Universitätsspital Basel

Herzzentrum

Cardiac Regeneration – Picking up the Pieces: *Cell Therapy*

Gabriela M. Kuster
Division of Cardiology and Department of Biomedicine
University Hospital Basel

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Disclosures: none

Departement Biomedizin Basel

Mechanisms of cell-based myocardial repair

Paracrine Effects

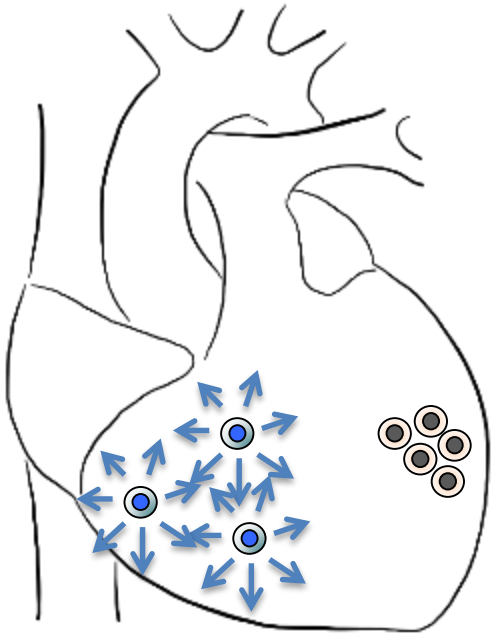
↓Apoptosis/Cell Death

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

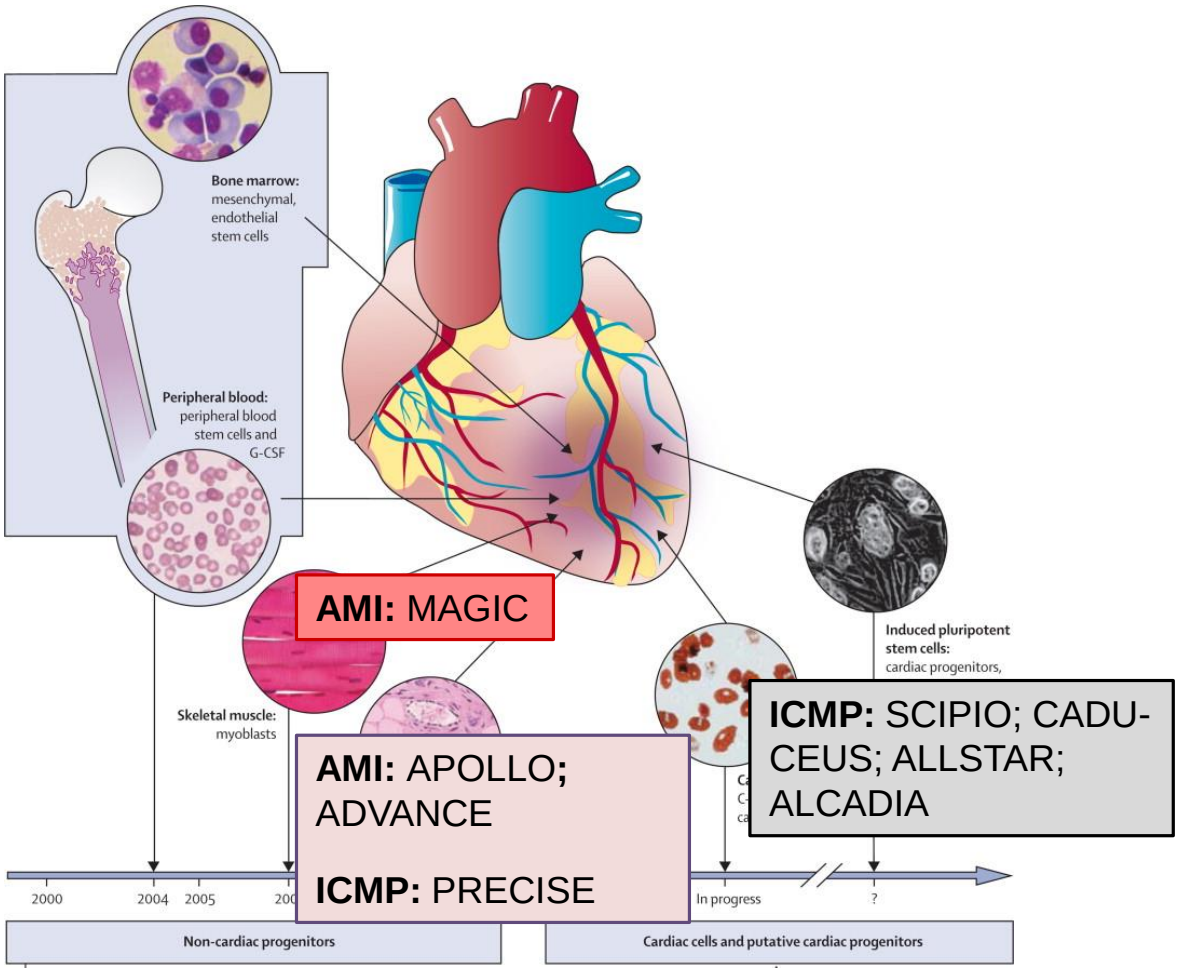
Timeline of clinical trials

