Stem Cell Therapy for Heart Failure: Is Anything on the Horizon?

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Regenerative Surgery: Undifferentiated Cells for Myocardial Regeneration

Undifferentiated Mononuclear Cells
Do not normally contribute to cardiac lineage cells

HSC (~2-4%): blood lineages
MSC (~0.01%): bone, cartilage, fat
1 CSC/10,000 cardiomyocytes
## Clinical Trials in Ischemic Cardiomyopathy 1st Generation

<table>
<thead>
<tr>
<th>Type of trial</th>
<th>Author</th>
<th>Age of Infarct</th>
<th>Treated/Control</th>
<th>Randomized</th>
<th>Change in EF (%) (Controls)</th>
<th>Change in EF (%) (Treated)</th>
<th>Duration of follow-up</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG + BMC</td>
<td>Stamm et al.(^{4})</td>
<td>&lt;3 months</td>
<td>6/no control</td>
<td>N</td>
<td>N/A</td>
<td>12.7</td>
<td>3-10 months</td>
<td>Echo</td>
</tr>
<tr>
<td>CABG + BMC</td>
<td>Zhao et al.(^{5})</td>
<td>~18 months</td>
<td>18/18</td>
<td>Y</td>
<td>4</td>
<td>13</td>
<td>6 months</td>
<td>Echo</td>
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<tr>
<td>CABG + BMC</td>
<td>Stamm et al.(^{6})</td>
<td>2 weeks to 3 yrs</td>
<td>20/20</td>
<td>Y</td>
<td>3.7</td>
<td>9.7</td>
<td>6 months</td>
<td>Echo</td>
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<tr>
<td>CABG + BMC</td>
<td>Ahmadi et al.(^{7})</td>
<td>&lt;3 months</td>
<td>18/9</td>
<td>N</td>
<td>5.2</td>
<td>3.7</td>
<td>14 months</td>
<td>Echo</td>
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<tr>
<td>CABG + BMC</td>
<td>Patel et al.(^{8})</td>
<td>Not available</td>
<td>10/10</td>
<td>Y</td>
<td>6.5</td>
<td>16.6</td>
<td>6 months</td>
<td>Echo</td>
</tr>
</tbody>
</table>

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**Supplemental Table 2. Summary of Stem Cell Trials in Subacute/Chronic Ischemic Heart Failure**

- **Type of trial**: CABG + BMC
- **Author**: Various authors
- **Age of Infarct**: Various durations
- **Treated/Control**: Various numbers
- **Randomized**: Various indications
- **Change in EF (%) (Controls)**: Various percentages
- **Change in EF (%) (Treated)**: Various percentages
- **Duration of follow-up**: Various durations
- **Assessment**: Echo

**Epicardial Injection**
### Clinical Trials in Ischemic Cardiomyopathy

**1st Generation**

<table>
<thead>
<tr>
<th>Type of trial</th>
<th>Author</th>
<th>Age of Infarct</th>
<th>Treated/Control</th>
<th>Randomized</th>
<th>Change in EF (%) (Controls)</th>
<th>Change in EF (%) (Treated)</th>
<th>Duration of follow-up</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intracoronary Infusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BMC or CPC</td>
<td>Assmus et al. 9</td>
<td>81 months</td>
<td>28/24/23*</td>
<td>Y</td>
<td>-1.2</td>
<td>2.9/-0.4</td>
<td>3 months</td>
<td>LVgram</td>
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<tr>
<td>BMC</td>
<td>Strauer et al. 10</td>
<td>27 months</td>
<td>18/18</td>
<td>N</td>
<td>-1</td>
<td>7</td>
<td>6 months</td>
<td>LVgram</td>
</tr>
<tr>
<td>BMC</td>
<td>Strauer et al. 11</td>
<td>~ 8.5 years</td>
<td>184/168</td>
<td>N</td>
<td>-3.5</td>
<td>6.2</td>
<td>60 months</td>
<td>LVgram</td>
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<tr>
<td>CABG + BMC</td>
<td>Hu et al. 12</td>
<td>&gt;3 months</td>
<td>31/29</td>
<td>Y</td>
<td>5.7</td>
<td>10.6</td>
<td>6 months</td>
<td>MRI</td>
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<tr>
<td><strong>Transendocardial Injection</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>BMC</td>
<td>Perin et al. 13</td>
<td>&gt;3 months</td>
<td>14/7</td>
<td>N</td>
<td>-4.15</td>
<td>5.5</td>
<td>2 months</td>
<td>Echo</td>
</tr>
<tr>
<td>BMC</td>
<td>Perin et al. 14</td>
<td>&gt;3 months</td>
<td>20/10</td>
<td>Y</td>
<td>4.8/0.9</td>
<td>3.5/4.5**</td>
<td>6 months</td>
<td>SPECT/LVgram</td>
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<tr>
<td>BMC or MSC</td>
<td>Williams et al. 15</td>
<td>4 months to 11 yrs</td>
<td>8/no</td>
<td>N</td>
<td>N/A</td>
<td>~3**</td>
<td>12 months</td>
<td>MRI</td>
</tr>
</tbody>
</table>

