Rab proteins are the largest subfamily of small GTPases that control vesicular transport by switching between inactive and active forms bound to nucleotides GDP or GTP, respectively. Active small GTPases recruit effectors to the membranes and trigger signal cascades (Fig. 1). After fulfilling their function, Rabs are switched off by GTPase activating proteins (GAPs) stimulating the intrinsic GTP hydrolysis activity. The abnormal activities of Rabs have been identified in several diseases, including cancer, immune and neurodegenerative diseases, diabetes, and diabetes-related complications.

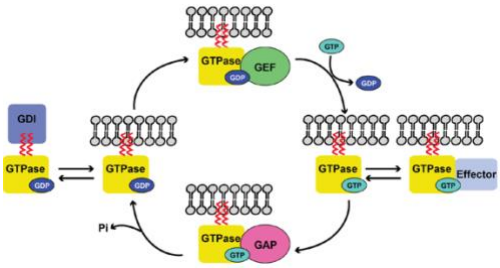

Figure 1. Activation/inactivation cycle of small GTPases is regulated by three types of controllers, the GTPase-activating proteins (GAPs), the guanine nucleotide exchange factors (GEFs), and the guanine nucleotide dissociation inhibitors (GDIs). GEFs are positive and GAPs are negative regulators

The activity of Rab GTPases tends to be downregulated in several diseases, such as diabetes. Therefore, the main objective of the project is to develop an innovative strategy to interrupt Rab−GAP interactions so as to activate Rabs. Due to the presence of α-helical interaction motif and the extensive, we hypothesize that the Rab−GAP interface might be a suitable system for targeting by α-helical peptides, which have proven successful in targeting diverse Rab−effectors interactions. We plan to verify this hypothesis by targeting interactions between Rab1b and Rab5 and their selective GAPs (TBC1D20 and TBC1D17, respectively).

Beyond serving as potential drugs, peptides targeting the Rab−GAP interaction will be valuable analytical tools for the study of 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. The obtained results will allow a better understanding of signaling pathways associated with diabetes.