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

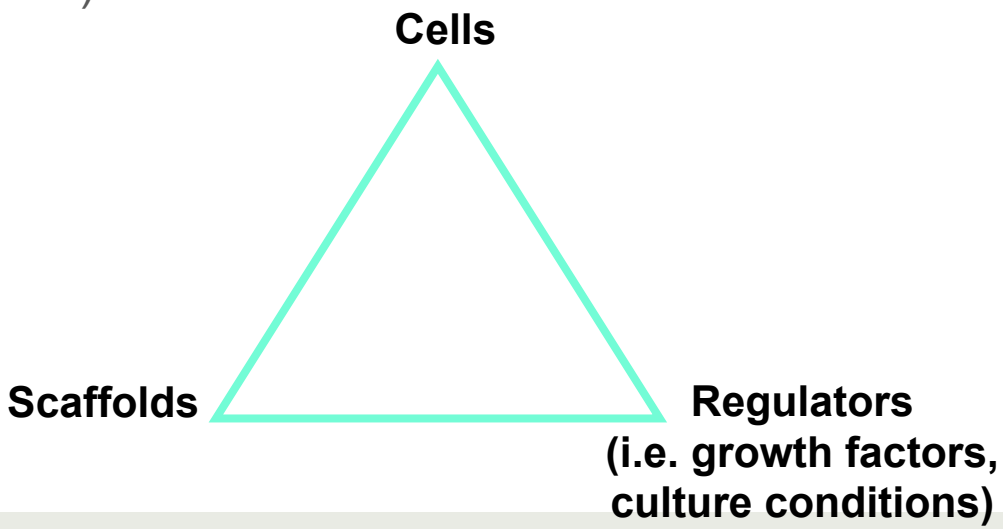
SLA 2013 Annual Conference

June 10, 2013

Disclosure: Co-Founder of Ventrix, Inc.

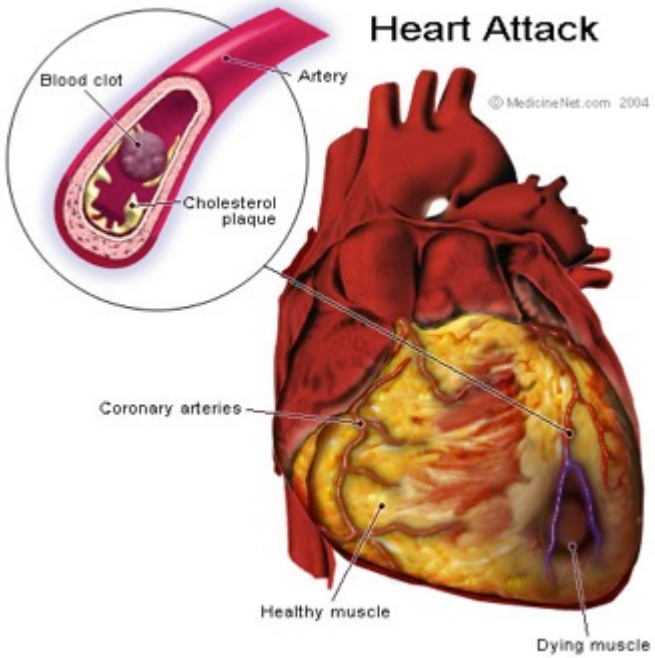
Definitions

- **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)



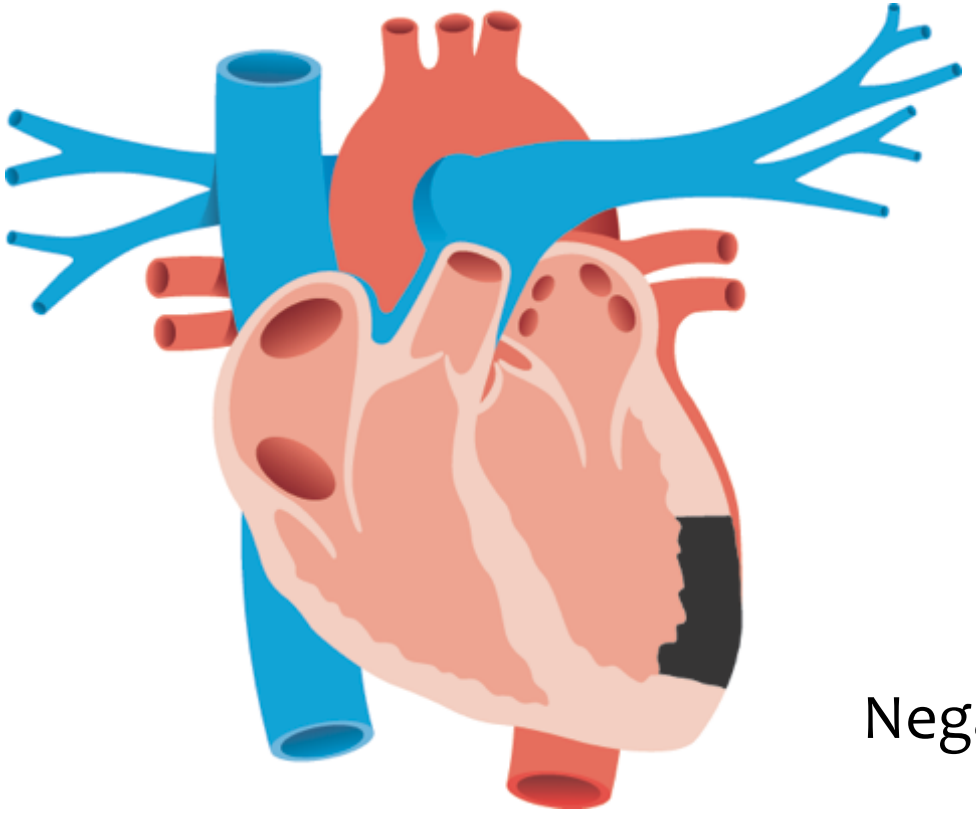
Myocardial Infarction

- 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



Modified from MedicineNet.com

Myocardial Infarction & Heart Failure



Myocardial infarction

↓

Death of cardiomyocytes

↓

Scar tissue formation

↓

Aneurysmal thinning

↓

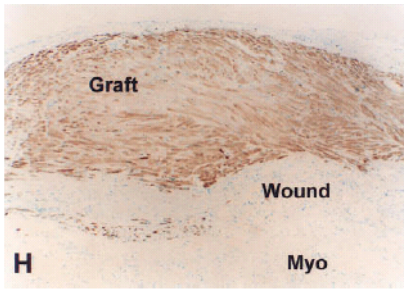
Negative left ventricular remodeling

↓

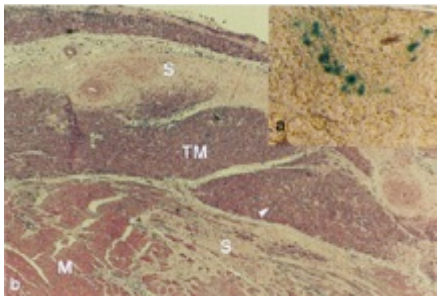
Decreased pumping capacity

Cellular Cardiomyoplasty

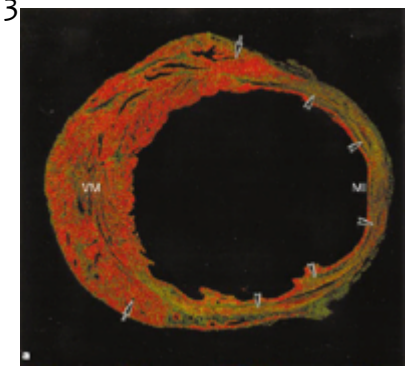
1



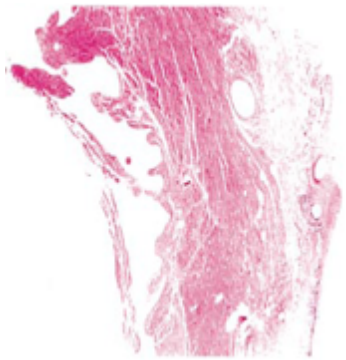
2



3



4



- 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

[1]Murry CE, et al. *J Clin Invest*. 1996. [2]Li RK, et al. *Ann Thorac Surg* 1996. [3]Orlic D, et al. *Nature* 2001. [4]Min JY, et al. *J Appl Physiol.* 2002.

Biomaterials for Treating MI

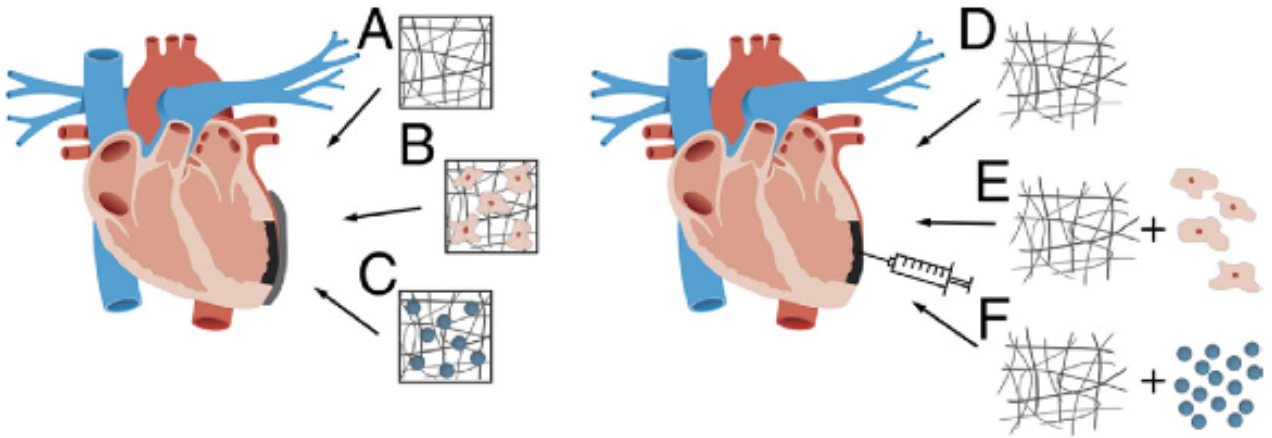
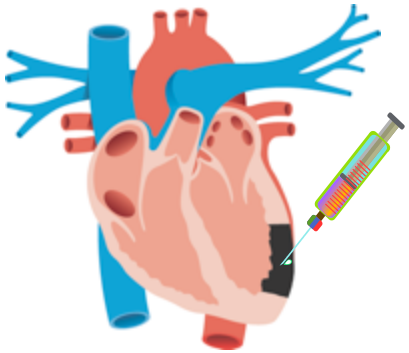


