Stem Cells for the Treatment of Heart Failure. What is Still Missing for a Prime Time Use?

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ISCT
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Stem Cells for the Treatment of Heart Failure. What is Still Missing for a Prime Time Use?

Outline

- Lack of thorough mechanistic understanding
- Optimization of cell retention
- Streamlined roadmap for clinical translability
Stem Cells for the Treatment of Heart Failure. What is Still Missing for a Prime Time Use?

Lack of Thorough Mechanistic Understanding

- Complexity of involved events
- Change in paradigm
- Basic research lagging behind clinical trials
Complexity of Involved Events

Drug-receptor interaction

Cell-triggered signalling pathways

Lack of Thorough Mechanistic Understanding

- Complexity of involved events
- Change in paradigm
- Basic research lagging behind clinical trials
Cell Therapy: A Changing Paradigm

Transplantation of cells ± biomaterial for replacing diseased host cells
Potential Mechanisms of Action of Stem Cells

- Injection of Stem Cells
- Activation of Endogenous Progenitors
- Differentiation into Cardiomyocytes
- Differentiation into Vascular Smooth Muscle Cells
- Differentiation into Endothelial Cells
- Inhibition of Apoptosis
- Extracellular Matrix Remodeling
- Neovascularization
- Attenuated LV Remodeling
- Enhanced Perfusion
- Improved Cardiac Function
- Improved Functional Capacity

Sanganalmath & Bolli Circ Research 2013;113:810-34.
Cell Therapy: A Changing Paradigm

Transplantation of cells ± biomaterial for replacing diseased host cells

Cellular graft-induced harnessing of endogenous repair pathways
Potential Mechanisms of Action of Stem Cells

Sanganalmath & Bolli Circ Research 2013;113:810-34.
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Early Cell Retention vs. Sustained Cell Survival

Rat model of MI; hMSCs encapsulated in alginate and mixed with a PEG-based hydrogel

Increased Retention

Levit R et al. J Am Heart Assoc 2013;2:e000367
Dissociation Between Sustained Cell Survival and Outcomes

Rat model of MI; hMSCs encapsulated in alginate and mixed with a PEG-based hydrogel

Reduced Remodeling and Improved Contractility – Assessment at 28 days

Levit R et al. J Am Heart Assoc 2013;2:e000367
Dissociation Between Sustained Cell Survival and Outcomes

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Dissociation Between Sustained Cell Survival and Outcomes

Rat model of MI; hMSCs encapsulated in alginate and mixed with a PEG-based hydrogel

Increased Angiogenesis - Assessment at 28 days

Levit R et al. J Am Heart Assoc 2013;2:e000367
Direct Comparison of Different Stem Cell Types and Subpopulations Reveals Superior Paracrine Potency and Myocardial Repair Efficacy With Cardiosphere-Derived Cells

Comparison of In Vitro Production of Growth Factors From Cultured Cells

Abstract 14862: Superiority of Human Pluripotent Stem Cell-Derived Cardiovascular Progenitors or Cardiomyocytes Over Bone Marrow Cells for Post-Infarction Ventricular Repair

- Nude rat model of MI

- Tx 4 days postMI

- At 32 days postMI, grafts from hESC-derived cardiovascular progenitors (11% of scar) and from hESC-derived cardiomyocytes (20% of scar) vs. no or few cells in the other groups (BM cells and hESC-derived noncardiac cells)

Chong et al. AHA Scientific Sessions, 2012
Cardiac stem cells in patients with ischaemic cardiomyopathy (SCiPIO): initial results of a randomised phase 1 trial

Roberto Bolli, Atul R Chugh, Domenico D’Amario, John H Loughran, Marcus F Stoddard, Sohail Ikram, Garth M Beach, Stephen G Wagner, Annarosa Leri, Toru Hosoda, Fumihiko Sanada, Julius B Elmore, Polina Goichberg, Donato Cappetta, Naresh K Solankhi, Ibrahim Fahsah, D Gregg Rokosh, Mark S Slaughter, Jan Kajstura, Piero Anversa

Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial


Cardiopoietic stem cell therapy in heart failure

The C-CURE multicenter randomized trial with lineage-specified biologics

Human Embryonic Stem Cell-Derived Cardiomyocytes
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Stem Cells for the Treatment of Heart Failure. What is Still Missing for a Prime Time Use?

