Chonnam Nat. Univ. Hosp.

Stem Cell Therapy in AMI

The optimal delivery strategy for stem cells

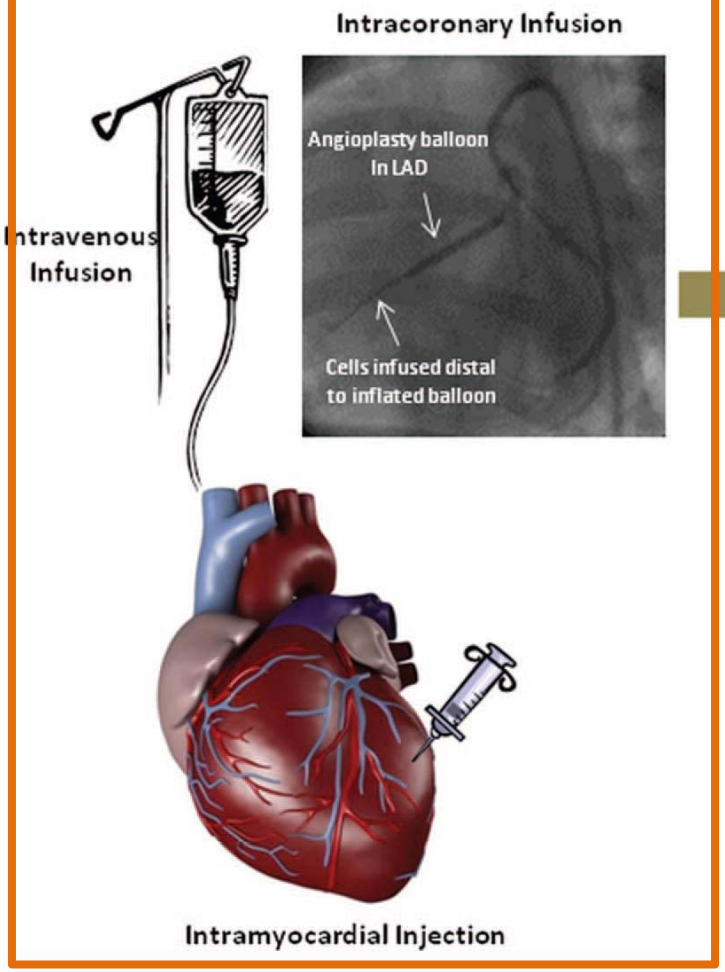
전남의대

안영근

Cardiac Regeneration : Stem Cell Therapy

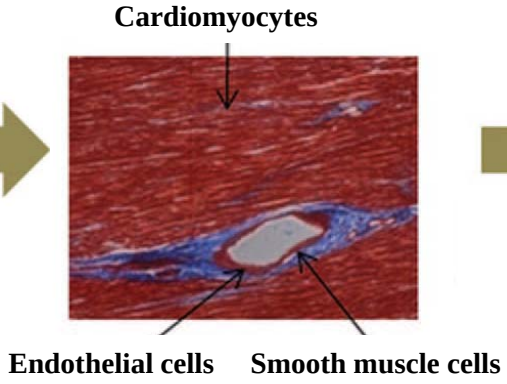
Potentially reparing myocardium

Delivery of MSCs



Mechanisms of action

- Engraftment and differentiation



- Angiogenesis
- Paracrine signaling
- Anti-inflammatory effects
- Activate endogenous cardiac stem cells

Functional and Structural Effects

- Reverse remodeling in chronic ischemic CMP
- Prevention of remodeling after AMI
- Scar size reduction
- Increase tissue perfusion
- Improved regional contractility
- Increased ejection fraction

Adam R, et al. *Circ Res. 2011;109:9923 –940*

Emerging Issues

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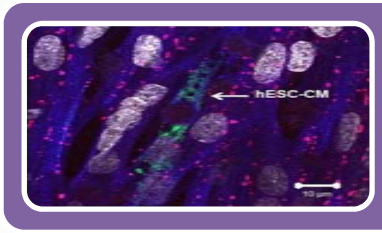
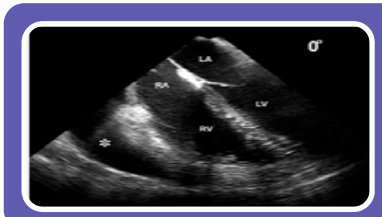
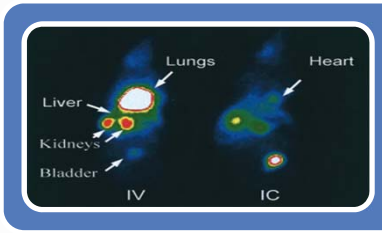


Engraftment



Procedural safety



Extracardiac retention of stem cells

Improvement of heart function

Which Route is Most Effective?

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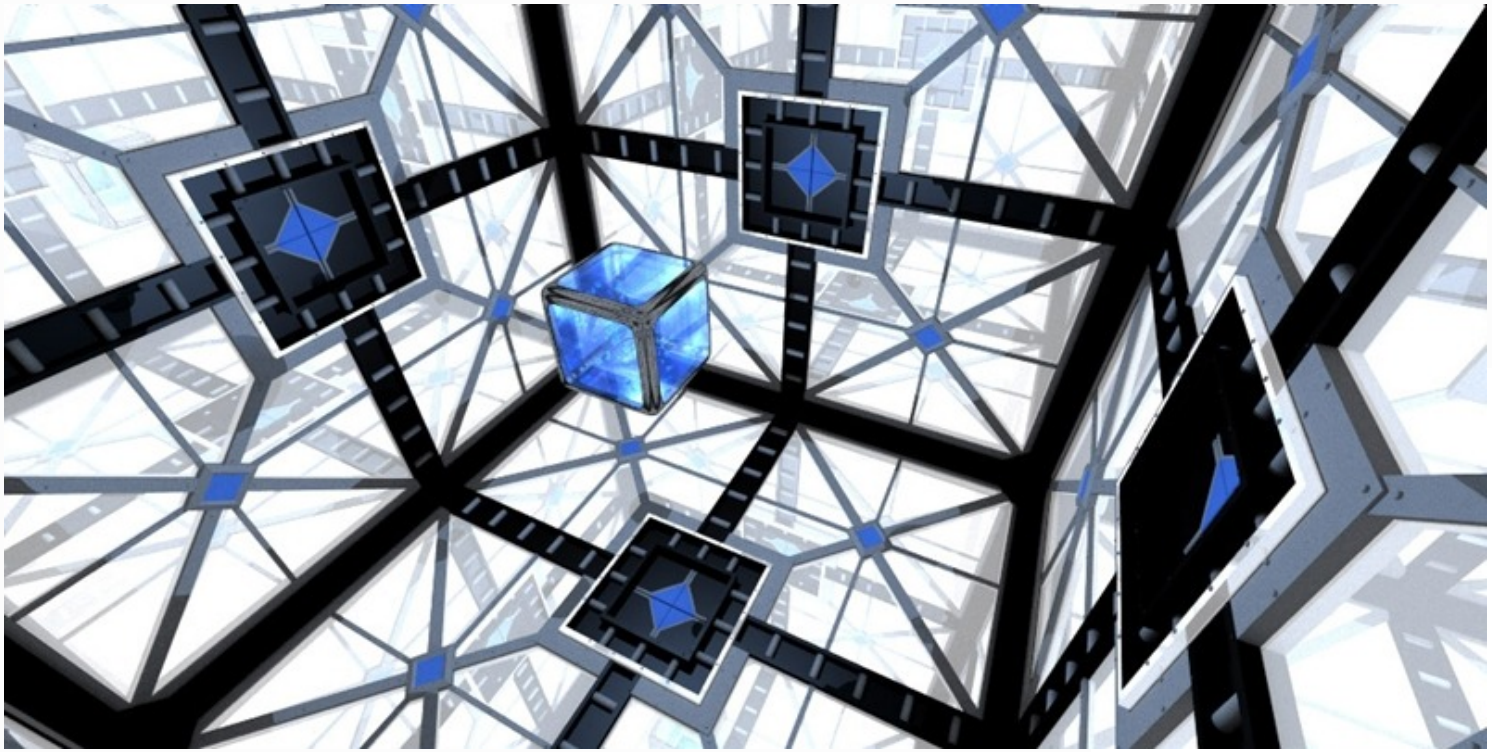
Methods of delivery will affect the outcome of stem cell therapies, perhaps significantly.



Injection Timing

Front Biosci. 2009 Jan 1;14:2845-56.

TNF-alpha enhances engraftment of mesenchymal stem cells into infarcted myocardium.

Kim YS, Park HJ, Hong MH, Kang PM, Morgan JP, Jeong MH, Cho JG, Park JC, Ahn Y.

Source

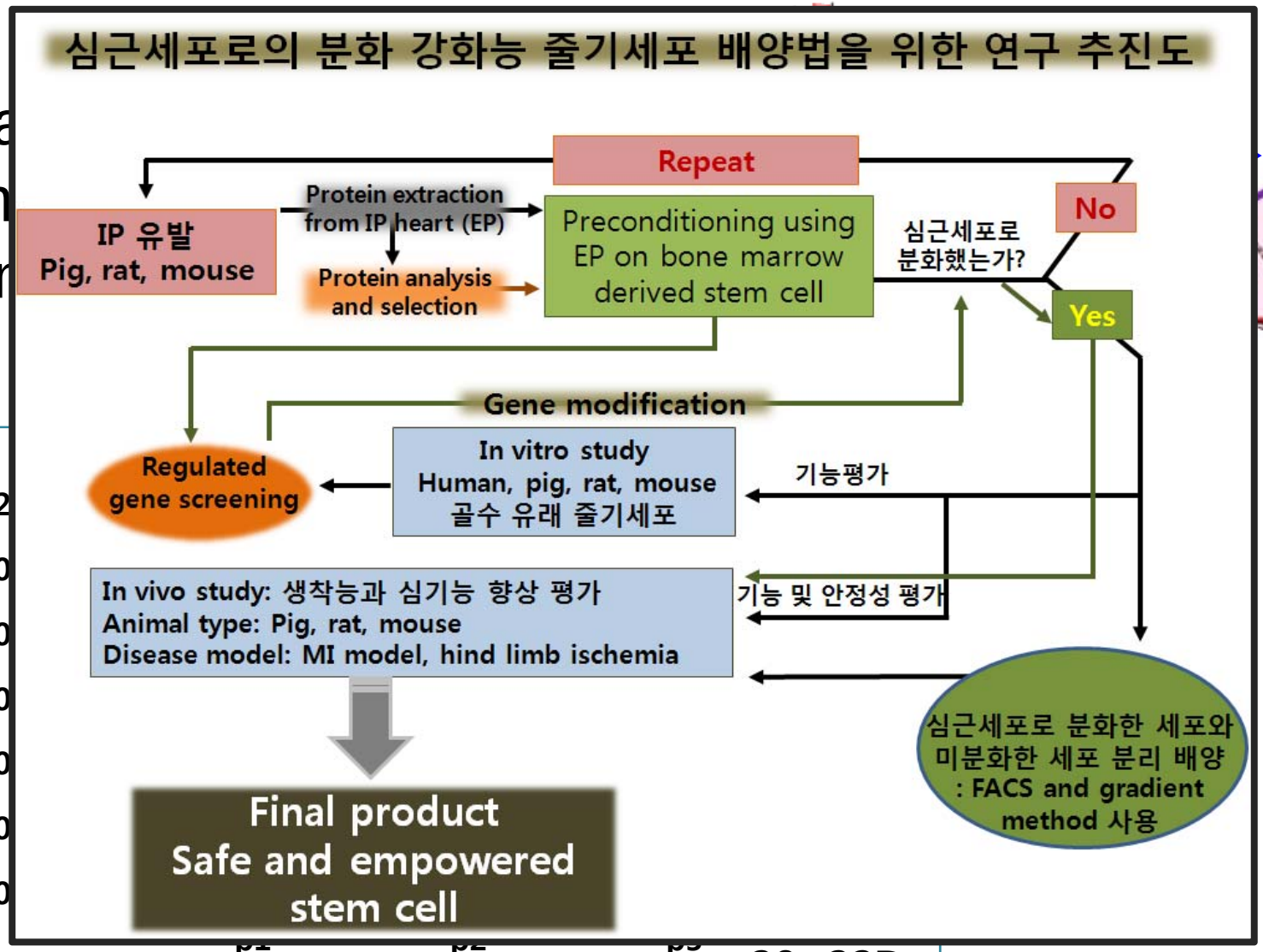
Cardiovascular Research Institute, Chonnam National University, Gwangju, South Korea

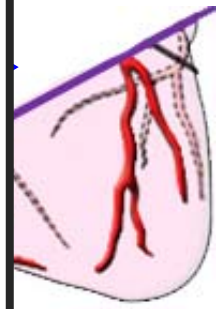
Between days 3 and 7 after AMI

B) by TNF-alpha", up-regulates the expression of molecules which are involved in inflammation and cell adhesion. For these reasons, we assessed the extent that treatment of MSC with tumor necrosis factor (TNF)-alpha modifies the characteristics of MSC, important to their engraftment in experimental myocardial infarct. Here, we show that pre-treatment of MSC prior to transplantation with tumor necrosis factor (TNF)-alpha increases adhesiveness, and migration of MSC in vitro and leads to increased expression of bone morphogenetic protein (BMP)-2 by MSC. Moreover, this treatment increases the rate of engraftment of MSC and improves recovery of cardiac function after myocardial infarction. These insights might provide better strategies for the treatment of myocardial infarction.

