Eukaryotic cells evolved abundance of specialized membrane-bound organelles. Rab GTPases (Rab proteins) have a prominent role in membrane trafficking and cell homeostasis. Their aberrant functioning lead to such disorders as cancer, diabetes, neurodegenerative diseases, making them very attractive therapeutic target.

The main objective of this proposal is to develop an innovative strategy to selectively target Rabs, with the aim of their up-regulation. For that purpose, we will design and synthesize peptides, which should disturb the interaction between Rab and GAP proteins stimulating the intrinsic GTP hydrolysis activity of Rabs. The use of therapeutic peptides gained significant importance over the last three decades in oncology, cardiovascular, and metabolic diseases. However, the idea that the activity of Rab GTPase can be upregulated by targeting their interactions with GAPs has not been studied yet.

Addressing this gap in knowledge will create significant opportunities for designing peptides for up-regulation of „undruggable“ protein targets. We also expect to achieve a selective response of the chosen Rab. Most of the existing strategies affect all Rabs by inhibiting the prenylating enzyme, Rab geranylgeranyl transferase (RGGT). However, such an approach leads to toxicity due to the reduction of activity of above 60 Rab proteins. The successful outcome of these studies will enable extending the methodology to Rab therapeutic targets in type 2 diabetes, allowing better understanding of signaling pathways associated with this condition. Developed peptides will become a robust tool for advancing the field of regulation of Rab. Such peptides will be valuable analytical tools for studying Rab function, enabling discovery or confirmation of biological insights, combining the advantages of small molecules with those of other gene silencing and/or editing techniques.