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

AMI: APOLLO; ADVANCE

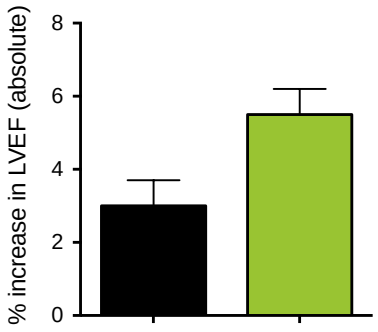
ICMP: PRECISE

ICMP: SCIPIO; CADUCEUS; ALLSTAR; ALCADIA

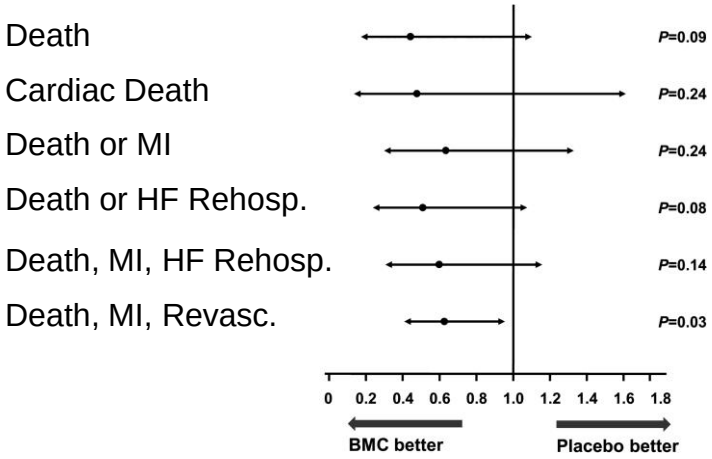
Adapted from: Ptaszek LM et al., Lancet 2012

Contradictory results from randomized controlled trials

Repair-AMI



N 103 101 3-7 d post-MI



Schachinger V et al., NEJM 2006
Assmus B et al., Eur Heart J 2014

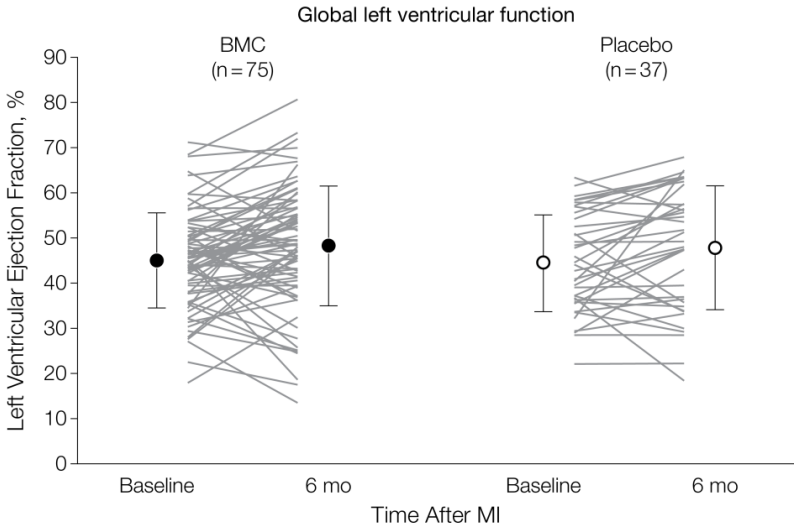
Cardiovascular Cell Therapy Research Network (**CCTRN**):

