Cardiac Regeneration : Mesenchymal Stem Cell Is it Enough?

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Limitations in Current Strategies

- **Pharmacotherapeutic intervention:** only provide a symptomatic relief
  - Angiotensin-converting enzyme inhibitor, β-blocker, diuretics, angiotensin receptors blockers

- **Device therapies** (specific to heart failure)
  - Cardiac resynchronization therapy, Cardiac defibrillators, ventricular assist devices

- **Cardiac revascularization procedures**
  - Coronary angioplasty, Coronary artery bypass grafting (CABG)

- **Heart transplantation** (end-stage heart failure): limited availability of donor heart

: There are the limitations of the currently available therapeutic approaches

▶ **Need for the development of principally new and efficient strategies (stem cell therapy)**

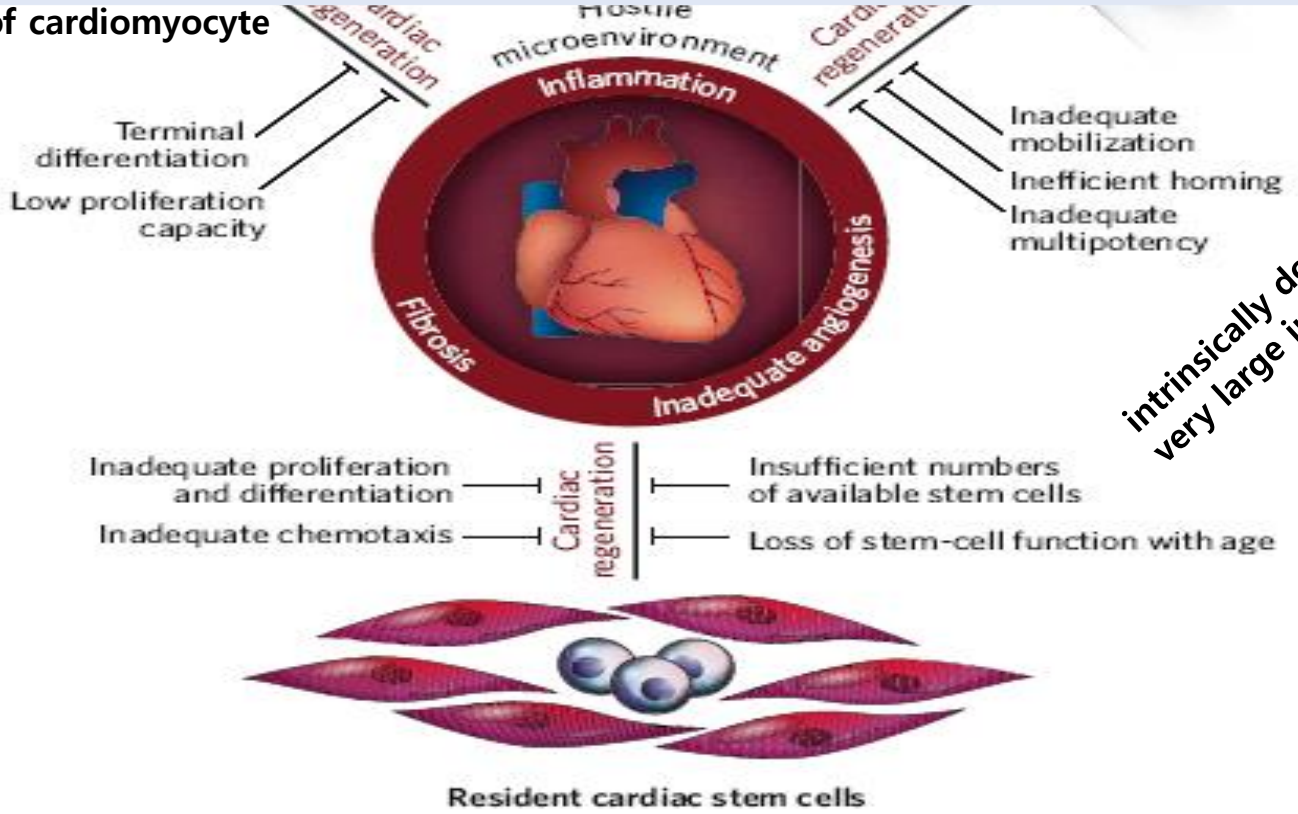
Limited Capacity of Innate Stem/progenitor Cells

Cardiomyocyte

Bone-marrow

▶**Need for the outside therapeutic intervention to compensate for the inept intrinsic repair mechanism.**

limited renewal of cardiomyocyte



intrinsically do not repopulate very large infarcts

Stem Cell (SC) sources for IHD

- Bone marrow-derived cells(unselected, CD 133+ , CD 34+)
- Circulating stem/progenitor cells
- Skeletal myoblasts
- Mesenchymal stem cells/ Adipose tissue-derived stem cells
- Resident cardiac stem/progenitor cells
- Inducible pluripotent stem cells
- Embryonic stem cells