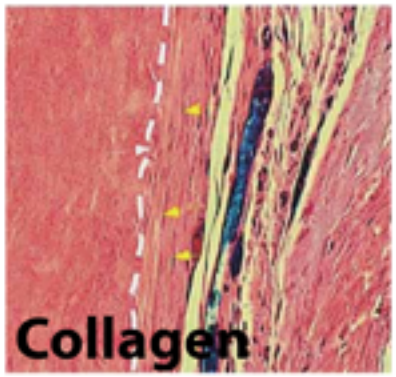
Figure 1 **Biomaterial Approaches to Treatment of MI**

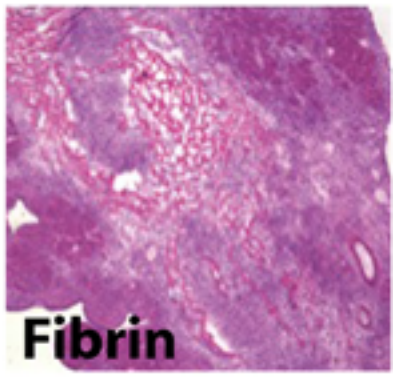
There are 3 strategies currently being examined for the treatment of myocardial infarction (MI): left ventricular restraints (not shown), cardiac patches, and injectable biomaterials. Cardiac patches and injectable materials can be either used as acellular scaffolds **(A and D)**, or delivery vehicles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

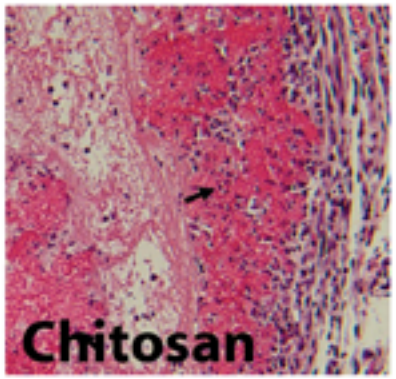
Rane & Christman, JACC, 2011

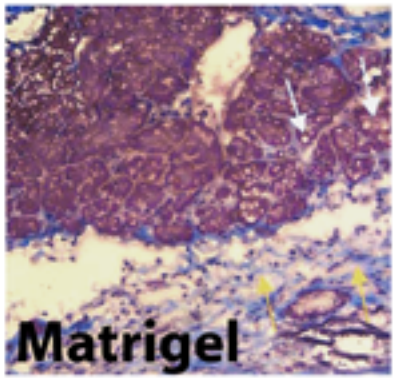
Injectable Biomaterials

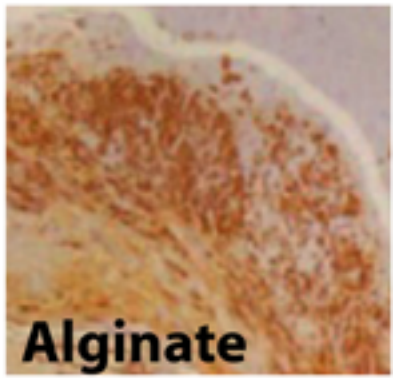


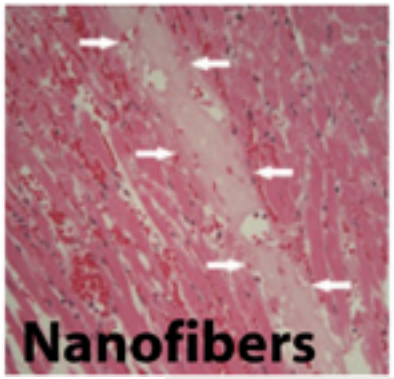


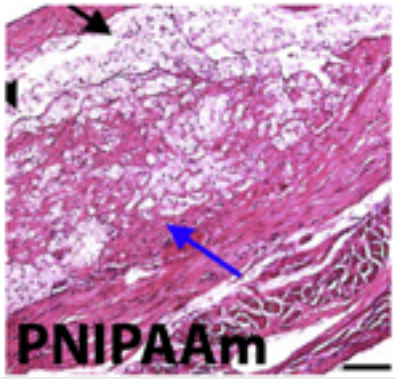


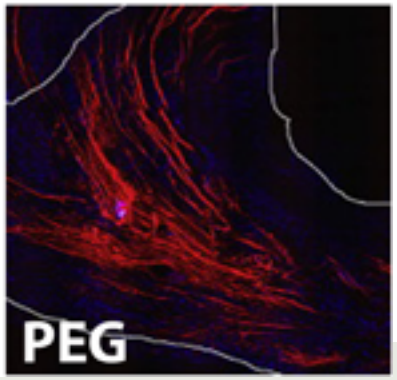










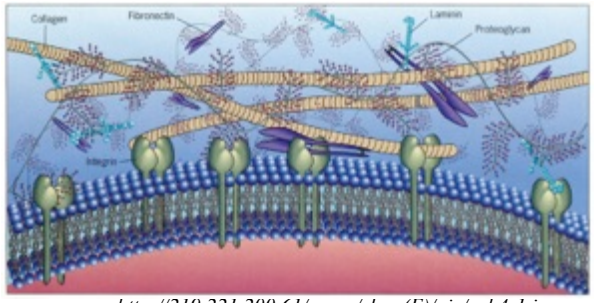


- Injectable Scaffold
  - Acellular or cellular
- Current materials do not mimic the native cardiac ECM
- Few have translated to catheter delivery

Dai W, et al. JACC2005
Christman KL et al. JACC 2004
Kofidis T, et al. J Thorac Card Surg 2004
Lu WN,, et al. Tissue Eng Part A 2008
Davis ME, et al.. Circulation 2005
Landa N, et al.. Circulation 2008
Dobner S, et al. J Card Fail 2009
Fujimoto KL, et al. Biomaterials 2009

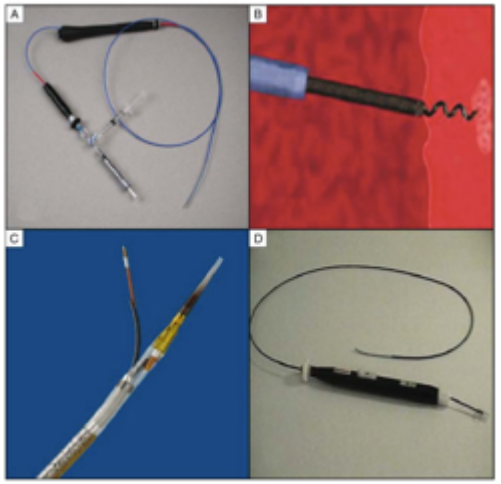
Ideal Scaffold Requirements

- Degradable/ Can be Remodeled
- Promote Cell Influx



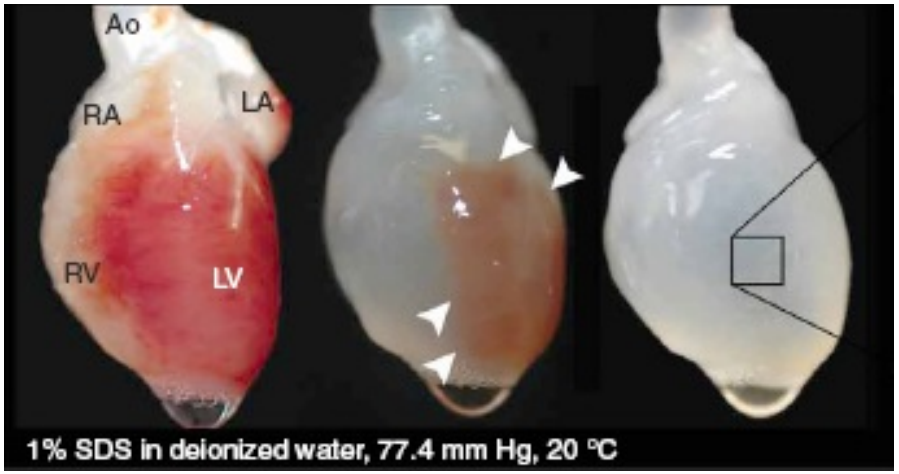
http://219.221.200.61/ywwy/zbsw(E)/pic/ech4-1.jpg

