Is Cell Therapy is (Necessary) for Ischemic Heart Disease?

- PRO -

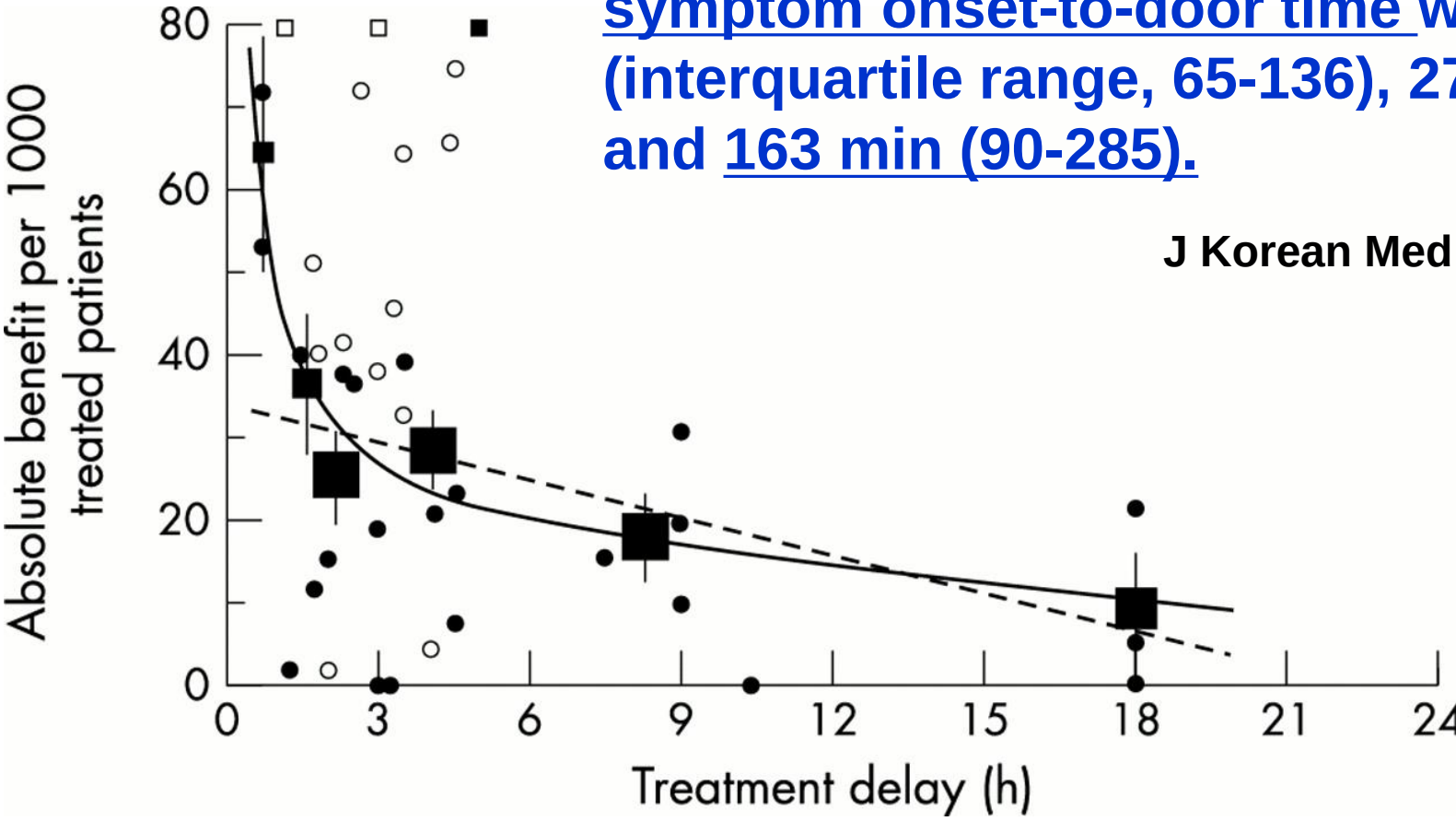
전남의대 심혈관센터
순환기내과

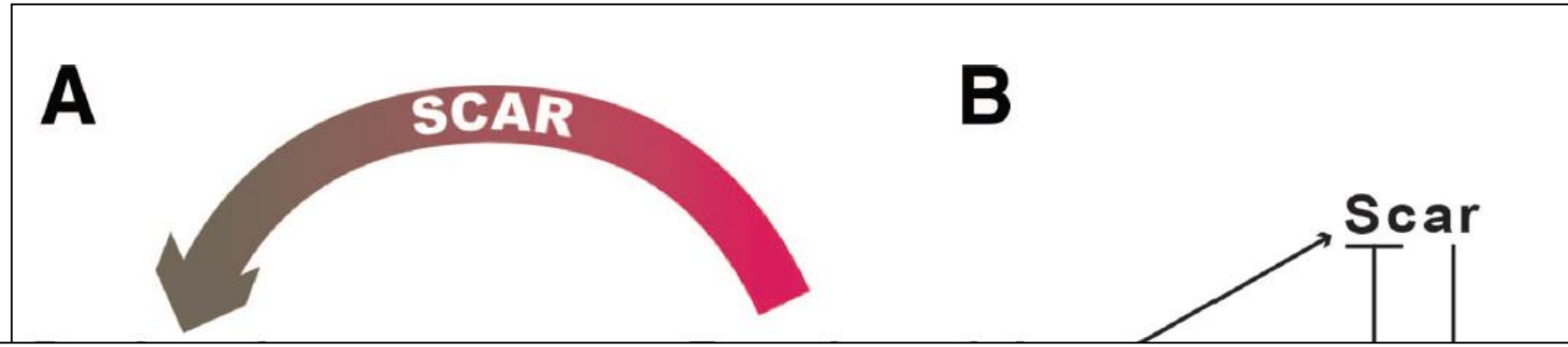
안영근

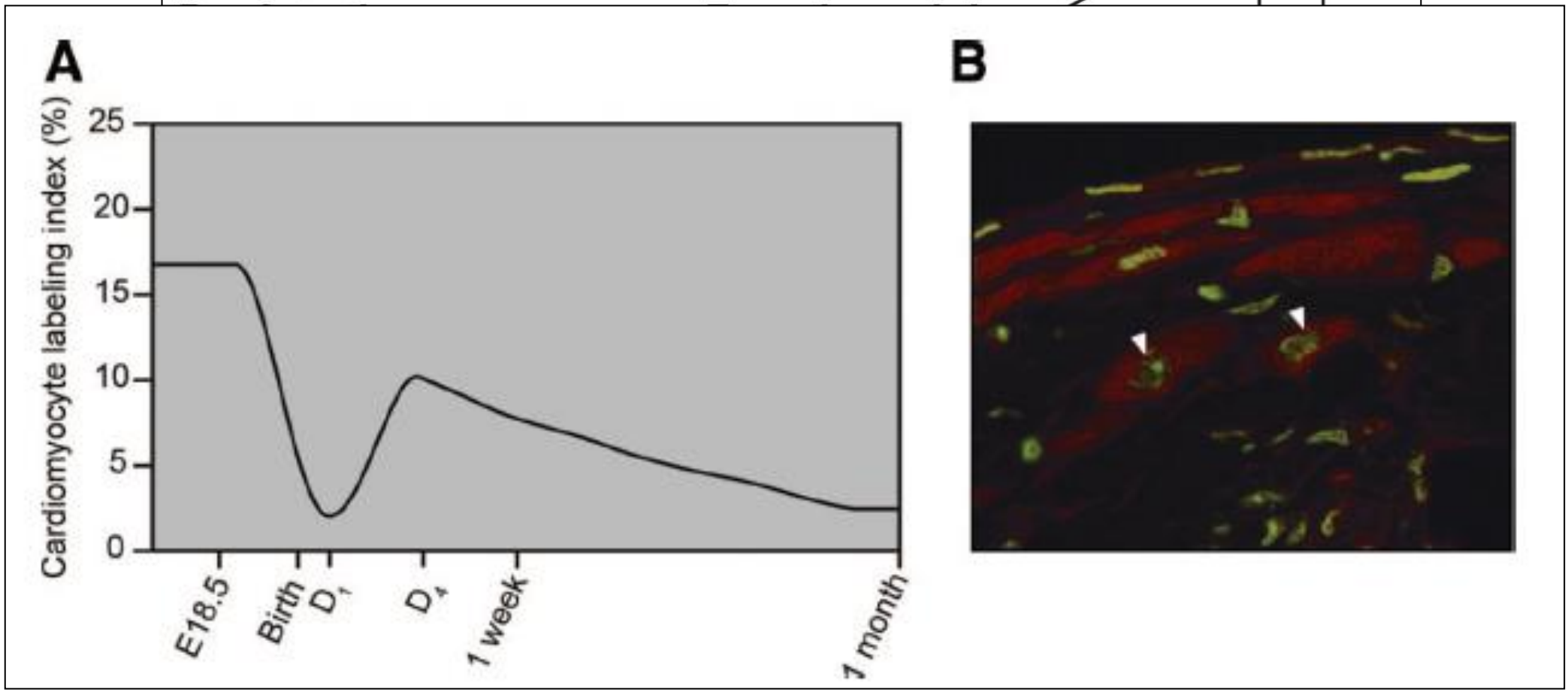
The Impact of Initial Treatment Delay Using Primary Angioplasty on Mortality among Patients with AMI: from the KAMIR

The medians of door-to-balloon time, symptom onset-to-balloon time, and symptom onset-to-door time were 90 (interquartile range, 65-136), 274 (185-442), and 163 min (90-285).

J Korean Med Sci 2008;23:357-64.







