Type 2 diabetes mellitus (T2DM) along with obesity are defined as the major threats of the present global public health. Even though muscles, liver and kidneys suffer detrimental impairment due to obesity-associated insulin resistance, it is the pancreatic β-cell failure that is the critical feature of T2DM occurrence. Such dysfunction is represented by aberrant secretory capacity and detrimental loss in β-cell mass and survival. Elevated level of free fatty acids (FAs) which is often accompanied by obesity, is one of the crucial factors which may lead to the compromised β-cell function and loss in T2DM. While FAs are necessary for normal β-cell functioning, prolonged exposure of islets to high concentrations of fatty acids result in an impaired insulin secretion coupled with decreased insulin gene expression, and diminished proliferation followed by induction of apoptosis. Generally, saturated fatty acids cause more severe effects on insulin secretory capacity and rates of apoptosis compared to monounsaturated fatty acids.

Cellular lipid storage varies, and reflects a balance between lipid arrival and lipid consumption. In this regard, storage reservoirs- lipid droplets (LDs) evolved for conserving metabolic energy and play a central role in the regulation of lipid homeostasis. Ultimately, LDs are believed to protect cells from lipotoxicity and provide them with substrates for energy metabolism but excessive accumulation of LDs is widely recognised as a hallmark of prevalent fat-related diseases, including obesity, diabetes, steatosis, myopathies, and arteriosclerosis. Almost all types of cells are capable to store TG in LDs, with the adipose tissue being predisposed to sustain excessive fat depots in the form of a single large LD. In contrast, non-adipocyte cells generally contain several LDs, with diameters in the low micrometre range.

Indeed, pancreatic β-cells possess a limited capacity for storage of lipids. Stearoyl-CoA desaturase (SCD1) is the rate limiting enzyme catalyzing the biosynthesis of monounsaturated fatty acids (MUFA). The current body of literature suggests that targeted SCD1 deficiency has potential to protect against many aspects of the metabolic syndrome in crucial tissues, including liver, muscle or adipose. Controversially, opposite appears to be true for pancreatic β-cells since recent evidence showed elevated SCD1 to protect common β-cell experimental models against lipotoxicity and improves their secretory function. Fairly recently we proposed a novel mechanism where the inhibition of SCD1 activity affected autophagy at the step of autophagosome-lysosome fusion due to perturbations in cellular membrane integrity, thus leading to an aberrant stress response and β-cell failure (Janikiewicz et al. 2015). How SCD1 can contribute to improvement of β-cell condition in the FAs overload context is awaiting further attention. Thus, the main objective of the proposed project is to define cellular and molecular mechanisms underlying SCD1-governed architecture, composition and metabolism of LDs in pancreatic islets in both, healthy and diabetic conditions.

To elucidate our hypothesis, experiments will be carried out on both *in vitro*, and *in vivo* models of type 2 diabetes mellitus. Therefore, overexpression of human SCD1 coding sequence and genetically/pharmacologically inhibited SCD1 will be introduced in the pancreatic β-cell line INS-1E. The latter model will employ adult mice fed a high-fat diet and already established β-cell obesity and lipotoxicity murine models. Genetically modified cells and pancreatic islets isolated from above described animals, will be further analysed with regard to molecular mechanisms implicated in fatty acids-induced lipid droplet formation in pancreatic β-cells. Proposed studies will include mainly: analysis of SCD1 localisation on LDs surface, isolation of LDs, lipid-protein interaction pull down assays alongside cell viability and proliferation assays. Next, in order to elucidate the role of SCD1 in LD biogenesis and its properties, we will perform following experiments: measurements of LD size, number, volume, velocity, pattern of cellular distribution and diversity, recruitment of perilipins, and comparative analysis of LD lipid composition. Furthermore, we will investigate the impact of SCD1 activity on LD metabolism and turnover. This part of the proposed project will be delineated by taking actions as follows: immunoanalysis of lipid metabolism-associated effectors, lipogenesis, lipolysis and lipophagy pathways. Finally, a possibility of SCD1-dependent LD turnover and fatty acid delivery to mitochondria will be deciphered by conducting analysis of *de novo* and remodelling phosphatidylcholine synthesis pathway, expression analysis of mitochondrially-encoded genes and proteins, and analysis of mitochondrial dynamics.

The expected impact of the project would significantly enhance the current state of knowledge upon pancreatic β-cell failure in lipotoxic environment. Our findings will add another piece of evidence to the emerging picture that an imbalance in lipid metabolism may contribute to the aetiology of type 2 diabetes. The obtained results will provide strong support that SCD1 contributions to LD properties and homeostasis could be a breaking point for potential therapeutic treatment in obesity induced pancreatic β-cell dysfunction.