- 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



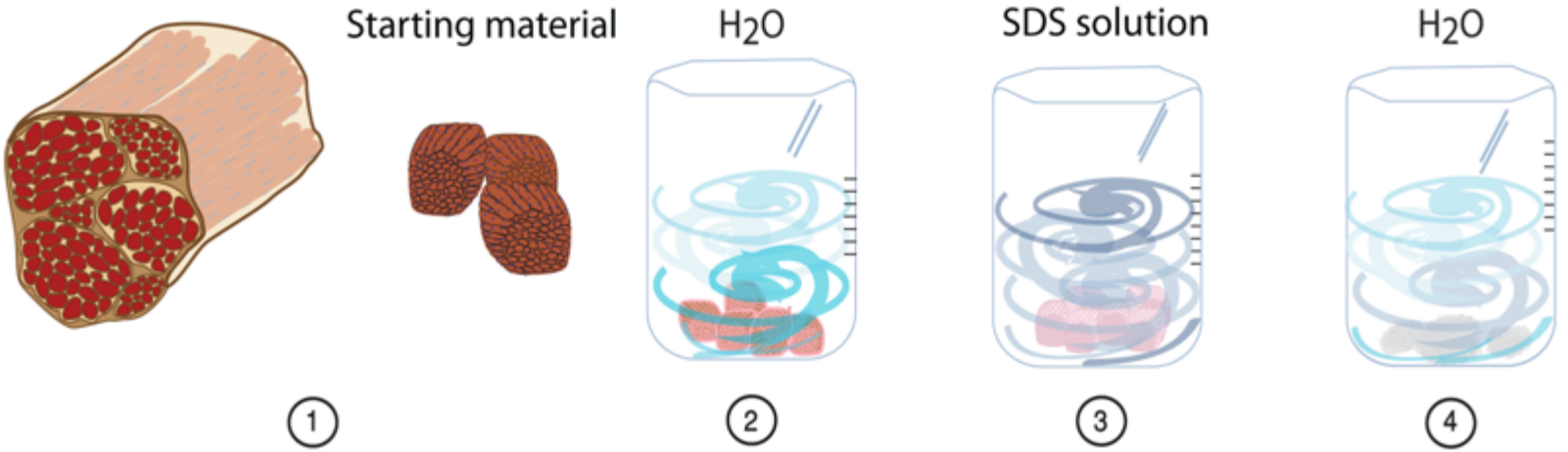
Decellularization

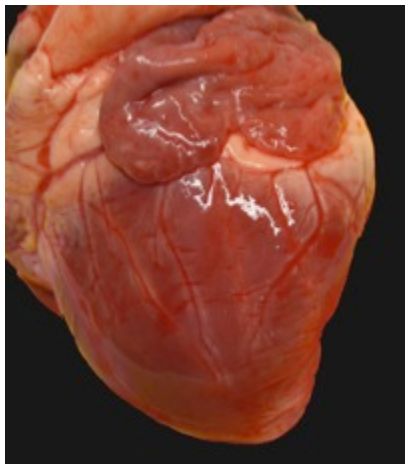
- Removal of cells from tissue
- Numerous FDA cleared devices
- Implanted in >2 million people
  - Small intestine submucosa
  - Pericardium
- Biocompatible
- Tissue Engineering scaffolds
- Injectable?

