

Title: “Role of DOC2A in asynchronous neurotransmitter release and neural network dysregulation in Alzheimer’s disease”

Project description:

In the nervous system, information processing relies on tightly regulated inter-neuronal communication mediated by the electrically evoked release of neurotransmitters. This process consists of two kinetically distinct components: one phase in which Ca²⁺ influx triggers rapid synchronous neurotransmitter release with a time course of several milliseconds and another slow asynchronous phase that can last for tens or hundreds of milliseconds at glutamatergic synapses. While fast synchronous release is essential for rapid communication with downstream neurons, asynchronous release allows for the modulation of postsynaptic excitability on relatively long timescales, which in turn can alter action potential firing patterns. Double C2 Domain Alpha (*DOC2A*) has been identified as a potential Ca²⁺ sensors for asynchronous neurotransmitter release in mouse hippocampal neurons (doi: 10.1016/j.cell.2011.09.046) and recent results from our laboratory suggests *DOC2A* as a genetic risk factor for Alzheimer’s disease (<https://doi.org/10.1038/s41588-022-01024-z>). We thus hypothesized that altered expression of *DOC2A* could contribute to disease onset/progression by affecting asynchronous neurotransmitter release and neural network activity. To address this possibility, we will use CRISPR/Cas9 gene-editing to generate isogenic human-induced pluripotent stem cells (hiPSCs) lines carrying mutations in the *DOC2A*. Next, hiPSCs will be differentiated into neurons in bi-dimensional cultures and cerebral organoids, allowing the functional characterization of these cells using state-of-art technologies, such as multi-electrode array (MEA) electrophysiology and single-cell RNA-sequencing (doi: <https://doi.org/10.1101/2022.01.18.476601>). These experiments will contribute to understanding the contribution of *DOC2A* to Alzheimer’s disease pathogenesis.

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