Proposal of Master Research Project / Trabajo fin de Master for the academic year 2022-23

Group name: **Cellular Plasticity and Neuropathology**
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Group web: **https://in.umh-csic.es/en/grupos/cellular-plasticity-and-neuropathology/**

Title of the MRP/TFM:

Understanding microglia phenotypes in Alzheimer's disease.

Summary of the Project:

Dementia is a term that describes a group of symptoms affecting cognitive functioning and behavioral abilities to the extent that it interferes with activities of daily living and quality of life. Memory loss and decline in thinking skills, language, problem-solving, and social abilities are symptoms of dementia. Dementia is present in most neurodegenerative diseases. A common pathological hallmark of diseases causing dementia is neuroinflammation. Moreover, growing evidence strongly suggests that inflammatory processes contribute to the progression of many neurodegenerative conditions, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (Jones et al., 2015; Labzin et al., 2018; Heneka, 2019). However, how brain-immune interactions modulate the underlying disease processes in dementia remains far from being understood.

The advent of singlecell RNA sequencing (scRNAseq) has greatly advanced the field by providing a highresolution view of brain microglia, in homeostasis, in ageing and in genetically modified mice that mimic human neurological diseases. There is now evidence from single cell profiling in mice and humans of an unprecedented diversity of activated microglia (Mathys et al., 2017; Keren-Shaul et al., 2017; Frieadman et al., 2018; Hammond et al., 2018; Sala Frigerio et al., 2019). More recently these analyses have been extended to human brain with Alzheimer's disease (Mathys et al., 2019; Zhou et al., 2020; Thrupp et al., 2020) revealing a strong component of neuroinflammation to Alzheimer's disease pathology.

This project seeks to contribute to our understanding of the functional correlate of the molecular phenotypes found in microglia. We also have particular interest in unveiling the molecular mechanisms regulating the transitions and maintenance of distinct phenotypic states of brain's innate immune cells present in the aged brain and in Alzheimer dementia. Our ultimate goal is to develop novel approaches for the treatment of Alzheimer's disease by modulating immunity and neuroinflammation.

To address these questions, the candidate will perform computational data analysis of high-throughput genomic data generated in our lab, from microglia of mouse models, including transgenic mouse models of AD, (RNA-seq and ATAC-seq from bulk population and single cells) to dissect the mechanisms orchestrating epigenome and transcriptome rewiring of microglia in response to environmental stimuli, such as neuronal damage.

We believe this is an exciting opportunity for an enthusiastic candidate to join a young team with a strong commitment to basic and translational research. You will receive help and supervision on the project at multiple levels, and will be offered possibilities to grow scientifically.

Methods and technology involved in the MRP/TFM Project:

The candidate will perform bioinformatic analysis of scRNA-seq, RNA-Seq, ATAC-seq, and ChIP-Seq datasets. The candidate should have basic programming abilities (R and/or phyton) and skills in statistics.

Member/s of the lab who will act as tutor/co-tutor of the project (if different from the group IP):

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