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Presenter Disclosure

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No Relationships to Disclose

Stem Cell Therapy for the Heart

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**American Society of Gene & Cell Therapy
May 19, 2010**



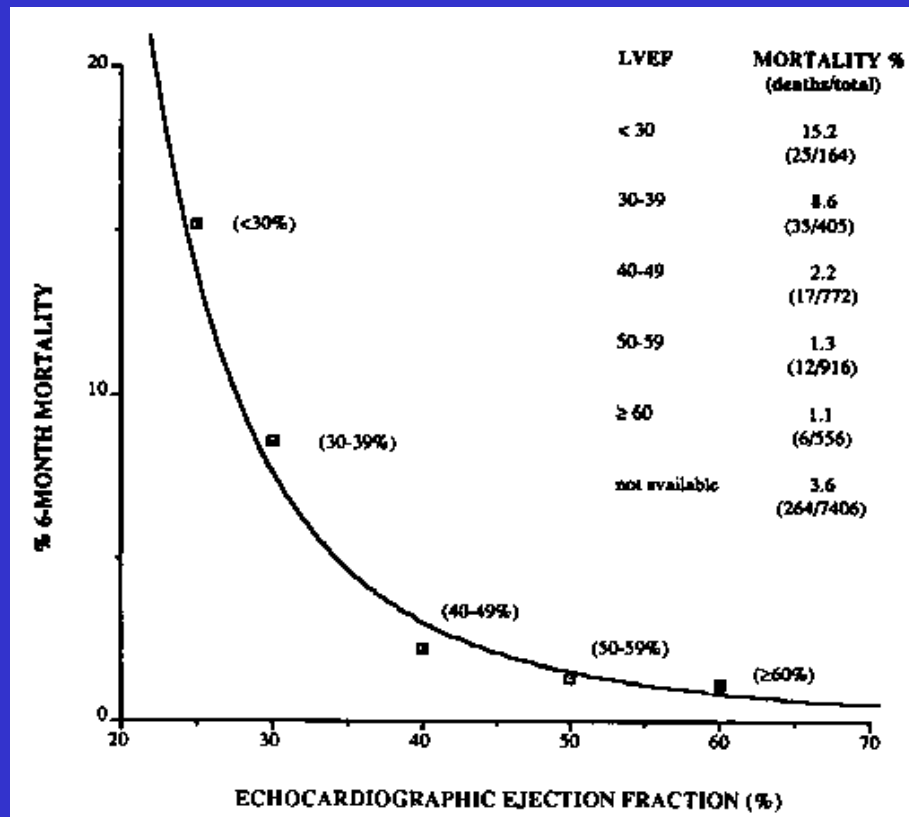
Congestive Heart Failure is a Common Problem

- 5.8 million Americans have congestive heart failure¹
- 70% of cases are due to ischemic cardiomyopathy
 - Framingham Study: 33.9% of patients develop CHF within 5 years of their first MI²
- An estimated \$39.2 billion will be spent on heart failure treatment in 2010¹

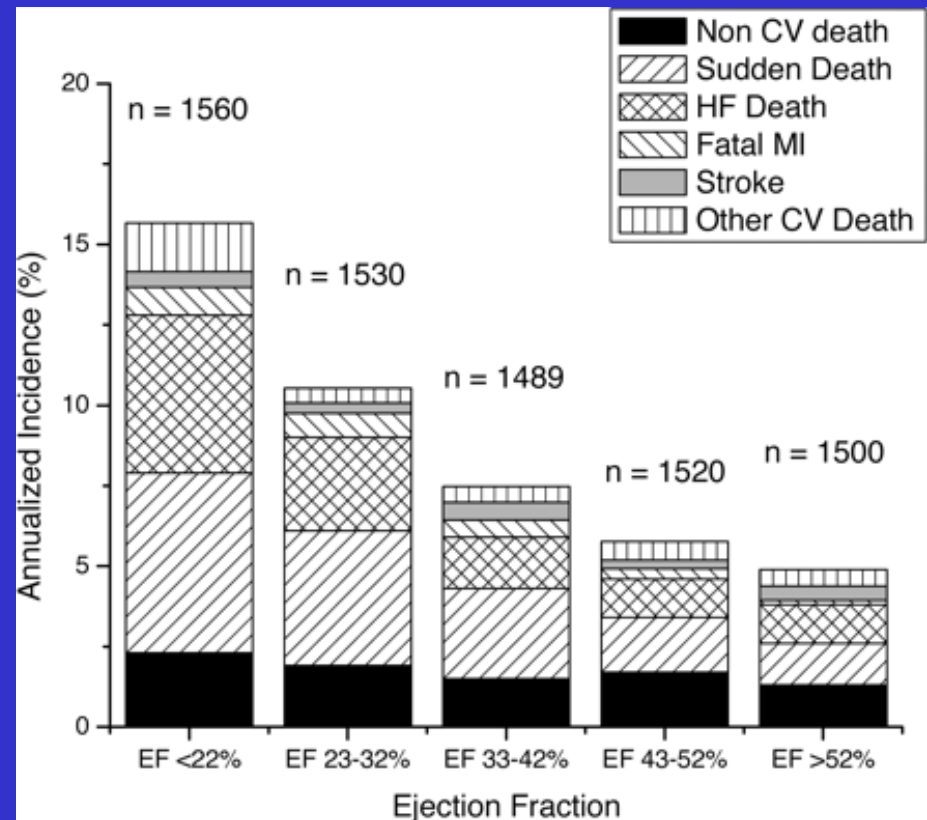
1. AHA Heart Disease and Stroke Statistics 2010