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

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

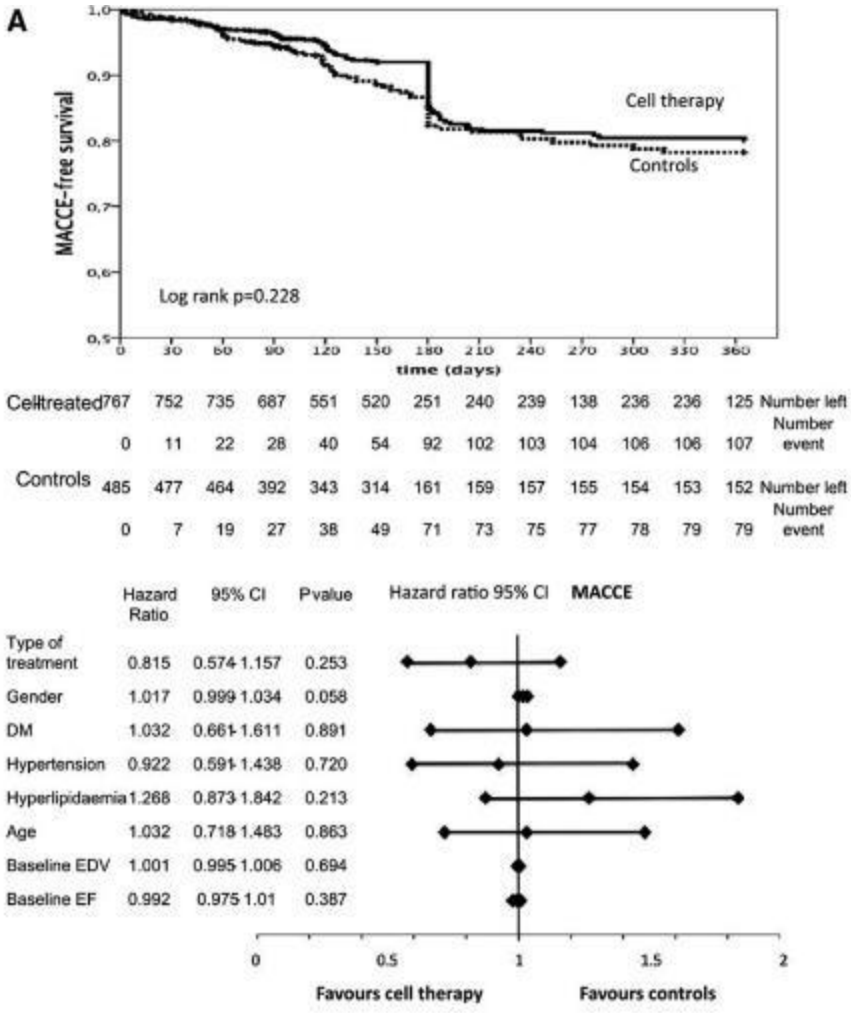
Swiss-AMI: N=200, 5-7d, 3-4wks, *Circ 2013*