Circulation. 2011;123:1771-1779

New drugs

Stents

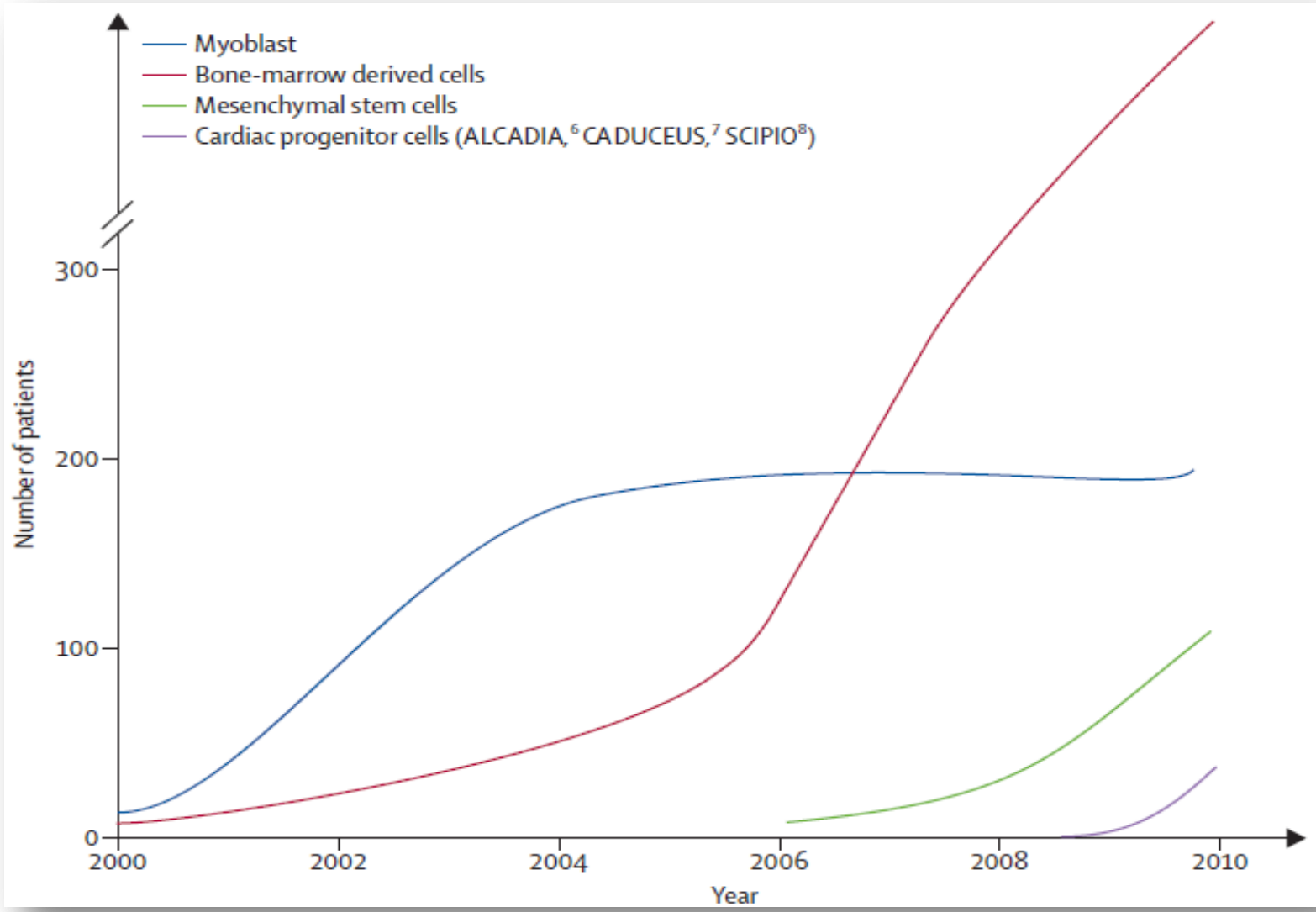
Adult stem cells
(Endogenous,
Exogenous)

iPS

Gene therapy

Prevalence of HF from post-ischemic cardiac dysfunction rather increases causing a substantial morbidity.

Clinical trials of stem cell therapy for cardiac repair



ALCADIA=AutoLogous human CArdiac-Derived stem cells to treat Ischemic cArdiomyopathy.
CADUCEUS=CArdiosphere-Derived aUtologous stem CElls to reverse ventricUlar dySfunction.
SCIPIO=cardiac Stem Cell Infusion in Patients with Ischemic cardiOmyopathy.

www.thelancet.com February 14, 2012

Review

http://dx.doi.org/10.4070/kcj.2012.42.2.71
Print ISSN 1738-5520 • On-line ISSN 1738-5555

kcj
Korean Circulation Journal

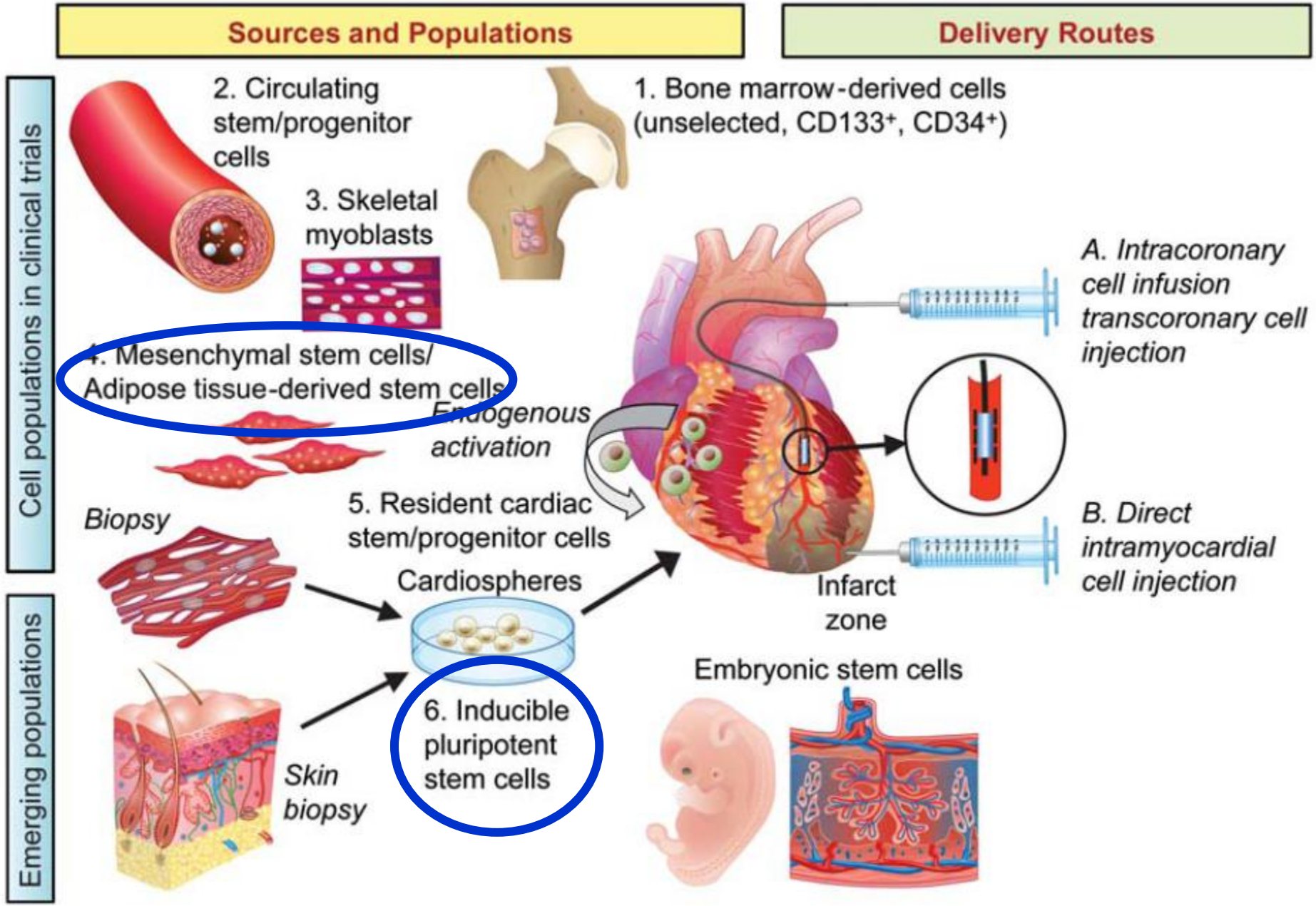
A Long Road for Stem Cells to Cure Sick Hearts: Update on Recent Clinical Trials

Yong Sook Kim, PhD[1] and Youngkeun Ahn, MD[1,2]

[1]*Heart Research Center,* [2]*Department of Cardiology and Cardiovascular Center, Chonnam National University Hospital, Gwangju, Korea*

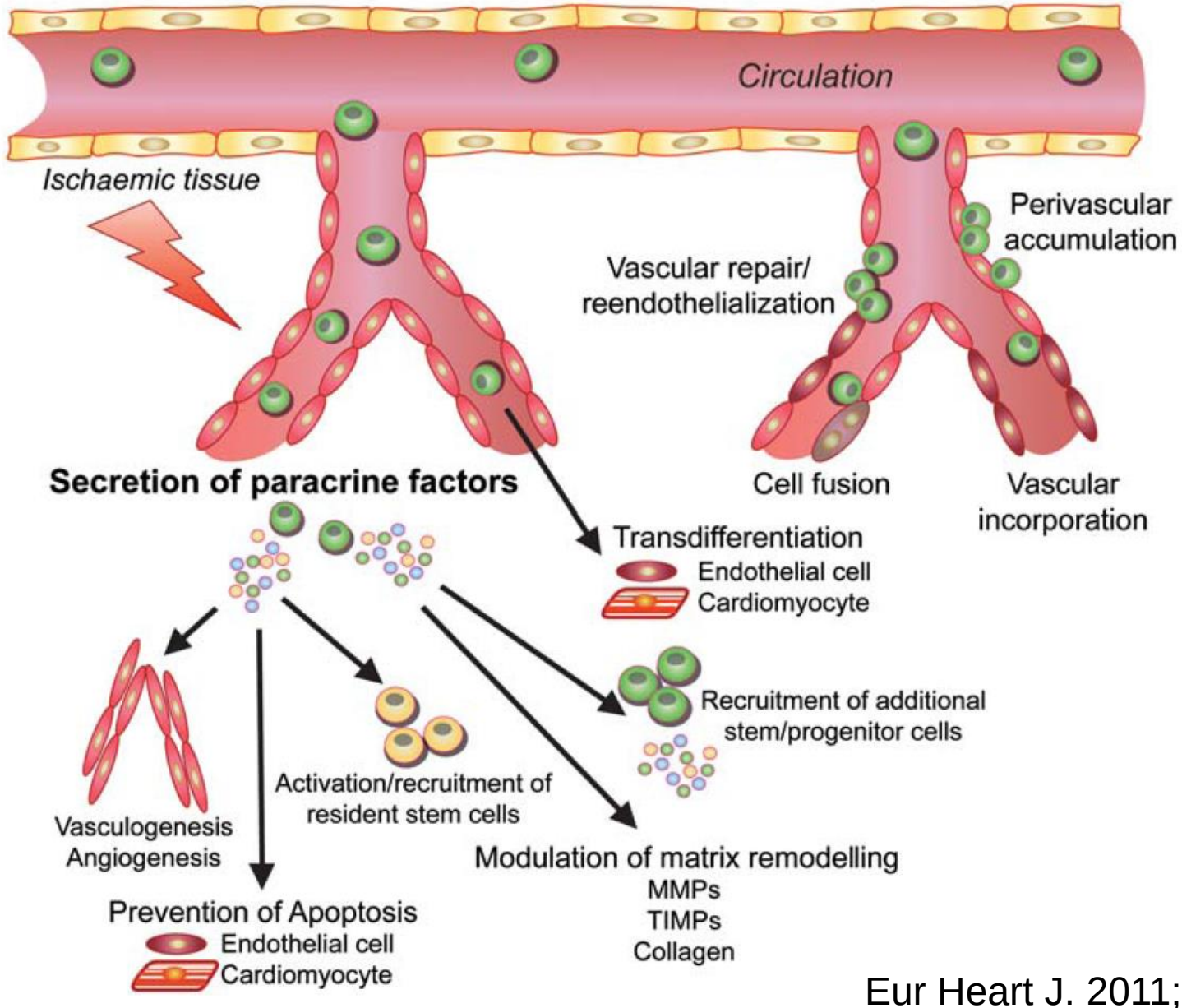
The contribution of stem cells to cure damaged hearts has finally been unraveled. A large number of preclinical and clinical studies have showed beneficial outcomes after myocardial infarction. In this review, the current understanding of stem cell therapy in preclinical and clinical experiences is summarized. Stem cells from bone marrow have shown a potential to improve cardiac performance after myocardial infarction in animal and early clinical studies. Clinical trials from all over the world have provided safety assessments of stem cell therapy with marginal improvement of clinical outcomes. Thus, further investigations should be encouraged to resolve the discrepancies between studies, clinical issues, and unclear translational findings. This review provides information and commentary on key trials for stem cell-based treatment of cardiovascular disease. **(Korean Circ J 2012;42:71-79)**