2. Velageti RS et al Circulation 2008;118:2057-62

Left Ventricular Ejection Fraction Predicts Mortality



Volpi A et al, *Circulation* 1993; 88:416-29

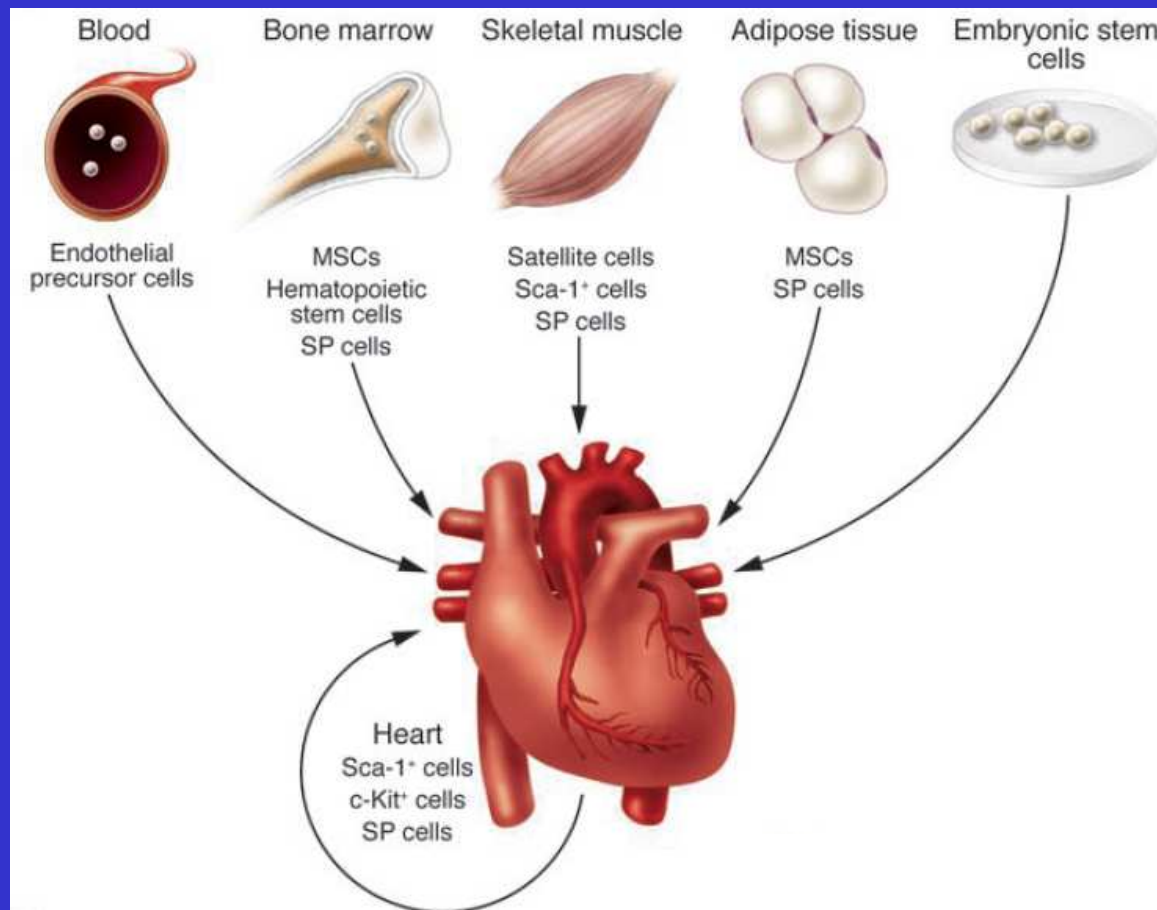


Solomon SD et al *Circulation* 2005;112:3738-44

Ideal Therapy for Congestive Heart Failure

- Repair & replace dysfunctional cardiac tissue
- Revascularize ischemic tissue
- Activate resident stem cells
- To:
 - Improve LV function and remodeling
 - Reduce symptoms and hospitalizations
 - Save lives

Sources for Cardiac Stem Cell Therapy



From: Dimmeler S et al, JCI 2005; 115:572-83

Clinical Trials of Stem Cell Therapy for the Heart are Actively Recruiting in the U.S.

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

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Search

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Found **113 studies** with search of: stem cells AND heart | Open Studies | United States

[Include studies that are not seeking new volunteers.](#)

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Rank	Status	Study
1	Recruiting	CARDIOSphere-Derived aUTologous Stem CELls to Reverse ventricUlar dySfunction Conditions: Myocardial Infarction; Ventricular Dysfunction; Congestive Heart Failure; Heart Failure Interventions: Other: Observation (Control Group); Biological: Autologous stem cell infusion
2	Recruiting	Prospective Randomized Study of Mesenchymal Stem Cell Therapy in Patients Undergoing Cardiac Surgery (PROMETHEUS) Conditions: Stem Cell Transplantation; Ventricular Dysfunction, Left Interventions: Genetic: Lower dose mesenchymal stem cell (MSC) injection; Genetic: Placebo; Genetic: Higher dose MSC injection
3	Recruiting	Myocardial Regeneration Using Cardiac Stem Cells Conditions: Coronary Artery Disease; Congestive Heart Failure Intervention: Procedure: Intracoronary Injection (cardiac stem cell therapy)

...and the World

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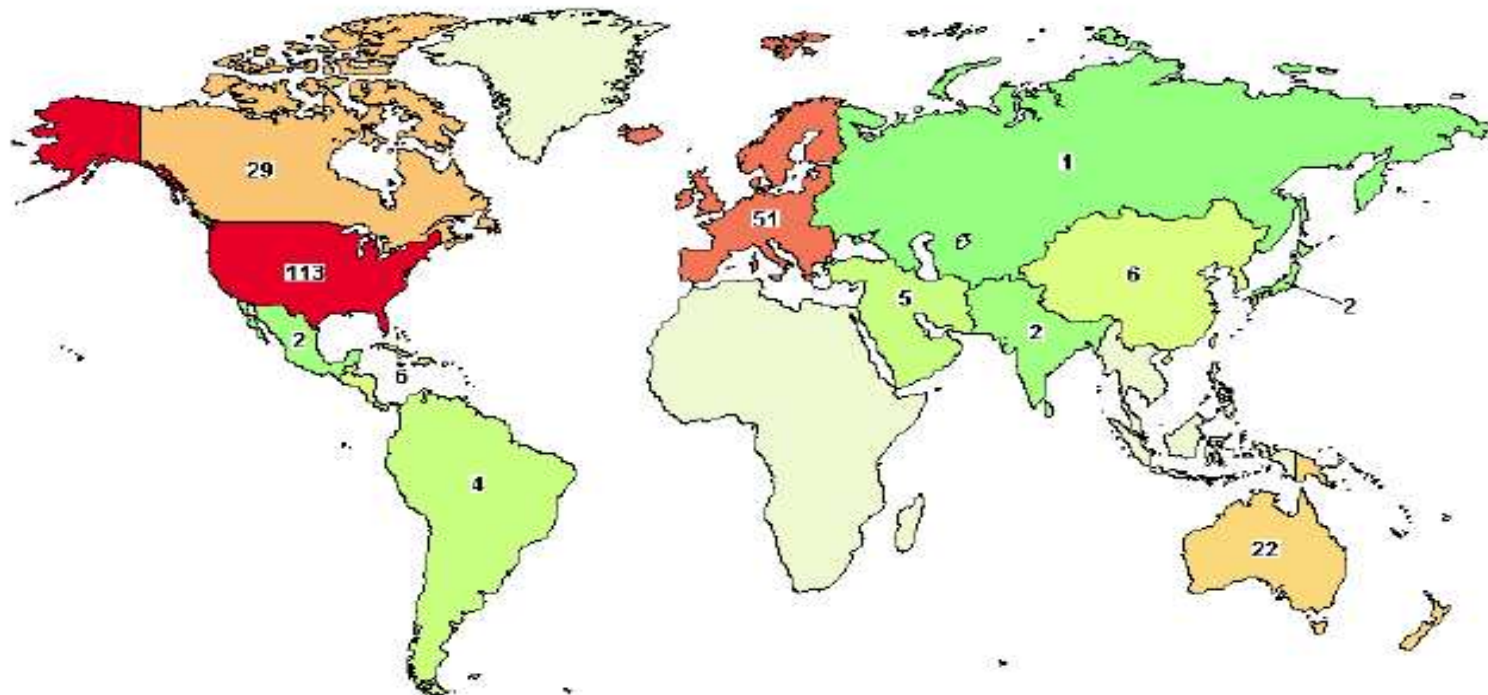
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Results on Map

