Abstract for general public

Parkinson's disease (PD) is a complex disorder that affects millions of people worldwide, causing difficulties with movement, balance, and everyday activities. It happens because special brain cells that produce the signaling molecule dopamine slowly die off during aging. But why these cells are lost and what role aging actually plays in this process remains a puzzle.

This project focuses on understanding one key piece of this puzzle: the role of the brain's immune cells, called microglia, which change as we age. Normally, microglia help keep the brain healthy by clearing away waste and protecting neurons. But as they age, microglia can become overactive, releasing harmful substances that might damage nearby neurons and worsen diseases like Parkinson's.

To study this, we use an exciting new approach: brain organoids grown in the lab. These are tiny, three-dimensional models of the human brain created from stem cells, that can differentiate in any type of the cells in human body and have unique property to self-organize in 3D structures (called induced pluripotent stem cells, iPSC). Such cells are obtained by "bringing back" to the primitive stage the cells that are differentiated and reside in the adult tissue. By using cells from Parkinson's patients (e.g. skin fibroblasts), including those with a specific genetic mutation linked to the disease, we can first obtain iPSC from this patient and then create realistic models of the midbrain, the area most affected in Parkinson's. By adding aged microglia to these models, we aim to recreate the interactions that happen in a real human brain.

In this project we will use control and diseased (derived from PD patient carrying SNCA-A53T mutation) iPSC cell lines to differentiate them into microglia and in parallel to create from them midbrain organoids. Microglia cell lines will be chemically stimulated or genetically engineered (to overexpress progerin – age related factor) to induce their aging and obtain aged microglia cell lines. The next experimental step will be introducing aged and control microglia lines to midbrain organoids and analyzing their influence on the progression of the PD pathology. One of the points to be assessed in the organoids assembled with microglia will be degeneration of the neurons that produce dopamine, critical neurotransmitter for PD pathology.

Our research asks crucial questions: How does aging affect microglia, and how do these changes interact with the toxic proteins that build up in Parkinson's? Can we identify ways to prevent microglia from becoming harmful? We also explore potential treatments, such as drugs that could clear out harmful cells or calm their overactive behavior, protecting neurons from damage.

This project has the potential to transform our understanding of how Parkinson's disease develops and progresses. It could pave the way for new treatments that target brain inflammation, offering hope for slowing or even stopping the disease. By using state-of-the-art lab models that mimic the human brain, we aim to bridge the gap between basic science and real-world solutions for patients and their families.