CCTRN TIME



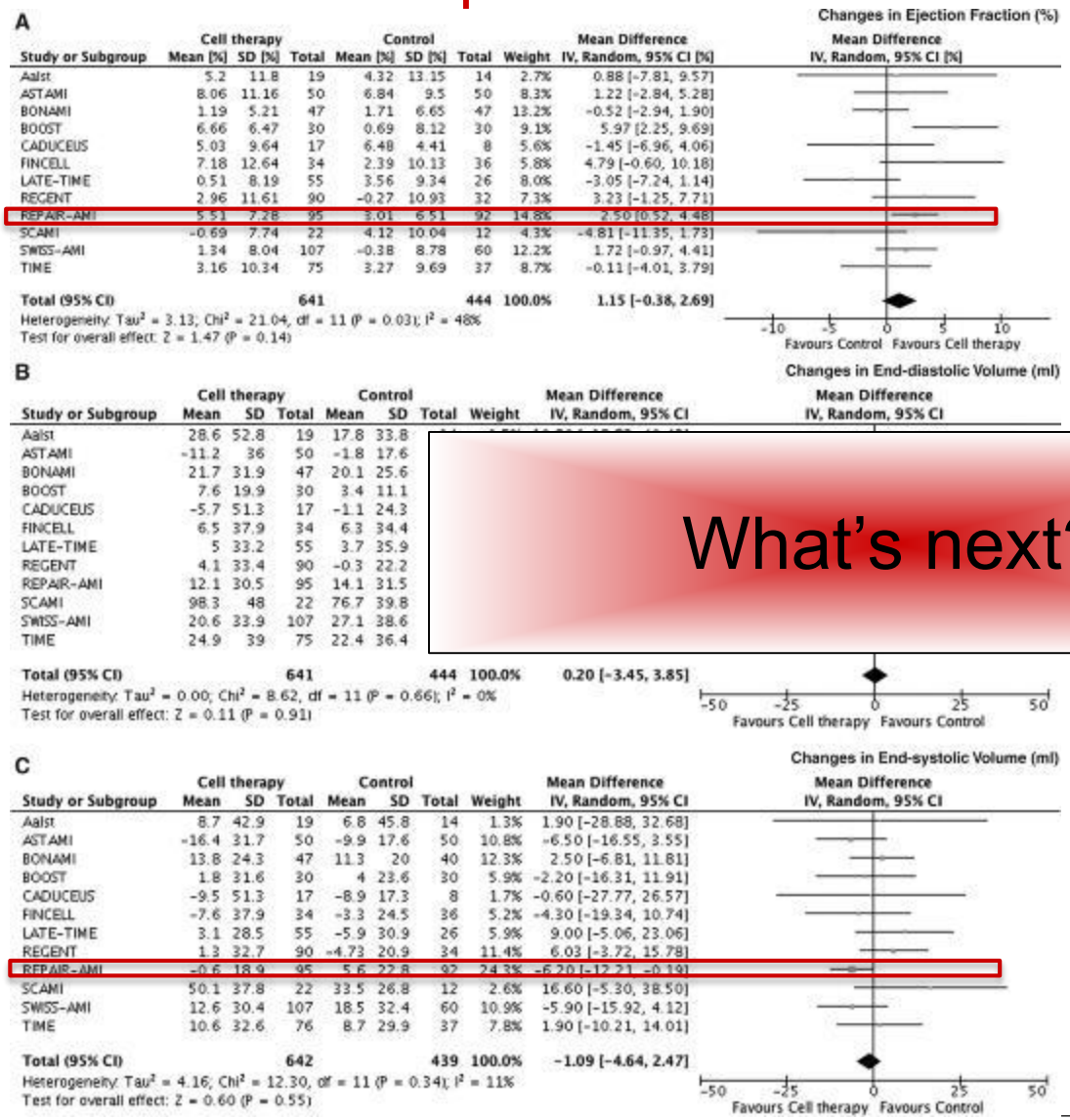
Traverse JH et al., JAMA 2012

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

Universitätsspital Basel
Kardiologie

BAMI. The effect of i.c. reinfusion of BMMNCs on all-cause mortality in acute MI

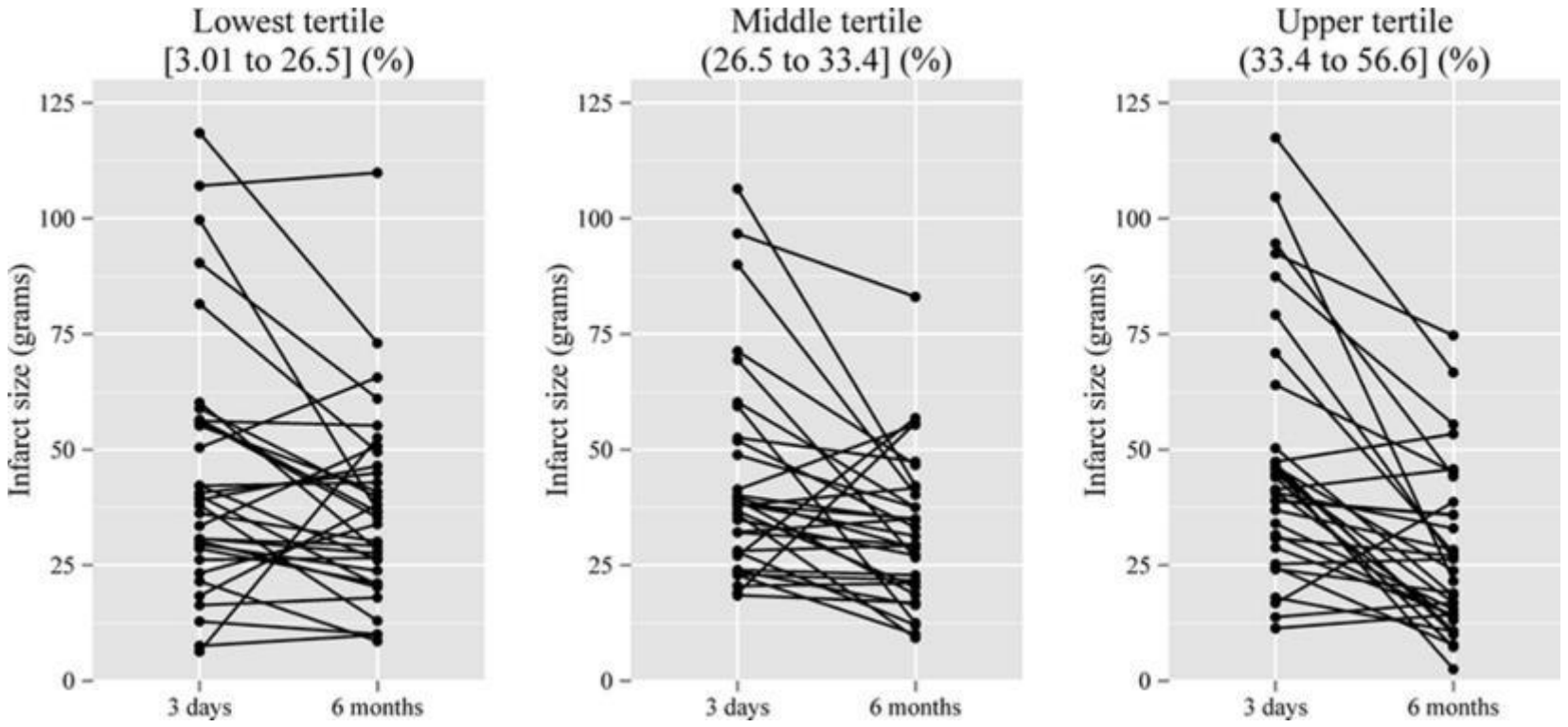
- Multinational, multicentre, randomised open-label, controlled, parallel-group phase III study (EC FP7).