Enhancement of Proliferation Activity

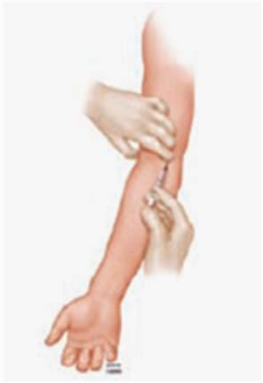
LAD
- Tota
- 5 m
- 4 tir



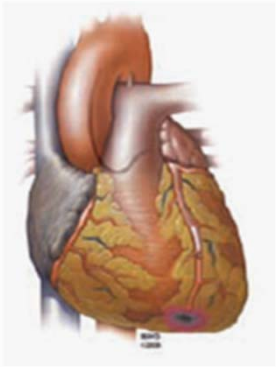


Stem Cells can be Delivered to the Heart

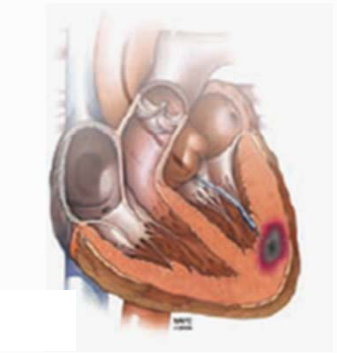
Intravenous



Intracoronary

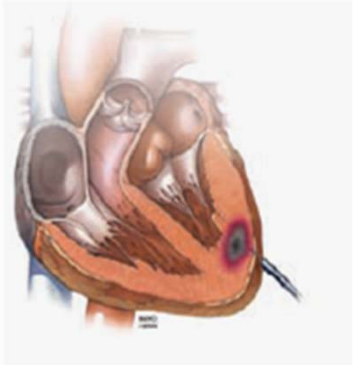


Direct endocardial

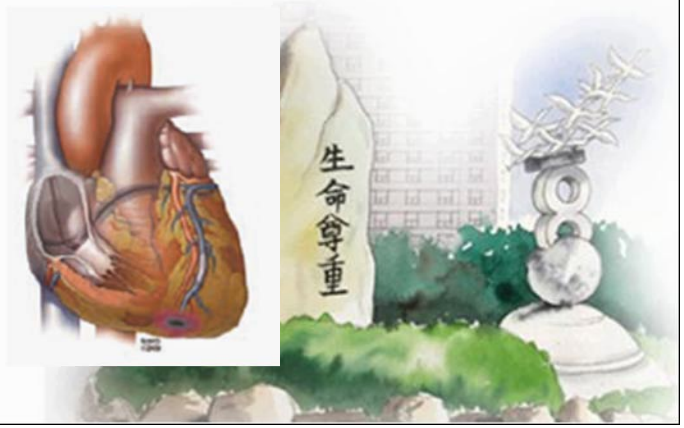


have been used in clinical trials

Direct epicardial



Coronary sinus



1. Intravenous Route

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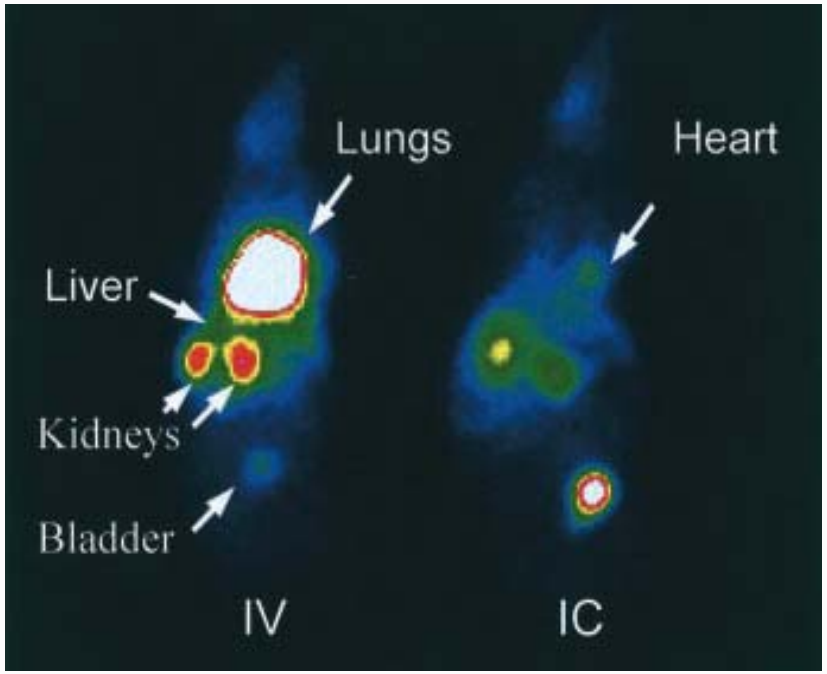
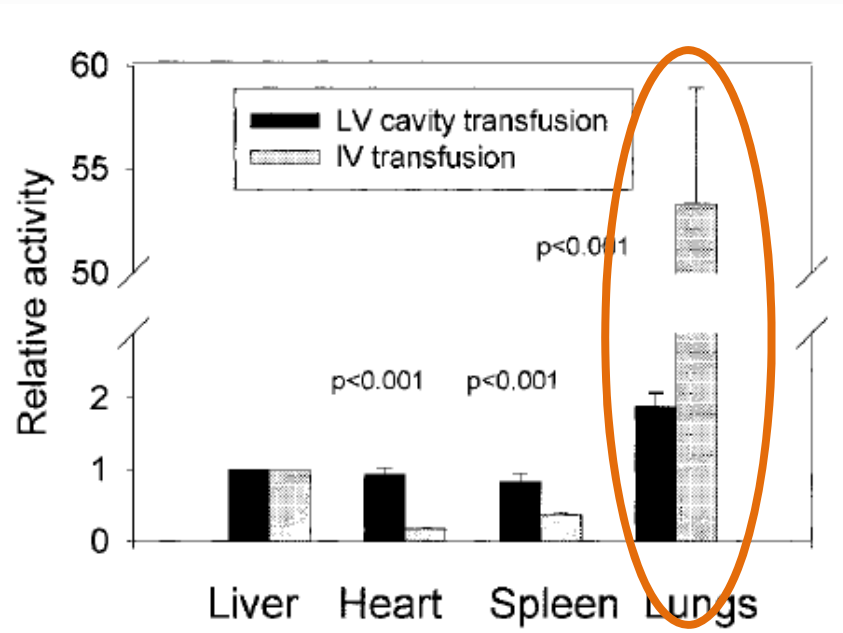
- **Advantage** : **Easiest and most practical method**
- **Disadvantage** : **Pulmonary entrapment**

BM-MSC 10 to 14 days after MI (Rat)





IV infusion **LV cavity infusion**

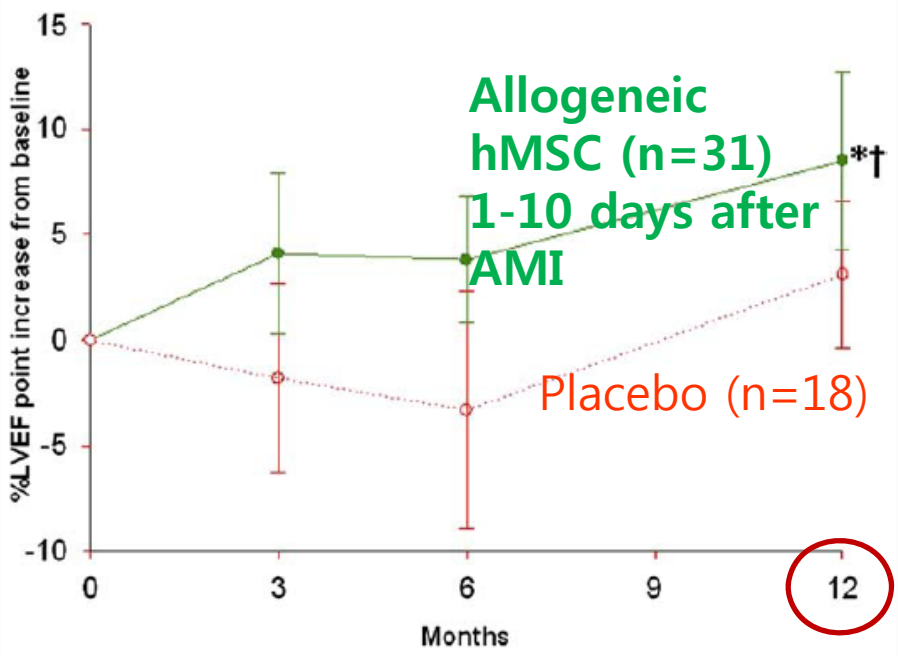
Barbash IM, et al. Circulation. 2003;108:863– 868.

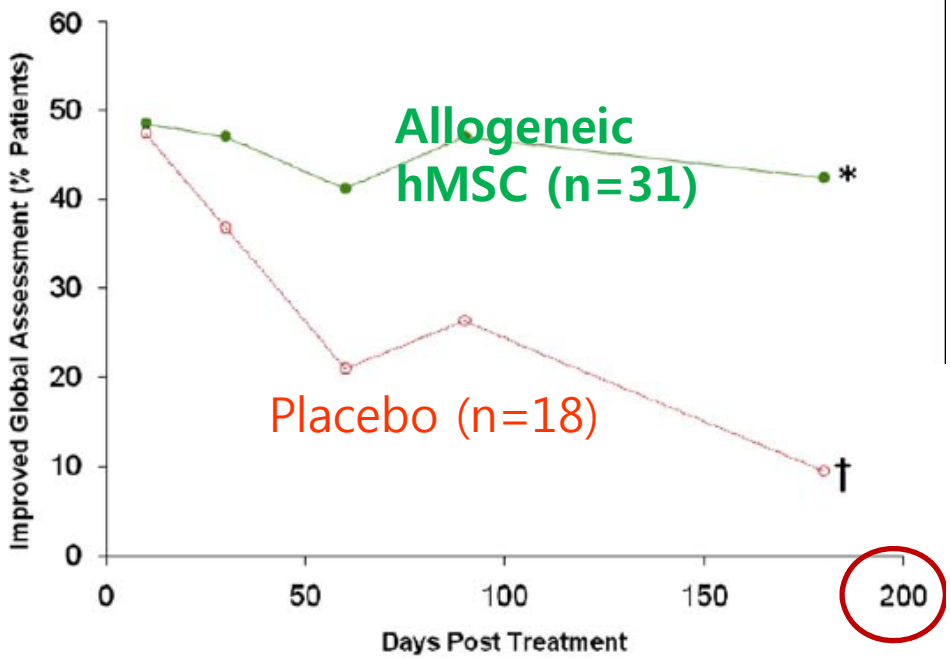
1. Intravenous Route

전남대학교병원

CLINICAL RESEARCH — Clinical Trials

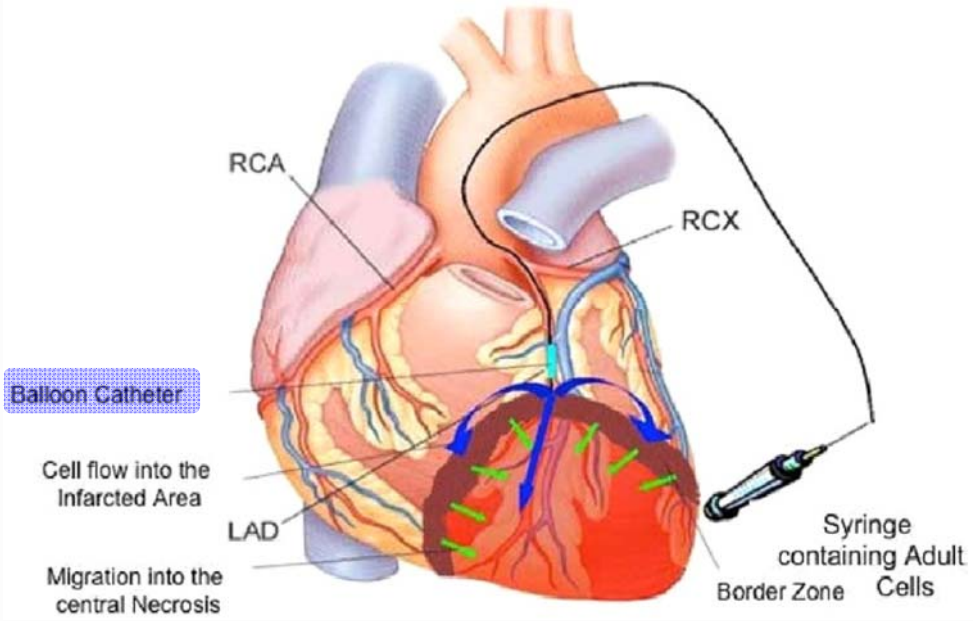
A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study of Intravenous Adult Human Mesenchymal Stem Cells (Prochymal) After Acute Myocardial Infarction

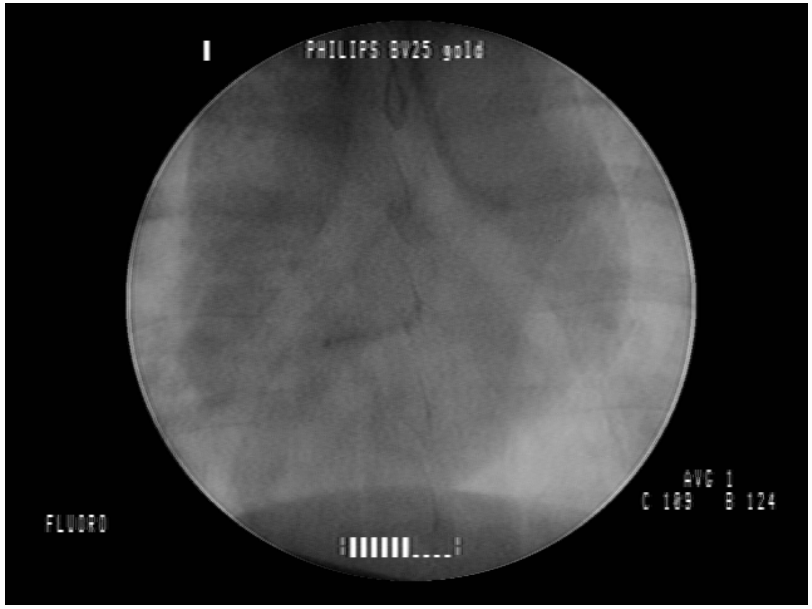




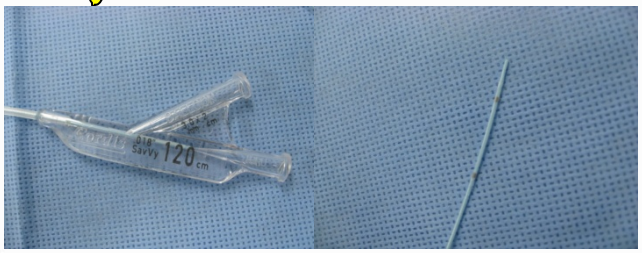
Hare JM, et al. J Am Coll Cardiol. 2009;54:2277– 86