SCIPIO supplemental Appendix 6
Regenerative Surgery

• Foundation established:
  – Safety
  – Feasibility
  – Efficacy: modest, inconsistent and often transient
    • Symptomatic/QOL
    • LVEF
    • LV geometry
    • Scar mass/Viable mass
Regenerative Surgery

• Mechanism of benefit in humans:
  – Myocardial regeneration (No evidence to date)
    • Myocytes
    • Blood vessels
  – Paracrine effects (Dominant mechanism)
    • Cytokines, chemokines, growth factors
    • Inhibit apoptosis
    • Inhibit fibrosis
    • Enhance contractility
    • Activate endogenous regeneration mechanisms
Regenerative Surgery

• Challenged to find clarity surrounding:
  – Cell type
  – Dose
  – Timing and method of delivery
  – Clinical indication:
    • Acute MI
      – Majority of trials and enrolled patients
      – Primary benefit appears to be in low EF patients
    • Chronic ischemia
    • Heart failure (ischemic and non-ischemic)
Effect of Transendocardial Delivery of Autologous Bone Marrow Mononuclear Cells on Functional Capacity, Left Ventricular Function, and Perfusion in Chronic Heart Failure
The FOCUS-CCTRN Trial

Evanescence C. Pita, MD, PhD, James T. Willerson, MD, Carl J. Pappas, MD, Timothy D. Henry, MD, Stephen S. Ellis, MD, David K. McNeal, MD, Georges N. Alex, MD, Devin Hay, MD, James D. Thomas, MD, Marvin W. Konysberg, MD, Daniel Martín, PhD, P. R., David Anderson, MD, Jay H. Towbin, MD, Nancy P. Pospisil, MD, PhD, Satinder Chadha, MD, Antonio R. Haterpoulos, PhD, Achillea P. Guo, PhD, Daniel A. Taitt, PhD, Christopher B. Cagle, MD, Dordove, Smith, RN, Lyndsay Westervelt, RN, James Chen, RN, Elizabeth Henderson, PhD, Rachel E. Gikon, RN, Miss Leslie Goldstein, RN, Sherry Bowman, RN, Judy Franzosen, RN, Sarah Bernatowicz, PhD, Linda B. Pillo, MD, MPH, Lara M. Simpson, PhD, Carola Logigian, MD, David Aguirre, MD, Eva Robinson, Charles Zerw:C, PhD, Judy Beltranescarr, MPH, Bradley R. Ebert, MD, Rachel W. Tepole, MPH, Sarah L. Sklarfl, PhD, David Z. Gordon, MD, PhD, Karl Z. Ebert, MD, Marcy Need, PhD, Leonard A. Morse, MD. PhD, Robert D. Settineri, MD, for the Cardiocalvear Cell Therapy Research Network (CCCTRN)

Context: Previous studies using autologous bone marrow mononuclear cells (BMACs) in patients with ischaemic heart Failu have demonstrated safety and suggested efficacy.

