PhD Student **Hüsün Sheyma Kizilkaya**, MSc

Place of enrolment: University of Copenhagen, Faculty of Health and Medical Sciences

Principal supervisor: Professor Mette M. Rosenkilde, University of Copenhagen, Department of Biomedical Sciences

Title of project: Impact of naturally occuring GIP receptor (GIPR) variants for GIPR function and interplay with the GLP-1R

ABSTRACT

Obesity and type 2 diabetes (T2D) have become global epidemics and heavy burdens on the public health system. Hence, there is a high demand for better and more personalized treatments for these diseases. One of the latest drugs showing great effect on both glycemic control and body weight in T2D patients combines a dual effect of the two incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon like polypeptide-1 (GLP-1) and is able to activate receptors for both hormones (GIPR and GLP-1R). Given the contradicting literature on whether GLP-1 should be combined with a GIPR agonist or antagonist for the most efficient treatment of obesity and T2DM, these recent results of the GIP-GLP1 coagonist, emphasize the need for better understanding of the GIP receptor system.
We have been able to identify 27 naturally occurring *GIP receptor (GIPR)* variants in a Danish populationbased T2DM cohort. A common variant among these, [E354Q], has been characterized functionally in our group and by others. The remaining 26 variants still need functional characterization. Hence, the first aim of this current project is to characterize these naturally occurring *GIPR* variants pharmacologically by investigating their ligand binding, receptor signaling and recycling properties (Aim 1a). Next, we will compare their pharmacological properties by studying their association with BMI, insulin resistance and T2D (Aim 1b). The second aim of this project will be to study the interplay of GIPR and GLP-1R to better understand the pharmacological cross-talk between these two receptors, and how this may explain the synergistic effect seen in co-agonists and whether GIPR agonists or antagonists are most effective as future therapies. This will be done in co-expression studies with the wild-type GIPR and GLP-1R, but also with selected *GIPR* variants with decreased or enhanced signaling activity. This will initially be done by stimulating the coexpressed receptors on HEK293 cells with GIPR and GLP-1R agonists separately as well as in combination with their respective antagonists, which have been developed/are available in the laboratory (Aim 2a). Subsequently, we also wish to investigate the effects of agonist/antagonist stimulation on the naturally expressed GIPR and GLP-1R on insulin secretion, using pancreatic β-cells, INS-1 (Aim 2b). Here we also wish to study the effects of selected GIPR variants effect on insulin secretion by introducing the variant into the INS-1 cells by CRISPR/Cas9 method. We expect this project to provide important new knowledge of the overall role of the GIP system by systematic studies of the naturally occurring GIPR variants and their importance for metabolic diseases. In addition, the improved knowledge about the interaction between the receptors will contribute to a better understanding of the pharmacological potential of the GIP system and the interplay between the two incretin hormones. This would form the basis for future GIP and GLP-1 related therapeutic interventions in the treatment of obesity and T2D.