Circulation. 2012;126:551-568



Eur Heart J. 2011;32:1197–1206

Proposed mechanisms of ischemic tissue repair



Eur Heart J. 2011;32:1197–1206

NATURE MEDICINE VOLUME 18 | NUMBER 3 | MARCH 2012

Korea okays stem cell therapies despite limited peer-reviewed data

Approved by Regulatory Authority

1) July 2011, Hearticellgram-AMI (Pharmicell, Seoul, Korea)

Acute Myocardial Infarction, Autologous BM-MSC

(n=59, EF 6% improvement (2% in std medicatin group))

2) Nov 2011, HEMACORD (New York Blood Center, USA)

Cord blood stem cell, for HSC infusion

3) Jan 2012, Cartistem (Medipost, Seoul, Korea)

Knee cartilage,Bbanked UCB stem cell

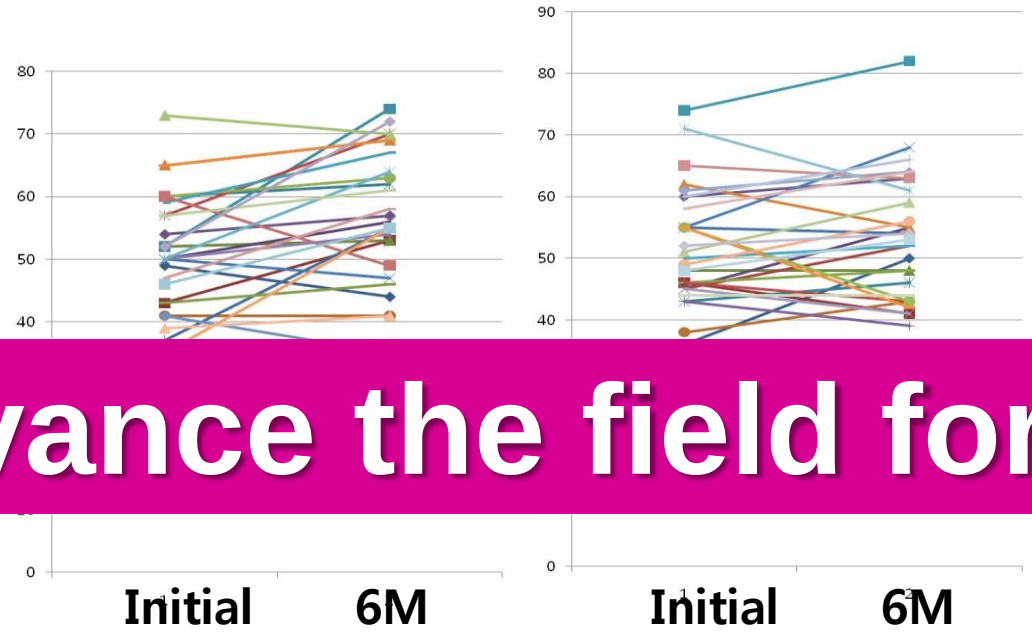
(n=89 pts, significant therapeutic effect in 26% of pts)

4) Cupistem (Anterogen, Seoul, Korea)

Autologous fat stem cell, Crohn's disease

A Randomized, Open labeled, multicenter trial for Safety and Efficacy of intracoronary adult human mesenchymal STEM cells after acute Myocardial Infarction (ROSE-STEMMI)

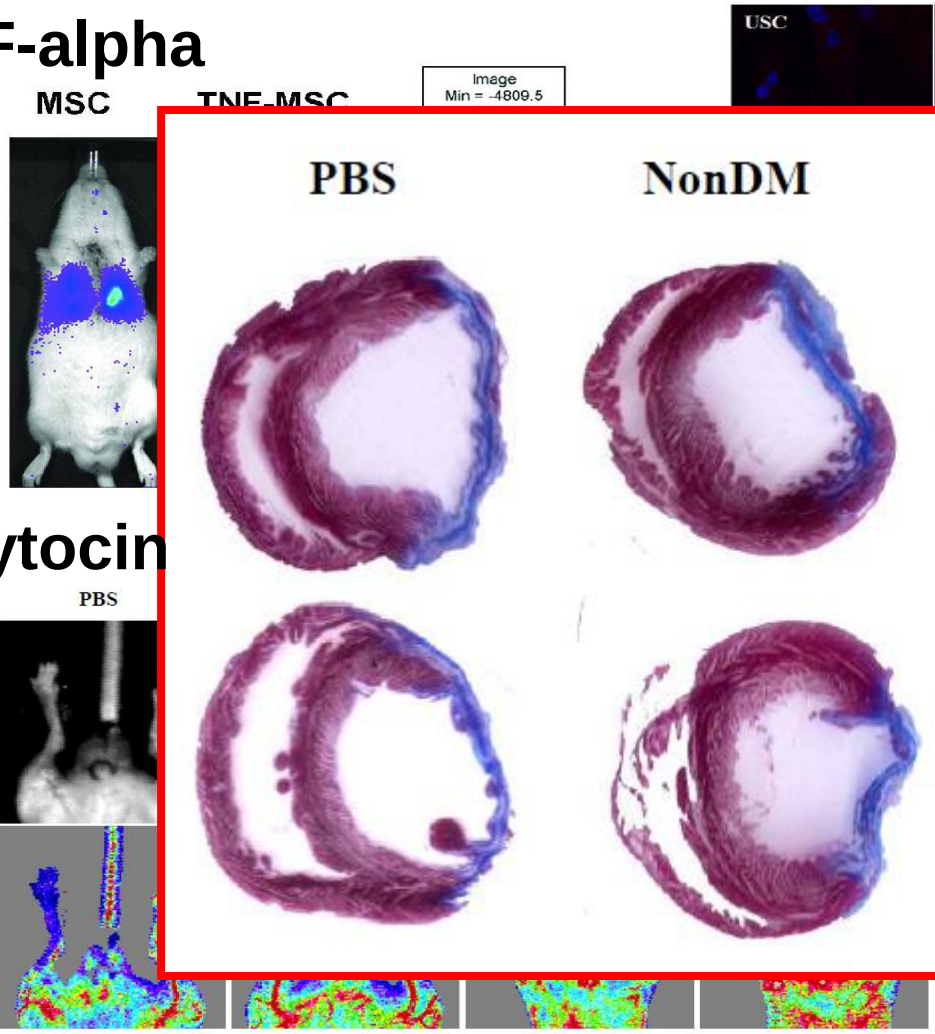
	Treatment N=30	Control N=29	P value
EF (SPECT)			
initial	49.0 ± 11.7	52.2 ± 9.1	0.256
6 M	55.0 ± 11.8	53.9 ± 10.0	0.718
EF difference	5.9 ± 8.5	1.8 ± 6.9	0.043



To advance the field forward

Priming of Cells

TNF-alpha



Oxytocin

G-POPs: G-CSF
BSC
by
ivated
t (on

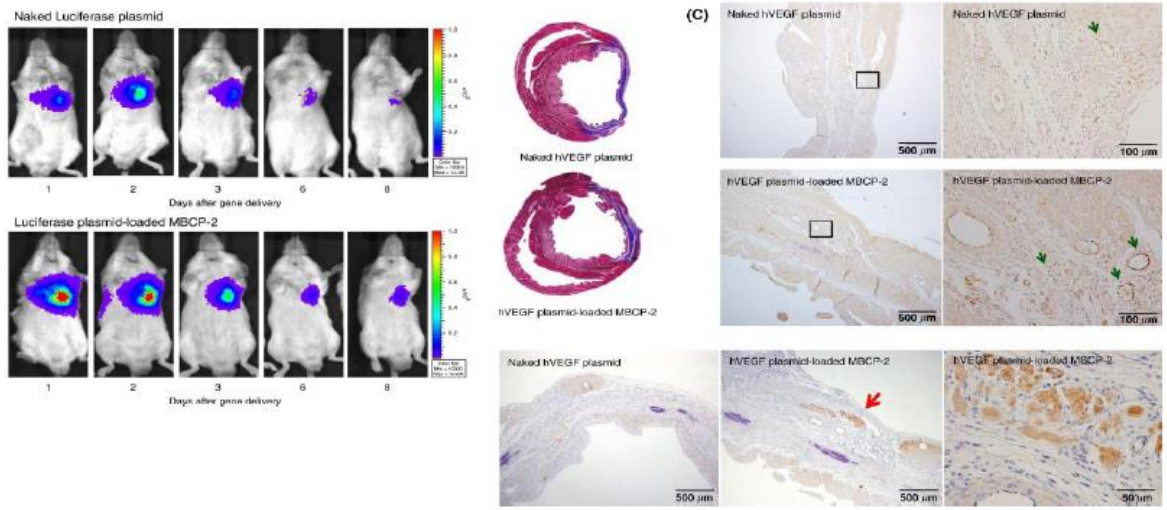
Front Biosci. 2009;14:2845-56
Circulation. 2006;114:18:171
Artif Organs. 2010;34:453-61

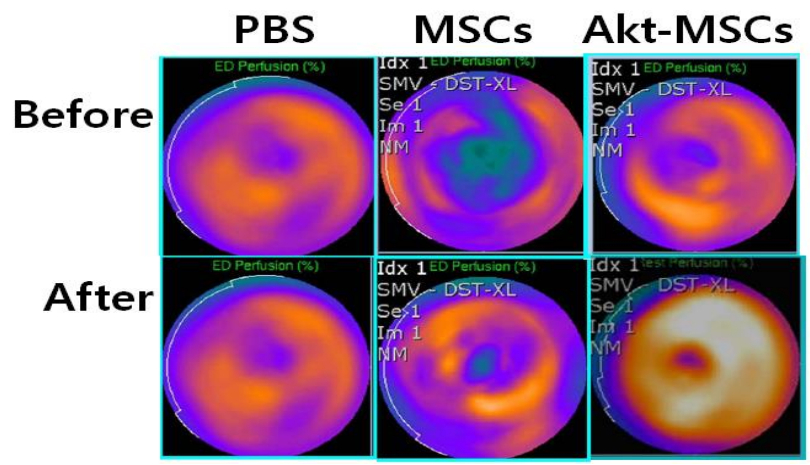
2009 KSC Young Investigator Award
Eur Heart J. 2010;31:83
Cells Tissues Organs. 2012;195:428-42