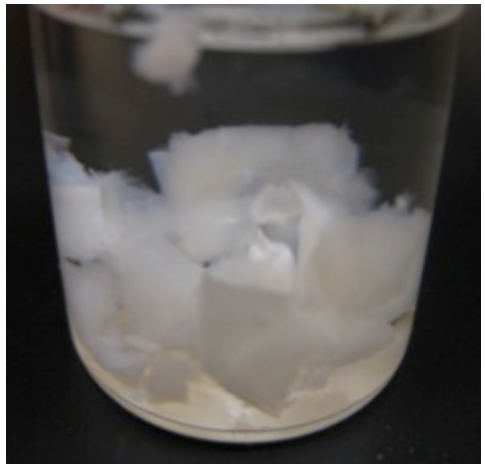


Ott et al, *Nature Medicine* 2008

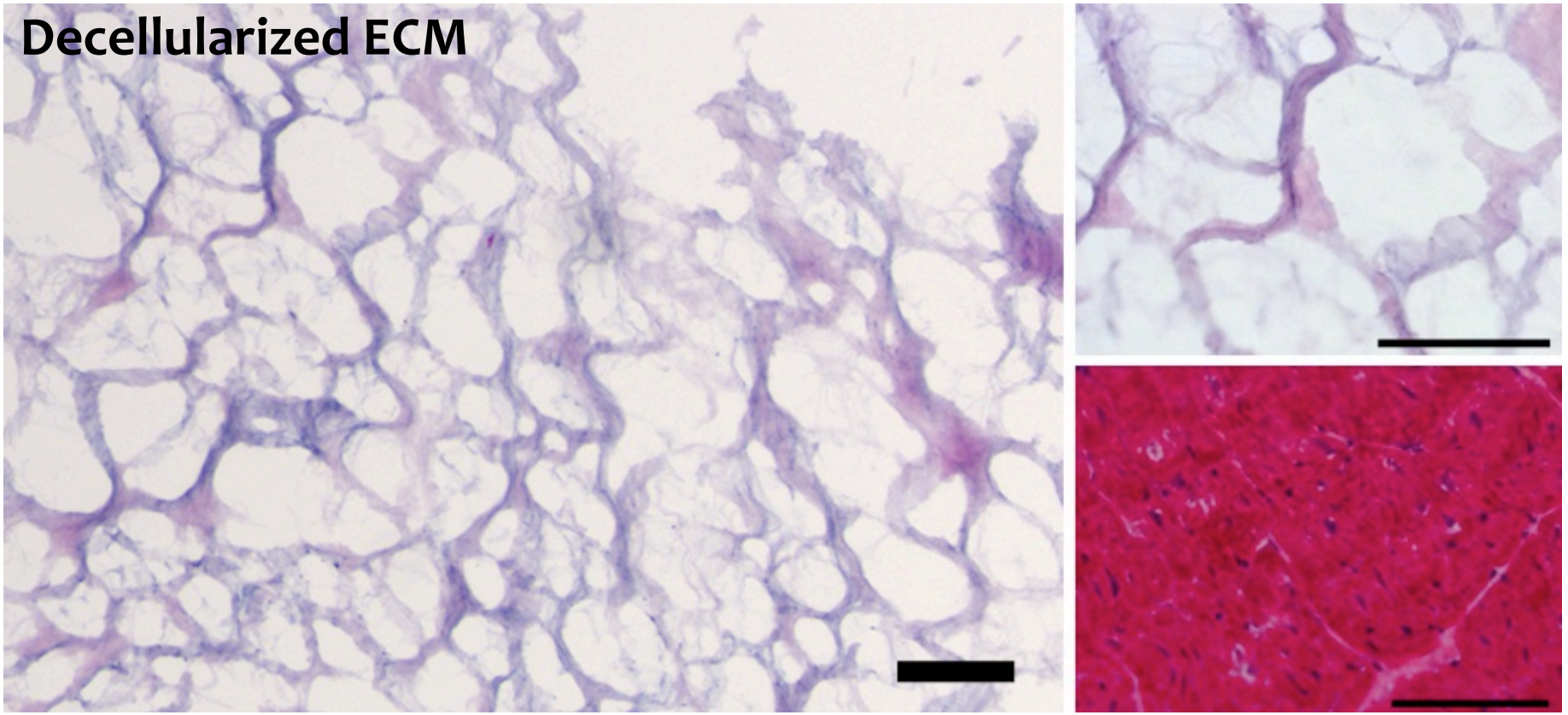
Decellularization Process







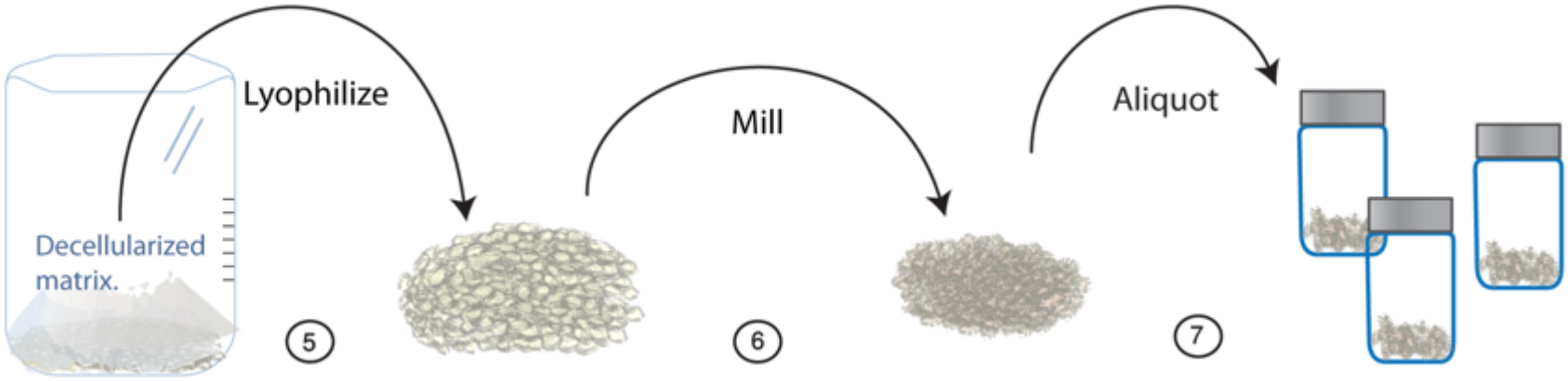
Decellularized Myocardium

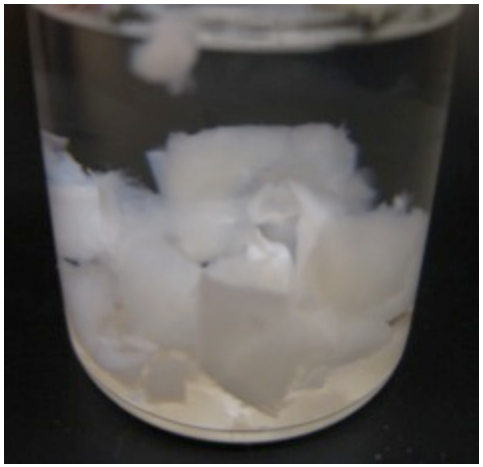


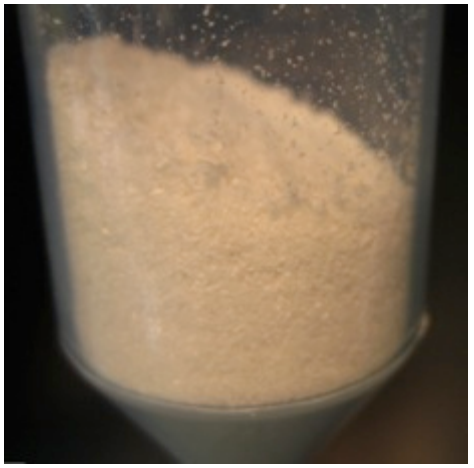
Scale bar: 100 um

Singelyn, DeQuach et al. Biomaterials, 2009

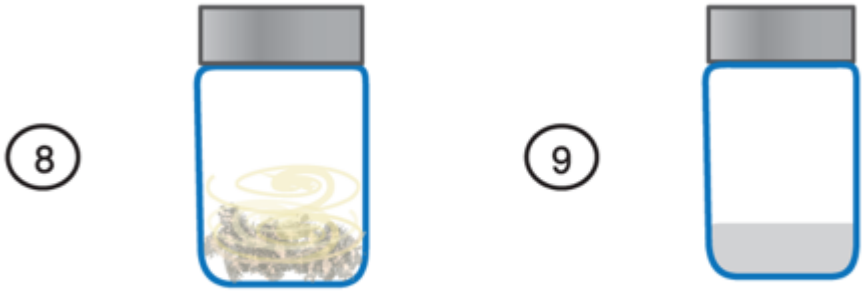
Injectable Matrix Processing

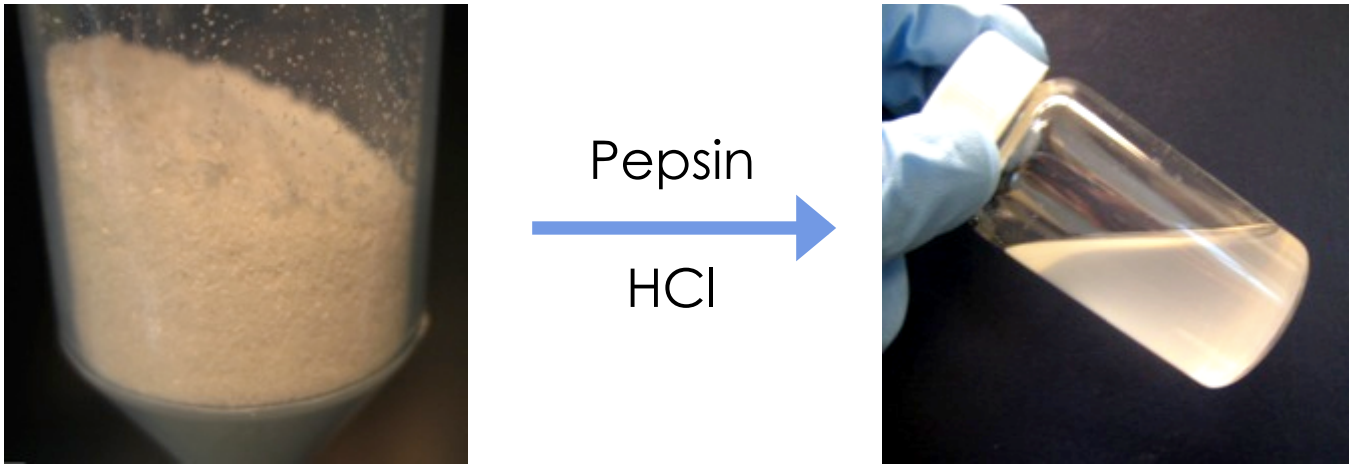






