Cardiac Scaffold for Human Mesenchymal Stem Cell Facilitated Autonomous Pacing

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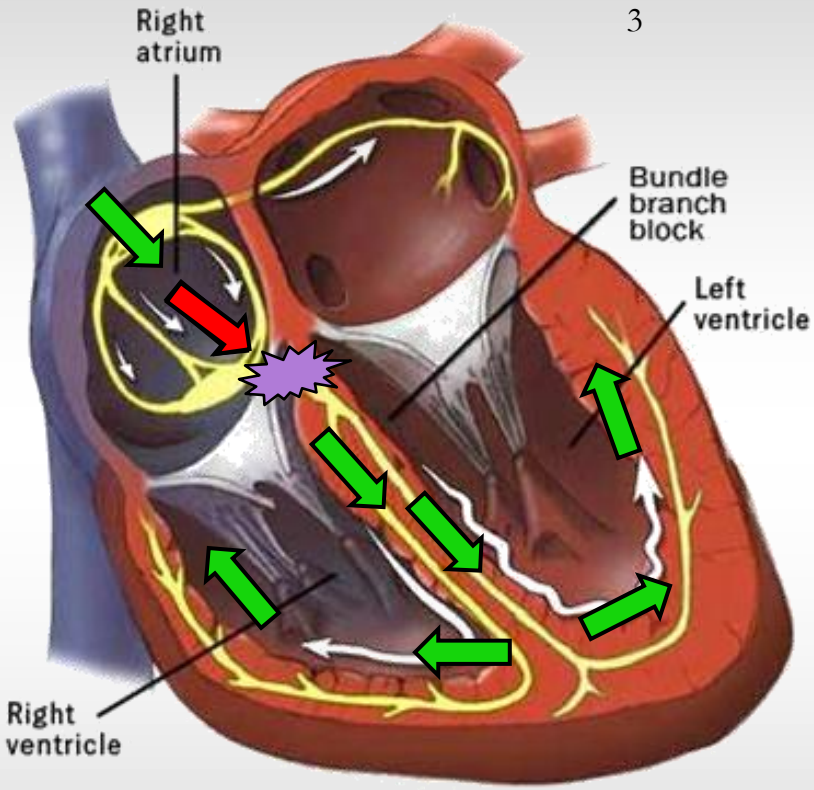
Clinical Significance

- Cardiac disease accounts for over 700,000 deaths/year - leading cause of deaths in United States[1]
- Arrhythmia – abnormal or disrupted propagation of the electrical impulses
- Roughly 400,000 pacemakers implanted each year[2]



3

1. Center for Disease Control, 2008. Available online at http://www.cdc.gov/heartdisease/
2. Ide, Hiroo. *Price differences between Japan and the US for medical materials and how to reduce them*. Health Policy Volume 28, 2007. Page 71.
3. Image available online from < http://www.ohiohealth.com/>

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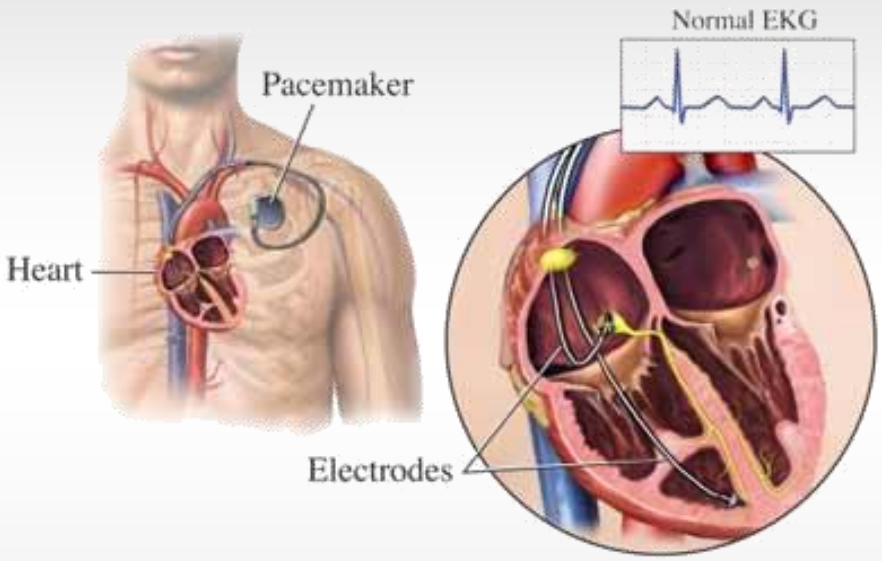
Current Solution

Electrical Pacemakers

- **Proven effective**
- **Limitations**
  - **Battery Life**
  - **Sensitivity to magnetic fields**
  - **Lead failure**
  - **Complications with implantation**
  - **Does not respond to physiological changes**



1

1. Image available online from <http:// services.epnet.com/GetImage.aspx>

Approach

Fencelin Stem Cells!

Stem Cell Migration is a large concern!

- **HCN Gene on Human Mesenchymal Stem Cell (hMSC)**
- **Modified hMSC + Cardiac Myocyte = I**
- **Communicate via**

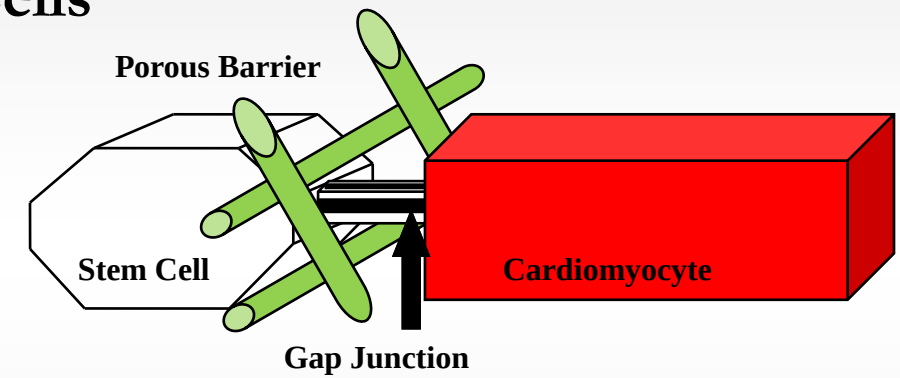
2

1

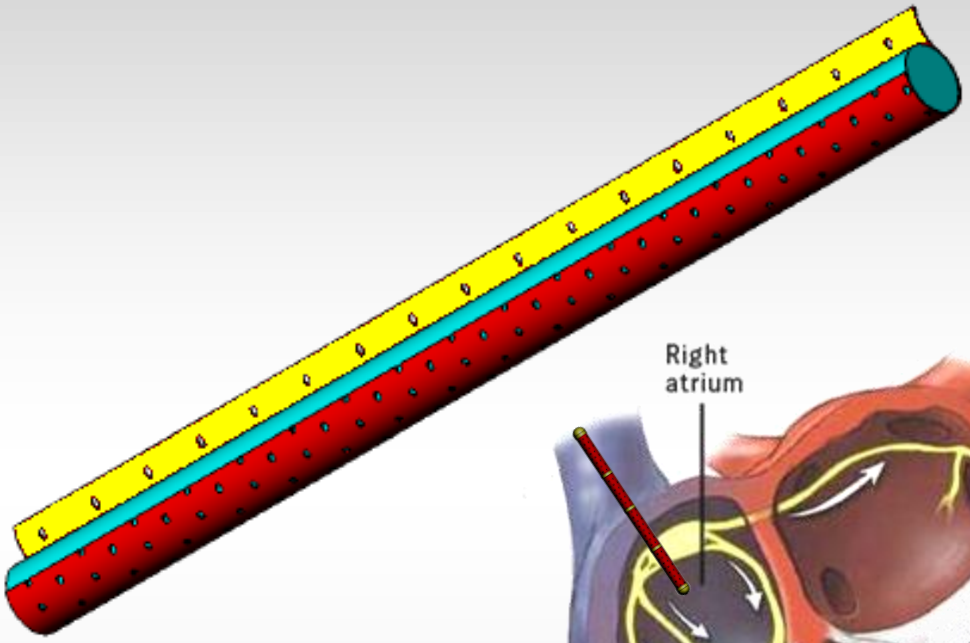
1. Rosen, M. R., Brink, P. R., Cohen, I. S., & Robinson, R. B. (2004). Genes, stem cells and biological pacemakers. *Cardiovascular Research, 64*(1), 12-23.
2. Image Retrieved 19-Mar-2009 from <http://cache.daylife.com/imageserve/0eVO4EY9yTcTM/610x.jpg>

