Stem Cell Therapy in Acute Myocardial Infarction: hype or reality?

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No disclosures

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Cardiac Regeneration in 2007:
the stem cell approach

Premise: myocyte deficit contributes to dysfunctional phenotype?

Pfeffer et al. NEJM 2003

Caulfield et al. Circ 1976
Full Regeneration of Myocardium in Zebrafish

Cardiac Regeneration: how it all started in 2001

Bone marrow cells regenerate infarcted myocardium


„Our studies indicate that locally delivered bone marrow cells can generate de novo myocardium, ameliorating the outcome of coronary artery disease.” (Nature, 2001)
When Bob Grinstead landed in Bangkok in March, he might have been mistaken for a typical tourist. But the 70-year-old retired salesman from Atlanta wasn’t in any shape for sightseeing. Since suffering a massive heart attack in 1990, he’d undergone two bypass surgeries and two dozen angioplasties. After his doctors told him there was nothing more they could do, Grinstead turned to the Internet for ideas…

Countless searches and phone calls later, he was on a plane to Thailand in a quest for the Holy Grail of 21st century medicine: Stem-Cell Therapy

(quoted from TIME magazine)

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Dr. Fulga's treatment repairs damaged heart tissue using adult stem cells harvested from the patient's blood.

The final product is injected into the patient's heart, where it helps the heart tissue recover its function.

„We don’t actually know the basis of the science,” Dr. Fulga cheerfully admits.

The process costs about $30,000.- per patient, plus physician's and travel expenses.

(quoted from TIME magazine)

Number of PubMed references on this type of treatment: 0
Cytokine/Growth Factor Response and BMC Mobilization after Myocardial Infarction

Mobilization:
- CD133+ (Ott, EHJ 2006)
- CD34+ (Crea, EHJ 2005)
- Mes SC (Kastrup, EHJ 2006)

Local:
- HIF1-a
- VEGF
- SDF-1

Early peak post-AMI

Systemic:
- EPO
- CRP, IL-6, IL-8,
- FGF2
- VEGF, SCF
- ....
Stem Cell Mobilisation by G-CSF after Subacute STEMI (44 Pts > 6 h and < 7 d after Primary PCI)

1. Kuethe et al. (Am Heart J 2005;150:115)
2. Ince et al. (FIRSTLINE-AMI, Circ 2005;112: 3097)
3. Valgimigli et al. (Eur Heart J 2005;26:1838)
4. Ripa et al. (STEMMI, Circ 2006;113:1983)
5. Zohlnhofer et al. (Revival 2, JAMA 2006;295:1003)

----> reassuring safety profile
----> not superior to placebo for LV function recovery
----> timing, dose, direct cellular effects?

G-CSF RCT Trials in Acute Myocardial Infarction
BOOST: LV-Ejection Fraction after 6 and 18 Months

Controls

BMC-Transfer

(Circulation 2006;113:1287-94)
LEUVEN STEM CELL TRIAL DESIGN

**AMI**: ST-$$\uparrow$$ mL 6 mm, Δt >2h + LV dysfunction post PCI

- Informed consent
- TTE & PET
- Bone marrow aspiration + randomization

24 hours

BMSC or placebo transfer in open IRA

Admission (4 d) | Follow-up (4 mo) | Follow-up (1 y)
---|---|---
- cine MRI - LE | - cine MRI - LE | - cine MRI - LE
- TTE | - TTE & PET | - TTE

Myocardial Infarction Imaging

Cx occlusion | LAD occlusion
---|---
1 week | 4 months
### CMR in Stem Cell Therapy (RCTs)

<table>
<thead>
<tr>
<th></th>
<th>EDV</th>
<th>EF</th>
<th>Mass WTh</th>
<th>WM</th>
<th>Area at Risk</th>
<th>MPI</th>
<th>CE-IR-MRI</th>
<th>IS</th>
<th>IT</th>
<th>MVO</th>
<th>Hem</th>
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<tbody>
<tr>
<td>BOOST</td>
<td>Y</td>
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<tr>
<td>Repair-AMI</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<td>Y</td>
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<tr>
<td>Leuven-AMI</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y (Y)</td>
<td>Y</td>
<td>Y (Y)</td>
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<td>ASTAMI</td>
<td>Y</td>
<td>Y</td>
<td>(Y)</td>
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<td>Y</td>
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<td>(SPECT)</td>
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<tr>
<td>STEMMI</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<td>MAGIC-3</td>
<td>Y</td>
<td>Y</td>
<td>(Y)</td>
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<tr>
<td>REVIVAL-2</td>
<td>Y</td>
<td>Y</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(SPECT)</td>
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<tr>
<td>G-CSF-STEMI</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
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<td>Y</td>
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### Bone Marrow Cell Transfer Post-AMI

