Technologies for the Heart: Biomaterials for Treating Myocardial Infarction

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The evolution of biomaterials...

**Historical examples:**

- **3000 BC:** Early Egyptians used linen sutures
- **600 AD:** Mayans fabricated teeth from sea shells
- **1930s:** First metal hip implants in Boston
- **1940s:** First papers on synthetic materials, polyethylene
- **1950+:** Appreciation for biocompatibility, how the body responds to implants

**Emerging examples:**

- Smart, responsive materials
- Control cell fate
- Dynamic properties
- Focus on designing for specific applications
Heart Attack Overview

- Millions suffer from myocardial infarction (MI) each year
- Heart disease is the leading cause of death in men and women
- Result of coronary artery disease, plaque build up and rupture

- Timing is everything, must treat the heart quickly to prevent significant damage
- Can lead to heart failure and arrhythmias (irregular beating)
- Current treatment: Blood thinning and reperfusion (dissolve clot, restore flow)

www.nhlbi.nih.gov
What happens after MI?

Status quo: restore blood flow, change lifestyle, hope for the best…
*New drug from Novartis

What are we forgetting?

• Post-MI Left Ventricular (LV) Remodeling
  – Hypoxia/Necrosis/Inflammation
  – ↑ LV wall stress
  – ↑ LV size, ↓ wall thickness
  – Geometry change
    • Ellipse to Sphere

• Changes in geometry and mechanics compromise regional and global LV function (ejection fraction), may lead to heart failure
How can we improve treatment options?

Treatment after remodeling (too late): Heart transplant, tissue engineering

Tissue Engineering
How can we improve treatment options?

Shifting the paradigm: Treat acutely
Limit the extent of remodeling
How can we limit adverse remodeling?

Acute therapies:

STEM CELLS: regeneration and repair

Examples: mesenchymal stem cells (MSCs) from bone marrow or adipose tissues, embryonic stem cells, induced pluripotent stem cells

Challenges: Positive results in clinical trials (e.g., bone marrow cells, muscle cells) have been transient due to issues with retention, survival, cell source, controlled differentiation

“Even the staunchest advocate of the use of cell-based therapies in cardiac repair would be forced to admit that progress has thus far been slow” (Henry Krum, Eur. Heart Journal, 2014)

How can we limit adverse remodeling?

Acute therapies:

- **Molecule Delivery**
- **Stem Cells**
- **Biomaterials**

What biomaterials?

**Hydrogels**: Water-swollen polymer networks
Tunable properties, biodegradable
Use alone, or to deliver cells/therapeutics

**Gelation**

- **Reactive Macromer (Hydrogel Precursor)**
- **Hydrogel**
  - polymer chain
  - polymer crosslink
Injectable Hydrogels

Mechanism 1: Mechanical (stress reduction)

Law of Laplace:
Correlation between wall thickness, volume, and wall stress

Mechanism 2: Biological (inflammation, molecule delivery)

Control cell recruitment
Therapeutic delivery
So, which hydrogel do we use?

Hydrogel Options: Natural versus Synthetic Materials (material chemistry)

Design considerations:
- Gelation/Injection/Distribution
- Mechanical Properties
- Degradation
- Timing/Location/Quantity
- Biocompatibility

Alginate
(Ikaria, LoneStar)

PolyNIPAAM

Decellularized Heart Tissue
(Ventrix)

Designing new hydrogels

Engineer specific and desired properties into hydrogels

Molecule Delivery:

Overcome issues with systemic delivery
Biological Targets

One target: Imbalance of MMPs/TIMPs results in LV remodeling

Previous administration of MMP inhibitors has not been successful in clinical trials due to off-target issues

Let’s deliver TIMP3 from gels
Releasing TIMPs from degradable HA gels

Inject array of 9 points in infarct region (swine model)

Release Profile of TIMP3

7 days later
TIMPs measured in tissue, higher than background levels

Releasing TIMPs from degradable HA gels

Animal Model

4 groups:
(1) Control
(2) MI Only
(3) MI/gel
(4) MI/gel/rTIMP-3

Patient Variability, Spatiotemporal Control

We may need better control over the delivery profiles of TIMP3

*Stimuli-responsive materials...*
What trigger can we use?

Release Mechanism: MMP Breakdown

Increased MMP

Cumulative Release (%)

Time

increasing:
- polymer concentration
- crosslink density
- polymer/molecule affinity
MMP degradation of hydrogels

Design material that is (1) injectable, (2) sequesters TIMP-3, (3) degrades with MMPs

Hyaluronic acid (HA)  \[ \text{NaIO}_4 \]  \[ \text{HA-aldehyde} \]

Dextran sulfate (DS)  \[ \text{NaIO}_4 \]  \[ \text{DS-aldehyde} \]

HA-maleimide  \[ \text{Gly-Cys} - \text{hydrazide} \]  \[ \text{HA-peptide-hydrazide} \]

Meets Design Goals

Other approaches for local molecule delivery

**Hydrogel Degradation (MMP2)**

![Graph showing mass loss over time for hydrogel degradation (MMP2)]

**Gel degrades and releases TIMP3 in response to MMPs**

![Diagram illustrating gel degradation and release of TIMP3 due to MMPs]

Assessment in Model of MI

Example outcome:

- MI/hydrogel/rTIMP-3
- MI/hydrogel
- MI

**Improved function and geometry**

**Increased TIMP levels**

**Decreased MMP activity**

*\( p < 0.05 \) vs. baseline +\( p < 0.05 \) vs. MI, #\( p < 0.05 \) vs. MI/gel

Can we move to a catheter?

- Percutaneous delivery
- Limitations of previous systems that require mixing of 2 components

Guest-Host Chemistry: Reversible interaction between $\beta$-cyclodextrin (CD) and Adamantane (Ad).

Synthesis:
Shear thinning hydrogel

Gelation:

Rapid Assembly

Shear-thinning

![Graph showing shear thinning behavior over time with different concentrations of CD-HA and Ad-HA](image)

![Images of vials with varying colors and states](image)
First, let’s try and prevent the initial heart attack.

Remodeling occurs after initial heart attack, this can lead to heart failure

Few current clinical treatment options, beyond repurfusion

Biomaterials may play a role

Long-term goal: engineering and integrating tissue constructs for repair
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