Cardiac Stem Cells

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Myocardial Infarction Mortality in U.S.A.

(Rosamund et al, Circulation 2007)
However...

Hospital discharges for heart failure by sex
(United States: 1979-2004). Source: NHDS, NCHS and NHLBI)
Damage → cell apoptosis and necrosis → scar formation → hypertrophy
LEFT VENTRICULAR REMODELING

POST-MI REMODELING

Acute Infarction

Infarct Zone Thinning & Elongation

Spherical Ventricular Dilation

Increased Interstitial Collagen

Fibrous Scar

Myocyte Hypertrophy
STEM CELL THERAPY
STEM CELL ORIGIN

- Blood
  - Endothelial precursor cells
- Bone marrow
  - MSCs
  - Hematopoietic stem cells
  - SP cells
- Skeletal muscle
  - Satellite cells
  - Sca-1+ cells
  - SP cells
- Adipose tissue
  - MSCs
  - SP cells
- Embryonic stem cells
  - MSCs
  - SP cells

Heart
- Sca-1+ cells
- c-Kit+ cells
- SP cells
HUMAN CARDIAC STEM CELL
THE HEART AS A SELF-RENEWING ORGAN

Bearzi C., Hosoda T, D’Amario D. PNAS, 2007
c-kit

CSCs are Self-Renewing and Clonogenic

Hosoda T, D’Amario D, Zheng H et al, PNAS, 2010
Hosoda T, D’Amario D., Zheng H et al., PNAS, 2010
SCIPIO

Stem Cell Infusion in Patients with Ischemic cardiomyopathy

Bolli R, Chugh A, D’Amario D et al., Lancet 2011
Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial

Overview

- Phase I, prospective, randomized, open label, human study enrolling a maximum of 20 patients to the treated arm and 20 controls scheduled to undergo on-pump CABG surgery.

- At the time of CABG, the right atrial appendage will be resected and harvested for CSCs.

- At 4 ± 1 months after CABG surgery, treated patients will undergo selective intracoronary injections of CSC solutions. All patients will be followed clinically for up to 2 years.

- Follow-up will include clinical assessment, laboratory studies, imaging and functional studies.

Bolli R, Chugh A, D’Amario D et al., Lancet 2011
Inclusion Criteria

• LVEF ≤ 40%

• A history of Q-wave (STEMI) MI with a residual akinetic and nonviable scar (as evidenced by a low-dose dobutamine stress echocardiogram and/or a thallium redistribution nuclear study for viability and/or an electrocardiogram and/or cardiac MRI and/or rest perfusion images on a sestamibi SPECT study)

• Patient scheduled for surgical revascularization within 2 weeks of the initial screening

Bolli R, Chugh A, D’Amario D et al., Lancet 2011
SCIPIO: Results

Ejection Fraction

SCIPIO: Results

Infarct size

Example of changes in the size of an infarct from baseline (before cardiac stem cell [CSC] infusion) to 4 and 12 months after CSC infusion.

Chugh A R et al. Circulation 2012;126:S54-S64.
Safety profile for intracoronary infusion of CSC is apparent

Feasibility of the procedure has been demonstrated

Preliminary results are more than encouraging and warrants investigation in a larger volume of patients

Paucity of surgical candidates implies need for other methods of tissue procurement

Bolli R, Chugh A, D’Amario D et al., Lancet 2011
CADUCEUS Trial (CArdiosphere-Derived aUtologous stem CElls to reverse ventricUlar dySfunction)

Malliaras et al, JACC 2014
- Second Generation of cells
- Selection of patients
- New technique for isolation
IGF-1R^{POS}hCSCs vs unselected hCSCs

infected with lentivirus carrying EGFP
Unselected hCSCs

IGF-1R^{pos} hCSCs

D’Amario et al, Circulation Research
The expression of IGF-1R identifies a pool of younger hCSCs with enhanced growth reserve in vitro and in vivo pointing to this hCSC subset as the ideal candidate cell for the management of human heart failure.
- Second Generation of cells
- Selection of patients
- New technique for isolation
SCIPIO: Results

Ejection Fraction

To define whether a pool of functionally competent hCSCs can be harvested from patients with ischemic cardiomyopathy, independently from age, sex and comorbidities.

To test whether CSC characteristics are critical determinants of LVR following complete revascularization at 1 year follow up.
17 Patients were lost at the FU:
10 = foreign residents
5   = not available for follow-up
2   = malignancies

55 Patients underwent CABG

2D Ecocardiography, laboratory tests, physical examination
NYHA class assessment
Growth Factors Serum Level