2. Intracoronary Route





Over the wire balloon

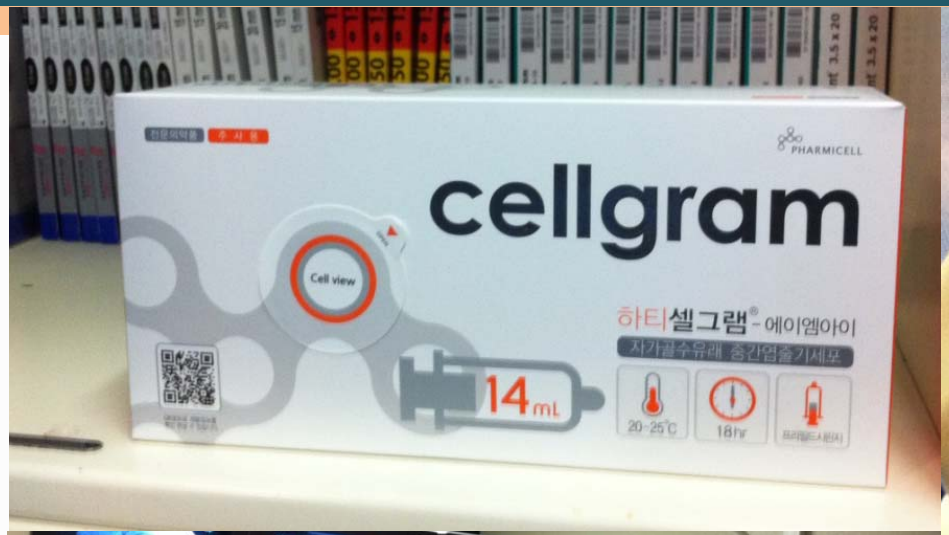


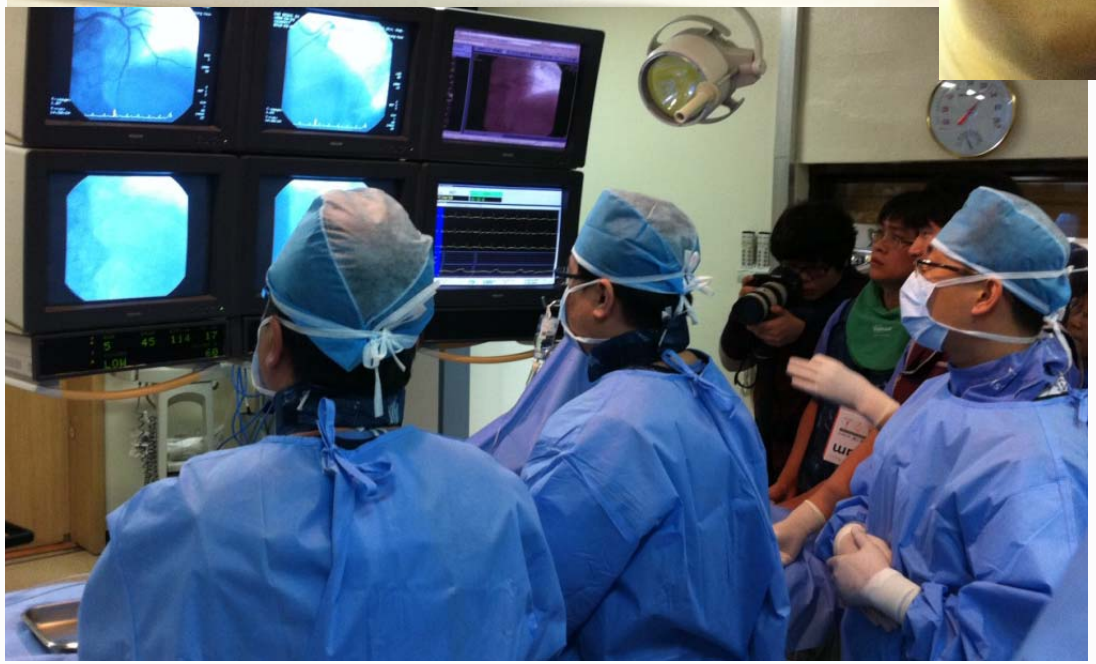
Connect to infusion pump
"Stem cell infusion"

Connect to inflator

Nabil Dib, et al. J Am Coll Cardiol Intv 2010;3:265-75

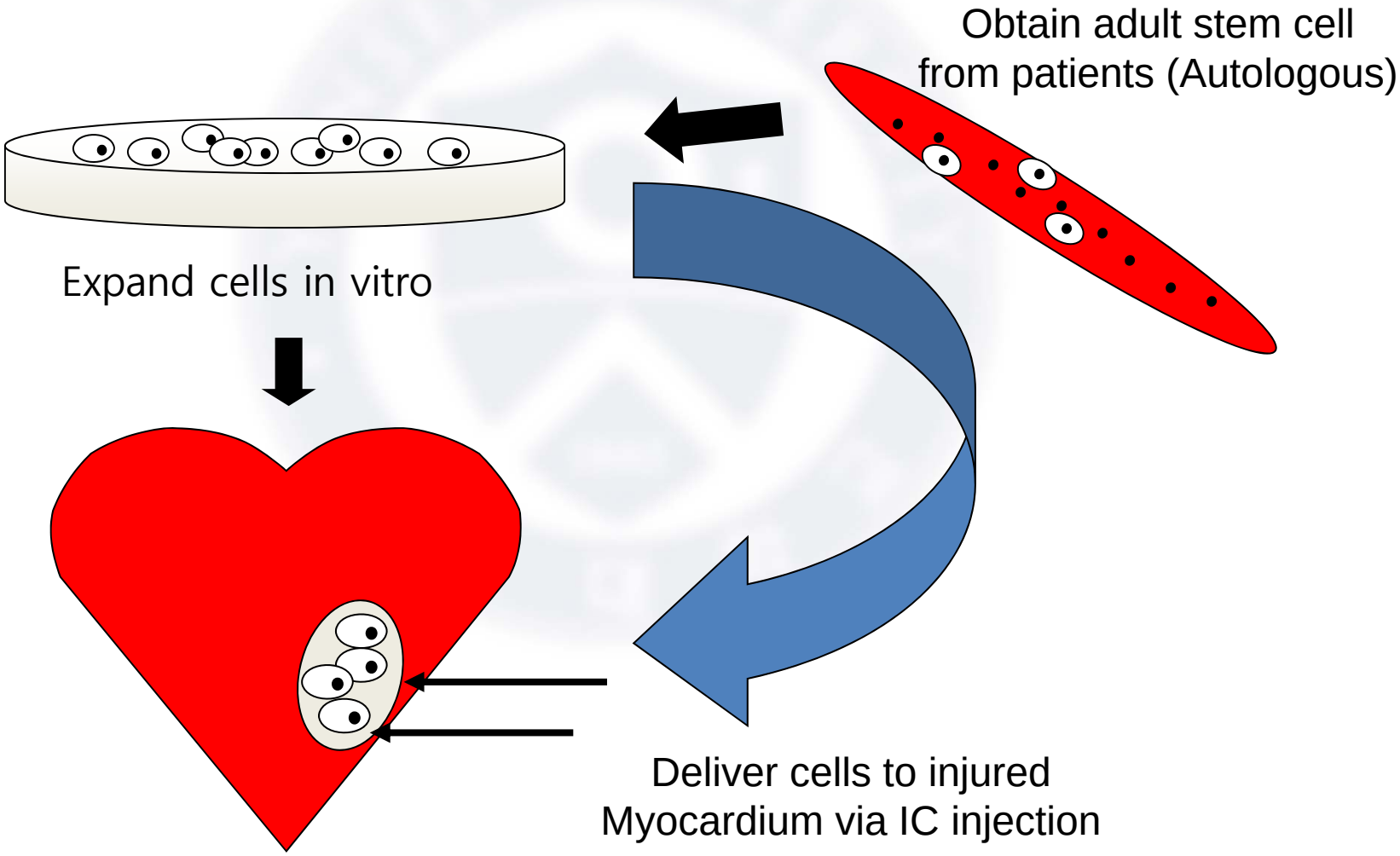
2. Intracoronary Route





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

Clinical steps of the procedure Using MSC in AMI patients



2. Intracoronary Route

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Advantages

1. Effectively deliver cells to ischemic tissue after full reperfusion therapy after AMI
2. Familiarity of angioplasty techniques to interventionist
3. Ability to deliver cells during PCI for Acute MI

Disadvantages

1. Concern about inducing ischemia during coronary artery occlusion
2. Lack of vessels in chronically
3. Occluded areas of scar tissue

Effect on Left Ventricular Function of IC transplantation of Autologous Bone Marrow MSC in Patients With AMI (PPCI <12 hr Sx onset)

Variables	BMSC Group	Control Group	p Value
Patients (n)	34	35	0.20
Functional defect (%)			
Just before BMSC implantation	32 ± 11	33 ± 10	0.20
At 3-mo follow-up	13 ± 5	28 ± 10	0.001
Infarcted area movement velocity (cm/s)			
Just before BMSC implantation	2.17 ± 1.3	2.19 ± 1.5	0.20
At 3-mo follow-up	4.2 ± 2.5	2.7 ± 1.7	0.01
Left ventricular ejection fraction (%)			
Just before BMSC implantation	49 ± 9	48 ± 10	0.20
At 3-mo follow-up	67 ± 11	53 ± 18	0.01
At 6-mo follow-up	67 ± 3	54 ± 5	0.01

Several imagining techniques demonstrated that bone marrow mesenchymal stem cells significantly improved left ventricular function.

Chen SL et al (Am J Cardiol 2004;94:92–95)

2. Intracoronary Route

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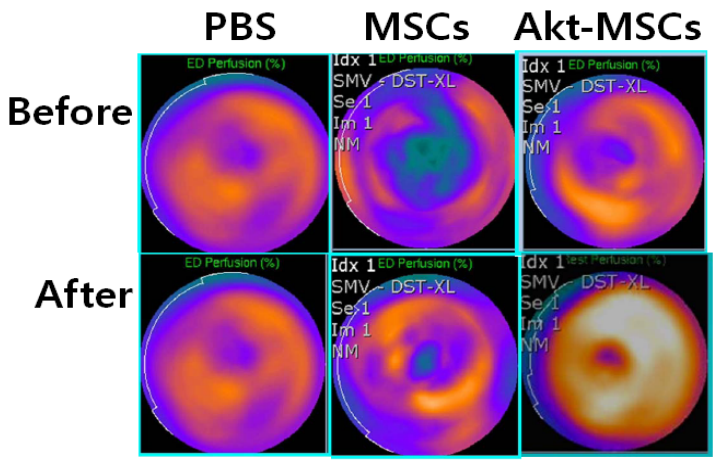
ELSEVIER

Cardiovascular Research 70 (2006) 530 – 542

Cardiovascular Research

www.elsevier.com/locate/cardiores



ells transduced with Akt in a porcine
farction model

Youngkeun Ahn [a,*], Myung Ho Jeong [a],
Kwang Il Nam [b], Jeong Gwan Cho [a],
Jong Chun Park [a]

Chonnam National University Hospital, 8 Hak Dong, Dong Ku,
57, South Korea
ional University Medical School, Gwangju, South Korea
lical Center and Harvard Medical School, Boston, USA

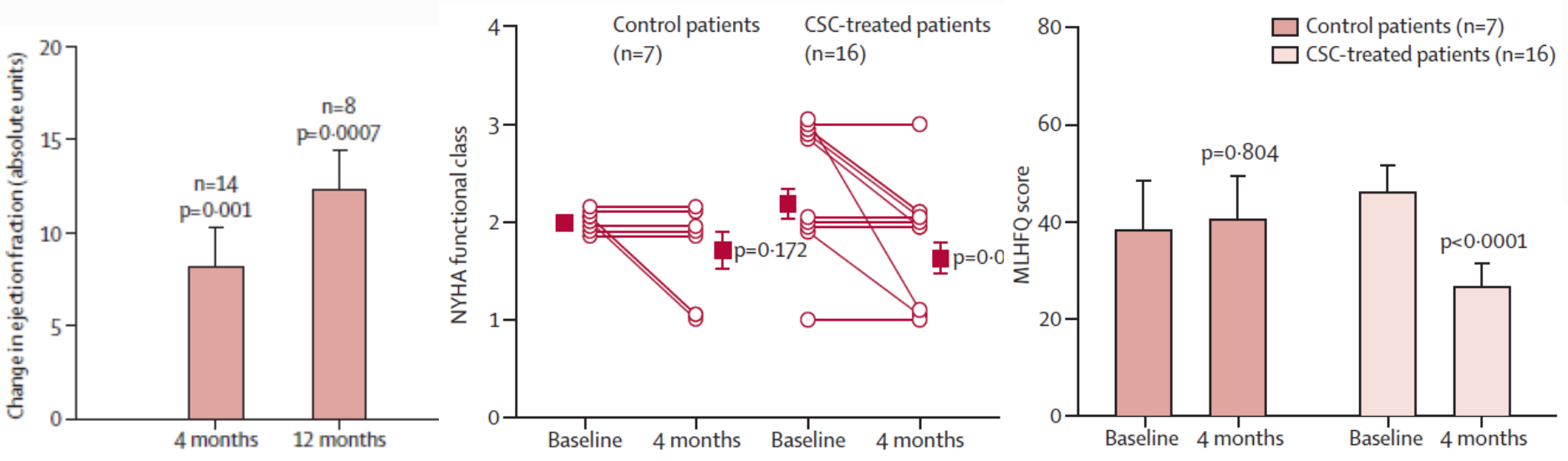
Cardiovasc Res 2006 (70:530-542)
IF 6.051 (89회 인용)

2. Intracoronary Route

전남대학교병원

Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial (EF ≤ 40%, 113 days after CABG)

Roberto Bolli, Atul R Chugh, Domenico D'Amario, John H Loughran, Marcus F Stoddard, Sohail Ikram, Garth M Beache, Stephen G Wagner, Annarosa Leri, Toru Hosoda, Fumihiro Sanada, Julius B Elmore, Polina Goichberg, Donato Cappetta, Naresh K Solankhi, Ibrahim Fahsah, D Gregg Rokosh, Mark S Slaughter, Jan Kajstura, Piero Anversa



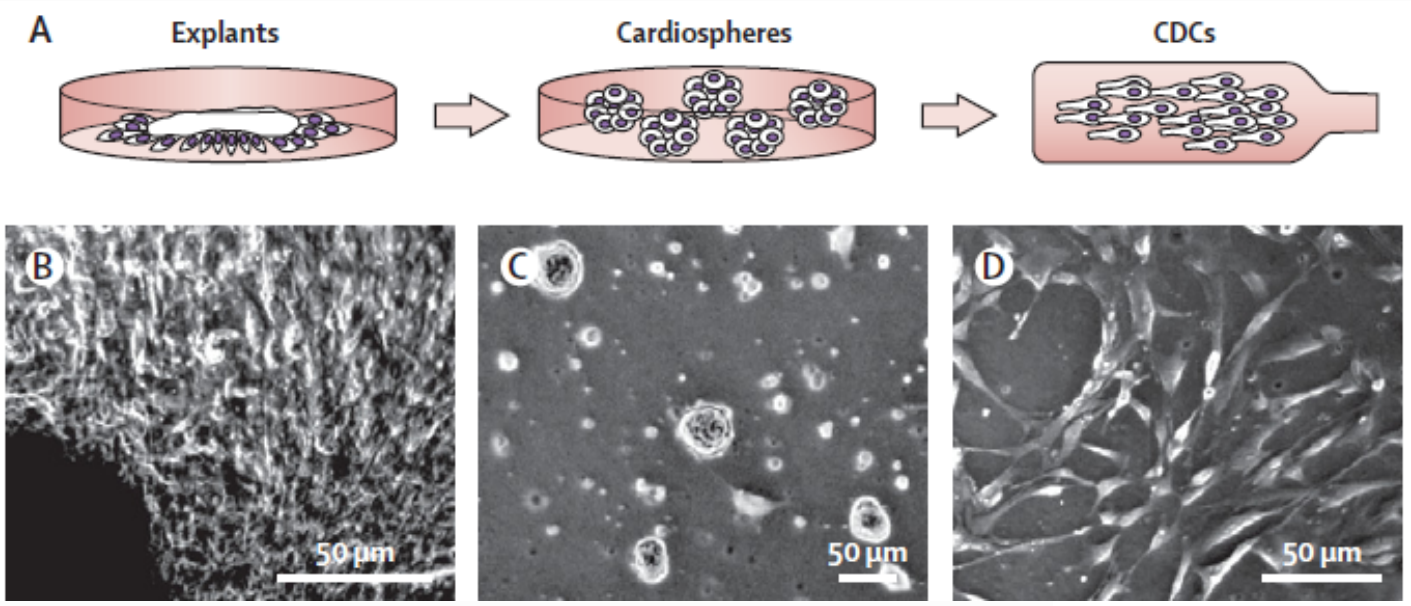
Bolli R, et al. Lancet 2011;378:1847– 57