Objective: To determine if administration of BMACs through transendocardial injection improves myocardial perfusion, reduces left ventricular end systolic volume (LVESV), or enhances maximal oxygen consumption in patients with coronary artery disease or LV dysfunction, and limiting heart failure or angina.

Design, Setting, and Patients: A phase 2 randomized double-blind, placebo-controlled trial of symptomatic patients (New York Heart Association classification II-III or Canadian Cardiovascular Society classification II-IV) with a left ventricular ejection fraction of 40% or less, a perfusion defect by single-photon emission tomography (SPECT), and coronary artery disease not amenable to revascularization who were receiving maximal medical therapy at 9 National Heart, Lung, and Blood Institute-sponsored Cardiocalvear Cell Therapy Research Network (CCCTRN) sites between April 29, 2009, and April 18, 2011.

Intervention: Bone marrow aspiration (obtaining BMACs using a standardized automated system performed locally) and transendocardial injection of 100 million BMACs or placebo (ratio of 2 for BMAC group to 1 for placebo group).

Main Outcome Measures: Co-primary endpoints assessed at 6 months, changes in LVEF, assessed by echocardiography, maximal oxygen consumption, and reversibility on SPECT. Phenotypic and functional analyses of the cell product were performed by the CCCTRN core laboratory.

Results: Of 635 patients who provided consent, a total of 92 (82 mm; average age, 63 years) were randomized (46 in BMAC group and 46 in placebo group). Changes in LVEF index (9 ± 0.6% vs 15 ± 0.6% CI, −6.1 to 4.31, P = .731), maximal oxygen consumption (10.05% vs 12.06% CI, −2.42 to 2.34, P = .17), and reversibility defect (1.295% vs 12.90% CI, 10.20% to 10.12%, P = .841) were not statistically significant. There were no differences found in any of the secondary outcomes, including percent myocardial defect, total defect size, heart defect size, regional wall motion, and clinical improvement.

Conclusion: Among patients with chronic ischemic heart failure, transendocardial injection of autologous BMACs compared with placebo did not improve LVEF, maximal oxygen consumption, or reversibility on SPECT.

Trial Registration: clinicaltrials.gov identifier: NCT00624005.

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Downloaded from jama.ama-assn.org at Montefiore Medical Center on March 28, 2012
Phase 2, double blind, randomized, control
  - 61 treated and 31 placebo
Autologous BMMNC: CD34+ and CD133+
Perfusion defect on SPECT
EF ≤ 45% and NYHA II-III
CAD not amenable to revascularization
Transendocardial infusion with NOGA mapping
  - 100 x 10^6 cells (≤12 hours of harvest)
FOCUS

- No improvement in LVESV or oxygen consumption at 6 months
FOCUS

• Mild improvement in LVEF (2.7%) at 6 months
Regenerative Surgery

- Clarity is developing around limited efficacy:
  - Insufficient number of cells
  - Poor retention (<10% @ 24 hours)
  - Poor engraftment (<1% @ 4 weeks)
  - Choice of stem cell
    - Lineage directed cardiac progenitor?
    - BMMNC is not normally “cardiac” lineage directed
    - If BMMNC, can it be coaxed to a cardiac lineage?
  - Homing mechanisms inadequate
    - Molecular homing signals intact and of sufficient duration?
  - Extracellular matrix abnormal
Promising New Cell Types
Here, we report the identification in vitro of a class of human c-kit-positive cardiac cells that possess the fundamental properties of stem cells: self-renewing, clonogenic, and multipotent.

