VI CONGRESSO INFERMIERISTICO
LA MALATTIA CARDIACA: … E DOPO ?

«Medicina rigenerativa: le prospettive future per il cuore malato … e non solo !»

16 Aprile 2016

Tiziano Moccetti

Direttore medico e primario di Cardiologia
Fondazione Cardiocentro Ticino

Associated Institute of the University of Zurich

University of Zurich[UZH]

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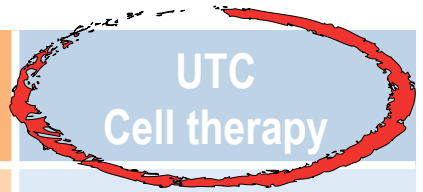
Areas of research

Imaging	Invasive Cardiology	Electrophysiology and heart failure	Clinical research	UTC Cell therapy
Cardiac CT	PCI	Cardiac implantable electronic devices	AMI	Clinical trials
Echocardio-graphy	Percutaneous Valve	Ablation	Stents	Clean Room
Cardiac MRI	Primary PCI	Heart failure	Heart failure	Basic cellular research
			Stem Cells	
			CIEDs	
			Pharmacology (SRC)	



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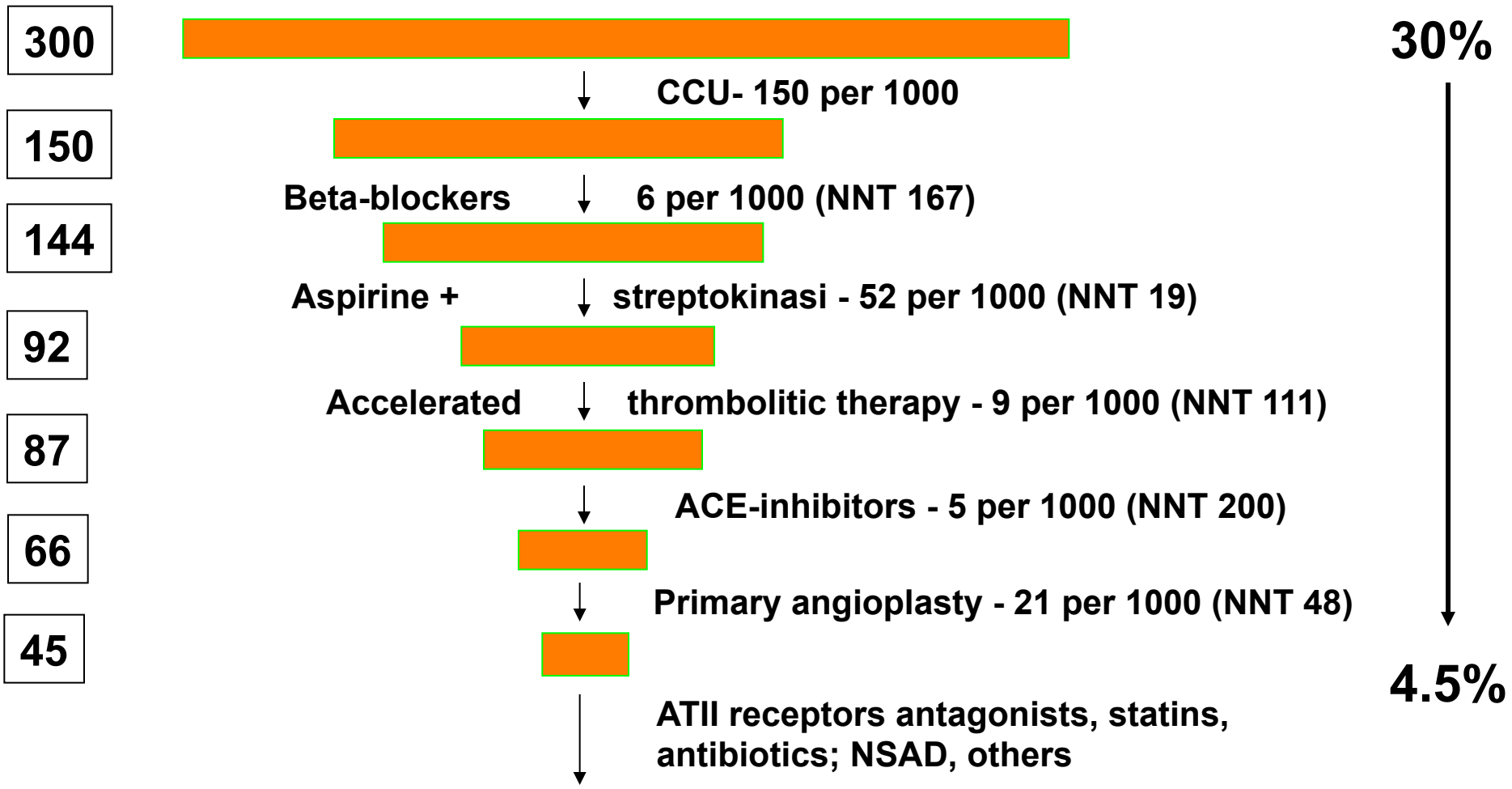
Acute myocardial infarction: a theoretic scenary
In-hospital-deaths *each 1000 patients*



? STEM-CELLS THERAPY ?

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Cellule staminali: promesse e realtà

Prometheus Attacked by Zeus's Eagle.

The NEW ENGLAND JOURNAL of MEDICINE

MEDICAL PROGRESS

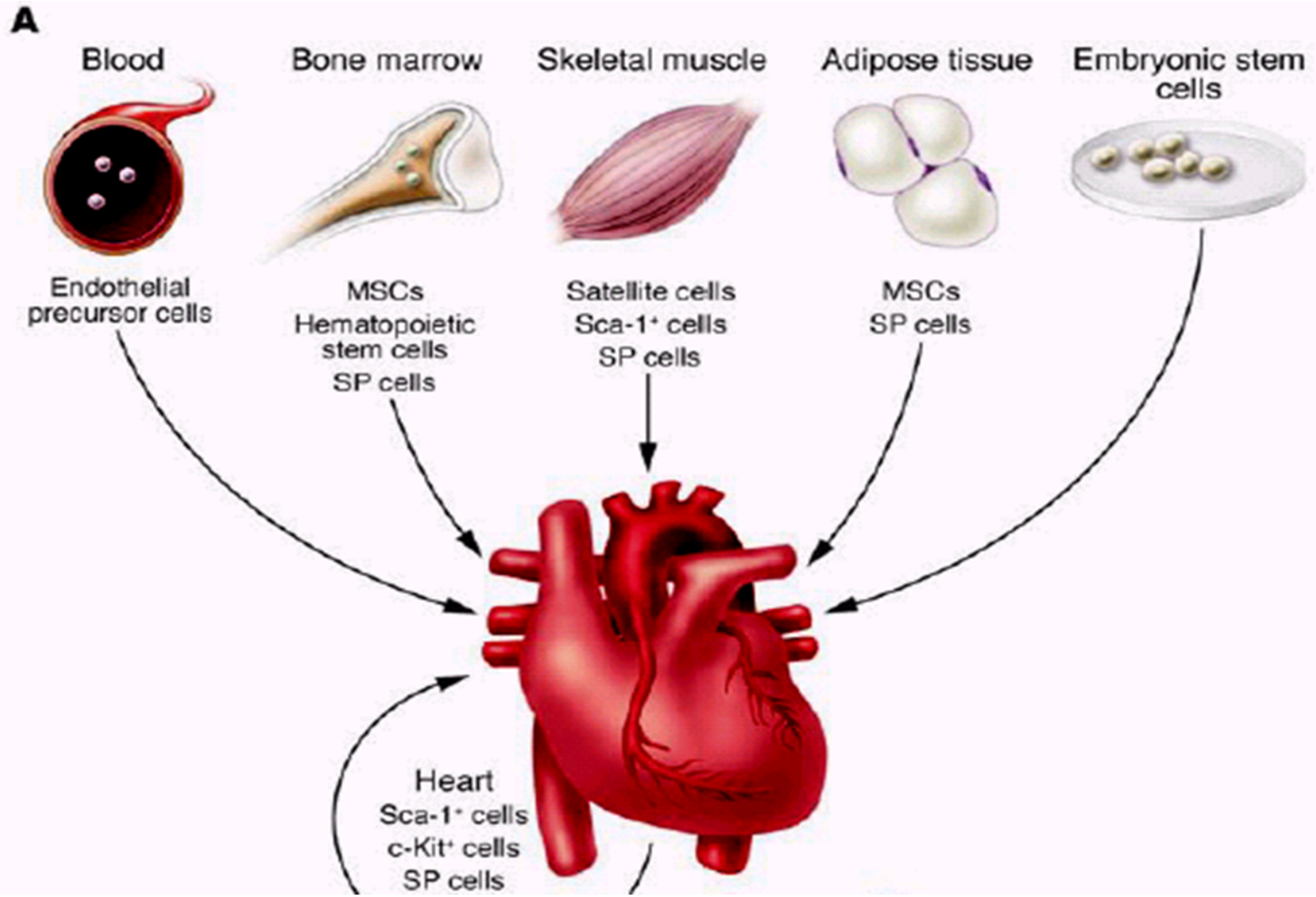
Prometheus's Vulture and the Stem-Cell Promise

Nadia Rosenthal, Ph.D.

WHEN PROMETHEUS TRANSGRESSED THE LAW OF THE ANCIENT GODS and stole fire for humankind, to teach them civilization and the arts, his punishment was typically brutal. Jupiter had the great Titan chained to the side of Mount Caucasus, where a vulture preyed daily on his liver, which was renewed as quickly as it was devoured.

We mere mortals do not possess livers with quite so vigorous a regenerative capacity, but the legend captures well the remarkable potential of the body to rebuild itself. Throughout our lives we sustain less gruesome injuries from which we recover spontaneously, often without realizing we were hurt. Wound healing involves the recruitment and proliferation of cells capable of restoring tissues and even organs to their original form and function. These cells must retain a collective memory of the complex developmental process by which the tissue was first constructed. Fortunately for Prometheus, whose name means forethought, his liver was well prepared for its daily renewal, since it is one of the most highly regenerative organs of the human body.

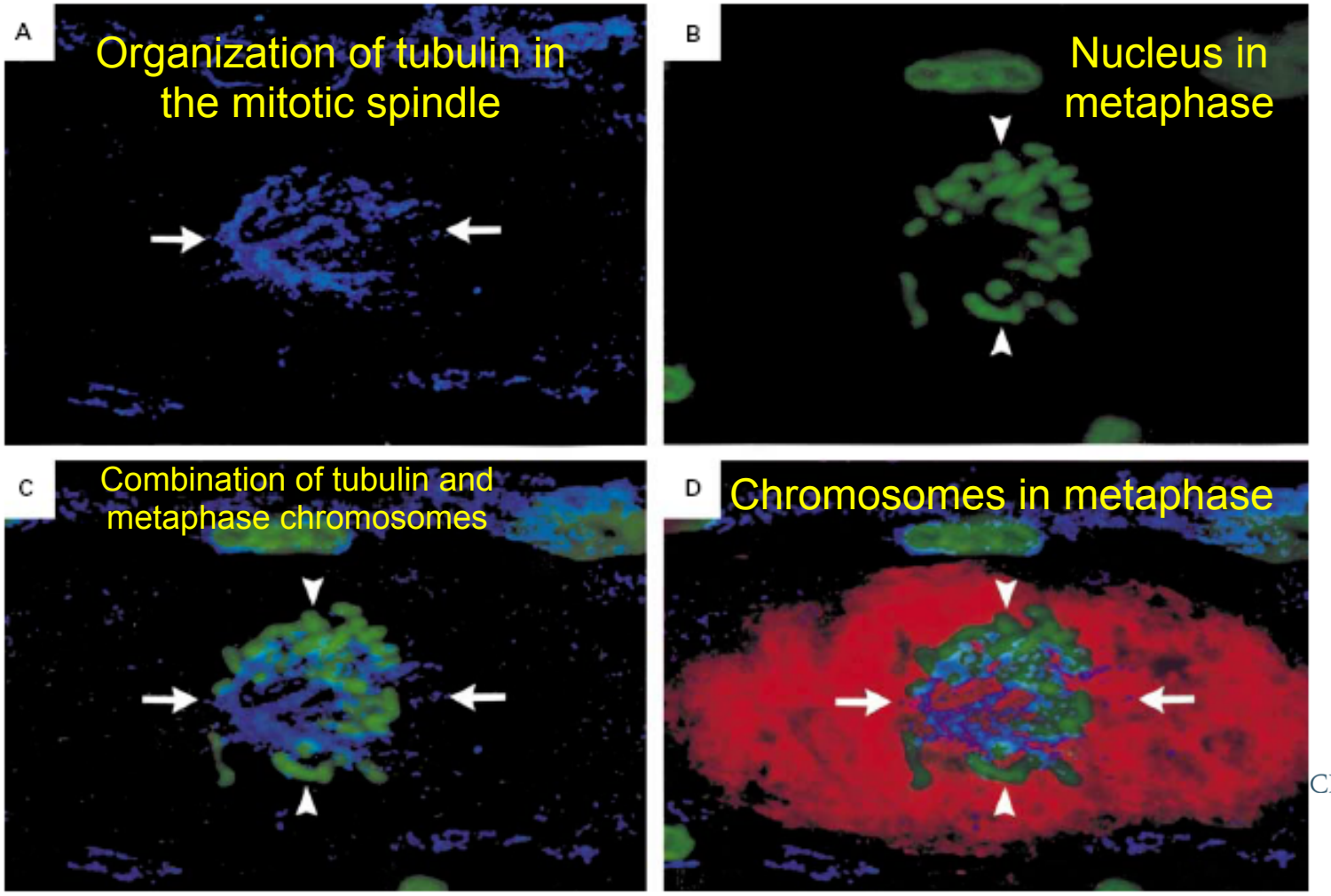
Sources of progenitor cells for cardiac regeneration in acute myocardial infarction



