During the development of the nervous system, stem cells pass through the metabolic and morphological changes to become specialized body cells, such as different types of neuronal and glial cells. The *PPARGC1A* gene, encoding PGC-1α protein, the positive regulator of mitochondrial biogenesis, was shown to be vital for the proper development of different types of cells in the brain, but the molecular mechanism of its effect on neural differentiation needs to be elucidated. Previous results from our group showed that PPARGC1A might be involved in the occurrence of "gliogenic switch", which happens in brain development after the wave of neuronal cells appearance (neurogenesis), when neural stem cells start to differentiate into glial cells: astrocytes followed by oligodendrocytes (gliogenesis), instead of neurons.

This project attempts to uncover how the PPARGC1A affects the specification of neural stem cells during human neurodevelopment. The brain organoid model derived from human induced pluripotent stem cells (iPSCs) will be used to address this question. The technology of iPSC generation and derivation of brain organoids are revolutionary achievements, enabling the study of brain development from their earliest stages without ethical issues. The advantage of the brain organoid model over 2D cell culture is the recapitulation in the dish of the natural brain metabolic functions and the complex 3D architecture with the content of interconnected different cell types. Using genetic engineering methods, the expression of *PPARGC1A* will be engineered in the human iPSC line to be silenced or increased, and the effect will be studied in dorsal forebrain (cortical) organoid development. The reflection of these changes will be investigated by the analysis of expression of genes involved in the gliogenic switch. The molecular mechanism of the PPARGC1A pathway will be investigated using sought-after whole transcriptomic analysis and identifying proteins directly interacting with PGC-1α. This approach will let to evaluate the role of PGC-1α in the neural stem cell fate decision, and uncover the exact mechanism.

We expect that changes in the PGC-1α expression level affect the occurrence of gliogenic switch, which will result in differences in proportions of cell populations present in the cortical organoids. The elucidation of the PPARGC1A pathway mechanism, which affects neural stem cell fate decision is necessary to know where to target the process of neurodevelopment and may lead to the development of new therapeutic strategies. Thus, this project uncovering the basic mechanisms of brain development will contribute to the society by possible future applications.