(randomized controlled trials 2006)

**Leuven AMI (n=67)
(Lancet 2006; 367:113-121)**

- **LVEF - MRI (%)**
  - CON + 2.2%
  - BMSC + 3.4%
  - Δ = +1.2% (P=NS)

**REPAIR-AMI (n=187)
(NEJM 2006; 355:1199-1221)**

- **LVEF - angio (%)**
  - CON + 3.0%
  - BMSC + 5.5%
  - Δ = +2.5% (P<0.05)

**ASTAMI (n=87)**

- **LVEF - MRI (%)**
  - CON + 4.2%
  - BMSC + 1.2%
  - Δ = -3% (P=NS)
### Mixed Results of Early RCT using BMC to be Expected in Absence of Gold Standard

BMC effect varies with timing, infarct severity, and cell preparation.

<table>
<thead>
<tr>
<th>Cell preparation</th>
<th>Timing (days)</th>
<th>LVEF (prim EP)</th>
<th>LVEDV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Boost</strong></td>
<td></td>
<td></td>
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<tr>
<td>(n=60)</td>
<td></td>
<td></td>
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<tr>
<td>Gelatine-polysucc</td>
<td>4.8</td>
<td>6 mo - MRI</td>
<td></td>
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<tr>
<td>24.6x10^6 (9.5 CD34+)</td>
<td>+6% → +2.8%</td>
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<tr>
<td><strong>2. Leuven-AMI</strong></td>
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<tr>
<td>(n=67)</td>
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<tr>
<td>Ficoll</td>
<td>1</td>
<td>4 mo - MRI</td>
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<tr>
<td>304x10^6 (2.8 CD34+)</td>
<td>+1.2%</td>
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<tr>
<td><strong>3. Repair-AMI</strong></td>
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<tr>
<td>(n=187)</td>
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<tr>
<td>Ficoll</td>
<td>3-7</td>
<td>4 mo - angio</td>
<td></td>
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<tr>
<td>280x10^6 (2.5 CD34+)</td>
<td>+2.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4. AST-AMI</strong></td>
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<tr>
<td>(n=87)</td>
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<td></td>
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</tr>
<tr>
<td>Lymphoprep</td>
<td>5</td>
<td>6 mo - MRI</td>
<td></td>
</tr>
<tr>
<td>68x10^6 (0.7 CD34+)</td>
<td>-3%</td>
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</tbody>
</table>

### Bone Marrow Cell Transfer Post-AMI
Infarct size and Timing of Cell Transfer

#### Multi-center (n=18)

**Baseline EF (%)**

(Schachinger et al., NEJM 2006; 355:1210-21)
MVO impairs LV Functional Recovery

• Early: present in 64% pts
  – Vol: 7.5 g / transmurality 51% / MVO-infarct ratio: 36%

Acute phase

FU (4 months)

3 min

20 min

20 min

LV-EF (%)

46 (8)  P=NS 47 (9)

3-4 d  4 mo

LV-EDV (mL)

162 (33)  P=0.014  175 (43)

3-4 d  4 mo

Bogaert et al. Eur J Rad 2007

How to Optimize Stem Cell Transfer?
Homing and Engraftment

IC injection

18F-FDG labeled BMSC:
1.3 - 2.6% homing infarct region

IV injection

18F-FDG labeled BMSC:
background

IC injection

18F-FDG labeled CD34+SC:
14 - 39% activity

Hofmann, Circ 2005
Global LV Function Recovery in AMI Patients with and without Microvascular Obstruction

![Graph showing LV-EF (%) over 1 week to 4 months with comparison between BMSC (n=17) and CON (n=19) with and without MVO.]

