Anti-inflammatory and neuroprotective effects of a new FPR2 receptor agonist evaluated in a human model of Fragile X Syndrome.

Fragile X syndrome (FXS) is an inherited genetic disorder caused by the expansion of the CGG triplet within the FMR1 gene, resulting in a reduction/loss of the FMRP protein. The latter regulates the expression of many genes, including those involved in synaptogenesis and neuroplasticity. Patients with FXS have neuropsychomotor alterations, intellectual disability, mood disorders, seizures, and Autism Spectrum Disorder (ASD). Preclinical studies have shown altered production of the pro-inflammatory cytokines in FXS patients and in Fmr1 knockout mice, suggesting that neuroinflammation might be a leading cause of neuronal and synaptic damage in FXS.
This proposal aims to investigate the link between neuroinflammation and neuronal dysfunctions in FXS and test whether these events could be rescued by treatment with the FPR2 receptor agonist MR-39, which is known to reduce neuroinflammation and improve neuronal plasticity in the mouse models of ASD (Cristiano et al., 2022). For this purpose, we will use as an experimental model neuronal cultures obtained from pluripotent stem cells of FXS patients and healthy donors (www.wicell.org) and treat them with MR-39. By combining cellular and molecular analyses, immunocytochemistry, confocal microscopy, and electrophysiology techniques, we propose to examine the effect of MR-39 treatment on:

1. The expression of genes involved in signal transduction pathways, that are dysregulated in FXS patients, such as mTORC1 and ERK/MAPK, using qRT-PCR and western blot.
2. The expression of specific microRNAs (miRNA), that are targets of FMRP and potentially involved in synaptic functions, such as mir-34b and mir-148.
3. The neuronal morphology changes, such as elongation and neurite branching, number, shape, and density of dendritic spines.
4. The synaptic transmission mediated by the AMPA and NMDA receptors using the patch-clamp technique.