The New England Journal of Medicine

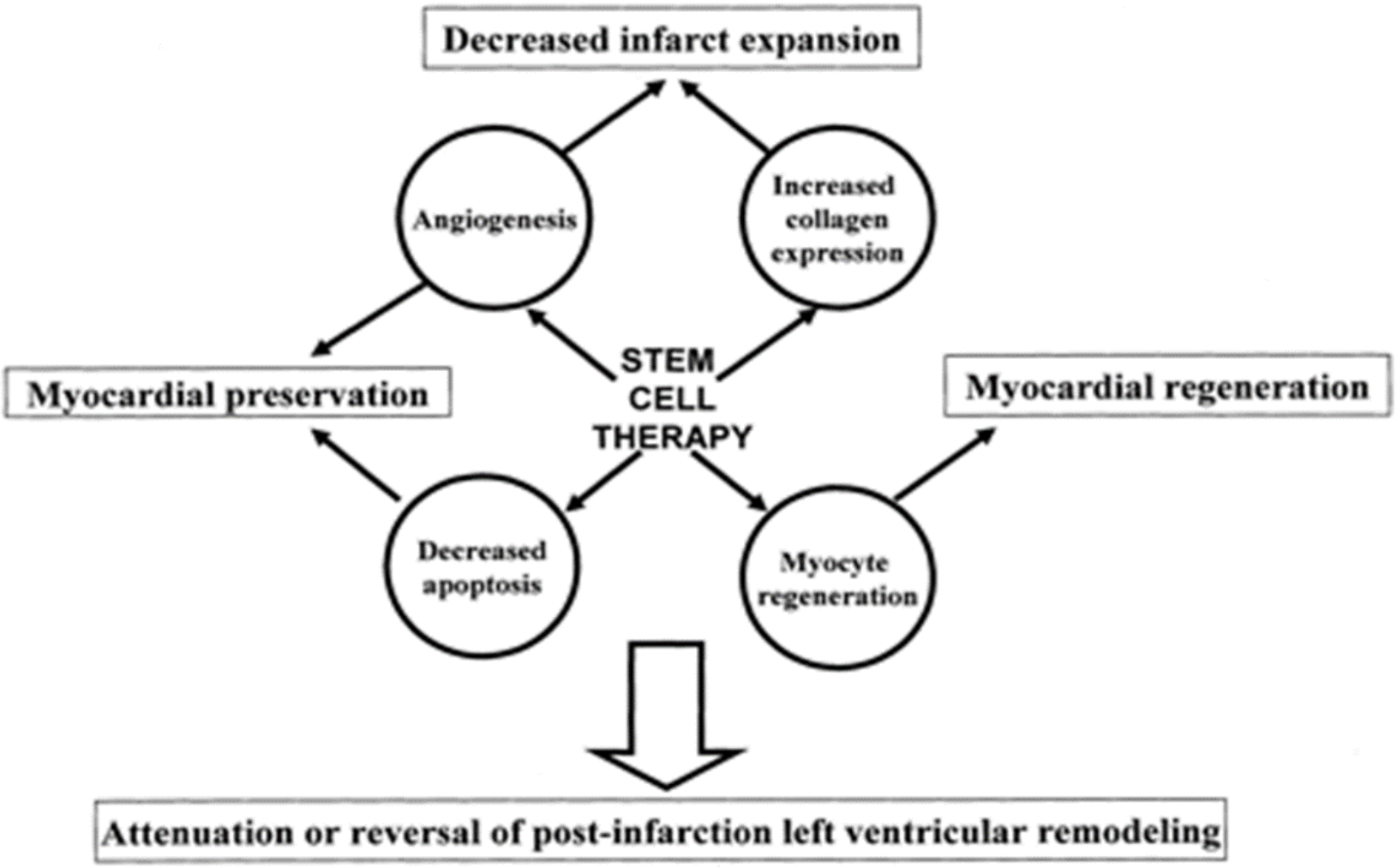
EVIDENCE THAT HUMAN CARDIAC MYOCYTES DIVIDE AFTER MYOCARDIAL INFARCTION

ANTONIO P. BELTRAMI, M.D., KONRAD URBANEK, M.D., JAN KAJSTURA, PH.D., SHAO-MIN YAN, M.D., NICOLETTA FINATO, M.D., ROSSANA BUSSANI, M.D., BERNARDO NADAL-GINARD, M.D., PH.D., FURIO SILVESTRI, M.D., ANNAROSA LERI, M.D., C. ALBERTO BELTRAMI, M.D., AND PIERO ANVERSA, M.D.



CINO

Potential beneficial mechanisms of stem cell therapy after myocardial infarction



Cardiac repair: Homing

1. Number of cells: CD 34+, CD 133
2. Colony formation
3. Signal
4. Adhesion/Migration
5. Invasion
6. Differentation

Migration and invasion of tissue are neccessary for integration

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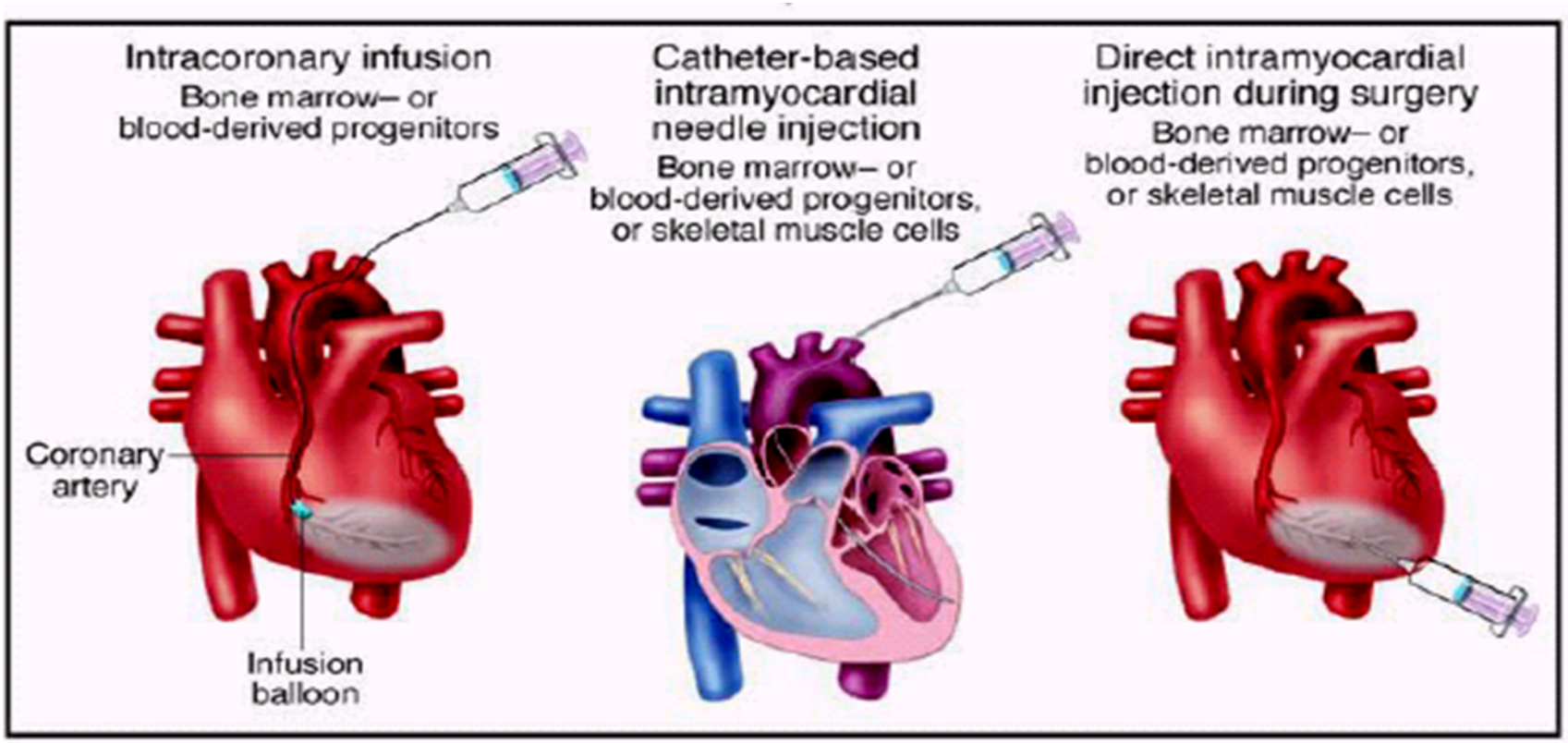
Injection methods



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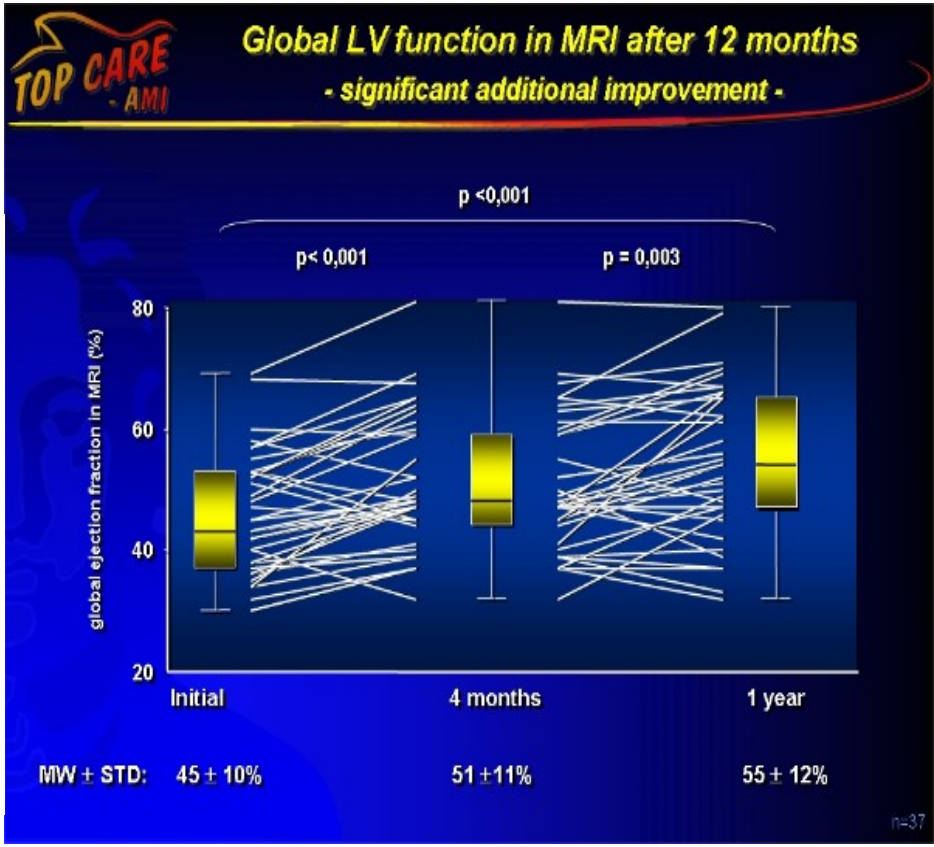
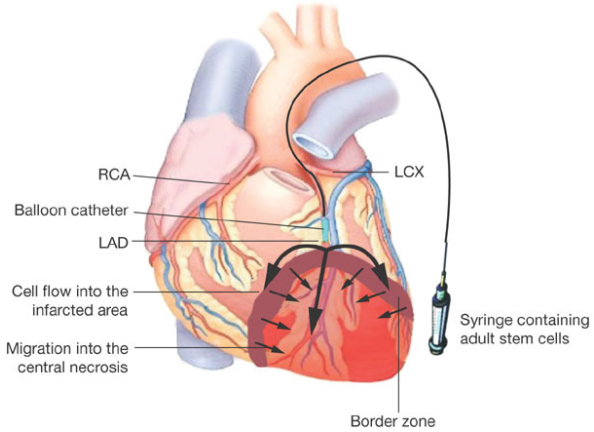
TOPCARE-AMI

