Stem Cell Therapy for Ischemic Dilated Cardiomyopathy

By

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Tanta University
Clinical Investigation and Reports

Repair of Infarcted Myocardium by Autologous Intracoronary Mononuclear Bone Marrow Cell Transplantation in Humans

Bodo E. Strauer, MD; Michael Brehm, MD; Tobias Zeus, MD; Matthias Köstering, MD; Anna Hernandez, PhD; Rudiger V. Sorg, PhD; Gesine Kögler, PhD; Peter Wernet, MD

Background—Experimental data suggest that bone marrow–derived cells may contribute to the healing of myocardial infarction (MI). For this reason, we analyzed 10 patients who were treated by intracoronary transplantation of autologous, mononuclear bone marrow cells (BMCs) in addition to standard therapy after MI.

Methods and Results—After standard therapy for acute MI, 10 patients were transplanted with BMCs via a balloon catheter placed into the infarct-related artery during balloon dilatation coronary angioplasty). Another 10 patients with acute MI were treated by standard therapy, followed by the infarct region (determined by left ventriculography) had decreased significantly (P = 0.005) and was also significantly smaller compared with wall movement velocity increased significantly only in 0.028. Further cardiac examinations (dobutamine stress echocardiography of the right heart) were performed for the cell therapy, left ventricular end-systolic volume index, and myocardial perfusion of the infarct region. These data demonstrate for the first time that selective intracoronary transplantation of BMCs seems to be effective under clinical conditions. The main indications for the cell transplantation seem to be myocardial regeneration and neovascularization.
In Other Words!

Hallelujah! Some day you may have hair again!!

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Mike Luckovich - dilute.com
Key Questions?

- Do patients still die from CHF despite improvements in medical and device therapy?
- Will LVADS and Heart Transplantation solve the unmet need?
- Would it be a good thing if we could prevent LV dysfunction or better yet improve LV function?
Therapy for AMI –
- Lysis v PPC
- Impact of time/treatment

1 million UK heart failure
5% all admissions
1-2% health budget

Heart failure -strategies-

Medical treatment
- Biventricular pacing
- Surgical cardiomyoplasty
- Left ventricular assist device
- Artificial hearts
- Heart transplantation
- Cell transplantation?
CONSENSUS I
All-cause mortality

SOLVD Treatment Trial
All-cause mortality


SOLVD Treatment Trial
Death or hospitalization for CHF

SOLVD Prevention Trial
Death or development of CHF


REMATCH Trial

Survival (% of patients)

Survival (% of patients)

Months

0  6  12  18  24  30

LVAD
OMM

Rose E et al. NEJM 2001; 345: 1435-1443.
Summary regarding Standard Of Care!

- Therapy for HF associated with low EF has improved significantly in the past 20 years, with major concomitant increased insight into the nature of the disease.
- The most successful therapies are based not on acute changes in hemodynamics or symptoms, but on interventions which improve the biology of the diseased ventricle.
- Device therapy may provide modest gains in survival, and significant improvement in outcome in selected patients.
- Ultimately, more fundamental insight is required into mechanisms of disease progression to definitively halt and reverse ventricular remodeling and dysfunction.
Will Stem Cell therapy play a key role in the Prevention and Treatment of CHF? HOW?

♦ STEMI

♦ CHF:
  ♦ Ischemic Cardiomyopathy
    ♦ With ongoing Ischemia: Hibernating Myocardium
    ♦ Without Ischemia: SCAR
  ♦ Nonischemic Cardiomyopathy
Embryonic stem cells
The whole body

Bone marrow stem cells
Specialised tissue (e.g. heart, blood vessels)

Resident stem cells
Repair of the organ (e.g. in heart, repairs heart)
Transplantation Pathways of Bone Marrow Cells

