Governance of stem cell therapy
Consequences of innovation

Prof. Dr. med. Gustav Steinhoff
Exchange of cardiomyocytes


- Method: Integration of carbon-14, generated by nuclear bomb tests indicates age of cardiomyocytes
- Results:
  1% turning over annually (age dependent)
  Fewer than 50% of cardiomyocytes are exchanged at the age of 75
- Conclusion: “… it may be rational to work toward the development of therapeutic strategies aimed at stimulating this process in cardiac pathologies.”
What are the effects of CABG surgery?


**Figure 1.** Left ventricular ejection fraction (LVEF) during 1-year follow-up — baseline LVEF (LVEF), after coronary artery bypass grafting (LVEF_1m), after 3 (LVEF_3m), 6 (LVEF_6m) and 12 (LVEF_12m) months of observation.

**Figure 2.** Wall motion score index (WMSI) during follow-up — baseline WMSI (WMSI), after coronary artery bypass grafting (WMSI_1m), after 3 (WMSI_3m), 6 (WMSI_6m) and 12 (WMSI_12m) months of observation.
Cardiac Stem Cell Therapy

mod. Dimmeler et al. JCI 2005
2001: First clinical stem cell application in heart disease (Strauer, Steinhoff)

1. Mobilization (G-GSF)
2. Systemic iv injection
3. Intracoronary injection
4. Endocardial injection

Stem / Progenitor Cell

Cardiology

Surgery

Local implantation im Patch TE Heart valve TE

Homing Extravasation

Integration Migration

Action

Action

Strauer, Düsseldorf
Intravascular application MNC BM 3/2001

Steinhoff, Rostock
Intramyocardial application CD133 BMSC 6/2001
<table>
<thead>
<tr>
<th>Cell type</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Mean follow-up duration (months)</th>
<th>Number of cells injected</th>
<th>Route of injection</th>
<th>Ejection fraction versus control (%)</th>
<th>Source</th>
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<tbody>
<tr>
<td>BMMNCC</td>
<td>R-SB</td>
<td>60</td>
<td>12</td>
<td>(10^8)</td>
<td>Intracoronary</td>
<td>+7.0 (P = 0.03)</td>
<td>Meluzin et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>R-SB</td>
<td>51</td>
<td>3</td>
<td>(2 \times 10^8)</td>
<td>Intracoronary</td>
<td>+4.1 (P = 0.001)</td>
<td>Assmus et al. (2006)</td>
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<tr>
<td></td>
<td>R-SB</td>
<td>66</td>
<td>3</td>
<td>(10^8)</td>
<td>Intracoronary</td>
<td>+3 (P = 0.04)</td>
<td>Meluzin et al. (2006)</td>
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<td></td>
<td>R-SB</td>
<td>204</td>
<td>12</td>
<td>(2.4 \times 10^8)</td>
<td>Intracoronary</td>
<td>Decreased mortality</td>
<td>Schächinger et al. (2006)</td>
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<td>20</td>
<td>6</td>
<td>(4 \times 10^7)</td>
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<td>+6.7 (NS)</td>
<td>Ge et al. (2006)</td>
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<td></td>
<td>R-SB</td>
<td>20</td>
<td>4</td>
<td>(6 \times 10^7)</td>
<td>TEIM</td>
<td>+2.5 (NS)</td>
<td>Hendriks et al. (2006)</td>
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<td></td>
<td>R-DB</td>
<td>67</td>
<td>4</td>
<td>(1.7 \times 10^8)</td>
<td>Intracoronary</td>
<td>+1.2 (NS)</td>
<td>Janssens et al. (2006)</td>
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<tr>
<td></td>
<td>R-SB</td>
<td>100</td>
<td>6</td>
<td>(8.7 \times 10^7)</td>
<td>Intracoronary</td>
<td>-3.0 (P = 0.05)</td>
<td>Lunde et al. (2006)</td>
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<td></td>
<td>R-SB</td>
<td>60</td>
<td>18</td>
<td>(2.5 \times 10^9)</td>
<td>Intracoronary</td>
<td>+2.8 (NS)</td>
<td>Meyer et al. (2006)</td>
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<td>CohortS</td>
<td>36</td>
<td>3</td>
<td>(3 \times 10^9)</td>
<td>TEIM</td>
<td>+4.0 (NS)</td>
<td>Mocini et al. (2006)</td>
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<td>R-SB</td>
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<td>4</td>
<td>(2.4 \times 10^8)</td>
<td>Intracoronary</td>
<td>+2.5 (P = 0.01)</td>
<td>Schächinger et al. (2006)</td>
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<td>3</td>