Lineage directed to cardiac, but not yet differentiated
Donor Female Dog → Explanted Heart → Mincing of tissue → Collagenase Digestion → Unfractionated Cardiac Cells

Donor Heart → Recipient Male Dog → Intracoronary Delivery → c-kit-positive CPCs → In vitro Expansion EGFP Lentivirus Infection → Selection
Progenitor Cells From the Explanted Heart Generate Immunocompatible Myocardium Within the Transplanted Donor Heart


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DOI: 10.1161/CIRCRESAHA.109.207266

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Myocardial Regeneration:
Differentiated and developing cells are indistinguishable from native myocardium
Current Research Studies

Cardiac stem cells in patients with ischaemic cardiomyopathy (SClPIO): initial results of a randomised phase 1 trial


Summary

Background c-kit-positive, lineage-negative cardiac stem cells (CSCs) improve post-infarction left ventricular (LV) dysfunction when administered to animals. We undertook a phase 1 trial (Stem Cell Infusion in Patients with Ischemic cardiomyopathy [SClPIO]) of autologous CSCs for the treatment of heart failure resulting from ischaemic heart disease.

Methods In stage A of the SClPIO trial, patients with post-infarction LV dysfunction (ejection fraction [EF] ≤40%) before coronary artery bypass grafting were consecutively enrolled in the treatment and control groups. In stage B, patients were randomly assigned to the treatment or control group in a 2:3 ratio by use of a computer-generated block randomisation scheme. 1 million autologous CSCs were administered by intracoronary infusion at a mean of 113 days (SE 4) after surgery; controls were not given any treatment. Although the study was open label, the echocardiographic analyses were masked to group assignment. The primary endpoint was short-term safety of CSCs and the secondary endpoint was efficacy. A per-protocol analysis was used. This study is registered with ClinicalTrials.gov, number NCT09474461.

Findings This study is still in progress. 16 patients were assigned to the treatment group and seven to the control group; no CSC-related adverse effects were reported. In 14 CSC-treated patients who were analysed, LVEF increased from 30.8% (SE 1.9) before CSC infusion to 38.5% (2.8) at 4 months after infusion (p=0.001). By contrast, in seven control patients, during the corresponding time interval, LVEF did not change (30.1% [2.4] at 4 months after CABG vs 30.2% [2.5] at 8 months after CABG). Importantly, the salutary effects of CSCs were even more pronounced at 1 year in eight patients (eg, LVEF increased by 12.3% after CABG) vs baseline, p=0.0007). In the seven treated patients in whom cardiac MRI could be done, infarct size decreased from 32.6 g (6.3) by 7.8 g (3.7; 24%) at 4 months (p=0.004) and 9.8 g (3.5; 30%) at 1 year (p=0.04).

Interpretation These initial results in patients are very encouraging. They suggest that intracoronary infusion of autologous CSCs is effective in improving LV systolic function and reducing infarct size in patients with heart failure after myocardial infarction, and warrant further, larger, phase 2 studies.

Funding University of Louisville Research Foundation and National Institutes of Health.
• CSC: c-kit (+), Lineage (-)
  – Endogenous cardiac stem cells
• Post MI: mean 3.7 yrs
• EF ≤ 40% in Stage A and B
• Intracoronary infusion after CABG
  – $1 \times 10^6$ cells
  – Mean 113 days after CABG
• 16 patients
SCIPIO: Ejection Fraction (%)

- Improvement in LVEF at 4 months and sustained at 1 year
- Mean: 5.6% at 4 mos and 8.2% at 1 yr
SCIPIO: Infarct Size

- Reduction in infarct size at 4 months and 12 months (cMRI)
Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial


Summary

Background Cardiosphere-derived cells (CDCs) reduce scarring after myocardial infarction, increase viable myocardium, and boost cardiac function in preclinical models. We aimed to assess safety of such an approach in patients with left ventricular dysfunction after myocardial infarction.

Methods In the prospective, randomised CARdiosphere-Derived autologous stem CELs to reverse ventricular dysfunction (CADUCEUS) trial, we enrolled patients 24 weeks after myocardial infarction (with left ventricular ejection fraction of 2545%) at two medical centres in the USA. An independent data co-ordinating centre randomly allocated patients in a 2:1 ratio to receive CDCs or standard care. For patients assigned to receive CDCs, autologous cells grown from endomyocardial biopsy specimens were infused into the infarct-related artery 15 months after myocardial infarction. The primary endpoint was proportion of patients at 6 months who died due to ventricular tachycardia, ventricular fibrillation, or sudden unexpected death, or had myocardial infarction after cell infusion, new cardiac tumour formation on MRI, or a major adverse cardiac event (MACE: composite of death and hospital admission for heart failure or non-fatal recurrent myocardial infarction). We also assessed preliminary efficacy endpoints on MRI by 6 months. Data analysers were masked to group assignment. This study is registered with ClinicalTrials.gov, NCT00893360.

