Integrating Biomaterials with Microfluidics to Model Physiological Angiogenesis *In Vitro*

Claire Komar, Ethan Boodey, Gregory Riddle, Matthew Ryan, Haley Royce, and Dr. Linqing Li
Department of Chemical Engineering and Bioengineering, University of New Hampshire, Durham, NH 03824

INNOVATION SCHOLARS

Background

- Vascularization is critical for tissue engineering as it provides blood flow to transfer oxygen, delivers nutrients, and removes waste.
- Engineering a functional vascular network enhances success of integration with host vasculature after implantation.
- Currently, *in vitro* models do not fully capture the dynamic and multicellular morphogenic process that occurs during angiogenesis, while current *in vivo* animal models suffer low throughput and are ethically controversial.
- **Project Goal: Engineer a unique organotypic model of angiogenic sprouting and neo-vessel formation by creating artificial vessels fully encapsulated within a 3D collagen hydrogel matrix. Mimicking vascularization provides knowledge of potential wound healing applications and cancer metastasis for personalized medicine.**

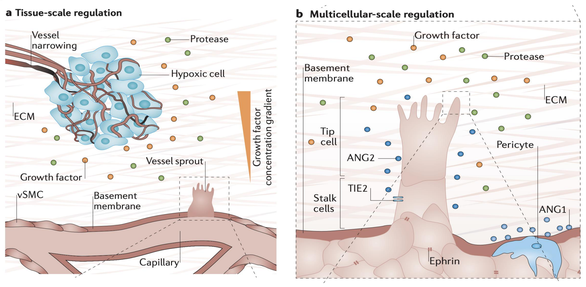


Figure 1. Endothelial cells proliferate in response to growth factors.

Materials and Methods

Using a PDMS (polydimethylsiloxane) microfluidic chip, an *in vitro* fluidic system was able to be successfully modeled, which demonstrated channel flow and new blood vessel growth.

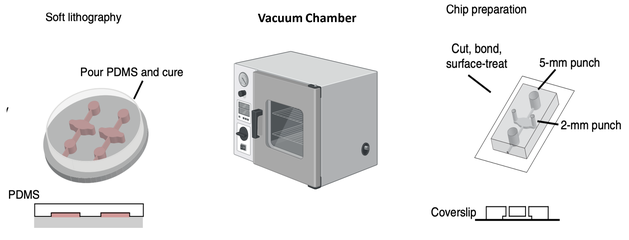


Figure 2. Pouring and curing of PDMS to create chip.

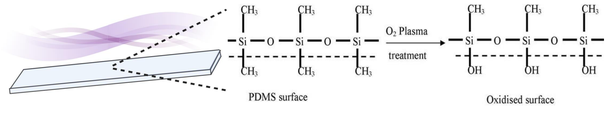


Figure 3. Chemistry of plasma treatment to seal chip to coverslip.

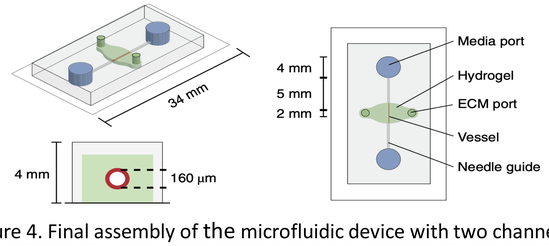


Figure 4. Final assembly of the microfluidic device with two channels.

Fabrication of Microfluidic Device: Single-Channel AngioChip

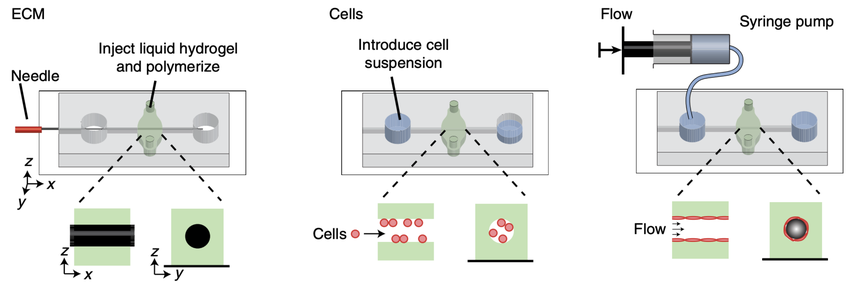
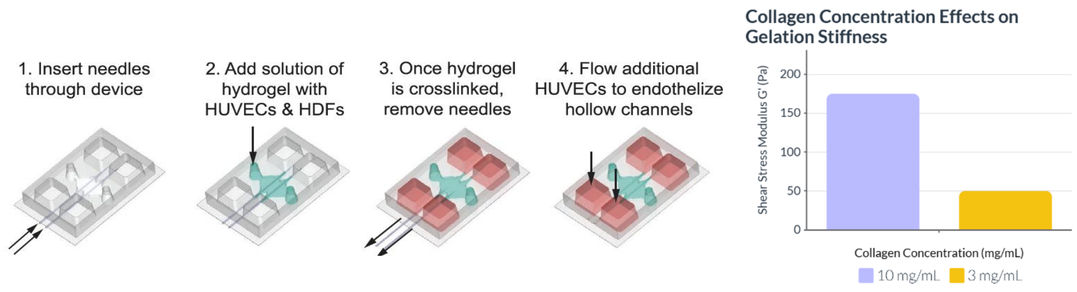


Figure 5. Schematic of hydrogel formation in a microfluidic device, cell seeding, and introduction of flow.