- 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.

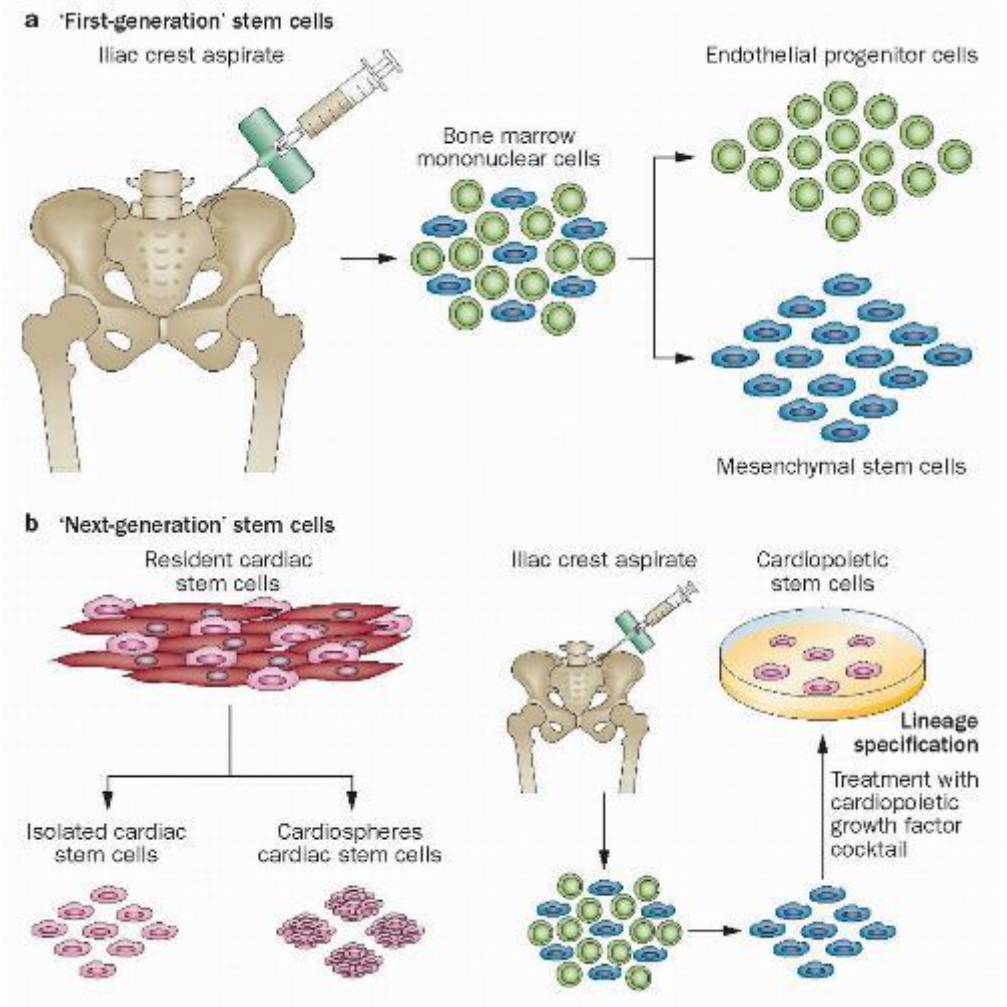
NCT01569178

Cell type analyses from the CCTRN TIME trial



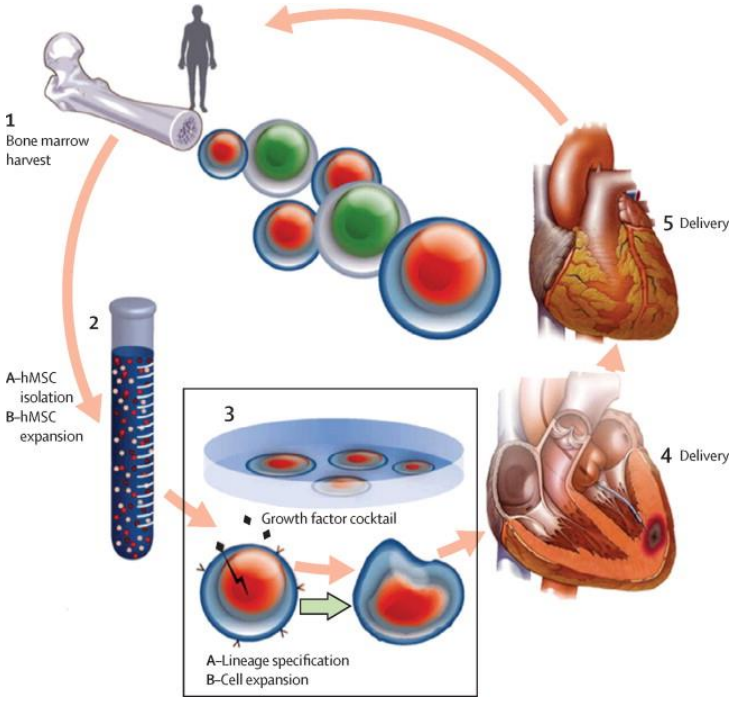
Shutt RC, Circ Res 2015

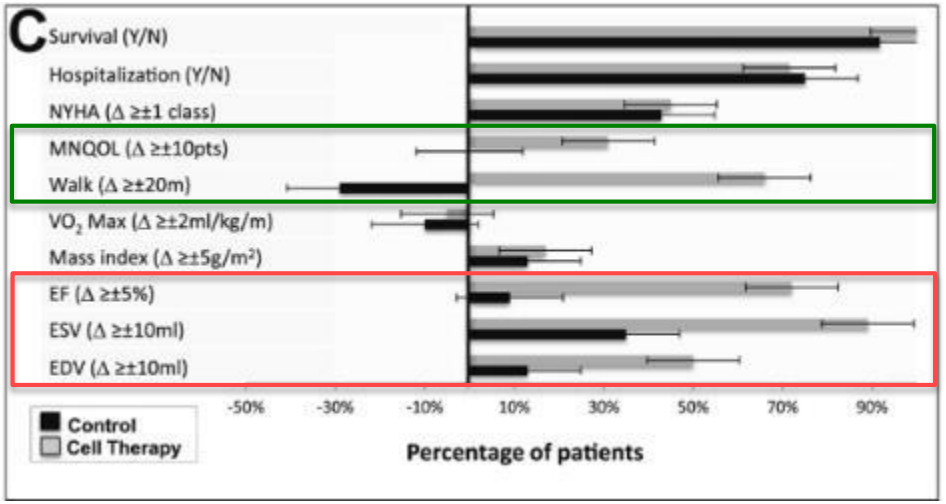
Cardiac derived cells and lineage specification



Behfar A et al., Nat Rev Cardiol 2014

C-Cure: cardiogenic lineage specification of BM-MSC



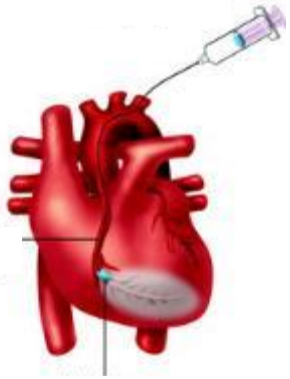


Bartunek J et al., JACC 2013

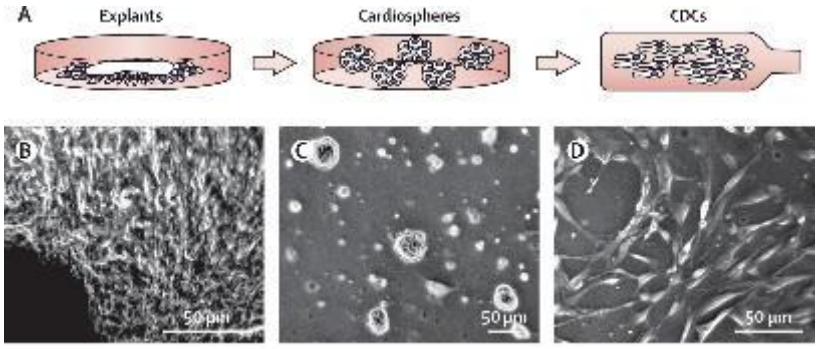
Advantages of mesenchymal stem cells (MSCs)