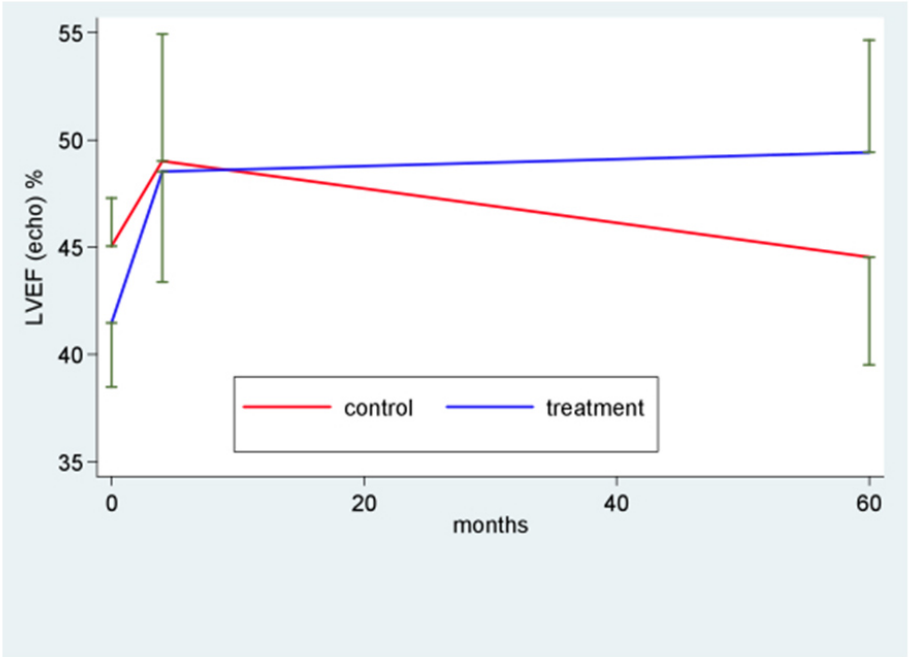
TABLE 2. LV Function Assessed by Analysis of LV Angiography in the Cell Therapy Group

	Baseline (n=19)	Follow-Up (n=19)	P
Ejection fraction, %	51.6±9.6	60.1±8.6	0.003
End-diastolic volume, mL	117.2±35.1	105.2±29.9	0.199
End-systolic volume, mL	56.1±20.0	42.2±15.1	0.011
Regional wall motion, SD/chord			
Infarct	−1.5±0.2	−0.5±0.7	<0.001
Infarct center	−1.5±0.5	−0.8±0.5	<0.001
Infarct border	−1.3±0.4	−0.4±0.6	<0.001