<td>(9 \times 10^7)</td>
<td>Intracoronary</td>
<td>+1.0 (P = 0.02)</td>
<td>Strauer et al. (2005)</td>
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<td>12</td>
<td>(2.6 \times 10^7)</td>
<td>TEIM</td>
<td>+8.1 (NS)</td>
<td>Perin et al. (2004)</td>
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<td>3</td>
<td>(2 \times 10^7)</td>
<td>Intracoronary</td>
<td>+1.0 (NS)</td>
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<td>CPC</td>
<td>CohortS</td>
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<td>6</td>
<td>(5 \times 10^9)</td>
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<td>+6.0 (P = 0.04)</td>
<td>Tatsumi et al. (2007)</td>
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<td>73</td>
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<td>+2.8 (NS)</td>
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<td>47</td>
<td>3</td>
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<td>Intracoronary</td>
<td>+0.8 (NS)</td>
<td>Assmus et al. (2006)</td>
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<tr>
<td></td>
<td>R</td>
<td>82</td>
<td>6</td>
<td>(1.4 \times 10^9)</td>
<td>Intracoronary</td>
<td>-0.2 (NS)</td>
<td>Kang et al. (2006)</td>
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<td>CohortS</td>
<td>70</td>
<td>6</td>
<td>(7.3 \times 10^7)</td>
<td>Intracoronary</td>
<td>+5.5 (P = 0.04)</td>
<td>Li et al. (2006)</td>
<td></td>
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<td></td>
<td>SB</td>
<td>26</td>
<td>3</td>
<td>(7 \times 10^7)</td>
<td>Intracoronary</td>
<td>+7.2 (NS)</td>
<td>Erbs et al. (2005)</td>
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<td>CD133</td>
<td>CohortS</td>
<td>27</td>
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<td>NA</td>
<td>Intramyocardial</td>
<td>NA</td>
<td>Ahmadi et al. (2007)</td>
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<td></td>
<td>CohortS</td>
<td>55</td>
<td>6</td>
<td>(6 \times 10^6)</td>
<td>Intramyocardial</td>
<td>+6.3 (P = 0.02)</td>
<td>Stamm et al. (2007)</td>
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<tr>
<td></td>
<td>CohortS</td>
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<td>Bartunek et al. (2005)</td>
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<td>CD34</td>
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<td>24</td>
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<td>(3.5 \times 10^7)</td>
<td>TEIM</td>
<td>NA</td>
<td>Losordo et al. (2007)</td>
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<td>SMB</td>
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<td>97</td>
<td>6</td>
<td>NA</td>
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<td>+3 (P &lt; 0.04)</td>
<td>MAGIC (2007)</td>
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<td></td>
<td>CohortS</td>
<td>26</td>
<td>12</td>
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<td>+14.5 (P &lt; 0.01)</td>
<td>Gaviria et al. (2006)</td>
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<td>CohortS</td>
<td>12</td>
<td>12</td>
<td>(2.1 \times 10^8)</td>
<td>TEIM</td>
<td>+11.6 (P &lt; 0.05)</td>
<td>Inc et al. (2004)</td>
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<tr>
<td>MSC</td>
<td>R</td>
<td>48</td>
<td>12</td>
<td>(5 \times 10^6)</td>
<td>Intracoronary</td>
<td>-3 (NS)</td>
<td>Chen et al. (2006)</td>
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<tr>
<td></td>
<td>R-SB</td>
<td>69</td>
<td>6</td>
<td>(6 \times 10^6)</td>
<td>Intracoronary</td>
<td>+12.0 (P = 0.01)</td>
<td>Chen et al. (2004)</td>
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<tr>
<td>MSC + EPC</td>
<td>CohortS</td>
<td>22</td>
<td>4</td>
<td>(3 \times 10^6)</td>
<td>Intracoronary</td>
<td>+0.3 (NS)</td>
<td>Katritis et al. (2005)</td>
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<tr>
<td>BMC</td>
<td>R-DB</td>
<td>20</td>
<td>6</td>
<td>NA</td>
<td>Intracoronary</td>
<td>+9.2 (P = 0.05)</td>
<td>Ruan et al. (2005)</td>
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</tbody>
</table>