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Map of **184 studies** found by search of: stem cells AND heart | Open Studies

Click on the map below to show a more detailed map (when available) or search for studies (when map not available).



What We've Learned So Far

I. Promise of stem cell therapy for the heart

- REPAIR-AMI Trial
- Prochymal Study
- Cardiac Stem Cells

II. Potential Pitfalls

- MAGIC Trial
- Embryonic Stem Cells

III. Future Questions

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Intracoronary Bone Marrow–Derived Progenitor Cells in Acute Myocardial Infarction

Volker Schächinger, M.D., Sandra Erbs, M.D., Albrecht Elsässer, M.D.,
Werner Haberbosch, M.D., Rainer Hambrecht, M.D., Hans Hölschermann, M.D.,
Jiangtao Yu, M.D., Roberto Corti, M.D., Detlef G. Mathey, M.D.,
Christian W. Hamm, M.D., Tim Süselbeck, M.D., Birgit Assmus, M.D.,
Torsten Tonn, M.D., Stefanie Dimmeler, Ph.D., and Andreas M. Zeiher, M.D.,
for the REPAIR-AMI Investigators*

- Randomized, double-blind, placebo-controlled study
- Patients with ST-elevation Myocardial Infarction treated with PCI and stenting of culprit vessel, and LV ejection fraction $\leq 45\%$
- Intracoronary infusion of autologous bone marrow progenitor cells or placebo 3-7 days after MI

Results of Repair-AMI

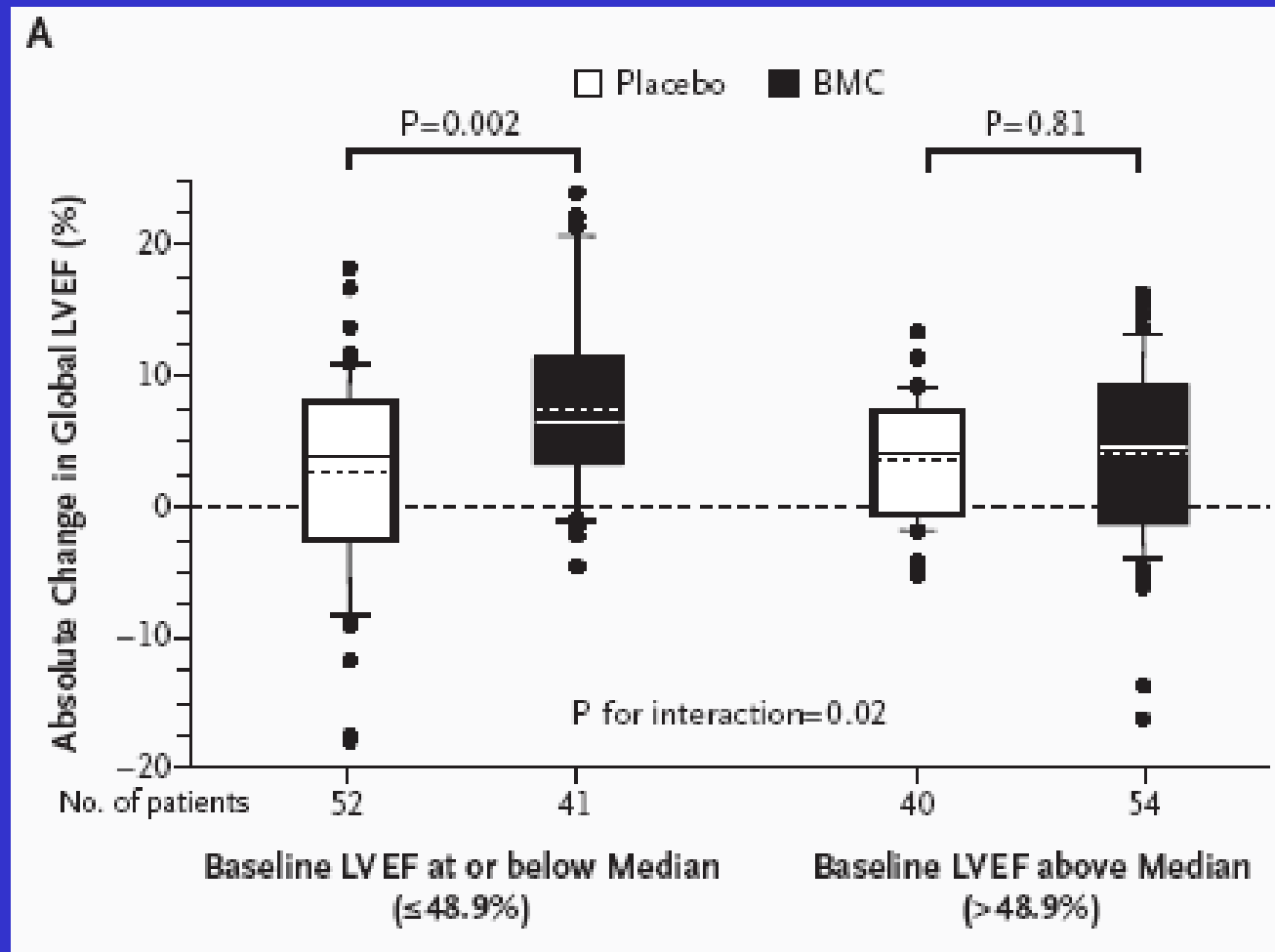
- 204 patients total:
 - 101 bone marrow cells (BMC), 103 placebo
- BMC-treated patients at 4 months had:
 - Higher LVEF: 53.8% vs 49.9%, $p=0.02$
 - Greater increase in LVEF: +5.5% vs +3.0%, $p=0.01$
- BMC-treated patients at 1 year had:
 - Lower rate of cardiovascular events (Death, recurrent MI, repeat revascularization): $p=0.01$

