Role of individually located beta cells in glucose homeostasis and diabetes

The endocrine pancreas is comprised of so-called islets of Langerhans, clusters of endocrine cells, which are scattered throughout the exocrine part of the pancreas. The cells of the islets, in particular the insulin secreting beta cells, are crucial for systemic blood glucose homeostasis and they play a significant role in the development of diabetes. Islets vary in composition, shapes and sizes. They can reach a diameter of several hundred micrometers, but can be also be comprised of only a few cells. Interestingly, almost 20% of endocrine objects observed in a non-diabetic human pancreas are single insulin producing beta cells (see figure), individually located within the exocrine tissue, without direct contact to other endocrine cells.

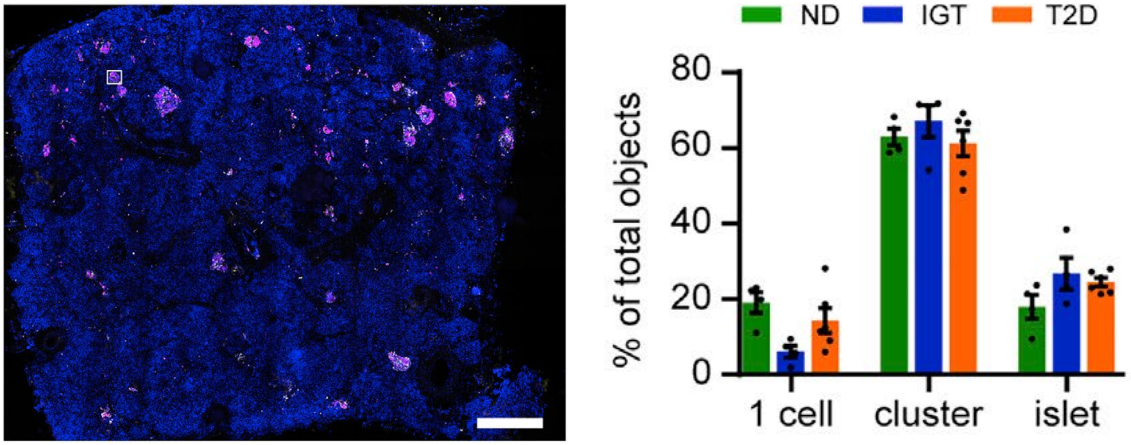

Figure: (left) Maximum intensity projection of an entire human pancreas tissue slice stained with antibodies against insulin (magenta), glucagon (grey), and somatostatin. (right) Mean percent of endocrine objects (K) grouped by appearance of single cells, cluster (up to 10 cells), and islets (>11 cells) for individual samples from non-diabetic (ND), impaired glucose tolerant (IGT), and type 2 diabetic (T2D) specimens. From Cohrs et al, 2020

Whereas the contribution of individually located beta cells to the overall endocrine cell mass of the pancreas is small, some reports suggest their fraction is changed in diabetes. However, it is still not known if these are functional hormone secreting cells, if they are remnants of development, or a potential source of regeneration, and if they are relevant to the pathogenesis of diabetes. The reason for this complete lack of knowledge is the previous absence of suitable techniques to study these cells. Using viable tissue slices of pancreas, a technology established and optimized in our lab, we can know study these cells and address the numerous open questions about their physiology.

We will investigate islet cell function by 4D live cell imaging (confocal and 2P-LSM) of functional cell markers like $[Ca^{2+}]_i$ and mitochondrial activity. Functional assessment will be complemented by molecular (e.g. spatial transcriptomics) and morphological analyses of markers, relevant for beta cell status and phenotype. Using animal models, we will follow the physiology of individually located beta cell throughout postnatal development, aging and disease pathogenesis. In addition, we will translate our findings to the human pancreas. Therefore, we will make use of our unique access to viable donor tissue and organs through local and international networks. Thus, this project aims to provide insight into the phentotype and role of individually located beta cells in glucose homeostasis and diabetes, or the first time.