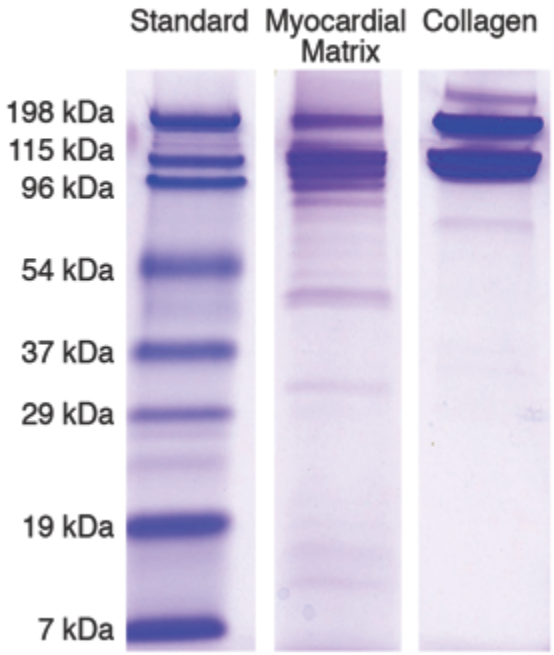
Injectable Matrix Processing





Biochemical Composition

- Biochemical composition should provide cues of native cardiac ECM
- Contains numerous ECM peptide fragments
- 23 ± 5 μg GAG per mg of matrix



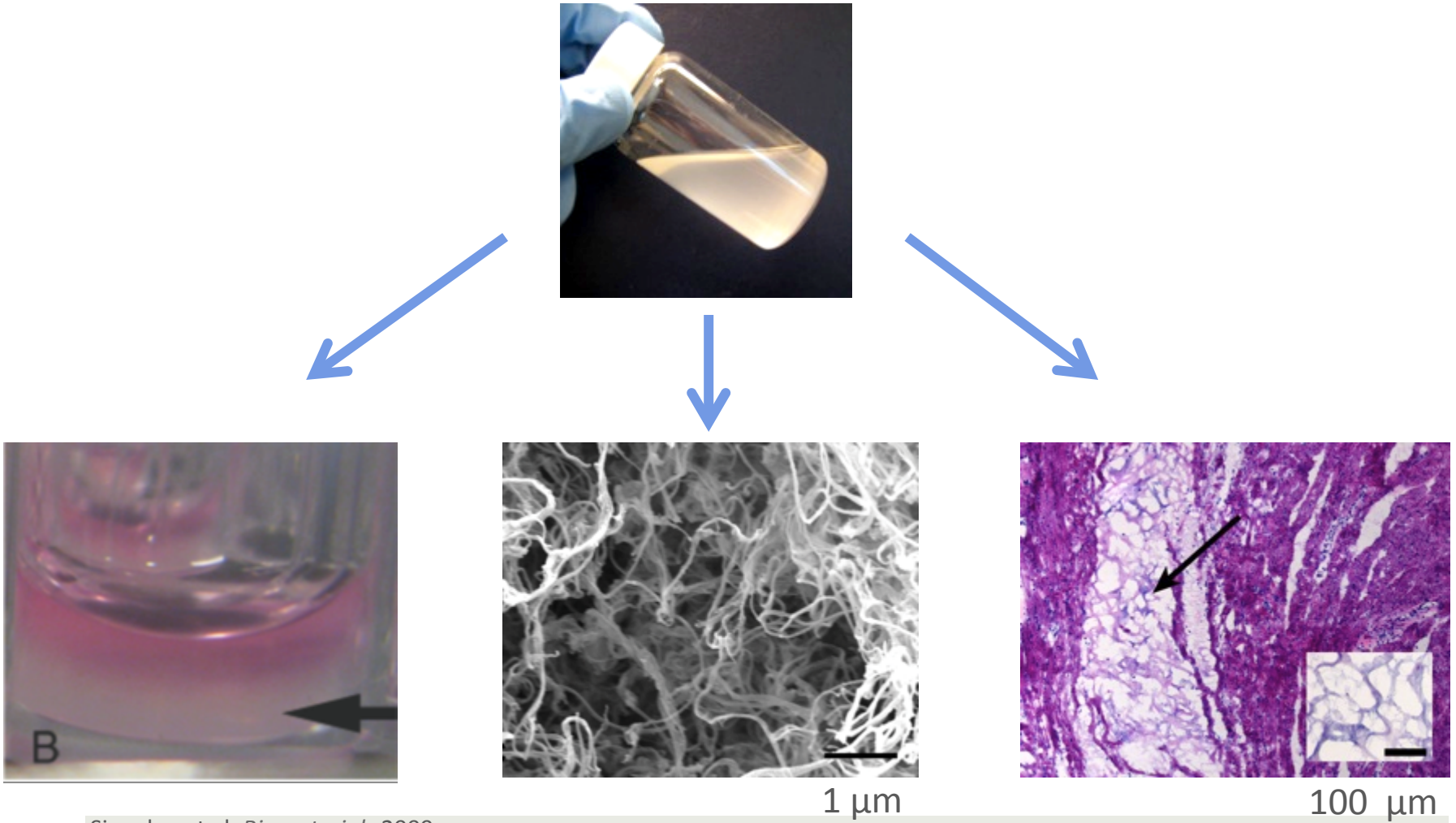
Mass Spec:

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

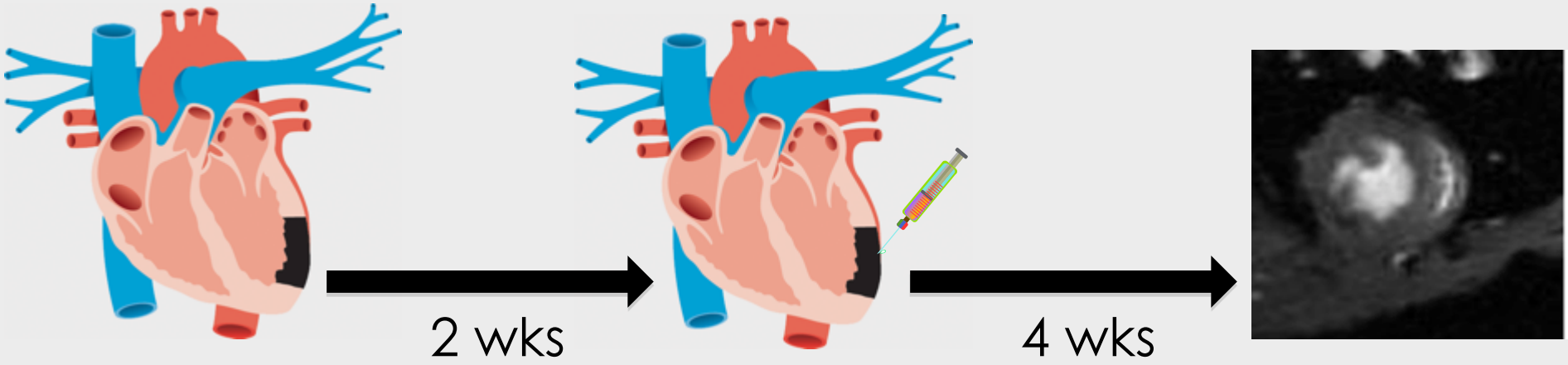
Self-assembles into a nanofibrous gel at physiological conditions



