Stem cell therapy for cardiovascular disease – where does it stand?

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Disclosures

I have nothing to disclose

Today's Topics

• Background on Stem Cells
• Update on Cardiac Stem Cell Therapies
• Update on Direct Differentiation
• Future of Stem Cell Therapy

Epidemiology of Myocardial Infarction and Angina in the U.S.

- Single Largest Cause of Death
  - >500,000 deaths in the U.S./year
  - 1 in every 4.8 deaths
- Incidence
  - 1,500,000 Americans will have a new or recurrent MI each year
- Prevalence
  - ~14,000,000 with a history of MI, angina, or both
  - ~5,000,000 Americans with Heart Failure

* Based on data from the Atherosclerotic Risk in Communities study (ARIC) of the National Heart, Lung, and Blood Institute, 1987-94. Includes Americans hospitalized with definite or probable MI or Non-CHD, not including silent MI.

American Heart Association, 2016 Heart and Stroke Statistical Update
Myocardial Infarction and Heart Failure

- Myocardial Infarction
- Death of cardiomyocytes
- Scar tissue formation
- Aneurysmal thinning
- Left ventricular remodeling
- Decreased pumping capacity

Current Therapeutic Options For Patients with Large MI and Severe Heart Dysfunction

- Revascularization therapy
- Medications — anti-platelet therapies, statin, ace-inhibitor, beta-blocker, aldactone
- Prophylactic ICD to decrease risk of sudden death
- Cardiac resynchronization therapy
- Biventricular assist devices
- Heart Transplantation

None of these therapies lead to myocyte generation

Stem Cell -- “Fountain of Youth?”

Potential Beneficial Mechanisms of Stem Cell Therapy after MI

- Decreased infarct expansion
- Improved collagen expression
- Increased capillary recruitment
- Myocardial preservation
- Myocardial regeneration

Attenuation or reversal of post-infarction left ventricular remodeling
Classification of Stem Cells

Primary distinction

1) Embryonic stem cells
2) Non-embryonic stem cells
   - adult stem cells (bone marrow cells; circulating endothelial progenitor cells; mesenchymal stem cell; native cardiac stem cells; adipose derived stem cells, skeletal myoblast cells ……)
   - cord blood
3) Induced Pluripotent Stem cells
4) Somatic cell nuclear transfer cells

Stem Cell Embryology

In the 3-5 day old embryo, called a blastocyst, a group of about 30 cells called the inner cell mass gives rise to specialized cells that make up an adult organism.

Embryonic Stem Cell Differentiation

Adapted from UCSF Program in Development and Stem Cell Biology

Induced Pluripotent Stem Cell Lines (IPS)

Four factors (Oct 4, NANOG, Sox 2, LIN28) sufficient to reprogram a human somatic stem cell (fibroblast) to a pluripotent cell with all the characteristics of hES

(Yu J, et al., Thomson J, Science 2007)

Generation of IPS from human dermal fibroblasts by transduction of four transcription factors (Oct3/4, Sox2, Klf4, and c-Myc). IPS with all characteristics of hES

(Takayashi K, et al., Yamanaka S, Cell 2007)
The Nobel Prize in Physiology or Medicine 2012

- Shinya Yamanaka (UCSF)
- Sir John B. Gurdon

Which Stem Cells to use?

Embryonic Stem Cells ➔ Adult Stem Cells

- iPS Cells

How many cells to use?
Which patients will benefit?
How to deliver the cells?
What is the fate of the cells?
What are the risks/benefits?
How are the benefits achieved?
Can we make the cells work better?
Many other questions …..

Human ESC vs. iPS cells

Advantages

- Highly Expandable
- Pluripotent

Disadvantages

- Ethical objections (not with iPS)
- Difficult to isolate
- Risk of rejection (not with iPS)
- Immune-suppressive Rx required (not with iPS)
- Arrhythmogenic potential
- Risk of teratocarcinomas
- Lack of specific markers

Strauer BE and Kornowski R 2003;107: 929-934
Adult Stem Cells

Advantages
- Likely more easily obtainable
- No ethical objections
- Highly compatible
- Autologous transplantation
- No need for immunosuppressive Rx
- Clinical application already realized

Disadvantages
- Lack of specific markers
- Arrhythmogenic

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Stem Cells used for Cardiac Repair in Clinical Trials
- Bone Marrow
  - Mononuclear cells (BMMNCs)
  - Mesenchymal stem cells
  - Hematopoietic stem cells (CD 34+)
- Blood Vessel
  - Endothelial Progenitor cells (Hemangioblasts)
- Skeletal Muscle
  - Satellite cells (myoblast)
- Heart
- Resident Cardiac Stem Cells