Source: Tongers et al. Eur Heart J 32: 1197-1206, 2011

Stem Cell (SC) Types for Ischemic Heart Disease

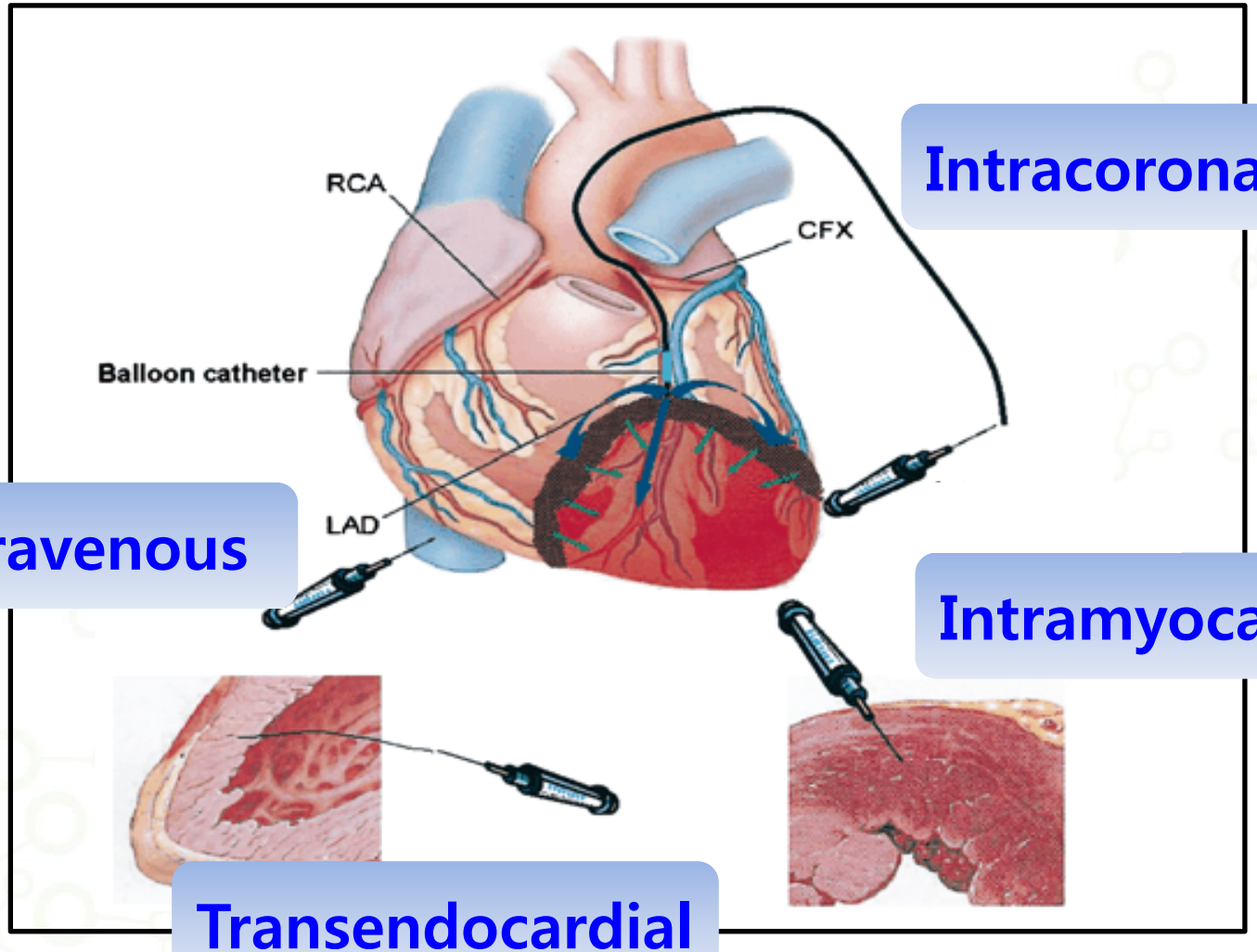
most clinical studies in ischemic heart disease have us… arrow mononuclear cells

가장 많은
임상 연구 진행

최근 임상 연구
증가 추세

	Stem/progenitor cell	Current clinical trial status
Em…	Embryonic stem cell (ESC)	-
Adult st… (fibroblast…)	Induced pluripotent stem (iPS) cell	-
Bone marrow/Blood	BM-Mononuclear cell	+++
	BM-Mesenchymal stem cell (MSC)	++
	Endothelial progenitor cell (EPC)	+
Fat…	Adipose-Mesenchymal stem cell	+
Sk…	Skeletal myoblast	+
Heart	Cardiac-derived stem cell (CSC)	+