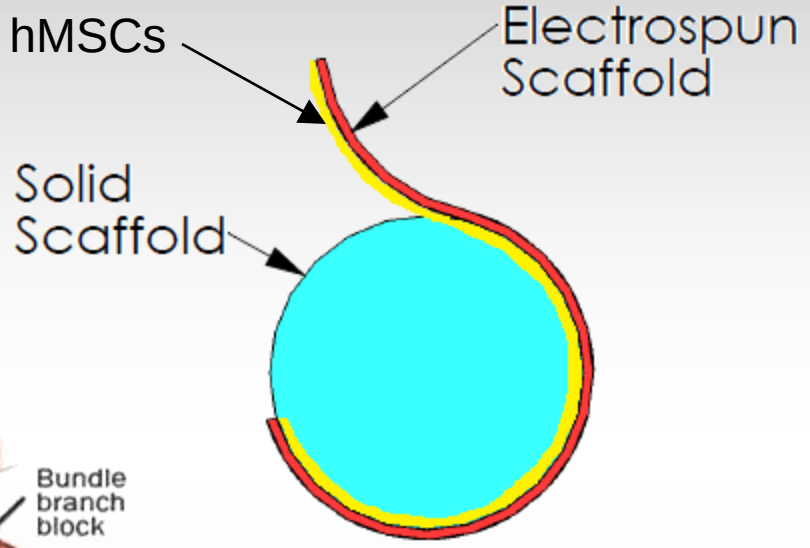
Objective

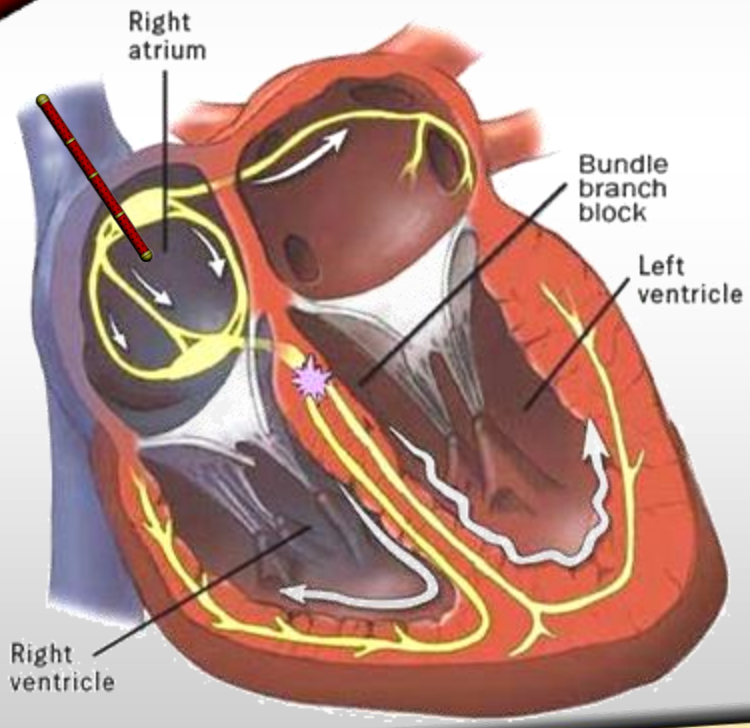
- **Mesenchymal Stem Cell Migration Inhibiting Scaffold**
  - **Prevent Migration of Stem Cells**
  - **Permanent and Durable**
  - **Allow Gap Junction Formation**
  - **Minimally Invasive Delivery**



Our Design







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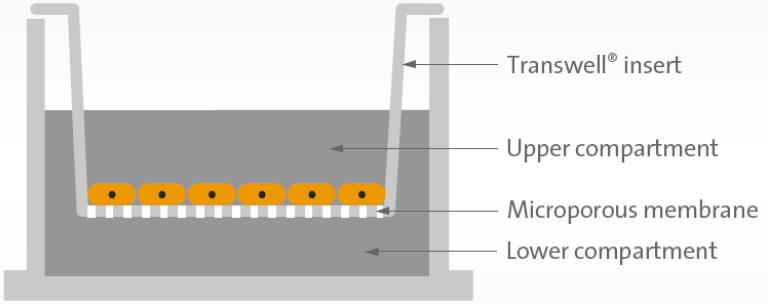
hMSC Migration Assay

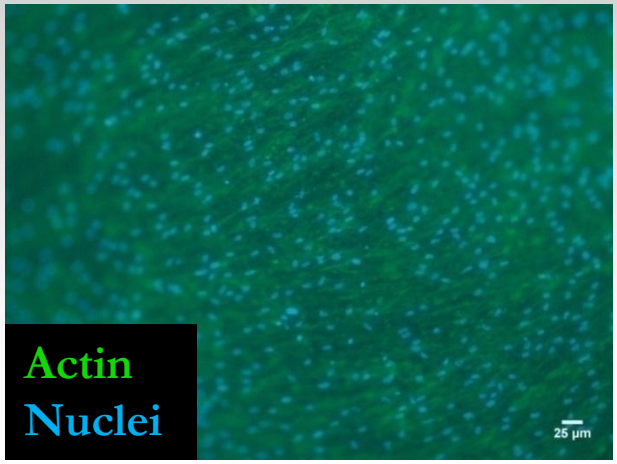
- Methodology
  - Pore sizes of 0.4, 3.0, 8.0 μm diameter
  - Which pore size inhibits migration?
  - Fibroblast Growth Factor
  - Incubate for 3 Days
- Evaluation
  - Staining to quantify migration
  - DAPI stain for the nuclei
  - Phalloidin stain for cellular cytoplasm



