute of Neuropathology
University of Zurich/ University Hospital Zurich
Schmelzbergstrasse 12
8091 Zürich

Lay summary of the project

Protein aggregation disorders affect millions of people and are essentially incurable. Protein aggregates "jump" from one neuron to another, infecting the entire brain and causing neurodegeneration. Here we propose to enumerate all genetic modifiers of transcellular transfer, using prion disorders as a prototypic model.

We will utilize two single-gene CRISPR-cut and CRISPR-activator libraries spanning the entire human genome and a highly prion-susceptible human cell line in which the human PRNP gene was replaced by its ovine homologue. We will perform pooled CRISPR activation and knock-out screens to identify modulators of prion uptake, and then validate our hits on human IPSC-derived neurons.

To assess their role in intercellular transfer and propagation, we will establish a genetically encoded reporter system that identifies newly infected and prion-propagating cells. Our study will shed light on the molecular mechanisms mediating cell-to-cell transfer of neurodegeneration-related amyloids and might lead to the identification of new druggable targets.