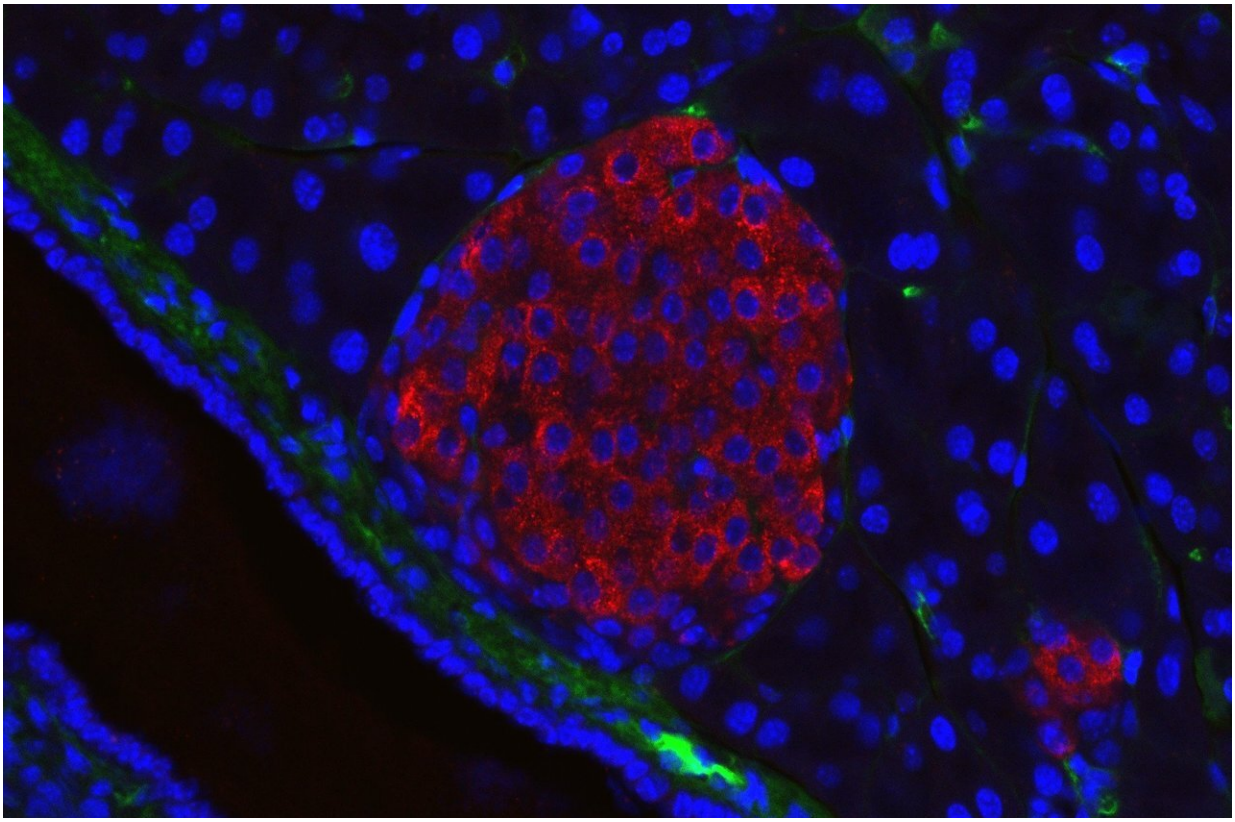
Every islet matters: New review on improving the impact of human islet research

September 8 2022



A pancreatic islet from a mouse in a typical position, close to a blood vessel; insulin in red, nuclei in blue. Credit: Generated in the Solimena lab, Paul Langerhans Institute Dresden

Affecting more than 500 million people worldwide, diabetes mellitus is a growing burden to patients' longevity and quality of life, as well as an

increasing challenge to health care systems. The disease ultimately results from the inability of pancreatic islet beta cells to produce enough insulin to meet metabolic needs. Thus, the study of pancreatic islets is critical for finding means to prevent the disease or treat the causes of beta cell failure.

