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. Image available online from <http://www.ohiohealth.com/>
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. Image available online from <http://services.epnet.com/GetImage.aspx>
**Approach**

**Fence in Stem Cells!**

- **Stem Cell Migration is a large concern!**
  - HCN Gene on Human Mesenchymal Stem Cell (hMSC)
  - Modified hMSC + Cardiac Myocyte = Pacemaker
  - Communicate via Gap Junctions


Objective

• Mesenchymal Stem Cell Migration Inhibiting Scaffold
  • Prevent Migration of Stem Cells
  • Permanent and Durable
  • Allow Gap Junction Formation

• Minimally Invasive Delivery
Our Design

- hMSCs
- Electrospun Scaffold
- Solid Scaffold
- Right atrium
- Bundle branch block
- Left ventricle
- Right ventricle
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
Pore Size – Representative Images

8.0 Micron Pores

Actin Nuclei

0.4 Micron Pores

Actin Nuclei

3.0 Micron Pores

Actin Nuclei

Control

Actin Nuclei
Deflection of a hMSC

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

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Materials

• Currently used in cardiovascular applications
  – Polyurethane
  – Dacron
  – ePTFE
  – Nitinol
• Good mechanical properties
• Biocompatibility and hemocompatibility
• Corrosion and wear resistance

Manufacturing Process

- **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

Objectives

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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

Gap Junctions
Nuclei
hMSC Migration – Polyurethane Scaffold

- hMSCs seeded on top layer of scaffold

- Staining of Scaffold Revealed no Cell Migration

- Gap Junctions Formed Through Scaffold Membrane

![Image of scaffold with labeled layers: Top Layer and Reverse Side with Actin and Nuclei staining.](image)
Objectives

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  • Allow Gap Junction Formation ✓

• Minimally Invasive Delivery
Final Design

- **2 Part Scaffold**
  - Solid cylinder (In Blue)
  - Provides structural support
  - Diameter: Catheter sizes available
  - Length: surface area for 700K cells

- **Porous membrane (In Red)**
  - Surrounds solid cylinder
  - Thickness: allows gap junction formation
  - Pore size: prevent migration

Contains cells in between the solid cylinder and the porous membrane

All units are in mm
Catheter Delivery
A Special Thanks To…

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<tbody>
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Questions?
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

\[ \Delta_{\text{max}} = \frac{5wL^4}{384EI} \]

- \( w \) = load per unit length
- load = intramyocardial pressure = 5mmHg
- \( L \) = length between fibers
- \( E \) = Young’s Modulus = 126±81Pa
- \( I \) = Moment of Inertia

Supplemental Slides

Moment of Inertia

\[ I = \frac{\pi ab^3}{16} \]

\[ \times 4 \]

\[ I = \frac{\pi ab^3}{4} \]
Supplemental Slides

Area of a Cell

\[ A_{\text{cell}} = \pi r^2 \]

where \( r = 0.5 \mu \text{m} \)

Surface Area needed for Scaffold

\[ A_{\text{cell}} = \pi r^2 \times 700,000 \]

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

\[ A_{\text{cell}} = 55.0 \text{mm}^2 \]
hMSC Migration Assay - Scraping

0.4 μm Pre-Scraping

3.0 μm Pre-Scraping

0.4 μm Post-Scraping

3.0 μm Post-Scraping