Findings Between May 5, 2009, and Dec 16, 2010, we randomly allocated 31 eligible participants of whom 25 were included in a per-protocol analysis (17 to CDC group and eight to standard of care). Mean baseline left ventricular ejection fraction (LVEF) was 39% (SD 12) and scar occupied 24% (10) of left ventricular mass. Biopsy samples yielded prescribed cell doses within 36 days (SD 6). No complications were reported within 24 h of CDC infusion. By 6 months, no patients had died, developed cardiac tumours, or MACE in either group. Four patients (24%) in the CDC group had serious adverse events compared with one control (13%; p=1.00). Compared with controls at 6 months, MRI analysis of patients treated with CDCs showed reductions in scar mass (p=0.001), increases in viable heart mass (p=0.01) and regional contractility (p=0.02), and regional systolic wall thickening (p=0.015). However, changes in end-diastolic volume, end-systolic volume, and LVEF did not differ between groups by 6 months.

Interpretation We show intracoronary infusion of autologous CDCs after myocardial infarction is safe, warranting the expansion of such therapy to phase 2 study. The unprecedented increases we noted in viable myocardium, which are consistent with therapeutic regeneration, merit further assessment of clinical outcomes.

Funding US National Heart, Lung and Blood Institute and Cedars-Sinai Board of Governors Heart Stem Cell Center.
CADUCEUS
(Acute MI)

- Cardiosphere-derived stem cells
  - c-kit+, CD 90+, CD 105+ and CD 45 (-)
  - Endomyocardial biopsy
- ≤ 4 weeks Post MI and PCI/Stent
- EF: 25 - 45%
- Intracoronary infusion after PCI/Stent
  - 12.5 - 25 x 10^6 cells
  - ≤ 90 days after MI
- 17 patients
CADUCEUS: Ejection Fraction

- No improvement in LVEF at 6 and 12 months
CADUCEUS

- Reduction in scar mass and increase in viable mass
- *Does this represent myocardial regeneration?*

Difference in scar mass

Change in viable mass
Interpatient variability limits therapeutic efficacy of stem cell therapy

Most patients derived from patients with heart disease lack efficacy

Rarely patients harbor reparative hMSC

Interpatient variability limits therapeutic efficacy of stem cell therapy

Mayo Clinic Experience
Humanized cardiogenic cocktail achieves cardiopoiesis of patient bone marrow-derived mesenchymal stem cells
C-Cure Clinical Trial

First-in-man Intervention with Lineage Specified BM Stem Cells

• Multicenter Phase II, randomized, prospective study with blinded analyses
• Patients randomized into standard of care + cells vs. standard of care
• Target cell dose 600-1,200 x 10^6 cells, endoventricular delivery

Ischemic cardiomyopathy

• NYHA class II-III
• LV ejection fraction ≥15% and ≤40%
• Systolic dysfunction
• History of previous myocardial infarction
• Stable treatment

Phase II (n = 45)

C-Cure (SOC + CP cells)

Control (standard of care)

All patients on ICD
C-Cure Phase II Clinical Trial

Late-Breaking Clinical Trial May 20, 2012

• First-in-class lineage-specified stem cell product developed for treatment of heart failure

• Clinical trial documents feasibility and safety of cardiopoietic stem cells in ischemic cardiomyopathy

• Complementing standard of care, cardiopoietic stem cell therapy improved cardiac function and clinical performance