Possible Routes for SC Therapy



Source: Strauer BE & Kornowski R. Circulation 107:929-934. 2003

Ongoing Clinical Trial Activity for Heart Disease

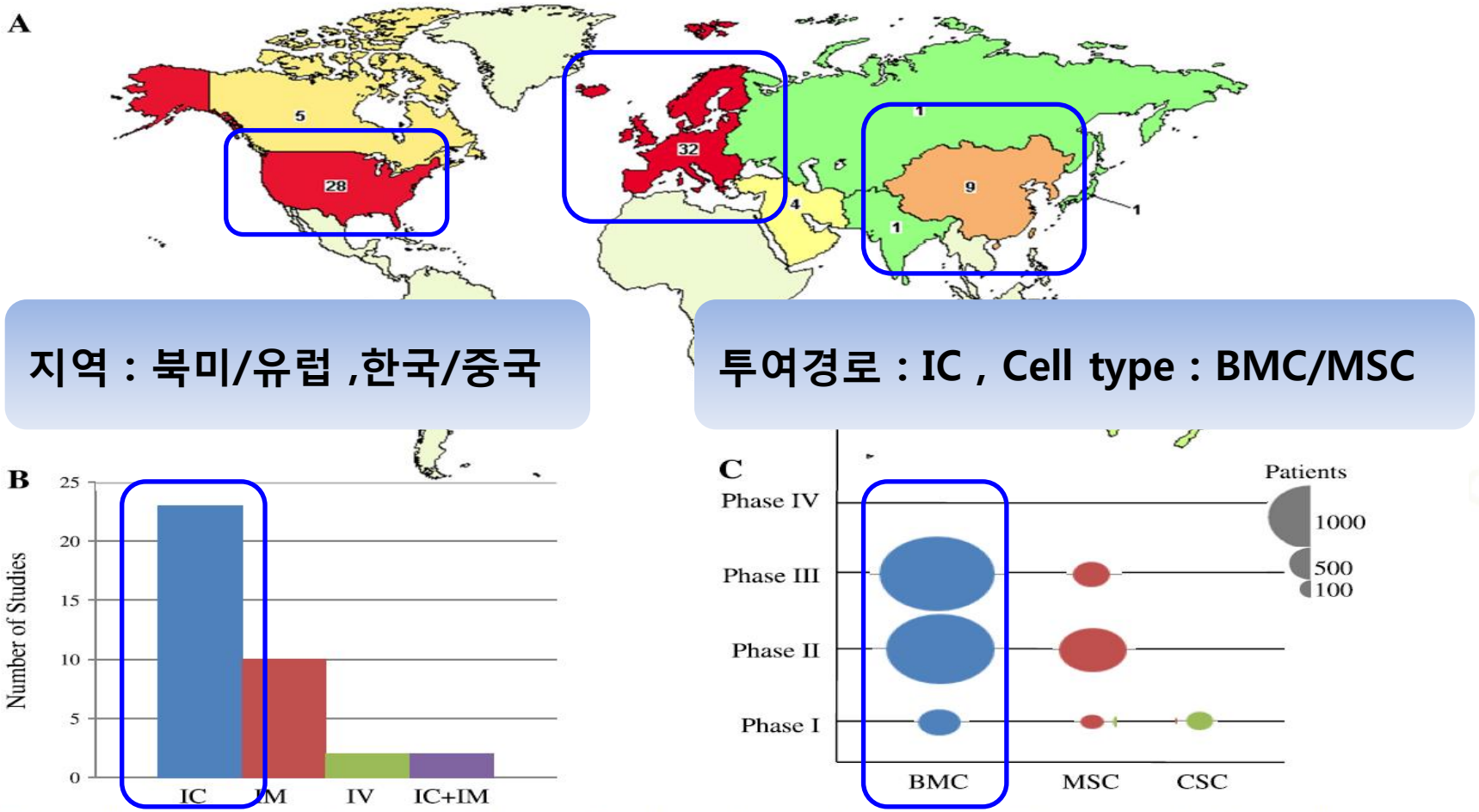


Fig. 1. Ongoing clinical trial activity evaluating cell-based therapy for heart disease. *A*: topographic representation of ongoing clinical trials currently registered with ClinicalTrials.gov employing stem cell therapy for myocardial infarction (map adapted from ClinicalTrials.gov). *B*: types of delivery systems. IC, intracoronary infusion; IM, intramyocardial injection; IV, intravenous infusion. *C*: number of patients enrolled in clinical trials of different phases. BMC, bone marrow-derived stem cells; MSC, mesenchymal stem cells; CSC, cardiac stem cells.

Source: Karantalis et al. Am J Physiol Heart Circ Physiol 303: H256–H270, 2012

BM-derived Mononuclear Cells (Clinical trial; MNC, PBSC)

▸ **The first clinical trial of stem cell (BM mononuclear cells) therapy for cardiac repair**

Repair of Infarcted Myocardium by Autologous Intracoronary Mononuclear Bone Marrow Cell Transplantation in Humans

Circulation 2002;106:1913-1918

- **Cell type :** autologous mononuclear bone marrow cell (BMCs)
- **Infusion :** intracoronary
- **Patients :** AMI 치료군 10명 / 대조군 10명
- **Result :** 3 months f/u
  - infarct region 30% → 12% 감소 (p=0.005)
  - infarction wall movement velocity 2.0cm/s → 4.0cm/s로 증가(p=0.028)
  - stroke volume index/LVESV volume & contractility/myocardial perfusion → 유의하게 개선

BM-derived Mononuclear Cells (Clinical trial; MNC, PBSC)

- So far, most clinical studies have used BM mononuclear cells and showed either no benefit or small (but possibly clinically important) improvements in cardiac function.

BMMNC를 이용한 치료에서...

-안전성 문제가 없음

-다수 논문에서 Improvement in LVEF

-Infusion : IC injection

		and GCSF				function
Assmus *et al.* [10] (TOPCARE-AMI)	NR	BMMNC or CPC	IC	3-7 days	PCI	Improvement in LVEF
Schächinger *et al.* [11] (TOPCARE-AMI)	NR	BMMNC or CPC	IC	3-7 days	PCI	Improvement in EF
Strauer *et al.* [9]	NRC	BMMNC	IC	5-9 days	PCI	Reduction in infarct region
Bartunek *et al.* [100]	NRC	BMMNC (CD133)	IC	11.6 days	PCI	Improvement in LVEF
Hirsch *et al.* [21]	RCT	BMMNC	IC	3-8 days	PCI	No effect on global or regional LV function
Tendera *et al.* [20]	RCT	BMMNC	IC	3-12 days	PCI	No significant improvement in LVEF
Chen *et al.* [101]	RCT	BMMNC	IC	18 days	PCI	Improvement in LVEF
Yousef *et al.* [15] (BALANCE)	NRC	BMMNC	IC	7 days	PCI	Improvement in LVEF, exercise capacity and mortality

Source: Arnous et al. Stem Cell Res Ther, 2012

BM-derived Mononuclear Cells (Clinical trial; MNC, PBSC)

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Cardiac Cell Therapy — Mixed Results from Mixed Cells

Anthony Rosenzweig, M.D.

Despite substantial advances in treatment, ischemic cardiac injury and the ventricular dysfunction it can provoke remain major causes of morbidity and mortality throughout the world. The endogenous regenerative capacity of the heart appears inadequate to repair injured myocardium, leading to the cumulative loss of cardiomyocytes over the lifetime of a patient. This may contribute to the prevalence of heart failure as a diagnosis at hospital admission — particularly among the elderly.

For these reasons, experiments in animals suggesting that the transfer of cells derived from bone marrow (BMC) could dramatically improve cardiac function after infarction through regeneration of the myocardium[1] or neovascularization[2] generated tremendous excitement. In addition, they stimulated clinical studies suggesting that this approach is feasible, safe, and potentially effective in humans.[3,4] In this issue of the *Journal*, Schächinger et al.,[5] Assmus et al.,[6] and Lunde et al.[7] — following authors of other recent reports[8,9] — provide a realistic perspective on this approach while leaving room for cautious optimism and underscoring the need for further study (Table 1).