RCA

CFX

Balloon catheter

Intracoronary

LAD

Intravenous

Intramyocardial

Transendocardial

Strauer & Kornowski, Circulation 2003;107:929-934
STEM CELL THERAPY

TRANSDIFFERENTIATION
Vessel regeneration

TRANSDIFFERENTIATION
Cardiomyocyte regeneration

PARACRINE EFFECTS

NEOVASCULARIZATION

CARDIOMIOGENESIS

CARDIAC REPAIR

CHRONIC PTS

ACUTE PTS

CHRONIC PTS
Study Flow

Screening 550 pts

2:1 Randomization 30 pts

Treatment Group 30x10^6 BMMNC 20 pts

LVA/ NOGA Cell Injection/ Mock Injection

Control Group Mock BM Harvest 10 pts

Early Assessments

3 Month Assessment
- CCS
- NHYA
- Holter
- SPECT
- Echo
- MVO2

6 Month Assessment
- CCS
- NHYA
- Holter
- NOGA
- SPECT
- Echo
- MVO2
- Cor/LVA

MRI Subgroup 17 pts

Crossover 8 pts
### Baseline and 3 Month Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 months</td>
</tr>
<tr>
<td><strong>Clinical Assessment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCS</td>
<td>3±0.8</td>
<td>2.2±0.8</td>
</tr>
<tr>
<td>NYHA</td>
<td>2.6±0.7</td>
<td>1.9±0.9</td>
</tr>
<tr>
<td><strong>Functional Assessment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVO2 (ml/Kg/min)</td>
<td>14.8±3</td>
<td>15.7±5</td>
</tr>
<tr>
<td>Echo EF (%)</td>
<td>39±9.1</td>
<td>41.1±8</td>
</tr>
<tr>
<td>SPECT % of reversibility</td>
<td>21.3±18</td>
<td>20.1±22</td>
</tr>
</tbody>
</table>
### 3 Month SPECT and MRI Results in the Injected Segments

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Treatment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPECT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest perfusion</td>
<td>0.94±1.1</td>
<td>0.99±1.06</td>
<td>0.5</td>
</tr>
<tr>
<td>Stress Perfusion</td>
<td>1.48±1.1</td>
<td>1.46±1.1</td>
<td>0.63</td>
</tr>
<tr>
<td>Reversibility</td>
<td>0.57±0.7</td>
<td>0.41±0.6</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest Perfusion</td>
<td>0.08±0.34</td>
<td>0.02±0.14</td>
<td>0.08</td>
</tr>
<tr>
<td>Stress Perfusion</td>
<td>1.02±0.78</td>
<td>0.86±0.66</td>
<td>0.03</td>
</tr>
</tbody>
</table>
LV ejection fraction after autologous myoblast transplantation – 12 months follow up

Dr. Tomasz Siminiak, University School of Medical Sciences related study as presented at the AHA meeting November 2003. Surgical (epicardial) study.
MYOHEART Study Design

A Phase 1, Multi-Center, Open Label, Dose Escalating Study

30-Day Safety Evaluation

First Cohort (n=5)
25 x 10^6 cells

Second Cohort (n=5)
75 x 10^6 cells

Third Cohort (n=5)
225 x 10^6 cells

Fourth Cohort (n=5)
675 x 10^6 cells

2 injections (.25 cc)

6 injections (.25 cc)

18 injections (.25 cc)

27 injections (.50 cc)
MYOHEART LVEF (MUGA)

Interim Analysis

Graph 1:
- Cohort 1: Baseline (N=17), 3-Month (N=14), 6-Month (N=14), 12-Month (N=10)
- Cohort 2: Baseline (N=17), 3-Month (N=14), 6-Month (N=14), 12-Month (N=10)
- Cohort 3: Baseline (N=17), 3-Month (N=14), 6-Month (N=14), 12-Month (N=10)
- Cohort 4: Baseline (N=17), 3-Month (N=14), 6-Month (N=14), 12-Month (N=10)

Graph 2:
- All Total: Baseline (N=17), 3-Month (N=14), 6-Month (N=14), 12-Month (N=10)

p = n/s
MYOHEART 6-Minute Walk

Interim Analysis

Absolute Improvement (m)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Baseline</th>
<th>3-Month</th>
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<tbody>
<tr>
<td>1</td>
<td>N=5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>N=4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>N=5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>N=1</td>
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Relative Improvement (%)

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<th>Cohort</th>
<th>Improvement</th>
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<tr>
<td>1</td>
<td>6%</td>
</tr>
<tr>
<td>2</td>
<td>10%</td>
</tr>
<tr>
<td>3</td>
<td>22%</td>
</tr>
<tr>
<td>4</td>
<td>20%</td>
</tr>
</tbody>
</table>

p = n/s
Improved Exercise Capacity and Ischemia 6 and 12 Months After Transendocardial Injection of Autologous Bone Marrow Mononuclear Cells for Ischemic Cardiomyopathy