55 Consecutive Patients

Enrollment < 1 Week

Tissue Harvesting

55 Patients underwent CABG

17 Patients were lost at the FU:
10 = foreign residents
5   = not available for follow-up
2   = malignancies

38 Patients

Follow-Up

D’Amario et al, Circulation 2014
<table>
<thead>
<tr>
<th>Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients (n)</strong></td>
</tr>
<tr>
<td><strong>Age-yr (mean±SD)</strong></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td>Female (n;%):</td>
</tr>
<tr>
<td>Male (n;%):</td>
</tr>
<tr>
<td><strong>Body mass index kg/m²</strong></td>
</tr>
<tr>
<td><strong>CV risk factors</strong></td>
</tr>
<tr>
<td>Family history (n;%):</td>
</tr>
<tr>
<td>Smoke (n;%):</td>
</tr>
<tr>
<td>Hypertension (n;%):</td>
</tr>
<tr>
<td>Hypercholesterolemia (n;%):</td>
</tr>
<tr>
<td>Diabetes mellitus (n;%):</td>
</tr>
<tr>
<td><strong>BUN ≥ 24 mg/dl (n;%)</strong></td>
</tr>
<tr>
<td><strong>Uric Acid ≥ 8 mg/dl (n;%)</strong></td>
</tr>
</tbody>
</table>

D’Amario et al, Circulation 2014
## Clinical Presentation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count (Percentage)</th>
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</thead>
<tbody>
<tr>
<td>Acute coronary syndrome</td>
<td>16 (42%)</td>
</tr>
<tr>
<td>Stable angina</td>
<td>22 (58%)</td>
</tr>
<tr>
<td><strong>NYHA functional class</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>II</td>
<td>21 (55%)</td>
</tr>
<tr>
<td>III</td>
<td>15 (40%)</td>
</tr>
<tr>
<td>IV</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Previous CV events</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Previous coronary revascularization</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Ejection fraction (EF) - mean $\pm$ SD</td>
<td>54±11</td>
</tr>
<tr>
<td><strong>Patients with EF&lt; 45%</strong></td>
<td>8 (21%)</td>
</tr>
</tbody>
</table>
Left Ventricular Remodeling and Cardiac Stem Cell

Population Doubling Time

Telomere/Telomerase

IGF-1R expression
Left Ventricular Remodeling and Cardiac Stem Cell

\[ \Delta \text{Ejection Fraction} \]

Population Doubling Time

Telomere Length

Telomerase Activity

IGF-1R^{pos} CSC

D’Amario et al, Circulation 2014
D’Amario et al, Circulation 2014
Left Ventricular Remodeling and Cardiac Stem Cell

Δ End Systolic Volume

Population Doubling Time

Telomere Length

Telomerase Activity

IGF-1R^pos CSC

D’Amario et al, Circulation 2014
<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>p</th>
<th>CI 95%</th>
<th>Cut Off</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDT</td>
<td>0.92</td>
<td>&lt; 0.001</td>
<td>0.78 – 0.98</td>
<td>&gt; 26.8</td>
<td>81.8</td>
<td>96.3</td>
</tr>
<tr>
<td>Telomere length</td>
<td>0.85</td>
<td>&lt; 0.001</td>
<td>0.70 – 0.94</td>
<td>≤ 7</td>
<td>90.9</td>
<td>59.3</td>
</tr>
<tr>
<td>Telomerase</td>
<td>0.75</td>
<td>0.002</td>
<td>0.59 – 0.88</td>
<td>≤ 1.6</td>
<td>63.6</td>
<td>88.9</td>
</tr>
<tr>
<td>IGF1-R</td>
<td>0.86</td>
<td>&lt; 0.001</td>
<td>0.71 – 0.95</td>
<td>≤ 39.0</td>
<td>72.7</td>
<td>81.5</td>
</tr>
<tr>
<td>IGF1</td>
<td>0.81</td>
<td>&lt; 0.001</td>
<td>0.66 – 0.92</td>
<td>≤ 52.7</td>
<td>72.7</td>
<td>96.3</td>
</tr>
<tr>
<td>IGF1 at follow-up</td>
<td>0.71</td>
<td>0.01</td>
<td>0.54 – 0.85</td>
<td>≤ 81.8</td>
<td>45.4</td>
<td>100</td>
</tr>
</tbody>
</table>
- Second Generation of cells
- Selection of patients
- New technique for isolation
D'Amario et al, Circulation Research 2011

- Biopsy
- Cell isolation
- Expansion: 17 ± 2 days
- C-kit sorting
- Expansion: 9 ± 2 days
- CSC collection
<table>
<thead>
<tr>
<th>Histopathological Diagnosis</th>
<th>33</th>
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</thead>
<tbody>
<tr>
<td>Amyloidosis</td>
<td>2</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>1</td>
</tr>
<tr>
<td>ARVC</td>
<td>4</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>12</td>
</tr>
<tr>
<td>Virus Genome Positivity</td>
<td>3</td>
</tr>
<tr>
<td>Idiopathic Dilated Cardiomyopathy</td>
<td>14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major Complications</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemopericardium/Tamponade</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor Complications</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient Chest Pain</td>
<td>0</td>
</tr>
<tr>
<td>Non Sustained VT</td>
<td>3</td>
</tr>
<tr>
<td>Transient Hypotension</td>
<td>0</td>
</tr>
</tbody>
</table>

**ARVC**

**Myocarditis**
• Heart Failure is an international public health problem of pandemic proportions. The epidemics of HF represents a challenge for the National Health System.

• Currently there are no effective intervention to regenerate lost myocardial tissue and reverse the resultant dysfunction and heart remodeling.

• hCSCs and CDCs entered in the clinical scenario resulting in significant improvement in LV systolic function, quality of life ponting to this class of cell as the ideal candidate cell to treat HF in humans.