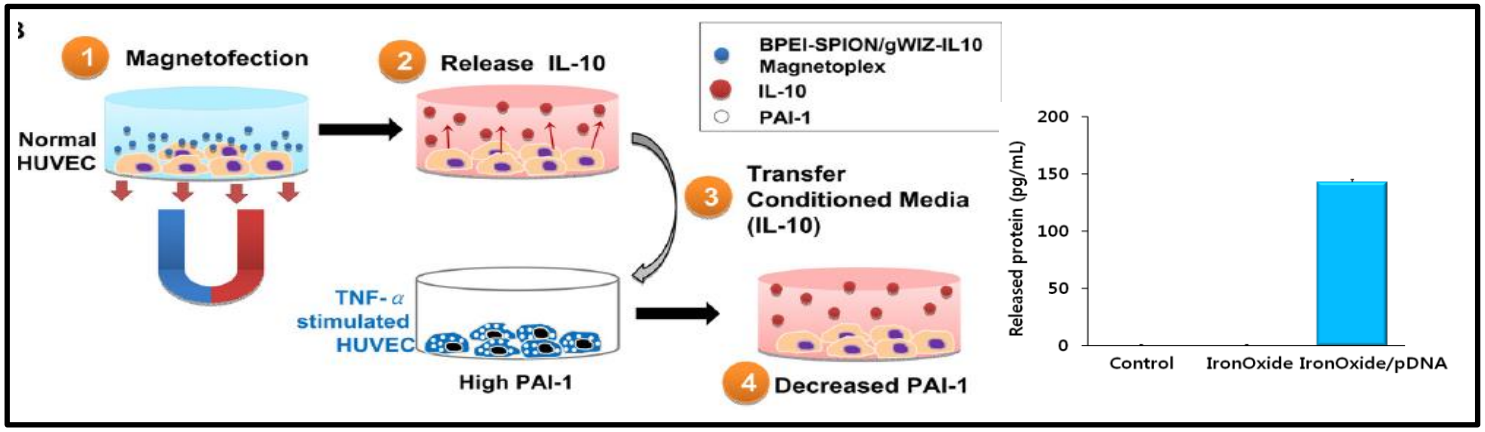
Genetic Modification

- Multi-block copolymer (MBCP)-2

  Highly efficient VEGF gene carrier to infarcted myocardium





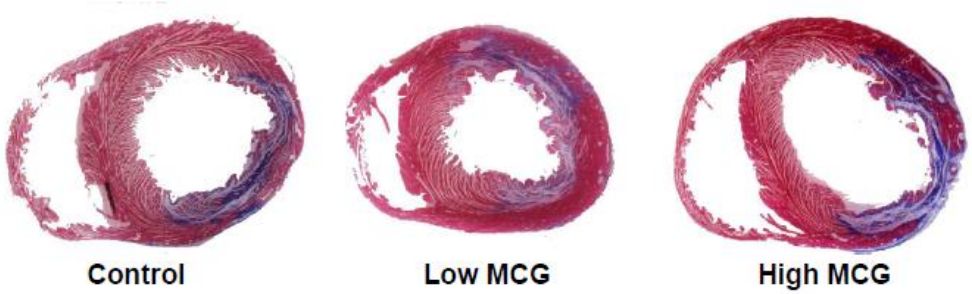


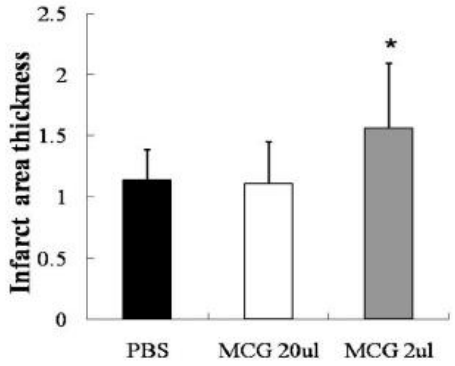
Angiogenesis
SPION
Akt

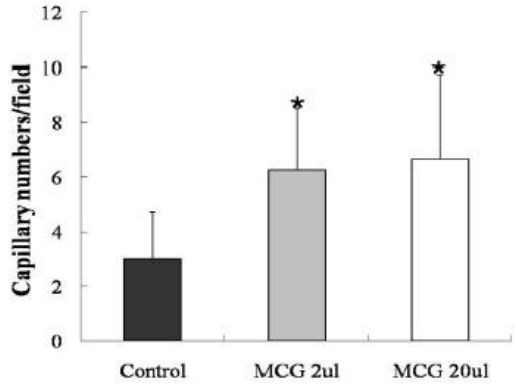
Cardiovasc Res. 2006;70:530-542
Journal of Controlled Release. 2009;138:168–176

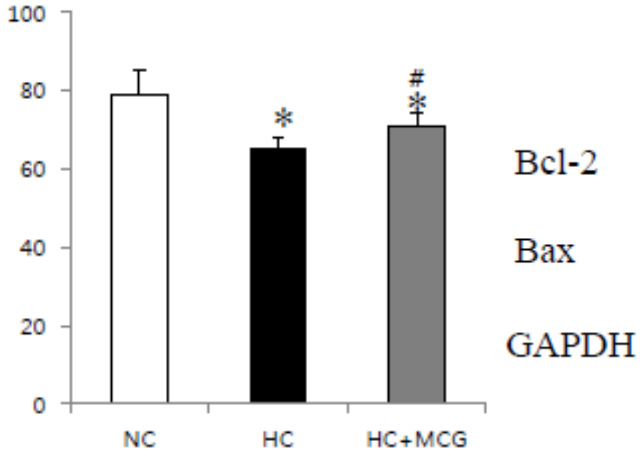
J Nanosci Nanotechnol. 2010;10:3170-4
J Nanosci Nanotechnol. 2011;11:1507-10
Biomaterials. 2010;31:4204-13

