

The gut-brain axis (GBA) is a critical communication system between the gastrointestinal (GI) tract and the central nervous system (CNS), playing a pivotal role in various aspects of health, including mood regulation, cognitive function, and immune response. Recent research has shown that disruptions in the gut microbiota, or gut dysbiosis, can lead to or exacerbate several neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. However, studying these interactions in traditional animal models presents challenges due to species differences and limitations in replicating the complexity of human biology. Therefore, there is an increasing need for advanced in vitro models to better understand the GBA and its involvement in neurological disorders.

This project aims to develop a cutting-edge Microbiota-Gut-Brain Axis on Chip (MGBA-on-Chip) platform, a type of organ-on-chip system. Organ-on-chip technology involves creating miniature, functional replicas of human organs within microfluidic devices, allowing for the study of disease mechanisms and testing of new therapies in a human-relevant environment. Our MGBA-on-Chip model will integrate human intestinal epithelial cells, neuronal cells derived from human pluripotent stem cells (hiPSCs), and microbiota. This model will simulate the complex interactions within the GBA, providing valuable insights into how the gut microbiota influences brain function and contributing to our understanding of neurodegenerative disorders.

The first step in the project is to design and fabricate the MGBA-on-Chip platform, which will involve the selection of biocompatible, transparent, materials, and the use of advanced techniques such as micromilling, 3D printing, and SU-8 lithography. These technologies will allow for the creation of a microfluidic system capable of supporting both the gut and brain compartments, ensuring that each organ's cells can be cultured and interact in a controlled environment. Fluid dynamics simulations will be performed to optimize flow rates and ensure cell viability.

Once the platform is constructed, we will introduce a variety of cell types, including intestinal epithelial cells (e.g., Caco-2, HT-29) and neuronal cells derived from hiPSCs. These cells will be cultured in the platform, and their interactions will be monitored using advanced imaging techniques and functional assays, such as calcium imaging and multi-electrode arrays, to assess cellular behavior and neuronal activity. In particular, we will explore the effects of the microbiota on the gut-brain communication by introducing microbiota or extracellular vesicles (EVs) into the system. These components will be pre-stained with fluorescent dyes for live imaging, and their impact on epithelial barrier integrity and neuronal function will be studied.

The final aim of the project is to validate the MGBA-on-Chip model by performing a comprehensive set of functional assays, including immunofluorescence staining, ELISA, Western blotting, and gene expression analysis. These tests will measure the expression of key markers involved in gut barrier integrity, neurotransmitter release, and neuroinflammation, which are critical for understanding the pathophysiology of neurodegenerative diseases. Additionally, the model will allow for the simulation of pathological conditions, such as dysbiosis and neuroinflammation, to observe the resulting changes in cellular behavior and communication.

By developing this advanced in vitro platform, the project aims to provide valuable insights into the complex interactions between the gut microbiota and the brain. It will also serve as a powerful tool for screening potential drugs or therapeutic strategies aimed at restoring gut-brain balance and preventing or treating neurodegenerative disorders. Ultimately, the MGBA-on-Chip model will contribute to the growing field of precision medicine, offering a more accurate, human-relevant model for the study of neurological diseases and the development of novel treatments.