Developing a Vascularized and Perfused Pancreatic Islet on a Chip for Diabetes Research

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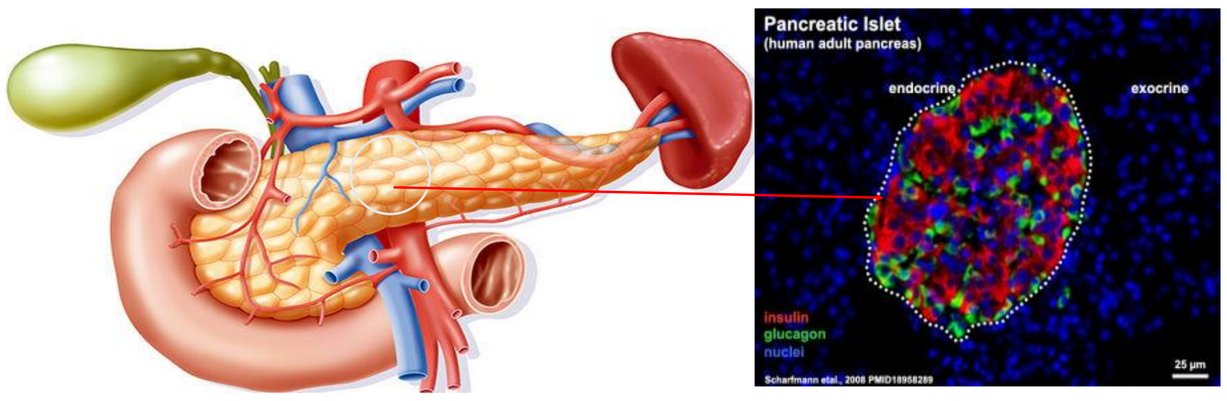
1. Introduction

Diabetes is one of the leading causes of non-communicable morbidity and early mortality in the world today, characterized by high blood sugar levels, resulting either from immune destruction or secretory failure of the insulin-releasing pancreatic islets of Langerhans.

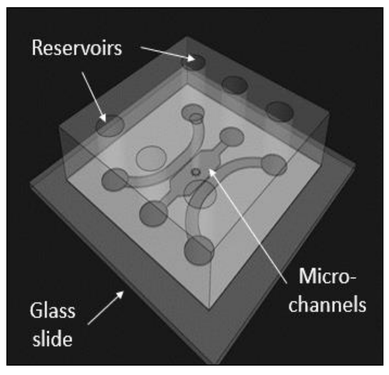


Organ-on-chip (OOC) technologies allow for the emulation of in vivo organotypic architecture, functionality, and physiochemistry, and promote the reduction and replacement of costly and less-ethical animal models. Current in vitro systems struggle to functionally interrogate islets over long time series, as these highly metabolically active micro-organoids become internally necrotic over the course of 48-72 hours. Furthermore, as islets are impossible to functionally image in vivo, the exact relationship between intra-islet blood flow and hormone secretory function remains fundamentally poorly understood.

2. Aims and Objectives

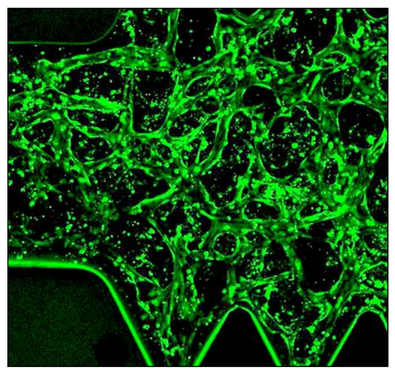
The aim of this project is to develop a vascularized islet-on-chip platform for long-term physiologically-relevant islet interrogation and experimentation, as well as the identification of new diabetes treatments and islet transplant strategies.

