Stem Cells for the Failing Heart

Zeljko J. Bosnjak, PhD, FAHA
Professor and Vice Chairman for Research
Departments of Anesthesiology and Physiology
The Medical College of Wisconsin, Milwaukee

3rd DUBROVNIK CARDIOLOGY HIGHLIGHTS
OVERVIEW

- New modalities for HF treatment
- Stem cell therapy - potentially disease modifying
- Individual clinical studies
- Meta-analyses
- Future directions and likely outcomes
New modalities for HF treatment

- The management of HF has extended the lifespan of this patient population; however, not able to reverse the disease

- Short of heart transplantation, there are currently limited options to overcome the poor prognosis of end-stage HF

- This urgent clinical need drives the exploration of cardiac repair with stem cells

- Many efforts aim to use the regenerative properties of stem cells for strategies to repair injured myocardium
**Post-MI cardiac adaptation**

- **Normal**
  - LV
  - Coronary artery
- **Myocardial infarction**
  - Infarction
  - Non-infarcted myocardium
- **Acute compensation**
- **Cardiac remodeling/HF**
- **Cardiac stabilization**

**Cell therapy goals**

**Prevent cardiac deterioration**
- Promote formation of new blood vessels
- Inhibit apoptosis
- Inhibit ROS production
- Prevent cardiac expansion
- Limit area of necrosis and scar size
- Alter scar content to improve mechanical support

**Restore pumping capacity**
- Promote formation of new blood vessels
- Replace lost cardiomyocytes
- Ventricle reconstruction
- Restore contractile tissue
- Restore elliptical shape
New modalities for HF treatment

- For nearly a century, the heart has been considered a terminally-differentiated post-mitotic organ unable to replace dying cardiomyocytes
- This premise is no longer valid
- Pool of resident cardiac stem cells (CSCs) that can acquire the cardiomyocyte, vascular smooth muscle, and endothelial cell lineages has been identified in the human heart
Birth date of cardiac cells
The role of hCSCs in restoring damaged myocardium

- Spontaneous cardiac repair is minimal; regenerative response to the non-infarcted tissue

- Spontaneous myocyte regeneration does not compensate for the loss of myocytes in the chronically pressure-overloaded heart

- Spontaneous cardiac repair may delay, but does not avoid or reverse the progression of HF
Sources of stem cells for cardiac regeneration and potential reparative mechanisms
Implantation of stem cells

**Intracoronary infusion**
Bone marrow– or blood-derived progenitors

**Catheter-based intramyocardial needle injection**
Bone marrow– or blood-derived progenitors, or skeletal muscle cells

**Direct intramyocardial injection during surgery**
Bone marrow– or blood-derived progenitors, or skeletal muscle cells

Coronary artery
Infusion balloon
Potential mechanisms of action of stem cells

Injection of Stem Cells

- Activation of Endogenous Progenitors
- Differentiation into Cardiomyocytes
- Differentiation into Vascular Smooth Muscle Cells
- Differentiation into Endothelial Cells
- Inhibition of Apoptosis
- Extracellular Matrix Remodeling
- Neovascularization

- Attenuated LV Remodeling
- Enhanced Perfusion
- Improved Cardiac Function
- Improved Functional Capacity

Sanganalmath S, Bolli R. Circulation Research 2013;113:810-834
Implantation of stem cells

- Most transferred cells are dead within a week
- Difficult for cells to engraft, survive, proliferate, and differentiate
- Clinical trials demonstrate that autologous cell based therapies for cardiovascular repair are feasible and safe
- Although efficacy of cell-based therapy has been limited, it holds enormous promise at preventing or reversing myocardial remodeling and promoting tissue regeneration
Clinical studies using MSCs

342 studies examining the effects of MSCs

160 studies examining the effects of MSCs in heart failure

http://clinicaltrials.gov (September 2013)
Use of various types of stem cell therapies in patients with cardiovascular disease

Sanganalmath S, Bolli R. Circulation Research 2013;113:810-834
Trials with Negative results:

✓ Late-TIME, Transplantation in Myocardial Infarction Evaluation
✓ Cardiovascular Cell Therapy Research Network [CCTRN]
✓ TIME

Trials with Positive results:

✓ Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis (POSEIDON)
✓ Cardiac Stem Cells in Patients with Ischemic Cardiomyopathy (SCIPIO)
✓ Cardiosphere-derived Autologous Stem Cells to Reverse Ventricular Dysfunction (CADUCEUS)
The acute and long-term effects of intracoronary Stem cell Transplantation in 191 patients with chronic heARt failure: the STAR-heart study

Bodo-Eckehard Strauer*, Muhammad Yousef, and Christiana M. Schannwell

- Open label, non-randomized, prospective study
- Intracoronary BMC therapy improves ventricular performance, quality of life, and survival in patients with heart failure
- These effects were present when BMC were administered in addition to standard therapeutic regimes
- No side effects were observed
Phase 1/2 randomized comparison with 13-month follow-up (n=30)