BMC Infusion Reduced Clinical Events at 1 Year in Repair-AMI

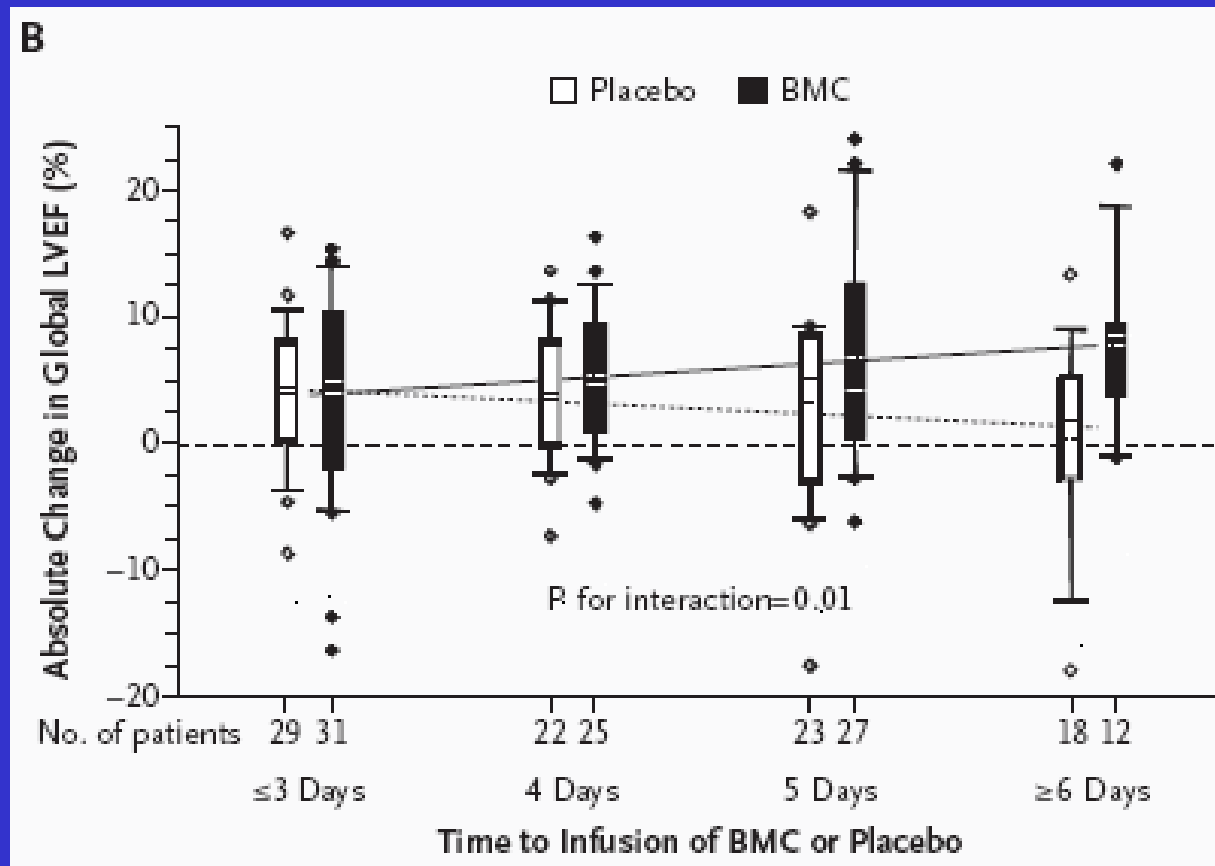
Table 3. Clinical Events during Follow-up.

Event	Placebo (N=103)	BMC (N=101)	P Value
	<i>no. of patients</i>		
1-Yr follow-up (cumulative)§			
Death	6	2	0.28 †
Myocardial infarction	5	0	0.06 †
Rehospitalization for heart failure	3	0	0.25 †
Revascularization	35	21	0.03 ‡
Target-vessel revascularization	24	16	0.18 ‡
Stent thrombosis	3	1	0.62 †
Non-target-vessel revascularization	16	6	0.03 ‡
Cerebral infarction	1	1	1.0 †
Documented ventricular arrhythmia or syncope	5	5	1.0 †
Combined events			
Death and recurrence of myocardial infarction	10	2	0.02 ‡
Death, recurrence of myocardial infarction, and any revascularization procedure	40	23	0.01 ‡
Death, recurrence of myocardial infarction, and infarct-vessel revascularization	29	18	0.08 ‡
Death, recurrence of myocardial infarction, and rehospitalization for heart failure	12	2	0.006 ‡

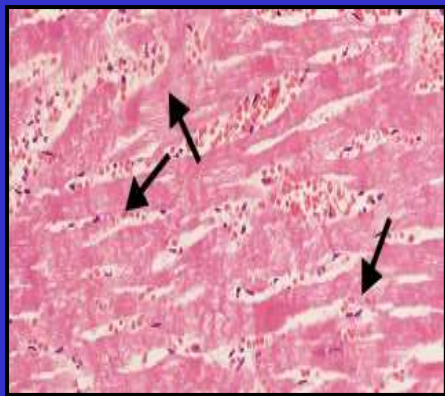
Degree of LV Dysfunction Predicted Effect of BMC Therapy in REPAIR-AMI



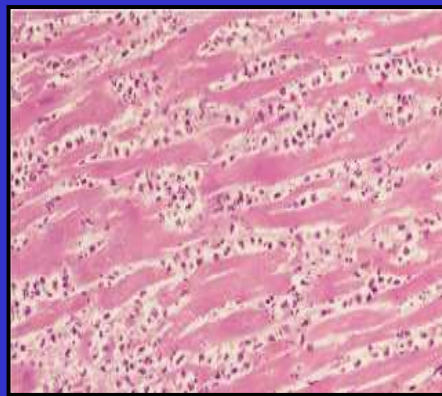
Later Cell Delivery Augmented Effect of BMCs on LVEF in REPAIR-AMI



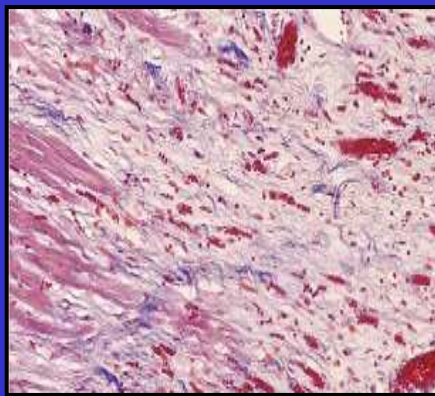
When is the Optimal Time for Cell Delivery after MI?



