Cellular therapy: where do we stand?

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Questions I need to be answered

• Which is the origin of the universe?

• Is Maradona better than Pelè?

• Cell therapy: where do we stand?

• Why cucumber in McD cheeseburger?
A CLINICAL OVERVIEW

• Have we done a good job?

• Is there (if any) a way to go?

• Our experience in Milan in RA
NEW CELLS IN OLD HEART

(Orlic D, Nature 2001)
Proposed mechanisms of ischemic tissue repair via stem and progenitor cell-based therapies

Tongers J, EHJ 2012
Cells are not molecules!

ATMP
Cell type/MoA Source Auto/Allo

Disease
Acute/Chronic STEMI/IHF/DCM

Cardiac Cell Therapy

Patient
Age Genetics Comorbidities Medications
CELLS IN THE SPOTLIGHT: THE SEARCH FOR POTENCY

FIRST GENERATION

SECOND GENERATION

THIRD GENERATION

Skeletal muscle derived cells
Bone marrow derived cells
Adipose derived stem cells
Cardiac derived stem cells
Cardiopoietic / Allogeneic BM-derived cells
“Combo” approach

Myoblasts
MNC EPC MSC
MSC
MSC
CPC MPC
MSC/ CSC
MSC/ M2like

MSC/M2like

Bone Marrow Cell Therapy for Ischemic Heart Disease
The Never Ending Story

Giulio Pompilio, Patrizia Nigro, Beatrice Bassetti, Maurizio C. Capogrossi

• **24 meta-analyses of about 80 RCTs,**
• **Heterogeneity of target disease, including criteria, surrogate endpoints, methods.**
• **Weak functional benefit (when present),**
• **No conclusive data about clinical impact.**
Where we stand…

- MoA: paracrine paradigm
- Few preclinical comparative studies
- Very few clinical comparative studies
- Mixed results very difficult to compare
Cell types in actively enrolling trials

Viewpoints

Power Is Nothing Without Control
The Enduring Search for the Best Cell in Cardiac Cell Therapy at a Crossroads

Beatrice Bassetti, Maurizio C. Capogrossi, Giulio Pompilio
Who may benefit?

- ADVANCED ISCHEMIC HEART FAILURE
- REFRACTORY ANGINA
Refractory ischemic cardiomyopathy

- More patients with refractory angina.
  - US: 100,000 - 200,000 new cases/year (Am J Cardiol 1999;84:598)
  - EU: 120,000 - 180,000 new cases/year
- Factors: aging, statins, better treatments
- Significant morbidity
- Frequent ER/hospital visits
When the going get tough..
Impact of Cell Therapy on Myocardial Perfusion and Cardiovascular Outcomes in Patients With Angina Refractory to Medical Therapy

A Systematic Review and Meta-Analysis

6 Studies with 353 participants included

**SPECT**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cell-based Therapy</th>
<th>Control</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>van Ramshorst et al, 2009</td>
<td>-3.4</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>Tse et al, 2007</td>
<td>-0.5</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Losordo et al (LD), 2011</td>
<td>-117.4</td>
<td>221.2</td>
<td>55</td>
</tr>
<tr>
<td>Jimenez-Quevedo et al, 2014</td>
<td>-0.5</td>
<td>2.2</td>
<td>17</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>116</td>
<td>97</td>
<td>100%</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.01, df = 3 (P = 0.80); I² = 0%
Test for overall effect: Z = 3.42 (P = 0.0006)

**A Frequency of Anginal Episodes**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Stem Cell</th>
<th>Control</th>
<th>Mean Difference</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
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<tr>
<td>Wang et al, 2010</td>
<td>-15.6</td>
<td>4</td>
<td>56</td>
</tr>
<tr>
<td>Losordo et al (LD), 2011</td>
<td>-16.6</td>
<td>8.9</td>
<td>55</td>
</tr>
<tr>
<td>Jimenez-Quevedo et al, 2014</td>
<td>-8.5</td>
<td>8.1</td>
<td>17</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>134</td>
<td>137</td>
<td>100%</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 38.50; Chi² = 28.43, df = 3 (P < 0.00001); I² = 90%
Test for overall effect: Z = 2.07 (P = 0.04)
Randomized, double-blind, multicenter trial comparing IM cell administration with no intervention (standard of care) or IM placebo injections (active control) in patients with refractory angina.

CD34+ cells using an ISOLEX 300i system after G-CSF mobilization (Baxter Healthcare Corporation).

NOGA XP-guided endocardial injections using MyoStar catheter (Biosense Webster)

Primary efficacy endpoint: TET at 12 months

Treated set: 112 patients randomized (28 SOC, 27 active control, 57 CD34+)

Premature termination by the Sponsor (Baxter HC) due to “strategic considerations” (at less of one quarter of planned enrollment).