FIRST SWISS CELL HEART THERAPY TRIAL

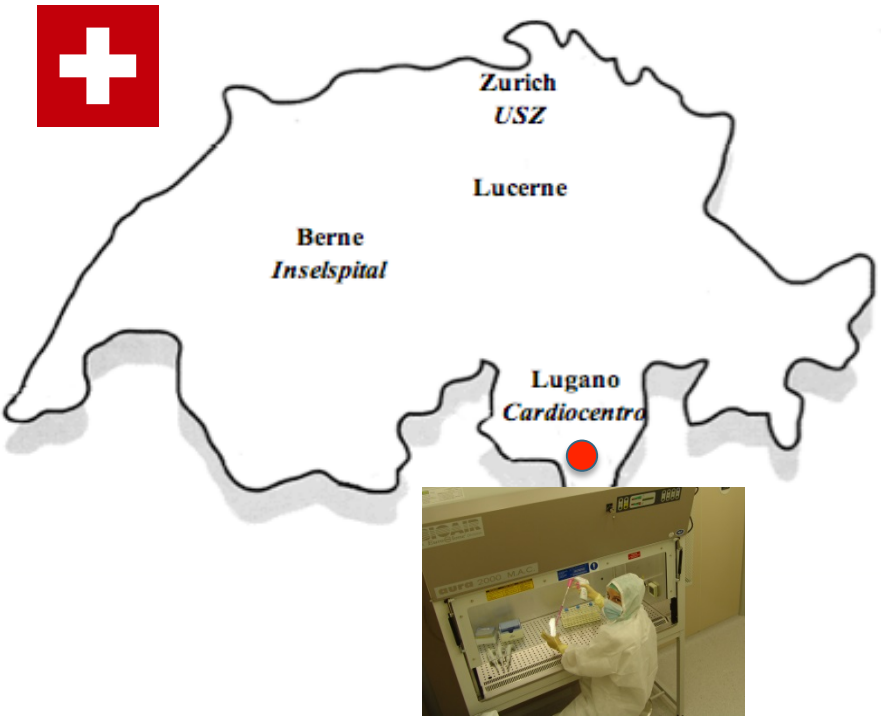


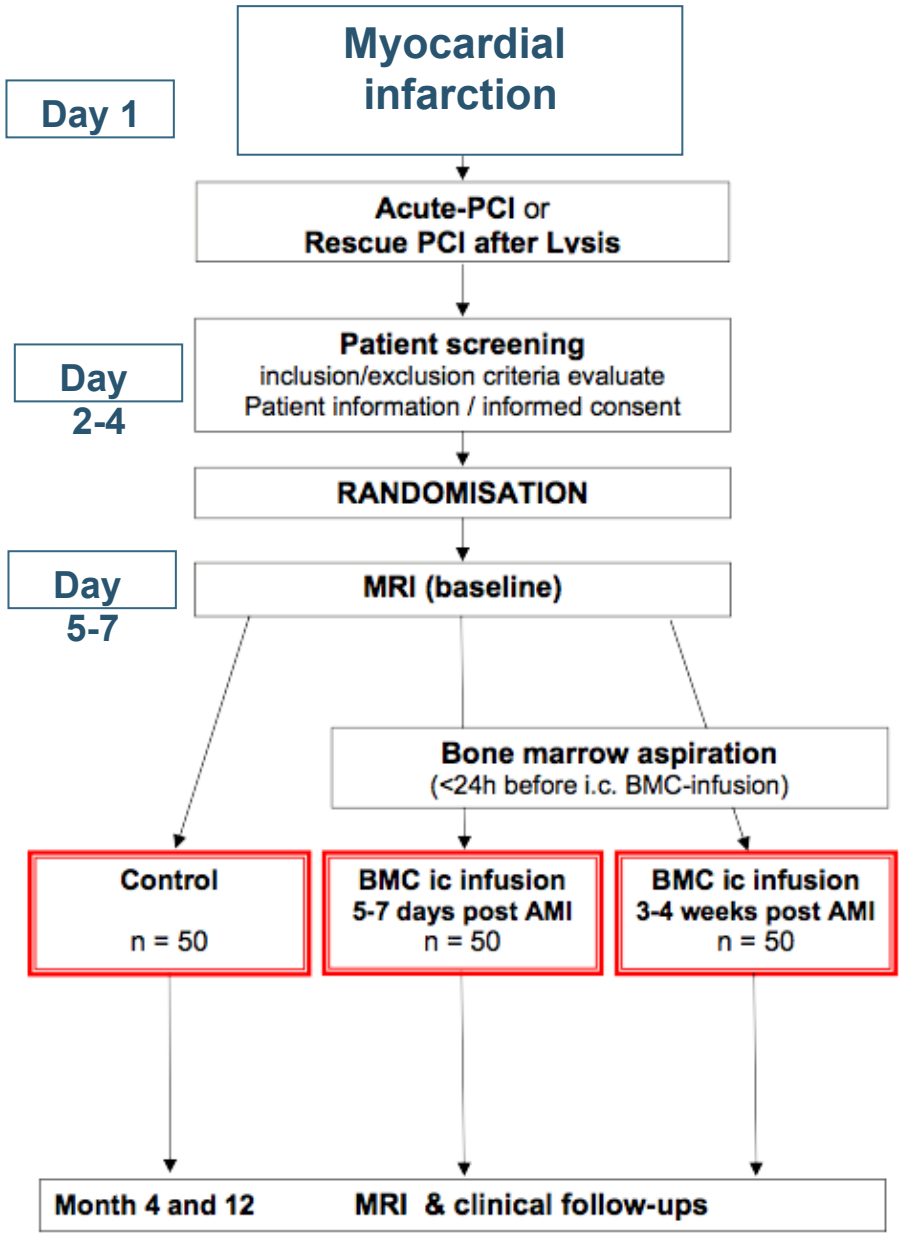


1st patient: August 24, 2004

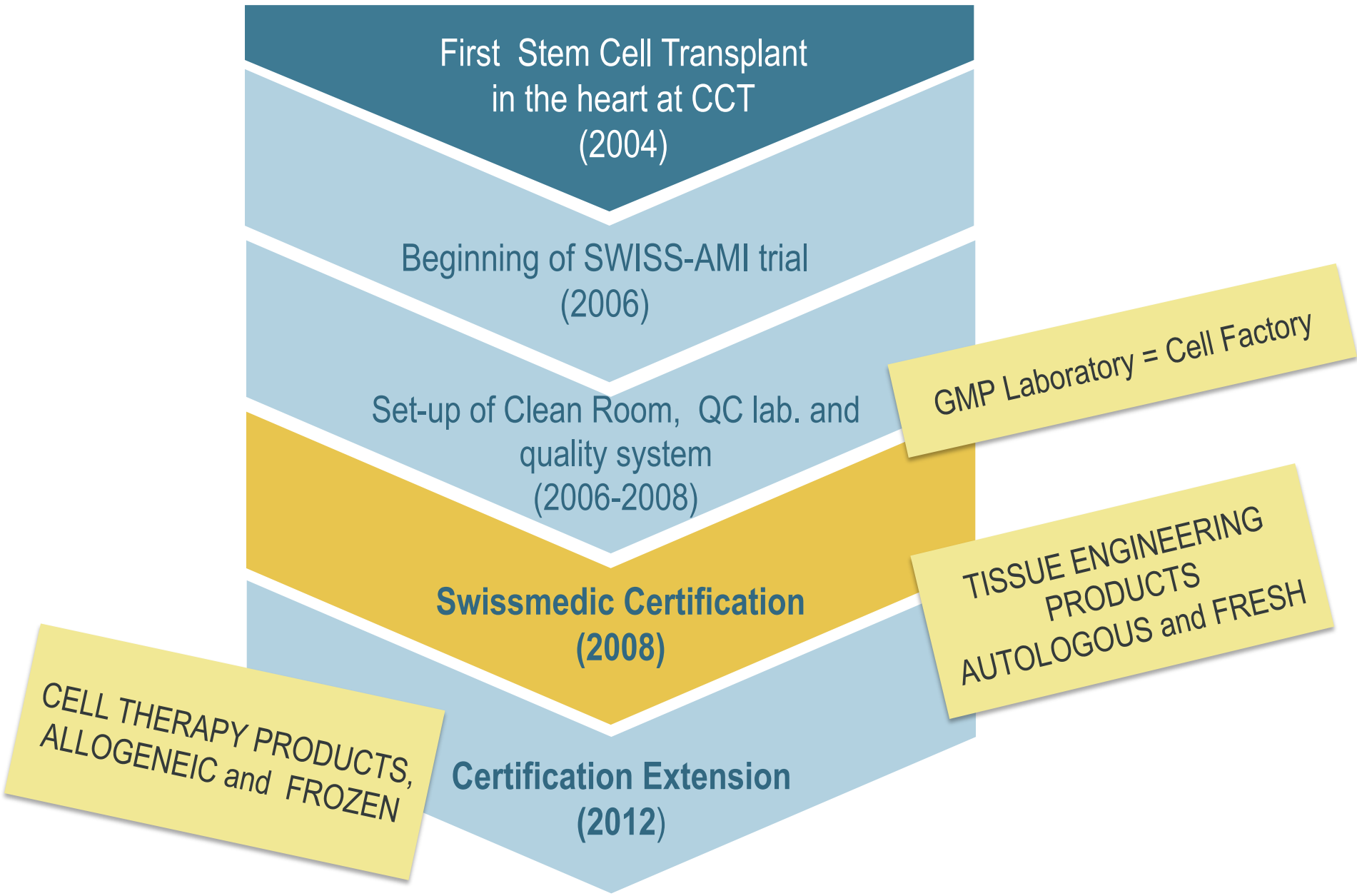
n= 23 treated
n=19 controls

THE SWISS-AMI TRIAL

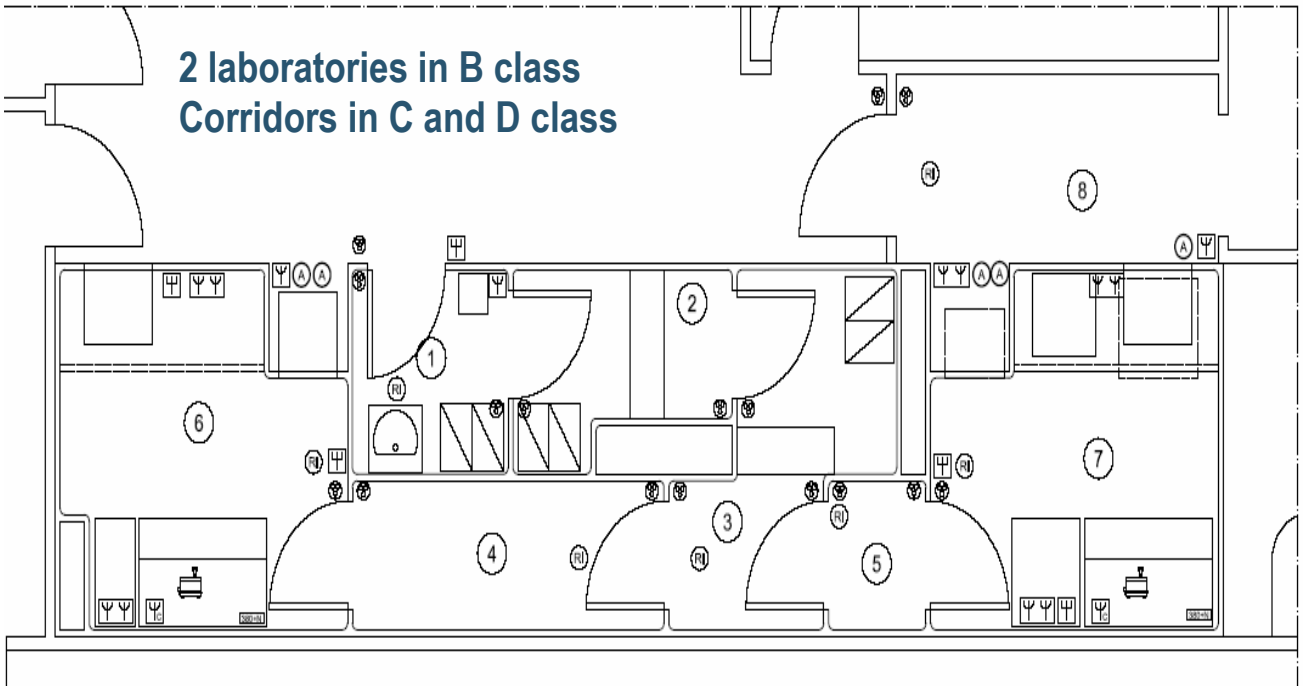




History of “Cell Factory”



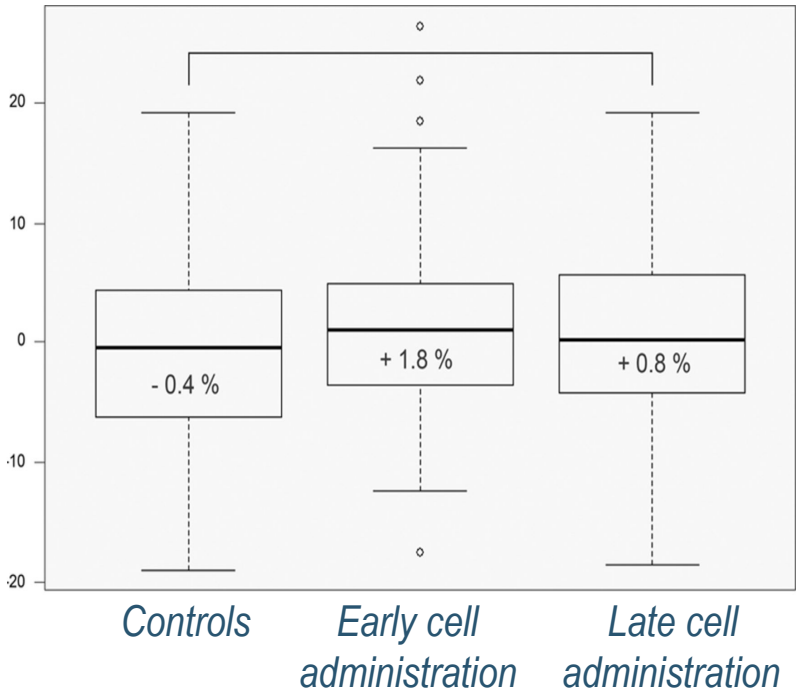
The Production Lab = Clean room



Operator in Clean Room

- **Cell Separation** from several biological tissues (bone marrow, pheripheral blood, adipose tissue)
- **Cell concentration**
- **Cell Culture**

Changes in left ventricular ejection fraction at 4 months



Sürder et al. Circulation 2013

A. Stem cells in the management of heart failure: What have we learned from clinical trials ?

Table 1. Outcome measures used in some clinical trials for stem cell therapy in acute myocardial infarction.

Trial	Stem cell type	1-Year outcome measure	Ref.
Chen *et al.* (2004)	Mesenchymal	Improved LVEF at 6 months	[51]
BOOST	Autologous BM	Improved LVEF at 6 months	[52]
REPAIR-AMI	BM progenitor	LVEF change/LV angiography at 4 months	[53]
Sun *et al.* (2010)	Different types	Cardiac remodeling (meta-analysis)	[54]
Perin *et al.* (2012)	Autologous ADH	LV end-systolic volume + maximum oxygen consumption	[40]
CADUCEUS	CSC	Scar mass + viable heart mass + regional contractility + regional systolic wall thickening	[55]
SCIPIO	CSC	LVEF Scar mass + viable infarct size	[16]

ADH: Aldehyde dehydrogenase; BM: Bone marrow; CSC: Cardiac stem cell; LV: Left ventricular; LVEF: Left ventricular ejection fraction.

Expert Review of Cardiovascular Therapy, November 2014

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B. Stem cells in the management of heart failure: What have we learned from clinical trials ?

Table 2. Major and relevant clinical trials in patients with chronic ischemic heart failure.

Trial/year	Delivery	Timing	1-Year endpoint	Ref.
MAGIC/2004	Transepicardial	>4 weeks	No change LVEF	[56]
Myoblast transplant/2005	Transendocardial	>10 years	Improved LVEF and viability	[57]
TOPCARE-CHD/2006	Intracoronary	81 ± 72 months	Improved LVEF	[58]
POSEIDON/2012	Transendocardial allogenic/autologous	30 days	Improved LVEF	[59]
C-CURE/2013	Endomyocardial	2 years	Improved LVEF	[60]

LVEF: Left ventricular ejection fraction.

Expert Review of Cardiovascular Therapy, November 2014

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European Heart Journal (2015) **36**, 1744–1753
doi:10.1093/eurheartj/ehv136

CLINICAL RESEARCH
Interventional cardiology

Bone marrow-derived mesenchymal stromal cell treatment in patients with severe ischaemic heart failure: a randomized placebo-controlled trial (MSC-HF trial)

Anders Bruun Mathiasen[1]*, Abbas Ali Qayyum[1], Erik Jørgensen[1], Steffen Helqvist[1], Anne Fischer-Nielsen[2], Klaus F. Kofoed[1,3], Mandana Haack-Sørensen[1], Annette Ekblond[1], and Jens Kastrup[1]

[1]Cardiac Catheterization Laboratory 2014 and Cardiology Stem Cell Laboratory, The Heart Centre, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, Copenhagen DK-2100, Denmark; [2]Department of Clinical Immunology 2034, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; and [3]Department of Radiology, Diagnostic Centre, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Received 11 August 2014; revised 12 March 2015; accepted 2 April 2015; online publish-ahead-of-print 29 April 2015

55 pts completed the 6-months FU (37 MSCs vs. 18 placebo)

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MSC-HF trial

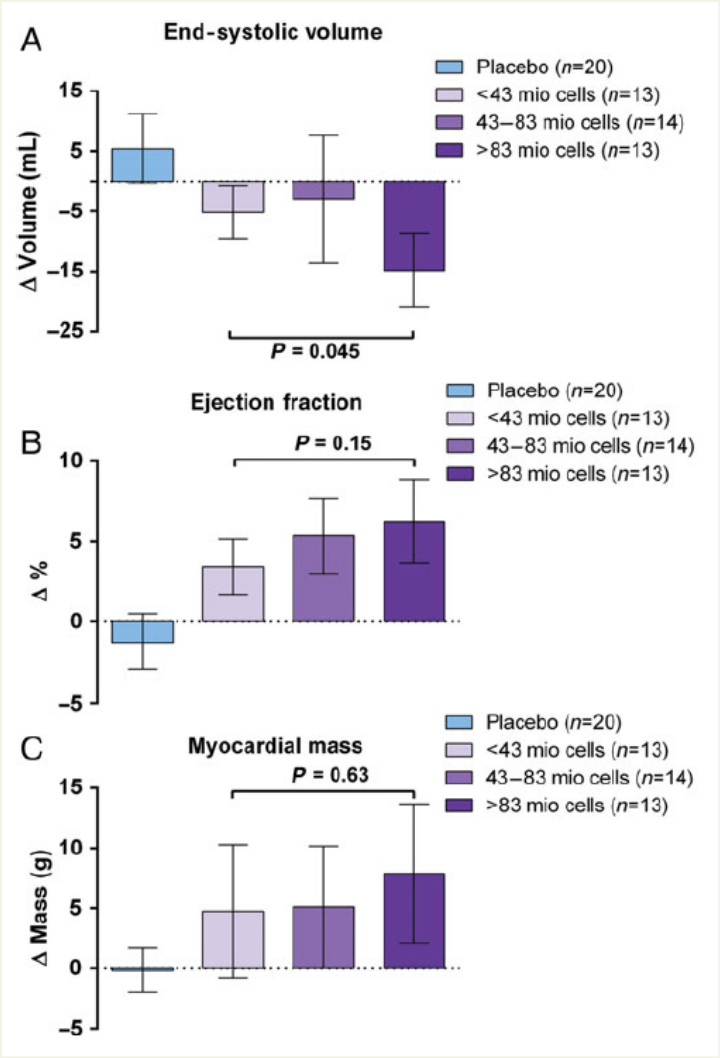

Figure 3 Dose–response effects: (*A*) end-systolic volume, (*B*) ejection fraction, (*C*) mean myocardial mass. *P*-values represent the differences between subgroups of the mesenchymal stromal cell group (One-way ANOVA. Bar values are mean ± 95% confidence intervals.).