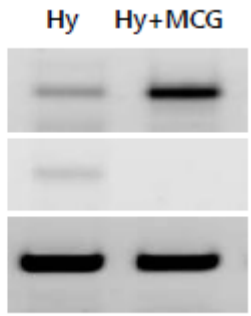
Microenvironment



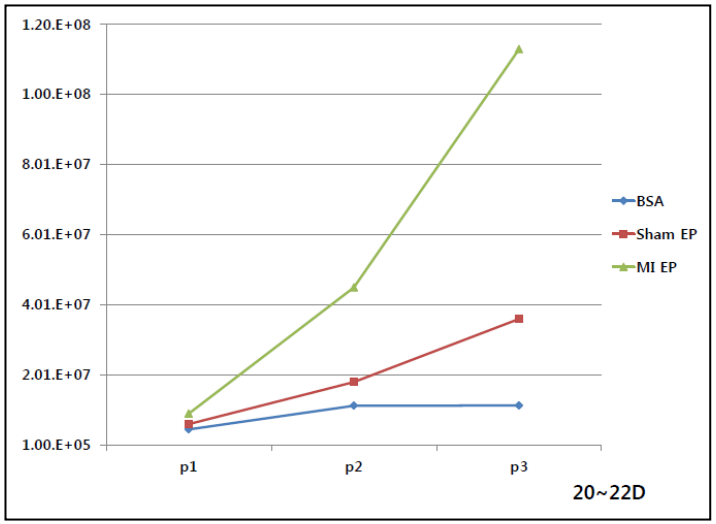




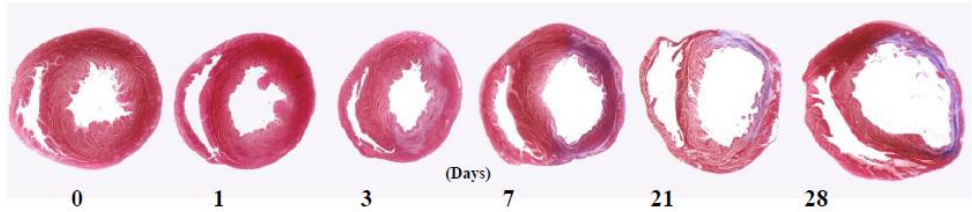


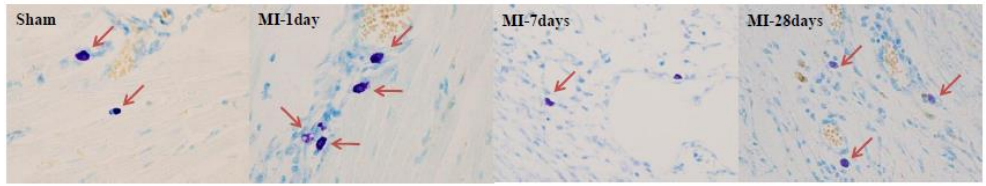


On going



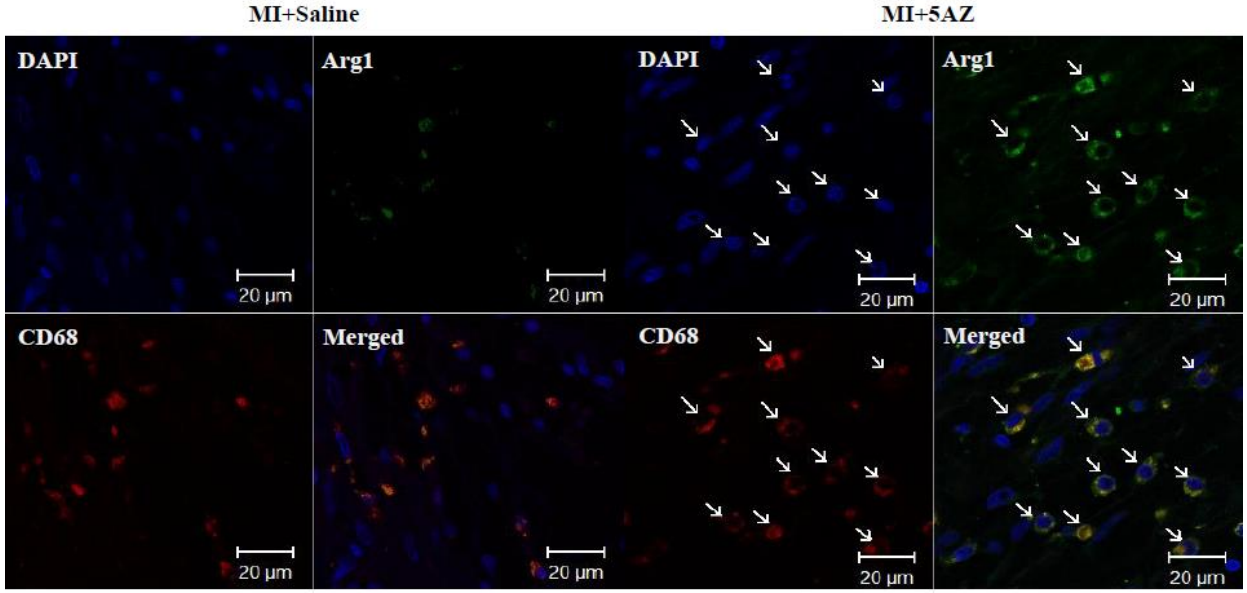
On going

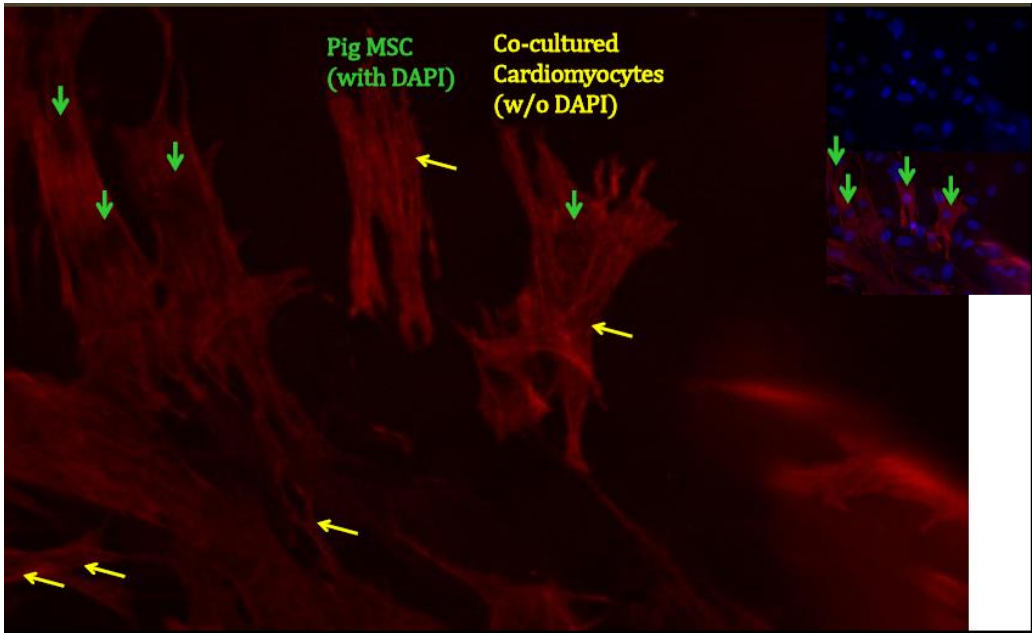


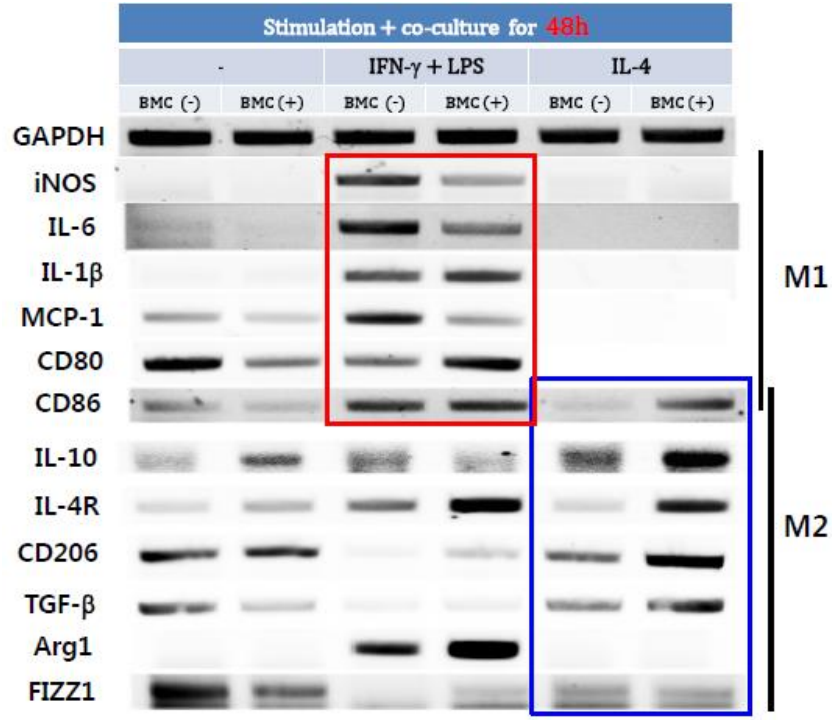


J Mol Cell Cardiol. 2011;50:814-25

Microenvironment (ongoing)





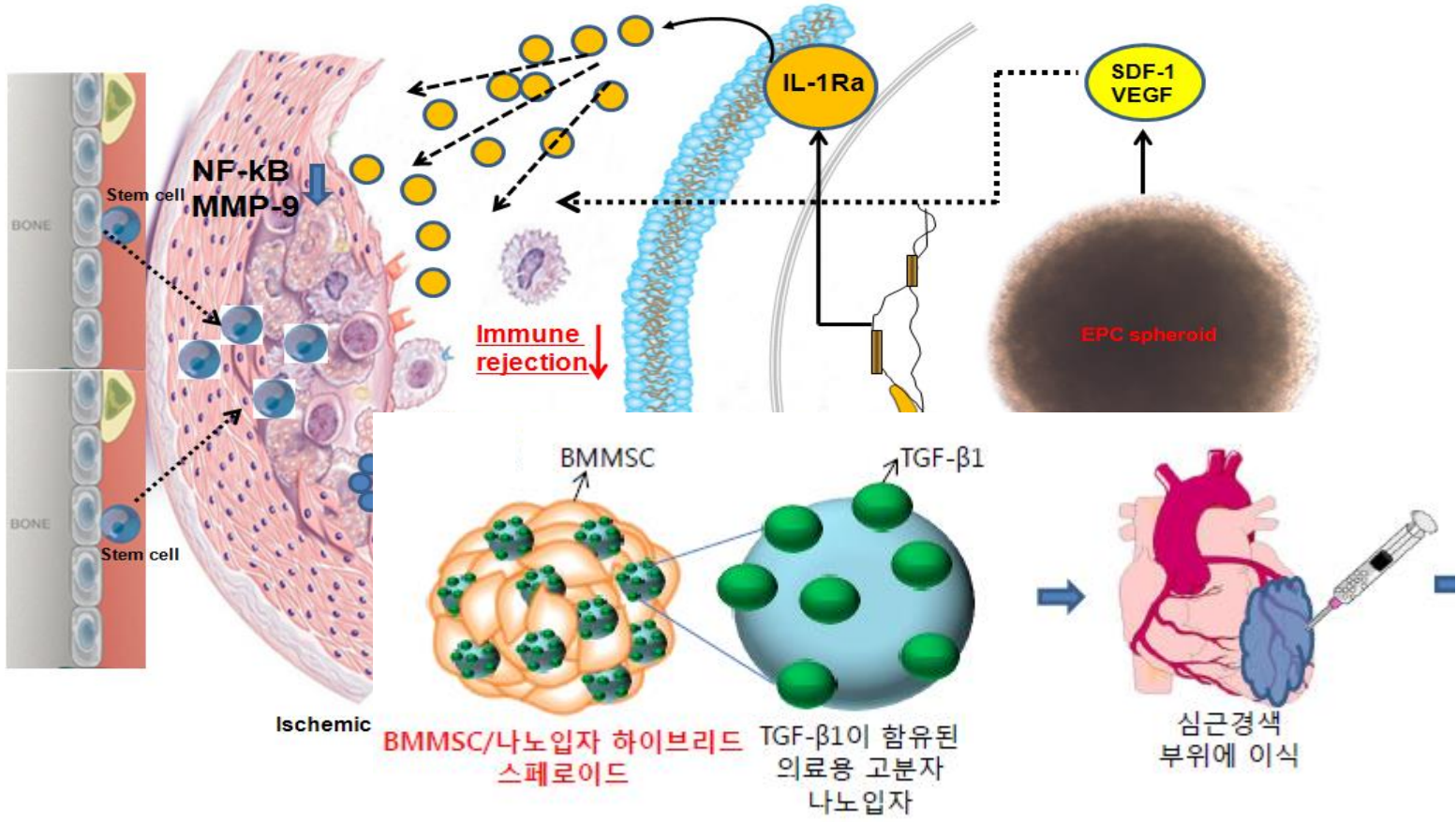


Effect of MSCs on Macrophages

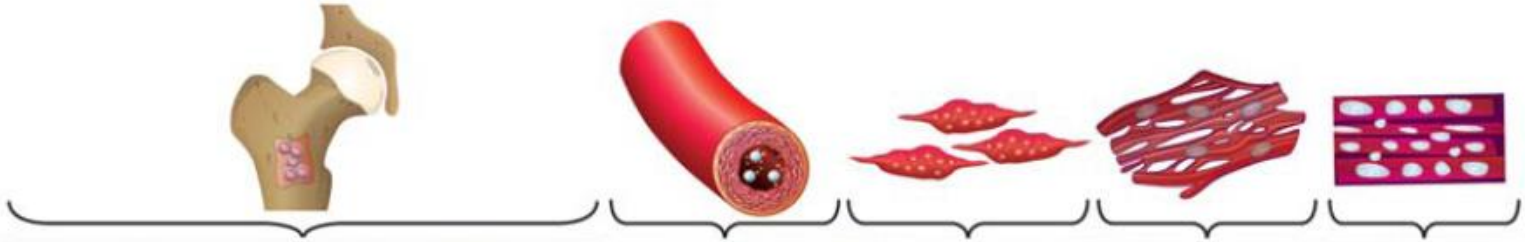
hMSC + hCMC

Optimization of Therapeutic Efficacy of Adult Stem Cells for Myocardial Infarction (supported by Korean Health Technology R&D Project, Ministry of Health & Welfare, Korea)

