Islet-on-a-chip:

Engineering the Microenvironment of Stem Cell-Derived β-cell (SCβ) Aggregates Towards Enhanced Glucose Response

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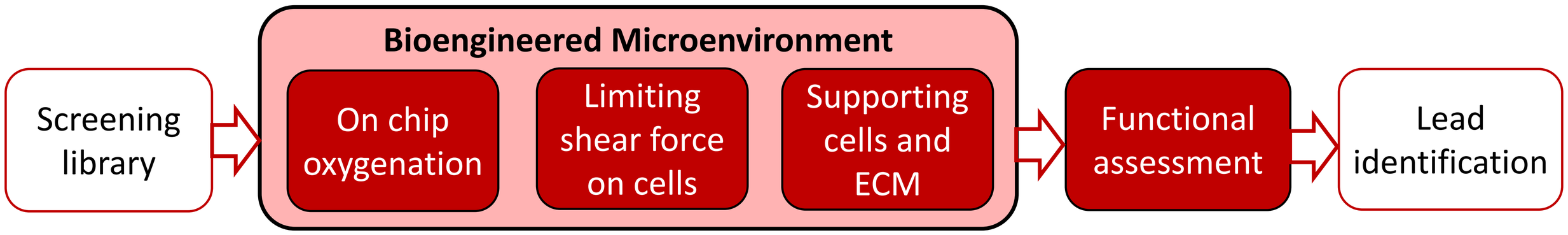
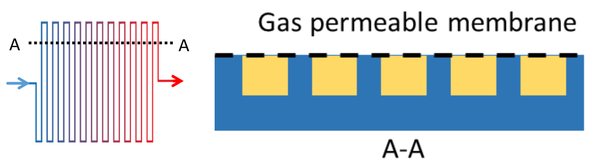


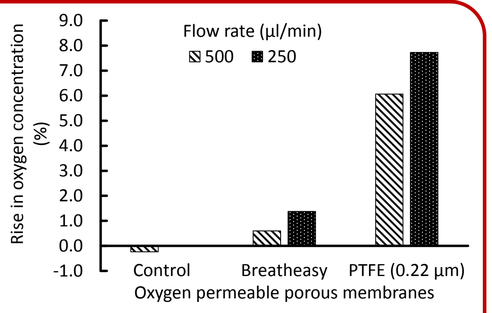
On-Chip-Oxygenation

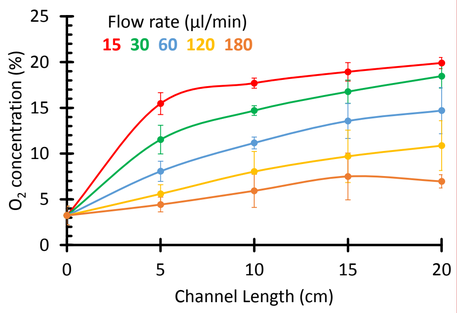


Motivation: It is difficult to meet high demand for O_2 by β-cells due its limited solubility in water. Fluid flow under a porous gas permeable membrane can enable continuous influx of O_2 while maintaining sterility of the fluid.

Progress:

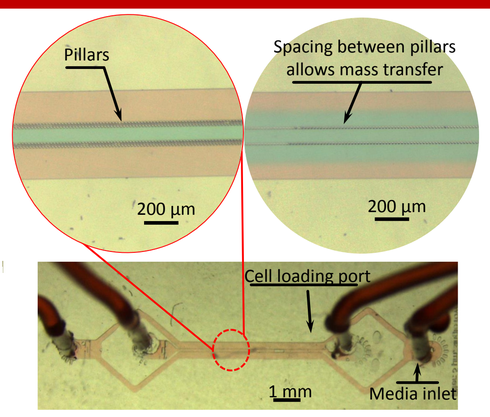
- A porous PTFE membrane (0.22 µm) enables continuous oxygenation of flowing media
- The oxygen level can be controlled by channel length and flow rate





Ongoing work: Integrate the oxygenation module with cell chamber

Cell Chamber Design



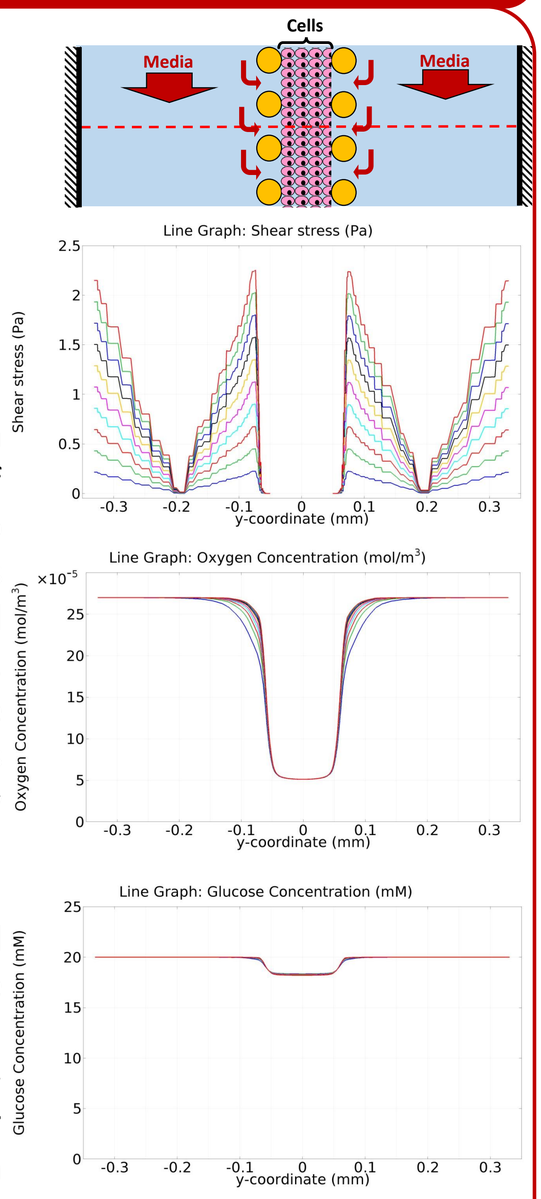
Motivation: Fluid flow around SCβ can provide a constant and controlled amount of nutrients around the cells. However, it also introduces unwanted shear stress. β-cells within islets are protected by endothelial cells from shear due to blood flow. Therefore we envision a device where the cells are protected from fluidic shear stress by rows of microfabricated pillars but allow for mass transport to and from the cells.