BMC, bone-marrow-derived cells (unspecified); BMMNCC, bone-marrow mononuclear cell; CPC, circulating progenitor cell; DB, double-blinded; EPC, endothelial progenitor cell; MSC, mesenchymal stem cell; NA, not available; NS, not significant; R, randomized; SB, single-blinded; SMB, skeletal myoblast; TEIM, transendocardial intramyocardial injection. *The number of patients is the sum of individuals in the control and treatment groups; almost all studies have equal numbers in each group. †Ejection fraction is the proportion of blood in the left ventricle that is ejected into the aorta during each heartbeat; this is a measure of cardiac function. ‡The author names refer to the original report, and the reference number cited indicates either the original report or a meta-analysis (or review) in which the original report is discussed. §Cohort denotes a non-randomized and non-blinded study. || Intramyocardial indicates injection through the epicardial side of the heart.
Clinical indication – acute/chronic ischemia, post infarction

**Combined Revascularization (Stent, CABG)**
- Acute myocardial infarction (immediately - days)
- Early after myocardial infarction (< 2 weeks)
- Chronic ischemia: Myocardial transition / remodeling phase (2 weeks – several months)

**Stand alone**
- Completed remodeling / scar postischemic cardiomyopathy (>6 months)
- Refractory angina
- Chagas disease
Stem cell “homing” and vascular activity

Role of endothelial NOS, SDF-1 alpha and local inflammation

Intravital fluorescence microscopy in murine cremaster muscle

Kaminski A et al. (Lab Investigation 2008)
Aspects of ventricular remodeling after infarction

Myocardial infarction in a mouse heart

Control

Hibernation

Connexin 43+ gap junctions

Fig. 1. Cardiomyocyte remodeling leading to hibernation.

- Chronic Ischemia
  - Repetitive Underperfusion
- Adaptive Response for Cell Survival
- Downregulation of Energy Utilization
- Oxidative → Glycolytic Metabolism
- Hemodynamic-Metabolic Balance-Adaptation
- ↓ Contraction
- ↑ Stress Proteins & Angiogenesis Genes
- Change of Phenotype
  - Cell Differentiation
  - Remodeling
- Fetal Metabolism
- Neonatal Appearance
- Hibernating Myocardium

Slezak et al. 2009
CD133+ cell product from human bone marrow

In vitro differentiation of endothelial cells from CD133-positive origin

Ong LL et al, Tissue engineering Part C, 2010

Biological Interaction Network

Effect of hypoxia on the differentiation of CD133
1.5% [vol/vol] oxygen and 5% [vol/vol] carbon dioxide
Hypothesis

Intramyocardial CD133\(^+\) stem cell treatment leads to better recovery of hibernating myocardium in addition to CABG surgery.
CD133\(^+\) stem cell preparation and transplantation
CD133^+ stem cell preparation and transplantation

Clinical setting: CD133^+ Isolation with CliniMACS-unit Miltenyi Biotec

Direct injection into myocardium

150–200ml
Target area for intramyocardial transepicardial injection

viability / stress induced ischemia / reduced wall thickening

LAD
Posterior interventricular
Analysis of stem cell related effects during CABG

A  Clinical case reports
   - \((CD133^+, n=\ldots)\)

B  Clinical trials
   - Rostock Phase I  \((CABG + CD133^+, n=15)\)
   - Rostock Phase II \((CABG + CD133^+, n=20)\)

Meta Analysis \((CABG + stem cells, n=94)\)
   - Phase III Trial \(PERFECT\)

C  Clinical \textit{real world}
   - Rostock REGISTRY \((CABG + CD133^+, n=99)\)
Case report stand alone CD133\(^+\) therapy

74 y.o. ♂
Stand-alone stem cell therapy
2 months after stented LAD-infarction

EF 32%

EF 47%
Rostock phase I/II study

**Phase I Trial / 18 months (n=15)**

- **LVEF (%)**
  - **preop**: 39±9
  - **discharge**: 47±6*
  - **6 months**: 50±8*
  - **18 months**: 48±6*

**Phase II Trial / 6 months (n=20 vs. control)**

- **CABG & CD133+ cells**
  - Increase in LVEF: **9.7%**
  - **p=0.0009**
- **CABG**
  - Increase in LVEF: **3.4%**


