Inflammation serves as our natural defense mechanism, safeguarding our bodies, organs, tissues, and cells against various external triggers. However, when left unchecked, the process becomes detrimental. Recent studies have shed light on the pivotal role of chronic inflammation in the development of various diseases, including neurodegeneration, arthritis, arterial sclerosis, irritable bowel syndrome, cancer, and depression. At the core of the inflammatory response lies a family of nuclear transcription factors called NF kappa B (NF-κB). NF-κB activation is prompted by a diverse array of harmful stimuli, such as bacterial toxins, viruses, physical injuries, and internal signaling elements, leading to the release of pro-inflammatory molecules. The crucial stage of this signaling cascade is governed by the serine-threonine protein kinase IKK-β, a key regulator of NF-κB activity.

The inhibitory kappa kinase beta (IKK-β) is a protein that controls the pro-inflammatory signal propagation also in the central nervous system. Inhibition of the local inflammatory response is a promising new approach to the treatment of neurodegenerative diseases. By developing a compound that can inhibit IKK-β in the central nervous system, we can potentially reduce pro-inflammatory signals and slow down the processes that lead to neurodegeneration and the development of diseases such as Alzheimer's disease.

The goal of this project is to understand the detailed interactions within the catalytic pocket, *"the mission control"* of IKK-β, and find an optimal drug-like molecule to stop its activity. The precise determination of the architecture of the pocket will serve as an introduction to the discovery and optimization of small molecules that can inhibit its activity and modulate the inflammatory response. The process of searching for the new molecule will be done by implementing computational methods based on classical and quantum mechanics calculations. Such an approach allows the large molecule like a protein to be treated in a classical *"ball-and-stick"* approximation, and the ligand binding region in the highest possible resolution, assured by quantum-mechanical based techniques. Selected compounds will be tested *in vitro* to experimentally check their activity and selectivity.

Thus far, protein crystallization remains the leading experimental technique capable of elucidating the structure of a protein-ligand complex, offering a unique opportunity to observe the ligand within the binding pocket. Bringing the protein to a solid form requires effort, which unfortunately contributes to structural flaws in the final structure. In this project, the crystallization and structure solution of the protein-ligand complexes is planned. Structures will be corrected and refined via sophisticated protocols and will serve as input for the further development of potent and selective inhibitors.

The chemical compounds resulting from this research and the detailed map of energetic interactions formed by specific protein residues will significantly advance our understanding of IKK-β kinase. Moreover, this knowledge will serve as a foundation for the development of potential medications targeting IKK-β.