PROJECT 1

DoS: Antonio Citro

Title: **Human Vascularized Islet Organ (hVIO) as an extracorporeal model for the study of physiopathology and drug screening in diabetes.**

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Curriculum: Cell and Gene Therapy

UniSR personal page: https://research.hsr.it/en/institutes/diabetes-research-institute/units/pancreas-bioengineering.html

Project description (*Number of characters*, *including spaces*: 2.000 - 3.000):

Background. Pancreatic endocrine disorders including T1D and T2D are increasing worldwide underlying the urgent need to generate better models to create specific interventional therapies. On the other hand, pancreas is an organ not directly accessible and this represent a strong limitation in drug discovery and therapeutic development.

AIM. Here, taking advantage of tissue engineering and ß cell replacement strategies, we intend to overcome these limitations bio-engineering, for the first time, a reliable ex-vivo human vascularized islet perfusable organ (hVIO) to bio-mimic the physiological endocrine islet niche function. This extracorporeal organ will model the pancreatic endocrine physiological activity generating a highly controlled, easy accessible and reproducible tool to investigate poorly understood physiological and immunological mechanisms beyond endocrine dysfunctions. Based on a decellularized lung left lobe scaffold repopulated with human blood outgrowing endothelial cells (BOEC) through organ vascular access and human islets through the airspace, we can model ex-vivo an extracorporeal human VIO (hVIO) that recapitulates integrated vascular and endocrine (islets) compartments. This innovative technology will represent the first human "pancreatic endocrine like close-concept organ".
Our hypothesis is that, in a highly controlled, easy accessible and reproducible way, hVIO will represent a unique predictive tool to investigate poorly understood physiological and immunological mechanisms beyond endocrine dysfunctions.

Expected Outcomes. hVIOs, generated using human primary cells, will be the first flexible platform to validate available drugs for diabetes and to study the interaction between the pancreatic endocrine niche and the immune system.

Skills to be acquired by the student:

Surgical skills for organ harvesting and transplantation. *Organ Engineering:* i) organ decellularization to obtain native extracellular matrix with defined access and spatial geometry, ii) bioreactor assembly for organ long term culture in a pressure controlled system iii) Organ recellularization for Vascularized islet Organ engineering. *Cell biology:* i) BOECs isolation, characterization and expansion and ii) Pancreatic islet culture and manipulation. *Flow cytometry*. *Functional vascular and endocrine test to validate the hVIO performance*: i) dynamic insulin secretion test, ii) vascular fluorangiography assay and confocal analysis for cell-to scaffold

distribution. *hVIO endocrine and vascular maturation signature*: single cell and spatial transcriptomics experiments.

References (max. 3)

1)Citro, A. *et al.* (2019) 'Biofabrication of a vascularized islet organ for type 1 diabetes', *Biomaterials*, 199. doi: 10.1016/j.biomaterials.2019.01.035.

2) Citro, A. and Ott, H. C. (2018) 'Can We Re-Engineer the Endocrine Pancreas?', *Current Diabetes Reports*, 18(11). doi: 10.1007/s11892-018-1072-7.

3) Peloso, A. *et al.* (2016) 'The human pancreas as a source of protolerogenic extracellular matrix scaffold for a new-generation bioartificial endocrine pancreas', *Annals of Surgery*, 264(1). doi: 10.1097/SLA.0000000000001364.