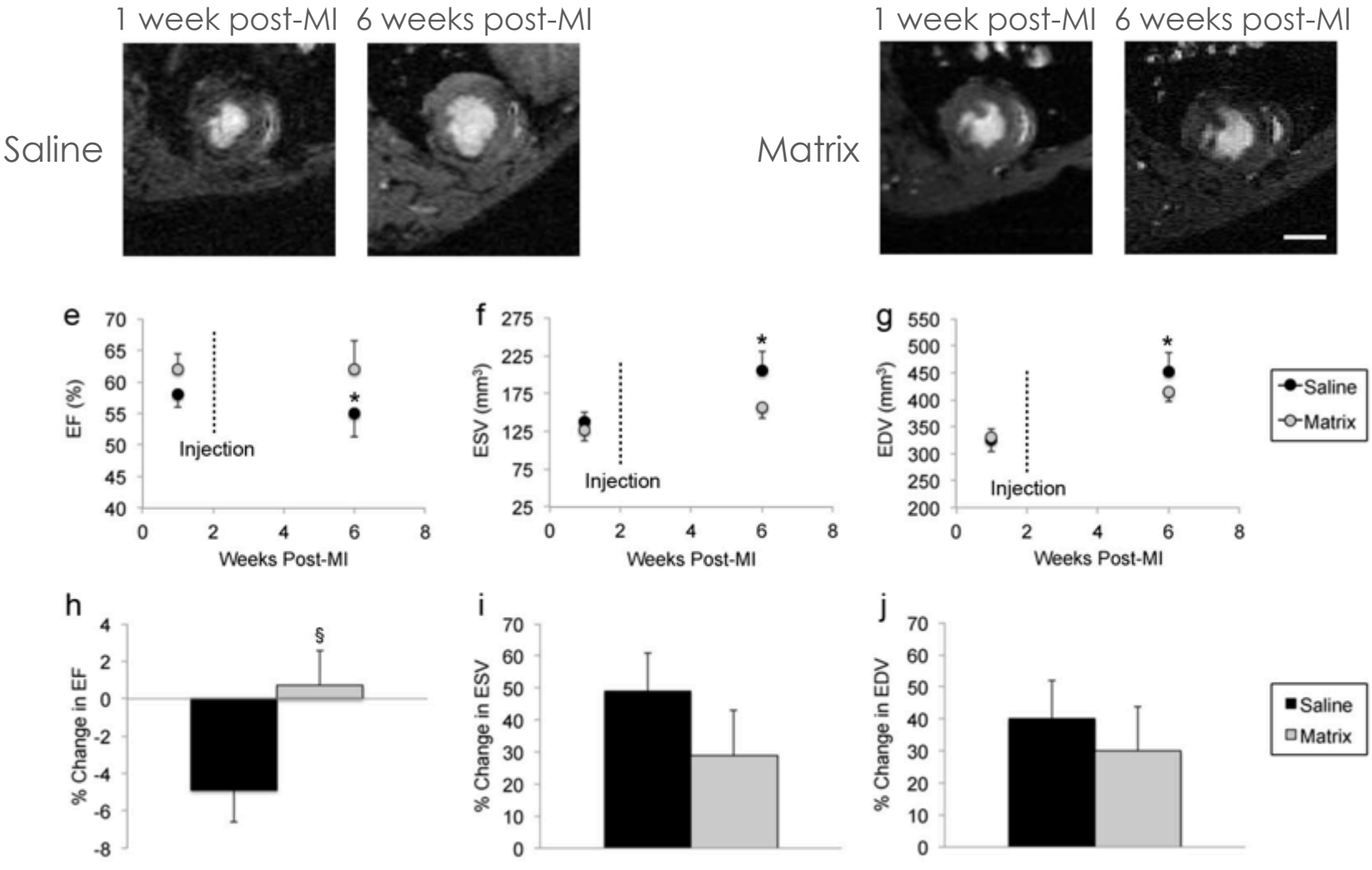
Singelyn et al, *Biomaterials* 2009

Rat MI Model

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



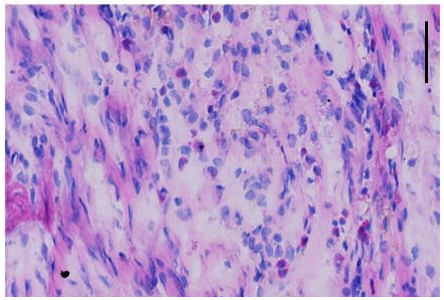
Preservation of Cardiac Function

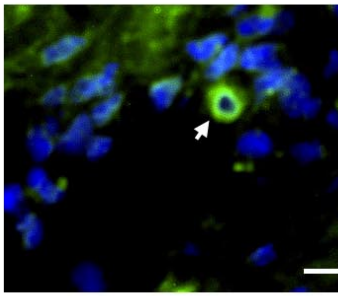


*p < 0.05 compared to baseline, §p = 0.054

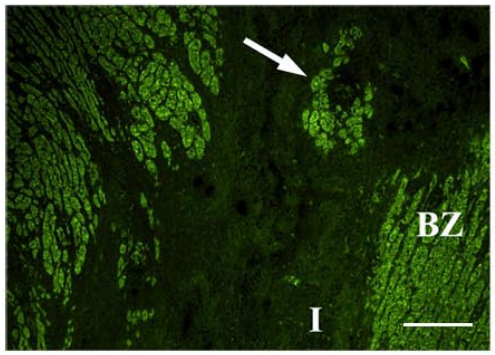
Singelyn et al, JACC, 2012

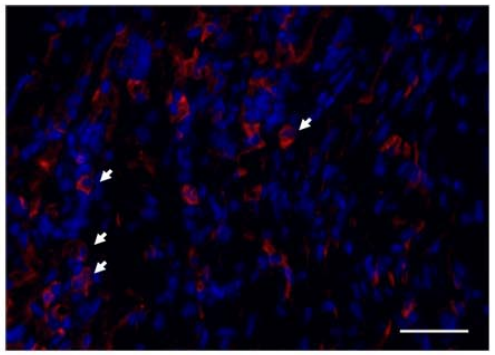
Cell Infiltration 1 Week Post-Injection

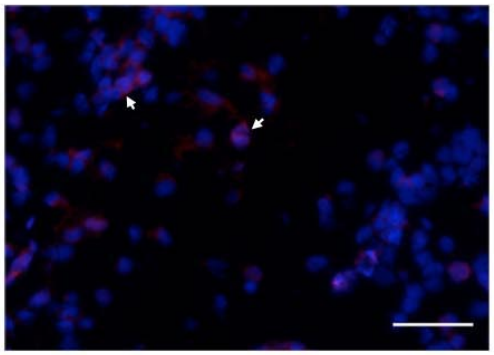


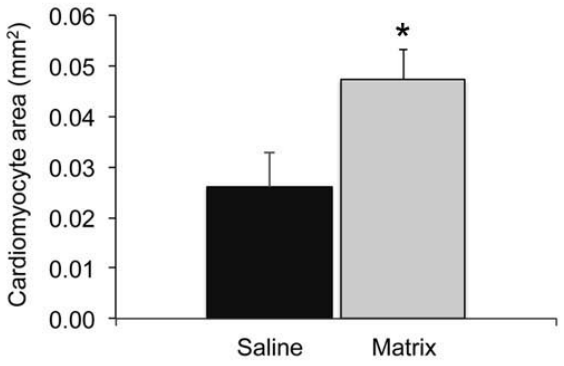


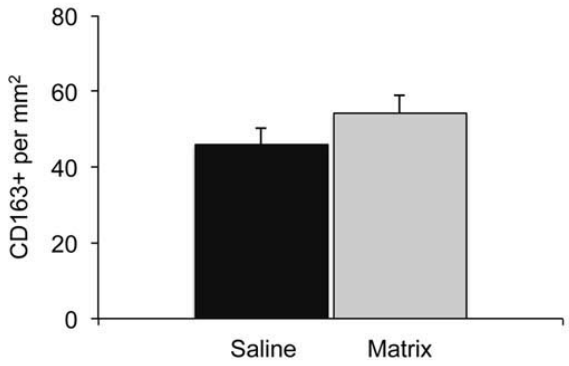
C-kit

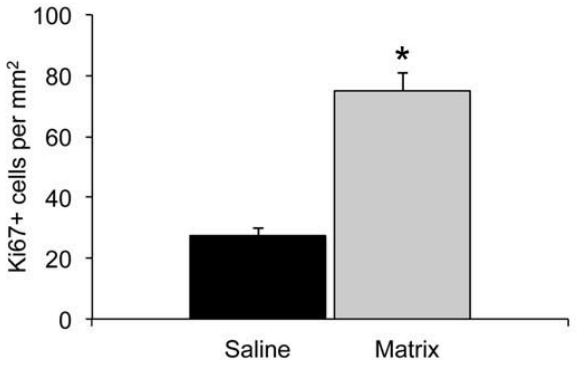






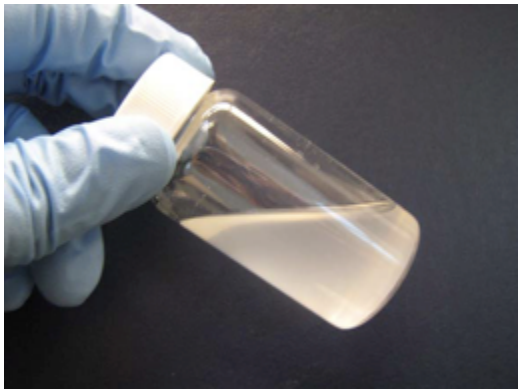




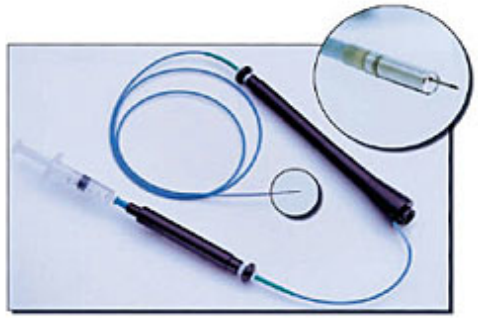


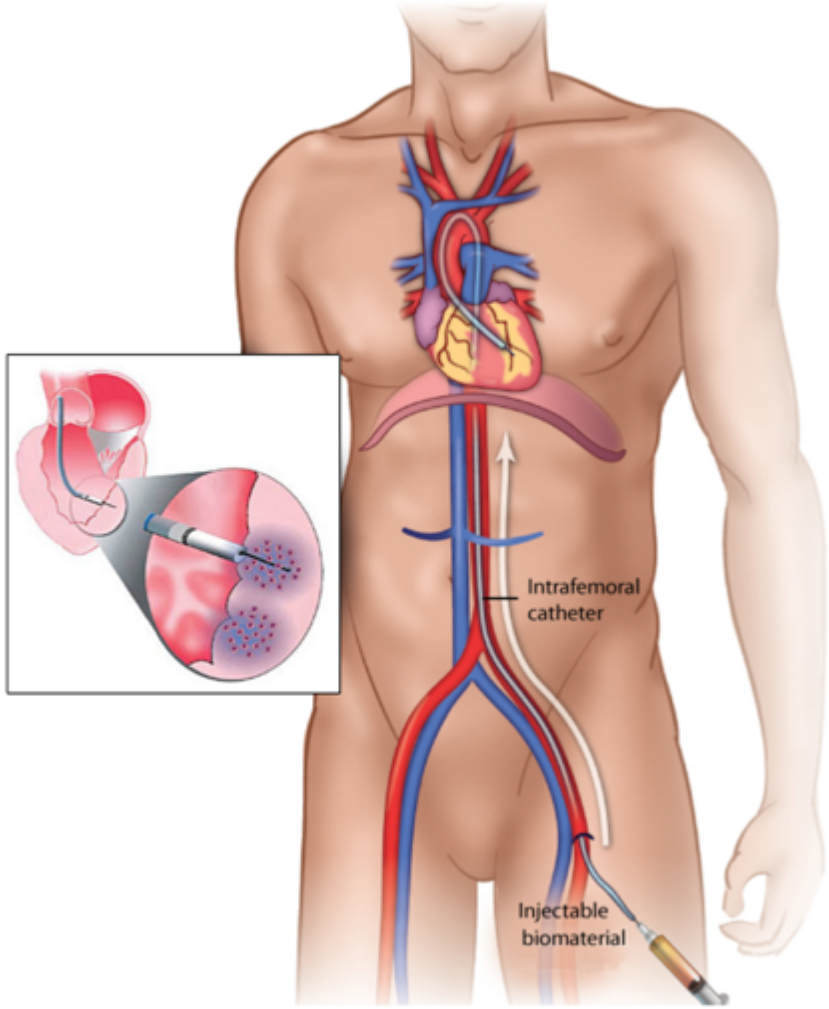
Singelyn et al, *JACC,* 2012.

In Vivo Catheter Trial – Porcine Model



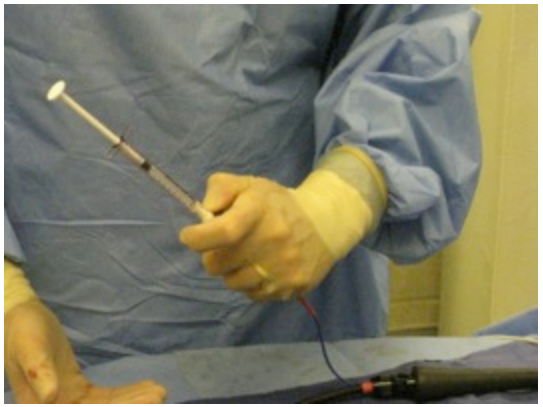
Biotin labeled Myocardial Matrix

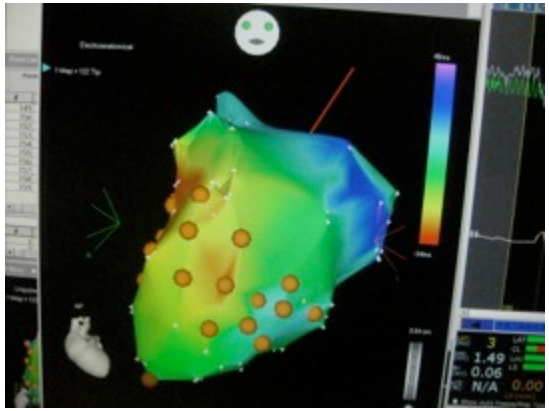


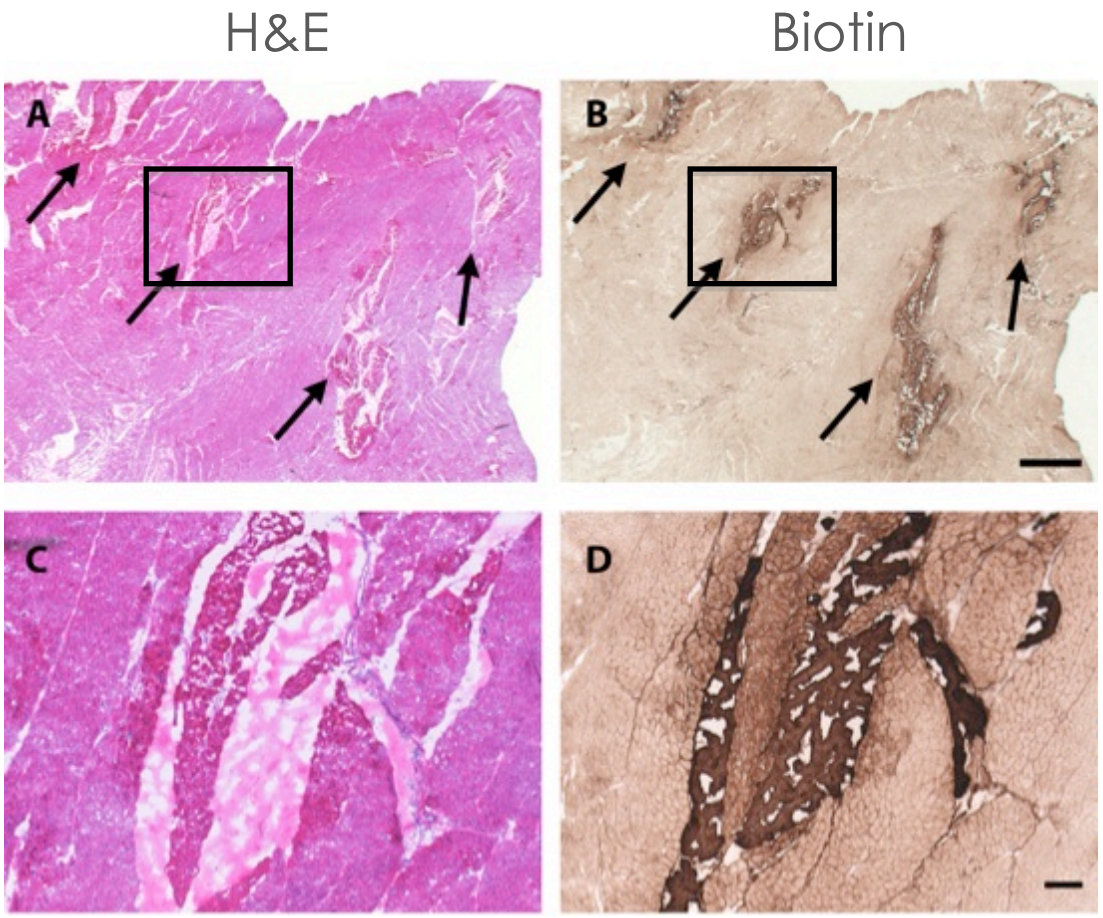


Singelyn et al, *JACC,* 2012.