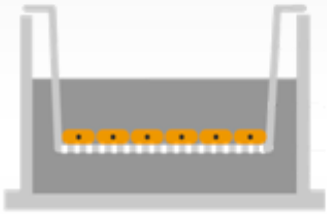
Corning Transwell® Permeable Supports

Pore Size – Representative Images

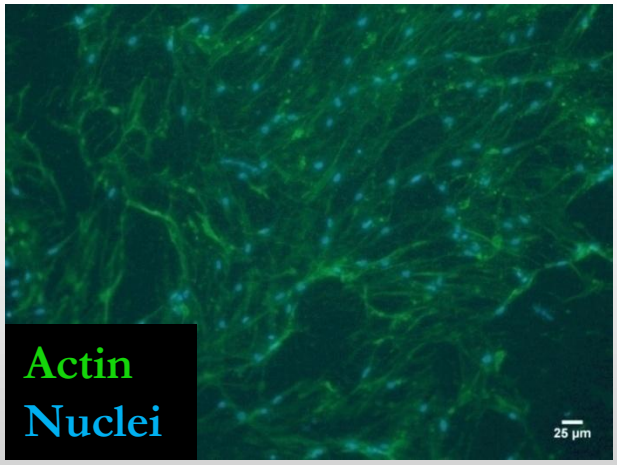
8.0 Micron Pores



0.4 Micron Pores

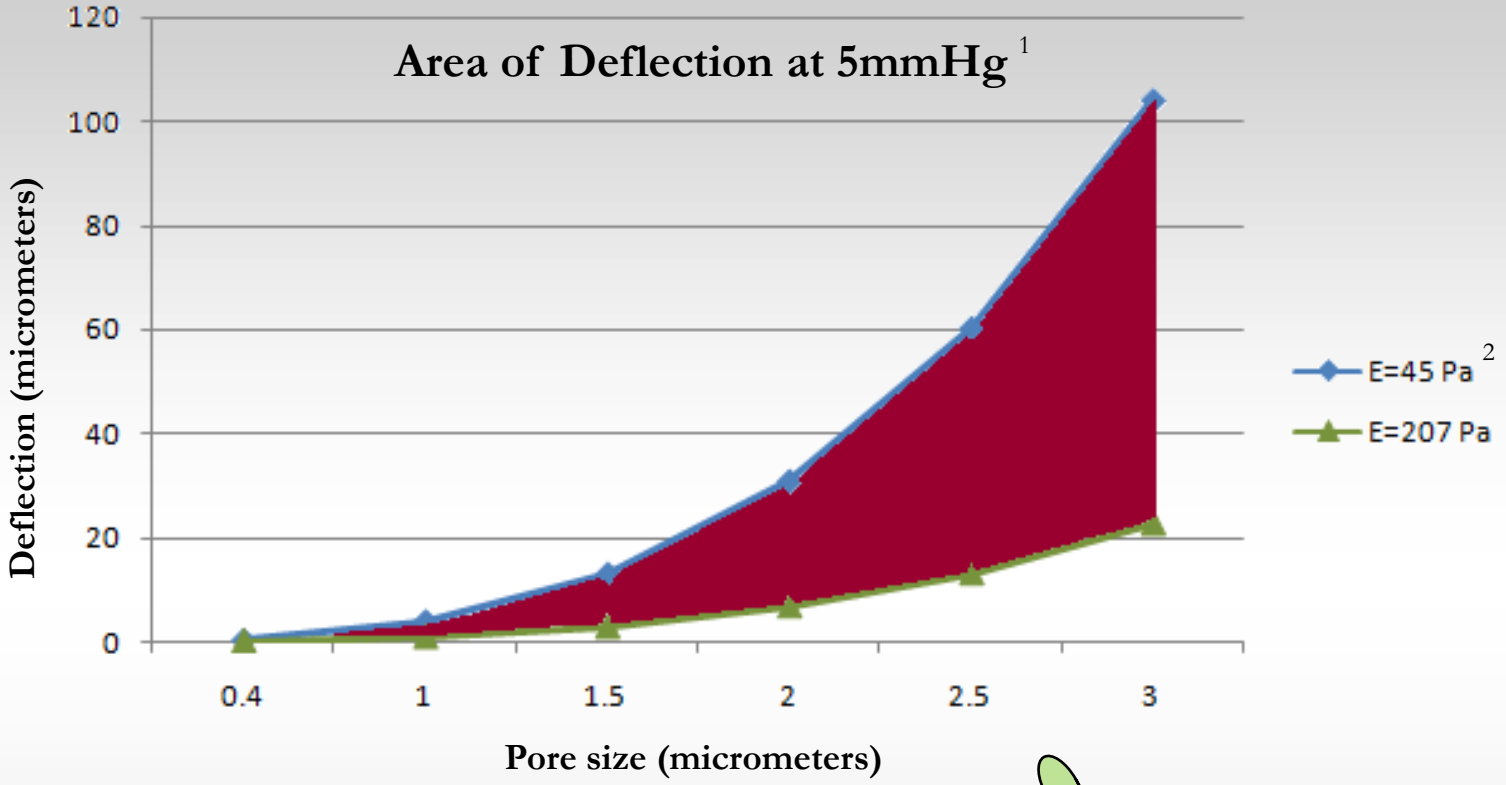


3.0 Micron Pores

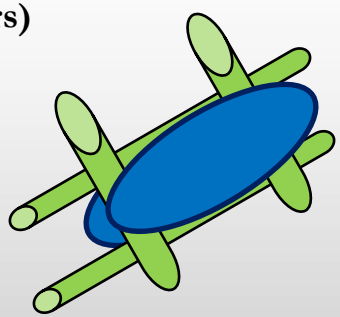


Control

Deflection of a hMSC



Pore Size = 2.0-2.5μm
Deflection = 15.0-30.0 μm
Fiber Diameter = 30.0-60.0 μm



1. Heineman, F. W., & Grayson, J. (1985). Transmural distribution of intramyocardial pressure measured by micropipette technique. *American Journal of Physiology of Heart and Circulatory Physiology, 249*(6), 1216-1223.
2. Tan, S., Pan, W., Ma, G., Cai, N., Leong, K., & Liao, K. (2008). Viscoelastic behaviour of human mesenchymal stem cells. *BME Cell Biology, 9*, 1-7.

WPI

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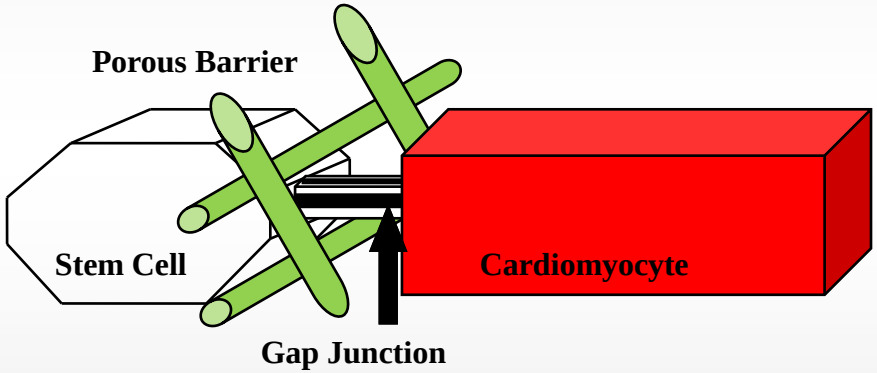
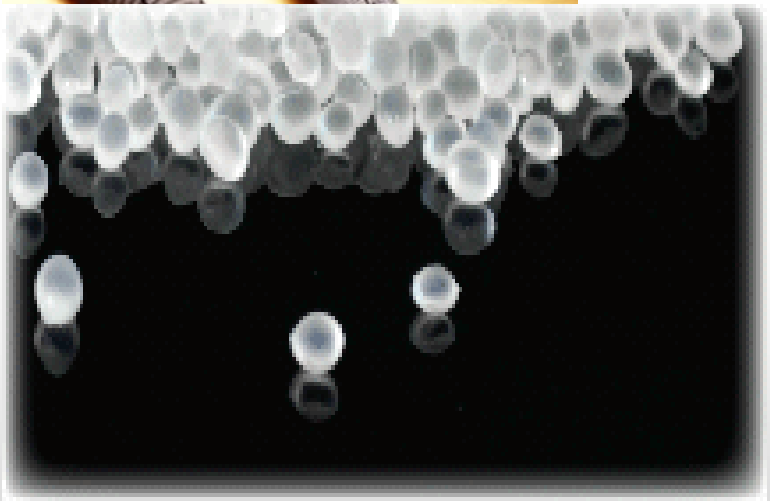
  - Minimally Invasive Delivery