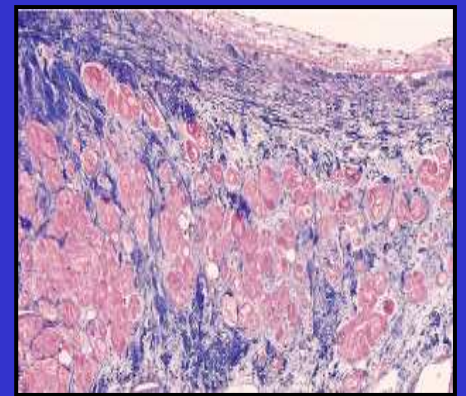
Immediate



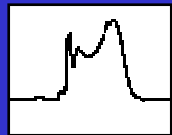
1-3 days



3 weeks



Chronic



MSCs



BMCs

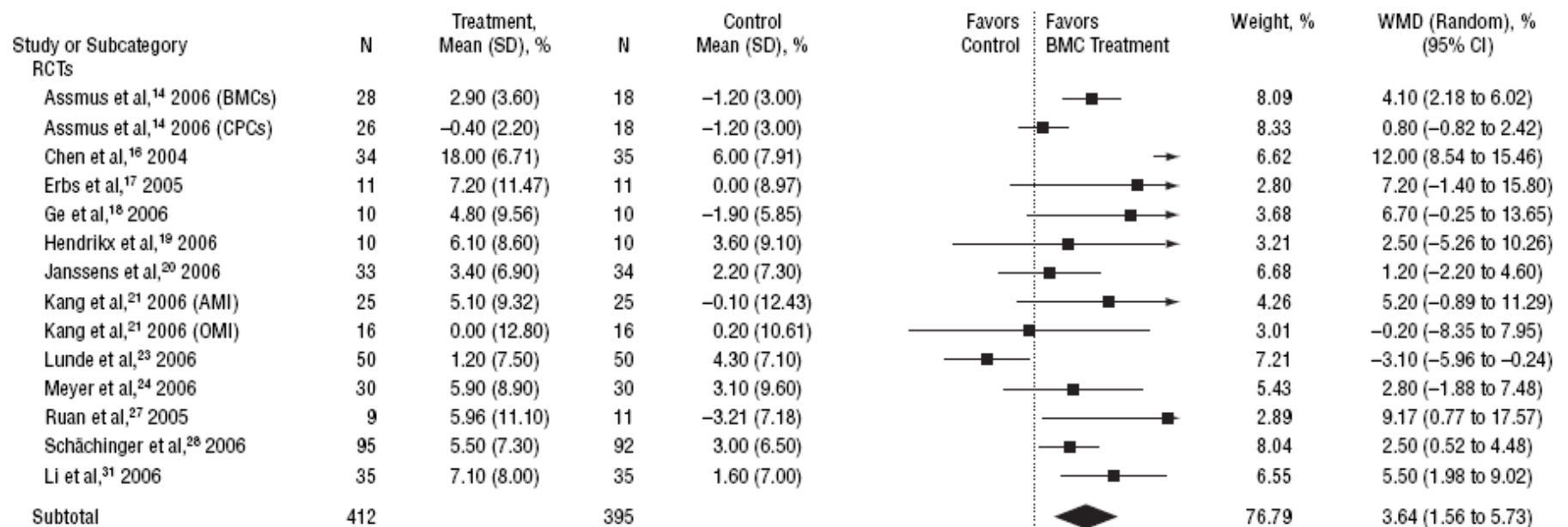


CSCs, EPCs

Summary of REPAIR-AMI

- Intracoronary infusion of autologous BMCs after acute MI appears beneficial in terms of LVEF and clinical events
- Patients with significant LV dysfunction had greater benefit
- Timing of cell delivery is important -- later appears better

BMC Infusion after MI is Beneficial Across Studies



Test for Heterogeneity: $\chi^2_{13} = 59.81$ ($P < .001$), $I^2 = 78.3\%$

Test for Overall Effect: $Z = 3.42$ ($P < .001$)

Abdel-Latif, A. et al. Arch Intern Med 2007;167:989-997.

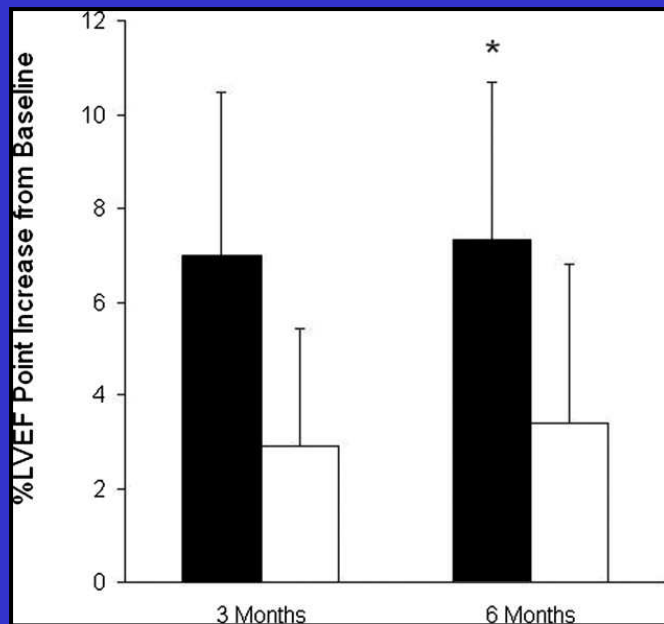
Mesenchymal Stem Cells (MSCs) for Cardiac Repair

- Subpopulation of adult bone marrow cells
 - CD 90+, CD 34-, CD 45-
 - Capable of multilineage differentiation
- Immune-privileged
 - Low levels of MHC II expression and co-stimulatory molecules
 - Allows for allogenic administration
- Promising results in pre-clinical models of infarction and ischemic cardiomyopathy

Prochymal Study: IV Delivery of MSCs after Myocardial Infarction

- Phase I, randomized, double-blind, dose-escalation study of intravenous allogeneic MSCs
- Patients within 10 days of first MI
 - LVEF 30-60%
 - Regional wall motion abnormality
- Randomized 2:1 MSC : Placebo for each dose
 - 0.5, 1.6, & 5 x 10⁶ MSCs/kg body weight
- 6 months of Follow-up
 - Clinical outcomes, echocardiography, rhythm monitoring