In the largest study of cardiac cell therapy to date, Schächinger et al. report the results of the greatest in patients with the worst LVEF at baseline. This double-blind and fully controlled trial provides the best evidence yet for beneficial effects of BMC after acute myocardial infarction. Enthusiasm is tempered somewhat by the modest size of the effect and by a recent report from the Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST) trial that the relative improvement in LVEF after infusion of BMC at 6 months, as compared with no infusion, was no longer significant at 18 months, suggesting that the main effect was an acceleration of recovery.[9]

It may be challenging to achieve significant improvements in LVEF in small cohorts of patients who have relatively preserved ventricular function and who are already receiving state-of-the-art therapy. Even some early trials of reperfusion in patients with acute myocardial infarction demonstrated either no improvement in LVEF[10] or a modest improvement.[11] Ultimately, the validation of cardiac cell therapy will require demonstration of benefit with regard to clinical outcomes — as was the case with reperfusion. Studies performed to date have not been designed or powered to evaluate clinical outcomes. Nevertheless, it is encouraging that the REPAIR-AMI

n engl j med 355;12 www.nejm.org september 21, 2006

BMMNC를 이용한 결과
→ Mixed Result

heterogenous cell population

보다 정교한 임상시험의 필요성 제기

BM-derived Mononuclear Cells (Clinical trial; MNC, PBSC)

The Effect of Intracoronary Reinfusion of Bone Marrow-derived Mononuclear Cells(BM-MNC) on All Cause Mortality in Acute Myocardial Infarction

- **BAMI Trial :** Phase Ⅲ 임상 진행중

-**Patients :** AMI (LVEF 45%이하) 3000명 enrollment 예정

- **Infusion :** intracoronary

- **Cell type :** Autologous bone marrow-derived mononuclear cells

- **Primary Outcome :** Time from randomization to death

- **Date :** 2012년 9월 ~ 2017년 1월

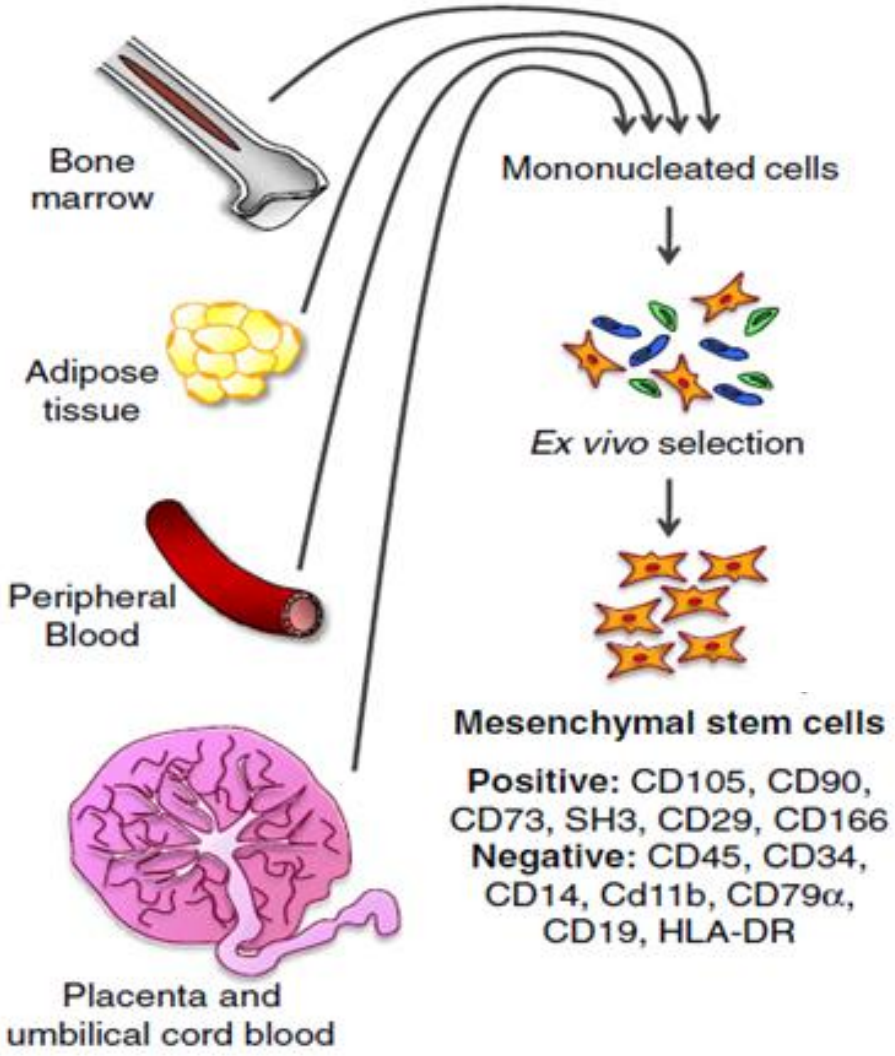
- **ClinicalTrials.gov Identifier:** NCT01569178

Mesenchymal Stem Cells (MSCs) (Good Candidate for Therapy)

Characteristics of MSC

1. Autologous/High capacity of cell proliferation
2. Differentiate into multiple cell types
3. Ability to migrate & integrate to host's target tissues
4. No safety concerns (tumor formation and allogenic rejection)
5. No ethical and political issues

MSCs (Sources)