Progress:

- Cell chamber designed and fabricated using soft-lithography after multiple iterations
- COMSOL™ simulations for fluid flow and β-cells [Buchwald 2013] show minimal shear stress and uniform nutrient distribution within the center channel with cells at multiple flow rates

Ongoing work:

- Culture cells in the cell chamber
- Modify the design to improve oxygen supply to the cultured cells



COMSOL™ simulation results for shear stress, oxygen and glucose concentration

Supporting Cells and ECM

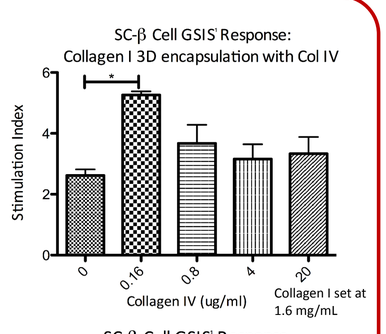
Motivation: Niche components such as surrounding endothelial cells (EC) and matrix proteins are essential for maintaining the normal function and phenotype of islets. We hypothesize that recapitulating the relevant microenvironmental cues will significantly facilitate the functional maturation of SCβ aggregates and boost their glucose response.

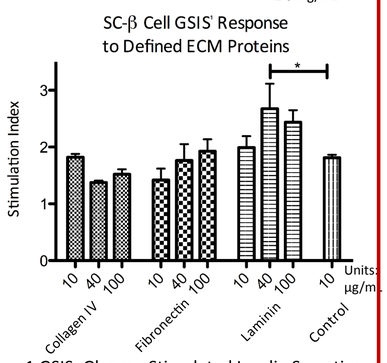
Progress:

- Direct contact MSC co-culture doesn't affect SCβ function
- Laminin improves GSIS response of SCβ 1.5 fold
- Collagen IV within collagen-I at 0.16 µg/mL improves GSIS response 2 fold
- Dissociated SCβ cells reaggregate with endothelial cells to form spherical cluster with well distributed ECs within the heterogeneous cluster

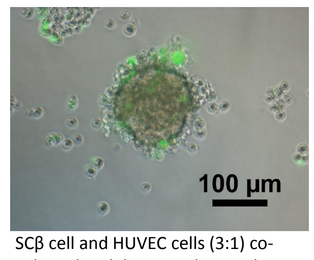
Ongoing work:

- We are refining matrix conditions and supporting cell ratio to improve SCβ function
- Evaluate effect of EC on function and viability of SCβ
- Culture SCβ and progenitor cells on the device in the presence of supporting cells and ECM





1 GSIS: Glucose Stimulated Insulin Secretion



SCβ cell and HUVEC cells (3:1) co-cultured with hanging drop technique (HUVEC cells stained with CellTracker™ Green CMFDA Dye)

Functional Assessment On Chip

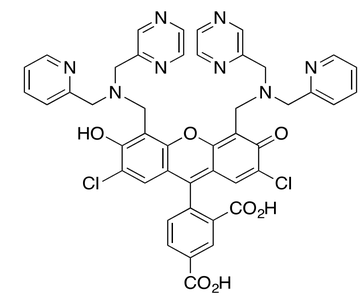
Motivation: Currently it is not possible to assess insulin secretion of β cells in real time. A sensor to continuously monitor co-secreted Zn^{2+} can enable indirect measurement of β cell functionality on chip in real time.

Progress:

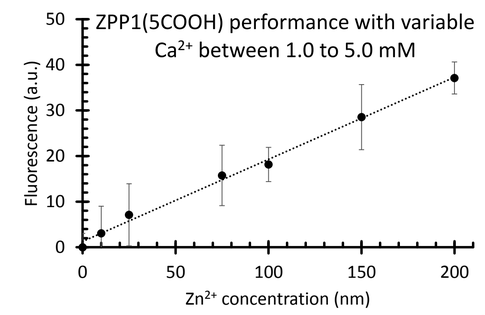
- ZPP1(5COOH) shows the highest sensitivity among the 6 sensors screened
- Unlike other sensors, ZPP1-(5COOH) shows limited sensitivity to other ions (e.g. Ca^{2+}) present in buffers used for islet stimulation

Ongoing work:

- Correlate Zn^{2+} and insulin secretion after glucose stimulation
- Integrate Zn^{2+} sensor with the device



ZPP1(5COOH)



Conclusion

- Multiple environmental parameters including oxygen, mechanical stress, supporting cells and ECM proteins are being investigated for their impact on SCβ survival and glucose response
- Laminin and collagen-IV significantly improved stimulation index of SCβ
- ZPP1-(5COOH) is identified as the robust Zn sensor that can enable real time functional assessment
- These approaches will collectively form the islet-on-a-chip that will enable a reliable platform for screening molecules to improve function of SCβ

Acknowledgements:

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