

# 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

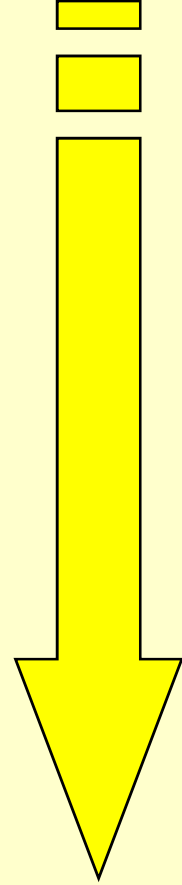
→ ORGAN/TISSUE	→ CONDITIONS	→ SETTINGS
<ul style="list-style-type: none"><li>- Heart</li><li>- Liver</li><li>- Skin</li><li>- Brain</li><li>- Cornea</li><li>- Tooth</li><li>- Inner ear</li><li>- Urinary bladder</li><li>- Cartilage</li><li>- Tendon</li><li>- Intervert. disc</li><li>- Vocal fold</li><li>- .....</li></ul>	<ul style="list-style-type: none"><li>- Myocardial infarction</li><li>- Diabetes</li><li>- Cerebral palsy</li><li>- Kidney failure</li><li>- Liver failure</li><li>- Parkinson's disease</li><li>- Critical limb ischemia</li><li>- .....</li></ul>	<ul style="list-style-type: none"><li>- Laboratory</li><li>- Small animal</li><li>- Large animal</li><li>- Human (phase I-II)</li><li>- Human (phase III)</li><li>- RCT</li><li>- Routine? NO</li></ul>
	→ SPECIALTIES	→ PROFIT vs NO PROFIT
	<ul style="list-style-type: none"><li>- Orthopedics</li><li>- Maxillofacial surgery</li><li>- Plastic surgery</li><li>- Internal medicine .....</li></ul>	

# Autologous transplantation of blood-derived stem/progenitor cells for ischaemic heart disease

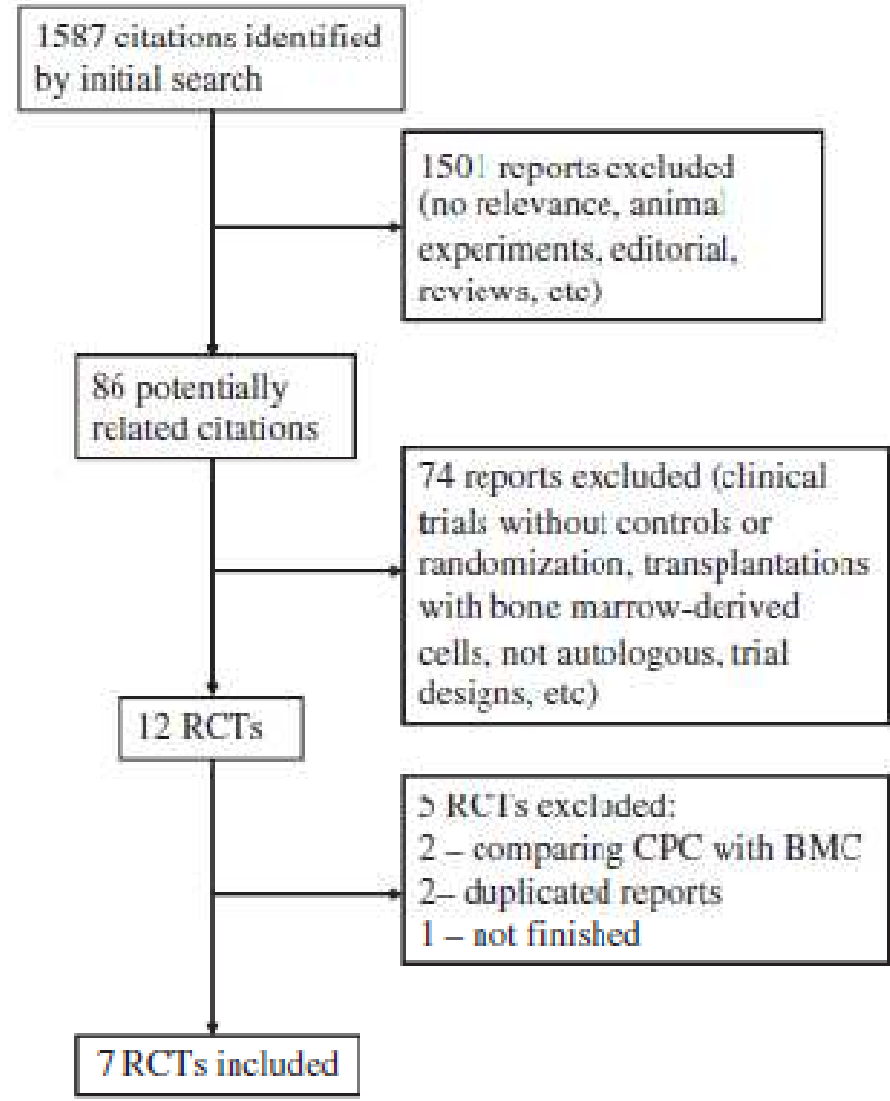
Y. Wen,<sup>1,2</sup> L. Meng,<sup>3</sup> Y. Ding,<sup>1,2</sup> J. Ouyang<sup>3</sup>