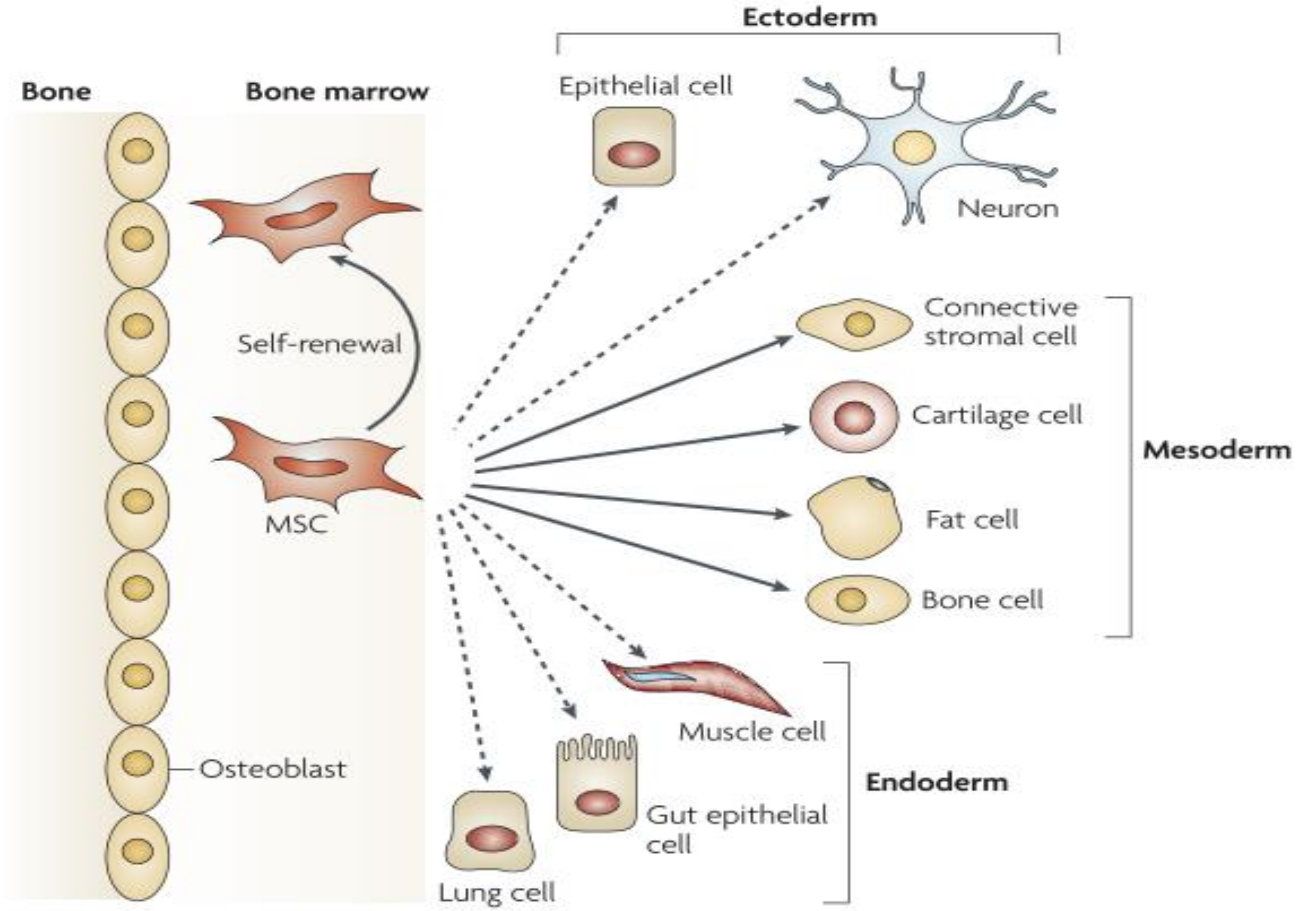


1. **Bone marrow**
2. **Adipose tissue**
3. **Peripheral Blood**
4. **Placenta & UCB**

Source: Gnecchi et al. Vascul Pharmacol 57: 48-55, 2012

MSCs (Plasticity)

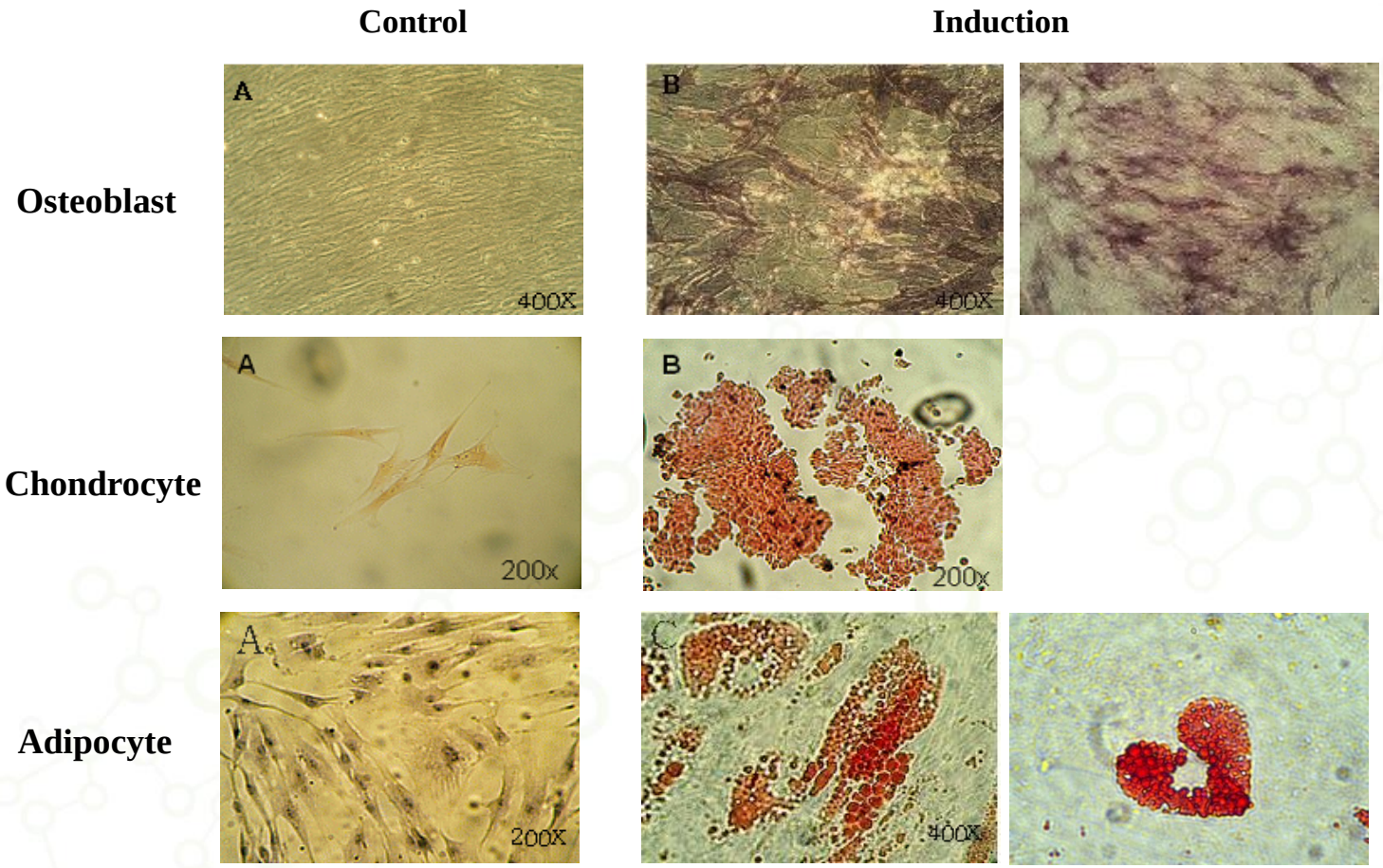
MSC는 중배엽성 세포외에 외배엽,내배엽성 세포로의 분화가 가능한 Plasticity가 있다



