Cellular Therapy and Myocardial Regeneration

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Stem cell sources

- Bone marrow
- Mobilized peripheral blood
- Cord blood
- Adipose tissue
- Amniotic fluid
- Placenta
- Limbus
- ........
- Selected organs/tissues
Pubmed search, 30 Jan 2011
Stem Cells and Organ Regeneration

- 510 articles, 333 reviews

<table>
<thead>
<tr>
<th>ORGAN/TISSUE</th>
<th>CONDITIONS</th>
<th>SETTINGS</th>
<th>SPECIALTIES</th>
<th>PROFIT vs NO PROFIT</th>
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<tbody>
<tr>
<td>Heart</td>
<td>Myocardial infarction</td>
<td>Laboratory</td>
<td>Orthopedics</td>
<td>NO PROFIT</td>
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<tr>
<td>Liver</td>
<td>Diabetes</td>
<td>Small animal</td>
<td>Maxillofacial surgery</td>
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<td>Skin</td>
<td>Cerebral palsy</td>
<td>Large animal</td>
<td>Plastic surgery</td>
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<tr>
<td>Brain</td>
<td>Kidney failure</td>
<td>Human (phase I-II)</td>
<td>Internal medicine</td>
<td>NO PROFIT</td>
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<tr>
<td>Cornea</td>
<td>Liver failure</td>
<td>Human (phase III)</td>
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<td>Inner ear</td>
<td>Critical limb ischemia</td>
<td>Routine? NO</td>
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<td>Urinary bladder</td>
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<td>Vocal fold</td>
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Figure 1 Flowchart of trial search and selection progress. Flowchart shows number of citations retrieved by individual searches and number of trials included in review. BMC, bone marrow cells; CPC, circulating progenitor cells; RCTs, randomised controlled trials.
Some non-hem stem cell experimental protocols

• **Myocardial ‘repair’?**
  - Vascular regeneration?
  - Cell fusion?
  - Is 4-6% LVEF increase clinically relevant?

• **Diabetes**
  - Studies ongoing, no firm conclusion yet

• **Cerebral palsy**
  - Large study ongoing, no firm conclusion yet
1. **SWiss Multicenter Intracoronary Stem Cells Study in Acute Myocardial Infarction (SWISS-AMI)**
   Condition: Acute Myocardial Infarction; Intervention: Procedure: intracoronary bone marrow cells infusion

2. **Trial of Hematopoietic Stem Cells in Acute Myocardial Infarction**
   Condition: Reperfused Acute Myocardial Infarction; Interventions: Other: Granulocyte Colony Stimulating Factor treatment (G-CSF); Other: Bone marrow mononuclear cells

3. **Bone Marrow Derived Adult Stem Cells for Acute Anterior Myocardial Infarction**
   Condition: Acute AMI; Interventions: Other: Bone marrow derived progenitor cells or placebo infusion; Other: Placebo infusion

4. **Use of Adult Autologous Stem Cells in Treating People Who Have Had a Heart Attack (The TIME Study)**
   Condition: Left Ventricular Dysfunction; Interventions: Biological: Adult stem cells; Biological: Placebo

5. **Treatment of Myocardial Infarction With Bone Marrow Derived Stem Cells**
   Condition: Acute Myocardial Infarction; Intervention: Procedure: Coronary catheterization and stem cell infusion

6. **Intracoronary Autologous Stem Cell Transplantation in ST Elevation Myocardial Infarction: TRACIA STUDY**
   Condition: Acute Myocardial Infarction, Intervention: Genetic: Stem Cell Transplantation

7. **Stem Cell Mobilization by G-CSF Post Myocardial Infarction to Promote Myocyte Repair**
   Condition: Myocardial Infarction; Intervention: Drug: Granulocyte Colony Stimulating Factor

8. **Prochymal® (Human Adult Stem Cells) Intravenous Infusion Following Acute Myocardial Infarction (AMI)**
   Condition: Myocardial Infarction; Interventions: Drug: Prochymal®; Drug: Placebo

9. **Study on the Efficacy and Mechanism of Cardiac Rehabilitation for Stem Cell Mobilization and Heart Failure Improvement**
   Condition: Myocardial Infarction; Intervention: Behavioral: cardiac rehabilitation

10. **Use of Adult Autologous Stem Cells in Treating People 2 to 3 Weeks After Having a Heart Attack (The Late TIME Study)**
    Condition: Left Ventricular Dysfunction; Interventions: Biological: Adult stem cells; Biological: Placebo

Other 39 registered clinical trials follow …
The ‘Franco Calori’ Cell Factory of Ospedale Maggiore Policlinico, Milan, Italy

A public hospital clean room for GMP preparation of clinical grade cellular therapy products accredited by AIFA (Italian Drug Agency) since July 2007