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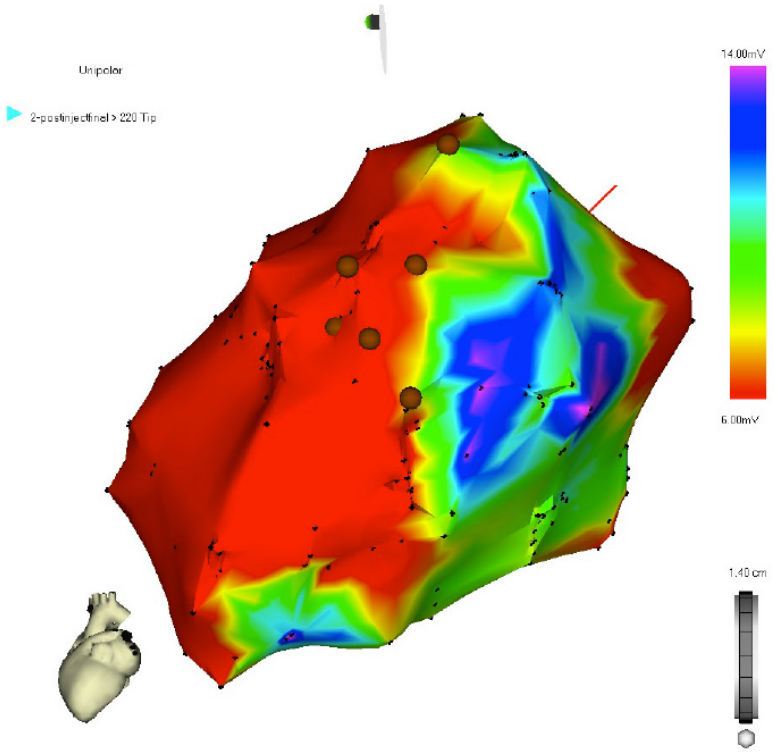
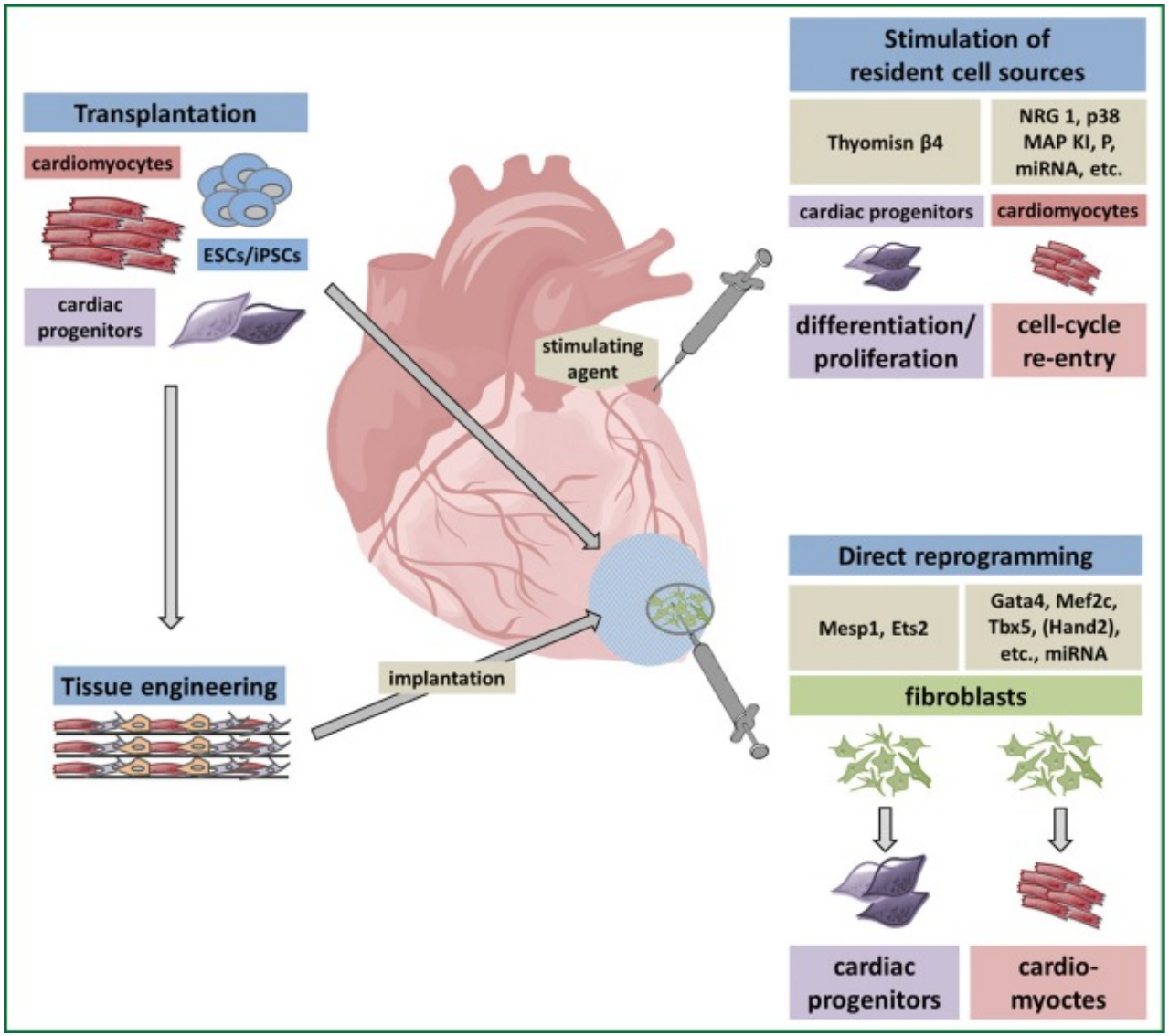
THE METHOD TRIAL

NOGA-guided intramyocardial bone marrow cell injection for chronic heart failure



Feasibility and safety study
(n = 10)



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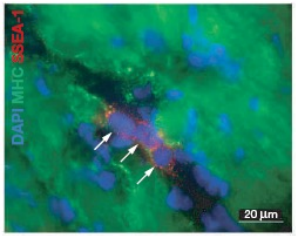
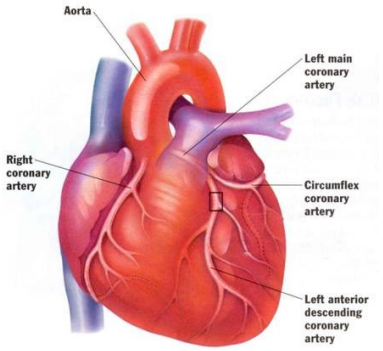
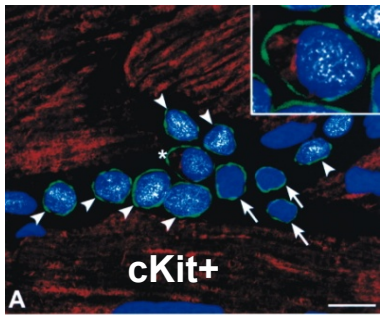
Resident adult Cardiac Progenitor Cells



Ott, H.Cet al. **The adult human heart as a source for stem cells: repair strategies with embryonic-like progenitor cells.** ***Nat. Clin. Pract. Cardiovasc. Med.,*** **2007**





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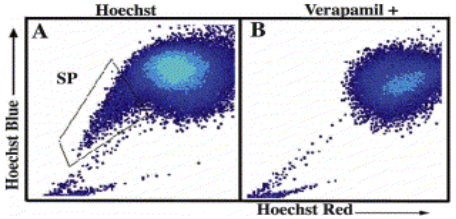
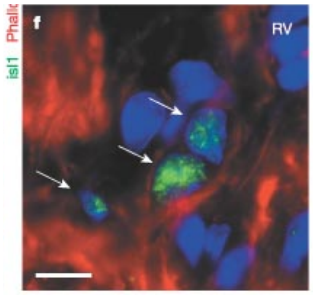


Hierlihy, A.M et. al. **The post-natal heart contains a myocardial stem cell population.** ***FEBS Lett.,*** **2002**



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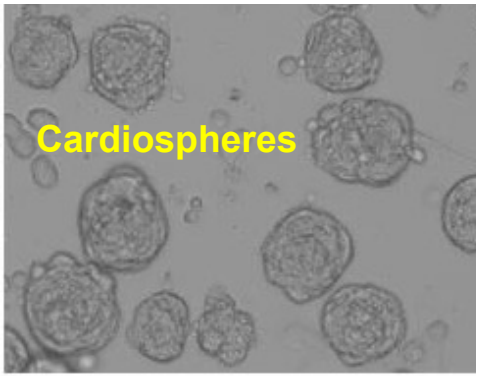

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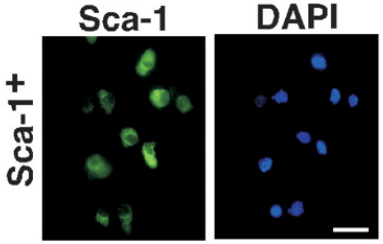

Oh, H.; et al. **Cardiac progenitor cells from adult myocardium: homing, differentiation, and fusion after infarction**. *Proc. Natl. Acad. Sci. USA,* **2003**,

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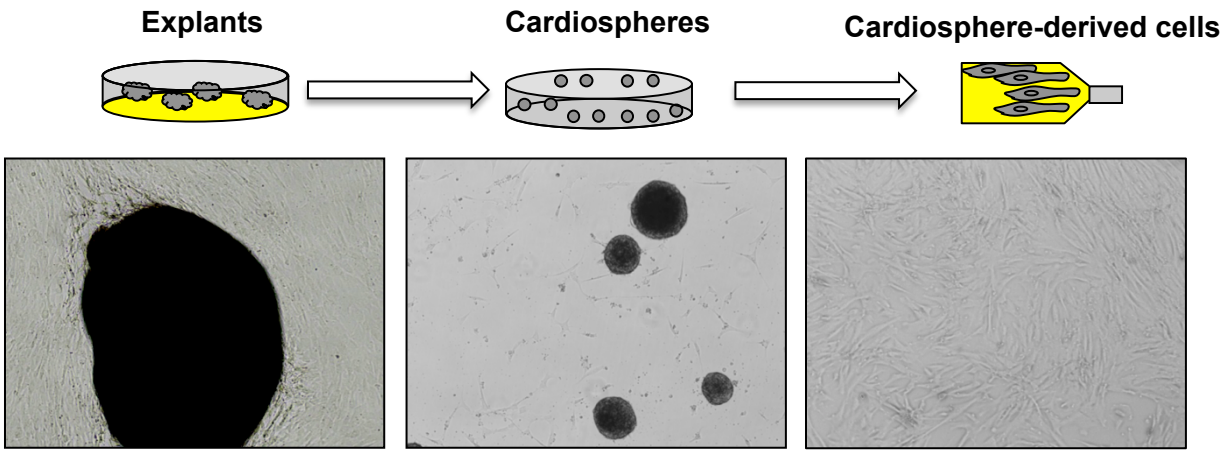
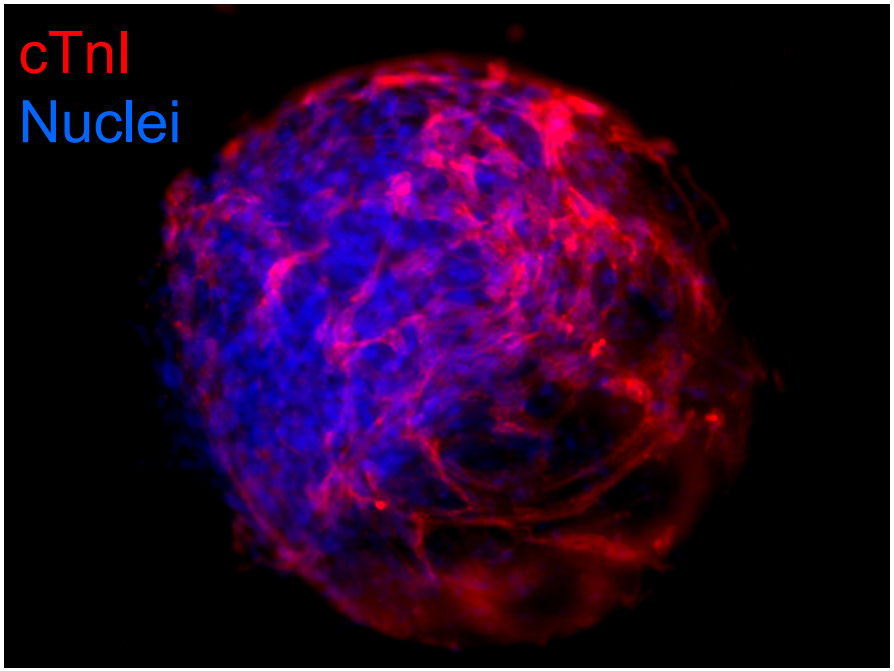
Cardiospheres