To aid in this quest, multiple academic and commercial entities around the world provide human pancreatic islets for research, with increasing data characterizing this important mini organ becoming available. However, critical questions remain about the significance and accuracy of the metabolic phenotyping of these donors and the modalities for islet collection and downstream analysis.

"We wrote the article with the intention to overview the status of the field, highlight the challenges and propose actions which could accelerate progress in the understanding of T2D and thus slow its pandemic spreading," says Prof. Michele Solimena, speaker of the Paul Langerhans Institute Dresden (PLID) of the German Center for Diabetes Research (DZD) and co-corresponding author together with Prof. Anna Gloyn of this perspective article.

Islets sources, their procurement and related limitations

"Human pancreatic islets can be obtained from various sources and both its source as well as the applied procurement technique have an impact on the information that can be obtained. While for example tissue samples from autopsy are useful for the histological study of islet cell morphology or morphometry, they lack functional data and provide only limited molecular information," says Prof. Michele Solimena.

In recent years, most information on human islets and the insulin-producing beta cells within the islet has come either from islets isolated

from brain-dead organ donors or, more recently, from surgical specimens of pancreatectomized patients. These living donors, most of whom have undergone a pancreatectomy due to pancreatic ductal adenocarcinoma, can be metabolically phenotyped prior to surgery, while their detailed family, clinical and pharmacological history, is available.

Islets within the surgical specimens can then be retrieved by laser capture microdissection for multi-omics profiling and characterized regarding their physiology and morphological features in fresh tissue slices or fixed sections. Although data on clinical and family history of brain-dead donors is more limited, islets isolated from these donors remain of great importance for research.

This approach involves the resection of the whole pancreatic gland, thereby enabling the enzymatic digestion and isolation of many islets, which could be then widely distributed to many laboratories for extensive imaging, functional, and -omics studies, also involving genetic and pharmacological perturbations.

Data analysis, integration and federation: What about FAIRness?

Research on the physiology and pathophysiology of human islets continues to be of paramount importance. To increase the possibilities of uncovering causal mechanisms for T2D, and the potential to address them prior to disease onset, changes to current operational models are required. These include the availability of additional islet sources, more powerful and reliable technological platforms for the standardized generation of quantitative islet data as well as the implementation of more transparent and coordinated interaction models for the sharing of samples and the integration of datasets.

"We believe that the FAIR principles, meaning Findability, Accessibility, Interoperability and Reusability are of tremendous importance for future studies," explains Michele Solimena. Currently only few international teams have established independent biorepositories of multi-omic data on human islets and many other existing cohorts still fall short on these basic principles.

"This is, in our opinion, an enormous loss to the field as individually these collections are underpowered for most analyses but collectively, they have the potential to make significant headway in understanding disease heterogeneity and diabetes pathogenesis," said Solimena.

"With our perspective article, we aimed to shed light on the current scientific situation regarding the opportunities associated with the use of pancreatic islets for the understanding of T2D, but at the same time to keep in mind their limitations. The availability of additional islet sources, more powerful and reliable technological platforms for the standardized generation of quantitative islet data as well as the implementation of more transparent and coordinated interaction models for the sharing of samples and the integration of datasets offer new opportunities to uncover such causal mechanisms and tackle them even prior to disease onset. This is especially timely in view of the recent identification of different prediabetes and T2D clusters, which argue for a more precise molecular taxonomy, including that of the islets," concludes Michele Solimena.

The research was published in the journal *Nature Metabolism*.

More information: Anna L. Gloyn et al, Every islet matters: improving the impact of human islet research, *Nature Metabolism* (2022). DOI: 10.1038/s42255-022-00607-8

Provided by Deutsches Zentrum fuer Diabetesforschung DZD