Priming + Spheroid



Superior Cell Population

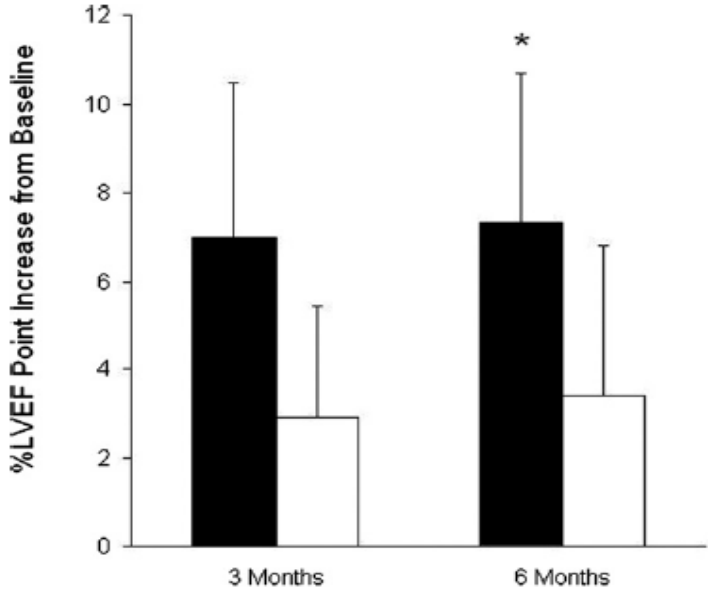


	Bone marrow-derived cells			Circulating/ mobilized stem/ progenitor cells	Mesenchymal stem cells/ adipose tissue-derived stem cells	Resident cardiac stem cells (cardiospheres)	Skeletal myoblasts
	Unselected	CD133+	CD34+				
Completed trials	ASTAMI Boost Cao *et al.* FINCELL HEBE Jannsen *et al.* MYSTAR Ramshorst *et al.* Repair-AMI	Bartunek *et al.*	Regent	ACT34-CMI TOPCARE-AMI TOPCARE-CHD	Hare *et al.*	n/a	MAGIC
Ongoing trials	Boost-2 SWISS-AMI TIME/Late TIME Cellwave REGENERATE-IHD FOCUS ... and others	SELECT-AMI Cardio-133		ENACT-AMI MAGIC Cell 5	PROMETHEUS C-Cure Prochymal® TAC-HFT Kastrup *et al.* APOLLO PRECISE ... and others	CADUCEUS SCIPIO	MARVEL

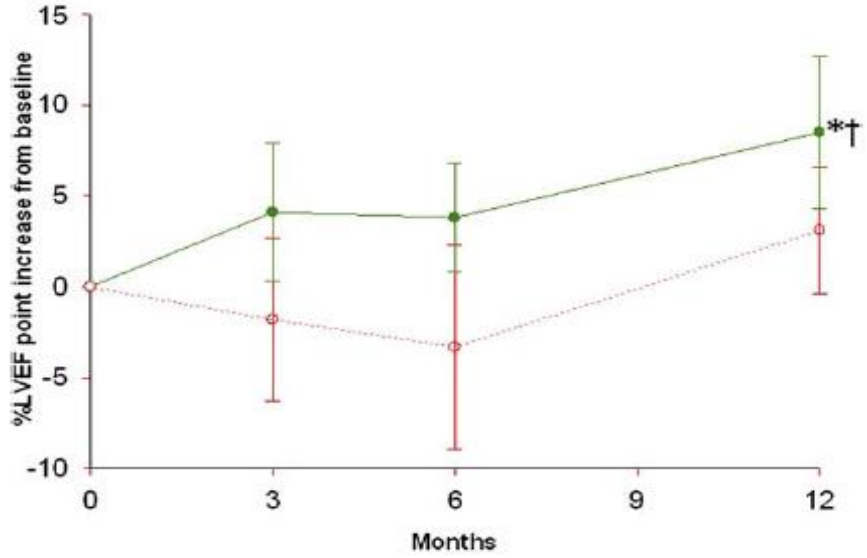
Compact bone cell

A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study of Intravenous Adult Human Mesenchymal Stem Cells (Prochymal) After Acute Myocardial Infarction

Increase From Baseline Values in % LVEF (≤60% and ≥30%) at 3 and 6 Months Post-Treatment in 53 Patients With Anterior MI



Impact of allogeneic hMSC Treatment on LVEF Evaluated by Cardiac MRI



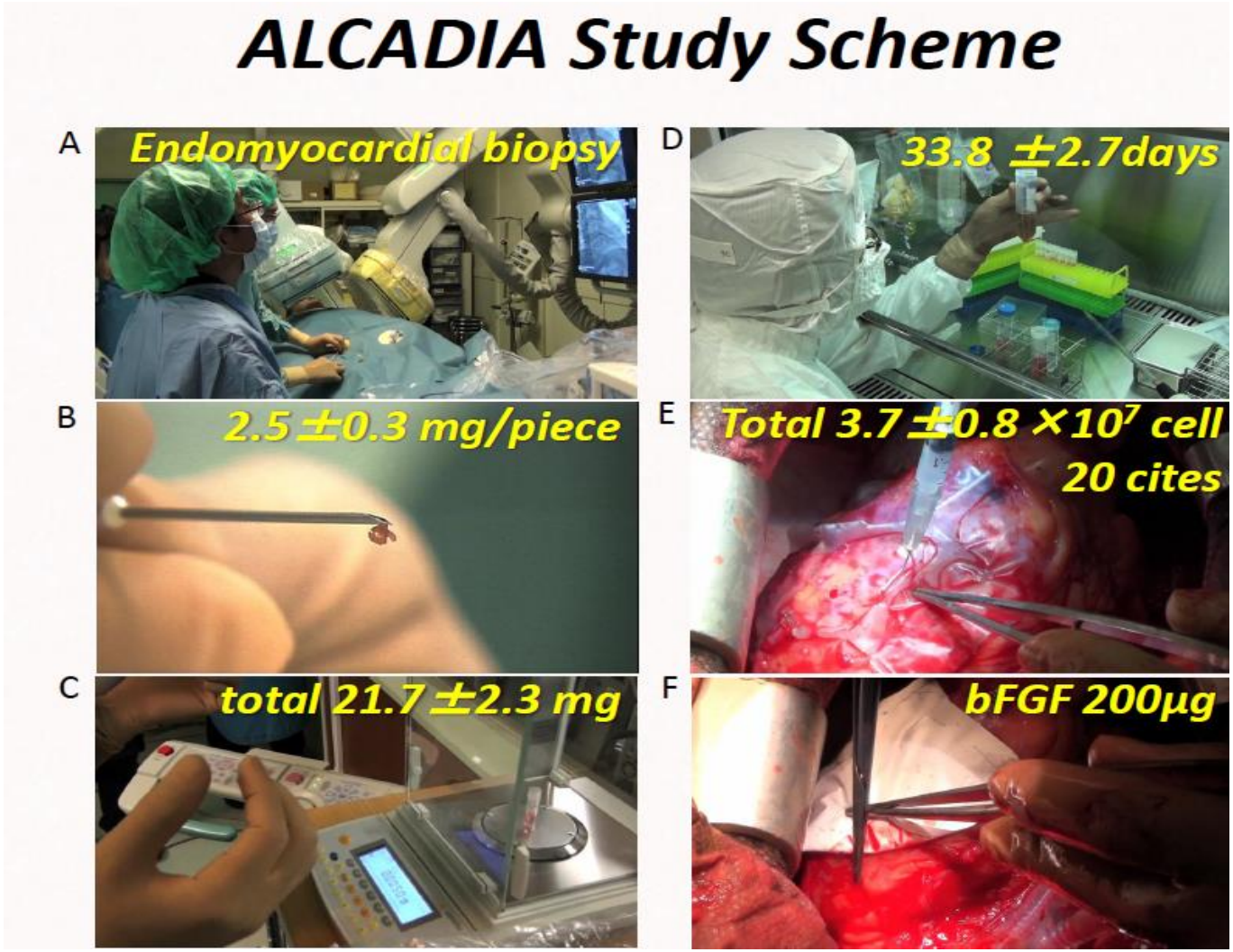
J Am Coll Cardiol. 2009;54:2277-86

Cardiac SCs (1)

The ALCADIA (AutoLogous Human CArdiac-Derived Stem Cell To Treat Ischemic cArdiomyopathy) Trial

EF ≧15% and ≦35%

ALCADIA Study Scheme



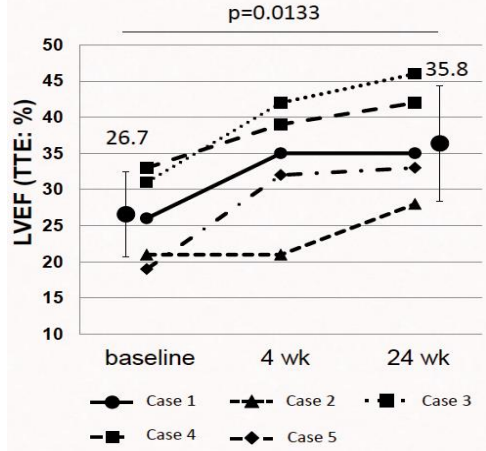
Interim Results : Safety of ALCADIA

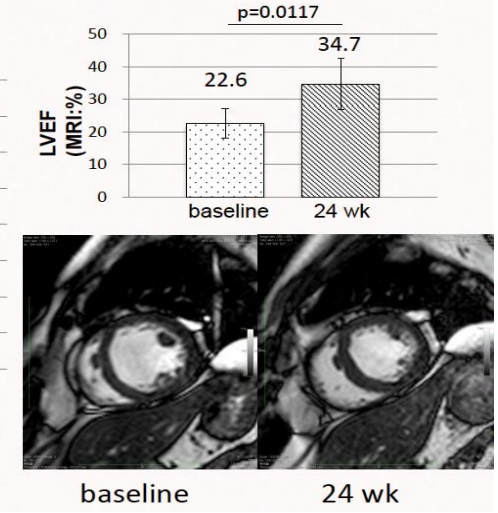
	ALCADIA
Serious Adverse event(SAE)	1/5
• Adverse event	0
• MACE (6Mo)	1
VT/Vf	0
Congestive Heart Failure	1
Tumor	0
Death	0

- No complication of right ventricular biopsy
- 1 graft occlusion within 3 weeks after cardiac bypass surgery (case 6)

Results: Efficacy of ALCADIA

~ Restore the loss of LV function ~

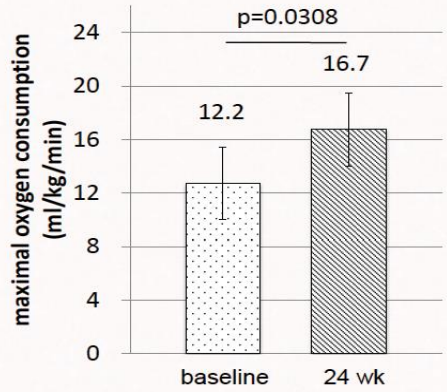


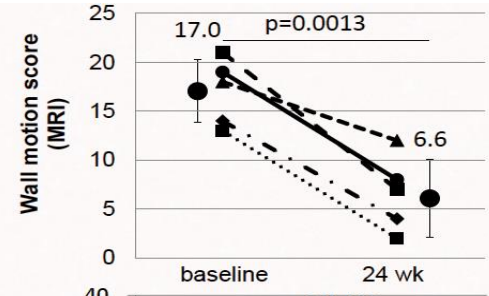


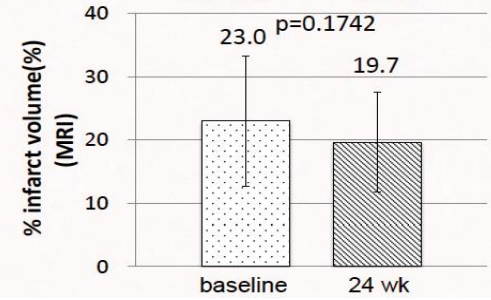
Results : Efficacy of ALCADIA

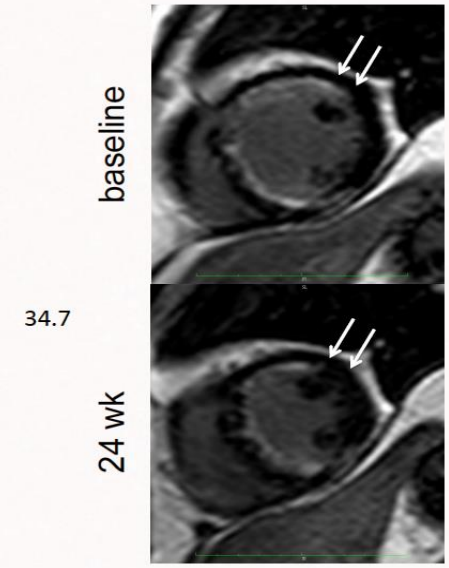
~ improve the symptom of heart failure and the exercise capacity ~

