Current Status of Cardiac Cell Repair Therapy

Banff 2017
Cell Therapy in Acute Myocardial Infarction

Therapeutic Targets

- Acute myocardial infarction
- Chronic heart failure
- Adverse LV remodeling
- Infarct expansion
- Chronic LV dilatation
- Regeneration?
- Paracrine factors?
- Vascularization
- Apoptosis

Stem cells
Patient Cohorts, Cell Types, Doses, Routes of Delivery and Clinical Endpoints Used in Adult Stem Cell Trials

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Adult Stem Cell Type</th>
<th>Dose and Delivery Route</th>
<th>Clinical End Point</th>
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<tbody>
<tr>
<td>Type of heart disease</td>
<td>Bone marrow-derived stem cells</td>
<td>Cell dosage</td>
<td>Imaging surrogate end points</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>Bone marrow mononuclear cells</td>
<td>High dose (&gt;100 M cells)</td>
<td>Left ventricular ejection fraction using echocardiogram</td>
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<tr>
<td>Chronic ischemia/angina</td>
<td>Mesenchymal stem cells</td>
<td>Low/medium dose (1M = 100 M cells)</td>
<td>Infarct size using magnetic resonance imaging</td>
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<tr>
<td>Ischemic cardiomyopathy</td>
<td>Adipose tissue- or umbilical cord-derived stem cells</td>
<td></td>
<td>Perfusion using SPECT</td>
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<tr>
<td>Nonischemic cardiomyopathy</td>
<td>Adipose tissue-derived SCs</td>
<td></td>
<td>Major adverse cardiac events</td>
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<td></td>
<td>Umbilical cord &quot;Wharton jelly&quot;-derived SCs</td>
<td></td>
<td>Death</td>
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<tr>
<td></td>
<td>Cardiac tissue-derived stem cells</td>
<td></td>
<td>Cardiovascular death</td>
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<tr>
<td></td>
<td>Cardiosphere derived cells</td>
<td></td>
<td>Myocardial infarction</td>
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<tr>
<td></td>
<td>Cardiac stem cells</td>
<td></td>
<td>Revascularization</td>
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<td></td>
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<td>Heart failure readmission</td>
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</tbody>
</table>

Patient characteristics

- Patient age: old vs young
- Time after myocardial infarction: days vs months
- Infarct size: small vs large
- Baseline LVEF: <35% vs <45%

Nguyen and Wu: JAMA Cardiology, 2016
Cell Repair Therapy – Phase 1
Lessons Learned – Clinical Studies

- Safe and feasible
- Studies predominantly in BMSC
- Ventricular arrhythmias with skeletal myoblasts

- Can *modestly* improve LV function (EF 3.0% ↑)
- Improved perfusion, remodeling and CFR after MI
- Clinical outcomes – *favorable trends* (trials underpowered for clinical endpoints)

- Majority of implanted cells disappear within 1 wk
- No evidence of myocyte regeneration using existing therapies
  - *Paracrine hypothesis as explanation for beneficial effects*
  - *Stimulation of endogenous cardiac progenitors*

Recent trials
- Mixed results
  - New questions generated
  - Reflect an incomplete understanding of basic mechanisms of benefit
  - New cells and innovative strategies to improve survival and proliferation under evaluation
Proposed Mechanisms of Benefit

Endothelial stem cells

Transplanted cells

Direct differentiation

Resident endothelial progenitor cells

Angiogenic stimulus

New blood vessels

Cardiogenic stimulus

Healthy myocardium

Resident cardiac stem cells

Direct differentiation

Homeostatic stimuli

Immunomodulation

Paracrine effects

Mesenchymal stem cells

Cardioprotection
The initial enthusiasm has been tempered and the number of unanswered questions increases. Nonetheless, the concept maintains its promise.