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# 1587



# 7



**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

# 1st 10 myocardial infarction stem cell experimental clinical trials listed at Clinicaltrials.gov

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 ...

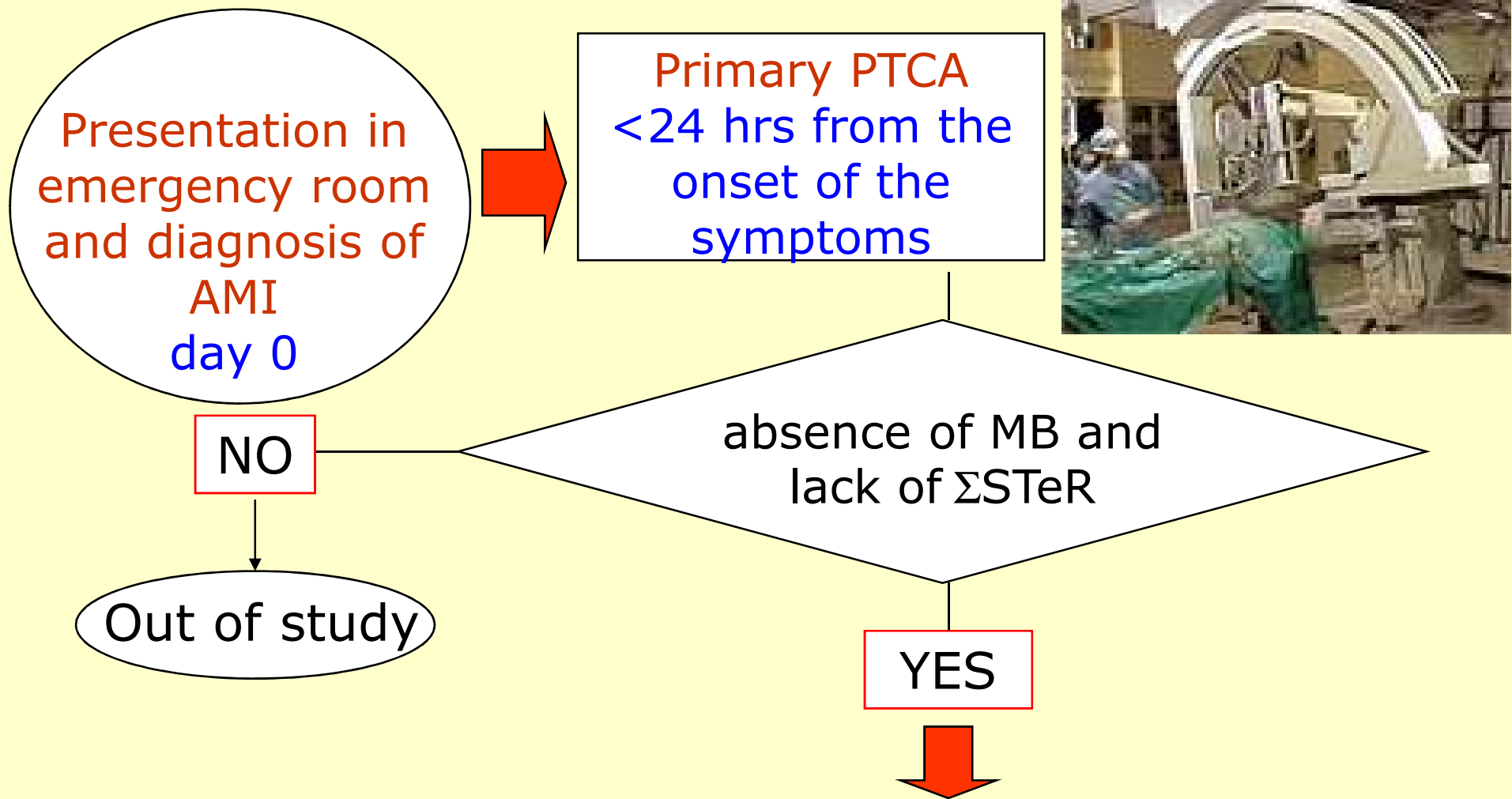
# The 'Franco Calori' Cell Factory of Ospedale Maggiore Policlinico, Milan, Italy