3. Methodology



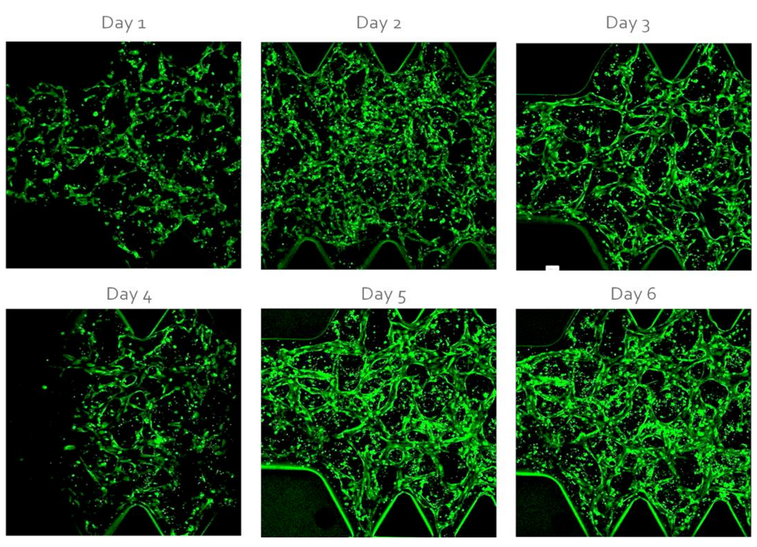
Stage 1. 3D design of a novel microfluidic platform in SolidWorks.

Stage 2. Micro-fabrication using SU-8 Soft-photolithography and practical analysis of fluid dynamics.

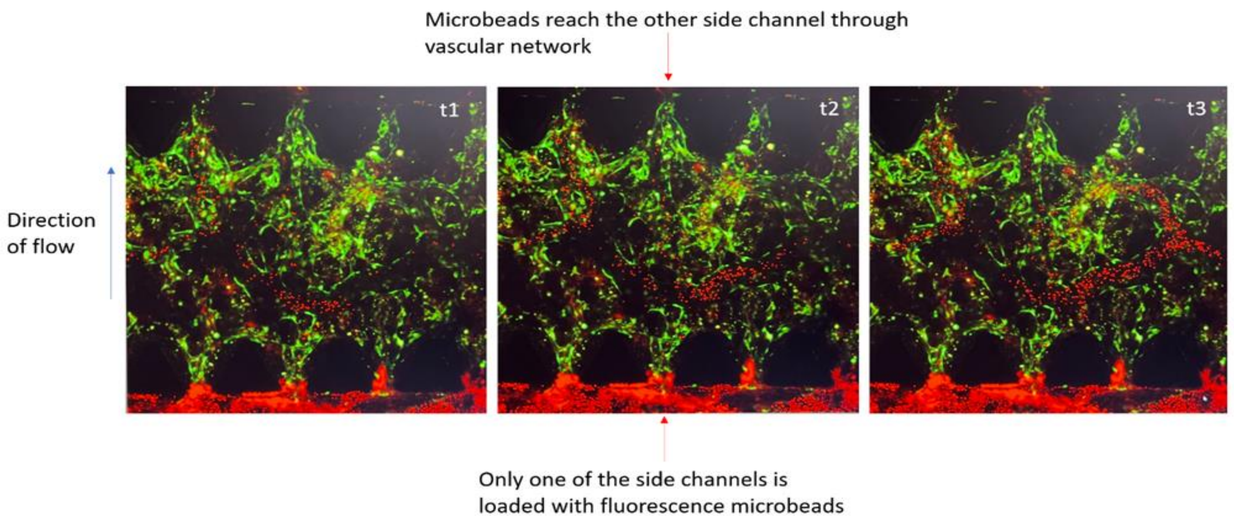


Stage 3. Vascularization of chip designs with HUVECs (Human Umbilical Vein Endothelial Cells)/MSCs (Mesenchymal Stem Cells) co-culture in fibrin.