Results of Prochymal

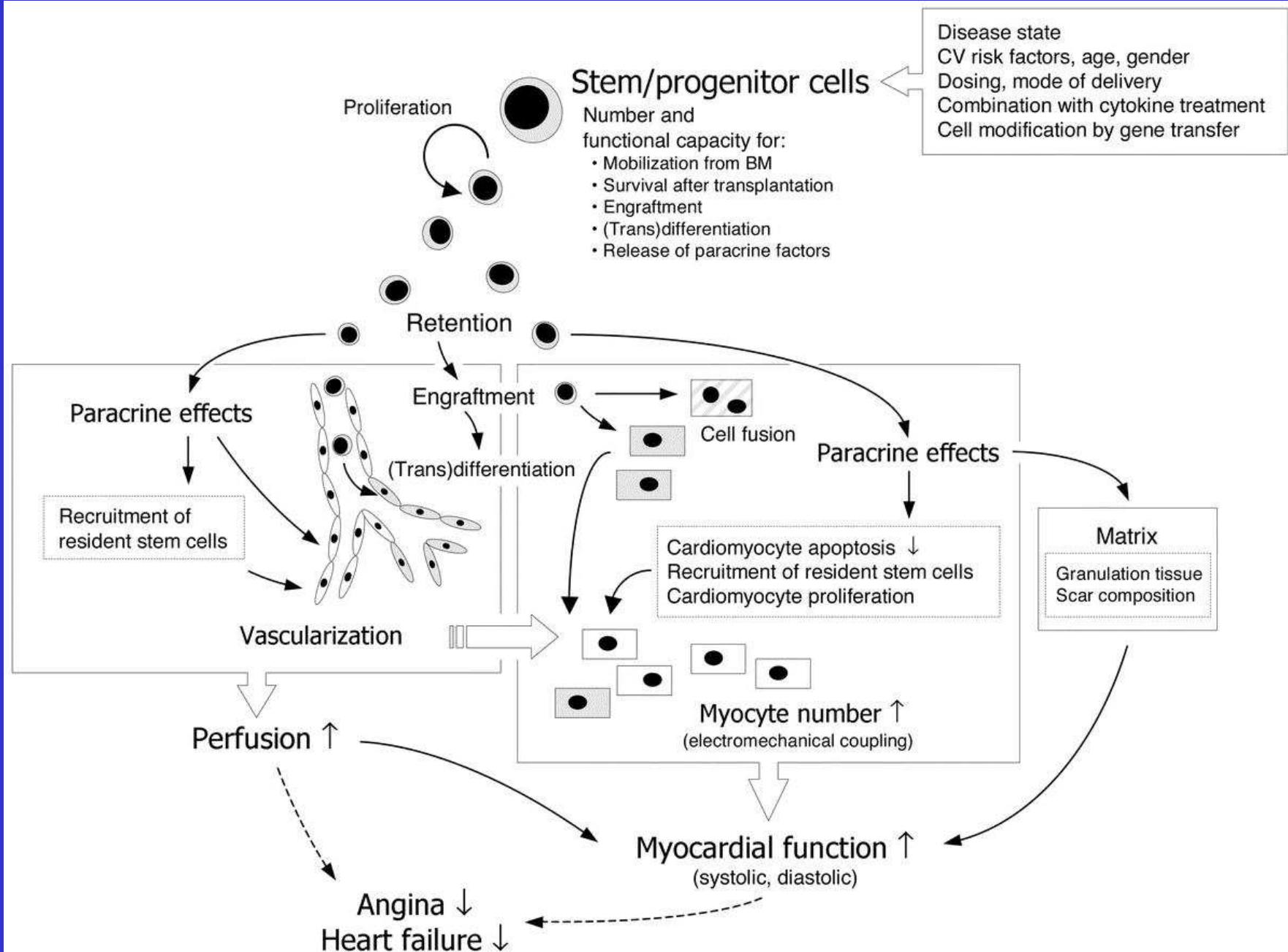


Hare JM et al JACC 2009; 54(24):2277-86

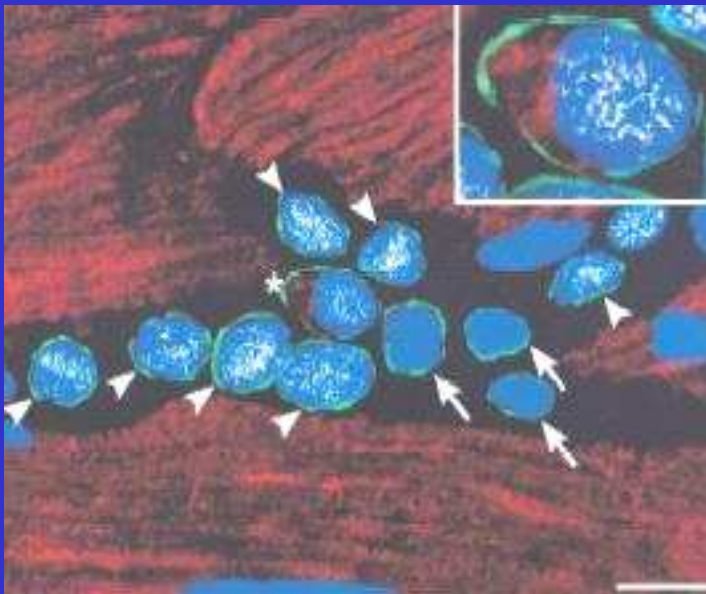
- 53 patients completed study (34 MSC, 19 placebo)
- No overall difference in LVEF between MSC-treated and placebo
 - In patient with anterior MI, MSC treatment significantly improved LVEF at 6 months ($7.3 \pm 3.4\%$, $p=0.044$, $n=12$), but not placebo ($3.4 \pm 3.4\%$, $p=NS$, $n=8$)
- MSC-treatment significantly reduced arrhythmic events
 - Patients with at least one arrhythmia: 8.8% (3/34) MSC-treated vs 36.8% (7/19) placebo, $p=0.025$
- MSC-treatment improved pulmonary function testing (FEV1) at 6 months

Summary of Prochymal

- IV administration of allogeneic MSCs after MI is safe and appears efficacious
- Effect of MSCs on LVEF most pronounced in anterior MI
 - Supports results of REPAIR-AMI
- Direct delivery to the heart may not be necessary in acute MI
 - Homing to area of injury & inflammation
 - Direct cell vs Paracrine effects



