PROJECT 2

DoS: Lorenzo Piemonti

Title: Vanguard: Bioartificial Pancreas to Cure Type 1 Diabetes

Curriculum: Gene and Cell Therapy

Link to OSR/UniSR personal page: https://www.unisr.it/docenti/p/piemonti-lorenzo

Project description:

Background. Forty million individuals worldwide suffer from type 1 diabetes(T1D). This disease is managed by insulin therapy in a vast majority of patients because of the limited accessibility of beta cell replacement therapies (pancreas or islet of Langerhans transplantation). There is an urgent need for the development of a beta cell replacement therapy that will be available to larger numbers of T1D patients. The VANGUARD project (an H2020 consortium project) aims to deliver an Advanced Therapeutic Medicinal Product (ATMP) of high translational potential in T1D field, with properties of increased functionality and implantability and protection from immune destruction.

AIM. In this project, we will construct a bioartificial pancreas by assembling insulin- producing organoids, composed of human islet cells, human amniotic epithelial cells (hAEC) and blood outgrowth endothelial cells (BOECs), into an amniotic membrane-derived hydrogel. Components of the amniotic membrane will provide extracellular matrix and mechanical protection and confer their well-defined anti-inflammatory and immunomodulatory properties to the constructs. In collaboration with our H2020 partners, hAECs will be genome-edited to overexpress and locally release immunomodulatory molecules (HLA-G, HLA-E, CD47 and PD-L1) and endothelial cells will enhance graft revascularization. Functionality, biocompatibility, potency and safety of the bioartificial pancreas will be assessed *in vitro* and *in vivo* in relevant pre-clinical model of T1D.

Expected outcome. The ATMP delivered upon completion of the project will provide a model for rapid development of a bioartificial pancreas, utilizing "infinite" sources of insulin-producing cells (stem cell-derived, xenogeneic), and available to all type 1 diabetic patients before they develop the devastating chronic complications of the disease.

Skills to be acquired by the student: The student will become expert in bioartificial pancreas assembly with a dedicated focus on i) Hydrogel generation (Amniogel)(ii) Insulin secreting organoids generation and integration within Amniogel (hydrogel based on human amniotic membrane ECM) to bioengineer a bioartificial pancreas and iii) bioreactor customization for bioartificial pancreas long term culture and in vitro testing. He/She will acquire the additional following skills: vascular and endocrine bioartificial pancreas characterization (cell culture, flow cytometry, immunofluorescence, Luminex proteic assay, endocrine performance evaluation by dynamic perfusion, vascular evaluation with confocal analysis and quantifications, animal handling and cell/bioartificial pancreas transplantation, analysis of data). The student

will collaborate with the Vanguard H2020 consortium for the definition of the functional criteria for ATMP in vivo eligibility.

References (max. 3)

1. Lebreton, F., Lavallard, V., Bellofatto, K., Bonnet, R., Wassmer, C. H., Perez, L., Kalandadze, V., Follenzi, A., Boulvain, M., Kerr-Conte, J., Goodman, D. J., Bosco, D., Berney, T. & Berishvili, E. Insulin-producing organoids engineered from islet and amniotic epithelial cells to treat diabetes. *Nat. Commun.* **10,** 1–12 (2019).

2. Lebreton, F., Bellofatto, K., Wassmer, C. H., Perez, L., Lavallard, V., Parnaud, G., Cottet-Dumoulin, D., Kerr-Conte, J., Pattou, F., Bosco, D., Othenin-Girard, V., Martinez de Tejada, B. & Berishvili, E. Shielding islets with human amniotic epithelial cells enhances islet engraftment and revascularization in a murine diabetes model. *Am. J. Transplant.* **20,** 1551–1561 (2020).

3. Citro, A. & Ott, H. C. Can We Re-Engineer the Endocrine Pancreas? *Curr. Diab. Rep.* **18,** (2018).