**Absolute LVEF Improvement in %**

- **Stem cell group**
- **Control group**

**Subgroup analysis**

- **n=35 vs. control**
- **n=20 at 6 months**

Increase in myocardial perfusion at 6 months
Myocardial perfusion after CD133 + CABG – 3 years

* \( p < 0.05 \) vs. control
CT-Scan

- No cardiac malformation in all analyzed hearts! (MRI/CT)
- One slight myocardial calcification without functional relevance in treatment group:
### Meta analysis

Intramyocardial bone marrow stem cell therapy during CABG

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Age</th>
<th>Sex</th>
<th>Baseline LVEF</th>
<th>Follow-up LVEF</th>
<th>Change of LVEF</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Control</td>
<td></td>
<td>Treatment</td>
<td>Control</td>
<td>Treatment</td>
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<tr>
<td>Stamm et al. 2007</td>
<td>20</td>
<td>20</td>
<td>62.0±10.2</td>
<td>63.5±8.4</td>
<td>75</td>
<td>80</td>
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<td>Hendrikx et al. 2006</td>
<td>10</td>
<td>10</td>
<td>63.2±8.5</td>
<td>66.9±6</td>
<td>100</td>
<td>70</td>
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<tr>
<td>Ahmadi et al. 2006</td>
<td>18</td>
<td>9</td>
<td>48.6±9.8</td>
<td>50.9±4.7</td>
<td>91.6</td>
<td>57.1</td>
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<td>Moccini et al. 2005</td>
<td>18</td>
<td>18</td>
<td>64.4±6.6</td>
<td>66.9±4.5</td>
<td>94.4</td>
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<tr>
<td>Patel et al. 2005</td>
<td>10</td>
<td>10</td>
<td>64.8±3.9</td>
<td>63.6±4.9</td>
<td>80</td>
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<tr>
<td>Zhao et al. 2006</td>
<td>18</td>
<td>18</td>
<td>60.3±10.4</td>
<td>59.1±15.7</td>
<td>83.3</td>
<td>83.3</td>
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</tbody>
</table>
Meta analysis Intramyocardial bone marrow stem cell therapy during CABG

Forrest Plot Fixed Effects

Major adverse cardiovascular events
Composite of cardiac death, recurrent MI, revascularisation procedure and stroke

Meta-analysis
Intramyocardial bone marrow stem cell therapy during CABG

n=179

Study
Stamm et al. 2007
Hendrikx et al. 2006
Ahmadi et al. 2006
Moccini et al. 2005
Patel et al. 2005
Zhao et al. 2006
Combined

Favours BMSC
Favours control

RR Cardiovascular Events (95% CI)
### Meta analysis

Intramyocardial bone marrow stem cell therapy during CABG

![Forest Plot Fixed Effects](image)

**LVEF change (95%CI)**

<table>
<thead>
<tr>
<th>Study</th>
<th>WMD (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stamm et al. 2007</td>
<td>6.30 (1.75, 10.85)</td>
<td>11.80</td>
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<tr>
<td>Hendrikx et al. 2006</td>
<td>2.50 (-5.26, 10.26)</td>
<td>4.05</td>
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<tr>
<td>Ahmadi et al. 2006</td>
<td>-1.40 (-5.57, 2.77)</td>
<td>14.04</td>
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<tr>
<td>Mocini et al. 2005</td>
<td>4.00 (-0.43, 8.43)</td>
<td>12.44</td>
</tr>
<tr>
<td>Patel et al. 2005</td>
<td>10.20 (7.92, 12.48)</td>
<td>47.14</td>
</tr>
<tr>
<td>Zhao et al. 2008</td>
<td>9.40 (4.58, 14.22)</td>
<td>10.53</td>
</tr>
<tr>
<td>Overall (I-squared = 81.7%, p = 0.000)</td>
<td>6.94 (5.38, 8.51)</td>
<td>100.00</td>
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</tbody>
</table>

*Favours Control* vs *Favours BMSC*
Meta analysis Intramyocardial bone marrow stem cell therapy during CABG

Forest Plot Fixed Effects

<table>
<thead>
<tr>
<th>Study</th>
<th>WMD (95% CI)</th>
<th>Weight</th>
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<tbody>
<tr>
<td>Stamm et al. 2007</td>
<td>-6.50 (-30.46, 17.46)</td>
<td>37.11</td>
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<tr>
<td>Ahmadi et al. 2006</td>
<td>-21.60 (-59.18, 15.99)</td>
<td>15.09</td>
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<tr>
<td>Patel et al. 2005</td>
<td>-18.00 (-39.11, 3.11)</td>
<td>47.81</td>
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<tr>
<td>Overall (I-squared = 0.0%, p = 0.715)</td>
<td>-14.28 (-28.87, 0.32)</td>
<td>100.00</td>
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</table>

LVEDV follow-up (95% CI)
Conclusion and plans

- **Phase-I** clinical feasibility and safety study in 15 CABG patients showed that intramyocardial injection of autologous CD133+ bone marrow cells was not associated with cell-related complications in longterm analysis 1,2.