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

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- **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)



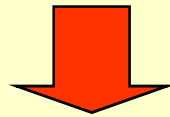
**ENROLLMENT AND INFORMED CONSENT (DAY 0 to 3)**



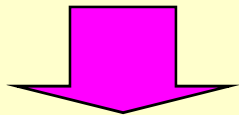
# STUDY FLOW CHART (2)

## BASELINE EVALUATION:

- $^{13}\text{NH}_3$  AND FDG PET
- ECHO 2D

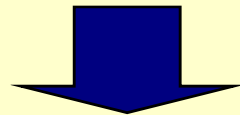


## RANDOMIZATION



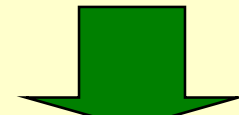
GROUP A

BM  
harvesting



GROUP B

GCSF  
administration  
and apheresis



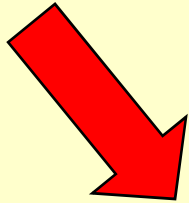
GROUP C

Controls:  
standard  
therapy

# STUDY FLOW CHART (3)

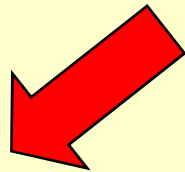
GROUP A

BM harvesting

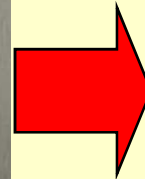


GROUP B

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)

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

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

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**
  - Giordano et al. Ex vivo expansion of cord-blood derived progenitor cells for allogeneic transplantation: a phase I-II clinical study.
    - EBMT Meeting Proceedings, 19-22 March, 2006.
  - Torrente et al. Autologous transplantation of muscle-derived CD133+ stem cells in Duchenne muscle patients.
    - Cell Transplant 2007;16:563-77.
  - Castellani et al. The role of PET with <sup>13</sup>N-ammonia and <sup>18</sup>F-FDG in the assessment of myocardial perfusion and metabolism in patients with recent AMI and intracoronary stem cell injection.
    - J Nucl Med 2010;51:1908-16.
  - 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 $^{13}\text{N}$ -Ammonia and $^{18}\text{F}$ -FDG in the Assessment of Myocardial Perfusion and Metabolism in Patients with Recent AMI and Intracoronary Stem Cell Injection

J Nucl Med 2010;51:1908-16.

