Cardiovascular Disease

- Effects 81.1 million Americans
- More women than men!
- 17.6 million Americans have coronary heart disease
- In every year since 1900 (except 1918) CVD has been the leading cause of death
**Cardiovascular Disease Deaths vs. Cancer Deaths by Age**

**United States: 2006**

Deaths in Thousands

<table>
<thead>
<tr>
<th>Age Group</th>
<th>CVD</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>45-54</td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td>55-64</td>
<td>81</td>
<td>101</td>
</tr>
<tr>
<td>65-74</td>
<td>120</td>
<td>138</td>
</tr>
<tr>
<td>75-84</td>
<td>242</td>
<td>165</td>
</tr>
<tr>
<td>85+</td>
<td>315</td>
<td>85</td>
</tr>
<tr>
<td>Total</td>
<td>831</td>
<td>560</td>
</tr>
</tbody>
</table>

*Source: NCHS*

---

**Percentage Breakdown of Deaths from Cardiovascular Diseases**

**United States: 2006 (Preliminary)**

- **Coronary Heart Disease**: 51%
- **Diseases of the Arteries**: 4%
- **Heart Failure**: 7%
- **High Blood Pressure**: 7%
- **Stroke**: 17%
- **Other**: 14%

*Not a true underlying cause. Heart failure, any mention mortality was 282,754 in 2006.*

*Source: NCHS.*

*Note: May not add to 100% due to rounding.*
Heart Attack
What’s the Big Deal Anyway?

The heart has limited regenerative capacity unlike other organs.

Most of the heart heals with scarring and not with new muscle.

This causes loss of function, heart failure and sets us up for electrical instability.
Treatment
Stem Cell Overview

**Embryonic**
- Blastocyst
- All cell and tissue types found in the developing fetus.

**Adult**
- Hematopoietic
- Blood Elements:
  - Red Blood Cells
  - White Blood Cells
  - Platelets
- Mesenchymal (MSC)
- Connective Tissues:
  - Marrow Stroma
  - Bone
  - Muscle
  - Cartilage
  - Ligaments and Tendons
  - Fat
How are stem cells defined?

1) Self-renewal
2) Multi-potential
3) Highly proliferative
Challenges

Which stem cell?
How to identify it?
How to isolate it?
Which disease process?
How to get it to the proper area?

How do you get them to engraft and survive?
Timing of injection?
How do we get them to function like the other cells around them?
Cardiomyocyte proliferation

Bone-marrow stem-cell mobilization

Cardiac regeneration

Cardiac regeneration

Hostile microenvironment

Inflammation

Fibrosis

Inadequate angiogenesis

Inadequate proliferation and differentiation

Insufficient numbers of available stem cells

Insufficient chemotaxis

Loss of stem-cell function with age

Inadequate mobilization

Inefficient homing

Inadequate multipotency

Terminal differentiation

Low proliferation capacity

Resident cardiac stem cells
Types of Stem Cells

Embryonic- derived from early embryos- pluripotent

iPSC- change somatic cells into pluripotent stem cells- 4 transcription factors

Bone Marrow Derived

Mesenchymal
<table>
<thead>
<tr>
<th>Source</th>
<th>Cell type</th>
<th>Potential mechanisms of action</th>
<th>Potential effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blastula</td>
<td>Embryonic stem cells</td>
<td>Differentiation into cardiomyocytes</td>
<td>Direct contribution to contractility</td>
</tr>
<tr>
<td>Skin fibroblasts</td>
<td>Cardiac stem cells</td>
<td>Differentiation into endothelial cells</td>
<td>Remodelling of electrical properties</td>
</tr>
<tr>
<td>Heart</td>
<td>Endothelial progenitor cells</td>
<td>Differentiation into smooth muscle cells</td>
<td>Remodelling of infarcts</td>
</tr>
<tr>
<td>Blood</td>
<td>Mesenchymal stem cells</td>
<td>Paracrine effects</td>
<td>Angiogenesis</td>
</tr>
<tr>
<td>Bone marrow</td>
<td></td>
<td></td>
<td>Remodelling of the extracellular matrix</td>
</tr>
<tr>
<td>Fat</td>
<td></td>
<td></td>
<td>Contribution to mechanical properties of the scar</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Activation of endogenous stem cells</td>
</tr>
</tbody>
</table>
Skeletal Myoblast