In perspective

Excitement/euphoria

Reality check

Depression

Progress
Barriers to Myocardial Regeneration

Cellular factors (injected cells)

- Inadequate number
- Low proliferative capacity
- Insufficient pluripotency

Tissue factors

- Lack of cell contact & integration
- Rapid washout of injected cells
- Fibrosis preventing tissue organization

Cell environment factors

- Stimuli for homing and/or engraftment and proliferation
- Inhibitory environment for survival, eg, inflammation and apoptosis

Hostile cardiovascular environment

Forrester: JACC Intv, 2009
Approaches to Isolation and Preparation of Stem Cells

**First-generation stem cells**
- Iliac crest aspirate
- Bone marrow mononuclear cells
- Endothelial progenitor cells
- Mesenchymal stem cells

**Next-generation stem cells and combinations**
- Resident Cardiac Stem Cells
- Iliac crest aspirate
- Isolated cardiac stem cells
- Cardiospheres cardiac stem cells
- Cardiopoietic stem cells

**“Guided” Cell Therapy**
- Lineage specification
- Treatment with cardiopoietic growth factor cocktail

Behfar: Nature CV Reviews, 2014
# Approaches to Enhance Cellular Function and the Environment

<table>
<thead>
<tr>
<th>Cell-directed</th>
<th>Enhancement of cellular function</th>
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<tbody>
<tr>
<td><strong>Nonpharmacologic</strong></td>
<td></td>
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<tr>
<td>Pharmacologic</td>
<td>Statins  SDF-1  NO synthase enhancers</td>
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<table>
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<tr>
<th>Substrate directed</th>
<th>Enhancement of (ECM) matrix and cellular environment</th>
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<tr>
<td>• Optimized delivery systems</td>
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Why Proceed Clinically While Basic Questions are Unresolved?

Trials provide some answers to preconceived hypotheses but also generate *new* questions

- Aspirin
- Statins
- ACE-inhibitors
- Aldosterone antagonists

Preclinical studies will not answer complex questions re timing and methods of cell delivery
Clinical Trials of Cardiac Cell Repair Therapy

Major Issues

- Statistical power
- Surrogate vs “hard” endpoints

Changing “unnatural” history of MI
Better prognosis

The critical importance of blinding

- Difficulties in enrollment
- Globalization of trials – does geography matter?
Cardiac Cell Repair Therapy is at a Crossroads

“The end of the beginning or the beginning of the end”? - Winston Churchill

Grounds for cautious optimism

- Ongoing basic research on multiple fronts and countries but “lost in clinical translation”

Clinical trial results

Safety Modest benefits Trends in the right direction

- Improved clinical trial design

Concerns

- Benefits – modest
- Neutral trials

- Unrealistic expectations

- Overreaction to neutral trial results

- Perceptions in scientific community over extent of stem cell research funding

- Concerns re scientific credibility – justified and unjustified
Ongoing Clinical Trials of Stem Cell Therapy

The field of stem cell research is active, robust international and encompasses both bench and bedside

- 39 trials – 1,675 pts (range 30-1,730)
- Ischemic and non-ischemic cardiomyopathy
- Phases 1, 2 and 3

Cell source
- Autologous
- Allogeneic
- Umbilical cord

Cell types
- 11 different cells and combinations

Delivery
- Intracoronary
- Intramyocardial
- Intravenous
- Transendocardial
- Precursor cells (mesoblast)
Autologous CD34+ Cells for Treatment of Refractory Angina
Meta-Analysis of 3 Randomized Double-Blind Studies

- ACT – 34
- ACT – 34 (24 mo extension)
- RENEW (prematurely terminated)
  - 303 pts

Mortality reduction
P=0.003 but not powered for this endpoint

![Total Exercise Time Chart]

**Total Exercise Time**

- Mod43: P=0.002
- MLL6: P=0.009
- MLL12: P=0.022

T Povsic: (Pers Comm)
Ixmyelocel-T for Pts With Ischemic Heart Failure
Randomized Double-Blind Trial