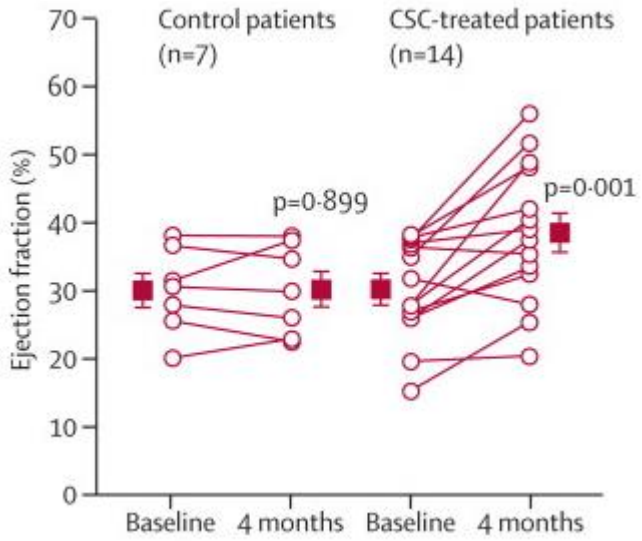
- Easily accessible either through bone marrow aspiration (bone marrow-derived) or liposuction (adipose tissue-derived)
- Identification through defined panel of surface markers and lack of hematopoietic markers
- Immunoprivileged: lack of MHCII, low expression of MHCI, immunomodulatory properties
-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

