Over the last decades, changes to the human lifestyle (i.e., diet, physical activity, and microbial exposure) have significantly increased overweight and obesity worldwide. The health consequences are associated with a wide range of problems and diseases that involve disruption to metabolic homeostasis, including diabetes, cardiovascular disease, neurodegenerative disorders, fatty liver disease, and cancer. The current classification of diabetes mellitus recognizes two forms: type 1 diabetes (T1D) and type 2 diabetes (T2D). Patients with type T1D dramatically reduce beta cell (β-cell) mass, leading to insulin insufficiency and hyperglycemia. In T2D, insulin resistance causes a compensatory expansion of β-cells and increased plasma insulin levels. Notably, most genes identified in genome-wide association studies of T2D regulate β-cell mass and/or β-cell function. Approaches increasing functional pancreatic β-cell mass are expected to improve therapeutic options. Current therapies are focused on lifelong artificial maintenance of insulin homeostasis. However, regeneration of β-cell mass and a real cure for diabetes is an important milestone yet to be achieved. Implementation of regenerative medicine into the clinical research canon offers strategies of a durable cure. We base our research on previous discoveries in the field of structural biology of proteins, small molecule inhibitors and human induced pluripotent stem cell (iPSC)-derived organoids to understand the mechanism of regeneration of pancreatic endocrine cell (beta cell) fraction.

Dual-specific tyrosine kinase DYRK1A and β-isoform of glycogen synthase kinase 3 (GSK3β) have been documented to inhibit pancreatic β-cell proliferation and activity. However, given the complexity of the disease mechanism, it is unlikely to be operated by single pathway. Therefore, we aim to better understand the molecular basis of β-cell modulation via inhibiting regulatory components of multiple targets. A major goal of this research is to develop specific inhibitors that will effectively improve β-cell function for extended periods of time. We plan to maximize efforts by using the best available diabetic models, including human cadaveric islet and diabetic mouse models.

Carefully selected experimental approach supported by thorough expertise, accompanied with an extensive international and inter-departmental academic collaboration and cooperation with clinicians will significantly support the project. The strategy proposed here outlines a plan of research aimed at obtaining new anti-diabetic therapeutic tools. We expect to confirm and document in detail the stimulatory effect of elaborated inhibitors on grafted β-cell proliferation and survival, first in *in vitro* and later in the living organism. This shall improve the glycemic control for which we seek the proof-of-concept in this study.

In the long run, the proposed strategy creates a vision for the development of therapeutic methods allowing to completely cure diabetes (instead of lifelong insulin supplementation), and consequently to improve of the quality of life and provide significant relief for health care systems worldwide.