2. Intracoronary Route

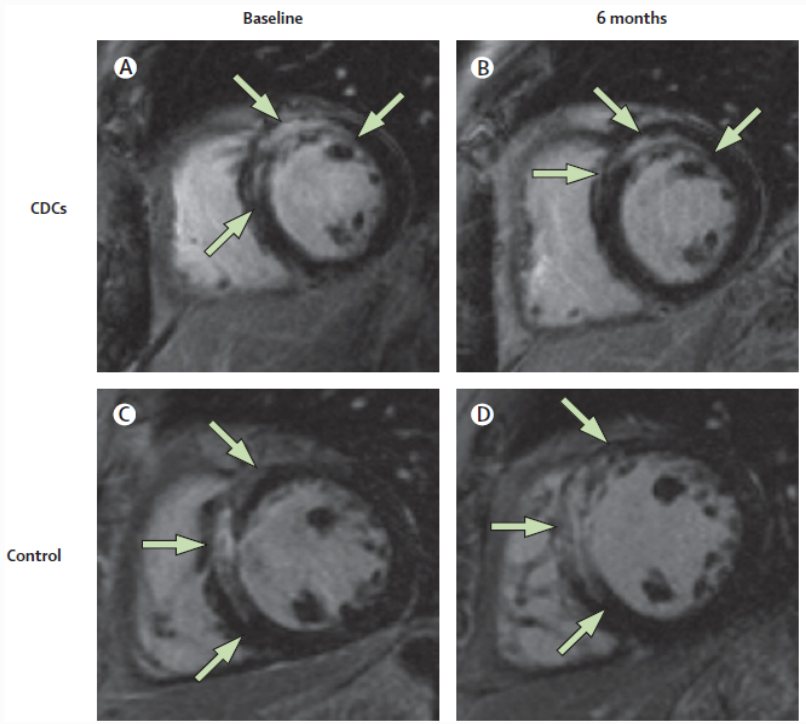
전남대학교병원

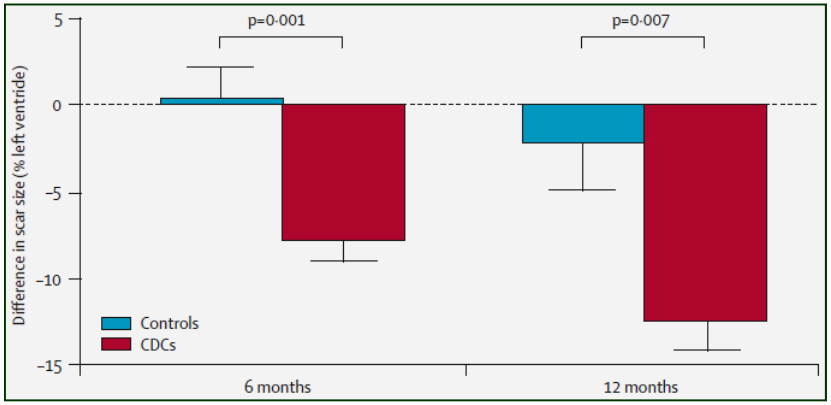
Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial (EF ≤ 25-45%, 2-4 wks after AMI)

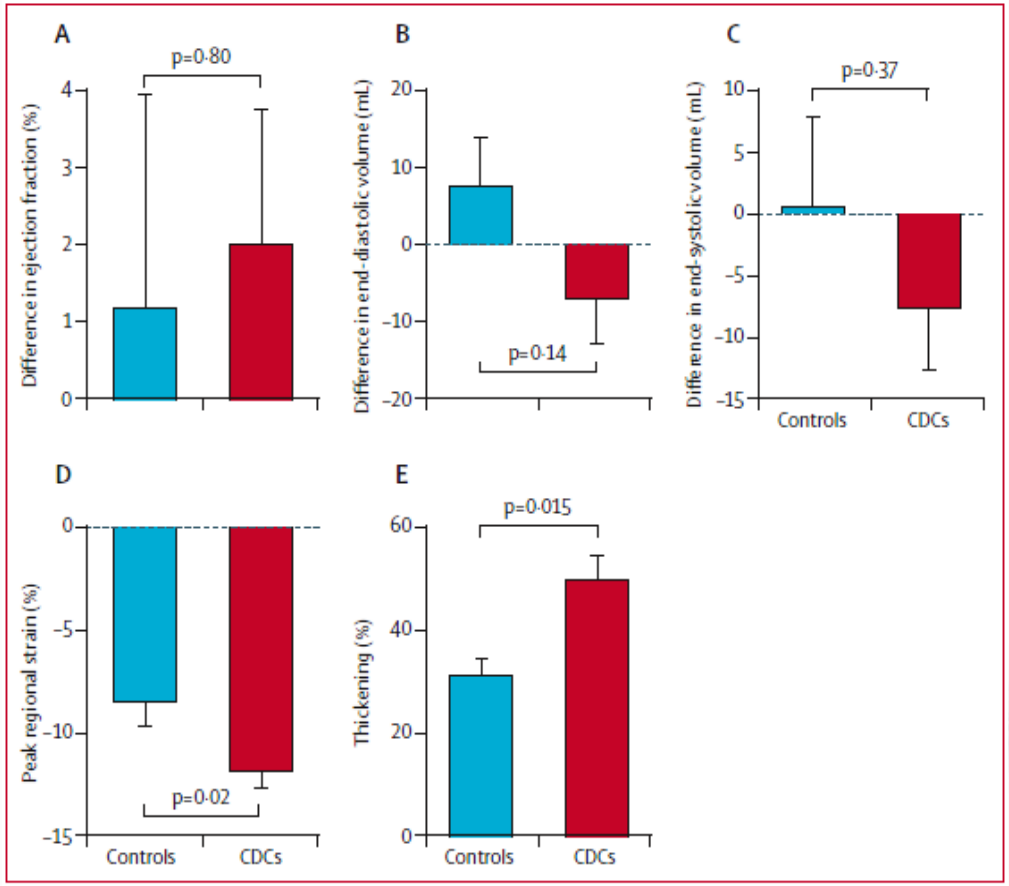
Raj R Makkar, Rachel R Smith, Ke Cheng, Konstantinos Malliaras, Louise E J Thomson, Daniel Berman, Lawrence S C Czer, Linda Marbán, Adam Mendizabal, Peter V Johnston, Stuart D Russell, Karl H Schuleri, Albert C Lardo, Gary Gerstenblith, Eduardo Marbán



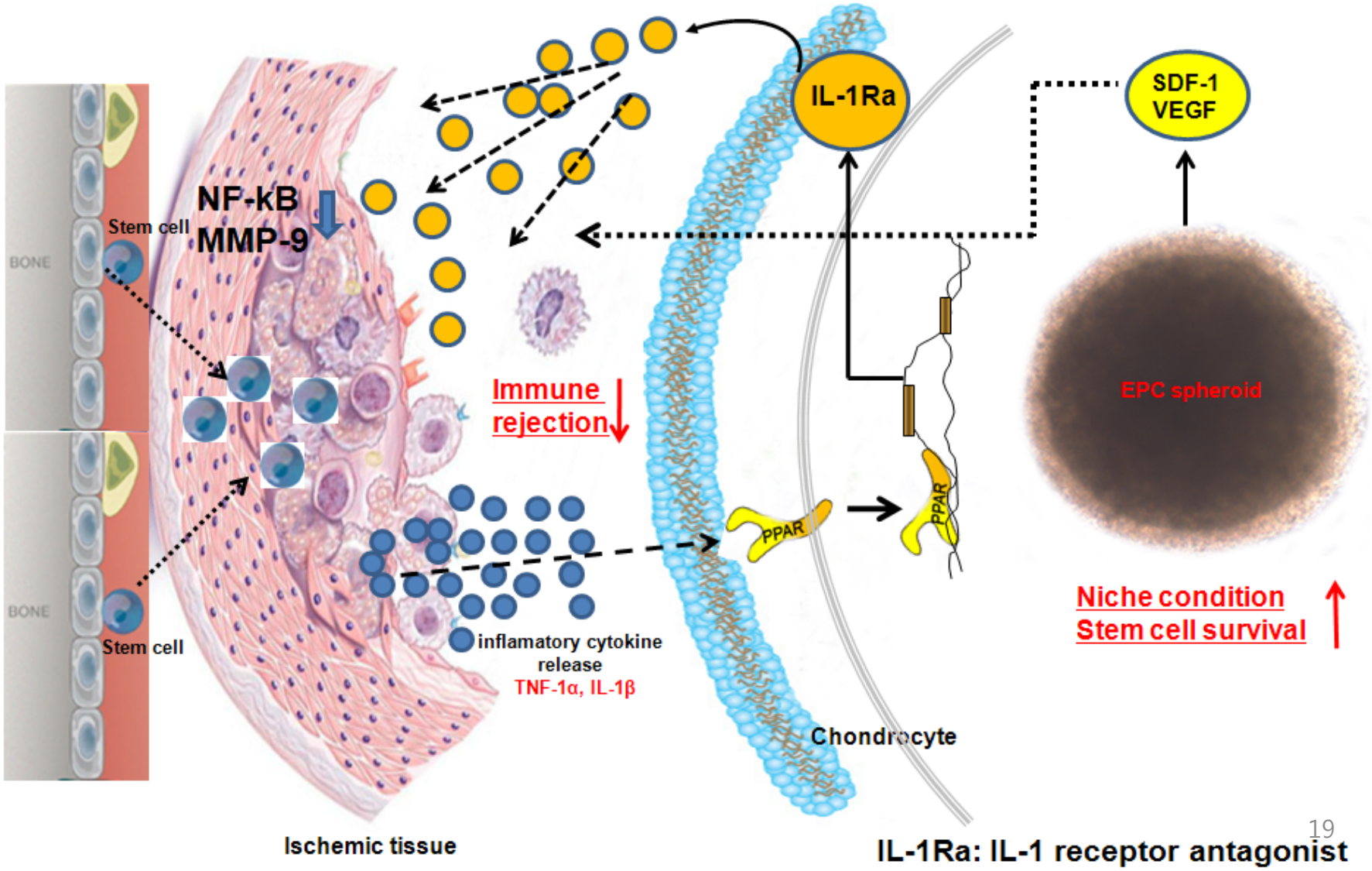
Makkar RR, et al. Lancet 2012;379:895– 904


Baseline
6 months
CDCs
Control
A
B
C
D

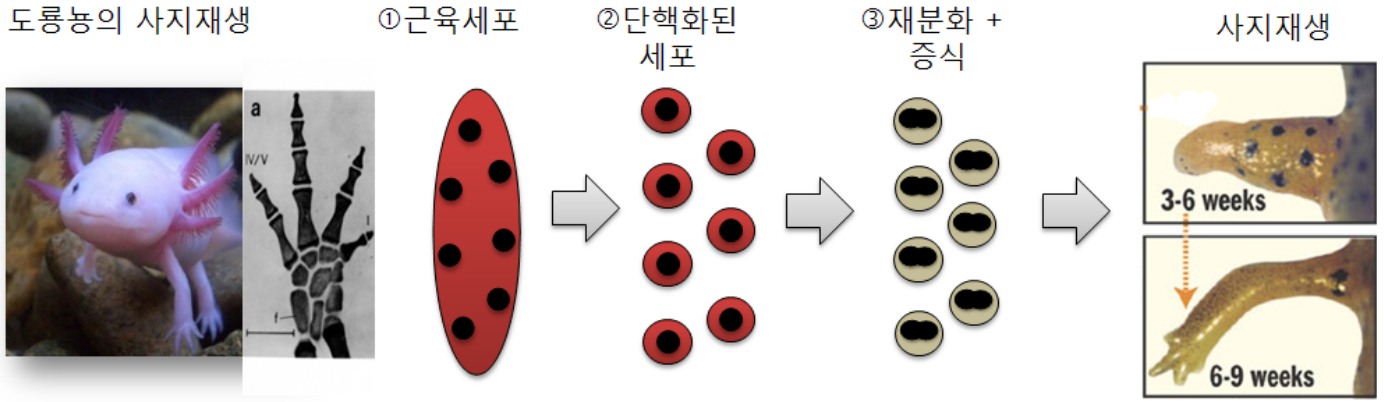

Difference in scar size (% left ventricle)
p=0·001
p=0·007
Controls
CDCs
6 months
12 months


A
p=0·80
Difference in ejection fraction (%)
B
p=0·14
Difference in end-diastolic volume (mL)
C
p=0·37
Difference in end-systolic volume (mL)
Controls
CDCs
D
p=0·02
Peak regional strain (%)
E
p=0·015
Thickening (%)