- Early Trials attempted to engraft skeletal myoblasts
- Resistant to ischemia
- Can differentiate into myotubes but not myocytes
- Worked in the lab!
- Don’t integrate electrically
Multinucleate
Negative for
Connexin 43
Desmosomes
Cadherin
No integration

MARVEL and Next Steps for Skeletal Myoblasts

Thomas J. Povsic M.D. Ph.D.
## MARVEL-1

### Serious Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Control (n=6)</th>
<th>Low-dose (n=7)</th>
<th>High-dose (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pts</td>
<td>Events</td>
<td>Pts</td>
</tr>
<tr>
<td>Sustained ventricular arrhythmias</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CHF</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Other: cardiovascular</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other: non-cardiovascular</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>3</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>
Bone Marrow Derived Cells

First evidence- Y chromosomes in female donor hearts of male recipients

Low differentiation into cardiomyocytes in human trials

Overall improvement in LVEF is minimal (5%)

Mesenchymal cells may be different
Reinfusion of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction

Study Design

Double-blind, Placebo-controlled, Randomized, Multicenter Trial

- **Study Design**
  - **acute ST elevation MI**
    - (successful acute reperfusion therapy)
  - bone marrow aspiration
    - (under local anesthesia)
  - **day 3 - 5**
  - **Placebo medium**
  - **Bone marrow progenitor cells**
  - **day 3 - 6**
  - intracoronary infusion
    - (& LV angiography)
  - **follow up LV angiography**
  - **4 months**
Study Procedures

Bone marrow aspiration
- 3 – 5 days after AMI
- local anesthesia
- 50 ml aspirate

Central Cell Processing Center
- Enrichment of progenitor cells (Ficoll density gradient centrifugation, release testing)
- GMP-compliant, licensed (PEI and the „Länder“, # 1034/01)
- Randomization
Institute for Transfusion Medicine, Red Cross Blood Donor Service/ J. W. Goethe University Frankfurt (T. Tonn / E. Seifried)

Intracoronary Infusion
- I.c. Infusion into infarct artery during stop flow
  - low pressure balloon inflation: 3 x 3 min, infusion of 3.3 ml each
  - Same or next day after bone marrow aspiration
Enhanced contractile recovery by BMC is confined to patients with failed initial recovery

Baseline LVEF by QLVA

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>BMC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EF below median (≤ 48.9 %)</strong></td>
<td>2.5 ±1.1</td>
<td>7.5 ±1.1</td>
</tr>
<tr>
<td><strong>EF above median (&gt; 48.9 %)</strong></td>
<td>3.7 ±0.7</td>
<td>4.0 ±0.6</td>
</tr>
</tbody>
</table>

p for interaction = 0.020

BMC therapy is associated with improved clinical outcome at 2 years

Event-free survival (%) (death, myocardial infarction, rehospitalization for heart failure)

Placebo 103 93 90 86 86
BMC 101 99 98 97 95

p = 0.009 (log rank)

CirculationHeartFail 2009
2 years clinical follow up
- Hazard Ratios -

Death
Myocardial infarction
Revascularization
Rehospitalization for heart failure
Combined
Death or MI
Death, MI or Rehospitalization for heart failure
Death, MI or Revascularization

CircHeartFail 2009
### Per patient analysis

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 100)</th>
<th>BMC (n = 100)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death (n)</strong></td>
<td>15</td>
<td>7</td>
<td>0.07</td>
</tr>
<tr>
<td>- Cardiac (n)</td>
<td>8</td>
<td>4</td>
<td>0.23</td>
</tr>
<tr>
<td>- SCD</td>
<td>3</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>- CHF-related death</td>
<td>3</td>
<td>0</td>
<td>0.08</td>
</tr>
<tr>
<td>- Cardiovascular (n) (stroke)</td>
<td>1</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>- Non-cardiovascular (n) (cancer, suicide, pneumonia)</td>
<td>3</td>
<td>2</td>
<td>0.65</td>
</tr>
<tr>
<td>- Cause of death unknown (registration office)</td>
<td>3</td>
<td>0</td>
<td>0.08</td>
</tr>
</tbody>
</table>

