Biomaterials and Their Use in Tissue Engineering:
Treating Cardiovascular Disease

Karen L. Christman, Ph.D.
Department of Bioengineering
Sanford Consortium for Regenerative Medicine
University of California, San Diego
SLA 2013 Annual Conference
June 10, 2013

Disclosure: Co-Founder of Ventrix, Inc.
• **Biomaterial**: material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body (D. F. Williams 1999)

• **Tissue Engineering**: is the regeneration and remodeling of tissue in vivo for the purpose of repairing, replacing, maintaining or enhancing organ function, and the engineering and growing of functional tissue substitutes in vitro for implantation in vivo as a biological substitute for damaged or diseased tissues and organs (NIH Bioengineering Consortium (BECON) symposium on tissue engineering, 2001)
Myocardial Infarction

- Leading cause of death in the western world
- 40% of those who experience an MI in a given year will die of it
- Two-thirds of heart attack patients do not make a complete recovery
- Heart transplantation and LVADs are only successful treatments for end-stage heart failure
Myocardial infarction

Death of cardiomyocytes

Scar tissue formation

Aneurysmal thinning

Negative left ventricular remodeling

Decreased pumping capacity
Cellular Cardiomyoplasty

- Injection of viable cells to replace necrotic cardiomyocytes
- Liquid solutions of cell culture media or saline
- Skeletal myoblasts, fibroblasts, cardiomyocytes, adult embryonic stem cells, iPSCs, cardiac stem cells
- Low cell transplant survival
- Paracrine mechanism of action

Figure 1: Biomaterial Approaches to Treatment of MI

There are 3 strategies currently being examined for the treatment of myocardial infarction (MI): left ventricular restraints (not shown), cardiac patches, and injectable biomaterials. Cardiac patches and injectable materials can be either used as acellular scaffolds (A and D), or delivery vehicles for cells (B and E) and/or biological molecules (C and F).
Injectable Biomaterials

- Injectable Scaffold
  - Acellular or cellular
- Current materials do not mimic the native cardiac ECM
- Few have translated to catheter delivery

Dai W, et al. JACC 2005
Christman KL et al. JACC 2004
Davis ME, et al.. Circulation 2005
Landa N, et al., Circulation 2008
Ideal Scaffold Requirements

- Degradable/ Can be Remodeled
- Promote Cell Influx
- Mimic native cardiac extracellular matrix (ECM)
  - Biochemical composition
  - Structural properties
- Minimally invasive catheter delivery
  - Injectable through 27G needle
  - Gelation in-vivo (at 37°C)
  - Appropriate gelation kinetics
Decellularization

- Removal of cells from tissue
- Numerous FDA cleared devices
- Implanted in >2 million people
  - Small intestine submucosa
  - Pericardium
- Biocompatible
- Tissue Engineering scaffolds
- Injectable?

Decellularization Process

1. Starting material
2. H2O
3. SDS solution
4. H2O
Decellularized Myocardium

Decellularized ECM

Scale bar: 100 um

Singelyn, DeQuach et al. Biomaterials, 2009
Injectable Matrix Processing

1. Lyophilize
2. Mill
3. Aliquot
Injectable Matrix Processing

8

9

Pepsin

HCl
• Biochemical composition should provide cues of native cardiac ECM

• Contains numerous ECM peptide fragments

• 23 ± 5 µg GAG per mg of matrix

Mass Spec:
- Fibrinogen
- Collagen I
- Collagen III
- Collagen IV
- Collagen V
- Collagen VI
- Lumican
- Perlecan
- Fibronectin
- Fibulin
- Laminin
- Elastin

Singelyn et al, Biomaterials 2009
Myocardial Matrix Hydrogel

Self-assembles into a nanofibrous gel at physiological conditions

Singelyn et al, *Biomaterials* 2009
Rat MI Model

Myocardial Infarction (MI) | Injection of Saline or Myocardial Matrix | Evaluation of LV with MRI

2 wks | 4 wks
Preservation of Cardiac Function

Singelyn et al., JACC, 2012

* $p < 0.05$ compared to baseline, $\S p = 0.054$
Cell Infiltration 1 Week Post-Injection

In Vivo Catheter Trial – Porcine Model

Biotin labeled Myocardial Matrix

Percutaneous Delivery

No Myocardial Matrix observed in other organs

Porcine MI Model

- Myocardial matrix improved global cardiac function
- Decreased end-systolic and end-diastolic volumes

Porcine MI Model

- Improved regional function
- Evidence of neovascularization and cardiac regeneration at endocardium
- Reduced infarct fibrosis

Myocardial Matrix

In vitro Stem Cell Studies

Matrix Alone

Matrix + Stem Cells

Matrix + Growth Factors
Growth Factor Delivery with ECM Hydrogel

**Myocardial Infarction (MI)**

1 week

**Injection**

5 days

ECM hydrogel, collagen, or saline +/- bFGF

**IHC**

Growth Factor Delivery with ECM Hydrogel

- ECM hydrogel retains growth factors through sulfated glycosaminoglycans
- Increased growth factor retention
- Increased neovascularization

Injectable ECM Hydrogels

Matrix Alone

Matrix + Stem Cells

Matrix + Growth Factors

In vitro Stem Cell Studies
CPCs on Myocardial Matrix

- Mike Davis & Kristin French, Bioengineering, Emory
- Mouse c-kit+ cardiac progenitor cells

Injectable Myocardial Matrix

- Compatible with transendocardial catheter delivery
- Improves cardiac function upon injection post-MI
- Biocompatible, hemocompatible, and no changes in arrhythmias
- Potential for enhancing cell and growth factor therapies
- Currently undergoing GMP manufacturing and first-in-human studies anticipated in late 2013 – beginning 2014
Acknowledgements

Christman Lab
Todd Johnson
Jean Wang
Sonya Seif-Naraghi, PhD
Adam Young
Nikhil Rao
Sophia Harrison
Greg Grover, PhD
Rebecca Braden

Former Lab Members
Jennifer Singelyn, PhD
Jessica DeQuach, PhD
Kevin Chung, MS
Priya Sundaramurthy, MS
Kristina Javor, MS
Aubrey Smith
Stephen Lin, MS
Airong Song, PhD
Pam Schup-Magoffin
Aboli Rane, PhD

Collaborators
Nabil Dib, MD
Anthony DeMaria, MD

BDS
Jonathan Wong
Mark Martin

Funding

National Heart Lung and Blood Institute
NIH Director’s NEW INNOVATOR AWARD
American Heart Association
The NIH Common Fund

UCSD Jacobs Department of Bioengineering