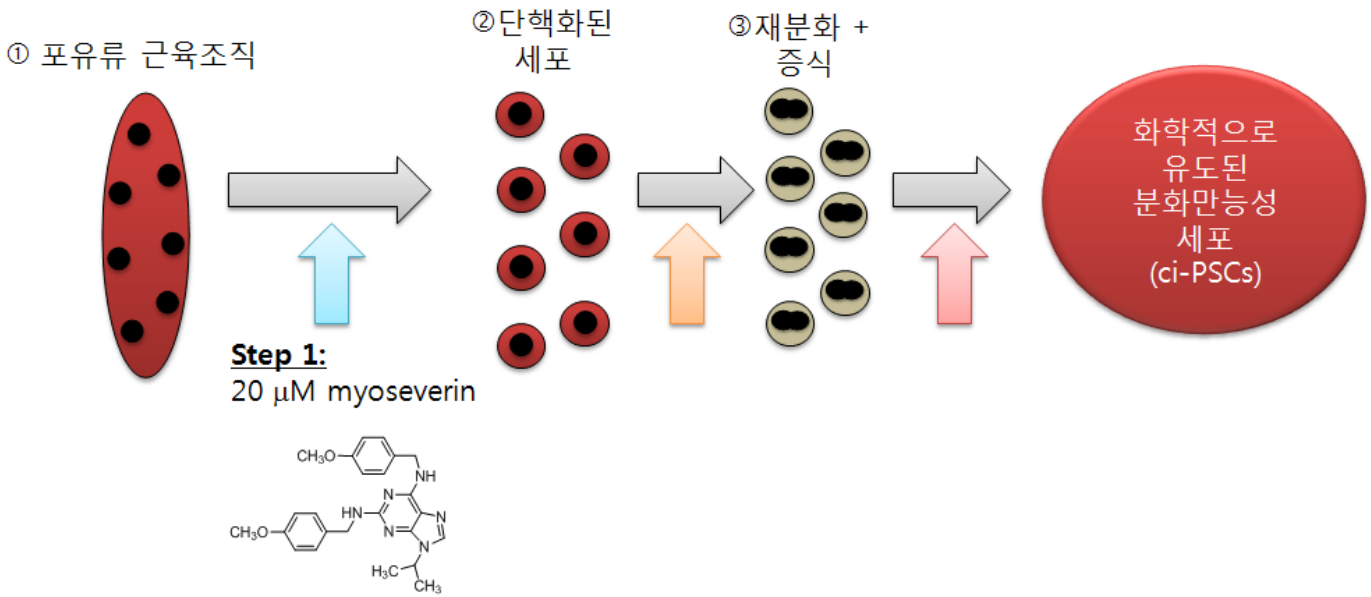
면역적합성 줄기세포 융합 치료제 개발 및 작용기전 연구



모델: 자연계에서의 조직 재생



본 연구진의 간단하고, 효과적인 화합물 칵테일



3. Endocardial Route

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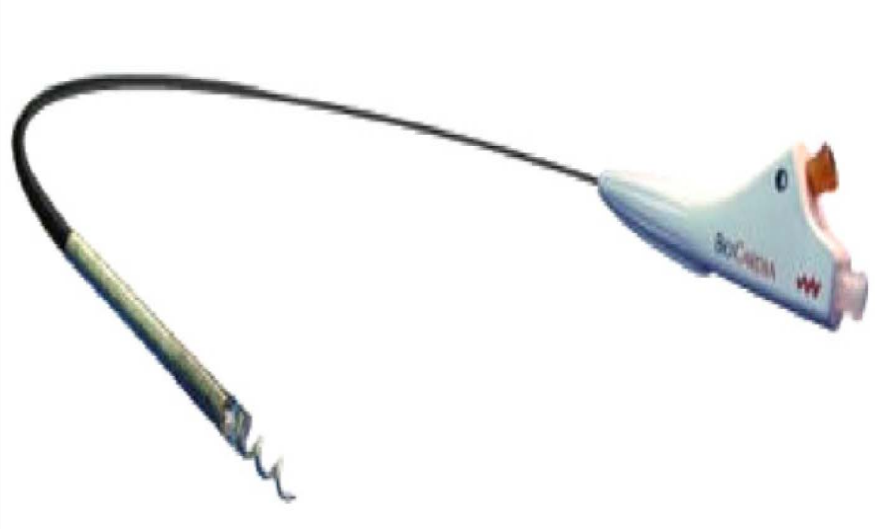
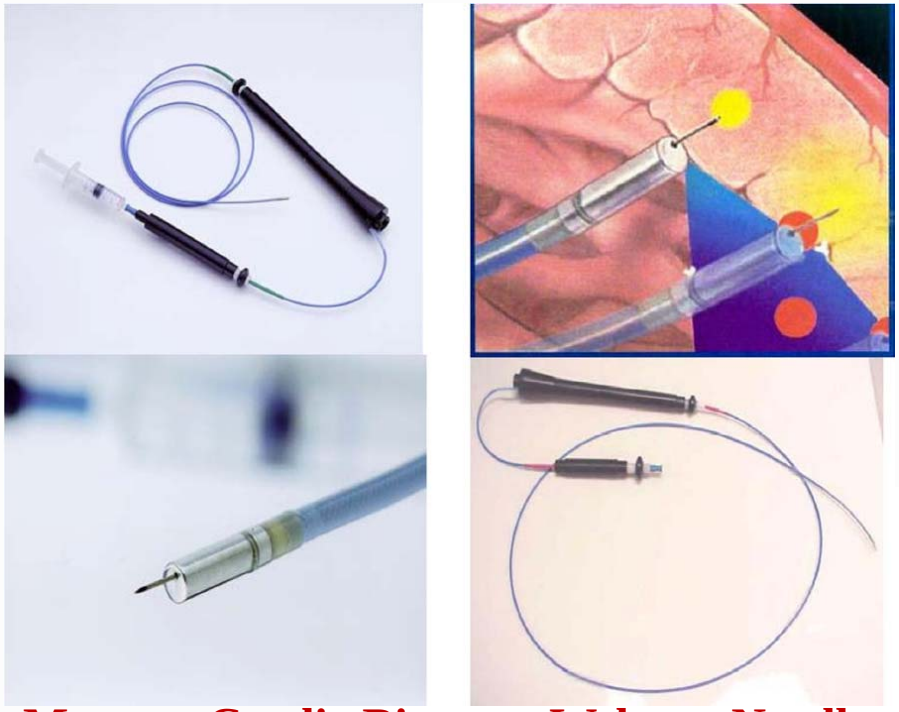
- **Device and method :** stem cell injection directly into the myocardium with a catheter navigated in the LV by fluoroscopic guidance or electroanatomic mapping



BioCardia Helical Infusion Catheter
: 2 fluid ports
1 for therapeutic agent and 1 for contrast.



Myostar Cordis-Biosense Webster Needle Injection Catheter

Sherman W, et al. Nat Clin Pract Cardiovasc Med. 2006;3:57–64

3. Endocardial Route

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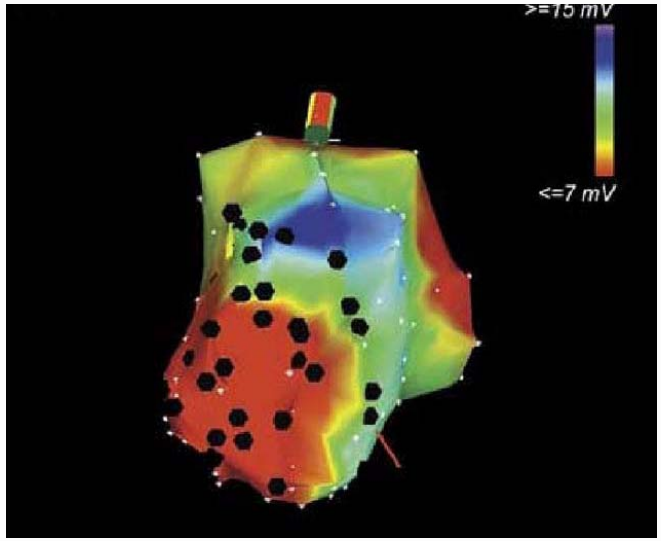
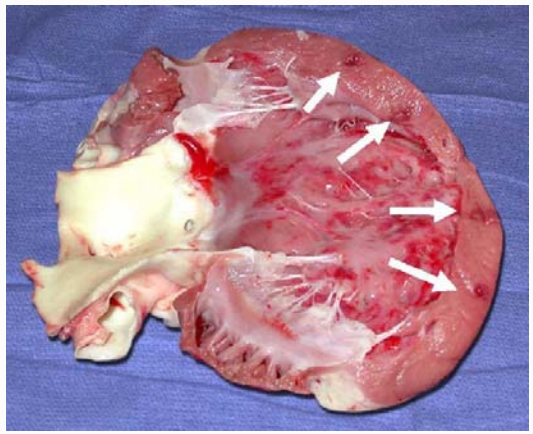
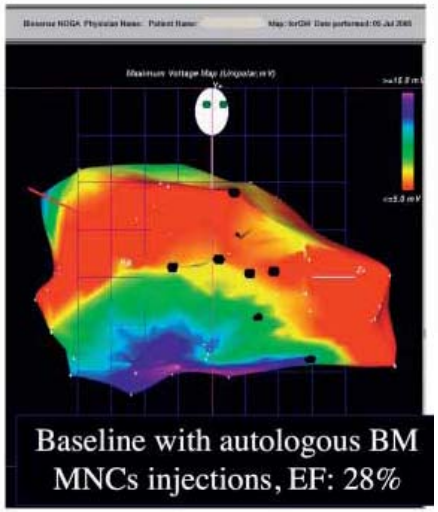
- NOGA mapping and 3D NOGA-guided intramyocardial injections

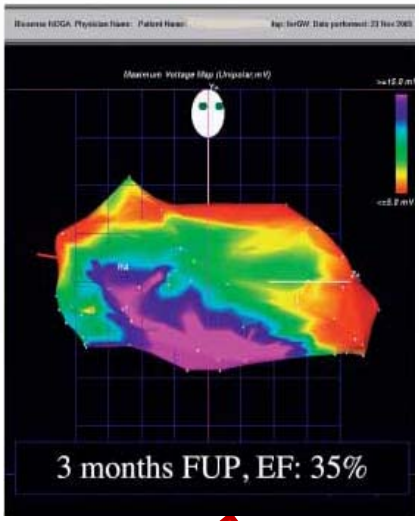




Arrows indicate site of injection

blue and green → normal myocardium
red → chronic infarction
yellow → border zone of infarction





3 months later

Silvia Charwat, et al. Thromb Haemost 2010; 103: 564
Dib N. Basic Research to Clinical Applications. 2006:213–30.

3. Endocardial Route

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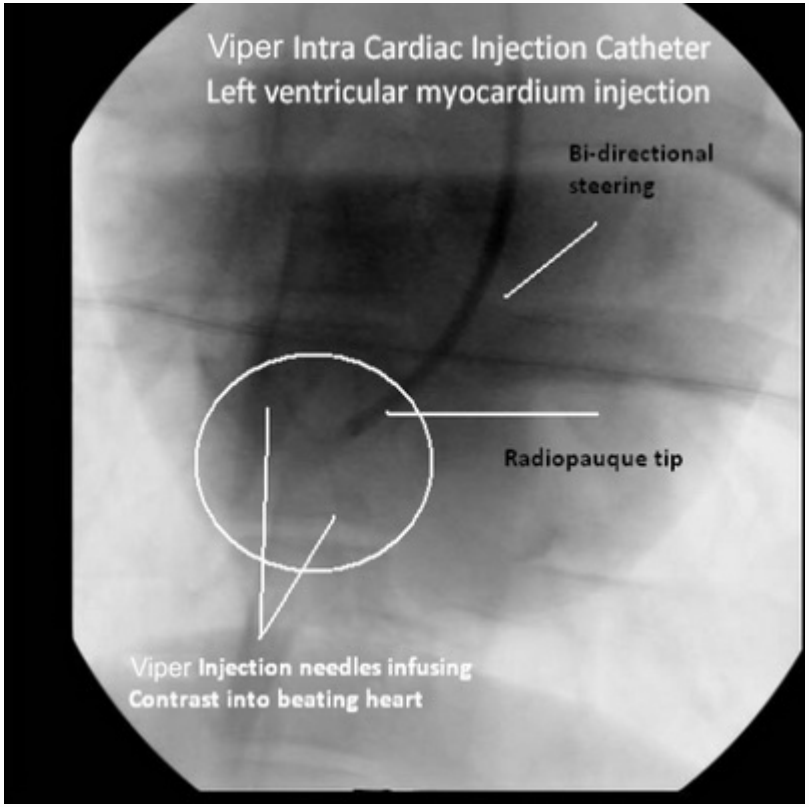
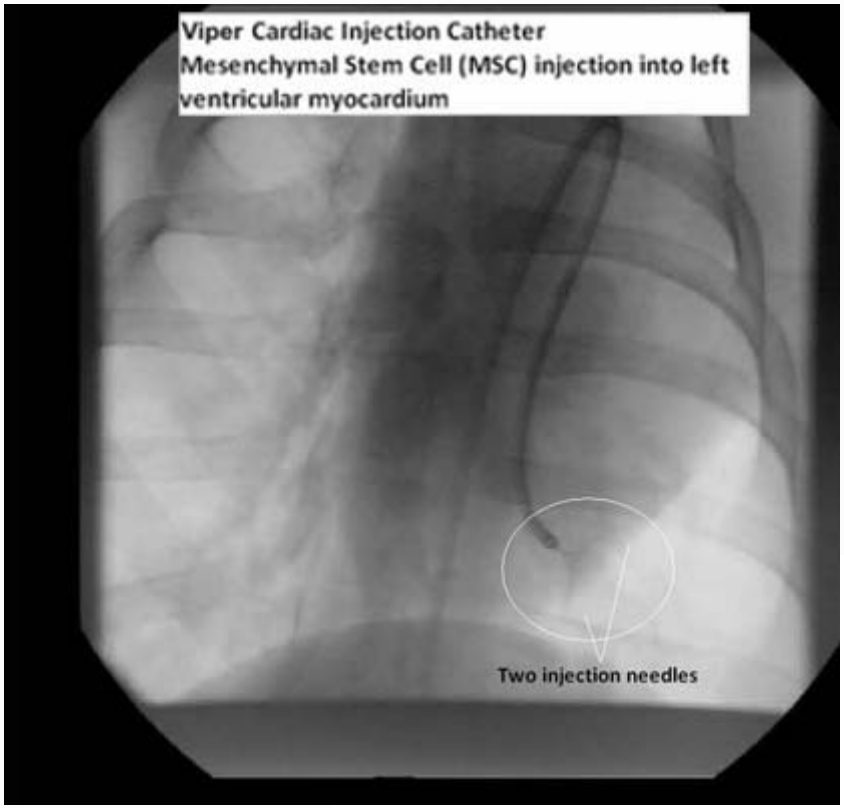
Viper cardiac injection catheter





www.bostontranstectec.com

3. Endocardial Route

전남대학교병원

Procedural safety

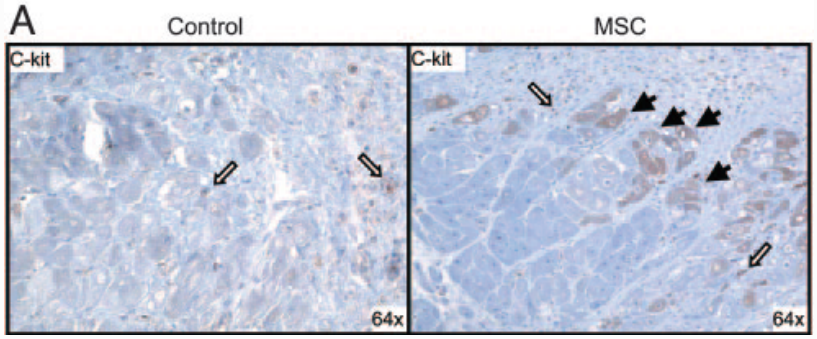
- Perforation of myocardium, with the potential for cardiac tamponade
- Induction of arrhythmias
- Scar formation of injection site

Gyongyosi M, et al. Circ Cardiovasc Imaging. 2008;1:94 –103

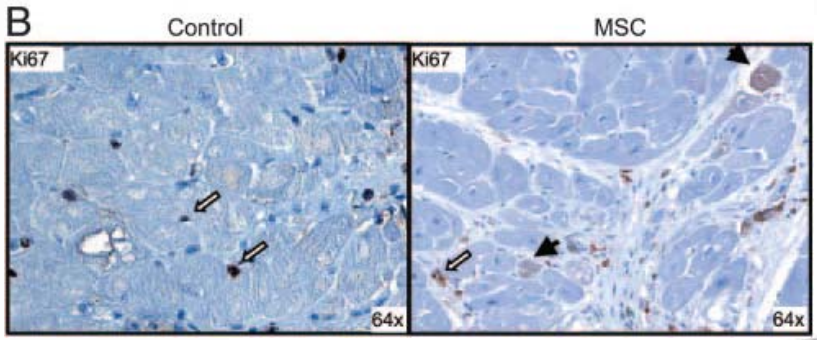
Efficacy

Pre-clinical: allo BM-MSC 3 days after AMI (Pig)

