Cardiac Regeneration – Picking up the Pieces:
Cell Therapy

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Disclosures: none
Mechanisms of cell-based myocardial repair

**Paracrine Effects**
- Apoptosis/Cell Death
- Recruitment and Activation of Resident Stem Cells
- Cardiomyogenic Differentiation of Resident Stem Cells
- Angiogenesis, Vasculogenesis
- Modulation of Matrix Remodeling

**Direct Effects**
- Creation of a Niche-like Environment
- Transdifferentiation into Cardiomyocytes, Endothelial Cells and Vascular Smooth Muscle Cells

Scar Stabilization
- Capillary Density
- Cardiomyogenic Rebuilding

**REVERSE REMODELING**
- Contractile Performance

*Adapted from: Kuster GM et al., in: Translational Regenerative Medicine, Elsevier, in press*
Timeline of clinical trials

**BMMNC:**
- AMI: TOPCARE-AMI; BOOST; REPAIR-AMI; ASTAMI; BONAMI; FINCELL; HEBE; TIME; Late TIME; Swiss AMI

**ICMP:**
- TOPCARE-CHD; FOCUS-CCTRN

**BM-MSC in ICMP:**
- POSEIDON; C-CURE

**AMI:**
- MAGIC
  - 2000
  - 2004
  - 2005
  - 2006

**ICMP:**
- PRECISE
  - In progress

**ICMP:**
- SCIPIO; CADUCEUS; ALLSTAR; ALCADIA

Adapted from: Ptaszek LM et al., Lancet 2012
Contradictory results from randomized controlled trials

**Repair-AMI**

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<tr>
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<th>Placebo</th>
<th>BMC</th>
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<td>% increase in LVEF (absolute)</td>
<td></td>
<td></td>
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<tr>
<td>N</td>
<td>103</td>
<td>101</td>
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<tr>
<td>3-7 d post-MI</td>
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**Cardiovascular Cell Therapy Research Network (CCTRN):**

**TIME** N=120; 3-7 d *JAMA 2012*

**Late-TIME** N=87; 2-3 wks *JAMA 2011*

**Swiss-AMI:** N=200, 5-7d, 3-4wks, *Circ 2013*

**CCTRN TIME**

Global left ventricular function

**Schachinger V et al., NEJM 2006**

**Assmus B et al., Eur Heart J 2014**

Traverse JH et al., *JAMA 2012*
The ACCRUE patient-level meta-analysis: primary EP

Gyöngyösi M et al., Circ Res 2015
The ACCRUE patient-level meta-analysis: Remodeling

What’s next?

Gyöngyösi M et al., Circ Res 2015
BAMI. The effect of i.c. reinfusion of BMMNCs on all-cause mortality in acute MI

- Multinational, multicentre, randomised open-label, controlled, parallel-group phase III study (EC FP7).

- Aim: to demonstrate that a single i.c. infusion of autologous BMMNCs is safe and reduces all-cause mortality in patients with reduced LVEF (<=45%) after successful reperfusion for acute MI when compared to a control group of patients undergoing best medical care.

- Study design based on Repair-AMI. Inclusion of 3000 patients (currently ongoing). Completion expected in 2018.

NCT01569178
Cell type analyses from the CCTRN TIME trial

Shutt RC, Circ Res 2015
Cardiac derived cells and lineage specification

Behfar A et al., Nat Rev Cardiol 2014
C-Cure: cardiogenic lineage specification of BM-MSC

Bartonuk J et al., JACC 2013
Advantages of mesenchymal stem cells (MSCs)

- Easily accessible either through bone marrow aspiration (bone marrow-derived) or liposuction (adipose tissue-derived)
- Identification through defined panel of surface markers and lack of hematopoietic markers
- Immunoprivileged: lack of MHCII, low expression of MHCI, immunomodulatory properties
- Suited for allogeneic transplantation and – hence – potential off-the-shelf use, enabling quality control and potency testing
SCIPIO and CADUCEUS

i.c. application of c-kit+ CPC

Bolli R et al., Lancet 2011

Makkar RR et al, Lancet 2012
Reprogramming and beyond

First Generation: BM-derived cell injection
- Intra-coronary or intra-myocardial injection

Second Generation: Cardiac-derived cell injection
- Purified, specific cardiac-derived populations obtained by biopsy or surgery
- Intra-coronary or intra-myocardial injection

Third Generation: in situ cell reprogramming, cardiomyocyte dedifferentiation, or stimulation of endogenous cardiac stem cells

Kovacic JC and Fuster V, Circ Res 2015
Reprogramming of dividing non-myocytes

Song K et al, Nature 2012
Conclusions and Outlook

- Transplantation of BMCs into the injured myocardium is safe, but clinical efficacy appears limited.

- Cardiac committed cells such as resident cardiac stem/progenitor cells (CPCs) or primed cardiogenic mesenchymal stem cells, with supposedly greater cardiomyogenic differentiation potential, may hold promise for the future.

- Alternative approaches include direct genetic reprogramming of dividing nonmyocytes into cardiomyocytes, induction of cardiomyocyte proliferation, stimulation of endogenous CPCs or use of induced pluripotent stem cells (iPS).

- Combination of cell therapy with tissue engineering strategies (use of matrices, decellularized scaffolds, biopolymers etc.) are under investigation.
Thank you for your attention