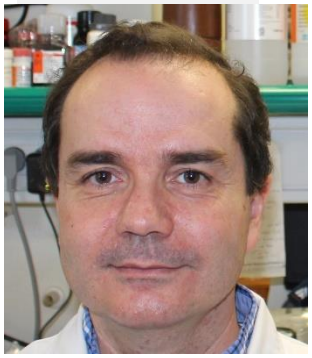
ImmunoTools *FlowISiAM* Award 2024



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GPR37 Processing in Neurodegeneration: A biomarker for Parkinson's disease progression rate

The orphan G protein-coupled receptor 37 (GPR37) is expressed primarily in the central nervous system, specifically in the corpus callosum, cortex, striatum, and substantia nigra[1]. This receptor has gained attention for its potential involvement in neurodegenerative processes, particularly in Parkinson's disease (PD). GPR37 is a substrate for parkin, an E3 ubiquitin ligase that is found to be mutated in patients with autosomal recessive juvenile PD[2]. The absence or overexpression of parkin has been associated with a higher propensity for GPR37 to misfold and aggregate, ultimately leading to cell death[3,4]. Interestingly, the N-terminal domain of GPR37 (ecto-GPR37) undergoes rapid and constitutive cleavage by ADAM-10[5,6], leading to the shedding of this ectodomain into the extracellular environment. Recently, we reported higher levels of GPR37 protein density and mRNA expression in postmortem substantia nigra samples from patients with sporadic PD[7]. Thus, our objective is to investigate the processing and density of GPR37 in the blood of patients suffering from various neurodegenerative diseases, including Lewy body disease (LBD), multiple system atrophy (MSA), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and Alzheimer's disease (AD). To this end, the presence of ecto-GPR37 peptides in peripheral blood activated monocytes from patients with PD, MSA, CBD, and PSP will be evaluated using flow cytometry-based intracellular staining or *FlowISiAM* technology (ImmunoTools and INVIGATE). Blood will be taken from several cohorts of patients from the Hospital de Bellvitge (Spain) and the Karolinska University Hospital Clinic (Sweden). In addition, these cohorts will be expanded with patients from other hospitals. Additionally, a parallel test of classical PD markers (i.e., α-synuclein, Tau) will be performed to establish potential correlations between these biomarkers and ecto-GPR37. Furthermore, we will investigate how the progression rate of PD affects the levels of ecto-GPR37 peptides in blood activated monocytes. Our preliminary data using an in-house nanoluciferase-based immunoassay in cerebrospinal fluid (CSF) obtained at the onset of the disease indicated that these peptides increased significantly in patients with PD that progressed slowly compared to patients with PD who progressed rapidly. These results indicate a possible role for GPR37 processing in the progression rate of PD. Therefore, the identification of GPR37 peptides in peripheral blood using *FlowISiAM* technology in patients with mild cognitive impairment will provide crucial information on its potential role as a predictor of progression rates of PD, as well as allowing the stratification of patients within the different neurodegenerative diseases assessed.

In general, this research will underscore the distinctive processing and density patterns of GPR37 in neurodegenerative diseases, providing crucial information on its potential role as a predictor of the progression rates of PD. This could have significant implications for treatment decisions, patient care, and prognosis. In many cases, interventions and therapies are tailored based on the expected speed of disease progression. Therefore, an accurate understanding of the progression rate is essential for the clinical management of PD.

Cooperation partner: Prof. Dr. Ciruela's group will cooperate with ImmunoTools to establish *FlowISiAM* analysis at the Institute of Neurosciences, University of Barcelona, and the Bellvitge Institute for Biomedical Research (IDIBELL). ImmunoTools and its partner SME, INVIGATE, will share specific know-how for computer-aided scoring from *FlowISiAM* raw data for optimal test results.

ImmunoTools' partner SME, INVIGATE, will take on the task of developing GPR37 peptide specific monoclonal antibodies and will support the initial evaluation. Furthermore, INVIGATE will provide other PD-related monoclonal antibodies from its own pipeline (α-synuclein, Tau) for experimental evaluation within *FlowISiAM* in PD blood samples. Optionally, ImmunoTools and INVIGATE's clinical network partners may be involved for control measurements in blood samples from patients with Alzheimer's disease.

Prof. Dr. Ciruela and Dr. Sebastian Krause (INVIGATE) seek to develop and permanently improve *FlowISiAM-based* strategies for the prediction of PD disease progression and for early detection of PD in patients with MCI.

References

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ImmunoTools *FlowISiAM* AWARD for **Francisco Ciruela,** includes antibodies for *FlowISiAM*, know how transfer and protocol, support regarding selection of specific antibodies against specific biomarkers from INVIGATE, expert assistance in evaluating the results obtained, and integration into the ImmunoTools *FlowISiAM* network.

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