Two-Channel AngioChip Assembly and Collagen Hydrogel Integration



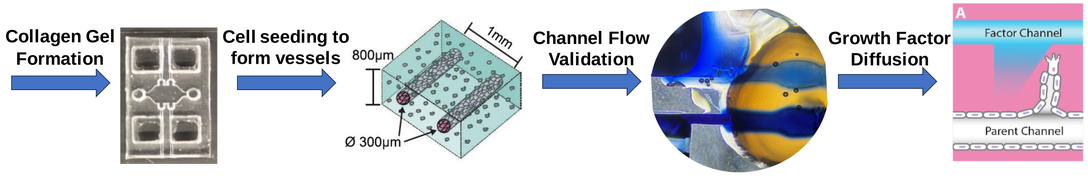


Figure 6. Collagen, an extracellular matrix protein, is placed in the center well to help support and stabilize cell morphology. The rheology, or elasticity, of collagen at a higher stiffness promotes more protein availability for attachment and smoother channel formation[1]. Channels encapsulating endothelial cells are created by extracting gelatin-coated acupuncture needles. The microfluidic devices demonstrates flow through these channels, offering a sealed, *in vitro* system for studying angiogenic processes.

In Vitro Vessel Formation and Angiogenic Sprouting

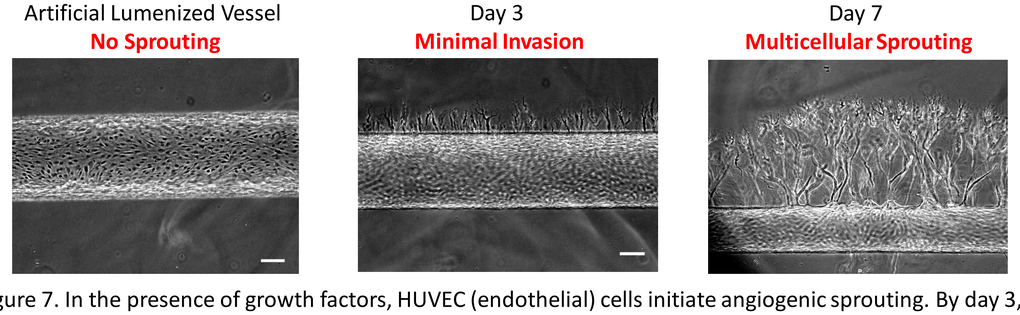


Figure 7. In the presence of growth factors, HUVEC (endothelial) cells initiate angiogenic sprouting. By day 3, sprouts begin to form primitive vascular structures. Stalk cells provide support while tip cells exhibit migratory behavior. After 7 days, the sprouts mature into functional blood vessels, allowing for oxygen and nutrient transfer to local tissues[2].

Future Directions

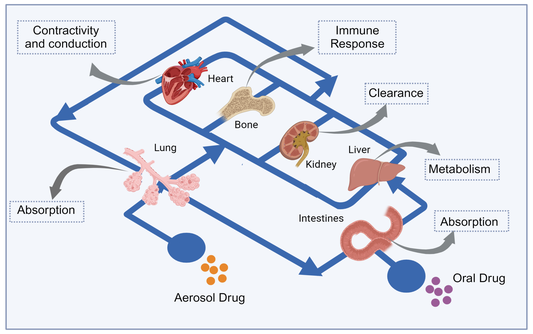


Figure 8. Human on a Chip – Connecting All Organs

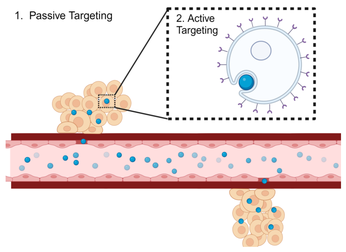


Figure 9. Drug Targeting Methods

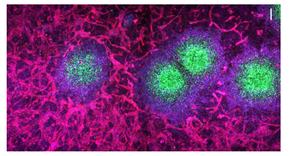


Figure 10. Vascularized Ovarian Cancer Spheroids with Human Dermal Fibroblasts in Fibrin gel

Conclusions

This project modeled *in vivo* vascularization with implementation of an *in vitro* microfluidic flow system. The microfluidic chips demonstrated necessary channel flow for proper nutrient delivery to the endothelial cells. **Evaluation of artificial vessels showed the successful formation of neo-vessels, an indication of early stage vascular formation.**

As a novel testing method, this research has great potential for the development of drug treatments and to combat the attrition rates of drug therapies in clinical trials. Microfluidic devices are able to recapitulate local tissue environments, model tumor penetrating therapeutics[3], and cancer induced angiogenesis, making this a compelling alternative for animal testing. Additionally, these chips have the potential to make personalized medicine more accessible by offering a cost-effective and portable method for efficient diagnostics.

Acknowledgments

Haley Royce; Dr. Linqing Li; Department of Chemical Engineering and Bioengineering; Innovation Scholars Program

References

1. Bubli, S. Y., Smolag, M., Blackwell, E., Lin, Y.-C., Tsavalas, J. G., & Li, L. (2023). Inducing an LCST in hydrophilic polysaccharides via engineered macromolecular hydrophobicity. *Scientific Reports*, *13*(1), 14896.
2. Nguyen, D.-H. T., Stapleton, S. C., Yang, M. T., Cha, S. S., Choi, C. K., Galie, P. A., & Chen, C. S. (2013). Biomimetic model to reconstitute angiogenic sprouting morphogenesis in vitro. *Proceedings of the National Academy of Sciences*, *110*(17), 6712–6717.
3. Sontheimer-Phelps, A., Hassell, B.A. & Ingber, D.E. Modelling cancer in microfluidic human organs-on-chips. *Nat Rev Cancer* 19, 65–81 (2019).
4. Bose, Tanima & Diane, bullet & Latawiec, Diane & Mondal, Partha & Mandal, Subhra. (2014). Overview of nano-drugs characteristics for clinical application: The journey from the entry to the exit point. Journal of Nanoparticle Research. 16. 2527. 10.1007/s11051-014-2527-7.