TE route group vs. Control group



c-Kit-positive myocytes



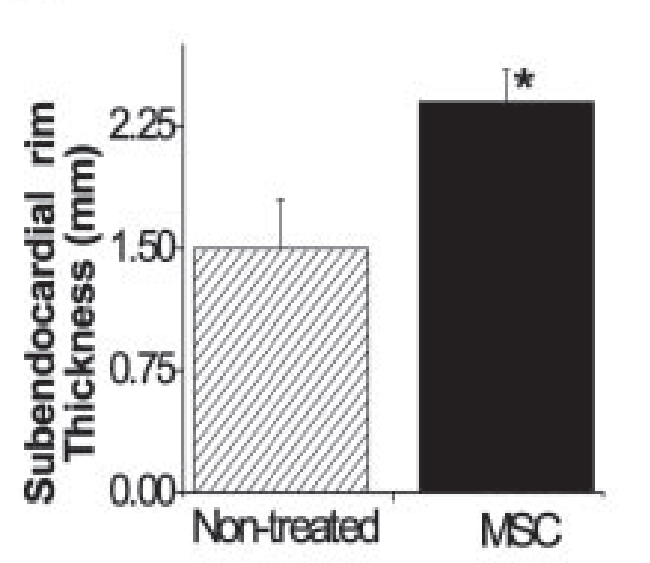
Ki67-positive myocytes

Amado LC, et al. PNAS 2005;102:11474 –11479

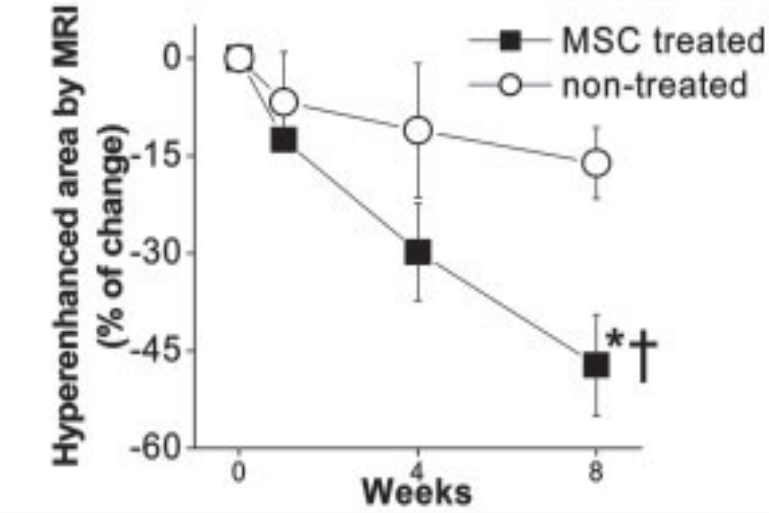
3. Endocardial Route

전남대학교병원

Subendocardial rim thickness



Hyperenhanced area by MRI



Ejection fraction: from 25% to 42% at 8 weeks after injection

Pressure-volume loops : improved LV relaxation and systolic compliance

Allogeneic MSCs injected into regions of damaged myocardium 3 d after MI engraft, stimulate cardiac regeneration, and profoundly decrease myocardial infarct size

Amado LC, et al. PNAS 2005;102:11474 –11479

3. Endocardial Route

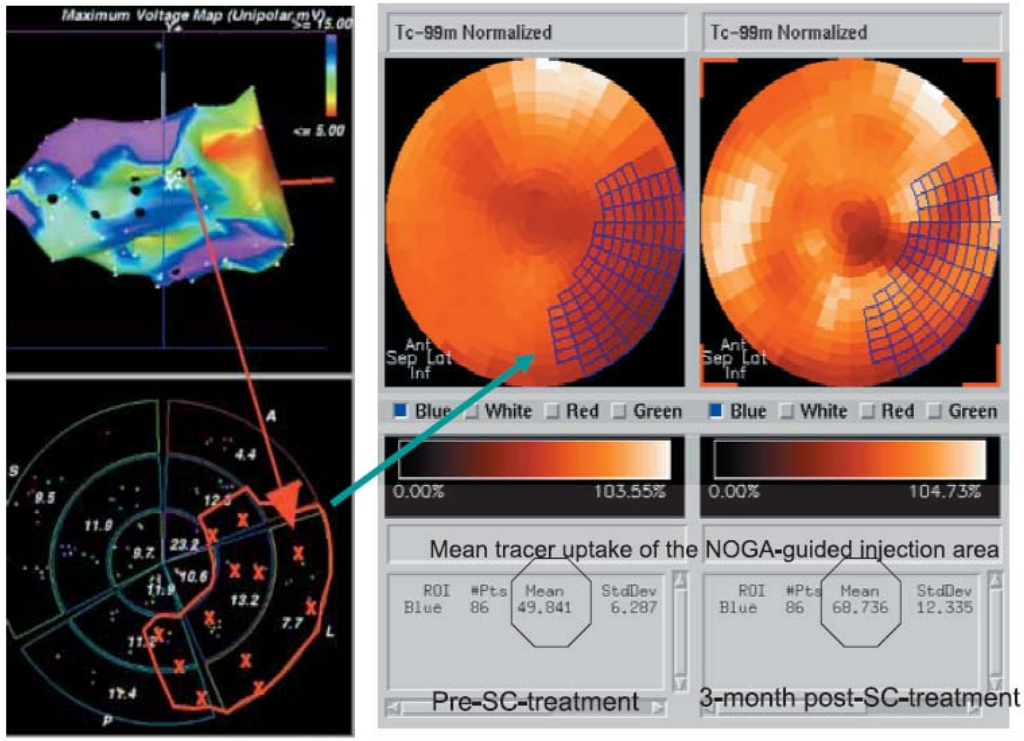
전남대학교병원

- **Efficacy**

Clinical: BM-MNC 68±34 days after AMI

NOGA-guided subanalysis of the MYSTAR prospective randomised study

TE route group vs. Control group



Inclusion criteria: Patients with recent AMI (STEMI) and post-infarction cardiac dysfunction (LVEF 30~45%)

Silvia C, et al. Thromb Haemost 103:564-571

3. Endocardial Route

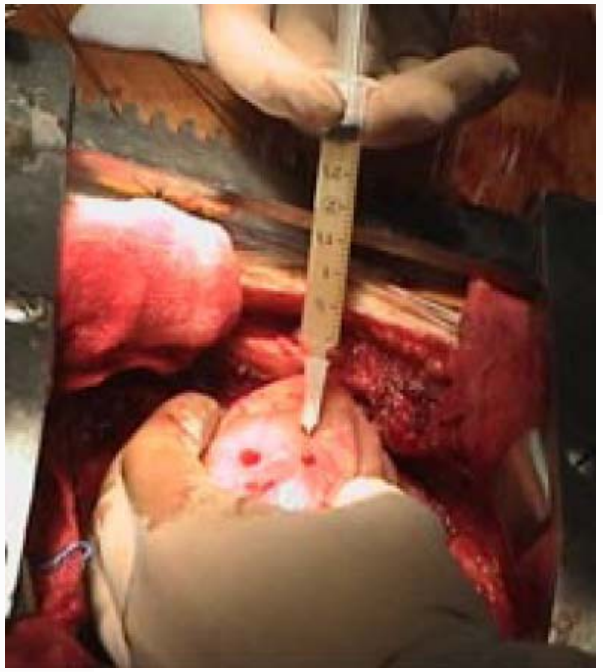
전남대학교병원

	Before BM-MNC therapy	Three months after BM-MNC therapy	P-value
Clinical data			
NYHA	2.0 ± 0.9	1.4 ± 0.6	<0.001
CCS	1.8 ± 0.7	1.2 ± 0.5	<0.001
Transthoracic echocardiography			
LA [mm]	53.6 ± 9.0	48.3 ± 7.8	<0.001
EDD [mm]	54.2 ± 7.0	51.9 ± 7.3	0.070
WMSI	1.8 ± 0.5	1.7 ± 0.4	0.200
Ventriculography			
EDP [mmHg]	23.4 ± 7.7	20.5 ± 8.8	0.186
Infarct size [%]	27.2 ± 10.7	24.1 ± 11.5	<0.0001
EF [%]	38.0 ± 6.1	41.5 ± 8.4	<0.0001
ESV [ml]	166.9 ± 78.2	137.6 ± 36.1	0.002
EDV [ml]	206.9 ± 69.2	207.4 ± 75.4	0.764

Silvia C, et al. Thromb Haemost 103:564-571

4. Epicardial Route

- Most reliable method
- Highly accessible, due to exposure by surgical incision
- Most invasive delivery technique
- Requires either a thoracotomy or sternotomy
- Injections can be made into a beating or arrested heart
- Computer-driven injection devices
- Epicardial application of cell-seeded biocompatible patches or even scaffold-free cell sheets



4. Epicardial Route

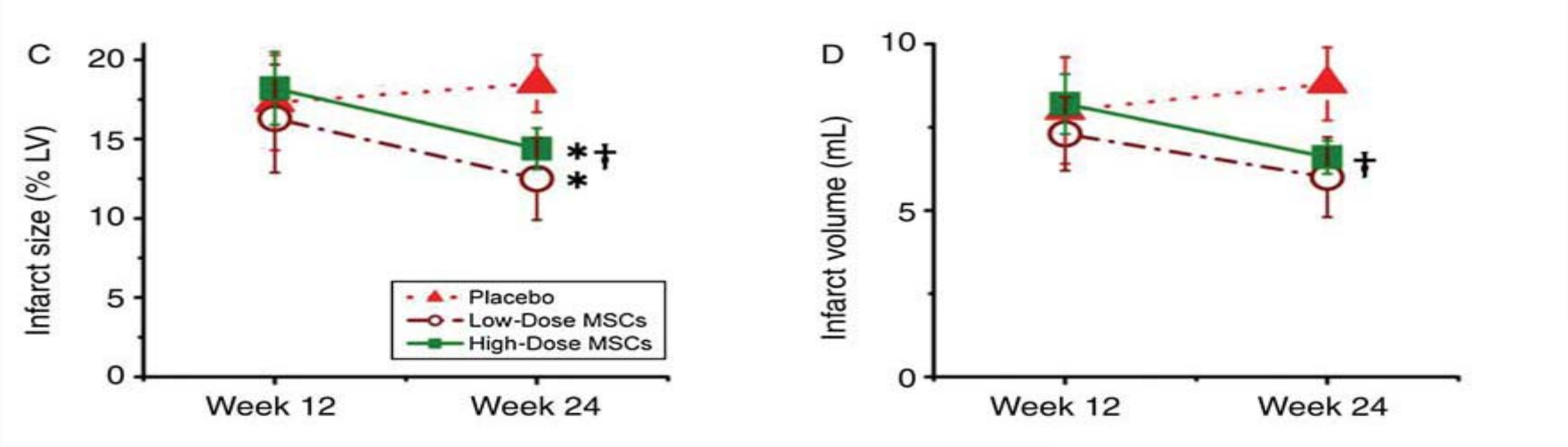
전남대학교병원

Efficacy

Pre-clinical: BM-MSC 12wks after AMI (Pig)

Injections were administered to the beating heart via left anterior thoracotomy.

Direct epicardial route
Group 1 (n=6): PBS group
Group 2 (n=3) : 2X10^6 MSCs/kg
Group 3 (n=6) : 20X10^6 MSCs/kg



Infarct size **Infarct volume**

Autologous MSCs can be safely delivered in an adult heart failure model, producing substantial structural and functional reverse remodelling

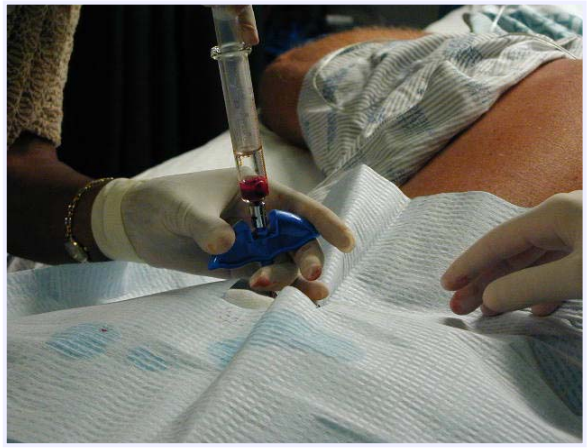
Karl HS, et al. Eur Heart J 2005;102:11474 –11479

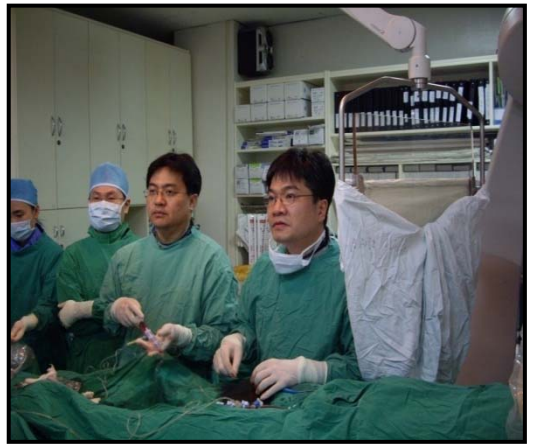
5. Coronary Sinus Route

- **Percutaneous retrograde coronary sinus delivery**
  - Very safe
  - Potential advantages for more homogenous delivery across the myocardium than IC, IM delivery
  - Placement of a catheter into the coronary sinus via either the internal jugular or femoral vein, with the infusion catheter placed over a wire
  - A single or double balloon is inflated, followed by infusion

Preclinical Trials

: Comparative studies of different methods





1. IC vs. EC vs. IV

전남대학교병원

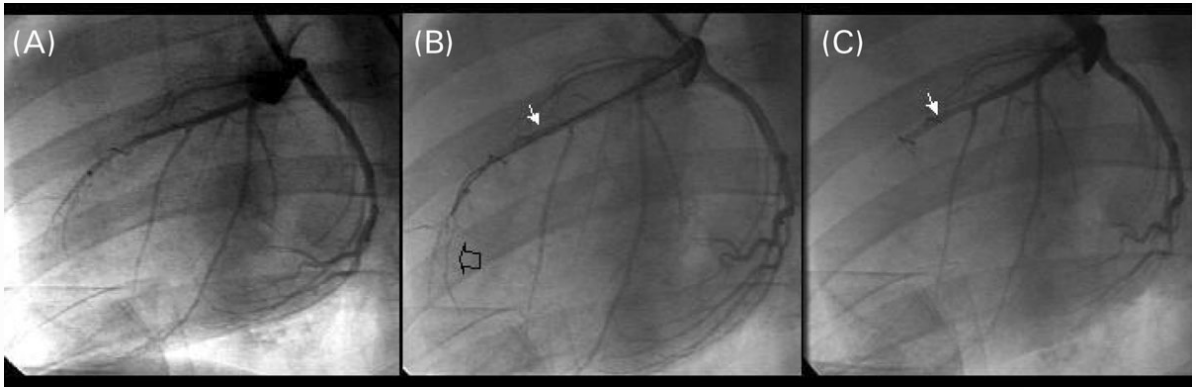
A quantitative, randomized study evaluating three methods of mesenchymal stem cell delivery following myocardial infarction

Pre-clinical: Allogeneic BM-MSC following AMI (Pig)

Group 1 (n=6): Intracoronary route
Group 2 (n=6): Endocardial route
Group 3 (n=6): Intravenous route

Sacrificed 14±3 days after transplantation
Confirmation of cellular engraftment
: DiI and FISH labelling techniques.