Absence of significant alloimmune reactions in patients receiving allogeneic MSCs

Cell therapy may not only improve left ventricular structure but may also improve quality of life and functional capacity
Left ventricular ejection fraction, %

Change in Ejection Fraction, %

Allogeneic MSCs (n = 14)  Autologous MSCs (n = 13)  Overall (n = 27)

End-diastolic volume, mL

Change in End-Diastolic Volume, mL

Allogeneic MSCs (n = 14)  Autologous MSCs (n = 13)  Overall (n = 27)

End-systolic volume, mL

Change in End-Systolic Volume, mL

Allogeneic MSCs (n = 14)  Autologous MSCs (n = 13)  Overall (n = 27)

End-diastolic myocardial volume, μL

Change in End-Diastolic Myocardial Volume, μL

Allogeneic MSCs (n = 14)  Autologous MSCs (n = 13)  Overall (n = 27)

JAMA. 2013 Aug 21;310(7):750
Change in New York Heart Association Classification Quality of Life
Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial


- Infusion of autologous CDCs after myocardial infarction is safe
- Significant increases in viable myocardium is consistent with therapeutic regeneration
- No differences in EF or volumes
Manufacture of cardiosphere-derived cells
CADUCEUS trial changes in scar size

Lancet 2012; 379: 895–904
CSC infusion produces a striking improvement in both global and regional LV function

Reduction in infarct size

Increase in viable tissue that persist at least 1 year and are consistent with cardiac regeneration
Baseline (27.5 ± 1.6%)
4 months after CSC infusion (35.1 ± 2.4%),
12 months after CSC infusion (41.2 ± 4.5%).

Circulation. 2012;126:S54–S64
Short- and long-term outcomes of intracoronary and endogenously mobilized bone marrow stem cells in the treatment of ST-segment elevation myocardial infarction: a meta-analysis of randomized control trials

Hendrik Zimmet¹, Pramote Porapakkham², Pornwalee Porapakkham³, Yusuke Sata⁴, Steven Joseph Haas¹, Silviu Itescu⁵, Andrew Forbes¹, and Henry Krum¹*

Meta-analysis of 29 studies (1830 patients)

- Intracoronary BMSC therapy post-STEMI improves LVEF beyond standard medical treatment, in both the short and longer term
Effect of intracoronary BMSC on LVEF at 3–6 months

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Weighted Mean Difference (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Ruan</td>
<td>2005</td>
<td>20</td>
<td>9.03 (-0.73, 18.79)</td>
</tr>
<tr>
<td>Ge</td>
<td>2006</td>
<td>20</td>
<td>2.30 (-4.21, 8.81)</td>
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<tr>
<td>Huang RC</td>
<td>2006</td>
<td>40</td>
<td>3.60 (-0.12, 7.32)</td>
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<tr>
<td>Janssens</td>
<td>2006</td>
<td>60</td>
<td>2.70 (-2.26, 7.66)</td>
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<tr>
<td>Lunde</td>
<td>2006</td>
<td>100</td>
<td>-0.20 (-4.17, 3.77)</td>
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<tr>
<td>Meyer</td>
<td>2006</td>
<td>60</td>
<td>4.70 (-1.60, 11.00)</td>
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<tr>
<td>Schachinger</td>
<td>2006</td>
<td>187</td>
<td>3.90 (0.54, 7.26)</td>
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<tr>
<td>Huang</td>
<td>2007</td>
<td>40</td>
<td>4.40 (0.81, 7.99)</td>
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<tr>
<td>Penicka</td>
<td>2007</td>
<td>24</td>
<td>-2.00 (-8.41, 4.41)</td>
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<tr>
<td>Suarez de Lezo</td>
<td>2007</td>
<td>20</td>
<td>13.00 (5.54, 20.46)</td>
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<tr>
<td>Huikuri</td>
<td>2008</td>
<td>72</td>
<td>3.00 (-2.62, 8.62)</td>
</tr>
<tr>
<td>Meluzin (high dose)</td>
<td>2008</td>
<td>40</td>
<td>3.00 (-2.54, 8.54)</td>
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<tr>
<td>Cao</td>
<td>2009</td>
<td>86</td>
<td>2.70 (1.14, 4.26)</td>
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<tr>
<td>Piepoli</td>
<td>2009</td>
<td>38</td>
<td>5.30 (3.93, 6.67)</td>
</tr>
<tr>
<td>Plewka</td>
<td>2009</td>
<td>56</td>
<td>6.00 (1.46, 10.54)</td>
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<tr>
<td>Silva</td>
<td>2009</td>
<td>20</td>
<td>5.84 (-9.90, 21.58)</td>
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<tr>
<td>Tendera (Non-sel)</td>
<td>2009</td>
<td>66</td>
<td>1.00 (-2.71, 4.71)</td>
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<tr>
<td>Yao</td>
<td>2009</td>
<td>24</td>
<td>3.30 (0.49, 6.11)</td>
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<td>Grajec</td>
<td>2010</td>
<td>45</td>
<td>2.90 (-4.15, 9.95)</td>
</tr>
<tr>
<td>Hirsh</td>
<td>2010</td>
<td>127</td>
<td>1.10 (-2.22, 4.42)</td>
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<td>Roncalli</td>
<td>2010</td>
<td>92</td>
<td>-2.00 (-6.08, 2.08)</td>
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<tr>
<td>Traverse</td>
<td>2010</td>
<td>40</td>
<td>-2.80 (-9.07, 3.47)</td>
</tr>
<tr>
<td>Wohrle</td>
<td>2010</td>
<td>40</td>
<td>-6.10 (-13.37, 1.17)</td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
<td></td>
<td>2.70 (1.48, 3.92)</td>
</tr>
</tbody>
</table>