Global versus Regional LV Function Analysis for Risk Stratification after AMI

**Predictors of mortality**
* (forward Cox PHA)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>P</th>
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<tbody>
<tr>
<td>Age (per 10y)</td>
<td>1.65</td>
<td>&lt;.0001</td>
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<tr>
<td>Kilip Class</td>
<td>1.44</td>
<td>&lt;.0001</td>
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<tr>
<td>(per 1 increase)</td>
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<tr>
<td>WMSI</td>
<td>1.15</td>
<td>&lt;.0001</td>
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<tr>
<td>(per 0.2 increase)</td>
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*(Moller et al. Am Heart J 2006;151:419-25)*
Powerful Technology to Detect Biological Signals: MRI and TDI Analysis
Infarct Transmurality & Segmental Contraction

Coronary occlusion

- LV

- 20 min
- 60 min
- 3h
- >6h

Improved Regional Contraction in Dysfunctional Segments indicates BMC Functional Repair

Improved contraction (%)

P<0.05 for interaction

Infarcted segments (n=232)

Baseline 5 d 2 mo 4 mo 1 yr

Baseline Strain Septum (%)

Strain Septum 4 months (%)

Baseline 5 d 2 mo 4 mo 1 yr

CONTROL BMC

BMSC

BMSC

BMSC

BMSC

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BMSC Treatment Effect* on Infarct Size

Infarct size (g) 28% treatment effect* P=0.036

CONTROL BMSC

* Expressed as ratios of adjusted squares means (ANCOVA) with 95% CI.

Lancet 2006; 367:113-121

BMSC Treatment Effect* on Infarct Size

Infarct size (g) 28% treatment effect* 23%

CONTROL BMSC

* Expressed as ratios of adjusted squares means (ANCOVA) with 95% CI.
# Meta-Analysis: LV Ejection Fraction 
(n=499 BMC, n=477 Controls)

## Pooled difference

3.66% 
95% CI [1.93% to 5.40%]  
P<0.001
Clinical Trials of Bone Marrow Cell Therapy

where are we?

- Growing consensus that improvement in cardiac function is largely independent of cardiac muscle regeneration.

- The mixed results in the 4 RCTs of BMC transfer post MI, should not defer from cell transfer studies.

  - *need for preclinical parallel mechanistic studies*
  - *focus on informative clinical trials*

Limitations of Bone Marrow Cell-mediated Repair after Myocardial Infarction

**In situ:**
- no cardiac differentiation
- impaired microcirculation (NO low) and angiogenesis
- death of cardiac progenitor cells
- cellular senescence (oxidative damage, telomere shortening...)

  Cardiac protection vs regeneration

**Systemic:**
- insufficient number and function of progenitor cells
- defective homing

  Enhancement strategies for BMC homing and survival?
Stem Cells: from Bench to Bedside
Cell Enhancement Strategies

- statins
- p38 inhibitors
- PPARγ
- eNOS enhancers
- Integrin activators
- Cardiac specification….
  (gene transduction)

Priming of Progenitor cells
Impaired EPC phenotype & non-responders
~ CV Risk factors
~ post MI cell modification

- Mechanical activation
- Cytokines / Growth factors:
  - IGF-1, HGF, SDF-1, PDGF,…. 
- NO

Priming of Target Tissue
Hostile target milieu
~ oxidant stress
~ microvascular obstruction
~ transmigration - residency

Comparison of Different Progenitor Cell Populations in the Infarcted Porcine Heart

T=0
90 min balloon occlusion Cx
Hemodynamics
TTE
Trop, CK-MB

T=1w
EPC/MSC/Plac IC Transfer
Hemodynamics
TTE - MRI
Trop, CK-MB

T=7w
Euthanasia
Lenti-GFP MSC
(n=11)
Labeled EPC
(n=10)
Placebo
(n=10)
Hemodynamics
TTE
Trop, CK-MB
Histology
Conclusions

• IC transfer of autologous BMSCs is safe and does not cause delayed major adverse clinical events.

• In early reperfused MI with moderate reduction in global LV function, BMSC transfer has variable effects on global function recovery, but significantly improves recovery of regional function.

• The challenge for future BMSC studies is to investigate whether observed paracrine effects translate in clinical benefit in AMI patients with greater baseline impairment in systolic function.
Future Directions: Optimizing Stem Cell Transfer?

- Large, multicenter, clinical outcome study in large AMI (?
  - Centralized hematology core
  - SOPs cell preparation
  - Q-control, financial support, 

- Focused clinical studies and parallel preclinical studies
  - Boost 2 (dose comparison)
  - NL interuniversity study - Poland (cell comparison)
  - Leuven/Frankfurt/Rome/Madrid/London: FP7
  - Leuven homing studies & differentiation studies (SCIL)

Stem Cell Therapy: Fountain of Eternal Youth?

Lucas Cranach (oil on canvas 1546)
Acknowledgments
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KU-Leuven, Belgium

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- SCIL, Laboratory for Exp Cardiology, and VIB