Resident Cardiac Stem Cells



Beltrami AP et al, Cell 2003; 114:763-776

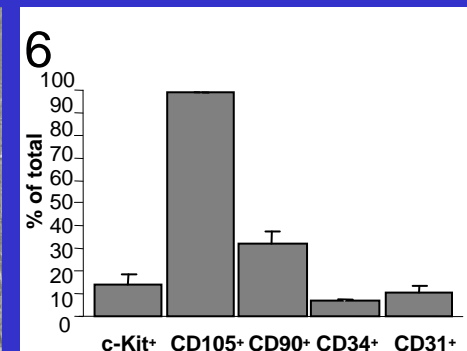
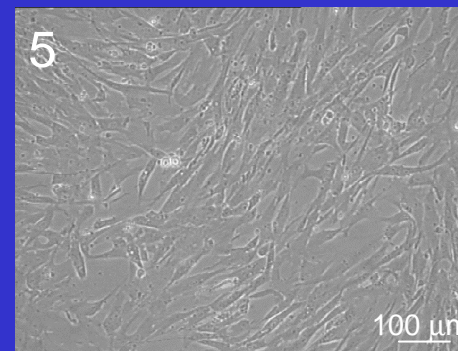
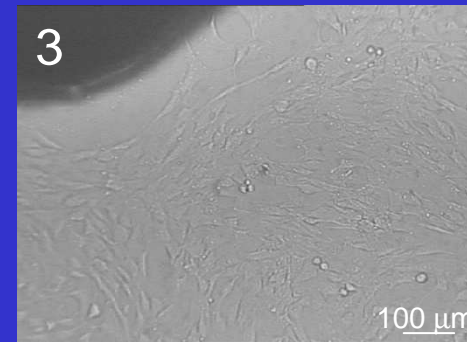
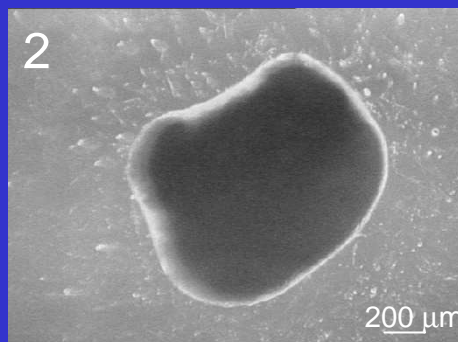
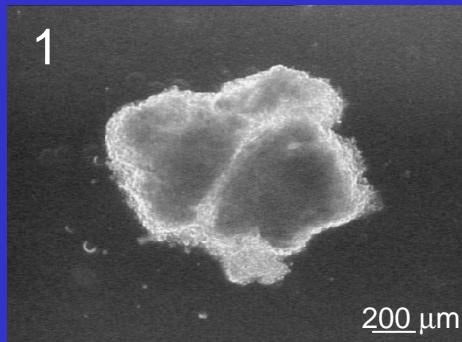
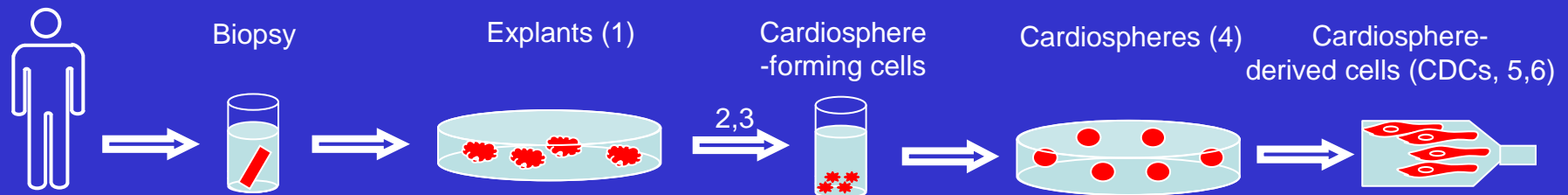
“...the adult heart, like the brain, is mainly composed of terminally differentiated cells, but is not a terminally differentiated organ...”

- Piero Anversa

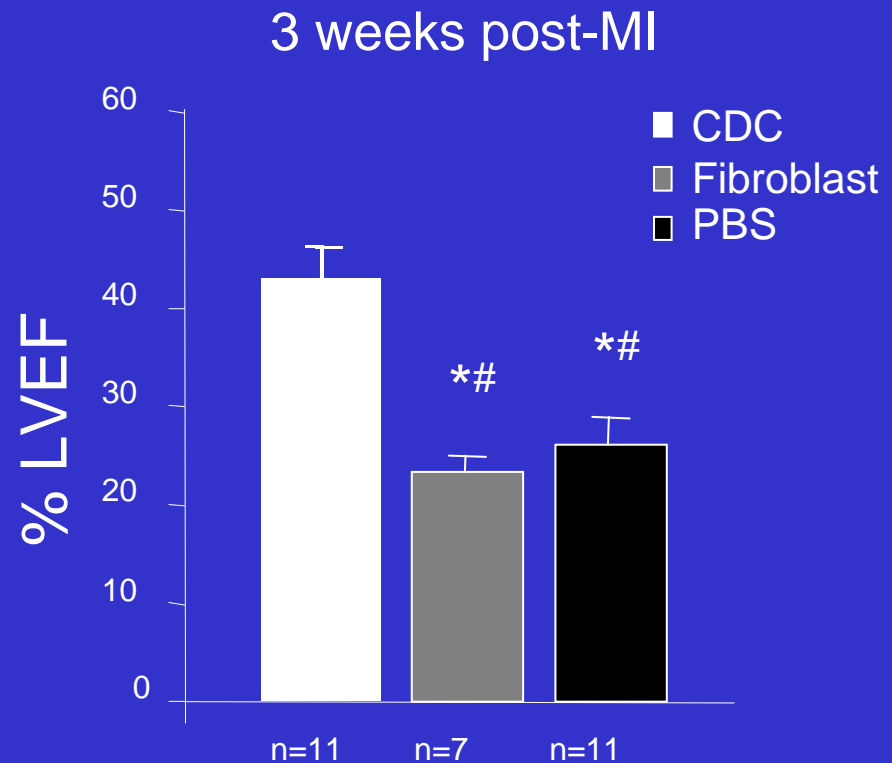
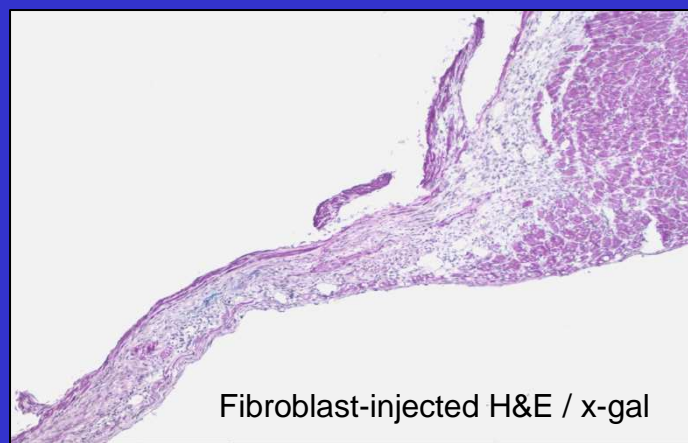
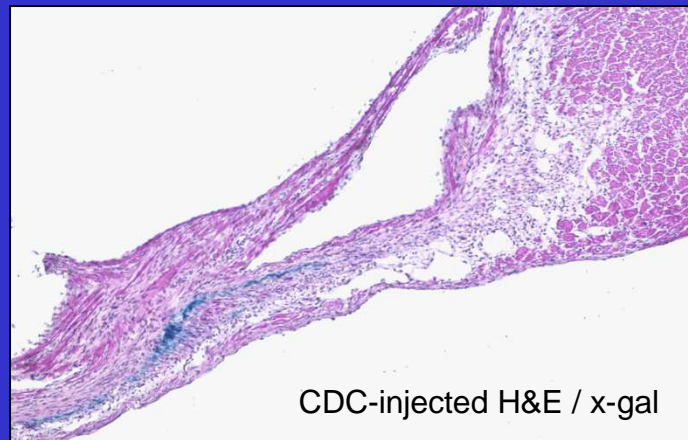
Cardiac-Derived Stem Cells