- In a subsequent **Phase-II** randomized, controlled, and prospective clinical trial in 40 patients, CABG & intramyocardial injection of CD133+ bone marrow cells resulted in better LV ejection fraction and perfusion than CABG only 3. Longterm safety of the treatment could be confirmed 4.

- **Phase-III** clinical study investigation (multicentre double-blinded randomized trial) is planned to finish in 2012 for definitive clinical introduction in the treatment of chronic ischemia after myocardial infarction.

1 Stamm et al. Autologous bone marrow stem-cell transplantation for myocardial regeneration. Lancet, 361(9351);45-6; 2003
2 Stamm et al. CABG and bone marrow stem cell transplantation after myocardial infarction. Thorac Cardiov Surg, 52(3):152-8; 2004
4 Yerebakan et al. Safety of intramyocardial stem cell therapy for the ischemic myocardium: Results of the Rostock trial after five year follow-up. Cell transplantation 2007; 16(9): 935-40.
PERFECT Phase III Study

a controlled, prospective, randomized, double blinded multicenter trial

PERFECT
INTRAMYOCARDIAL TRANSPLANTATION OF BONE MARROW STEM CELLS FOR IMPROVEMENT OF POST-INFARCT MYOCARDIAL REGENERATION IN ADDITION TO CABG SURGERY

Principal investigator: Prof. Dr. G. Steinhoff
Sponsor: Miltenyi-Biotec GmbH

German study centers: Berlin Heart Center
Medical School Hannover
University of Rostock

Approved (Phase III clinical trial) by Paul Ehrlich Institute June 2009
First patient: October 2009
Recruitment: 24 months
Planned final evaluation: 2012

CLINICAL OUTCOME STUDY
Inclusion:

Postinfarction (2w-6m), reduced LVEF (25-40%MRI), regional hibernation (MRI), indication CABG, 18-79y

Objectives:

学前教育

Primary objective: To determine whether injection of autologously-derived bone marrow stem cells yields a functional benefit in addition to the coronary artery bypass graft (CABG) operation as determined by left ventricular heart function (LVEF-MRI).

Secondary objectives: To determine the effects of an injection of autologously-derived bone marrow stem cells on physical exercise capacity, cardiac function, safety and quality of life (QoL).
PERFECT Phase III Study

a controlled, prospective, randomized, double blinded multicenter trial

142 Patients
estimated drop-out rate
15%, randomized in
an 1:1 ratio, bone marrow
aspiration
prior to CABG surgery

71 Patients
to provide 60 evaluable
patients
for stem cell group
200 ml BM harvest

5ml CD133+ cells (1-10x10⁶)
suspended in
physiological saline + 10%
autologous serum
intramyocardially

71 Patients
for placebo group
200 ml BM harvest

5ml physiological saline +
10% autologous serum
intramyocardially
**Ziele**

**Primärziel:** Zusätzlicher positiver Funktionseffekt einer Injektion autologer CD133⁺ Knochenmarkstammzellen im Vergleich zur Bypassoperation alleine

**Sekundärziel:** positive Effekte auf körperliche Leistungsfähigkeit, Herzfunktion und Lebensqualität sowie Nachweis der Sicherheit der Anwendung

**Patientenbehandlung**

**Entnahme** von Knochenmark (150-200 ml) und einer Blutprobe (20 ml) vor Bypass-Operation.

**Behandlung:** intramyokardiale Injektion von
- Verum: 5 ml CD 133⁺-Zellen (1-10 Mio.) in NaCl und 10% autologem Serum während der OP
- Placebo: 5 ml NaCl + 10% autologem Serum

