Microfluidics to Study Huntington's Disease by Visual Proteomics

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Stereotypic spatiotemporal spreading of pathological lesions through the nervous system is a hallmark of many neurodegenerative diseases. The prion-like spreading model provides an elegant explanation for this observation [1], postulating that misfolded proteins (amyloids) can disease healthy cells by imprinting their misfold onto endogenous proteins. However, the precise spreading mechanism and information carrier is still unknown. Huntington's disease (HD) is an archetypical example of the prion-like spreading phenomena: dominantly inherited mutations lead to the misfolding and aggregation of the huntingtin (HTT) protein and the onset of the lethal disease in a patient's age of around 35 years. HD is manifested by uncontrolled movements, depression, and a loss of cognition.

The project is based on our recently developed platform for microfluidics-based sample preparation for electron microscopy (EM) called 'cryoWriter' [2,3] which allows novel strategies for single-cell analysis by 'differential visual proteomics' [4] and 'interaction-labeling' [5]. Furthermore, we developed a microfluidic platform for the co-culture of diseased and healthy cells, assuring exclusive communication via neurites. A primary task will be to further develop the cryoWriter system for the integration of the cell-culturing chip to allow direct investigation of the neurite interaction region between two cells by electron tomography.

We are looking for a PhD student with a strong background in engineering and microfabrication, who is interested in working in a highly interdisciplinary group and has a keen interest in biomedical questions.

The specific aims of the project are (I) to study the transmission pathway of the misfolded mutant huntingtin protein (mHTT) from diseased to healthy cells, (ii) to study the fate and effects of these amyloid nanoparticles in the cell using our recently developed `visual proteomics' approaches, and (iii) to develop a new microfluidics platform that allows precise studying of the synaptic interaction between neurons by cryogenic electron microscopy (cryo-EM) tomography at nanometer-scale precision.

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[4] A. Syntychaki et al., 'Differential visual proteomics': Enabling the proteome-wide comparison of protein structures of single- cells. J. Proteome Res., 2019 (in press).
[5] D. Giss et al., Exploring the interactome: Microfluidic isolation of proteins and interacting partners for quantitative analysis by electron microscopy. Anal. Chem., 86(10):4680–4687, 2014.