A Human Multicellular Neuroimmune Component Cortical Organoid Model to Study Alzheimer`s Disease

Ira Espuny-Camacho, Associate Professor

GIGA-Neuroscience, GIGA Institute, University of Liège, Liège 4000, Belgium.

Abstract: Alzheimer's disease (AD) is neuropathologically characterized by the presence of amyloid-beta (Aβ) plaques and neurofibrillary tangles. Increasing evidence highlights microglia cells (MC) as key mediators in AD pathogenesis with recent reports showing a contribution of MC to Aβ plaque formation at early stages of the pathology in *in vivo* mouse models. However, their role in human systems remains poorly understood, emphasizing the need for novel and improved human models.

Here, we optimized a model to derive human microglia from pluripotent stem cells (hPSC) that results in a cell population with enriched microglial-specific gene expression and typical microglia morphology. Upon exposure to Aβ fibrils, microglia efficiently phagocytosed Aβ, leading to a decrease in microglia speed and changes in its transcriptomic profile with downregulation of phagocytosis related genes and cytoskeleton and extracellular matrix-associated pathways, suggesting a state of progressive microglial dysfunction. Next, we generated a multicellular neuroimmune competent human cortical organoid model (hmCO) that includes the presence of microglia, astrocytes and neurons in a 3D *in vitro* system. Interestingly, whereas AD hCOs without MC successfully model small Aβ aggregate formation, incorporating MC exacerbates Aβ accumulation and induces pronounced astrocyte reactivity.

Together, these results establish hmCOs as a valuable human platform for investigating microglia-driven mechanisms in neurodegenerative diseases, such as AD.

Short Bio: "*My research aims at deciphering early Alzheimer's disease phenotypes to unravel new targets for disease treatment through the use of cutting-edge in vitro human brain organoid models".*

Ira Espuny-Camacho was born in an olive tree region of the south of Spain, where her passion for science started. She completed her Bachelor and Masters degree in Chemical Sciences, Biochemistry and Molecular Biology at the University Autonoma in Madrid. Soon after, she enrolled in the Ph.D program in Biomedical sciences at the KU Leuven University in Belgium. During her doctoral work, in the laboratory of Bart De Strooper, she focused on the search of new therapeutic molecular targets for the treatment of Alzheimer's neurodegenerative disease patients. She was awarded a Ph.D by the KU Leuven University in 2007. In 2008, she moved to the laboratory of Pierre Vanderhaeghen, at the ULB, Brussels, where she pioneered a model for the differentiation of human pluripotent stem cells (hPSC) towards cortical neurons *in vitro* and its application to study cortical development and brain repair. Further, her postdoctoral work established a novel xenotransplantation human model for the study of Alzheimer's disease in vivo, that revealed that human neurons present species-specific features that drive degeneration and neuronal death. In 2017 she moved to the laboratory of Elena Cattaneo in the University of Milan, Italy, where she was awarded a Marie Sklodowska-Curie Individual fellowship and

specialised in *in vitro* 3D human stem cell-derived brain organoid models to study Huntington's disease. In late 2019 she moved back to Belgium where she became an Associate Professor at GIGA/Uliege.

Her scientific team at GIGA, Uliege, currently formed by 3 Ph.D students and 2 postdoctoral scientists, is focused on the study of early cellular and molecular pathological mechanisms in Alzheimer's disease using novel *in vitro* multicellular human brain organoid models.