Emerson C. Perin, MD, PhD; Hans F.R. Dohmann, MD; Radovan Borojevic, PhD; Suzana A. Silva, MD; Andre L.S. Sousa, MD; Guilherme V. Silva, MD; Claudio T. Mesquita, MD, PhD; Luciano Belém, MD; William K. Vaughn, PhD; Fernando O.D. Rangel, MD; Joao A.R. Assad, MD; Antonio C. Carvalho, MD, PhD; Rodrigo V.C. Branco, MD; Maria I.D. Rossi, PhD; Hans J.F. Dohmann, MD, PhD; James T. Willerson, MD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2max, mL/kg per min</td>
<td>17.3±6</td>
<td>17.5±6</td>
<td>0.03</td>
</tr>
<tr>
<td>METS</td>
<td>5.0±2.3</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td>30±6</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

Functional class:

- NYHA: 2.2±0.9, 2.7
- CCSAS: 2.6±0.8, 2.9
- PVC, ms: 2507±6243, 672
- dQRS, ms: 130±15, 145
- LAS 40, ms: 50±24, 70
- RMS 40, µV: 22.2±22, 23.9

SPECT indicates single-photon emission computed tomography; low-amplitude signal less than 40 µV; RMS 40, root mean square of the 40 ms interval; NYHA, New York Heart Association; CCSAS, Canadian Cardiovascular Society Classification System.

*P for comparisons between treatment and control groups.

Figure 1. A and B, Unipolar voltage map showing an area of inferobasal scar (red) on both AP (A) and inferior (B) views. C, DE-MRI short-axis slice through the base of the left ventricle showing transmural scar, which corresponds to the bright signal.
Transcoronary Transplantation of Functionally Competent BMCs Is Associated With a Decrease in Natriuretic Peptide Serum Levels and Improved Survival of Patients With Chronic Postinfarction Heart Failure
Results of the TOPCARE-CHD Registry

The acute and long-term effect of intracoronary Stem cell Transplantation in 191 patients with chronic heart failure:

A new STAR in the cardiac cell therapy sky

Francisco Fernández-Avilés
Department of Cardiology
Hospital General Universitario Gregorio Marañón
Complutense University of Madrid – School of Medicine
faviles@secardiologia.es
Study design: Recruitment of patients

Patients with acute myocardial infarction treated by PCI (1995-2001)

8.5±3.2 years Medication treatment

n=391 Patients with LVEF≤35% due to ischemic heart disease admitted to the university clinic (2003-2005)

BMC treatment has been proposed to all patients

n=191 patients accepted the BMC therapy
= BMC group

n=200 refused the BMC therapy
= Control group

Invasive diagnostics and therapy (PTCA, Stent) and cell therapy

Invasive diagnostics and therapy (PTCA, Stent), no cell therapy

Invasive diagnostics and follow-up after 3, 12 and 60 months

Invasive diagnostics include coronary angiography, left ventriculography, right heart catheterization and determination of derived parameter (cardiac index, EF, wall stress etc.)

PCI= percutaneous coronary intervention, LVEF= left ventricular ejection fraction, BMC= bone marrow cell, PTCA= percutaneous transluminal coronary angioplasty
(3) Bone Marrow Cell Preparation

Autologous Heparinized Bone Marrow Cells

Ficoll Density Separation
H₂O Lysis of Residual Erythrocytes

Differentiated Cell Count
Sterility Testing

Mononuclear Bone Marrow Cells

Differentiated Cell Count
Viability Testing

Cultivation over Night

- Teflon Bag
- X-Vivo15 Medium, Supplemented with 2% Autologous Plasma
- 1x10⁶ Cells/ml

Cultivated Mononuclear Bone Marrow Cells

Differentiated Cell Count
Sterility Testing
Viability Testing
Biological and Functional Characterisation

Harvest and Filtration of the Cultivated Cells

Mononuclear Bone Marrow Cells in 20 ml heparinized Saline
(4) Intracoronary Transplantation Technique

Balloon catheter
Cell inflow into infarct border zone
Cell migration into central infarct zone

Syringe with adult stem cells
Border zone

RCA
RCX
AD

Strauer et al., Circulation 2002;106:1913-1918
(5) Hemodynamics of the left ventricle

