The most common form of pathologically accelerated cognitive decline is Alzheimer's disease (AD). The hallmarks of AD are extracellular plaques containing amyloid beta (Aβ) and intracellular neurofibrillary tangles (NFTs) containing hyperphosphorylated tau protein. Functional significance of amyloid plagues and NFTs in neuronal damage during the course of the disease is yet to be determined, and pharmacotherapy trial to eliminate the plagues or tangles produced moderate results. Recently, as the target of pharmacotherapy the blood-brain barrier (BBB) has gained a particular interest, as its dysfunction has been confirmed in the brains of AD patients. Significantly, BBB damage precedes the development of clinical symptoms in AD patients and is strongly associated with the progression of dementia. The role of the BBB in maintaining homeostasis is undeniable. It is known that it limits the transport of large molecules and immune cells from the blood to the brain. In the opposite direction, BBB transport systems eliminate neurotoxic molecules and "metabolic waste" from the brain. When BBB is damaged, lymphocytes, macrophages, and plasma proteins infiltrate the brain in uncontrolled manner, triggering the excessive activation of glial cells and consequently, they exacerbate neuroinflammatory processes, which promote neurodegeneration. Tight junctions (TJs), which seal intercellular gaps between brain microvascular endothelial cells (BMECs), are crucial for the proper function of the BBB. Their formation and proper maintenance are regulated by communication between BMECs and other brain cells, such as pericytes, astrocytes, microglia, oligodendrocytes, and indirectly with neurons by releasing soluble factors. The profile of mediators released by these cells, therefore, determines the function and integrity of the BBB. However, under conditions of prolonged neuroinflammation, these cells also release substances that are harmful to the BBB. Therefore, BBB dysfunction may be determined by an extracellular component, including inflammatory mediators originating from BBB surrounding cells, and a cellular component, e.g., receptors on the surface of these cells, the activation of which via intracellular signal transduction pathways affects the integrity of the BMECs in the brain. We hypothesize that both of these components may strongly influence BBB dysfunction in age-dependent brain pathologies such as AD. Therefore, we propose a new strategy to restoring normal function of BBB through specific activation of the FPR2 receptor present on BBB-forming cells to resolve inflammatory processes, thereby limiting the sustained release of pro-inflammatory mediators. This approach is innovative and has not yet been the goal of research. Moreover, the research will use newly synthesized compounds - FPR2 receptor agonists, whose impact on BBB parameters has not been studied so far. In the project, we will conduct comprehensive in vitro and in vivo studies to assess the usefulness of the newly synthesized compounds. We will use BMEC and primary astrocyte cultures, which will be obtained from control mice (WT, C57BL/6J) and transgenic $APP^{NLF/NLF}$ knock-in (KI) well-verified as an animal model of AD. The use of BMECs treated with conditioned medium obtained from astrocytes and next combined primary co-cultures will allow us to investigate the role of interactions between cells via soluble factors in maintaining the proper integrity of the BBB after immunological challenge. This rigorous and comprehensive approach will enable us to select the most promising compounds that will be administered chronically to $APP^{NLF/NLF}$ animals in the prodromal phase of AD. We will assess their usefulness in modulating the age- and sex-dependent properties of the BBB in brain areas and the panel of mediators released by its cells, neurodegeneration parameters, the peripheral immune response (serum and spleen) as well as behavioral/cognitive parameters also after a systemic immune challenge. Our project focuses on finding new targets for potential drugs for the treatment of neurodegenerative brain diseases and therefore has potential translational value. The proposed innovative and highly promising strategy has the potential to significantly slow down neurodegenerative processes. This approach, based on an original hypothesis and preliminary results of our international collaboration, is poised to revolutionize the field. The use of state-of-the-art methods, highly advanced in vitro and in vivo models, and the extensive experience of our researchers ensure that the results obtained will significantly expand knowledge about the molecular mechanisms of BBB functioning in pathological conditions. We anticipate that the results of our approach will not only contribute to expanding basic knowledge about the effectiveness and mechanism of action of unique compounds on BBB properties but also open new horizons in the treatment of AD and other neurodegenerative diseases.