Percutaneous Delivery





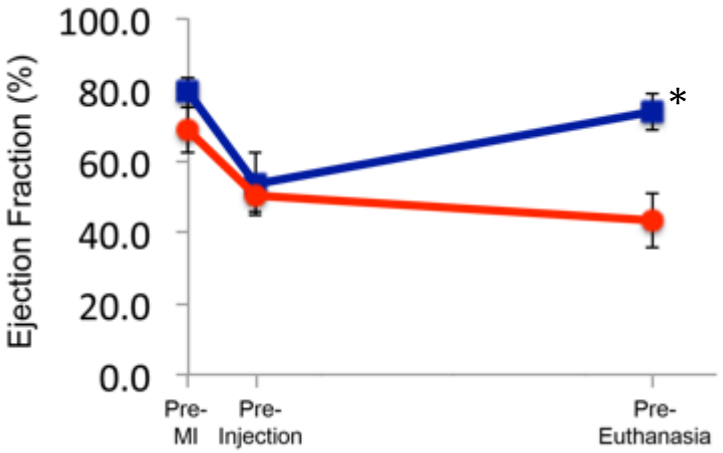


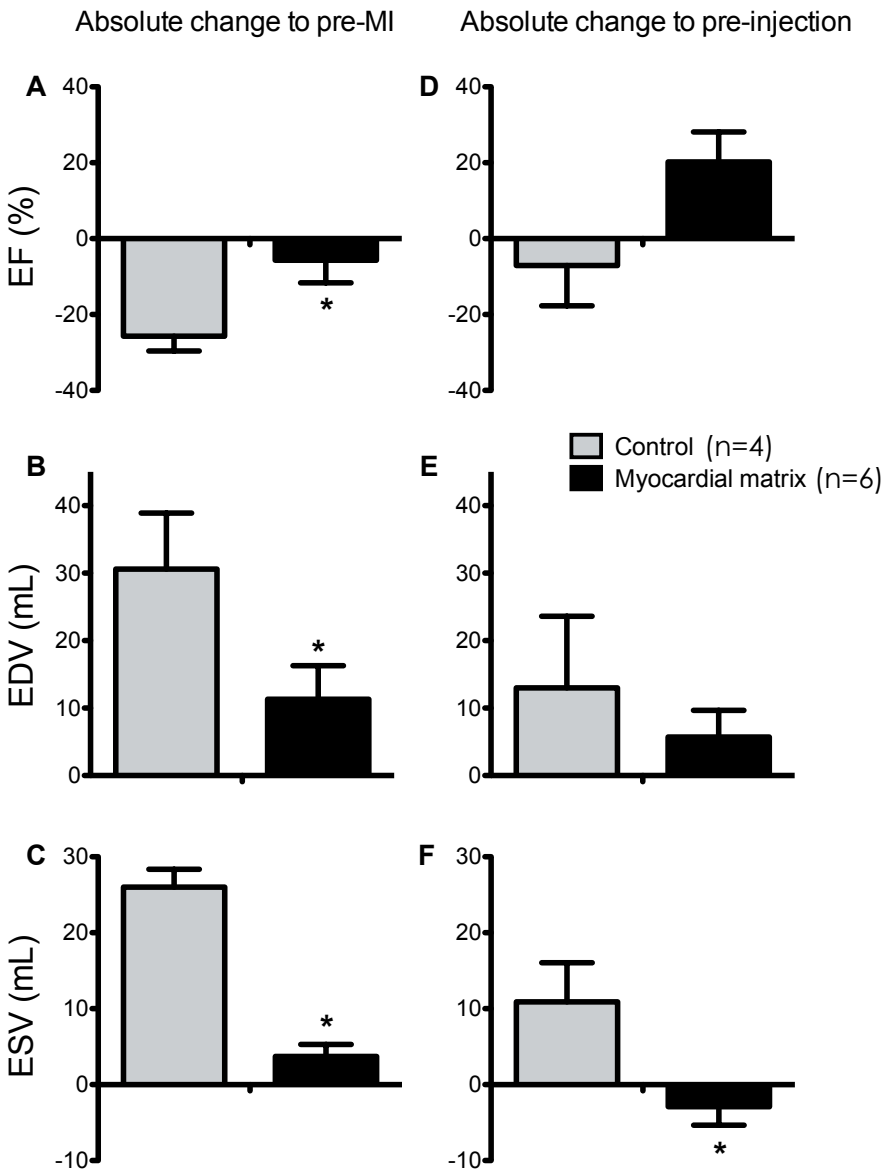
No Myocardial Matrix observed in other organs

Singelyn et al, *JACC,* 2012.

Porcine MI Model

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

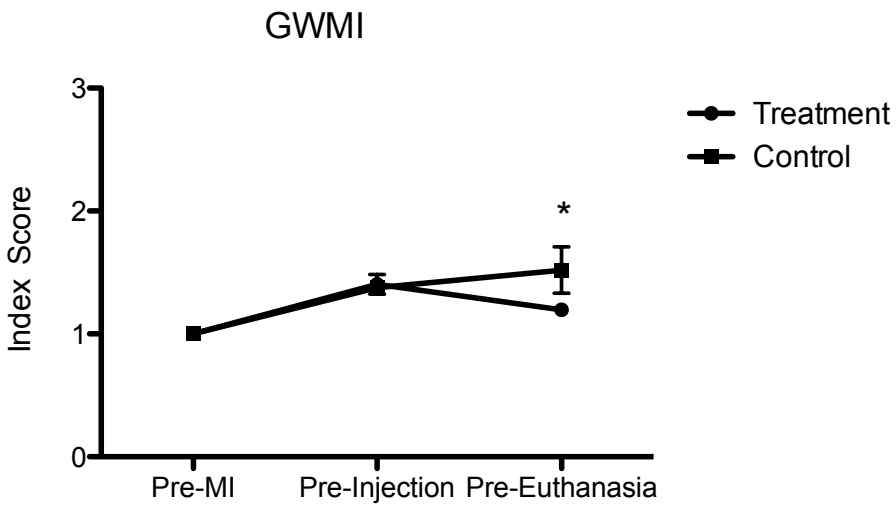


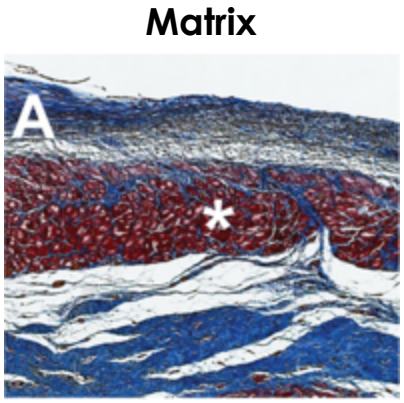


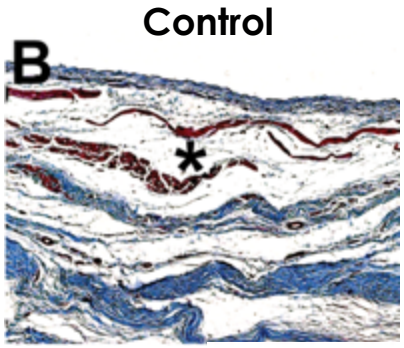
Seif-Naraghi et al, *Science Translational Medicine*, 2013

