Rapid Prototyping and Development of Advanced Multi-lumen Bioreactor for Study of Cerebral Aneurysm Formation

CNS 2018 ANNUAL MEETING
HOUSTON, TEXAS
OCTOBER 6-10, 2018

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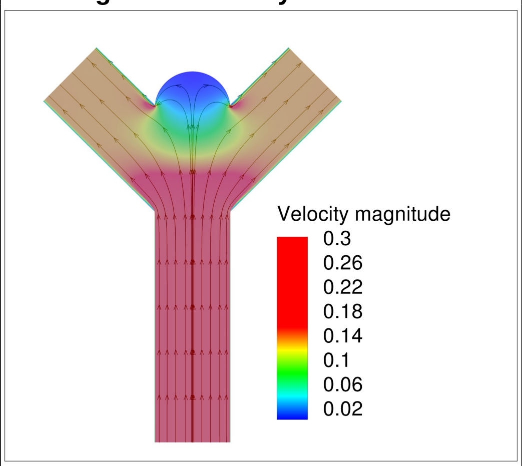
Introduction

Cerebral aneurysms form due to complex interactions between hemodynamic shear stress and inflammation. Current in vivo models are costly and time consuming, while described in vitro models lack the complexity of in vivo systems. We set out to develop an advanced, multi-lumen flow chamber bio-reactor that would allow for inflammatory, endothelial, and smooth muscle cell interactions to study cerebral aneurysm formation. First, we used a previously published flow chamber design as a starting point. Specifically, we used a flow field that was described and studied using both *in silico* and *in vitro* methods (Figure 1).

Figure 1. Velocity Streamlines



CFD simulation showing velocity streamlines at high perfusion flow rate

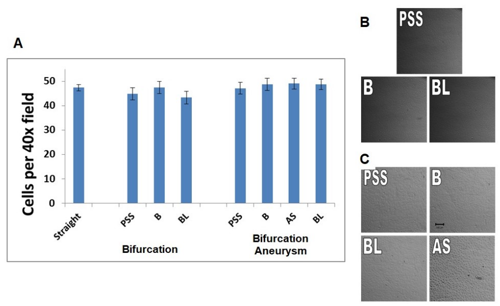
Methods

We have shown that human endothelial cells and smooth muscle cells can be successfully studied on semi-permeable membrane and exposed to pulsatile flow at wall shear stress of 10 dynes/cm2 (unpublished data) (Figure 2 and 3). For this project, we used rapid 3D printing to design (Figure 4) a multi-lumen flow chamber bioreactor. The components were then manufactured (Figure 5) and validated.

Results

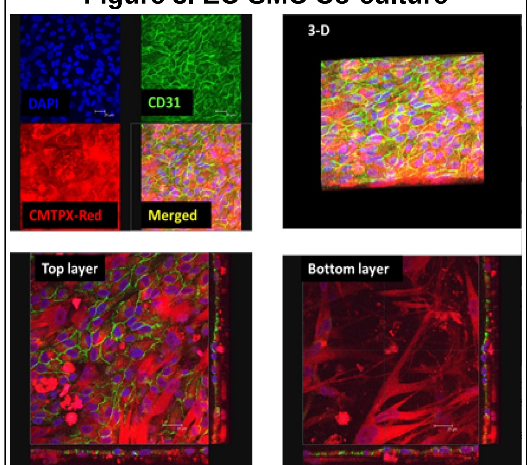
Rapid prototyping is an efficient method in development of next generation bioreactor to study cerebral aneurysm formation (Figure 6 and 7). Semi-permeable membrane allows for separation of endothelial and smooth muscle cell populations, while allowing for cell-to-cell communication (Figure 3).

Figure 2. Cell Density in Systems



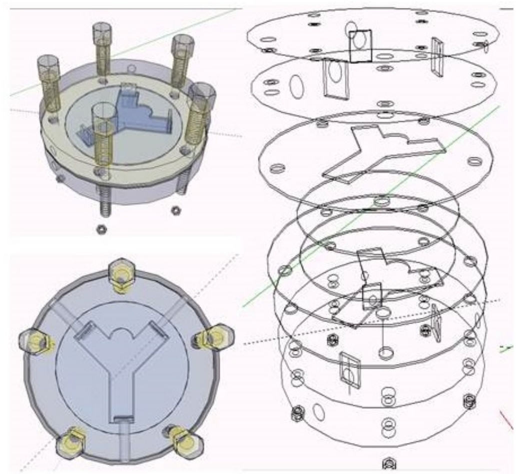
Endothelial cell density did not show any significant differences across different systems or sub-locations

Figure 3. EC-SMC Co-culture



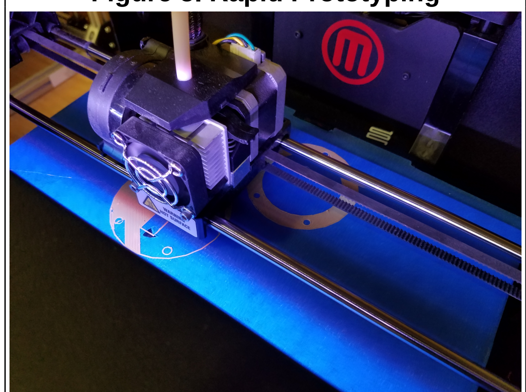
Co-culture of endothelial and vascular smooth muscle cells in the flow chamber systems shows fairly uniform layering

Figure 4. Advanced Cerebral Aneurysm Flow Chamber Mk2



Design drawings for 2nd generation cerebral aneurysm flow chamber

Figure 5. Rapid Prototyping



Makerbot 3D printer was used to create a mock up prototype

Conclusions

We used rapid prototyping and 3-D printing to manufacture an advanced multi-lumen flow chamber bioreactor for study of inflammatory interactions in cerebral aneurysm formation (Figures 4-7). This device allows for sampling of individual cell populations and high-throughput discovery of inflammatory factors.

Figure 6. Perfusion System in Experimental Application

Figure 7. Flow Chamber Prototype

Construction and validation of component fit using 3D-printed elements

Learning Objectives

A next-generation, multi-lumen flow chamber bio-reactor can be used to study advanced inflammatory cell-vascular cell interactions in cerebral aneurysm formation. Future studies will involve using the device as a platform for biomarker discovery.

References

KW Nowicki, K Hosaka, Y He, PS McFetridge, EW Scott, BL Hoh. A novel high-throughput in vitro model for identifying hemodynamic-induced inflammatory mediators of cerebral aneurysm formation. Hypertension, 2014.