Cell Mimetics

- Conditioned medium
- Microvesicles (microparticles and exosomes)
- Biomimetic polymers
Stem Cells for the Treatment of Heart Failure. What is Still Missing for a Prime Time Use?

Cell Mimetics

- Conditioned medium
- Microvesicles (microparticles and exosomes)
- Biomimetic polymers
MVs and exosomes dock at the plasma membrane of a target cell

Bound vesicles either fuse directly with the plasma membrane or are endocytosed.

Endocytosed vesicles may then fuse with the delimiting membrane of an endocytic compartment.

**Raposo & Stoorvogel JCB 2013;200:373-83.**
The F1 fraction represents an homogeneous exosome population purified from the CM by HPLC fractionation.

Stem Cells for the Treatment of Heart Failure. What is Still Missing for a Prime Time Use?

Cell Mimetics

- Conditioned medium
- Microvesicles (microparticles and exosomes)
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Improved Bioactivity by Scaffold Functionalization

**Functionalization by:**
- The incorporation of biologics
- The mechanical properties of the scaffold

**Added bioactivity**
- Displayed epitopes, released molecules, genetic materials, binding sequences, biopolymers...

**Functional groups**
- Hydrophobicity, signaling...

**Cross-linking**
- Stiffness, degradation...

**Geometry**
- Isotropic, aligned, fibrous, porous...
Injectable Small Intestine Submucosal Extracellular Matrix in an Acute Myocardial Infarction Model

Mouse model of MI; Treatment 7 days postMI; Assessment after 3 weeks

LV Function

CACs : Circulating Angiogenic Cells

Injectable Small Intestine Submucosal Extracellular Matrix in an Acute Myocardial Infarction Model

Mouse model of MI; Treatment 7 days postMI; Assessment after 3 weeks

LV Function

CACs : Circulating Angiogenic Cells

Why Have’t Stem Cells Fulfilled Their Clinical Potential

Lack of Thorough Mechanistic Understanding

- Complexity of involved events
- Change in paradigm
- Basic research lagging behind clinical trials
Intracoronary, human autologous stem cell transplantation for myocardial regeneration following myocardial infarction.

[Article in German]


Abstract

OBJECTIVE:
The regenerative potential of human autologous adult stem cells on myocardial regeneration and neovascularisation after myocardial infarction may contribute to healing of the infarction area. But no clinical application has previously been reported. We here describe for the first time the results of this method applied in a patient who had sustained an acute myocardial infarction.

HISTORY AND CLINICAL FINDINGS:
14 hours after the onset of left precordial pain a 46-year-old man was admitted to our hospital for interventional diagnosis and treatment. Coronary angiography demonstrated occlusion of the anterior descending branch of the left coronary artery with transmural infarction. This was treated by percutaneous transluminal catheter angioplasty and stent placement.

THERAPY AND RESULTS:
Mononuclear bone marrow cells of the patient were prepared and 6 days after infarction 1.2 infinity 10^7 cells were transplanted at low pressure via a percutaneous transluminal catheter placed in the infarct-related artery. Before and 10 weeks after this procedure left ventricular function, infarct size, ventricular geometry and myocardial perfusion were measured by (201)thallium SPECT both at rest and on exercise, together with bull's-eye analysis, dobutamine stress echocardiography, right heart catheterisation and radionuclide ventriculography. At 10 weeks after the stem cell transplantation the transmural infarct area had been reduced from 24.6 % to 15.7 % of left ventricular circumference, while ejection fraction, cardiac index and stroke volume had increased by 20-30 %. On exercise the end diastolic volume had decreased by 30 % and there was a comparable fall in left ventricular filling pressure (mean pulmonary capillary pressure).

CONCLUSION:
These results for the first time demonstrate that selective intracoronary transplantation of human autologous adult stem cells is possible under clinical conditions and that it can lead to regeneration of the myocardial scar after transmural infarction. The therapeutic effects may be ascribed to stem cell-associated myocardial regeneration and neovascularisation.
Stem Cells for the Treatment of Heart Failure. What is Still Missing for a Prime Time Use?

Still Unsolved Key Basic Issues

- Cell phenotype and dosing
- Autologous vs. allogeneic origin of the cells
- Optimal timing of cell delivery
- Interactions between the grafted cells and the microenvironment of the target area
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Routes of Cardiac Cell Delivery

Intracoronary

Intramyocardial

Effect of Timing of Injection by Different Routes on Cardiac 99mTc-Labeled BMC Retention

Stem Cells for the Treatment of Heart Failure. What is Still Missing for a Prime Time Use?

