Introduction: To address the critical role of γ-secretase in amyloid plaque clearance, we focused our work on studying the involvement of microglia in this process. The microglial phagocytosis can be triggered via the Low density lipoprotein receptor related protein (LRP). LRP is a type I membrane protein and a γ-secretase substrate. It interacts with APP and facilitates its trafficking and processing. LRP uses Aβ as a ligand and controls its uptake and transport to the lysosomes.

Aims: The proposed project aims to elucidate the γ-secretase dependent functions of Aβ clearance by microglial cell.

Methods: We chose different approaches to study the γ-secretase functions in microglial cell lines- BV2 and ES derived microglia (EsDM). Genetic mutations of the Presenilin (PS) gene and pharmacological component (DAPT) were used to inhibit the γ-secretase activity.

Results: Our results showed that γ-secretase is involved in Aβ uptake and decrease in this process was seen after γ-secretase inhibition. We reported that Aβ’s receptor LRP is expressed in microglial cells where its processing and endocytosis is γ-secretase dependent. Cells with inhibited γ-secretase activity demonstrated impaired LRP endocytosis, and Aβ cellular uptake. This also correlated with a decrease in degradation and changes in the lysosomal structure and localization. Opposite effects were shown in microglia cells overexpressing PS1 where the rate of Aβ uptake and its degradation was significantly high.

Conclusion: Our results indicate that γ-secretase inhibition contribute to Aβ accumulation in the brain. Modulation of γ-secretase activity could be used as a promising therapeutic target.