Procedural safety: no adverse events
: following IC infusion, half of the pigs exhibited decreased blood flow distal to the infusion site



Freyman F, et al. Eur Heart J. *2006;27:1114-1122*

1. IC vs. EC vs. IV

전남대학교병원

Infarct zone engraftment rate of MSCs : IC >> EC >> IV
Extracardiac entrapment rate : EC << IC & IV

Table 2 Engraftment of MSCs in tissues varies by delivery technique

	Mesenchymal stem cell engraftment 14 days after delivery			
	Infarct zone (cells)	Infarct zone (cells/g)	Liver (cells/g)	Lung (cells/g)
IC	2 864 000 ± 983 000	106 000* ± 43 000	1000 ± 1000	11 000 ± 2000
EC	1 393 000 ± 618 000	51 000** ± 24 000	700 ± 700	4000 ± 3000***
IV	None detected	None detected	9 ± 20	13 000 ± 2000

*IC vs. EC ($P = 0.01$), IC vs. IV ($P = 0.0008$).
**EC vs. IV ($P = 0.003$).
***EC vs. IC ($P = 0.06$), EC vs. IV ($P = 0.02$).

- IC was more efficient than EC and IV
- IC delivery was associated with decreased coronary blood flow.
- EC delivery was safe and well tolerated and decreased remote organ engraftment with compared with IC and IV deliveries.

Freyman F, et al. Eur Heart J. 2006;27:1114-1122

2. IC vs. IM (epicardial) vs. EC

전남대학교병원

Analysis of Different Routes of Administration of Heterologous 5-Azacytidine–Treated Mesenchymal Stem Cells in a Porcine Model of Myocardial Infarction

Pre-clinical: Allogeneic 5-aza treated BM-MSC following AMI (Pig)

Group 1 (n=5): Intracoronary route
Group 2 (n=5): Intramyocardial route
Group 3 (n=5): Endocardial route

Sacrificed 30 days after transplantation
Confirmation of cellular engraftment
: DiO and DAPI

Procedural safety: no adverse events

Moscoso I, et al. Transplantation Proceedings 2009;41:2273–2275

2. IC vs. IM (epicardial) vs. EC

전남대학교병원

Infarc zone engraftment rate of MSCs : IC >> IM & EC

	IC	IM	EC	NI
Infarcted zone	$85.96 \pm 19.95 (\times 10^{-3})$	$12.39 \pm 6.7 (\times 10^{-3})$	$8.09 \pm 3.3 (\times 10^{-3})$	$0.3 \pm 0.06 (\times 10^{-3})$
Healthy zone	$1 \pm 0.53 (\times 10^{-3})$	$0.94 \pm 0.67 (\times 10^{-3})$	$0.75 \pm 0.16 (\times 10^{-3})$	$0.36 \pm 0.17 (\times 10^{-3})$

- The mean number of engrafted cells within the infarct zone was significantly greater after IC infusion than either IM or EC injection.
- Fluorescent cells were not observed in healthy zones of the myocardium or in healthy animals.

Moscoso I, et al. Transplantation Proceedings 2009;41:2273–2275

3. IC vs. EC

전남대학교병원

Effects of Adipose Tissue-Derived Stem Cell Therapy After Myocardial Infarction: Impact of the Route of Administration

Pre-clinical: Adipose Tissue-Derived Stem Cell following AMI (Pig)

Group 1 (n=4): intracoronary PBS
Group 2 (n=5): intracoronary ADSCs
Group 3 (n=4): endocardial PBS
Group 4 (n=6): endocardial ADSCs

Sacrificed 21 days after transplantation
Echocardiography and histopathology

Procedural safety: no adverse events

Rigol M, et al. J Cardiac Fail 2010; 16:357–366

3. IC vs. EC

전남대학교병원

Infarct zone engraftment rate of ADSCs : IC (80%) = EC (79%)

Neovascularization : IC > EC

	Intracoronary Administration		Transendocardial Administration	
	Culture Medium (Control) n = 4	ADSCs n = 5	Culture Medium (Control) n = 4	ADSCs n = 6
Small vessels	141 ± 26	223 ± 40*	162 ± 37	168 ± 35
Large vessels	31 ± 4	38 ± 11	32 ± 14	34 ± 5
Total number of vessels	172 ± 25	261 ± 40*	194 ± 24	201 ± 34

Rigol M, et al. J Cardiac Fail 2010; 16:357–366

3. IC vs. EC

전남대학교병원

Improvement of LV function : IC = EC = control

	Intracoronary Administration		Transendocardial Administration	
	Culture Medium (Control) n = 4	ADSCs n = 5	Culture Medium (Control) n = 4	ADSCs n = 6
3 weeks after administration				
LVEF (%)	49 ± 2*	49 ± 10*	51 ± 8*	51 ± 12*
LVEDV (mL)	27.3 ± 3.9	32.0 ± 4.8	34.1 ± 5.9	38.4 ± 13.9
LVESV (mL)	13.8 ± 1.3*	16.2 ± 2.7*	16.6 ± 3.2*	17.7 ± 2.9*

▪ Both pathways of ADSCs delivery are feasible, producing a similar number of engrafted and differentiated cells, although intracoronary administration was more effective in increasing neovascularization

Rigol M, et al. J Cardiac Fail 2010; 16:357–366

4. IC vs. EC

전남대학교병원

Comparison of intracoronary and transendocardial delivery of allogeneic mesenchymal cells in a canine model of acute myocardial infarction

Pre-clinical: allogeneic BM-MSC at 7 days after AMI (Canine)

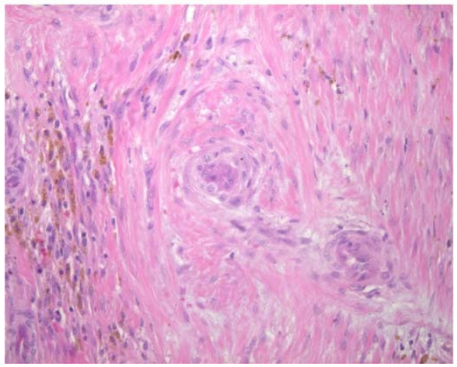
Group 1 (n=7): Intracoronary route
Group 2 (n=6): Endocardial route
Group 3 (n=6): Control

Sacrificed 21 days after transplantation
Echocardiography and histopathology

Procedural safety: 2 dogs died after randomization and IC infusion of MSCs

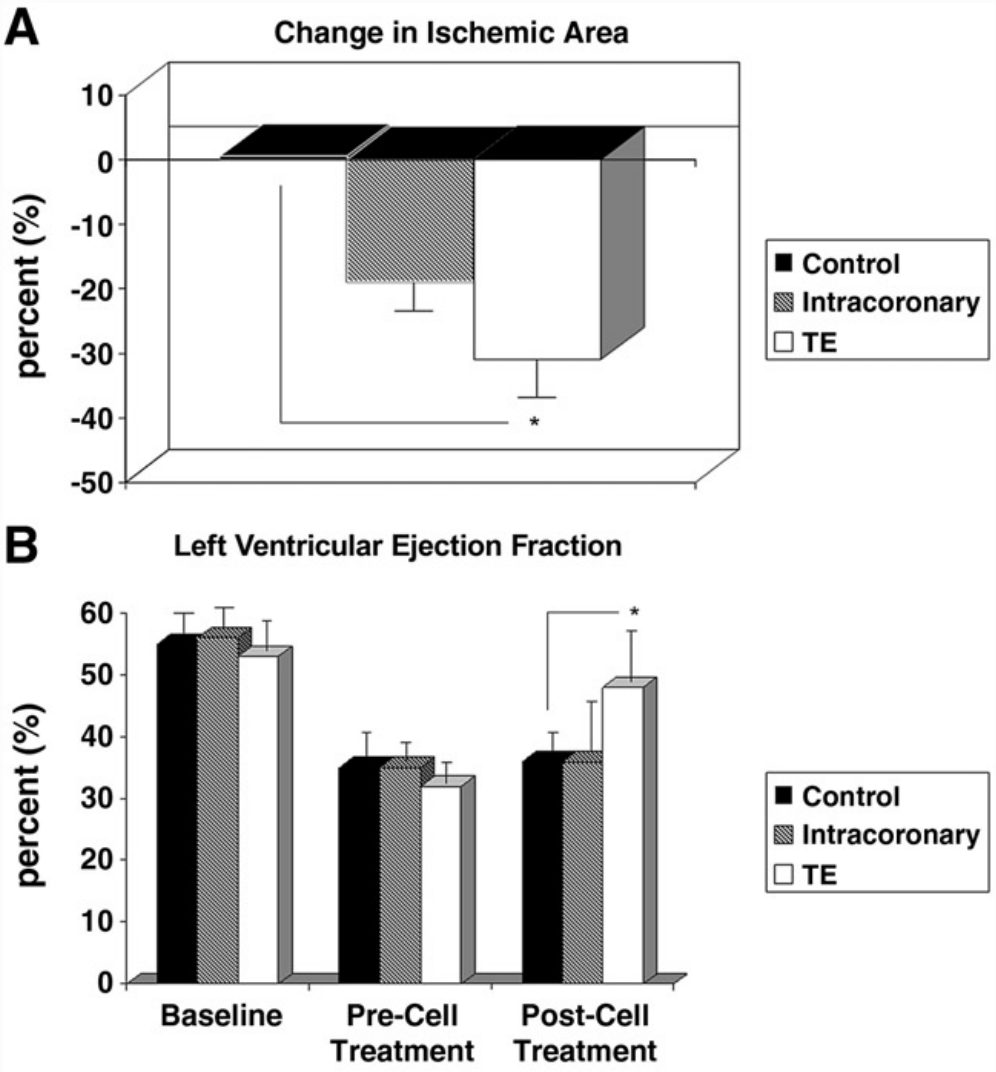
Dog1: extensive **microvascular "plugging"** associated with MSCs

Dog2: **intestinal ischemia/infarct**



Perin EC, et al. J Mol Cell Cardiol 2008; 44:486–495

4. IC vs. EC

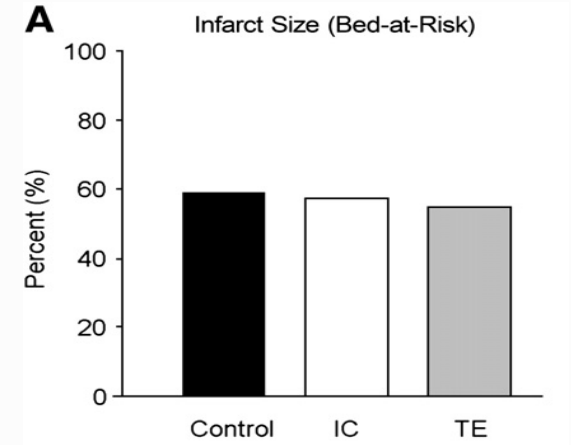


Reduction of ischemic area:
EC > control (p=0.03)
IC = control (p=0.08)
EC = IC (p=0.13)

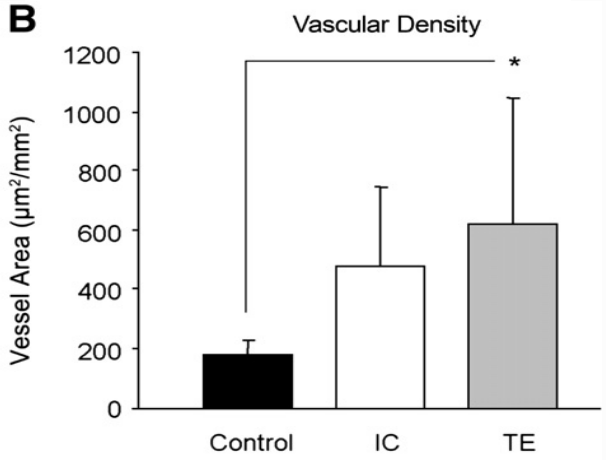
Improvement of LVEF:
EC >> control (p=0.01)
IC = control (p=0.83)
EC = IC (p=0.63)

Perin EC, et al. J Mol Cell Cardiol 2008; 44:486–495

4. IC vs. EC



Infarct Size:
EC = IC = control (p>0.05)



Vascular density:
EC >> control (p=0.01)
IC = control (p>0.05)
EC = IC (p>0.05)

▪ EC : safe, higher cell retention with an increased vascularity and greater functional improvement than did the IC group

Perin EC, et al. J Mol Cell Cardiol 2008; 44:486–495

5. IM (epicardial) vs. EC

전남대학교병원

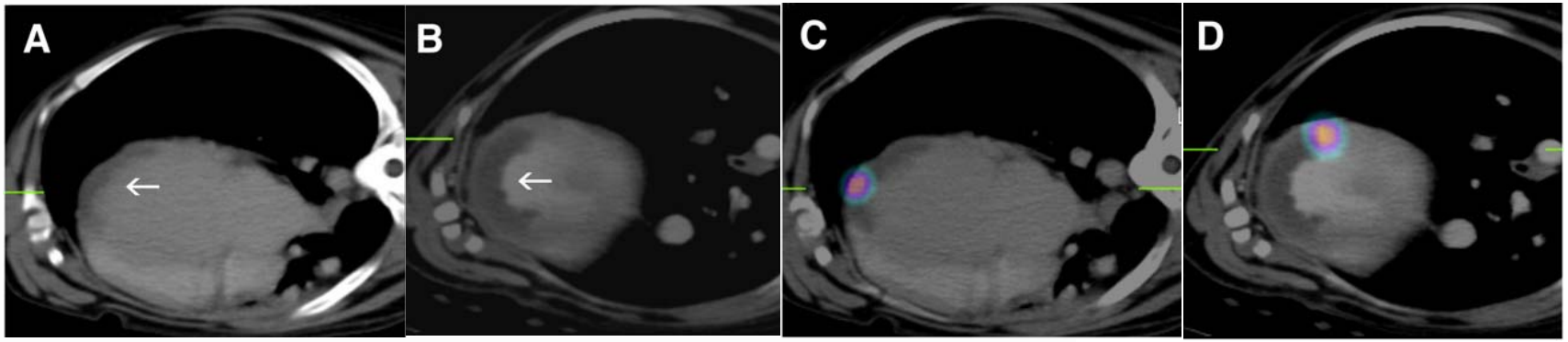
Comparison of Initial Cell Retention and Clearance Kinetics After Subendocardial or Subepicardial Injections of Endothelial Progenitor Cells in a Canine Myocardial Infarction Model

Pre-clinical: EPC following AMI (Dog)