- Undifferentiated c-kit⁺, lin⁻ cells reside in niches within the adult heart
- CSCs are clonogenic, self-renewing, and multipotent
 - Form cardiac myocytes, blood vessels, and smooth muscle
 - Responsible for cell turnover, routine repair
- May be isolated from myocardial tissue and expanded *ex vivo*

Cardiac Stem Cells from Human Biopsy Samples



Cardiosphere-Derived Cells Engraft and Preserve LVEF in a Pre-clinical Model of MI

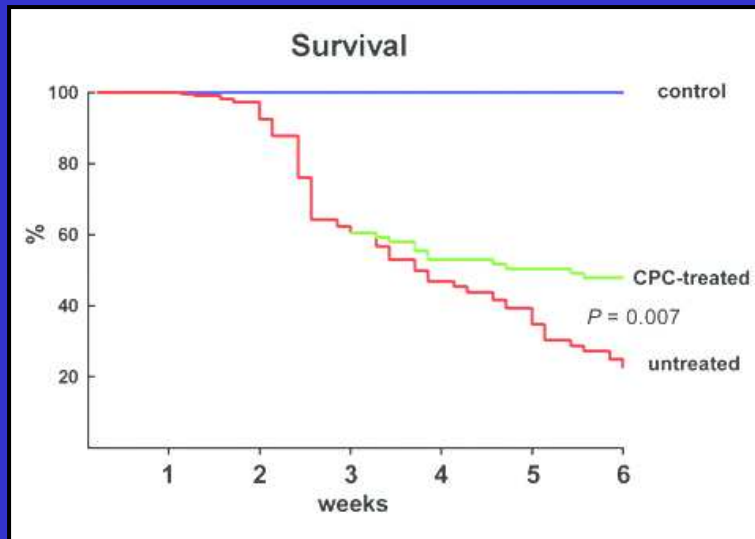


Smith et al, *Circulation*. 2007;115:896-908

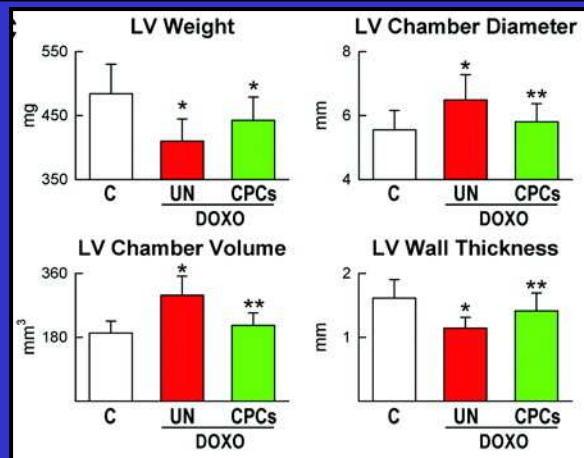
Clinical Trials of Cardiac Stem Cell Therapy for Infarction

- Cardiosphere-Derived Autologous stem Cells to reverse ventricular dysfunction (CADUCEUS) Trial
 - Phase I/II randomized dose-escalation of study of cardiosphere-derived cells after myocardial infarction with LV dysfunction (LVEF 25-45%)
 - CDCs isolated from endomyocardial biopsy sample
 - Intracoronary delivery
- Myocardial Regeneration Using Cardiac Stem Cells (Scipio) Trial
 - Myocardial infarction with LVEF < 40% referred for CABG
 - Right atrial appendage used as source for CSCs
 - Intracoronary delivery

Cardiac Stem Cells Reverse Anthracycline Cardiomyopathy



- Death of resident cardiac progenitor cells may be a cause of chemotherapy-induced cardiomyopathy
- In a rodent model of anthracycline cardiomyopathy, delivery of syngeneic cardiac progenitor cells resulted in preserved EF & reduction in adverse remodeling compared to placebo



Potential Pitfalls for Cardiac Stem Cell Therapy

- MAGIC Trial of skeletal myoblasts
 - Cell-treated patients had trend toward higher rates of arrhythmias compared to placebo

Table 4. Safety End Points

	Placebo (n=34)	Low Dose (n=33)	High Dose (n=30)	HR (95% CI)	P*
Six-month MACE,‡ n (%)	7 (21)	13 (39)	6 (20)	1.6 (0.7; 3.8)	0.29
Six-month mortality, n (%)	2 (6)	5 (15)	4 (13)	2.6 (0.6;12.1)	0.20
Six-month ventricular arrhythmias, n (%)	2 (6)	4 (12)	5 (17)	2.7 (0.6; 12.6)	0.18

Menasché et al *Circulation* 2008;117:1189-1200

- Embryonic stem cell (ESC) therapy
 - Delivery of undifferentiated ESCs to the heart cause teratoma formation in rodent model

Nussbaum et al *FASEB* 2007;21:1345-1357

Summary

- Myocardial infarction and heart failure are common problems in need of novel therapies
- Bone marrow and mesenchymal stem cells have shown promise in clinical trials for treatment of myocardial infarction
- A population of multipotent stem cells resides in the heart and is capable of myocardial repair
- Stem cell therapy for the heart is not without risk, necessitating rigorous investigation

Future Questions for Cardiac Stem Cell Therapy

- Who stands to benefit?
- What cell type is best?
- When should cells be given?
- How should cells be delivered?

- Are cells necessary?