Source: Uccelli et al, Nature Reviews 8: 726-736, 2008

MSCs (Differentiation)

MSC의 분화를 특이적 염색으로 확인



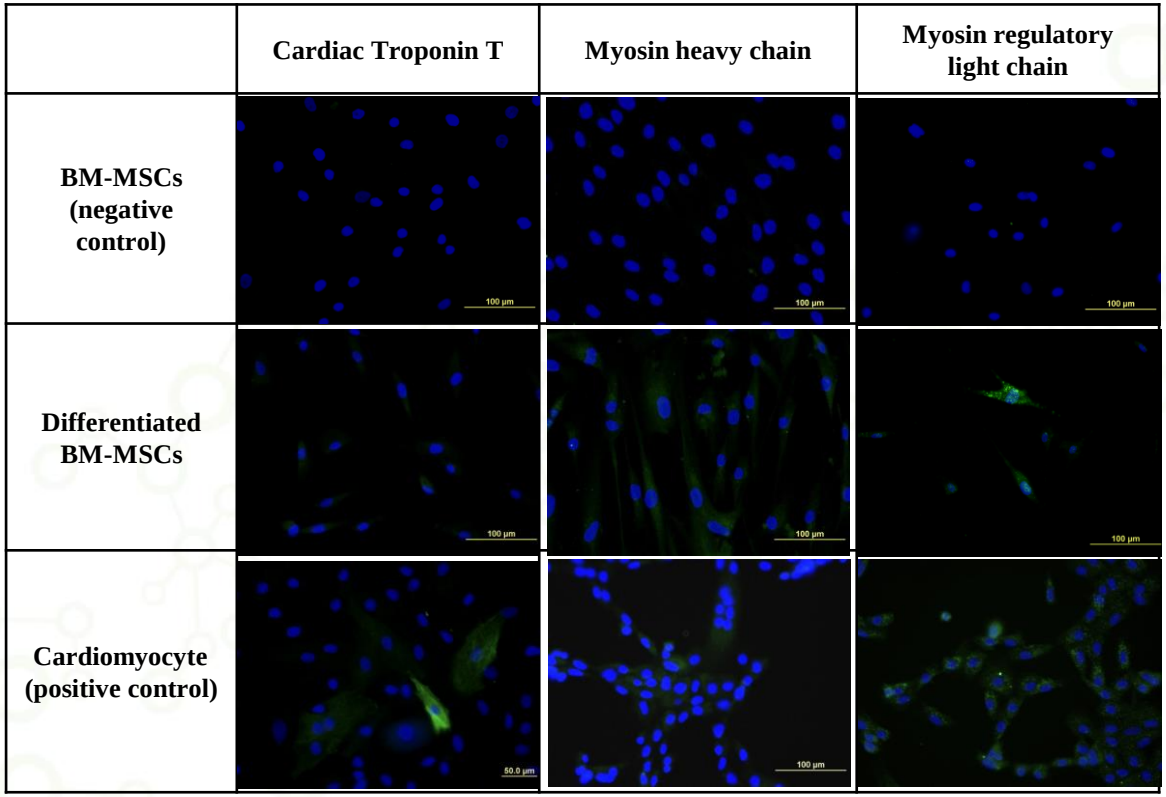
Source: Pharmicell Co., Ltd

MSCs (Differentiation)

미분화 MSC (음성 대조군) vs. 분화유도 MSC vs. 심근세포 (양성대조군) 분화 유도 확인

5-azacytidine + bFGF (10 – 14 days)