Massimo Castellani<sup>1</sup>, Alessandro Colombo<sup>2</sup>, Rosaria Giordano<sup>3</sup>, Enrico Pusineri<sup>4</sup>, Cristina Canzi<sup>1</sup>, Virgilio Longari<sup>1</sup>, Emanuela Piccaluga<sup>2</sup>, Simone Palatresi<sup>4</sup>, Luca Dellavedova<sup>1</sup>, Davide Soligo<sup>7,5</sup>, Paolo Rebulli<sup>3</sup>, and Paolo Gerundini<sup>1</sup>

Group A: CD 133+ cells from bone marrow

Group B: CD 133+ cells from mobilized peripheral blood

Group C: Controls

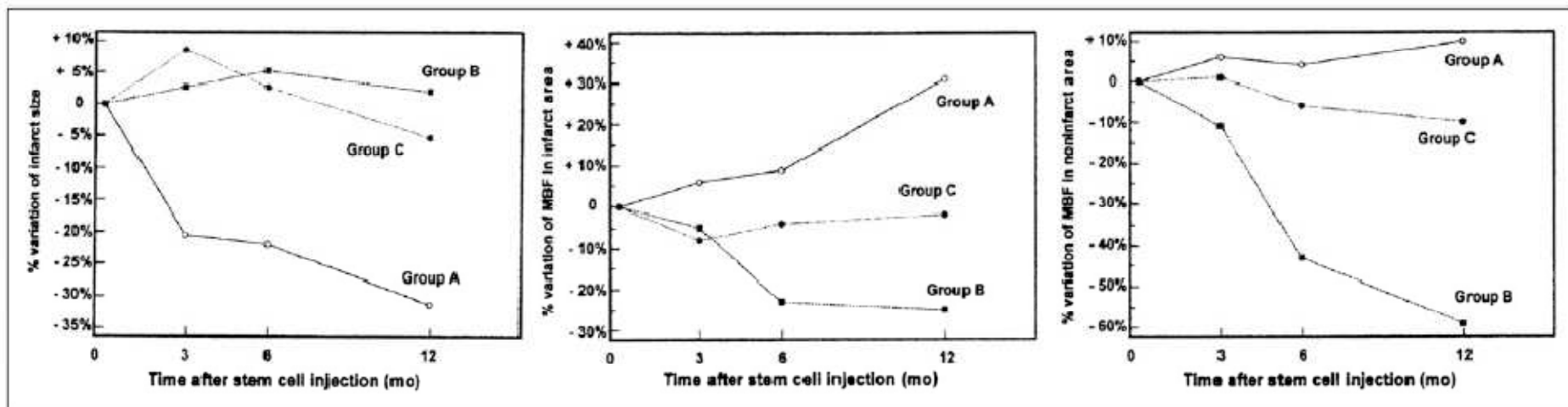
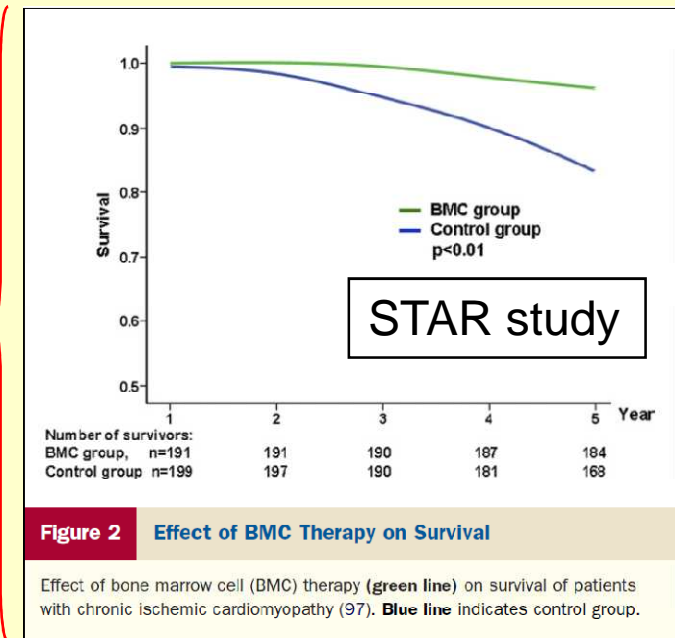


FIGURE 4. Mean percentage variation in infarct size and MBF in patients of the 3 groups during follow-up.

- 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?