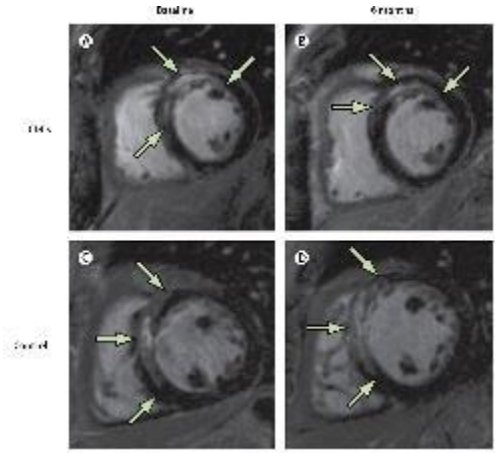
SCIPIO and CADUCEUS

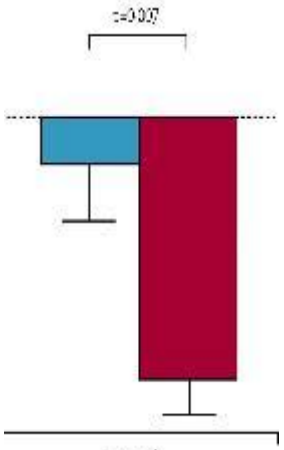


i.c. application of
c-kit+ CPC





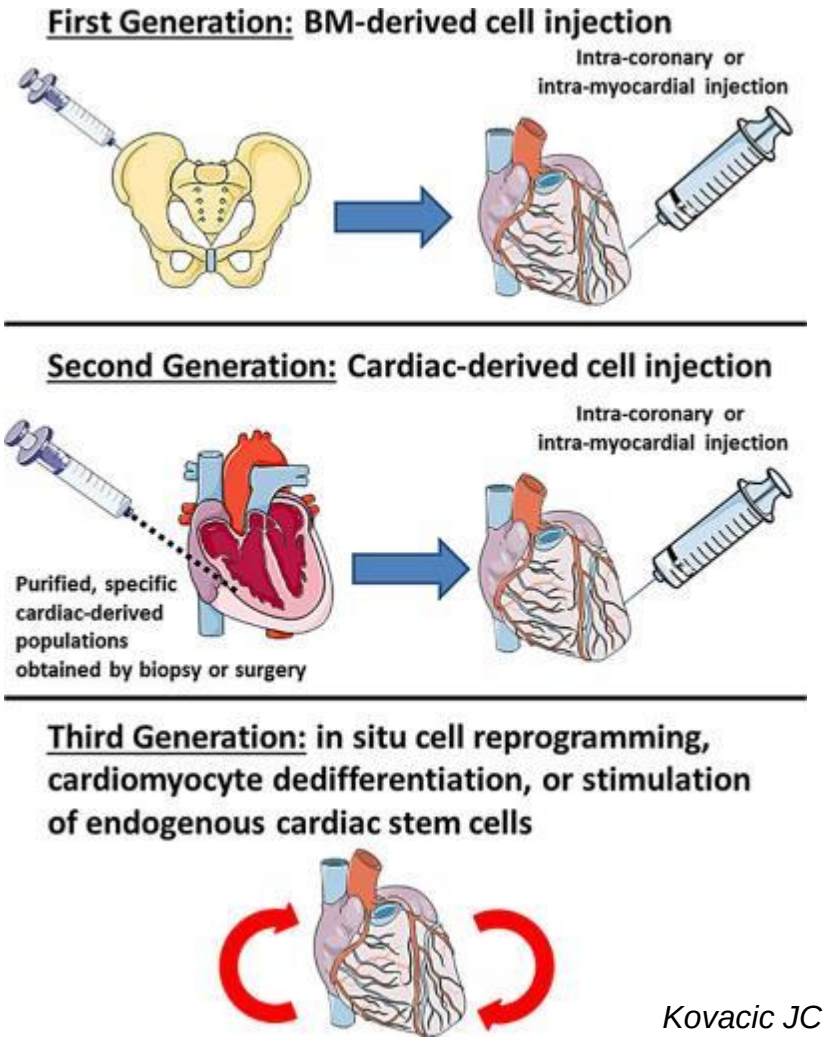




Bolli R et al., Lancet 2011