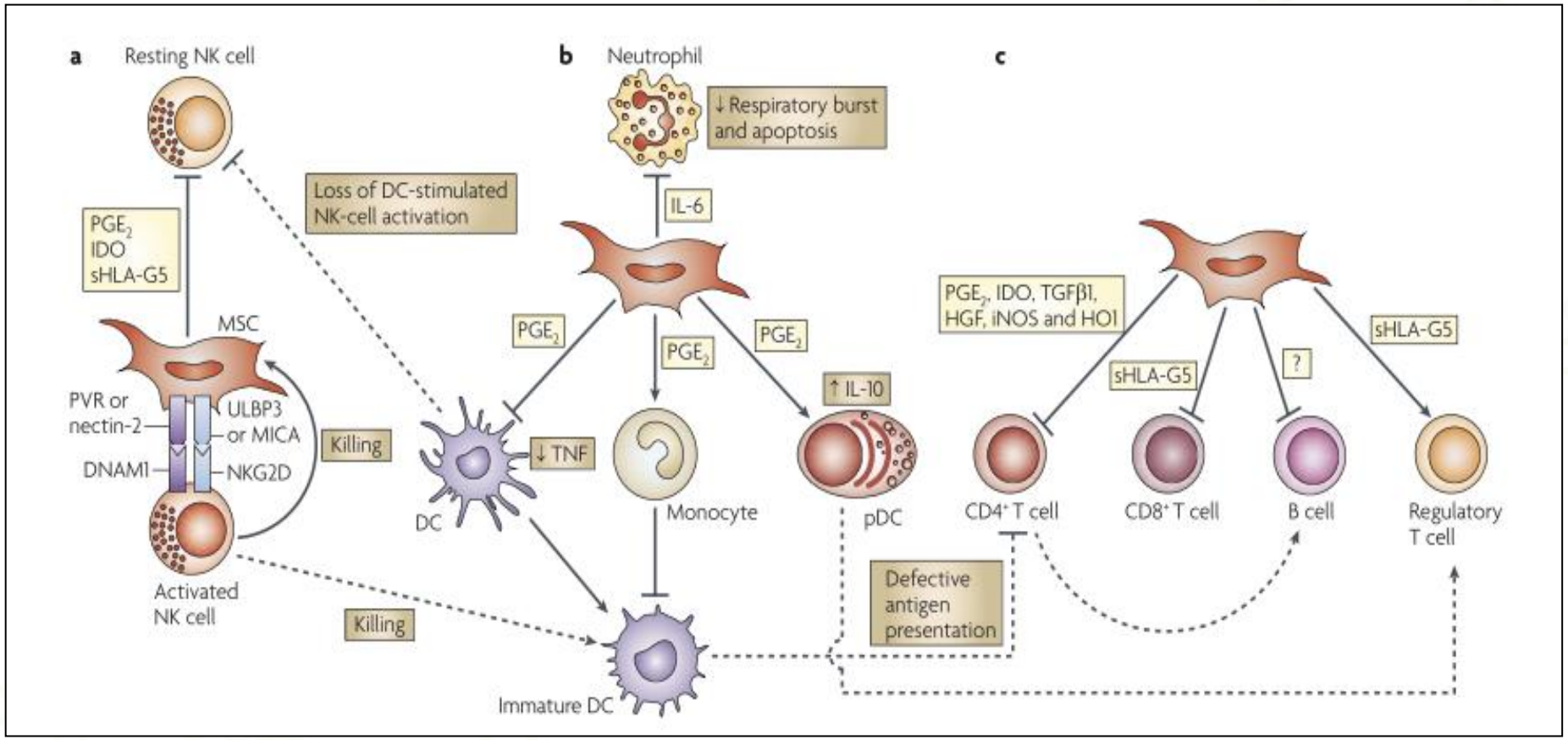
Cardiomyocyte



Source: Pharmicell Co., Ltd

MSCs (Immune Modulation)

MSC는 다양한 면역세포의 활성화를 억제하여 면역기능을 조절하는 능력이 있다



Source: Uccelli et al, Nature Reviews 8: 726-736, 2008

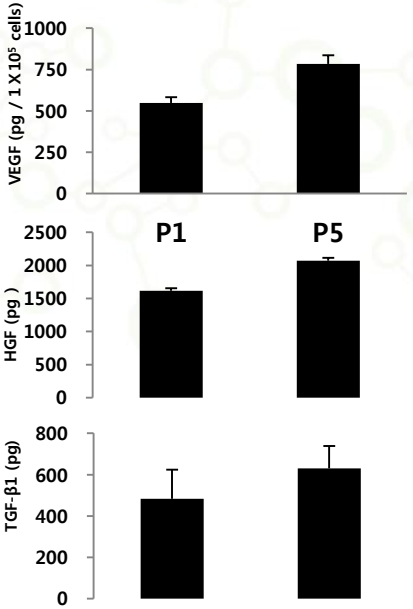
MSCs (Paracrine Factor Secretion)

MSC가 분비하는 다양한 factor로 paracrine effect를 실험을 통해 확인

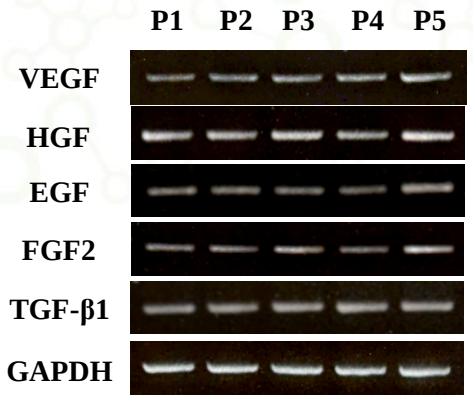
Table 1. Classification of paracrine factors secreted by mesenchymal stem cells (MSCs).