24 wk \ baseline		NYHA classification III	NYHA classification IV
NYHA classification	I	1	1
	II	1	2
	III	0	0
	IV	0	0





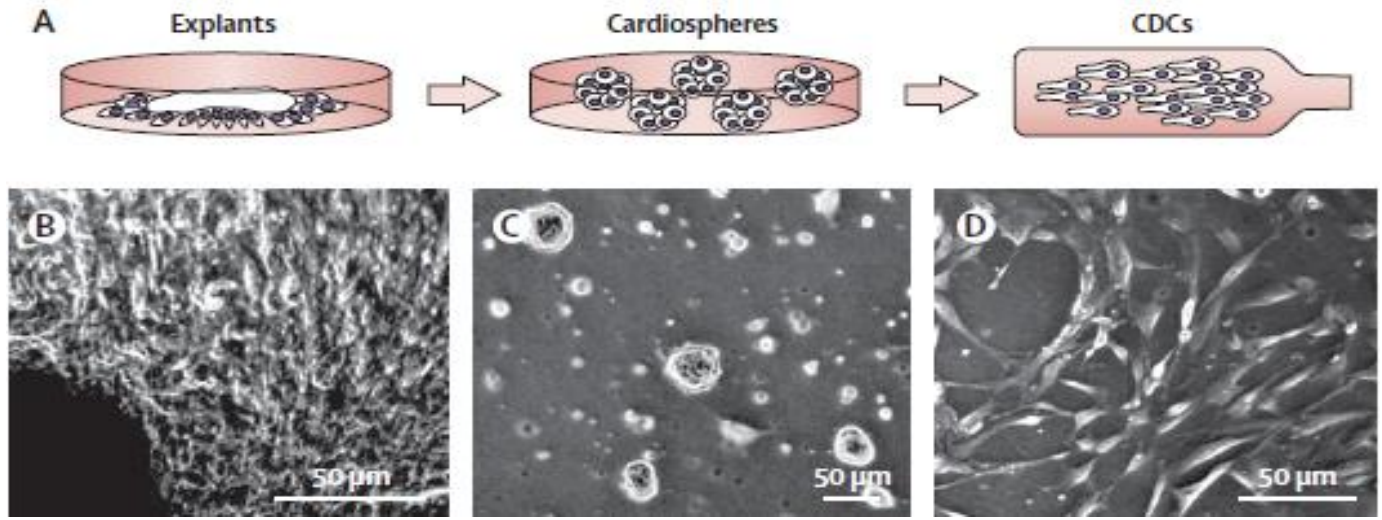




Cardiac SCs (2)

Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial

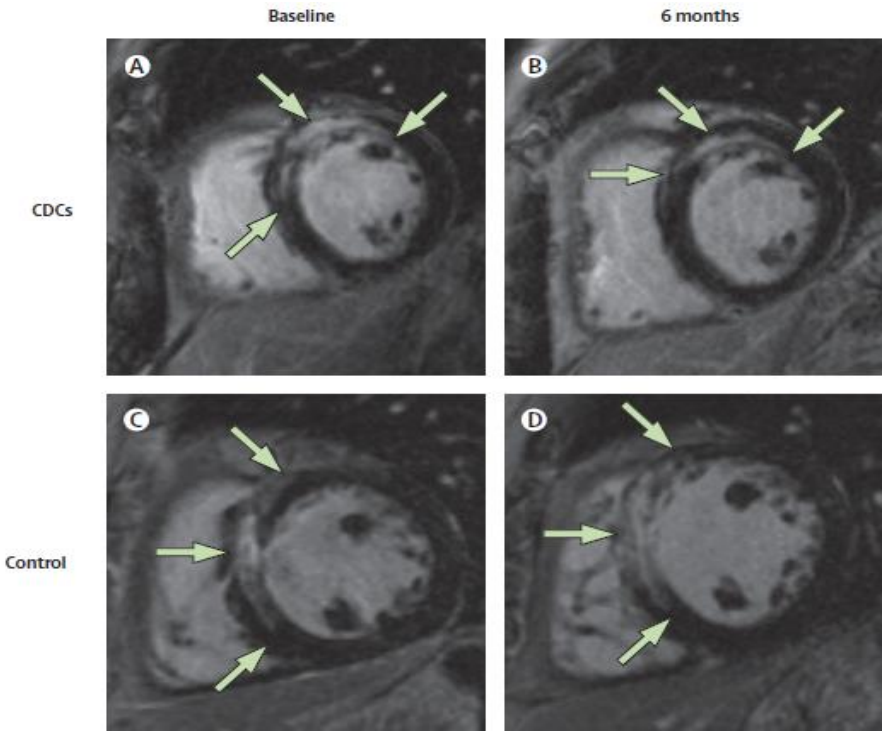
Raj R Makkar, Rachel R Smith, Ke Cheng, Konstantinos Malliaras, Louise E J Thomson, Daniel Berman, Lawrence S C Czer, Linda Marbán, Adam Mendizabal, Peter V Johnston, Stuart D Russell, Karl H Schuleri, Albert C Lardo, Gary Gerstenblith, Eduardo Marbán



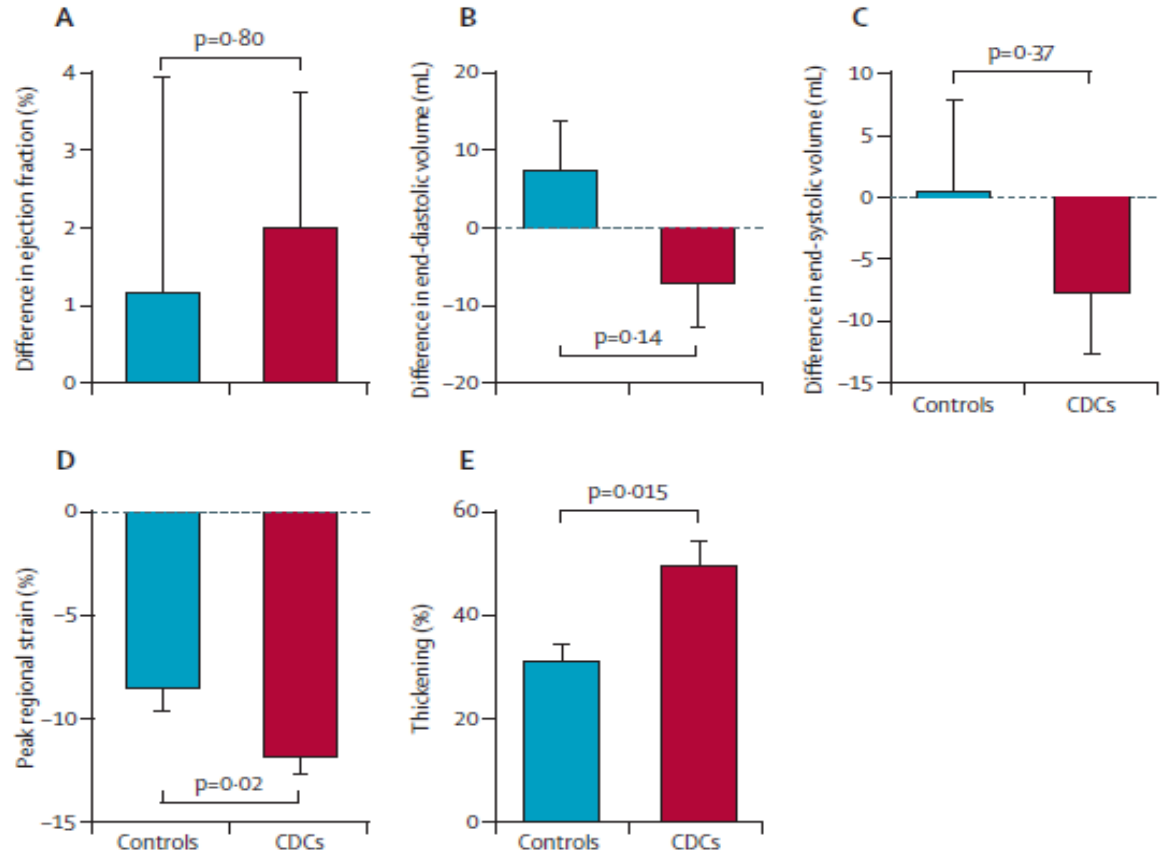
25 patients 2-4 weeks after MI (with LVEF of 25-45%), EMB

Lancet. 2012;379:895-904

Representative MR



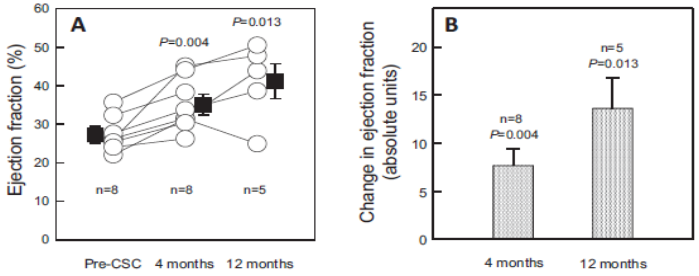
Global function, chamber volumes, and regional function in participants in the CADUCEUS study

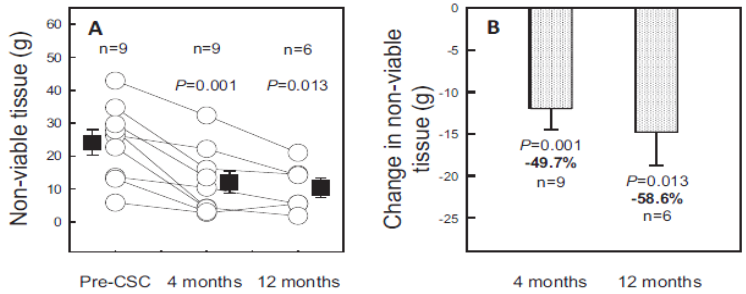


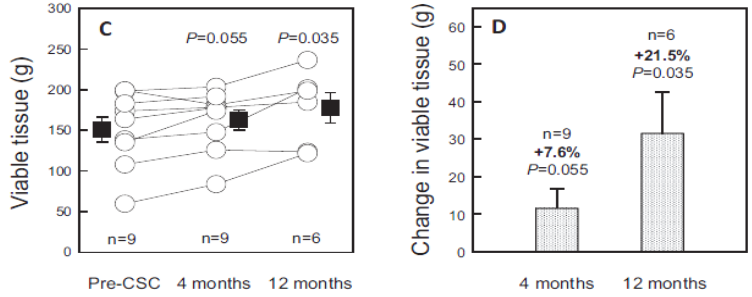
Cardiac SCs (3)