Povsic TJ et al., JACC Cardiovasc Int 2016
CHANGE IN TOTAL EXERCISE TIME

Povsic TJ et al., JACC Cardiovasc Int 2016
## The cell product PTC-CD133

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Analytical Procedure</th>
<th>Specification</th>
<th>SOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purity (%CD133+ cells on CD45+ viable cells)</td>
<td>Flow Cytometry</td>
<td>≥80%</td>
<td>LABTCG-SV-POS 141005-090.2</td>
</tr>
<tr>
<td>Viability (% negative cells to Propidium Iodide)</td>
<td>Flow Cytometry</td>
<td>≥80%</td>
<td>LABTCG-SV-POS 141005-090.2</td>
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<tr>
<td>Cellularity (number of total viable nucleated cells)</td>
<td>Trypan blue exclusion method</td>
<td>1-12 x 10^6</td>
<td>LABTCG-SV-POS 061204-014.4</td>
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<td>Sterility</td>
<td>Sterility test (Eu Farmacopeia)</td>
<td>Negative</td>
<td>Validation report by Eurofins Biolab n° CC130.07</td>
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<tr>
<td>Endotoxin</td>
<td>LAL test</td>
<td>&lt;0.5 EU/mL</td>
<td>LABTCG-SV-POS 171204-027.3</td>
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**AIFA-approved cardiac CT**
"Phase I trial of endocavitary injection of bone-marrow derived CD133^+ cells in ischemic refractory cardiomyopathy (RECARDIO Trial)

- Phase I, prospective, multicentric to assess safety and preliminary efficacy of endocavitary injection of autologous BM-derived CD133^+
- 10 patients with refractory cardiomyopathy (CCS III-IV; EF >45%)
- Efficacy follow-up 6 months; safety follow-up 12 months
- Sponsored by Ministry of Health (RF2010)
STUDY POPULATION

• Milano - CCM
• Monza - H San Gerardo (GMP)
• Torino - Molinette

INCLUSION CRITERIA

• Ischemic heart failure not amenable to any type of revascularization procedure,
• CCS and/or NYHA class III/IV under state-of-the-art maximal therapy,
• LVEF between 20% and 45%,
• Peak V0₂ ≤ 21 mL/Kg/min,
• Presence of a reversible perfusion defect ≥ 10% of the LV myocardium as determined by gated-SPECT,
• 18 years ≤ Age ≤ 80 years.
**PRIMARY ENDPOINTS**

- **MACE up to 12 months:**
  - Death
  - Non fatal MI
  - Hospitalization due to IHF

- **SAEs up to 6 months:**
  - Cardiac perforation
  - Pericardial tamponade
  - Sustained VT
  - Ectopic tissue formation
  - Malignant arrhythmias

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**EFFICACY ASSESSMENT**

- An increase of Summed Stress Score (SSS) or Summed Difference Score (SDS) on regional perfusion at stress gated-SPECT
TRIAL FLOW CHART

**Screening**
- Inclusion/exclusion criteria check
- Informed Consent signed

**Treatment**
- Bone marrow harvest
- GMP grade immunomagnetically selection of ATMP-CD133
- Endocavitary intramyocardial administration of ATMP-CD133

**Follow-up**
- Efficacy: SPECT and CPET at 6 and 12 months
- Safety: cardiovascular events up to 12 months
TREATMENT

A) Bone marrow aspiration from the iliac posterior crest

B) CD133+ cells immunomagnetically selected at GMP facility

C) Patient referred to the CathLAB the day after

D) Percutaneous inoculation of CD133+ cells into ischemic regions of the LV through an endocavitary flouroscopy-based approach
BIOCARDIA HELIX INFUSION CATHETER SYSTEM

- Intended for the infusion of agents into myocardium
- Endovascular route
- Fluoroscopy-based navigation

Retrograde
Novel Application of 3-Dimensional Real-Time Cardiac Imaging to Guide Stem Cell-Based Therapy

Corrado Carbucicchio, MD, Michela Casella, MD, Valentina Catto, BE, Beatrice Bassetti, MSc, Alberto Bestetti, MD, and Giulio Pompilio, MD

Can J Cardiol, 2015
<table>
<thead>
<tr>
<th>Patients</th>
<th>BM volumes</th>
<th>CD133 x 10^6</th>
<th>Purity</th>
<th>Vitality</th>
<th>Nº of injections</th>
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<td>1-001</td>
<td>328</td>
<td>7,62</td>
<td>93,76</td>
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<tr>
<td>1-002</td>
<td>309</td>
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<td>1-008</td>
<td>390</td>
<td>11,47</td>
<td>87,34</td>
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<td>280</td>
<td>2,66</td>
<td>89,1</td>
<td>99,89</td>
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<tr>
<td>Mean ± SD</td>
<td>362 ± 49</td>
<td>6,57 ± 3,27</td>
<td>87,71 ± 4,98</td>
<td>99,77 ± 0,38</td>
<td>12 ± 1</td>
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## SAFETY PROFILE

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<tr>
<th>Patients</th>
<th>In-hosp Mortality</th>
<th>In-hosp Morbidity</th>
<th>3 months Mortality</th>
<th>3 months Morbidity</th>
<th>6 months Mortality</th>
<th>6 months Morbidity</th>
<th>12 months Mortality</th>
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<td>Subdural hematoma</td>
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<td>1-008</td>
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<td>1-009</td>
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<tr>
<td>3-001</td>
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<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>Right sup fem PCI</td>
<td>no</td>
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</table>

No SAEs up to 6 months / 1 MACE at 12 months
CLINICAL BENEFIT

Changes of Canadian Class

*** p < 0.0001

Nitrates assumption per week

* p < 0.05

T0  T6

T0  T6
Summed stress (SSS) rest (SRS) and difference (SDS) scores at gated-SPECT

* $p<0.05$
CONCLUSIONS

- **Refractory ischemic cardiomyopathy/refractory angina** appear to be a good target for cardiac cell therapy (cCT);

- **Patients to be entered in future pivotal trials** need to be carefully selected for high likelihood to benefit;

- **In the Nederlands cCT is reimbursed on a hospital-based exception (Leiden)** for the treatment of refractory angina.
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