Materials

- Currently used in cardiovascular a
  - Polyurethane
  - Dacron
    - Good mechanical properti
  - ePTFE
    - Biocompatibility and hemocompatibility
  - Nitinol
  - Polyurethane
    - Corrosion and wear

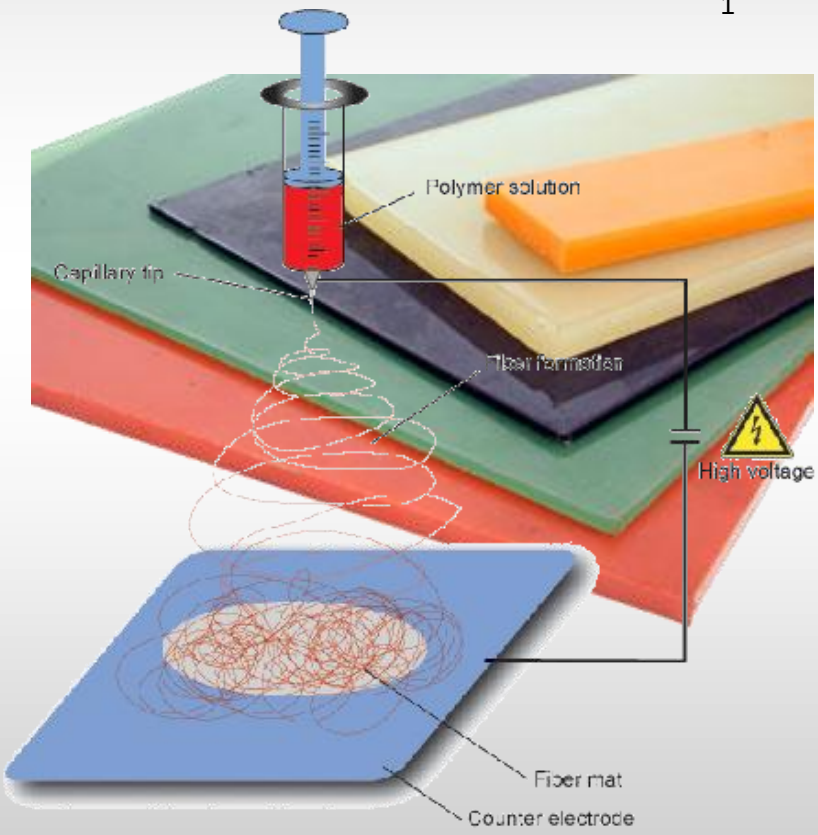
to our



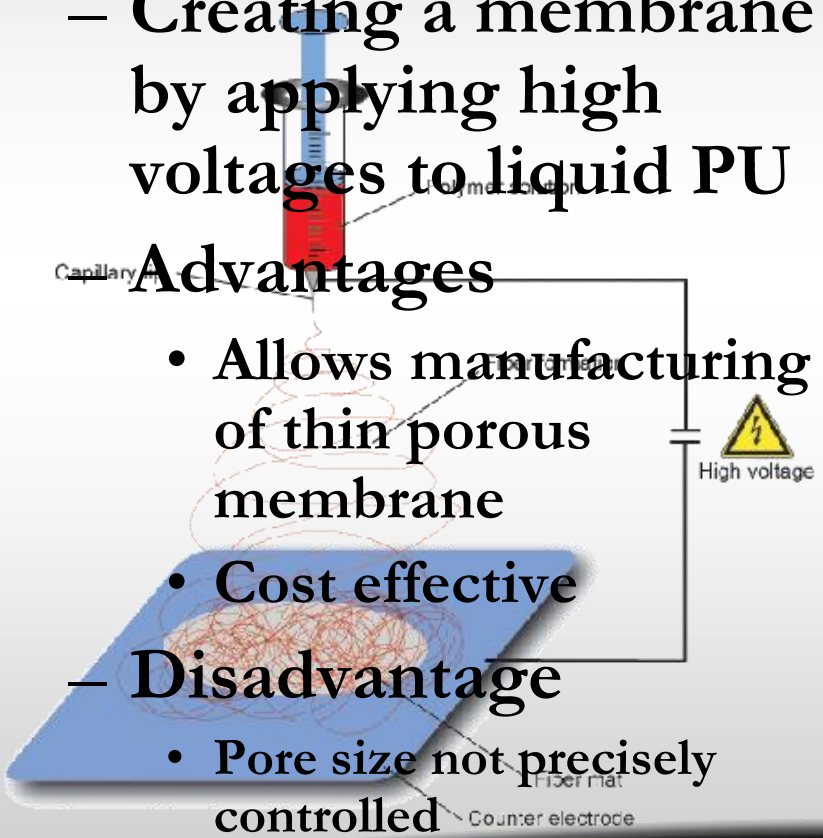
1. http://www.alibaba.com/product/in102647177-101650137-100652054/coronary_stents.html
2. http://www.biomed.metu.edu.tr/courses/term_papers/Blood-Vessel-Substitutes_durmus.htm
3. http://www.advbiomaterials.com/images/clearpelletstop.gif

Manufacturing Process

BioSurfaces, Inc.



- Electrospinning
  - Creating a membrane by applying high voltages to liquid PU
  - Advantages
    - Allows manufacturing of thin porous membrane
    - Cost effective
  - Disadvantage
    - Pore size not precisely controlled



1. Image Retrieved 2-April-2009 from <http://www.urethanespecialties.com/sheetsandpads1.jpg>
2. Image Retrieved 2-April-2009 from <http://www.uni-marburg.de/fb15/ag-wendorff/research/Electrospinning/es-setup>

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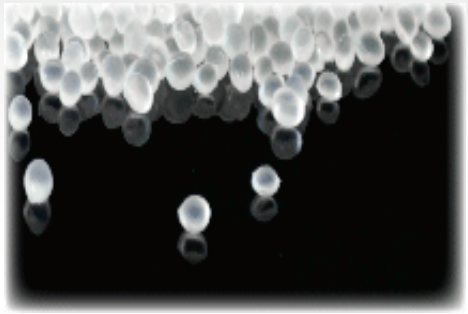

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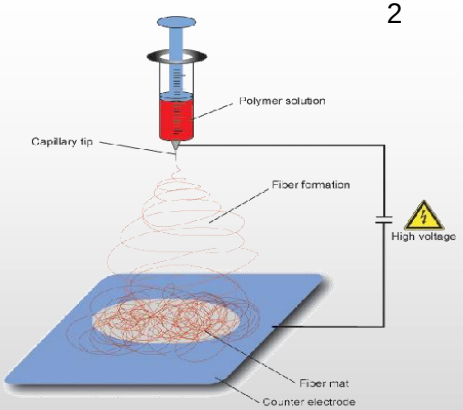