Catheter-Based Cell Delivery

Optimization of Cell Transfer

- Enhancement of homing signals
- Improved delivery devices
- Incorporation of cells into biomaterials
Importance of the SDF-1:CXCR4 axis in myocardial repair

Marc S. Penn, MD, PhD

An Open-Label Dose Escalation Study to Evaluate the Safety of Administration of Nonviral Stromal Cell-Derived Factor-1 Plasmid to Treat Symptomatic Ischemic Heart Failure

Stabilization of Functional Parameters

Stem Cells for the Treatment of Heart Failure. What is Still Missing for a Prime Time Use?

Catheter-Based Cell Delivery

Optimization of Cell Transfer

- Enhancement of homing signals
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Optimized Delivery System Achieves Enhanced Endomyocardial Stem Cell Retention

GFP positive cells per gm of heart tissue ($10^5$)

- Straight + end holes
- Curved + side holes

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Catheter-Based Cell Delivery

Optimization of Cell Transfer

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Approaches to Tissue Engineering of Heart Muscle

Layered cell sheets

Mechanical stimulation of cells in hydrogel

Electrical stimulation of cells in a porous scaffold

Decellularized heart

Perfusion of a channeled scaffold, blood supply

In situ polymerization of cell-loaded hydrogel

Cardiosphere-derived cells (CDCs) grown from adult human cardiac biopsy specimens, incorporated within an *in situ* polymerizable hydrogel made of hyaluronan and porcine gelatin (*Hystem®-C™*) and injected intramyocardially in acutely infarcted SCID mice.

Stem Cells for the Treatment of Heart Failure: What is Still Missing for a Prime Time Use?

Surgical Cell Delivery

From intramyocardial injections...

...To epicardial patches
Cardiac Patches

Advantages

- To overcome the limitations of cell injections
- To strengthen the infarcted myocardium
- To provide a template enhancing cell survival, proliferation, differentiation and migration
- To serve as a platform for drug/factor delivery
In Vivo Cardiomyocytic Differentiation of Beating hESC

Beating I6 human ESC embedded into a fibrin scaffold
Explantation 48 h after transplantation in an infarcted rat heart

Immunostaining anti-slow MHC
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The Gatekeepers

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC
and Regulation (EC) No 726/2004

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

U.S. Department of Health and Human Services
Food and Drug Administration
Stem Cells for the Treatment of Heart Failure. What is Still Missing for a Prime Time Use?

Guidelines

- Full traceability of clinical-grade source materials
- Robust, scalable and quality-controlled manufacturing process ensuring product consistency in GMP-approved facilities
- Accurate characterization of batch release criteria
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Release Criteria

- Viability
- Sterility
- Purity (phenotyping)
- Potency (functional testing)
- Oncogenicity if culture-expanded cells (karyotype, FISH, CGH-arrays)
Advantages of Allogeneic Cell Therapy Products

- Off-the-shelf availability
- Consistent functionality
- Simplification of logistics
- Reduced costs
Does Transendocardial Injection of Mesenchymal Stem Cells Improve Myocardial Function Locally or Globally? An Analysis From the POSEIDON Randomized Trial

Stem Cell Clinical Trials (All Phases) by Indication. 2012

Source: visiongain 2012
## Regenerative Therapy Market
### Current Perspectives

<table>
<thead>
<tr>
<th>Area</th>
<th>World market (billion €)</th>
<th>Projected time</th>
<th>Estimation</th>
</tr>
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<tbody>
<tr>
<td>Cell therapy</td>
<td>10</td>
<td>2020</td>
<td>20 à 40 % annual growth</td>
</tr>
<tr>
<td>Gene therapy</td>
<td>2</td>
<td>2020</td>
<td>30 % annual growth</td>
</tr>
<tr>
<td>Reconstruction of reimplantable tissues/organs</td>
<td>15</td>
<td>2025</td>
<td>Evolving market</td>
</tr>
<tr>
<td>Biomaterials</td>
<td>87</td>
<td>2017</td>
<td>15% annual growth</td>
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« If I had six hours to chop down the tree, I would spend the first four sharpening the axe. »

Abraham Lincoln
Take-Home Message

Translational Imperatives

- Embrace complexity
- Engineer versatility
- Deliver simplicity

G.D. Prestwich
Co-founder of Glycosan