• Favorable profile supports follow-up pivotal studies
Human Cardiac Stem Cells

Identification of a coronary vascular progenitor cell in the human heart

Claudia Bearzi, Annarosa Leri, Francesco Lo Monaco, Marcello Rota, Arantxa Gonzalez, Toru Hosoda, Martino Pepe, Khaled Qanud, Caroline Ojaimi, Silvana Bardelli, Domenico D’Amario, David A. D’Alessandro, Robert E. Michler, Stefanie Dimmeler, Andreas M. Zeiher, Konrad Urbanek, Thomas H. Hintze, Jan Kajstura, and Piero Anversa


- Endogenous coronary vascular progenitor cell (VPC)
  - c-kit +
  - vascular endothelial growth-factor receptor 2 (KDR)
Homing Mechanisms
Stem Cell Based Tissue Repair

• Natural process, but clinically inefficient
• Short duration of expression of key molecular homing signals to direct stem cells to the injury
  – Stromal cell-Derived Factor (SDF-1)
Stromal Cell-Derived Factor-1 (SDF-1)

- Naturally occurring chemokine:
  - Upregulated during tissue injury
  - Short duration of expression (~7 days in acute MI)
  - Receptor: CXCR4
- Key regulator of stem cell migration to areas of tissue injury
- Trophic effect: Injured cardiomyocytes express CXCR4 and bind circulating SDF-1 blocking apoptotic cell death
- Increases vasculogenesis
- Down regulates inflammatory mediators (e.g. IL-8)

Courtesy of Marc S. Penn, MD, PhD, FACC
SDF-1 Plasmid (Non-Viral) for NYHA Class III CHF – Phase I Trial

- JVS -100
  - Naked plasma DNA used to deliver the therapeutic protein SDF-1

Sponsor: Juventas Therapeutics, Inc.
PI – Doug Losordo

Courtesy of Marc S. Penn, MD, PhD, FACC
JVS-100 Phase I Clinical Trial
Enrollment completed in Q4 2010

• Open-label dose-escalation trial
  • Class III heart failure
  • EF < 40%, post-MI

• JVS-100 delivery
  • 15 injections (1 ml each) of JVS-100
  • BioCardia Helical Infusion Catheter

• Primary Endpoints
  • Major Adverse Cardiac Events @ 1 mo
  • Efficacy @ 4 months

Courtesy of Marc S. Penn, MD, PhD, FACC
JVS-100
Improvement in QOL and 6MWD at 4 months

Quality of Life (QOL)
(10 pt change is clinically relevant)

Median Change from Baseline

6-Min Walk Distance (6MWD)
(30 m change is clinically relevant)

P-value relates to change from baseline

Courtesy of Marc S. Penn, MD, PhD, FACC
Summary

• JVS-100 is well tolerated at all doses with no adverse events related to drug

• SDF-1 expression late in patients with chronic heart failure leads to improvement in clinical status

• Phase 2 randomized placebo control multicenter clinical trial in Class III CHF
Inflammatory reaction and ECM degradation prevents normal stem cell adherence, migration, proliferation.
Biomaterial Scaffolds
CoreMatrix

Courtesy of Rob Matheny, MD
Biomaterial Scaffolds
CoreMatrix

Courtesy of Rob Matheny, MD
Porcine: Chronic CHF Study
Absolute LV Ejection Fraction Change, original EF<45

Ejection Fraction, %

- Control-no EMU
- EMU 2 mos post MI

post-MI | 36.05 | 35.9
4 mos   | 47.5
8-9 mos | 51.8

Courtesy of Rob Matheny, MD
Phase 1 LVAD Therapy: Effect of CoreMatrix Emulsion
LVAD Therapy: Effect of Intramyocardial Injection of Mesenchymal Precursor Cells on Myocardial Function
Angioblast: Revascor™

- Allogeneic mesenchymal stem cells
- Immunoselected & expanded from a single bone marrow donor
- Novel “off the shelf” product
- Promote neovascularization & angiogenesis
  - *In vitro* and in animals
- Evade immune recognition: lack HLA DR antigens
Key Efficacy Endpoint

Functional status & ventricular function (while weaned) at 90 d post intervention:
On the Horizon

- Stem cell therapy proven safe and feasible
- New candidate cell types with directed lineage
- Adjuvant homing and EC matrix therapy