Eukaryotic cells evolved abundance of specialized membrane-bound organelles. Rab proteins have a prominent role in membrane trafficking and cell homeostasis. Their aberrant functioning lead to multitude disorders, making them very attractive target for anti-cancer and antiviral therapy. As a prerequisite for Rabs function, they need to undergo post-translational modification with lipophilic geranylgeranyl chain. Such prenylation takes place thanks to Rab geranylgeranyl transferase (RGGT). Therefore, one strategy to control Rabs and reduce adverse effects of their dysregulation, is to inhibit RGGT.

The main objective of this proposal is to develop an innovative strategy to target RGGT, using a new pharmacological approach for controlled protein degradation - PROteolysis TArgeting Chimera (PROTAC). For that purpose we will use previously developed by us RGGT inhibitors and strengthen their activity by modifying them with proteosom targeting moiety. Besides the design and synthesis of new compounds, the project will involve proteomic studies, which will enable us to verify the second hypothesis: if the PROTAC targeting RGGT will also degrade its partner protein, Rab, which forms a multiprotein complex with RGGT.

Developed PROTACs will become a robust tool for advancing the field by extending the applicability of PROTAC strategy to novel class of proteins and determining the mechanism by which RGGT influences prenylation of different Rabs. In the future, these molecules can find application as potential therapeutics for diseases connected with dysregulated prenylation.