- Clinical ‘stem cell’ protocols developed during 2000-2011
  1. Allogeneic transplant of ex-vivo expanded cord blood
     - n=3 oncohematology patients, Dept of Pediatrics Pavia University
  2. Autologous transplant of muscular stem cells
     - n=8 DMD patients, Dept of Neurology, Milan University
  3. Intracoronary autologous transplant of CD133+ cells from bone marrow vs peripheral blood in acute myocardial infarction
     - n=15 AMI patients, Cardiology Cooperative Group
  4. Vocal Fold Repair (study of MSC in fat, in progress)
     - n=12 patients, cooperation with Otolaryngology Unit
  5. Cellular therapy for liver failure (in progress)
     - n=12 cirrhotic patients, cooperation with Bologna University
  6. Cellular therapy for Progressive Supranuclear Palsy (in progress)
     - n=20 patients, cooperation with Parkinson Center, ICP, Milan
STUDY FLOW CHART (1)

Presentation in emergency room and diagnosis of AMI day 0

Primary PTCA <24 hrs from the onset of the symptoms

absence of MB and lack of SSTEr

NO

Out of study

YES

ENROLLMENT AND INFORMED CONSENT (DAY 0 to 3)
BASELINE EVALUATION:
- $^{13}$NH$_3$ AND FDG PET
- ECHO 2D

RANDOMIZATION

GROUP A
BM harvesting

GROUP B
GCSF administration and apheresis

GROUP C
Controls: standard therapy
STUDY FLOW CHART (3)

GROUP A
BM harvesting

GROUP B
GCSF administration and apheresis

CD133+ cell
GMP production

Intracoronary administration
Assessed for eligibility (n= 355)

Enrollment n=16*

Randomization 15

Allocation n=15

Unmet inclusion criteria: * 1 denied consent ** heart transplantation

GROUP A
Allocated to intervention n=5
Received intervention n=5

GROUP B
Allocated to intervention n=5
Received intervention n=5

GROUP C
Allocated to intervention n=5
Received intervention n=5

Follow-Up

Lost to follow-up (n= 0 )
Discontinued intervention (n=0) GROUP A

Lost to follow-up (n= 0 )
Discontinued intervention (n= 0) GROUP B

Lost to follow-up (n= 0 )
Discontinued intervention (n=1) ** GROUP C

Analysis (3, 6 and 12 months)

Analyzed: @6 n= 5 @12 n=4

Analyzed: @6 n= 4 @12 n=3

Analyzed: @6 n= 5 @12 n=4**
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• Published reports from clinical ‘stem cell’ protocols developed during 2000-2011
  – Torrente et al. Autologous transplantation of muscle-derived CD133+ stem cells in Duchenne muscle patients.  
  – Castellani et al. The role of PET with 13N-ammonia and 18F-FDG in the assessment of myocardial perfusion and metabolism in patients with recent AMI and intracoronary stem cell injection.  
  – Colombo et al. Myocardial blood flow and infarct size after CD 133+ cell injection in large myocardial infarction with good recanalization and poor reperfusion: results from a randomized controlled trial.  
    • J Cardiovasc Med 2011, in press
The Role of PET with $^{13}$N-Ammonia and $^{18}$F-FDG in the Assessment of Myocardial Perfusion and Metabolism in Patients with Recent AMI and Intracoronary Stem Cell Injection


Massimo Castellani¹, Alessandro Colombo², Rosaria Giordano³, Enrico Pusineri⁴, Cristina Canzi¹, Virgilio Longari¹, Emanuela Piccaluga², Simone Palatresi⁴, Luca Dellavedova¹, Davide Soligo⁵, Paolo Rebulla³, and Paolo Gerundini¹

**Group A:** CD 133+ cells from bone marrow  
**Group B:** CD 133+ cells from mobilized peripheral blood  
**Group C:** Controls

**FIGURE 4.** Mean percentage variation in infarct size and MBF in patients of the 3 groups during follow-up.
• Cell Transplant?
• Cell Regeneration?
• Tissue Repair?
Clinical results of cellular therapy protocols in heart disease (2001-2011)

- **Acute myocardial infarction**
  - LVEF +11.4%
  - Infarct size -34%

- **Chronic infarction/ischemic heart disease (+CABG)**
  - LVEF +10%

- **Dilated cardiomyopathy**
  - LVEF: two studies, +5.4% and +8%

Source: Strauer & Steinhoff. 10 years of intracoronary and intramyocardial bone marrow stem cell therapy of the heart. From the methodological origin to clinical practice. J Am Coll Cardiology 2011; 58:1095-104
Cell type and possible mechanisms for myocardial regeneration

- **CD34+ & mixed BM cells**
  - Transdifferentiation? No ...
- **CD133+**
  - Neovascularization
- **MSC (from BM, AT, CB)**
  - Drugstore
Conclusions

• Further studies ....
  - What cell(s)?
    ➔ purified populations
  - What administration technique?
  - What patients?
    ➔ more severe
  - What time?
    ➔ 2nd week post AMI?