Diabetes mellitus (DM) is a disease that has reached epidemic proportions over the last century, becoming a significant burden on the healthcare system and society. The pathogenesis of diabetes is determined by the progression of pancreatic islet beta-cell (β-cell) dysfunction. The aberrant Insulin secretion, which is the main hormone performing anabolic function in the human body entails series of medical events. Insulin supplementation brings this deadly disease into a chronic state, but it does not provide a cure. Reconstitution of pancreatic islets provides an opportunity for effective diabetes therapy, which is the theme of this project. Recent high-throughput inhibitory studies revealed that Dual-specificity tyrosine-(Y) phosphorylation Regulated Kinase 1A (DYRK1A) and glycogen synthase kinase-3 β (GSK3β) regulate beta cell activity. The inhibition of both kinases enhances beta cells proliferation, suggesting the potential use of this mechanism in diabetes therapy. Optimization and use of specific inhibitors form the basis for innovative regenerative therapies. The primary idea of this project is to utilize the previously selected set of own DYRK1A inhibitors, newly optimized inhibitors of dual or single specificity (with the focus on GSK3β as a new target) in combination with nanoencapsulation for optimized targeting and delivery to regenerate pancreatic islets.

Small molecule inhibitor triggered β-cell proliferation and resultant restoration of hormone secretion remains the main objective of this project and will be gradually approached through: (i) defining the primary target kinase in addressing improved beta-cell proliferation. (ii) optimizing of the efficacy and target selection (ie. DYRK1A, GSK3 or dual) of our primary compounds through fragment decoration and/or selection of nanotechnology-based strategies to improve the delivery system. Structure based rational design will help selective targeting of GSK3β protein. (iii) tracking the kinase signaling to connect the critical key components directly interacting with the diabetic kinome. (iv) ultimately, combining all above findings and evaluating the efficacy in in vivo animal models of diabetes.

We envision, that **this project will provide effective tool compounds capable of modulating the proliferative potential of residual islet cells and a proof-of-concept that such an approach may ameliorate the underlying cause of diabetes**. In a long run, the proposed strategy creates a vision of a permanent cure for diabetes, a potential breakthrough in therapy, improving the quality lives of millions of people and provides significant relief to healthcare systems.