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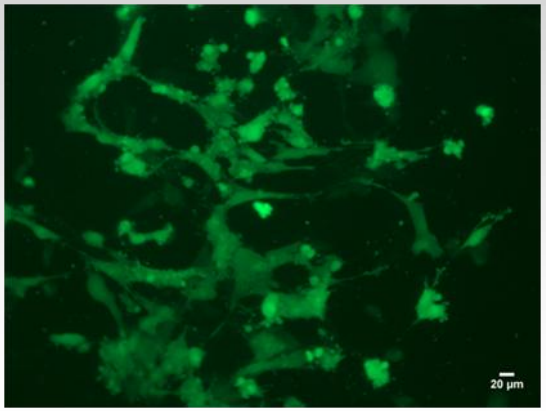
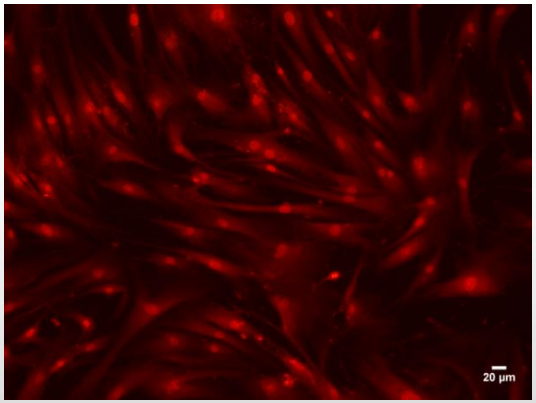
Cell Viability