**Endpunkte**

**Primärer Endpunkt:** LVEF 6 M nach OP / MRT i.R.

**Sekundärer Endpunkte:**
- LVEF (MRT/Echo) 6 M vs Prä-/Früh-Post-OP
- LVESD / LVEDD (Echo) 6 M vs Prä-/Früh-Post-OP
- körp. Leistungsfähigkeit (6-MWT) 6 M vs Prä-/Früh-Post-OP
- NYHA / CCS 6 M vs Prä-/Früh-Post-OP
- MACE
- QoL Score 6 M vs Prä-OP und nach 3 M

---

**Inclusion criteria**

- Previous MI (2w–6m)
- CABG indicated
- LVEF 25–40%

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**Exclusion criteria**

- Mitral regurgitation
- Emergency
- Cancer
- Claustrophobia
- Chronic Hepatitis

---

**Secondary endpoints**

- physical exercise capacity
- cardiac function
- safety and quality of life (QoL).
Concomitant research to PERFECT

1. Cell-/Blood analysis: time points

- pre OP
  - screening
  - BM aspiration
- OP
  - 6h
  - 24h
  - 72h
- post OP
  - discharge
  - 6 month
Concomitant research to PERFECT

2. Cell analysis

- max 10% of aspired bone marrow
- Isolation of CD133⁺ cells
- miRNA profile
- Characterization (sub-populations, FACS)
- Parvo-Virus
- Vitality and proliferation (FACS, CFU-Assay)
- Angiogenesis *in vitro* und *in vivo*
Concomitant research to PERFECT

3. Blood analysis

All patients (Rostock, Hannover, Berlin):
- Angiogenesis (VEGF, FGF)
- Stem cell factors (SCF, SDF-1, GCSF)
- Heart failure (myoglobin)
- Inflammation reaction (IL-6, IL-8, TNFα)
- Immune suppression (IL-10)
- Endothelial activation (sE-Selectin)
- Monitoring (CMV, EBV, Parvo, HAMA, AFP)
- Identification of diagnostic markers (miRNA, protein patterns)

Add. Rostock patients:
- ca. 90 ml blood
- additional time points
- Angiogenesis in vivo
- Mobilization of endothelial progenitor cells (FACS, CFU-Hill)
Clinical *real world* – the REGISTRY program

- REGISTRY-program
  - treatment of additional cardiovascular indications
  - long time FU
  - documentation at Rostock University since 2001
  - inclusion of further SC-therapy-centers in Germany
  - start national SC-register for cardiac application
Content of the REGISTRY-Database

- Patient data
- Information about surgery / product
- Indication
- Follow-Up's (Laboratory, MRT, Scintigraphy, ECG)
- Screening (Laboratory, MRT, Scintigraphy, ECG)
- Check lists, printed forms
Improvement in LVEF 6 months after CD133 + CABG treatment: (n = 56)

\[ \text{mean } 3.4 \pm 10.1 \text{ (50% change LVEF > 5%)} \]

*p=0.005 vs. preop.*
Median change in number of ventricular ES / h

Mean change in VES / all beat percentage: -0.8%
REGISTRY / Survival

Survival 93% in CABG + CD133⁺(93 out of 99)

vs. 88% in Control Phase II

patient 1 – 10 months (Phase II)
patient 2 – 02 months (Registry)
patient 3 – 74 months (Phase I)
patient 4 – 07 months stroke (Phase I)
patient 5 – 81 months (Phase I)
patient 6 – 62 months (Registry)
Update 2010

- 1988 - 2009 Animal models, mechanism and safety research
- 2001: worldwide first application and phase I study of intramyocardial injection of purified CD133+ bone marrow stem cells in coronary bypass patients
- Since 2006 Reimbursement by German health insurance companies (sDRG)
- 2008 Establishment of national reference center for cardiac stem cell therapy (RTC, Rostock)
- 2001-2009 Clinical safety and efficacy approval in longterm vigilance studies
- 9/2009 Start of Phase III clinical outcome study (Sponsor: Miltenyi-Biotec GmbH)
Intramyocardial CD133+ Bone Marrow Stem Cell Therapy,
Standardization of cardiac stem cell therapy

• Indication
  (ischemia/postinfarction/cardiomyopathy/Htx)
• Safety (arrhythmia, tumor, calcification)
• Dosage/Toxicity
• Standardization of cell preparation
• Efficacy (longterm, quality of life)
• Biodistribution of cells (migration, survival)
• Tumorogenicity
• Mechanism of action (paracrine, cellular)
• Comparison of different stem cell types

• CLINICAL OUTCOME (PE, MACE, QoL)
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