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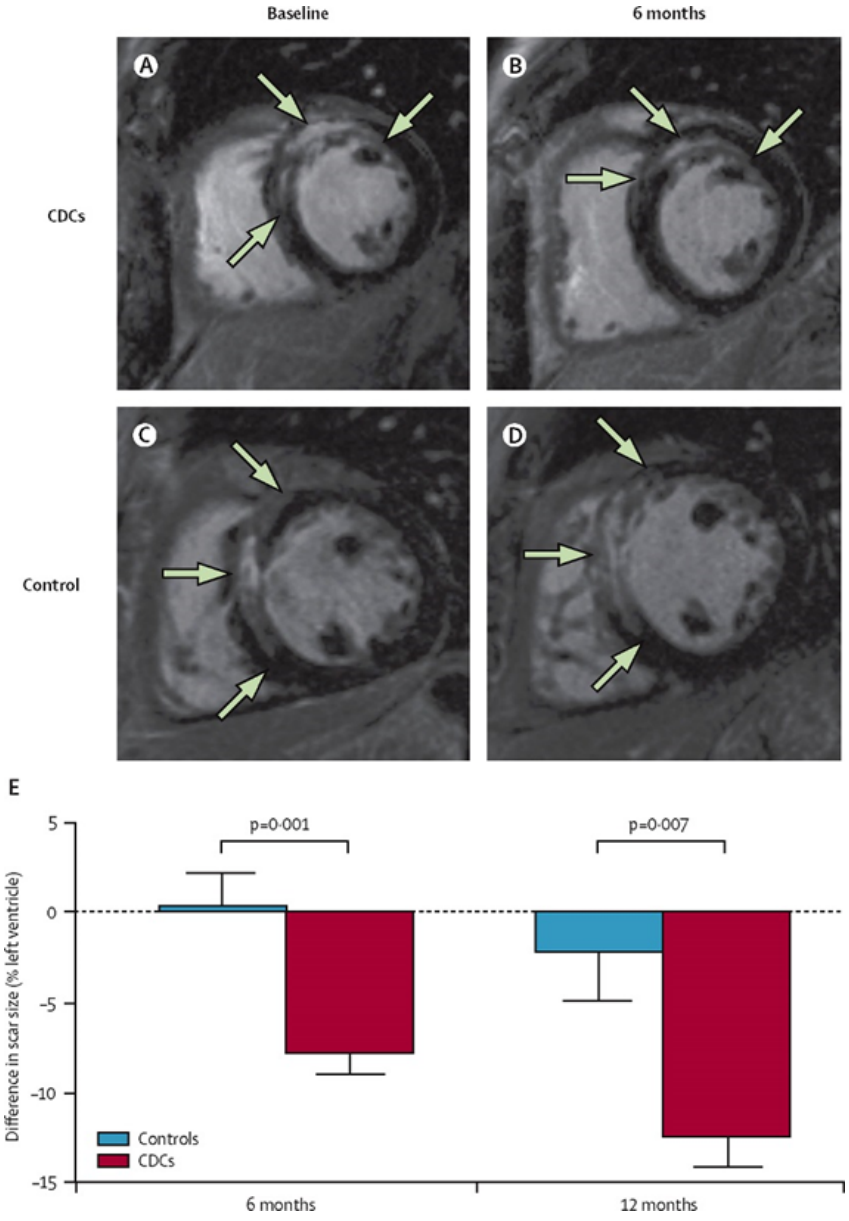
CADUCEUS



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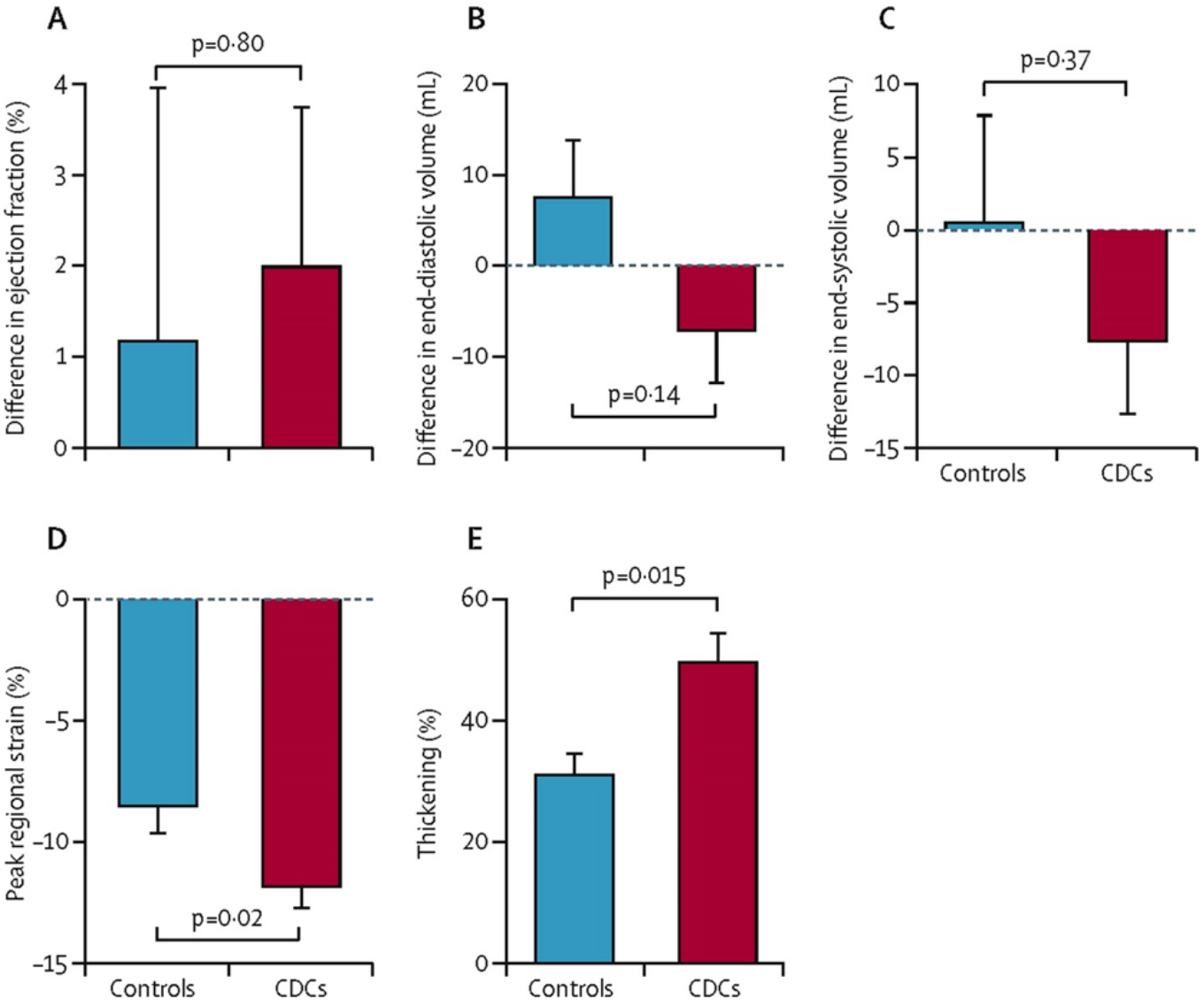

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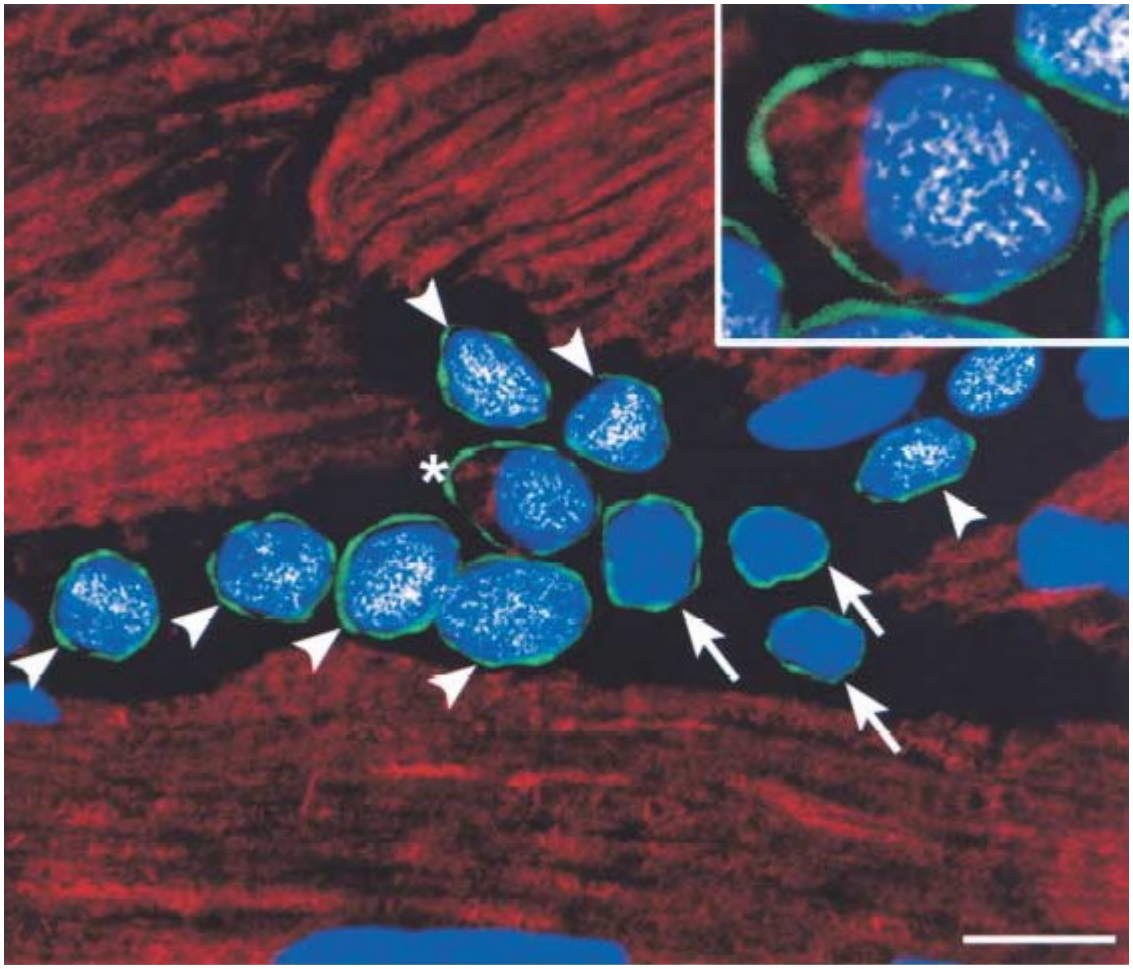
Human Cardiac Stem Cells