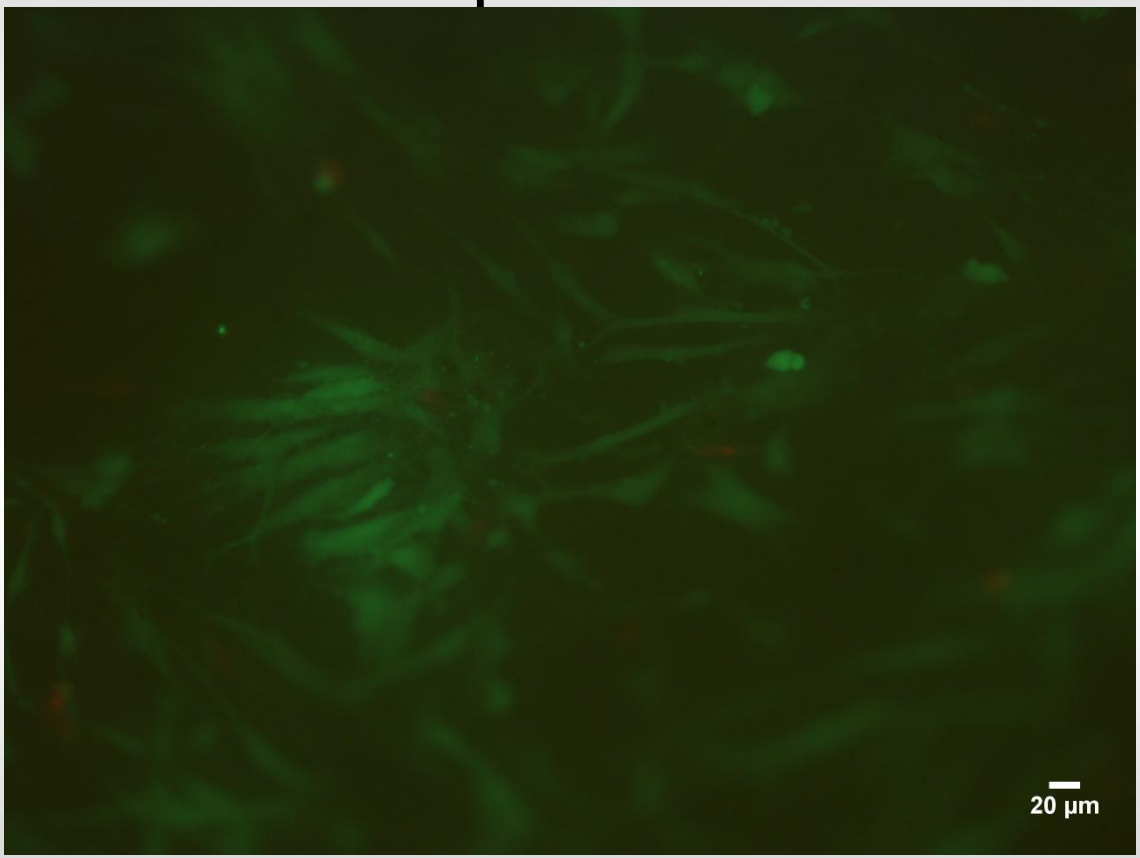


Live Control



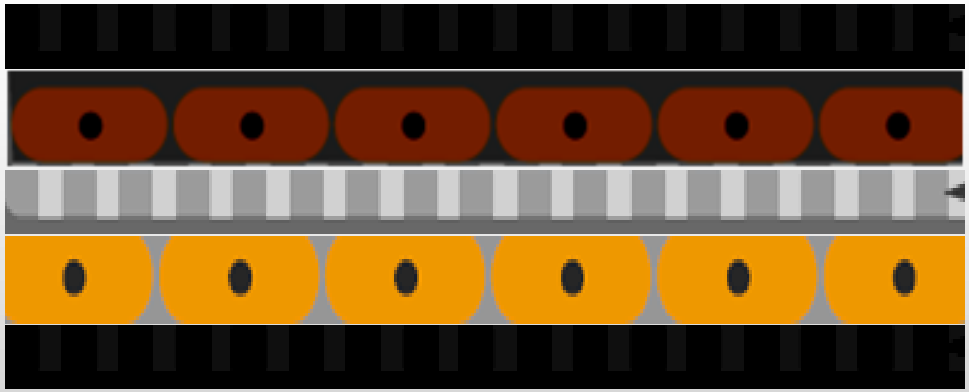
Dead Control

Sample Results

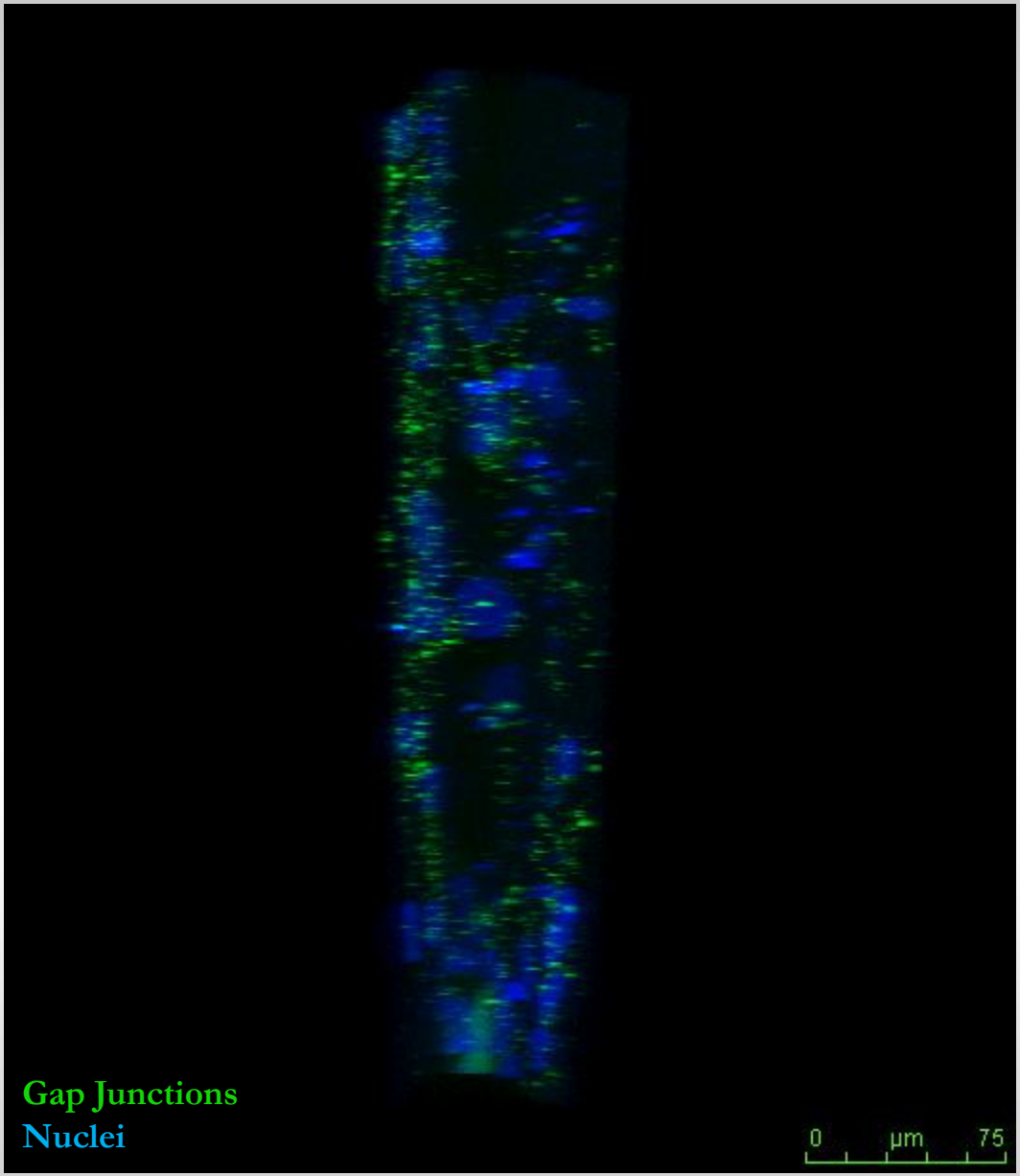


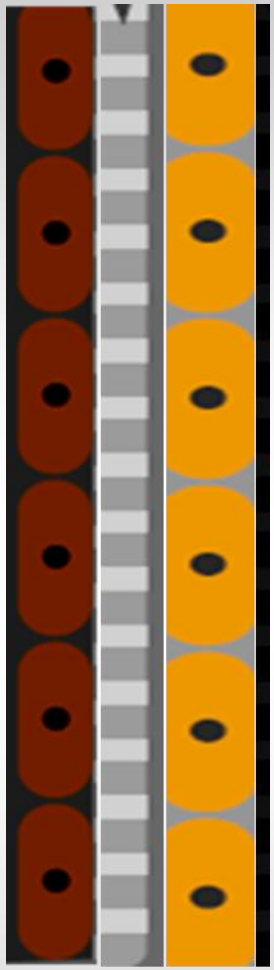
Gap Junction Formation through Pores

- Custom Gaudette-Pins Dual Wells
- hMSC On Both Layers of Scaffold
- Connexin 43 Immunohistochemistry for Gap Junction Formation



Results

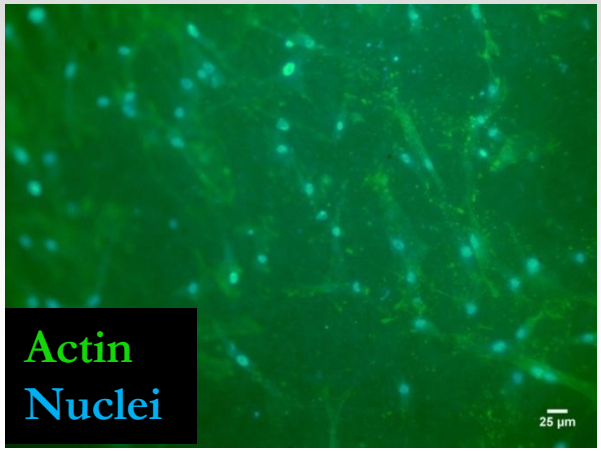




hMSC Migration – Polyurethane Scaffold

- hMSCs seeded on top layer of scaffold
- Staining of Scaffold Revealed no Cell Migration
- Gap Junctions Formed Through Scaffold Membrane

Top Layer



Reverse Side

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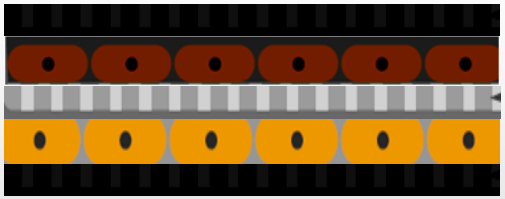
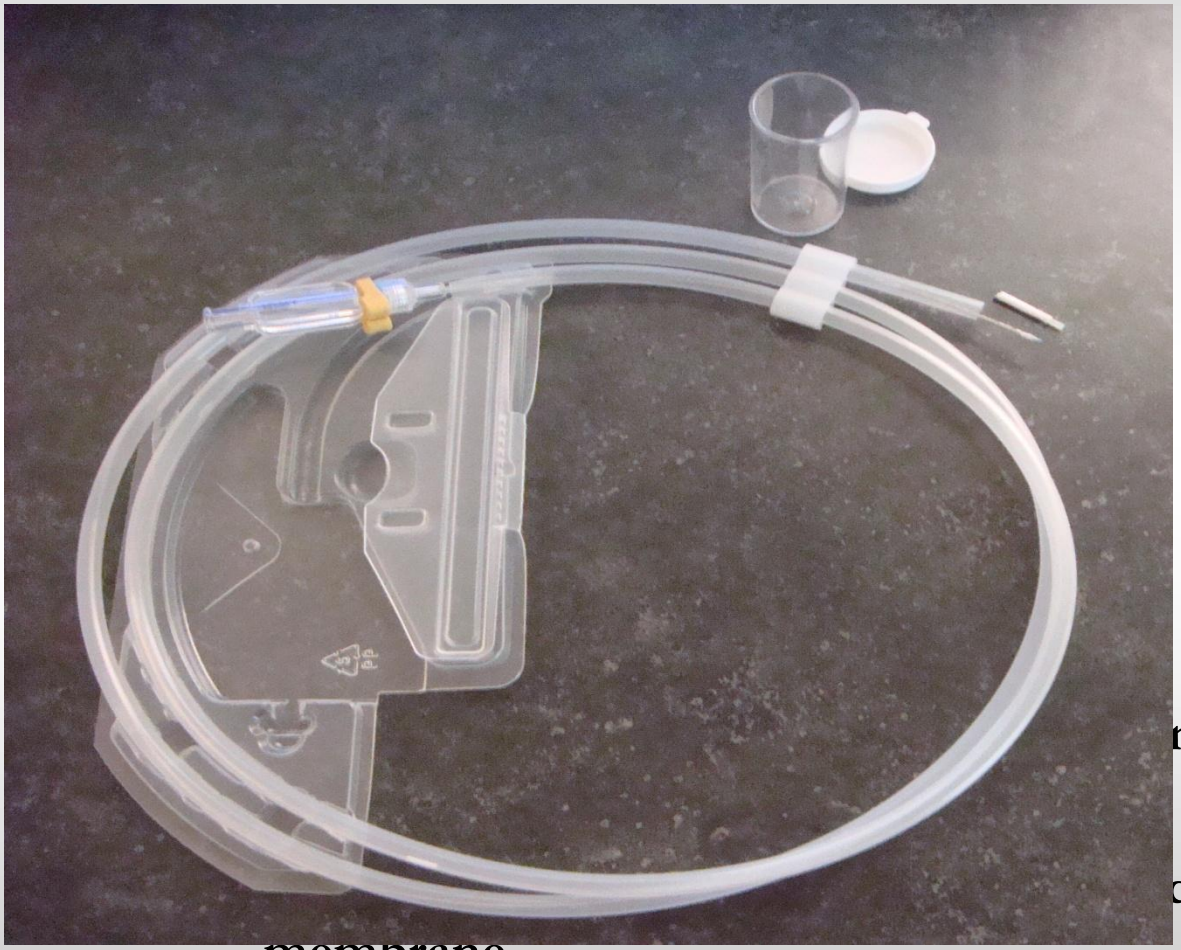
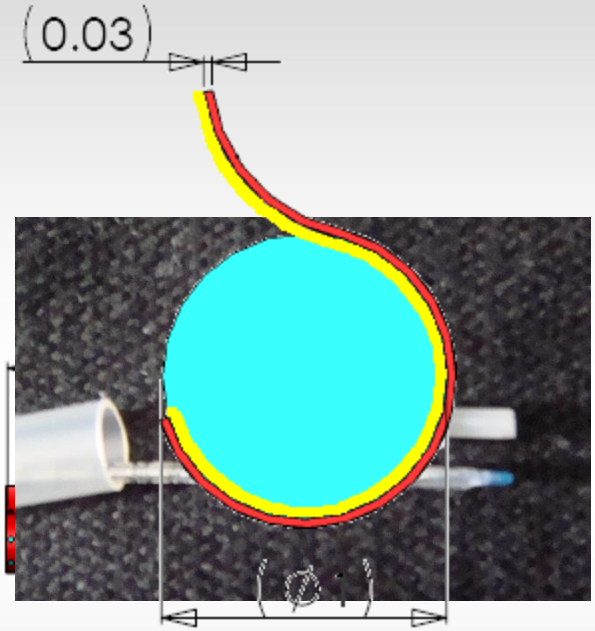


