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Supervisor's contact details

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Title of the project

Large-scale synaptic imaging approaches to identify druggable mechanisms of synaptopathy

MSCA-PF Research Panel

☐ Chemistry (CHE)

☐ Social Sciences and Humanities (SOC)

☐ Economic Sciences (ECO)

☐ Information Science and Engineering (ENG)

☐ Environment and Geosciences (ENV)

☒ Life Sciences (LIF)

☐ Mathematics (MAT)

☐ Physics (PHY)

Description of the project

Neurological disorders are often caused by pathological defects in synapses, but studying these defects is challenging due to the small size, heterogeneity and high abundance of synapses. The impact of specific disease-associated synaptic changes on the function of interconnected neurons can be unclear, undermining the search for druggable mechanisms.

This project addresses this challenge by combining optical actuator, optical reporter, and subcellular targeting approaches to generate a synaptic tool set. By using this tool set in conjunction with conventional reporters, longitudinal high-throughput imaging over large fields, and machine learning algorithms, we aim to establish causal relationships between properties of individual synapses and functional neuronal consequences, improving the understanding of how disease-associated synaptic defects impact on interconnected neurons. Synaptic proteomics, including single synapse analysis and proximity proteomics, will be used to identify proteome changes and heterogeneity between synapses in synaptopathies, in particular Alzheimer's Disease and SynGAP syndrome. The project's novel approach and advanced methods will improve our ability to identify druggable changes at synapses that contribute to neurological phenotypes.

The research will be carried out at the Turku Bioscience Center, which hosts research groups with expertise in high-end infrastructure available to the local research community.

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Facilities for this project include the Turku Screening unit, equipped with 3 customised high throughput microscopes and lab automation devices, the Turku Proteomics core with FAIMS-equipped Orbitraps for the highest selectivity and detection limits, and the Cell Imaging core hosting a wide range of imagers including super-resolution microscopes. We will also use the supercomputer facilities at the Center for Scientific Computing (CSC) to support data analysis.

Research objectives or research questions of the project

The overall aim is to identify mechanisms by which disease-associated changes in the proteome of synapses impact on the signalling and function of the neurons possessing the altered synapses. An emphasis is made on changes to signalling processes as these are often druggable.

The project addresses this aim through the following specific objectives:

1. The identification of new approaches for reliable synaptic targeting and multiplexing of optical probes and actuators.
2. The combination of these newly developed synaptic reporters with existing reporters indicating whole cell state, using large-field imaging. This is for simultaneous monitoring and actuation of synaptic changes and changes at the whole cell level across large numbers of interconnected neurons, in high throughput and over prolonged periods of time.
3. The effects on the relation between synapse-specific and whole cell signalling is systematically monitored with and without the synaptic proteome changes identified in models of Alzheimer's disease and SynGAP syndrome, This is to identify and clarify how early changes at even a limited number of synapses can lead to impacts at the whole neuron level.