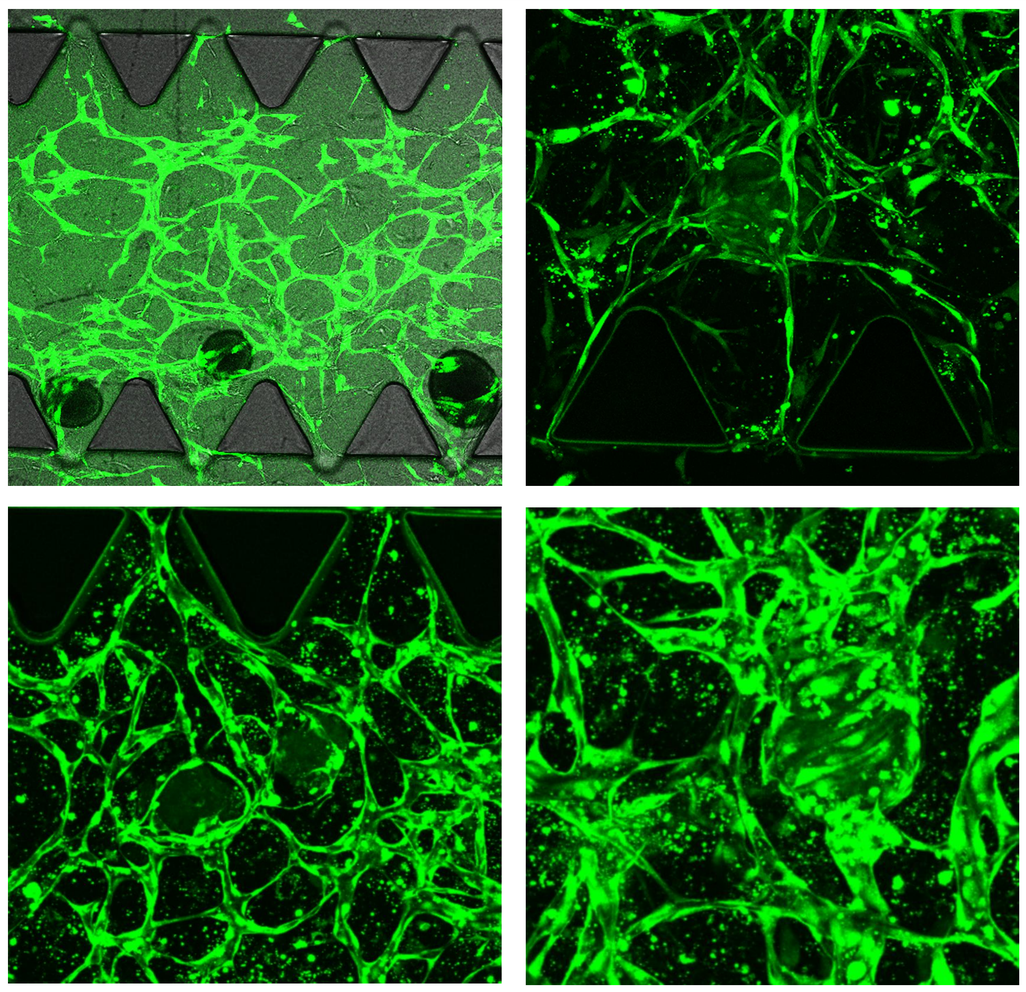
4. Results



Microvessel networks were imaged using confocal inverted laser-scanning microscopy. HUVECS pre-treated with green generational CellTracker (CMFDA) were cultured for 6 days under an alternating pressure gradient. These results emphasize the necessity of co-culture with stromal cells, as well as the importance of a mechanically stimulating pressure gradient, as networks failed to form in the absence of either of these conditions.



Red polystyrene microspheres (red channel) were used to visualize and verify perfusability and lumen integrity in networks. Spheres were added one side channel reservoir, and a cross-channel flow was generated via hydrostatic pressure differential (t1=frame 59, t2=117, t3=208).



Murine isolated islets (C57B6 WT mice) were co-loaded into chips alongside HUVECs and MSCs. Microvessels cluster and wrap around seeded islets, forming diffuse networks to provide the islets with nutrients delivered from the side channels. Islet viability appears to have been extended up to a period of 7-10 days post-isolation, a significant improvement over monolayer or even perifused conventional culture, yet these results are nascent and require thorough confirmation.

5. Conclusion

Current results illustrate the validity and robustness of a novel vascularized chip platform in the ability to develop microvessel networks and support islet viability over extended periods of culture/experimentation. While much work remains regarding characterization, quantification, and verification of these results, our vascularized platforms represent a promising and viable alternative to established in vitro models for islet implantation and interrogation. Further experiments are necessary to assess perfusability, viability, and functionality of islets implanted into vascularized chips.

6. Reference

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