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline/post cell therapy</th>
<th>Chronic heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cell therapy</td>
</tr>
<tr>
<td>CI-rest (l/min x m²)</td>
<td>baseline</td>
<td>2,7±0,63</td>
</tr>
<tr>
<td></td>
<td>post</td>
<td>3,3±0,6***</td>
</tr>
<tr>
<td></td>
<td>Abs.</td>
<td>0,56±0,5 (+ 22%)</td>
</tr>
<tr>
<td>VO₂peak (ml/min)</td>
<td>baseline</td>
<td>1515±506</td>
</tr>
<tr>
<td></td>
<td>post</td>
<td>1681±527***</td>
</tr>
<tr>
<td></td>
<td>Abs.</td>
<td>158±365 (+ 11%)</td>
</tr>
<tr>
<td>O₂-Pulse (ml/beat)</td>
<td>baseline</td>
<td>12,8±3,4</td>
</tr>
<tr>
<td></td>
<td>post</td>
<td>13,6±3,4**</td>
</tr>
<tr>
<td></td>
<td>Abs.</td>
<td>0,52±2,1(+ 6,3%)</td>
</tr>
<tr>
<td>Ergometry (Watt)</td>
<td>baseline</td>
<td>78,7±30</td>
</tr>
<tr>
<td></td>
<td>post</td>
<td>90,7±33,6***</td>
</tr>
<tr>
<td></td>
<td>Abs.</td>
<td>11,3±22,9 (+15,4%)</td>
</tr>
</tbody>
</table>

Abs. = absolute difference to baseline, CI = cardiac Index, PAP = pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, CPI = cardiac power index, VO₂peak = peak oxygen uptake, O₂-Pulse = oxygen pulse. Hemodynamics of the left ventricle before and after BMC therapy in patients with chronic ischemic cardiomyopathy in comparison to control group. 3 months after BMC therapy significant improvements of CI, PAP, PCWP, CPI, VO₂peak, O₂-Pulse and exercise capacity were documented.

*** p<0,01 (pre/post), ** p<0,05 (pre/post), * p<0,1 (pre/post)
## (6) Quantitative ventriculography

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline/post cell therapy</th>
<th>Chronic heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cell therapy</td>
<td>Control</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>baseline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>184±52</td>
<td>184±49</td>
</tr>
<tr>
<td></td>
<td>post</td>
<td>174±48***</td>
</tr>
<tr>
<td></td>
<td>Abs.</td>
<td>-9,9±33,3 (-5,5%)</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>baseline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>128±53</td>
<td>118±43</td>
</tr>
<tr>
<td></td>
<td>post</td>
<td>110±47****</td>
</tr>
<tr>
<td></td>
<td>Abs.</td>
<td>-15,9±30,2 (-14,1%)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>baseline</td>
<td>29,4±12,7</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>36±13,3****</td>
</tr>
<tr>
<td></td>
<td>Abs.</td>
<td>6,1±6,3 (22,4%)</td>
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<tr>
<td>SVI (ml/m²)</td>
<td>baseline</td>
<td>33,1±11,2</td>
</tr>
<tr>
<td></td>
<td>post</td>
<td>37,3±12****</td>
</tr>
<tr>
<td></td>
<td>Abs.</td>
<td>4,45±10,4 (+12,4%)</td>
</tr>
<tr>
<td>Infarct size (%)</td>
<td>baseline</td>
<td>28,1±17</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>24,9±16,4**</td>
</tr>
<tr>
<td></td>
<td>Abs.</td>
<td>-4,5±9,8 (-11,4%)</td>
</tr>
</tbody>
</table>

Abs. = absolute difference to baseline, EDV = end-diastolic volume, ESV = end-systolic volume, SVI = stroke volume index. Quantitative analysis of the left ventricle before and after BMC therapy in patients with chronic ischemic cardiomyopathy in comparison with the control group. 3 months after BMC therapy a significant improvement of EDV, ESV, EF and SVI was seen. A significant decrease of the infarct size was documented.