**5 years clinical follow up**

„Status alive“ patients (n=4; information of registration office) are only included into mortality analyses.
## 5 years clinical follow up

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>BMC</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Per patient analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>n = 99</strong></td>
<td><strong>n = 97</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Myocardial reinfarction (n)</strong></td>
<td>7</td>
<td>5</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Acute coronary syndrome (n)</strong></td>
<td>3</td>
<td>4</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Rehospitalization for heart failure (n)</strong></td>
<td>9</td>
<td>5</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Revascularization (n)</strong></td>
<td>42</td>
<td>30</td>
<td>0.10</td>
</tr>
<tr>
<td>- Target vessel revascularization (n)</td>
<td>28</td>
<td>18</td>
<td>0.11</td>
</tr>
<tr>
<td>- Stent thrombosis (n)</td>
<td>3</td>
<td>1</td>
<td>0.32</td>
</tr>
<tr>
<td>- Non-target revascularization (n)</td>
<td>18</td>
<td>14</td>
<td>0.48</td>
</tr>
</tbody>
</table>
### 5 years clinical follow up

**Per patient analysis**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo n = 99</th>
<th>BMC n = 97</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular arrhythmia or syncope (n)</td>
<td>7</td>
<td>6</td>
<td>0.80</td>
</tr>
<tr>
<td>PM / ICD Implantation (n)</td>
<td>11</td>
<td>5</td>
<td>0.13</td>
</tr>
<tr>
<td>Stroke (n)</td>
<td>7</td>
<td>3</td>
<td>0.21</td>
</tr>
<tr>
<td>Cancer (n) (lung, colon, sigma, prostate)</td>
<td>7</td>
<td>4</td>
<td>0.37</td>
</tr>
</tbody>
</table>

**Combined**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo n = 99</th>
<th>BMC n = 97</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI</td>
<td>18</td>
<td>12</td>
<td>0.26</td>
</tr>
<tr>
<td>Death, Rehosp. for heart failure (n)</td>
<td>20</td>
<td>11</td>
<td>0.09</td>
</tr>
<tr>
<td>Death, MI, Rehosp. for heart failure (n)</td>
<td>23</td>
<td>15</td>
<td>0.17</td>
</tr>
<tr>
<td>Death, MI, Revascularization (n)</td>
<td>52</td>
<td>36</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Embryonic Stem Cells

Prototypical stem cell-Pluripotent

1. Immunological rejection
2. Teratoma formation

How do we control them?
How complex are the interactions?
Is it worth the trouble?
Endogenous Cardiac Stem Cells

Small resident population in the heart
Avoid immunologic issues
How do we isolate them?
Will they differentiate and grow?
Will they be diseased like the heart we took them from?
Are they capable of self renewal?
iPSC

Somatic cells turned back into stem cells with the addition of 4 transcription factors

Similar in morphology, proliferation, gene expression and pluripotency

They are not homogenous

2009- functional cardiomyocytes have been created as well as nodal tissue
iPSC Potential

- Blastocyst embryo
- Healthy or diseased patient: skin fibroblasts
- Reprogramming
- hESC/IPS
- Self renewal
- Differentiation
- Cardiomyocytes
- Genetic engineering

- Mechanism of disease
- Transplantation
- Drug & toxicology testing
iPSC

Avoid the controversies of embryonic stem cells

Most importantly - Can we use these cells to create disease specific cell lines?