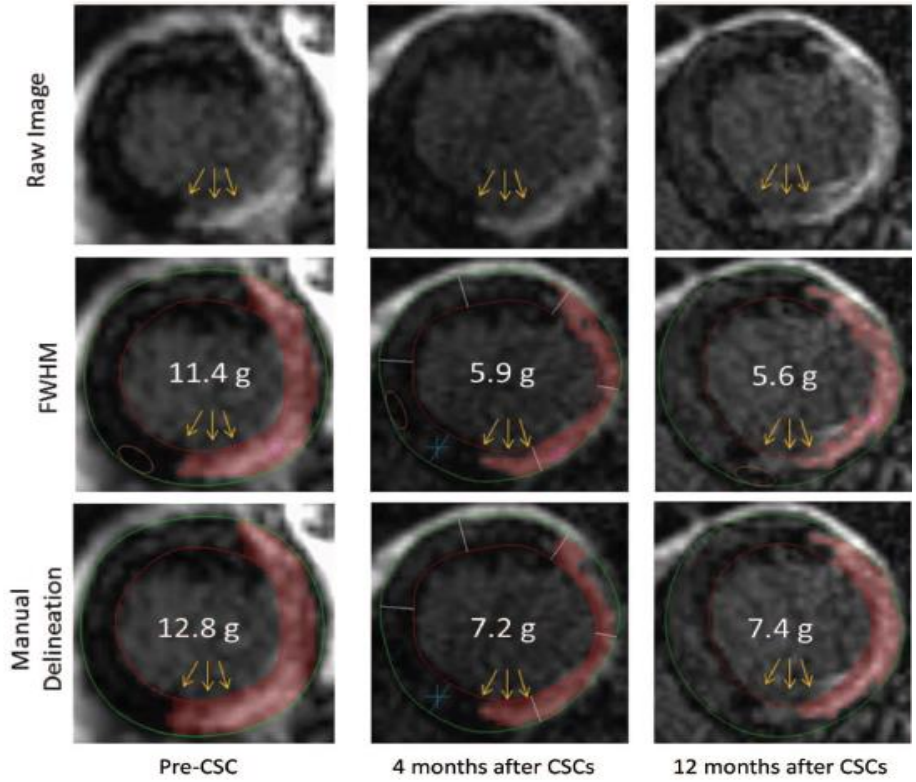
Administration of Cardiac Stem Cells in Patients With Ischemic Cardiomyopathy: The SCIPIO Trial

Surgical Aspects and Interim Analysis of Myocardial Function and Viability by Magnetic Resonance





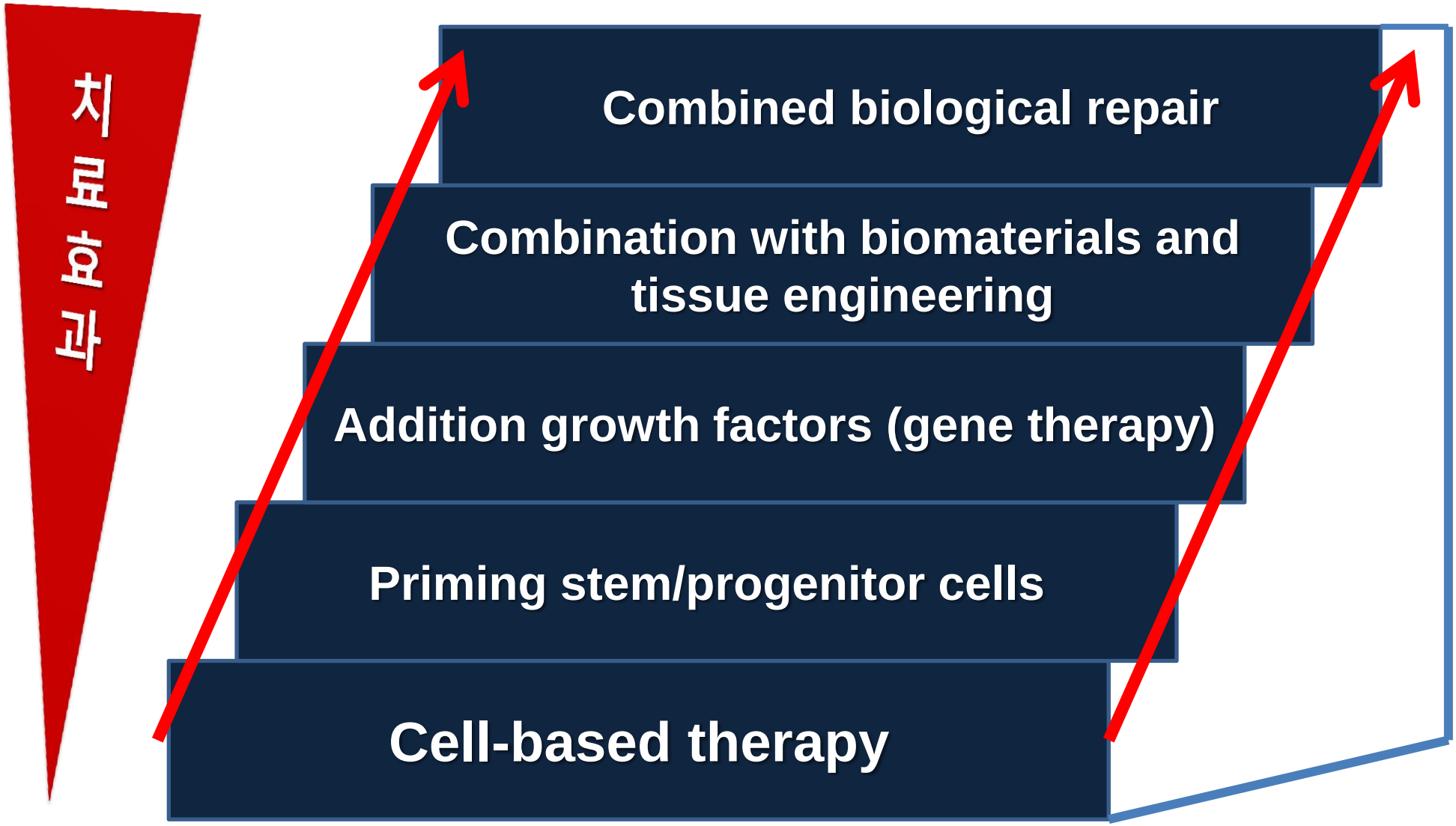




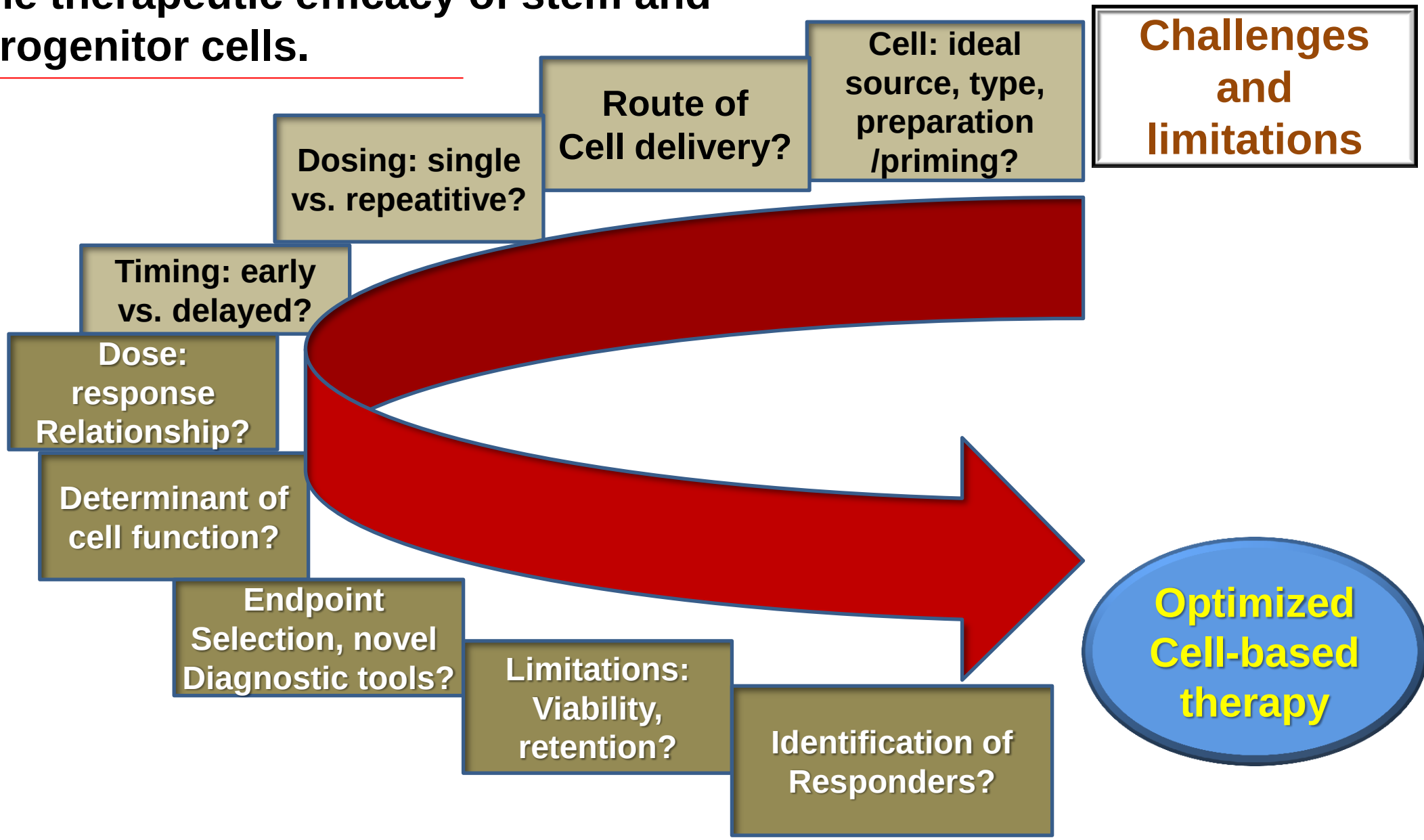
LVEF <40%, 33 patients, CSC from RAA, IC injection

Circulation. 2012;126:S54-64

Combined strategies of biological cardiac repair



Open questions for the optimization of the therapeutic efficacy of stem and progenitor cells.



Conclusion

We are challenged to show robust effects on disease progression, morbidity, and mortality associated with an acceptable safety profile to advance the promising concept of cell-based therapy to clinical routine.


경청해 주셔서 감사합니다.