Group 1 (n=7): epicardial route
Group 2 (n=7): endocardial route

Sacrificed 15 days after transplantation
Serial SPECT/CT

Procedural safety: no adverse events



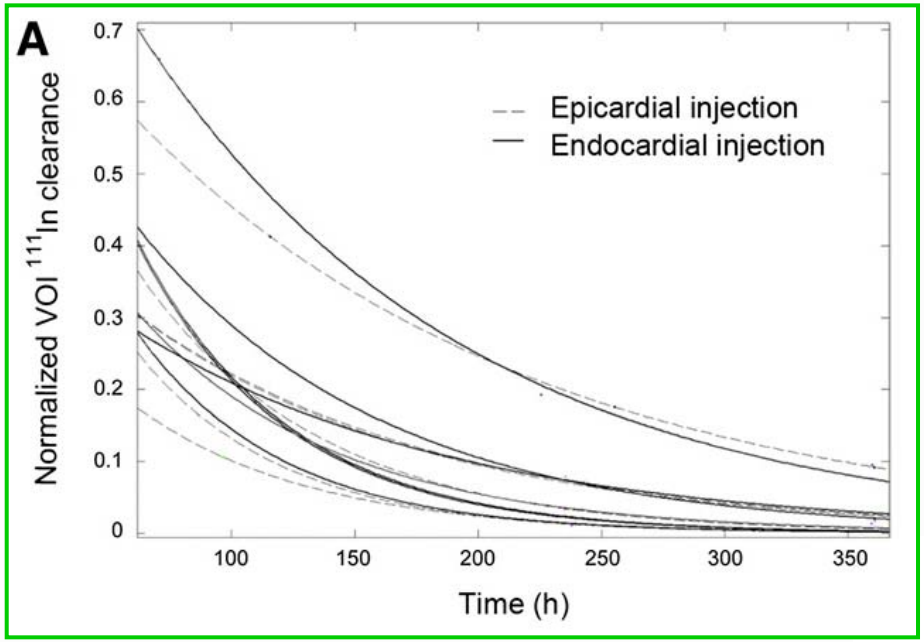
Day 0 Day 0 Day 15 Day 15

Mitchell AJ, et al. J Nucl Med 2010; 51:413–417

5. IM (epicardial) vs. EC

전남대학교병원

Initial EPC retention rate: IM (57 %) = EC (54%) (p=0.53)
Clearance half-life: IM (69hr) = EC (60hr) (p=0.81)



- Subendocardial injections, clinically more practical, show clearance kinetics comparable to those of subepicardial injections and will facilitate the ultimate clinical use of this treatment modality

Mitchell AJ, et al. J Nucl Med 2010; 51:413–417

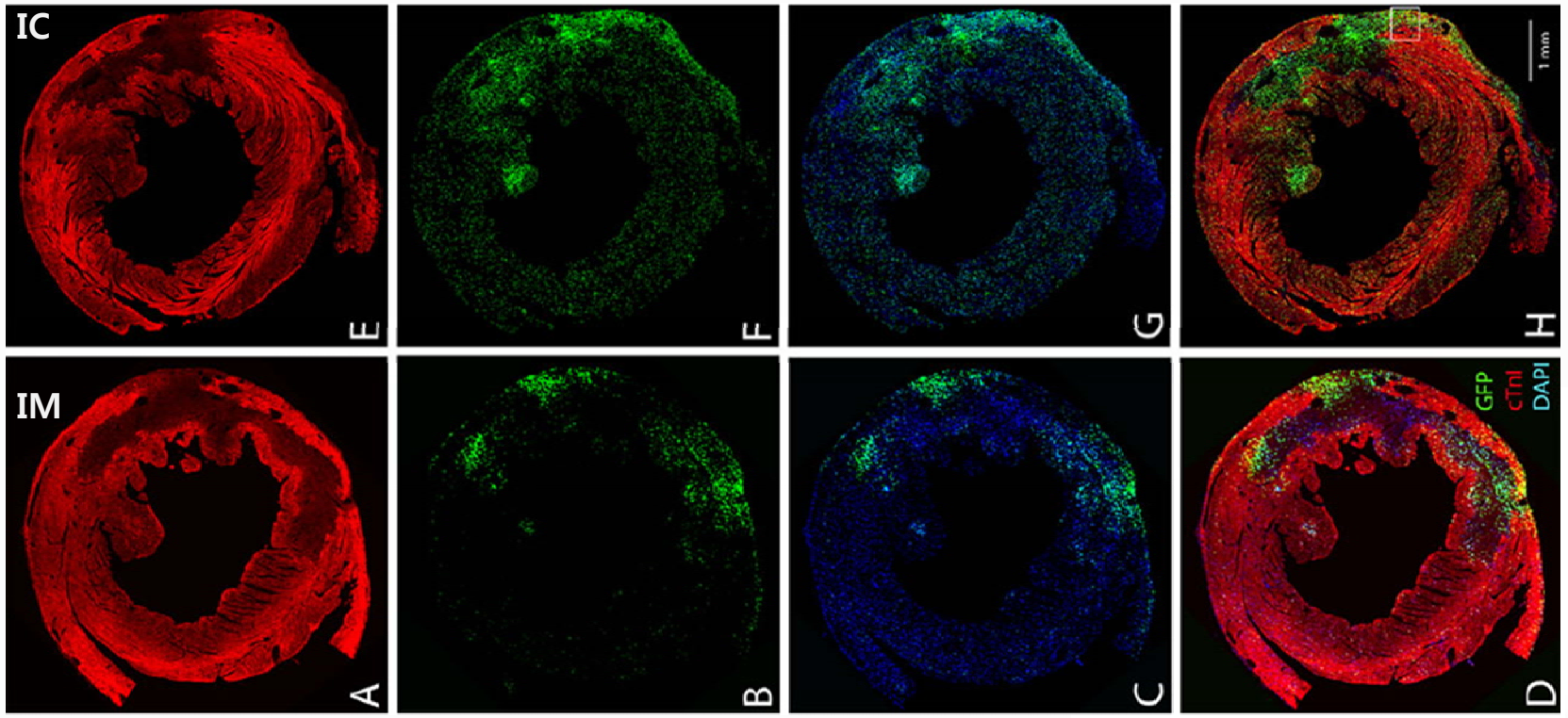
6. IC vs. EC

전남대학교병원

Intracoronary administration of cardiac stem cells in mice: a new, improved technique for cell therapy in murine models

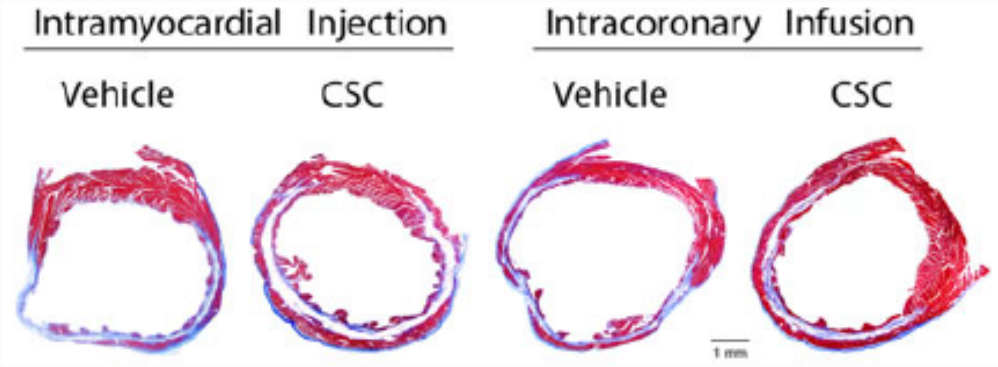
Qianhong Li · Yiru Guo · Qinghui Ou · Ning Chen · Wen-Jian Wu · Fangping Yuan · Erin O'Brien · Tao Wang · Li Luo · Gregory N. Hunt · Xiaoping Zhu · Roberto Bolli

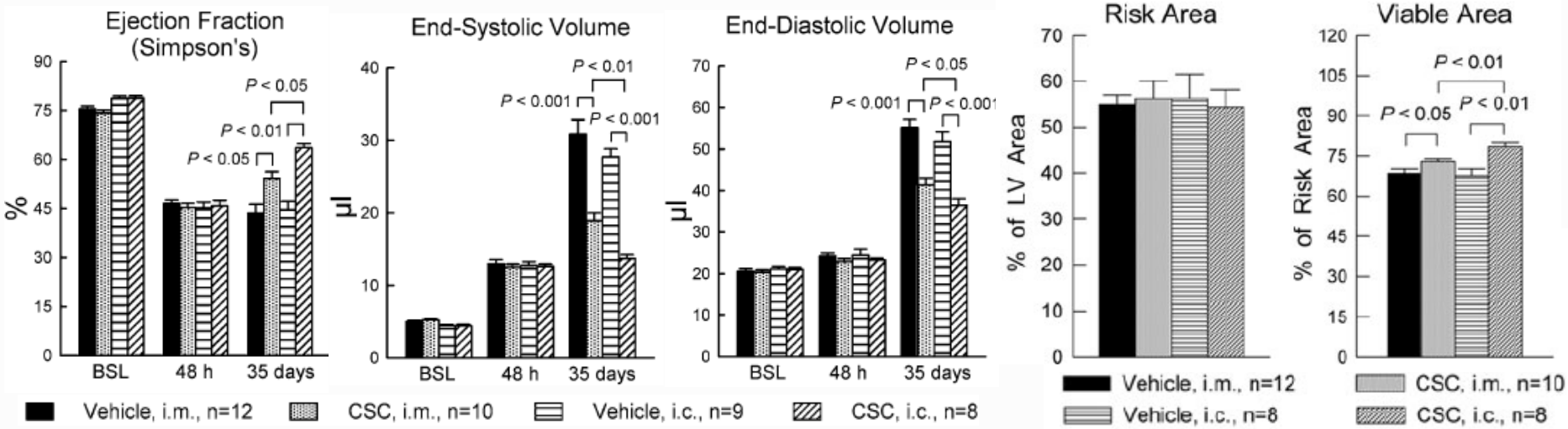
IC: More homogeneous distribution



Li Q, et al. Basic Res Cardiol 2011;106:849– 64

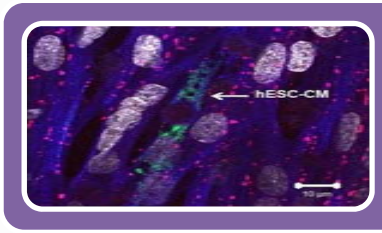
6. IC vs. EC



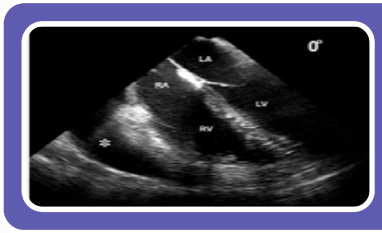


Li Q, et al. Basic Res Cardiol 2011;106:849– 64

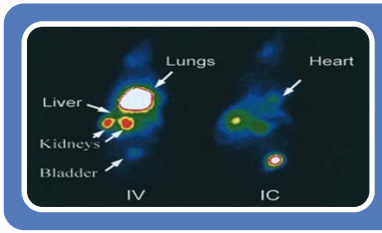
Summary and Conclusion



Engraftment → **IC ≥ EC=IM**



Procedural safety → **All methods are relatively safe**
IC => microvascular "plugging"



Extracardiac retention of stem cells → **EC=IM ≤ IC & IV**

Improvement of heart function → **IC = EC = IM (?)**

Intramyocardial Delivery in Clinical Trials

전남대학교병원

Trial	Cell	Time of Delivery	Results	F/U
van Ramshorst et al., 2009	Autologous BM-MNC, 1×10^8 cells, intramyocardial injection	Chronic MI	Modest improvement of summed stress score, LVEF in BMC group at 3 mo, increase of quality of life at 6 mo	3, 6
Williams et al., 2011	transendocardial, intramyocardial injection of auto BM-MNC (1 or 2×10^8), or MSC (1 or 2×10^8)	ICMP	EDV (208.7±20.4 to 167.4±7.32mL), infarct size ↓, regional function ↑ at 3 mo, changes in chamber dimensions not diff at 6 mo	12
Ahmadi et al., 2012	BM-CD133+BMC, $1.77\times10^6\pm1.14\times10^6$ CD133+ cells, intramyocardial transplantation	Candidate of CABG after MI	Safe, no benefit	60

Kim YS and Ahn Y, Korean Circ J 2012;42:71– 9

Intravenous Delivery in Clinical Trials

전남대학교병원

Trial	Cell	Time of Delivery	Results	F/U
Hare et al., Prochymal, 2009	Allogeneic BM-MSC, 0.5, 1.6, 5×10^6 cells/kg, iv	1-10 d	EF ↑	12
Moreira et al., 2011	BM-MNC 1×10^8, anterograde intra-arterial coronary (IAC) or retrograde intravenous coronary (IVC)	24h < MI, infract size > 10%,	Comparison of cell retention: IAC (16.14%), IVC (4.62%) at 4h, IAC (10.29%), IVC (3.13%) at 24h	24h

Kim YS and Ahn Y, Korean Circ J 2012;42:71– 9

Intracoronary Delivery in Clinical Trials

Trial	Cell	Time of Delivery	Results	F/U
Meyer et al., BOOST trial, 2009	Autologous BMC, 24.6×10^8	5 d	EF ↑	61
Tendera et al., REGENT trial, 2009	BM-MNC (1.78×10^8), CD34+ (1.9×10^6)	PCI after 12h	EF ↑	6
Beitnes et al., ASTAMI trial, 2009	BMC, 7×10^7	4-7 d	Safe, exercise time ↑, no other effects	36
Assmus et al., REPAIE-AMI, 2010	Auto BMC, $236\pm174\times10^6$	3-7 d after reperfusion	Still safe	24
Grajek et al., 2010	BMC, $2.34\pm1.2\times10^9$	4-6d after PCI	No differences in EF, LVEDV, LVESV, and spiroergometric stress test	6, 12
Arnold et al., TECAM study, 2010	BM-MNC, $97.6\pm61.4\times10^6$	STEMI, <9±3d of reperfusion	No difference in stenosis, plaque volume	9
Strauer et al., STAR-heart study 2010	BMC, $6.6\pm3.3\times10^7$	Chronic HF EF<35% (mean post MI interval: 8.5 yr)	Haemodynamics, exercise capacity, oxygen uptake, LV contractility, long-term mortality↑ in BMC group	3, 12, 60
Seth et al., ABCD Trial, 2010	BM-MNC	DCMP EF<35%	EF ↑, ESV ↓ at 6 mo EF ↑, ESV ↓ at 36 mo	36
Traverse et al., 2010	auto BMC 1×10^8	STEMI	EF ↑, LVEDP ↓	6
Mansour et al., COMPARE-AMI, 2011	CD133+ HSC, 1×10^7	3~7 d after PCI	Safe, EF ↑	12
Hirsch et al., HEBE trial, 2011	BM $296\pm164\times10^6$ or peripheral MNC $287\pm137\times10^6$	IC 4-7 d after MI	No difference	4
Penn et al., 2011	Allo MultiStem, 2×10^7, 6×10^7, 1×10^8	2-5 d after AMI	EF ↑, LV stroke volume↑	4
Bolli et al., SCIPIO, 2011	CSCs, 1 million	EF<40%, CABG, ICMP	EF ↑, Infarct size ↓	12
Solheim et al., 2011	BM-MNC 68×10^8	6d after the STEMI	No changes in prothrombotic markers	3
Roncalli et al., BONAMI trial, 2011	auto BMC	9.3 d after STEMI	Myocardial viability ↑	3
Makkar et al., CADUCEUS, 2012	Autologous cardioshpere, 12.5 ~ 25 million	2-4wk after MI (EF 25-45%)	Scar mass ↓, viable heart mass ↑, regional contractility ↑, no changes in EDV, ESV, LVEF	6

Thank you for your attentions!

Chonnam Nat. Univ. Hosp.

3rd Gwangju-Boston Joint Cardiology Symposium

Date: 25th - 26th May, 2012
Venue: Deok-Jae Hall/Myung-Hak Hall,
Chonnam National University Medical School, Gwangju