Final Design





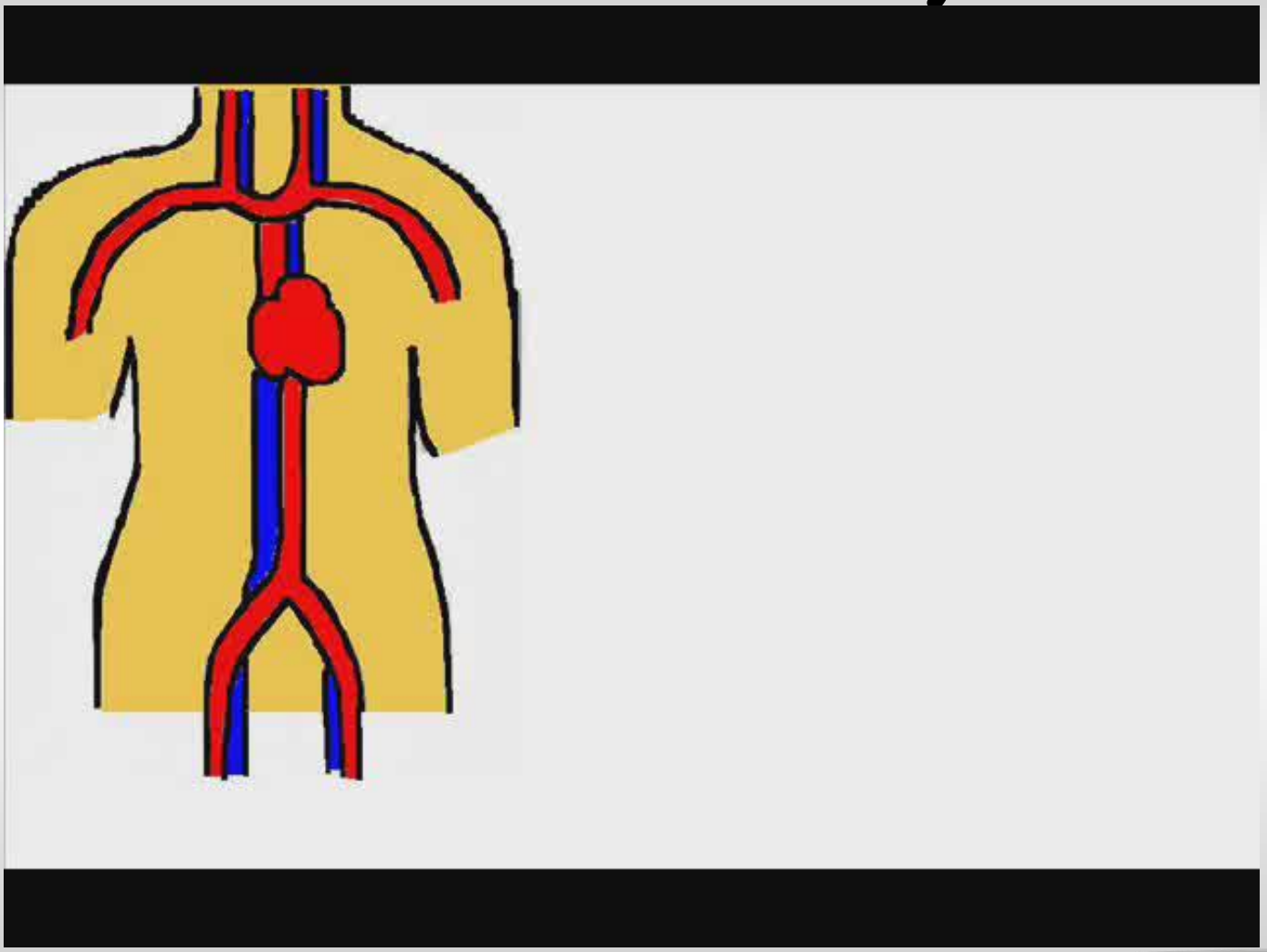
All units are in mm

n

der and the porous

membrane

Catheter Delivery



A Special Thanks To…

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Vicky Huntress
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Meghan Pasquali

George Pins
Michael Rosen
Jill Rulfs
Sharon Shaw
Lisa Wall

Questions?