Procedure of Intracoronary Cell Transplantation into Infarcted Myocardium in Humans

Strauer BE et al Circulation 2002;106: 1913-1918
Transendocardial Injection Technique

NOGA Myostar injection catheter
Injection catheter Advanced into LV

Perin EC et al Circulation 2003;107: 2294-2302

First Bone Marrow Cell Therapy Report

- 10 patients following MI vs 10 historical controls
- Stop-flow balloon technique
- BMMNCs down the infarct artery

Strauer BE et al Circulation 2002;106: 1913-1918

Use of various types of stem cell therapies in patients with cardiovascular disease

Sanganalmath S, Bolli R. Circulation Research 2013;113:810-834

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REPAIR-AMI Trial (Schachinger V. et al)

ST-elevation MI (Rx ed <24 hrs)
Bone Marrow Aspiration (days 3-5)
Placebo #103
B.M. treated #101
Intracoronary Infusion (236 million cells; 98% viable)
Baseline and F/U LV-angiogram at 4 months

AHA 2005

Copyright © American Heart Association
**Improvement in ejection fraction (%) from baseline (3-6 days post MI) to four months**

<table>
<thead>
<tr>
<th>Group</th>
<th>Stem cells</th>
<th>Placebo</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>All patients</td>
<td>5.5</td>
<td>3</td>
<td>0.014</td>
</tr>
<tr>
<td>Patients with baseline EF&lt;49%</td>
<td>7.5</td>
<td>2.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Patients with baseline EF&gt;49%</td>
<td>4.0</td>
<td>3.7</td>
<td>0.81</td>
</tr>
<tr>
<td>Patients treated within 5 days of MI</td>
<td>4.5</td>
<td>3.9</td>
<td>0.62</td>
</tr>
<tr>
<td>Patients treated after 5 days</td>
<td>7.0</td>
<td>1.9</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**Clinical events at four months**

<table>
<thead>
<tr>
<th>Event</th>
<th>Events in stem-cell group, n</th>
<th>Events in placebo group, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Recurrent MI</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Hospitalization for CHF</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Revascularization</td>
<td>19</td>
<td>28</td>
</tr>
</tbody>
</table>

**Benefits with BMC Therapy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2007 (18 trials, 999 patients)</th>
<th>2012 (50 trials, 2,625 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>↑ 3.7%</td>
<td>↑ 3.96%</td>
</tr>
<tr>
<td>Infarct scar size</td>
<td>↑ 5.5%</td>
<td>↑ 4.03%</td>
</tr>
<tr>
<td>LVESV</td>
<td>↓ 4.8 ml</td>
<td>↓ 8.91 ml</td>
</tr>
<tr>
<td>LVEDV</td>
<td>No change</td>
<td>↓ 5.23 ml</td>
</tr>
</tbody>
</table>

Most recent Cochrane Database Systematic Review 2015:
- 41 clinical trials, 2732 participants
- Cell therapy was safe but found no improvement in LVEF or quality of life in the short or long-term

**TIME, Late-TIME – U.S. Trials**

- NHLBI sponsored
- Patients with MI, treated with primary PCI
- Intra-coronary BMMNCs at 3 days, 7 days or 2 weeks post-MI.
- Controls received cell-free medium using stop-flow technique.
- No effect on regional or global LV function.

Traverse J, et al. JAMA 2012
Traverse J, et al. JAMA 2012
**BAMI Trial – Bone Marrow Derived Mononuclear Cell administration in acute MI**

- 1:1 Randomized, controlled (3,000 patients)
- no placebo group
- IC BMC vs. standard of care
- Primary endpoint: All-cause mortality
- Inclusion: LVEF < 45%, 3-6 days after successful reperfusion
- Aim: to reduce 2-year mortality by 25%
- 11 European countries

**POSEIDON-DCM: Allogenic vs. Autologous Stem Cells in Non-Ischemic Dilated Cardiomyopathy –**

- Randomized, parallel study
- Patients with nonischemic dilated cardiomyopathy randomized to transendocardial injection in 10 left ventricular sites with the NOGA catheter of allogenic (n = 18) versus autologous stem cells (n = 16)
- LVEF < 40%; f/u 12 months
- The primary safety outcome, treatment-emergent serious adverse events within 30 days, occurred in none of the allogenic stem cell group versus none of the autologous stem cell group
- Change in LVEF: 8.0% in the allogenic group versus 5.4% in the autologous group (p = 0.49)
- Change in 6-minute walk test: 37 m in the allogenic group versus 7.3 m in the autologous group (p = 0.012)

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**Cardiac Repair in Humans**

**Traditional View**

The adult heart is a terminally differentiated organ without regenerative capacity after injury.

