Press AD Abstract

It is widely accepted that synaptic alteration/loss is the strongest predictor of cognitive decline in Alzheimer's disease. However, this has mainly been based on histopathological studies in post-mortem brains which do not capture dynamic events that precede the observed synapse loss and in particular fall short in providing information on the impaired physiological function of synapses. In the PreSSAD project, we aim at addressing presymptomatic synaptic deficits in the context of the human AD pathology, by combining the expertise of five groups spanning from the identification of CSF biomarkers in preclinical AD cohorts to human synaptic biology. A major originality of the proposal is in the use of innovative human biological samples: 1) grafting human neurons with Cre-dependent null alleles for SNARE proteins in newborn mouse neocortex, 2) cerebral organoids derived from human induced pluripotent stem cells (iPSCs) and 3) organotypic cortical cultures obtained from human surgical resections. All models of human neurons and circuits will be genetically targeted to assess the early physiopathological stages of synapse dysfunction and loss, in combination with a proteomic and transcriptomic analysis of synaptic biomarkers. This project will help identifying new pre-diagnostic markers linked to altered presynaptic function in presymptomatic forms of AD.