Tests for heterogeneity: p = 0.003, I-squared = 50.3%
Test for overall effect: p < 0.001

Zimmet H et al. Eur J Heart Fail 2012;14:91-105
Effect of intracoronary BMSC on LVEF at 12–18 months

Zimmet H et al. Eur J Heart Fail 2012;14:91-105

Tests for heterogeneity: p = 0.123, I-squared = 38.5%
Test for overall effect: p < 0.001
Meta-analysis of 50 studies (2625 patients)

- Improvement of LV function, infarct size, and remodeling in patients with ischemic heart disease compared with standard therapy
- Benefits persist during long-term follow-up
- Reduction in deaths, recurrent myocardial infarction, and stent thrombosis

*Circulation, 126(5):551-568, 2012*
Transplantation of BMCs resulted in a 4% increase in mean LVEF
Transplantation of BMCs resulted in a 4% decrease in infarct scar size
Transplantation of BMCs resulted in a 9% decrease in mean LVESV
Transplantation of BMCs resulted in a 5% decrease in mean LVEDV
# Cell types used for cardiac repair

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Source</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow</td>
<td>BM</td>
<td>Autologous</td>
<td>Pluripotency</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>Paracrine effects</td>
<td>uncertain</td>
</tr>
<tr>
<td>Adult cardiac progenitor cells</td>
<td>Cardiac</td>
<td>Autologous</td>
<td>Invasive cardiac biopsy</td>
</tr>
<tr>
<td></td>
<td>biopsy</td>
<td>Differentiate into all cardiac lineages</td>
<td>Xenogenic antibodies used for isolation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paracrine effects</td>
<td></td>
</tr>
</tbody>
</table>
To improve the outcome of current cell therapy for cardiac regeneration in the future:

- Resolve the issues concerning optimal cell type, factors, dosage, patient population, and route and timing of administration
- Proceed with rigorous, large-scale, rationally designed, and randomized clinical trials
- Tissue engineering
- MicroRNA regulation of cardiac regeneration
- Reprogramming the fibroblasts
Approaches to direct cardiac reprogramming

Cardiac Fibroblasts

Gata4, Mef2c, Tbx5

Gata4, Mef2c, Tbx5, Hand2

miR-1, -133, -208, -499

In vitro iCMs

Adult Injured Heart

Gata4, Mef2c, Tbx5

Gata4, Mef2c, Tbx5, Hand2

miR-1, -133, -208, -499

In vivo iCMs

Qian L, Srivastava D. Circulation Research 2013;113:915-921
Likely outcomes in the future

✓ Off-the-shelf products likely in decade or so
✓ Different mixture of cells for patients with recent MI and those with chronic HF
✓ Infused into the coronary arteries for patients with dilated nonischemic cardiomyopathy
✓ Transendocardial injection to patients with major coronary blockages
✓ Cell therapy unlikely a sole treatment for HF, but an important adjunct to other therapeutic approaches, (prolonged LVA, microRNA, and gene therapy)
Thomas E. Starzl MD, PhD
(“The father of modern transplantation”)

“The history of medicine is that what was inconceivable yesterday and barely achievable today often becomes routine tomorrow”
Thank you
MicroRNA regulation of cardiac regeneration

Cardiomyocyte Proliferation

Cardiomyocyte Reprogramming

Cardiomyocyte Survival

Cardiomyocyte Differentiation

Regeneration

miR-1
miR-133a
miR-15 family

miR-199a-3p
miR-590-3p
miR-1825
miR-33b*

miR-1
MI-133a
MI-208
MI-499

miR-34
miR-1
miR-29
miR-320

miR-21
miR-221
miR-24
miR-199a-5p

Circ Res 2013;112:1412-1414
Remuscularising the Failing Heart

- Myocardial infarction - one billion myocytes dead
- Intramyocardial cell injection - over 95% of the cells are lost
- Calculated therapeutic cell dose - 20 billion myocytes
- Total myocytes number of the heart is 4 billion