Can we test medications, therapies etc to treat specific diseases?
A Phase II multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of PROCHYMAL® (ex vivo cultured adult human mesenchymal stem cells) intravenous infusion following acute myocardial infarction

UC Davis is currently enrolling patients
Prochymal

(IV human mesenchymal stem cells)
Mesenchymal Stem Cell Activity

- Prevent Scarring
- Down Regulate Inflammation
- Tissue Protective
  - Anti-apoptotic
  - Anti-fibrotic
- Tissue Regenerative
  - Bone
  - Tendon
  - Cartilage
  - Muscle
  - Ligament
  - Fat
  - Stroma
- Anti-inflammatory
  - TNF Suppression
  - IL-10 Production
  - IL-4 Production
  - Blocks T Cell Proliferation

Promote Tissue Regeneration
In infants, MSCs are present in very large numbers, resulting in tremendous regenerative capabilities, with little inflammation and fibrosis.

As we age, the number of MSCs in the body declines along with our ability to optimally respond to injury.
Post MI, the heart wall becomes fibrotic resulting in electrical and mechanical dysfunction.

Prochymal blocks pathological remodeling.
Outcomes

- We will follow patients for 2 years.
- How are they doing?
- How is their ventricular function?
- Have they had a recurrent event?
- MRI to assess scar formation
Cardiac MRI
TAC-HFT: A Phase I-II US Heart Failure Stem Cell Trial Design

Post MI Heart Failure Patients Consented and Enrolled

n=68

Bone Marrow Aspiration

34 pts

Adult Autologous Mesenchymal Cell Derived from Bone Marrow (3 wks later delivery)

24 pts

Adult Autologous Mononuclear Cell Derived from Bone Marrow (Same day delivery)

10 pts

Therapy

Control

Control

Therapy

Safety measures, including ectopic tissue formation, arrhythmias
Functional performance, QOL
Serial cardiac MR/CT evaluation of LV function
BIOCARDIA, INC
Helical Infusion System
BioCardia® Helical Infusion Catheter
CE Marked and under investigational use in USA

Therapeutic Lumen (distal tip)
Contrast Lumen (base of helix)
Contrast Lumen
Therapeutic Lumen
BioCardia ® Morph ® Steerable Guide Navigation
FDA approved and CE Marked
Helical Infusion System
Two catheter system with three degrees of control
Delivery Strategy

- MRI
- CT-Scan
- Echo

Choice of target territory

Ventriculography RAO/LAO

Drawing overlays

Navigation with fluoroscopic guidance
Navigation is Fluoroscopy-based

Left Anterior Oblique (LAO)  Right Anterior Oblique (RAO)

Aortic valves  Aortic valves

Septal  Lateral  Anterior

Apex  Inferior  Apex
Contrast at Base of Helix Confirms Engagement
Helix penetrates 4mm
WHAT ABOUT THE FUTURE OF CARDIAC STEM CELL THERAPY AT UC DAVIS?
HSC therapy for vascular disease

Bone Marrow Harvest

GMP Facility

Clinical trial with UC Davis GMP Facility.
About 6 hours

Quality Control and Quality Assurance

Stem Cell Sort
UC Davis Institute for Regenerative Cures at the UC Davis Medical Center in Sacramento
The Stem Cell Program received 20 million dollars in funding from the CIRM large facilities grant to build the UC Davis Institute for Regenerative Cures.
Manufacturing room for cellular manufacturing

The actual work environment
Are We Doing Enough?

Data would suggest that we need to do more

Extracellular matrix?

Growth factors?

Optimal timing?

Cell type?

Do we need cells at all?
Summary

- Cardiovascular disease remains the leading cause of death in the United States
- Medical therapy is not enough
- Stem cell therapy IS happening now
- UC Davis will be part of the solution
UC Davis Cardiac Stem Cell Team

- Jan Nolta, Ph.D
- Gerhard Bauer, Ph. D
- Carol Richman, MD
- Kori Harder, RN, MS
- Kimberley Book, RN, BS
- Helen Dobbins, RN
- Janine Carlson, RN, BSN
- Richard Rodriguez
- Betty Ratliff
- Kent Foley
- Eva Lewalski