**Current View**

The adult heart has some regenerative capacity after injury and several stem/progenitor cells have been identified.

**Endogenous cardiac stem cells**

Advantage of cardiac stem/progenitor cells:
- differentiate into cardiac cells; unlikely to form teratomas
- can be isolated and expanded from myocardial biopsy
- can be used for autologous transplantation
Method of Isolating CSs

- Cut heart to small piece (2 mm³) and digest by enzymes
- Culture the small piece (explants) for 1 to 7 weeks
- Fibroblast-like cells grow out from adherent explants first
- Small, phase-bright cells (putative CS forming cells) appeared on top of the fibroblast-like cells
- Harvest putative CS forming cells and transfer them to Poly-D-lysine coated plate

Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial

Lancet 2012
E. Marban and colleagues
How about combined cell therapy?

- Ixmyelocel-T – combination of two bone marrow cells: mesenchymal stem cells and activated macrophages
- Treated patients with ischemic heart failure
- Prospective, randomized double-blind trial (51 Placebo vs. 58 Ixmyelocel-T)

Ixmyelocel-T Trial (continued)

- Patients treated with ixmyelocel-T had a significant reduction in the primary endpoint
- 37% to 48% reduction in cardiac events compared to placebo
- Driven by a reduction in mortality and cardiac hospitalizations
- Fewer patients with SAEs observed in the ixmyelocel-T group compared to the placebo group
- No significant changes in LVEF or LV volumes, NYHA or 6-minute-walk

Potential Mechanisms for the Observed Benefits with Stem Cell Therapy after Acute MI?

- Progenitor Cells
- Cell transdifferentiation
- Cell fusion
- Soluble factors
- Cell-to-cell contact
- Other

- ? Improved cardiac function
- ? New muscle
- ? Less apoptosis
- ? New blood vessels
UCSF Translational Cardiac Stem Cell Program

• Tale of Three Cells:
  → Bone Marrow Derived Cells
  → Native Cardiac Stem Cells
  → Human Embryonic Stem Cells

Bone marrow cells injection 3 days after MI

Less left ventricular dilatation with cell therapy

Infarct size smaller with cell therapy

Change of LVEF 25 days post-injection of different cells
In detailed histologic analysis, we saw no new cardiomyocytes forming and in fact, very rare GFP+ cells were even identified in the hearts.

Limitation of infarct size in BMC and extract groups

Enhanced vascularity at the infarct border zone

Reduction in cardiomyocyte apoptosis in the extract group

Injection of Bone Marrow Cell Extract Into Infarcted Hearts Results in Functional Improvement Comparable to Intact Cell Therapy


We compared therapeutic benefits of intramyocardial injection of unfractionated bone marrow cells (BMC) versus BMC extract as treatments for myocardial infarction (MI) using closed-chest ultrasound-guided

Molecular Therapy vol. 17 no. 7 July 2009
What is in the extract?
Protein(s)?
Extracellular vesicles (exosomes)?
MicroRNA?

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How about a bioartificial heart?

- Decellularized hearts by coronary perfusion with detergents
- Preserved the underlying extracellular matrix
- Produced an acellular perfusable vascular architecture
- Reseeded the construct with cardiac and endothelial cells
- To establish function, maintained the hearts for up to 28 days by coronary perfusion in a bioreactor that simulated cardiac physiology

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**Issues for cardiac stem cell therapy**

- Which cell (viability/potency)
  - Bone marrow cells from older patients with CV risk factors and post-MI might be less functional than cells from healthy younger donors
- How many cells
- What disease (acute MI vs. chronic HF vs. ischemic/non-ischemic CMP)
- Mode of Delivery
- Timing of Delivery
- Single versus multiple
- Combinations of cells
- Cells + scaffolds or cytokines
- Who pays?

**Conclusion**

- Therapy with some of the cells appears safe but more research is certainly required
- Understanding the components of the extract derived from bone marrow cells is a must
- Improving cell retention using biodegradable scaffolds after delivery is under investigation and appears promising
- Direct Reprogramming of non-CM into CM is of great interest
- Bioartificial organs potentially have a bright future

**THANK YOU**