Inflammation is a term that covers the innate defence response of a human immune system to various exogenous stimuli. Despite being engineered as a protective mechanism, there are situations where it takes a chronic form. Recently, an increasing number of research demonstrated that **chronic inflammation underlies the aetiology of many disease states**, like arthritis, arterial sclerosis, irritable bowel syndrome, cancer, and even depression. The key component of an inflammatory response regulation system is the nuclear transcription factor NF kappa B (**NF-κB**). Diverse noxious stimuli, such as bacterial toxins, viruses, or mechanical injuries, and the following inflammatory cytokines of a signalling cascade trigger its activation. The critical points of this cascade are regulated by serine-threonine protein kinases **TAK1 and IKKβ** – two crucial NF-κB activity modulators. **The classical approach** to block the inflammatory response via hampering the NF-κB performance would be to block the activity of these kinases by the molecules with inhibitory activity. The efficacy of such compounds relies on the constant maintenance of high intracellular concentration, **which often results in many side effects.**

Targeting protein degradation with PROTAC (PROteolysis-TArgeting Chimera) molecules offers a new paradigm in drug discovery. PROTACs mimic endogenous protein degradation system by tagging the protein of interest for proteasomal breakdown. These proteins – TAK1 and IKKβ – are bound by the terminal part of PROTAC molecule, and, via a linker, are connected to the ligase which guides the protein to proteasomal degradation. Protein breakdown, in contrast to its inhibition, requires substantially lower compound concentration, thus enabling toxicity reduction, selectivity enhancement, and resistance mechanisms alteration, and finally – **giving hope for safer therapy.**

The aim of our project is to obtain the first-in-class PROTAC molecules degrading the protein kinases TAK1 and IKKβ with anti-inflammatory activity. The project will be carried out by the interdisciplinary, international scientific team involving researchers from Poland and Slovenia. In the first stage using our knowledge and experience, with the aid of molecular modelling techniques and crystallography methods, we will design new PROTACs targeting TAK1 and IKKβ. The designed compounds will be synthesized and their biological activity evaluated *in vitro*. The results will allow for a detailed characterization of compounds in terms of their ability to degrade established kinases and to determine whether this activity translates into an anti-inflammatory effect in a variety of cell models. Further *in vitro* and *in vivo* tests we will determine physicochemical and pharmacokinetic properties which reflect the behaviour of compounds (ability to reach the site of action or toxicity) in a living organism. The final verification of the anti-inflammatory activity of the selected PROTACs will be conducted in a rheumatoid arthritis rat model.

The results of the project will be an invaluable contribution to the development of novel therapies for inflammatory-based diseases.