DEMENTIA
RESEARCH

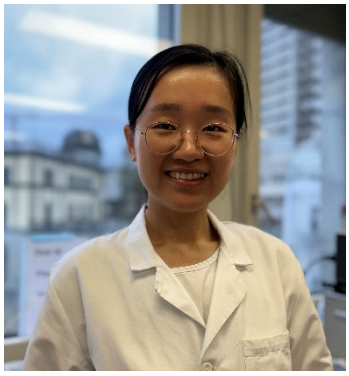
SYNAPSIS FOUNDATION SWITZERLAND

Career Development Award

Project

Tingting Liu:
"Unraveling the Roles of Primary Cilia and Microvilli in Transducing Protein Aggregates-Induced Toxicity in Neurodegenerative Diseases"

Granted amount	CHF 200'000
Starting date	1.1.2024
Duration	24 months



Main applicant

Tingting Liu, PhD
Institute of Neuropathology
University of Zurich
Schmelzbergstrasse 12
8091 Zurich

Unraveling the Roles of Primary Cilia and Microvilli in Transducing Protein Aggregates-Induced Toxicity in Neurodegenerative Diseases

Despite significant advances in our understanding of neurodegenerative diseases (NDs) in the past decades, the limited success in their treatment indicates gaps in our knowledge. Compared to the intensive studies on the replication/transmission of protein aggregates, the detrimental effects of these aggregates on recipient cells are overlooked and the factors influencing the toxicity remain largely unknown.

Through a genome-wide CRISPR activation synthetic lethality screen, we identified that primary cilia and microvilli mediate prion toxicity. Inhibition of ciliogenesis halted neuronal loss induced by prion infection in cultured organotypic cerebellum slices. The functions and underlying mechanisms of primary cilia and microvilli by which they contribute to the pathogenesis of NDs have been poorly studied.

To investigate the roles of primary cilia and microvilli in transducing protein aggregates-induced toxicity, we aim to: 1) examine the involvement of cilia/microvilli in prion toxicity; 2) explore the ciliary/microvillar regulation of distribution/expression of prions, and the associated signaling pathways in modulating prion toxicity; and 3) investigate a possible broader effect of these membrane structures in TDP43 and α-synuclein proteinopathies.

All this will open up an important direction for studying the membrane protrusion structures and potentially provide druggable targets for treating neurodegenerative diseases.