*** p<0.01 (pre/post),  ** p<0.05 (pre/post),  * p<0.1 (pre/post)
(8) Arrhythmogenic indexes

<table>
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<tr>
<th>Parameter</th>
<th>Baseline/post cell therapy</th>
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<tbody>
<tr>
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<td>Cell therapy</td>
<td>Control</td>
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<tr>
<td>Heart rate variability (HRV):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD of the RR-Intervals (ms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>31,7±19,2</td>
<td>34±15,2</td>
</tr>
<tr>
<td>Post</td>
<td>37,2±23,2***</td>
<td>32,6±14,1</td>
</tr>
<tr>
<td>Abs.</td>
<td>5,7±15,8 (+17,4%)</td>
<td>-2,67±9,8</td>
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<tr>
<td>Lown classification</td>
<td></td>
<td></td>
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<tr>
<td>baseline</td>
<td>2,49±1,5</td>
<td>2,31±1,6</td>
</tr>
<tr>
<td>Post</td>
<td>1,96±1,6**</td>
<td>2,5±1,7</td>
</tr>
<tr>
<td>Abs.</td>
<td>-0,46±1,1 (-21,3%)</td>
<td>0,2±1,1</td>
</tr>
</tbody>
</table>

Abs. = absolute difference to baseline. Arrhythmogenic indexes before and 3 months after BMC therapy. Significant improvements of HRV and Lown classification were documented.

*** p<0,01 (pre/post),  ** p<0,05 (pre/post),  * p<0,1 (pre/post)
Ejection fraction (EF) in the course of time in BMC group in comparison to control group
Effect of BMC therapy on survival in patients with chronic ischemic cardiomyopathy

Number of survivors:

<table>
<thead>
<tr>
<th>Year</th>
<th>BMC group</th>
<th>Control group</th>
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<tbody>
<tr>
<td>1</td>
<td>191</td>
<td>197</td>
</tr>
<tr>
<td>2</td>
<td>191</td>
<td>190</td>
</tr>
<tr>
<td>3</td>
<td>190</td>
<td>190</td>
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<tr>
<td>4</td>
<td>187</td>
<td>181</td>
</tr>
<tr>
<td>5</td>
<td>184</td>
<td>168</td>
</tr>
</tbody>
</table>

p<0.01
<table>
<thead>
<tr>
<th></th>
<th>BMC group, n=191</th>
<th></th>
<th></th>
<th></th>
<th>Control group, n=199</th>
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</thead>
<tbody>
<tr>
<td>Number of survivors:</td>
<td>191</td>
<td>190</td>
<td>187</td>
<td>184</td>
<td>197</td>
</tr>
</tbody>
</table>

(12) The results demonstrate that in chronic heart failure there may be cell-induced improvements:

- of hemodynamics at rest (cardiac index, stroke volume, ejection fraction etc.,

- of exercise capacity (NYHA, oxygen uptake at rest and exercise)

- of LV contractility (shortening velocity, Psyst/ESV) and of LV geometry (EDV, ESV, infarct size)

Another important result refers to the decrease in mortality which indicates that cell therapy may prolong life.
The STAR-Heart Study

CONTRIBUTION

- Open label non-randomised trial
- Largest trial (391 pts) comparing BMNCs vs conventional therapy in patients with heart failure due to healed infarction. Simple method of delivery. Largest (60 moths) follow-up. Comprehensive assessment
- BMNCs safely produced a sustained benefit on clinical outcome and LV performance not observed before
- This STAR sheds light on the mechanisms of LV benefit of cell therapy
The STAR-Heart Study

CONTRIBUTION

Open label non-randomised trial

...but RELEVANT:

- Largest trial with the longest follow-up comparing BMSCs vs conventional therapy in patients with heart failure due to healed infarction

- Simple, cheap, elegant and reproducible method of delivery (feasible only for patients without occlusion)

- Comprehensive and precise structural, functional and clinical baseline and FU assessment

- BMCs safely produced a sustained benefit not observed before on clinical outcome and LV performance (EF, regional function and geometry)

- Insights into stem cell mechanisms of left ventricular benefit
The STAR-Heart Study

INSIGHTS INTO
STEM CELL MECHANISMS OF BENEFIT

Cells to be supplied:
- >1 Billion cardiomyocytes
- Supportive cells

66 x 10^6 BMCs not enough to improve LV performance

Transdifferentiation is not the mechanism

Viability is the answer and should be clarify:
- No viability: Pure scaffolding effect
- Viability: Rescue of hibernating myocardium through paracrine-mediated neovascularization
Cellular Cardiac Repair

Possible Mechanisms of Action

- Paracrine Effect (↓ apoptosis)
- Mechanical Advantage from ↑ LV wall thickness
- Improved LV Function
- Direct Cellular Benefit
  - Transdifferentiation
  - Fusion
- Angiogenesis
The STAR-Heart Study

OPPORTUNITIES

Double-blinded mechanistic trials in big animal models and humans using imaging surrogates are warranted to:

1. Compare the STAr-HEART delivery system with intramyocardial injection

2. Identify the subgroups of patients with highest benefit

3. Assess the effect of different doses of BMCs

4. Compare different types of cells in this scenario:
   - Autologous expanded stem cells (MSCs from bone marrow or adipose tissue, iPSCs)
   - Autologous adipose-derived fresh MSCs
   - Allogenic stem cells
CONCLUSIONS

The results of the STAR-Heart trial suggest that intracoronary transfer of BMNCs safely improves outcomes of patients with chronic symptomatic heart failure due to healed infarction.