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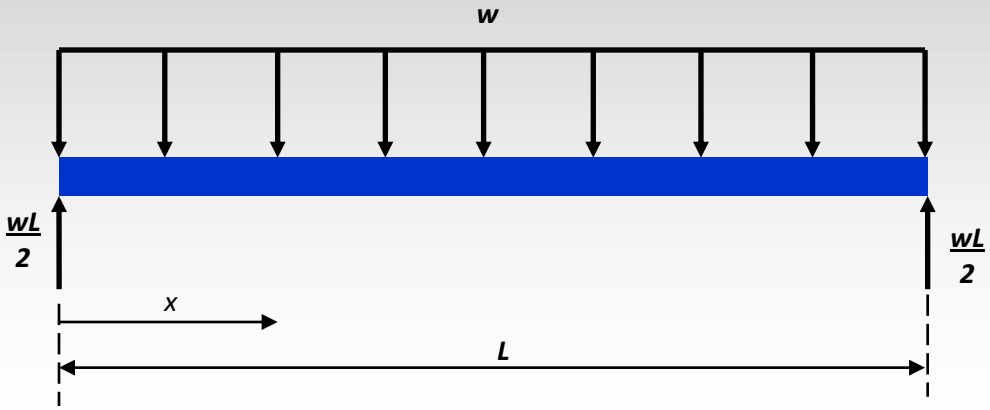
Future Recommendations

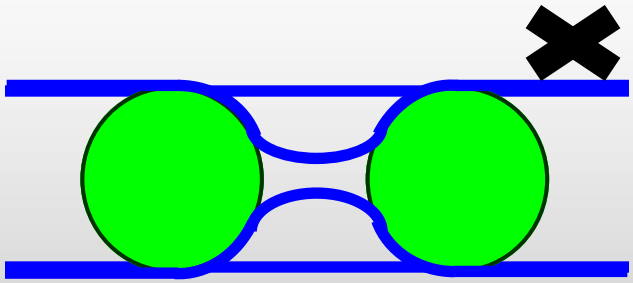
- In vitro studies proving cell viability in the final design configuration
- In vivo functional testing with canine or murine models
- Mechanical testing to ensure long term viability of scaffold in vivo
- Catheter delivery mechanism

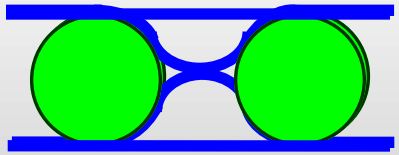
Deflection of a hMSC



$$\Delta_{max} = \frac{5wL^4}{384EI}$$

w =load per unit length
load=intramyocardial pressure=5mmHg[1]
L=length between fibers
E=Young's Modulus = 126±81Pa[2]
I=Moment of Inertia





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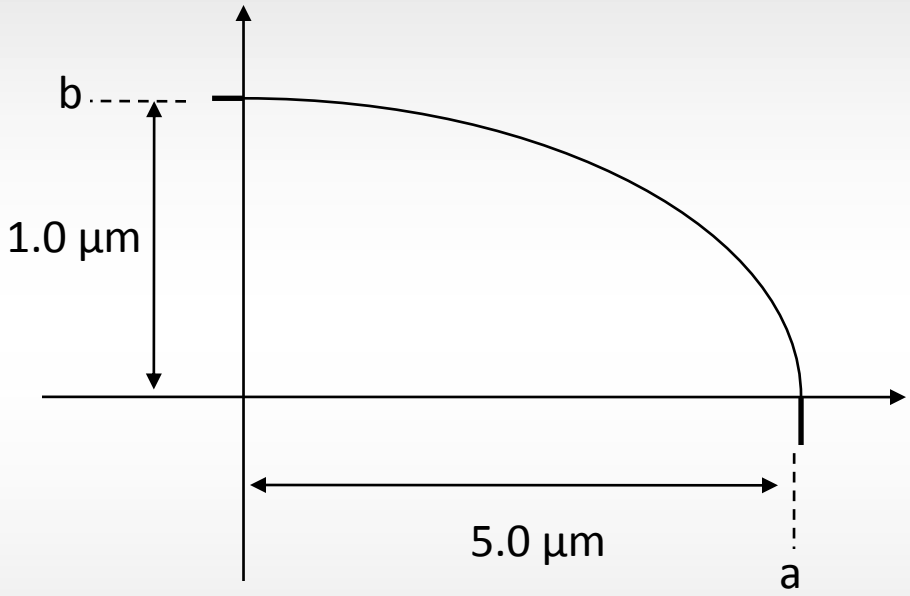
Supplemental Slides

Moment of Inertia



$$I = \frac{\pi a b^3}{16} \xrightarrow{\text{x } 4} I = \frac{\pi a b^3}{4}$$

Supplemental Slides

Area of a Cell

$$A_{cell} = \pi r^2$$

where r = 0.5μm

Surface Area needed for Scaffold

$$A_{cell} = \pi r^2 * 700{,}000$$

Need 700,000 cells to allow for a safety factor of 2

$A_{cell} = 55.0 mm^2$

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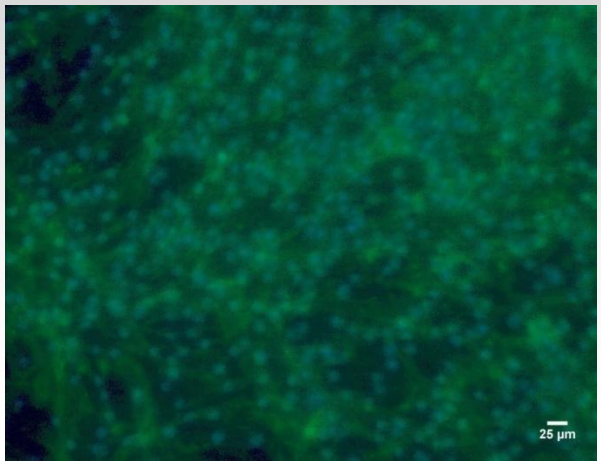
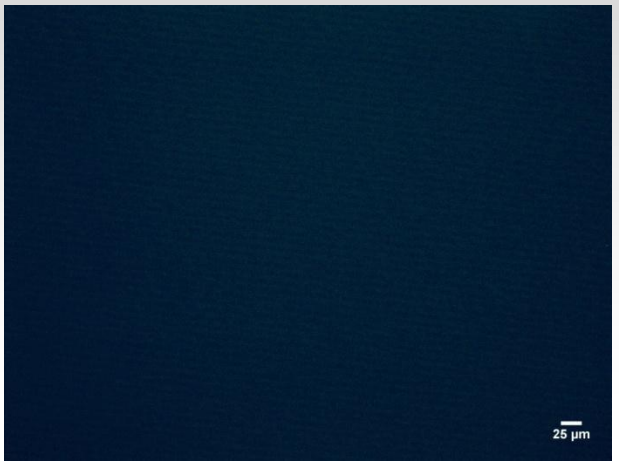
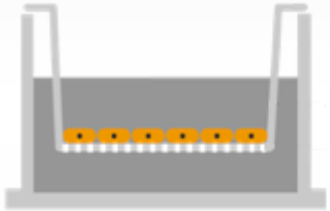
hMSC Migration Assay - Scraping

0.4 µm Pre-Scraping

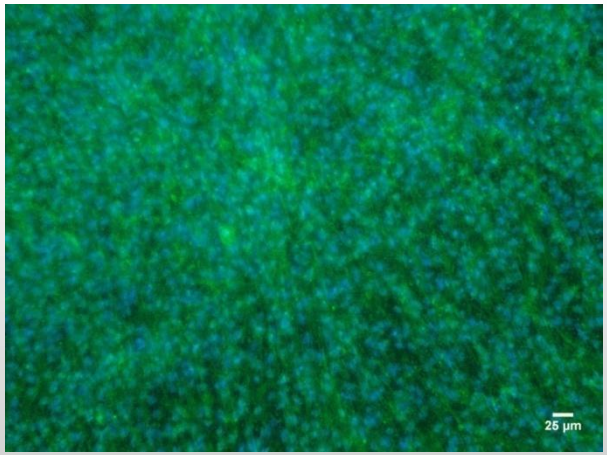


0.4 µm Post-Scraping





3.0 µm Pre-Scraping



3.0 µm Post-Scraping