- 126 patients
- NYHA class III-IV
- EF <0.35
- Non-revascularizable

**Ixmyelocel-T**

**Expanded BMC**

CD

CD 90+

MSC

CD 45+fx

CD 14+

Activated macrophages

**Time of Occurrence Primary End-Point**

All-cause death/
Hospital CV admissions/
Unplanned visits for decompensated HF

Survival (%)

Elapsed time to 1st event (mo)

HR 0.67 (95% CI 0.38-1.19)
P=0.1667

109 pts – per protocol efficacy analysis

RR 0.63 (0.42-0.97)
P=0.0344

No changes in LV function,
6 min walk or NYHA class

Patel: Lancet, 2016
Congestive Heart Failure Cardiopoietic Regenerative Therapy (CHART-I) Trial

- 315 pts randomized
- Endomyocardial delivery
- Cell product – C3BS-CQR-1

Primary Efficacy Endpoint (Hierarchical Composite)
- All-cause mortality
- No. of worsening HF events
- Change MLHFQ
- Change in 6-min walk
- Change in LVESV
- Change in LVEF

Outcomes

| Patients with baseline LVEDV 200-370 mL | Overall study population () | 0.54 (0.47, 0.61) | P=0.27 |
| Patients with ≤19 injections | | | |
| Baseline LVEDV 200-370 mL and ≤19 injections | | | |
| 0.4 0.5 0.6 0.7 0.8 | Mann-Whitney Estimator (95% CI) | 0.61 (0.52, 0.70) | P=0.015 |
| | | 0.59 (0.51, 0.67) | P=0.034 |
| | | 0.70 (0.59, 0.81) | P<0.001 |

Bartunek: EHJ, 2016
Cell Repair Therapy – a Time for Cautious Optimism?

Enthusiasm and allure ahead of the science?
Lessons to be learned from developments in angiogenesis and gene therapy
Rapid progress in clinical and translational science
Collaborative approach to design of future focused trials is crucial
Use of control experiments and blinding

“If we don’t succeed we run the risk of failure
President George W. Bush
Cardiac Cell Repair Therapy
Conclusions

• A pivotal trial demonstrating significant benefits on LV function (eg, EF 10%↑)  
  Will change clinical practice

• Resident cardiac stem cells and guided MSCs are promising

• Larger trials are needed to assess relative benefits compared to BMSC and other progenitors

• Enhancement strategies are needed to improve current results
Allogeneic cells likely to be the predominant cell type

- Evidence for the paracrine hypothesis is strengthening
- Prospect of cell-free cell repair therapy is realistic
- For surrogate endpoints blinding is essential
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure


THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

The Path to an Angiotensin Receptor Antagonist-Neprilysin Inhibitor in the Treatment of Heart Failure

Eugene Braunwald, MD*

JACC, 2015
Clarifying Stem-Cell Therapy’s Benefits and Risks

Peter W. Marks, M.D., Ph.D., Celia M. Witten, Ph.D., M.D., and Robert M. Califf, M.D.
Prometheus Bound

Paul Rubens

Philadelphia Museum of Art
Cardiac Cell Repair
The Magnitude of the Task

Leapfrog 15,000 yr
of evolutionary biology
Cardiac Cell Repair
The Magnitude of the Task

Stone age man
Cardiac Cell Repair
The Magnitude of the Task

MI vulnerable

Cardiac disease in the elderly?
Mortality would have little impact on survival of the species

MI vulnerable

Mortality would have little impact on survival of the species.
Conclusions

The mesenchymal stem cells of whales and mice are alike, in both morphology and size.
... and if mouse or whale adipose tissue were being considered for study or perhaps for veterinary therapeutic applications, the option would be to breed a large number of mice, or wait for a whale to become stranded on a beach.

The authors therefore call on investigators with access to beached blue whales or with mesenchymal stem cells from the African pygmy mouse or bumblebee bat, to come forward and collaborate with us.
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