



Principal Investigator Grant

Project

«Regulation of reversible amyloids and stress granule maturation by cytosolic pH»

Granted amount	CHF 273'248
Starting date	1.5.2021
Duration	24 months



Main applicant

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Lay summary of the project

Evidence is accumulating that precursors of disease-related aggregates are RNA-protein (RNP) granules forming as part of a physiological stress response. Why these RNP-granules develop into irreversible structures remains unclear. Interestingly, we found that cytosolic pH directly regulates protein aggregation. Indeed, the amyloid core of the yeast pyruvate kinase Cdc19 and its mammalian homologue PKM2 rapidly respond to physiological pH changes by forming reversible amyloids, which converge into irreversible structures upon extended stress conditions. Since cytosolic pH is a conserved cellular signal driving cell growth and aging, we speculate that protonation of specific residues in amyloid core motifs promotes amyloid formation and RNP maturation.

In this project, we propose to combine different approaches to unravel the molecular mechanism and function of pH-dependent amyloids and their role in driving RNP-maturation. We expect to gain insights into the complex processes underlying reversible aggregates and establish a mechanistic basis to understand age-related neurodegenerative diseases.