BWH BRIGHAM AND WOMEN'S HOSPITAL
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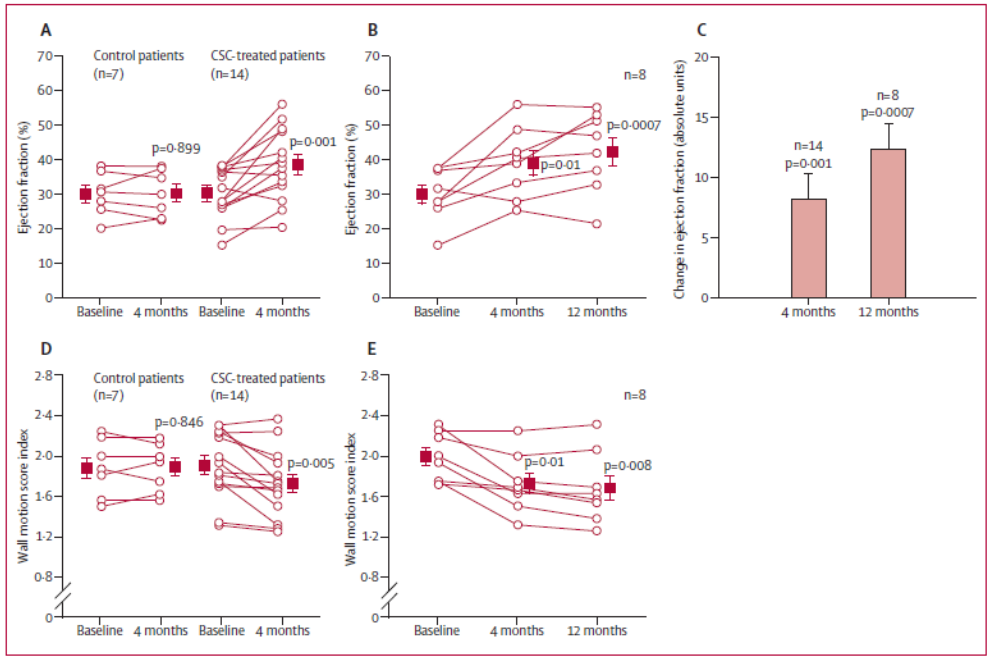
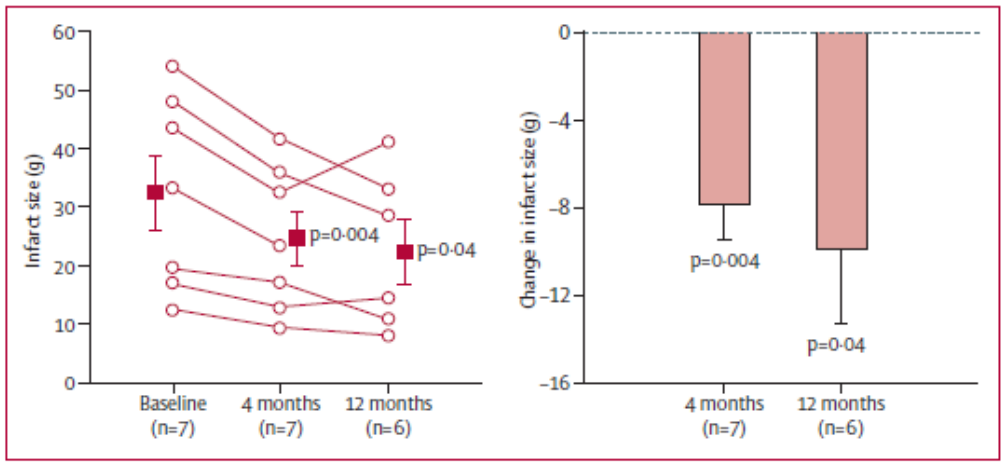
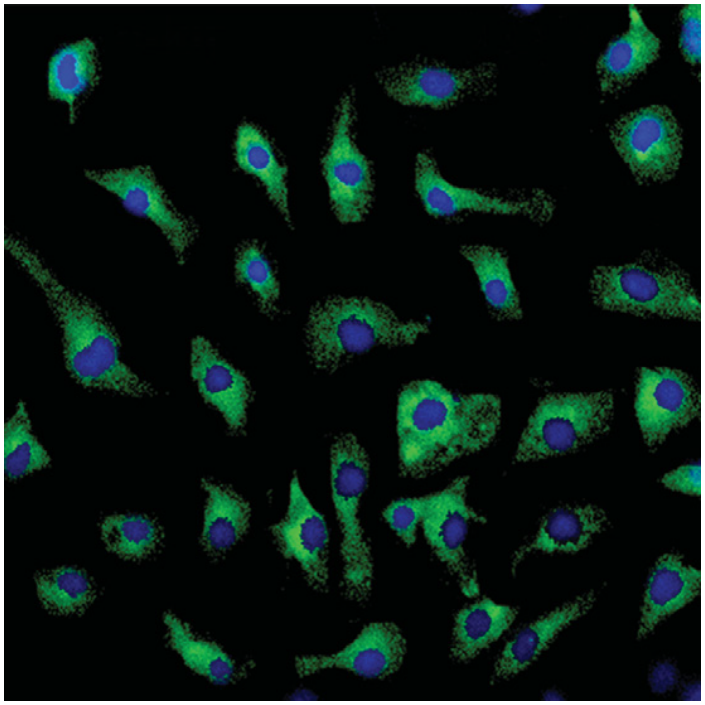
SCIPIO TRIAL







Bolli R et al., The Lancet 2011

BRIGHAM AND WOMEN'S HOSPITAL
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Direct regeneration versus paracrine effects … Exosomes in human CS

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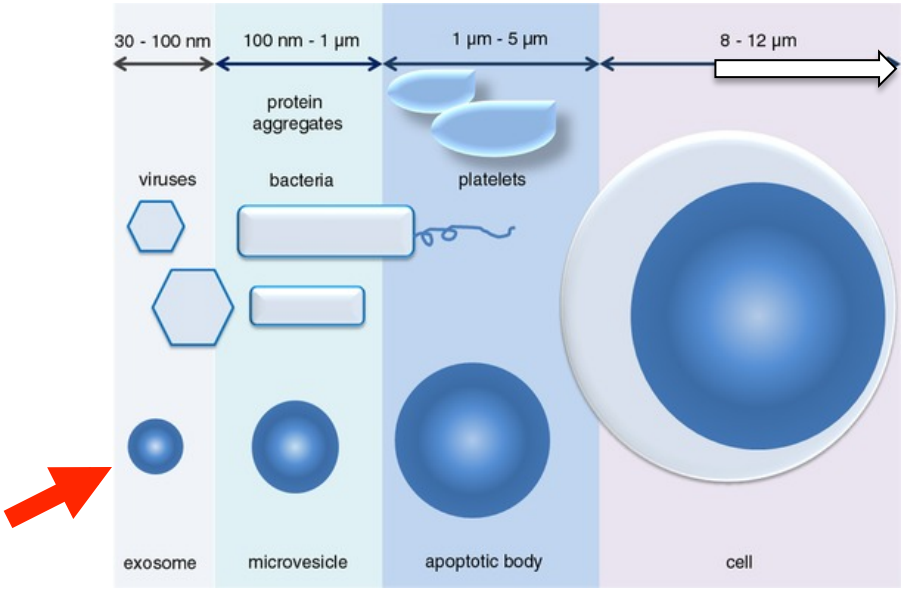
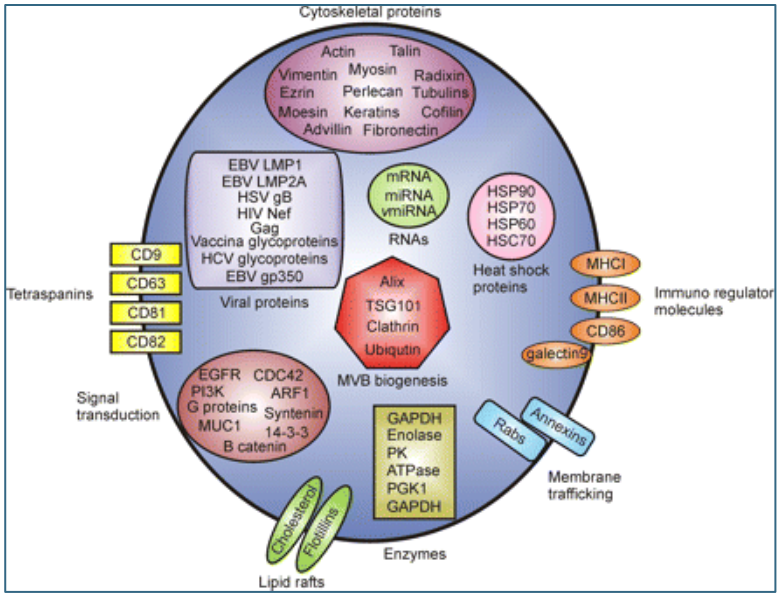
Direct regeneration versus paracrine effects…..Exosomes





- Exosomes are small membrane vesicles with a lipid bilayer,secreted by many, if not all, cells.
- Exocytosed internal vesicles of endosomal origin range in size between 50 and 100 nm
- Exosomes contain many different proteins, including growth factors and cytokines, and coding and non-coding RNA molecules

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Regenerative therapy in chronic HF: ongoing trials

- CHART
- DREAM-HF
- BAMI

FUTURE ?

- Exosomes + micro RNA
- c-kit

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CHART-1

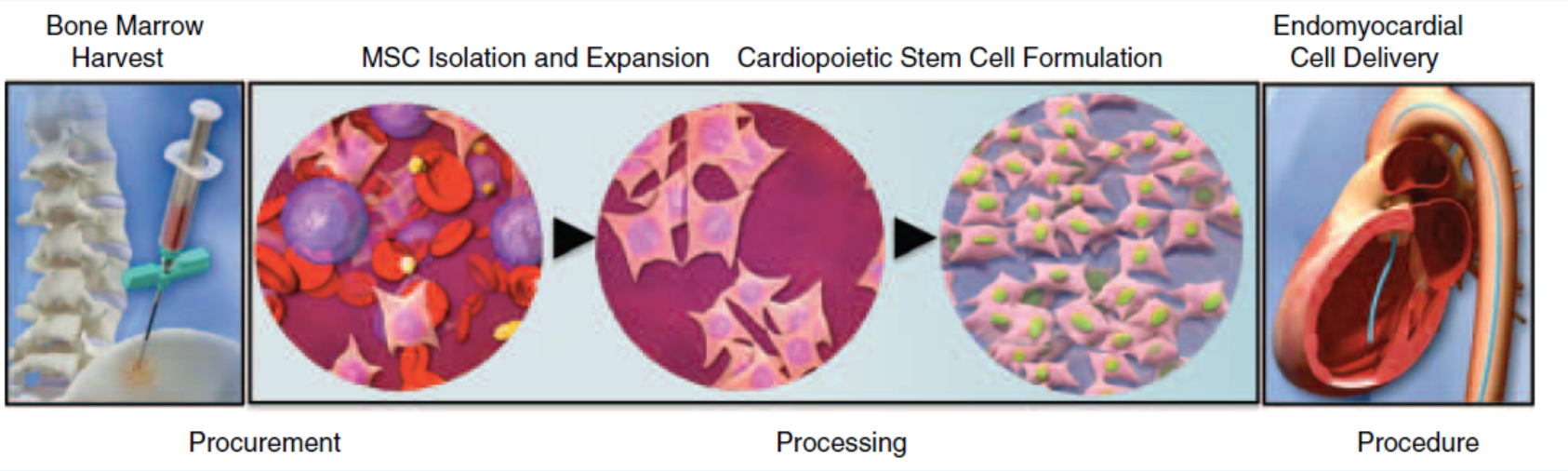

Figure 2 Cardiopoietic stem cell procurement and processing prior to the delivery procedure. Following bone marrow harvest, mesenchymal stem cells (MSCs) are purified and expanded. Following standard operating procedures, cardiopoiesis is imposed for lineage guidance of MSCs to derive cardiopoietic stem cells. Stem cells meeting pre-defined release criteria are delivered in an autologous fashion to patients with ischaemic cardiomyopathy using a catheter-based endomyocardial delivery procedure.