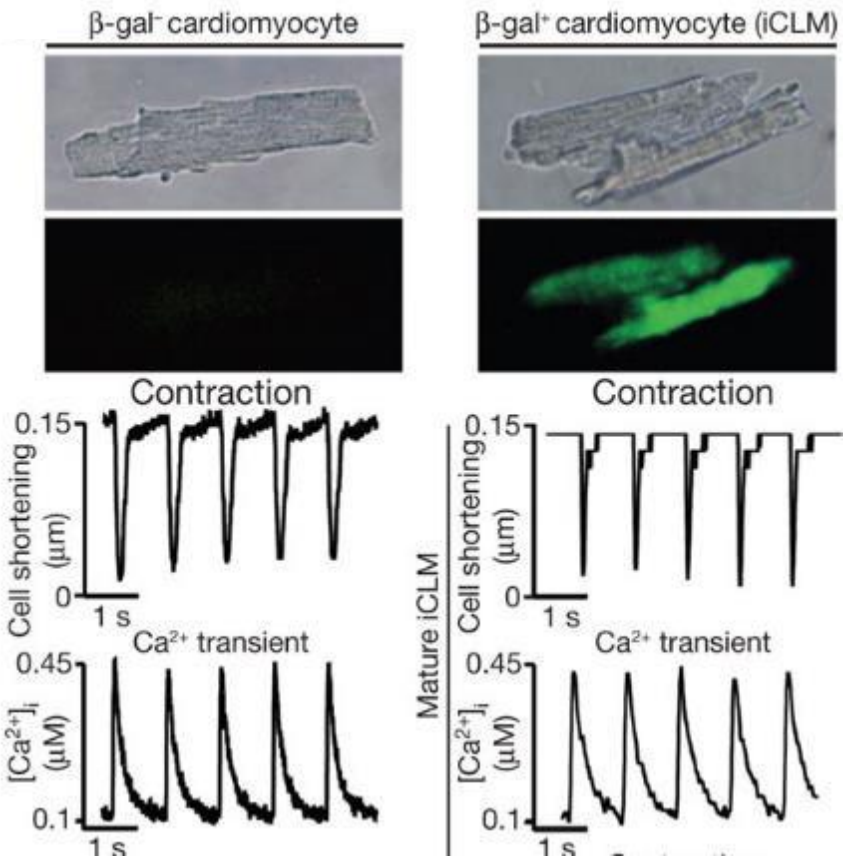
Makkar RR et al, Lancet 2012

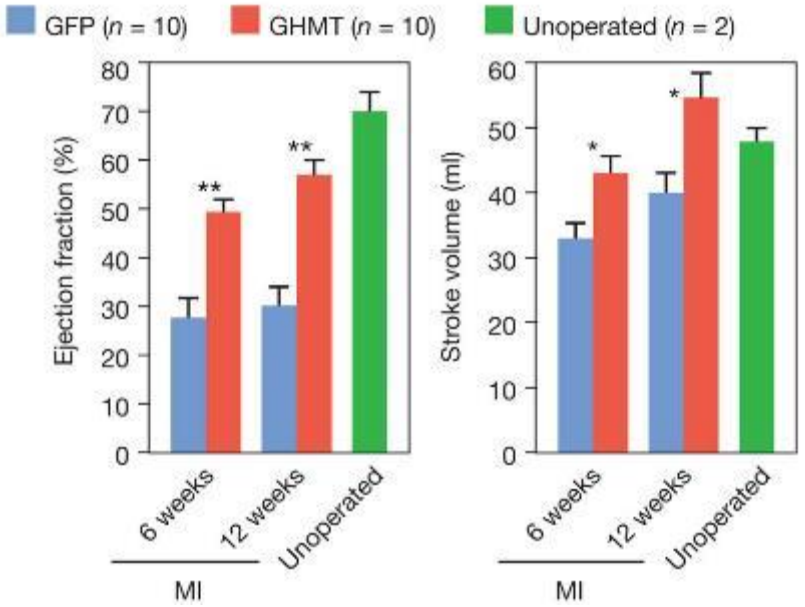
Reprogramming and beyond



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