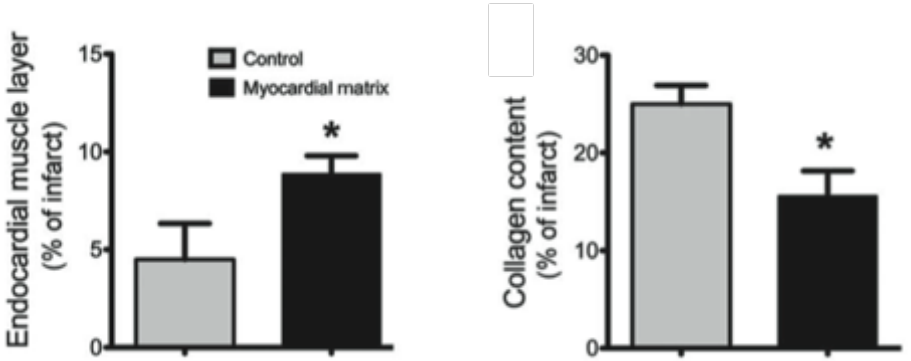
Porcine MI Model

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



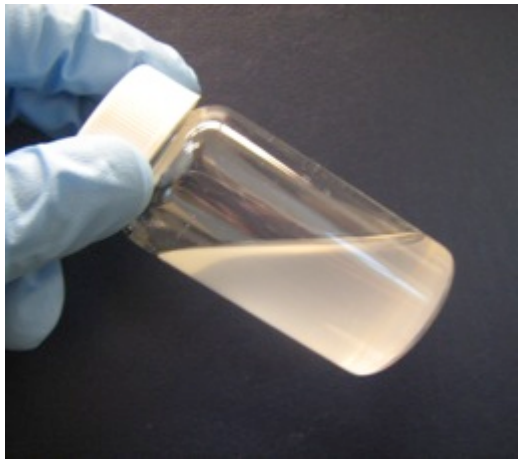


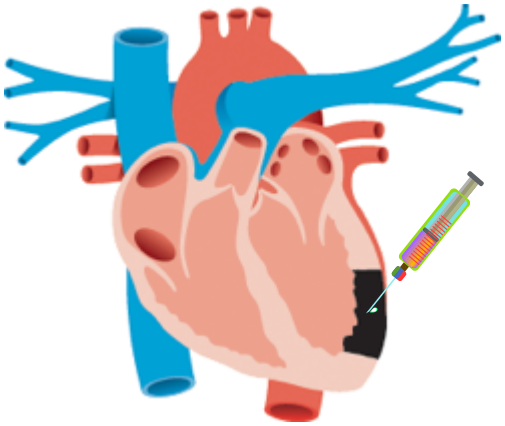


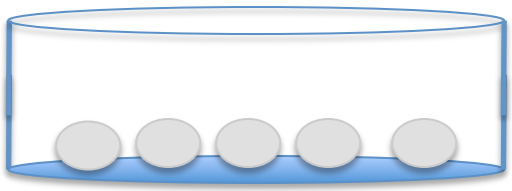


Seif-Naraghi et al, *Science Translational Medicine,* 2013

Myocardial Matrix







In vitro Stem Cell Studies

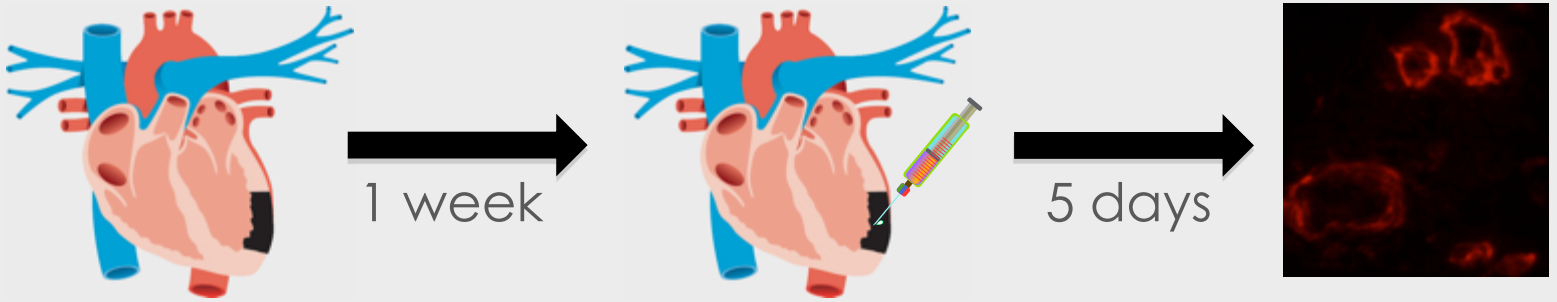
Matrix Alone

Matrix + Stem Cells

Matrix + Growth Factors

Growth Factor Delivery with ECM Hydrogel

Myocardial Infarction (MI) → 1 week → **Injection** → 5 days → **IHC**

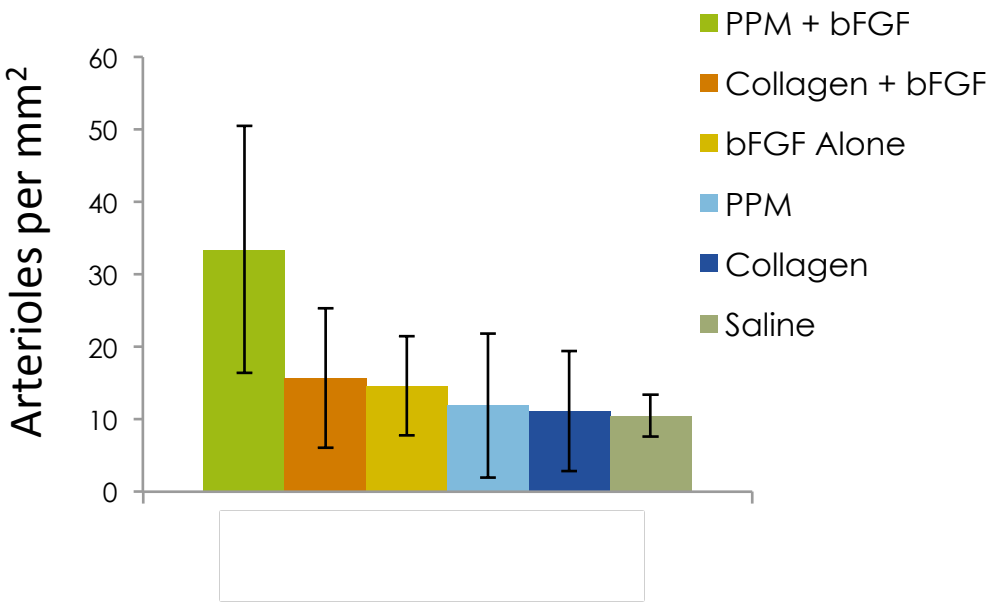


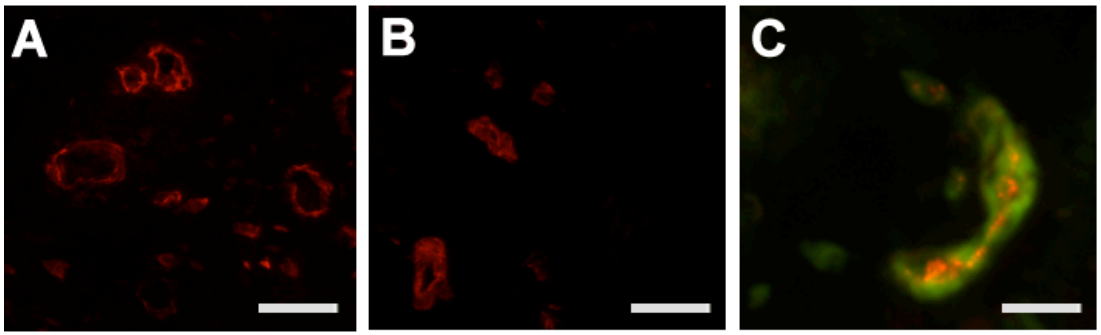
ECM hydrogel, collagen, or saline +/- bFGF

Seif-Naraghi et al, *Tissue Engineering* 2010, and *Acta Biomaterialia*, 2012

Growth Factor Delivery with ECM Hydrogel

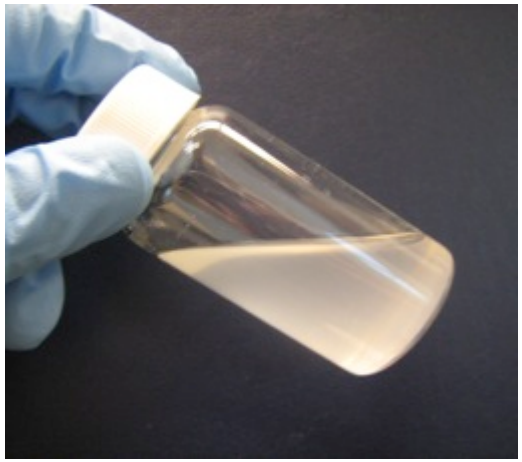
- ECM hydrogel retains growth factors through sulfated glycosaminoglycans
- Increased growth factor retention
- Increased neovascularization

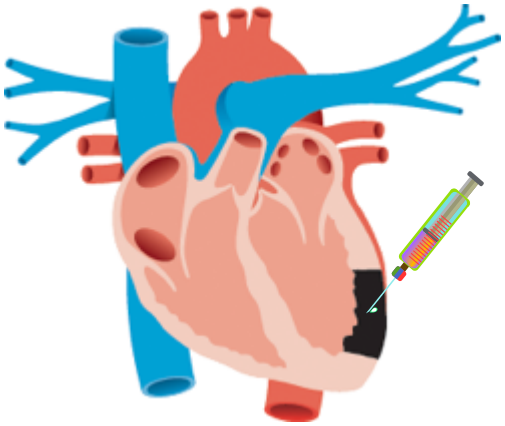




Seif-Naraghi et al, *Tissue Engineering* 2010, and *Acta Biomaterialia*, 2012

Injectable ECM Hydrogels

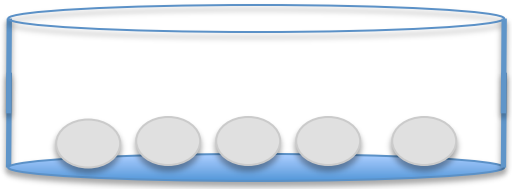




Matrix Alone

Matrix + Stem Cells

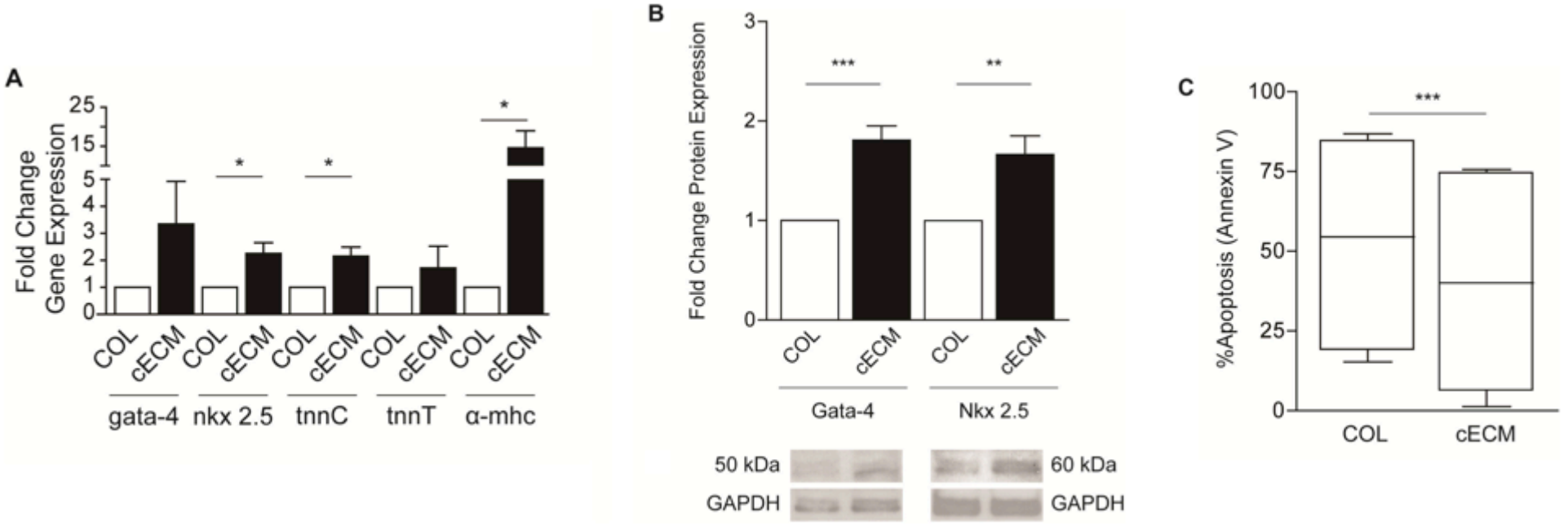
Matrix + Growth Factors



In vitro Stem Cell Studies

CPCs on Myocardial Matrix

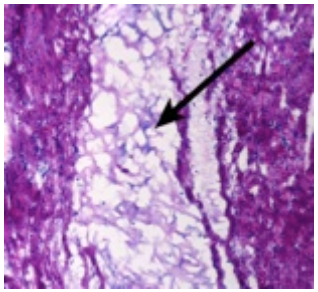
- Mike Davis & Kristin French, Bioengineering, Emory
- Mouse c-kit+ cardiac progenitor cells

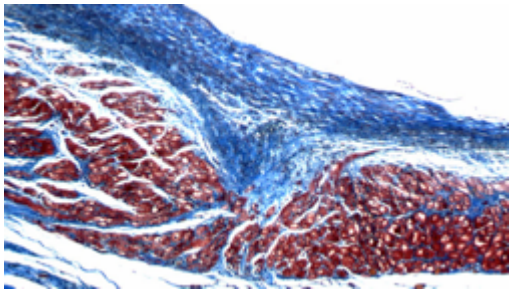


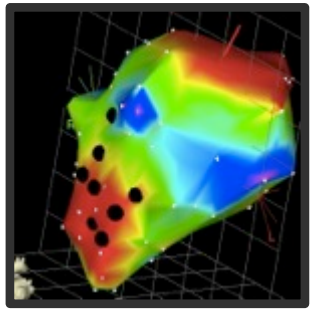
French et al, *Acta Biomaterialia*, 2012

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

Collaborators

Nabil Dib, MD
Anthony DeMaria, MD

BDS

Jonathan Wong
Mark Martin

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

Ventrix, Inc.

Adam Kinsey, PhD
Mike Salvatore

Funding

National Heart Lung and Blood Institute

NIH DIRECTOR'S NEW INNOVATOR AWARD

The NIH Common Fund

American Heart Association.

Wallace H. Coulter Foundation

iem

UCSD Jacobs | Department of Bioengineering