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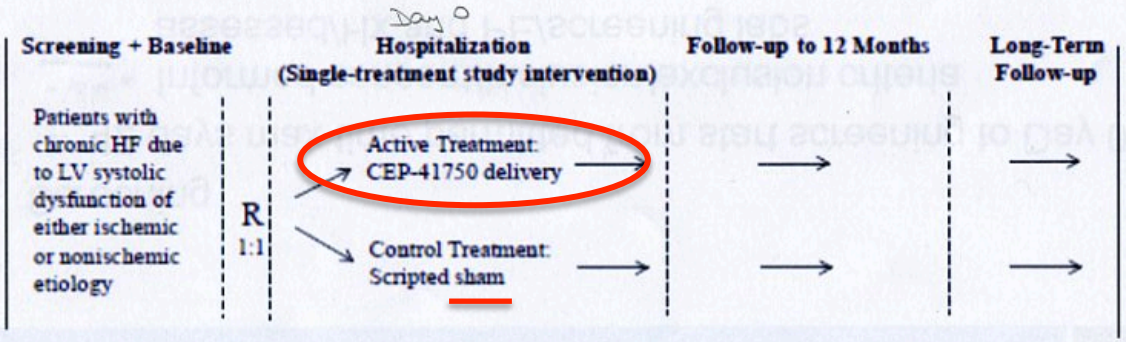
DREAM-HF

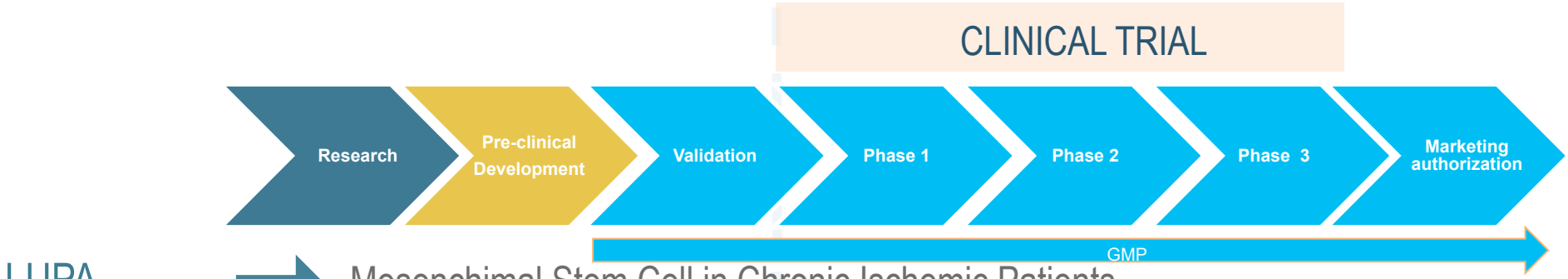
Heterologous cells (young donors) from BM with GF cocktail

Study Design

- Multicenter, randomized, double-blinded, sham-procedure controlled, parallel group design
- Treatment: A single dose of transendocardially administered MPCs (150 million cells versus control using a 1:1 randomization) in conjunction with optimal medical/revascularization therapy in patients with advanced chronic HF due to LV systolic dysfunction
- Consists of 3 main time points:
  - Screening
  - Day 0



Progress of On going Projects



LUPA — Mesenchimal Stem Cell in Chronic Ischemic Patients

EXOSOMES — Human Cardiac Progenitor Cell-derived Exosomes

C-Kit+ CELLS — Human Cardiac c-Kit+ Stem Cells

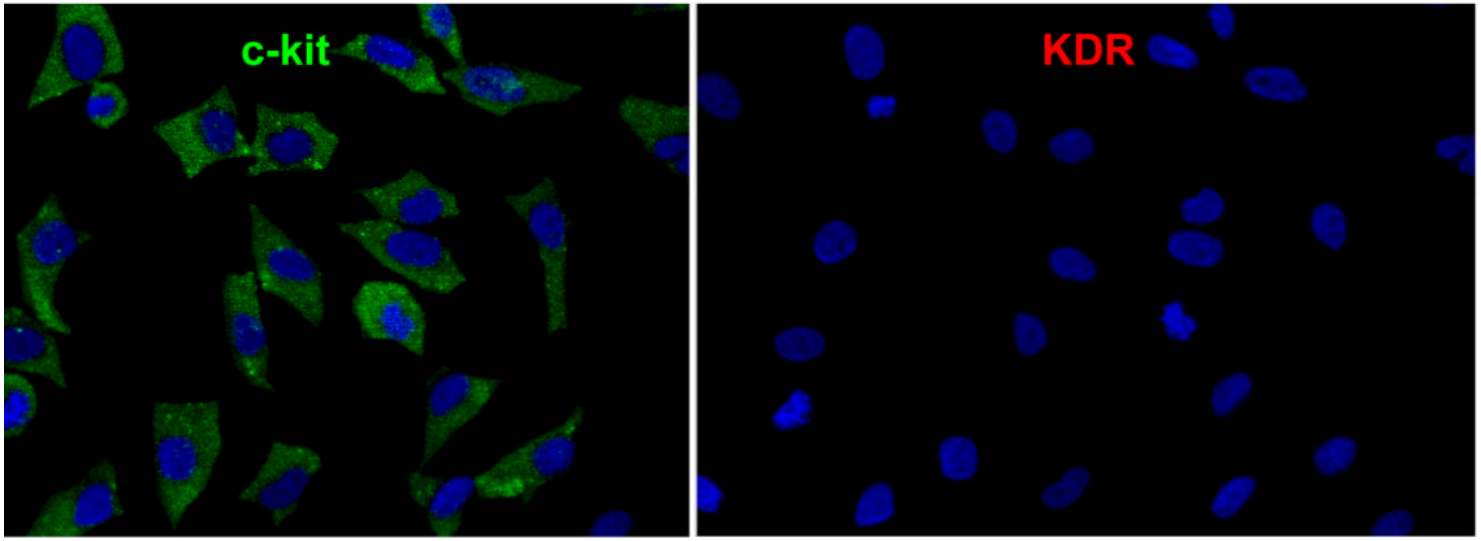
MULTIPLE SCLEROSIS — Autologous Neural Progenitors Cells (European Clinical Trial)

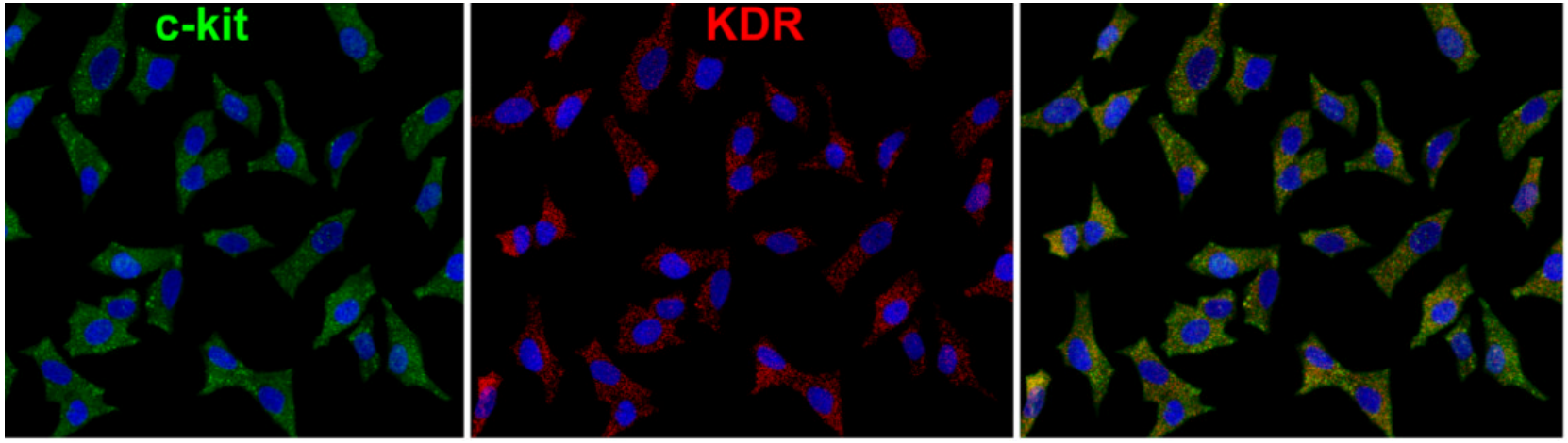
CIRCULATE — Bone Marrow derived Cells for PAD

METHOD — Bone Marrow derived Cells for Chronic Ischemic Patients

Swiss-AMI — Bone Marrow derived cells for AMI

Endomyocardial biopsies





D'Amario D. et al., Circ Res 2011

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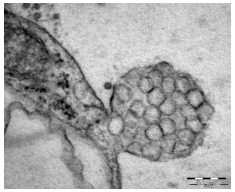
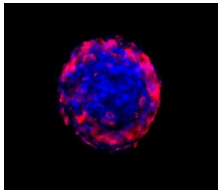
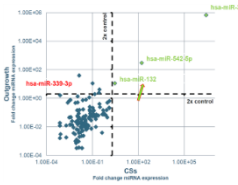
Exosomes



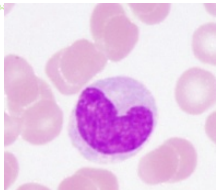
Cardiospheres



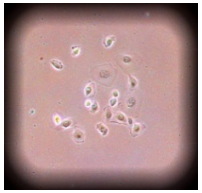
Micro RNA



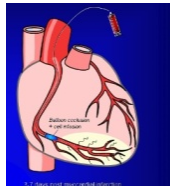
Monociti



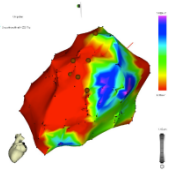
c-kit+ cells



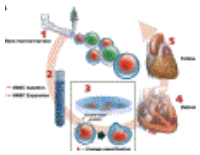
BAMI trial



METHOD trial



C-CURE trial



BASIC AND TRANSLATIONAL PROJECTS → CLINICAL STUDIES

G. Vassalli

L. Barile

E. Cervio

T. Tallone

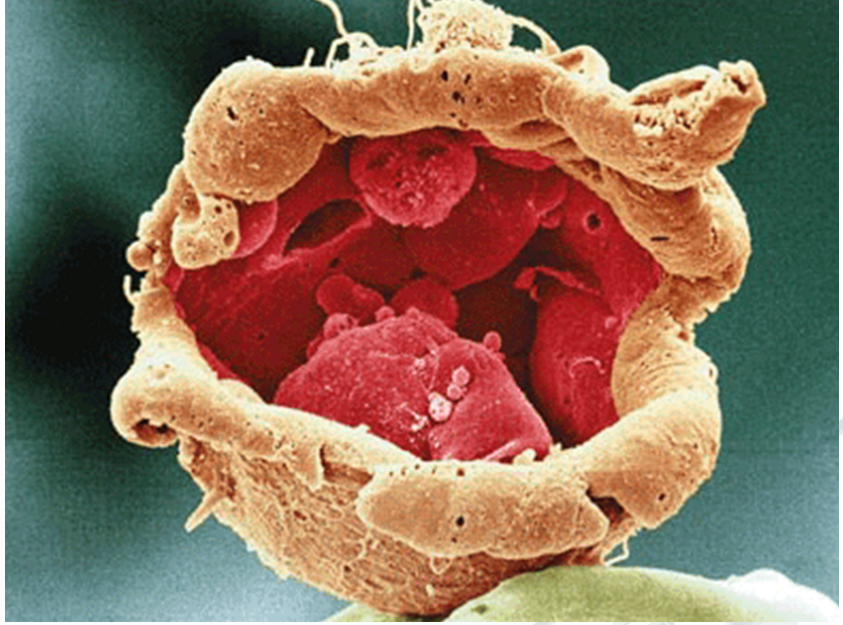
S. Bardelli

P. Anversa

A. Leri

D. Sürder

M. Moccetti



GRAZIE

Per la vostra attenzione

Associated Institute
of the University of Zurich

University of Zurich[UZH]

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