These results support scaffolding effect or paracrine activation as the main mechanisms of benefit of available cells in this population. Clarification of myocardial viability will help to distinguish between both possibilities.

Before conducting large scale clinical trials, translational, randomized, double-blinded, mechanistic studies are necessary to confirm these results, to further elucidate mechanisms, to identify subgroups of highest benefit and to compare different cells and different methods of delivery.
Stem cell therapy for heart repair
CURRENT STATE

The regeneration capability of the mammalian heart can be enhanced by transferring embryonic or adult stem cells (partial repair, total reconstruction)
Stem cell therapy for heart repair
CURRENT STATE

The regeneration capability of the mammalian heart can be enhanced by transferring embryonic or adult stem cells (partial repair >>> total reconstruction)

Clinical research limited to ischemic heart disease:
- BMNCs benefit LV beyond conventional therapy in STEMI
- Scant data in chronic patients.

Mechanisms of benefit poorly understood:
- Independent of transdifferentiation
- Scaffolding effect?
- Paracrine effect?

Embryonic (Cao T, Circulation 2008)
Bone Marrow (Crist CD, PNAS 2001)
Stem cell therapy for heart repair
CURRENT STATE

The regeneration capability of the mammalian heart can be enhanced by transferring embryonic or adult stem cells (partial repair, total reconstruction).

Clinical research limited to ischemic heart disease. Encouraging results (clinical setting).

<table>
<thead>
<tr>
<th>Stem Cell Therapy for Ischemic Heart Disease - 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reperfused STEMI</strong></td>
</tr>
<tr>
<td><strong>Bone marrow cells in &gt;1000 pts</strong></td>
</tr>
<tr>
<td>-Safe improvement of LV recovery beyond current medical and interventional therapies</td>
</tr>
<tr>
<td>-Large-scale trials warranted</td>
</tr>
<tr>
<td><strong>Chronic CAD</strong></td>
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<tr>
<td>≈325 pts</td>
</tr>
<tr>
<td><em>Populations (ischemia, LV dysfunction with or without viability)</em></td>
</tr>
<tr>
<td><em>Cells (bone marrow, myoblasts, adipose)</em></td>
</tr>
<tr>
<td><em>Delivery (IC, surgical, NOGA)</em></td>
</tr>
<tr>
<td><em>Safe benefit (symptoms, perfusion, LV performance)</em></td>
</tr>
</tbody>
</table>
Stem cell therapy for heart repair
CURRENT STATE

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Mechanisms of benefit in each situation poorly understood:
- Independent of transdifferentiation
- Scaffolding effect?
- Paracrine effect?

CARDIAC CELL THERAPY - MECHANISMS

CELLULAR
- Transdifferentiation into cardiomyocytes and supporting cells
- Fusion
- Scaffolding effect

PARACRINE
- Resident cells activation
- Cytokine-induced residual myocytes proliferation
- Angiogenesis
- Inflammation
- Metabolic modulation
- < Apoptosis

PREVENTION OF EXPANSION
TISSUE REGENERATION

CARDIOPROTECTION
RESTORATION

CARDIAC REPAIR
Alternative Therapies For the Treatment of Ischemic Cardiomyopathy

LVEF/NYHA IMPROVEMENT AT SIX MONTHS

<table>
<thead>
<tr>
<th></th>
<th>Bi-V Pacing</th>
<th>MyoCell</th>
<th>Bi-V Pacing</th>
<th>MyoCell</th>
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<tbody>
<tr>
<td>LVEF</td>
<td>14%</td>
<td>24%</td>
<td>25%</td>
<td>37%</td>
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<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
<td>37%</td>
</tr>
</tbody>
</table>


3 month, P=0.009, n=5; 6 month, P= 0.23, n=5.
Thank You