Microglia are resident immune cells of the brain with phagocytic capabilities. This means they can engulf and destroy microorganisms, as well as eliminate damaged or dying cells. Microglia play crucial roles in the brain, one of the most important being the support for neurons. These cells can undergo numerous morphological and functional changes, depending on the type of stimulus they encounter.

A widely used approach to investigate microglial function involves their temporary depletion from the brain using pharmacological inhibitors targeting the colony-stimulating factor 1 receptor (CSF1R), a signaling pathway essential for microglial survival. Upon cessation of CSF1R inhibition, microglia rapidly repopulate, restoring their population within a short time.

Our multiomics research demonstrates, at the single-cell level, that using a CSF1R inhibitor results in the near-complete removal of microglia. Importantly, the population of these cells functionally reconstitutes within 7 days after the inhibitor is withdrawn, both in young and aging brains. However, transcriptomic analyses have revealed that while microglia in young brains return to a state of homeostasis, in aging brains, the cells appear to get stuck at the maturation stage and fail to acquire the phenotype of fully mature, functional microglia. We suspect the repopulation process becomes impaired with age, potentially affecting later brain function.

This project aims to investigate the mechanisms underlying microglial repopulation in the context of aging. We are going to determine whether the ability of microglia to repopulate and regain their homeostatic functions diminishes with age, potentially compromising their key roles in brain health. To achieve this, we will use flow cytometry and next-generation sequencing to analyze the process at the single-cell level. Additionally, we will perform morphological analysis using confocal microscopy and 3D cell reconstruction.

In conclusion, understanding the molecular mechanisms driving microglial repopulation could provide valuable insights into the fundamental aspects of microglial behavior and the defects associated with aging. Identifying the key signaling pathways involved in this process may pave the way for developing novel therapeutic strategies to treat age-related neurodegenerative diseases.