Function	Factors	Ref.
Trophic	VEGF	[14-16]
	bFGF	[14]
	IL-6	[14]
	MCP-1	[14]
	HGF	[15]
	TGF-β	[15]
	EGF	[16]
	IGF	[16]
	SDF-1	[16]
	Angiopoietin-1	[16]
	Macrophage inflammatory protein	[16]
	Keratinocyte growth factor	[16]
	Erythropoietin	[16]
Immunomodulatory	PGE2	[20]
	HLA-G5	[23]
	HGF	[24]
	TGF-β	[24]
	IDO (induced by IFN-γ)	[39]
Chemoattractant	CCL2 (MCP-1)	[43]
	CCL3 (MIP-1α)	[43]
	CCL4 (MIP-1β)	[43]
	CCL5 (RANTES)	[43]
	CCL7 (MCP-3)	[43]
	CCL20 (MIP-3α)	[43]
	CCL26 (eotaxin-3)	[43]
	CX3CL1 (fractalkine)	[43]
	CXCL1 (GROα)	[43]
	CXCL2 (GROβ)	[43]
	CXCL5 (ENA-78)	[43]
	CXCL8 (IL-8)	[43]
	CXCL10 (IP-10)	[43]
	CXCL11 (i-TAC)	[43]
	CXCL12 (SDF-1)	[43]

실험상 mRNA 발현 확인



세포배양액내에서 인자 분비 확인



Source: Wang et al., Expert Opin. Biol. Ther., 2011 Pharmicell Co., Ltd

MSCs (Clinical Applications)

MSC를 통해 다양한 질환 치료 임상 연구가 활발하게 진행

임상 연구 분야

Immunosuppression

Regeneration

Phase III completed	Phase I–II	Phase III	Completed (I–II, III)
Graft versus host disease	14	1	I–II: 3, III: 1
Crohn's disease	4	3	I–II: 1, III: 1
Kidney injury	1		N/A
Cirrhosis	17		I–II: 3
Pulmonary diseases	5		I–II: 1
Fistula	1		N/A
Total	176	10	34

Source: Francois M & Galipeau J. J Cell Physiol 2012

MSCs (Clinical Applications for Cardiac Diseases)

- In comparison with the BM mononuclear cells, a few number of clinical studies using MSCs have been reported for cardiac regeneration

MSC 임상연구 (AMI)

Group	Dose(cells)	Follow up (months)	Results
Chen et al. [2004]	8-10 × 10^9 (IC)	3	Myocardial Perfusion, LVEF & LV chamber ↑
Hare et al. [2009]	0.5, 1.6, and 5 × 10^6 (IV)	3	Ventricular arrhythmia , LVEF ↑
Williams et al. [2011]	Chronic ischemic cardiomyopathy secondary to MI	10 repeated injections of 0.5mL of cell suspension (TESI)	3-12	↓Cardiac remodeling,↓ ESV and EDV, and↑ regional contractility
Bartunek et al. [2011] (C-CURE)	Heart failure secondary to ischemic cardiomyopathy	6-12 × 10^8 (EMG)	6	↑LVEF and↓ESV and EDV

IC, intracoronary infusion; DI, direct intramyocardial injection; IV, intravenous infusion; TEST, transendocardial stem cell injection; EMG; electromechanical guidance; ↑, increase; ↓, decrease.

Source: Elnakish et al. Stem Cells Int, 2012

MSCs (Clinical Applications for Cardiac Diseases) – Chen

► **The first clinical trial of stem cell (BM mononuclear cells) therapy for cardiac repair**

Effect on Left Ventricular Function of Intracoronary Transplantation of Autologous Bone Marrow Mesenchymal Stem Cell in Patients With Acute Myocardial Infarction

Am J Cardiol 2004;94:92-95

- **Cell type :** Autologous bone marrow MSC
- **Infusion :** intracoronary
- **Patients :** AMI 치료군 34명 / 대조군 35명
- **Result :** After 3 months LVEF 18% 상승후 6 months 까지 유지($p<0.05$)

MSCs (Clinical Applications for Cardiac Diseases) – Hare

► **The first clinical trial of allogenic MSC therapy for AMI repair**

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

J Am Coll Cardiol 2009, 54: 2277–86

- **Cell type :** Allogenic bone marrow-derived human MSC (prochymal)
- **Infusion :** intravenous
- **Patients :** AMI 치료군 39명 / 대조군 21명
- **Result :** After 12 months LVEF 5.2% 상승(Cardiac MRI)

MSCs (Clinical Applications for Cardiac Diseases) – Ongoing

Table. Ongoing Clinical Trials using MSCs in ischemic heart diseases (www.clinicaltrials.com)

Tri					Patient	
RELIE						
Angio						
Stemp						
Osins						
ESTIM						
Natio						hy
AHEP/						
RIMEC des						
Helsir						
ESTIM						
The P						
Natio						hy
Rigsh						
AHEP/						hy
University Hospital, Toulouse	1/2	BM(Auto)	Transendocardial	Safety	10	Chronic Myocardial Ischemia

- Trial Name or Sponsor : RELIEF / Pharmicell Co., Ltd
- Phase III Trial
- Source : BM(Autologous) [Hearticellgram]
- Route : Intracoronary
- Endpoint : LVEF
- Patient : 135
- Condition : Acute Myocardial Infarction

Proposed Mechanisms of SC Therapy for Ischemic Tissue Repair

1. 직접 작용

- Transdifferentiation

2. Paracrine Effect

- Angiogenesis
- Prevention of apoptosis
- Modulation of matrix remodelling

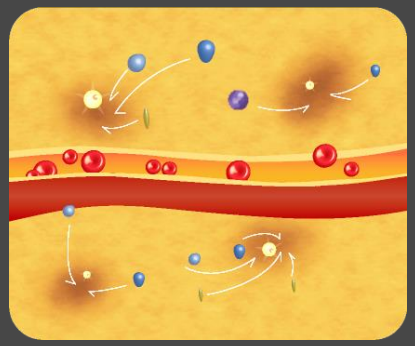
Figure 3 Proposed mechanisms of ischaemic tissue repair via stem and progenitor cell-based therapies.

Source: Tongers et al. Eur Heart J 32: 1197-1206, 2011

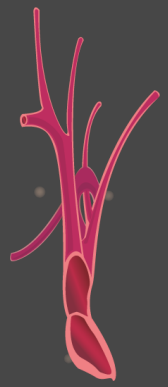
Putative Paracrine Effects of SCs in Ischemic Heart Disease

Stem Cells homing

SDF-1
VEGF-A
FGF-2
CCL2
SCF



Angiogenesis



VEGF-A
ANGPT-1
TGF- β1
IL-6
PDGF-A
ANG

STEM CELL

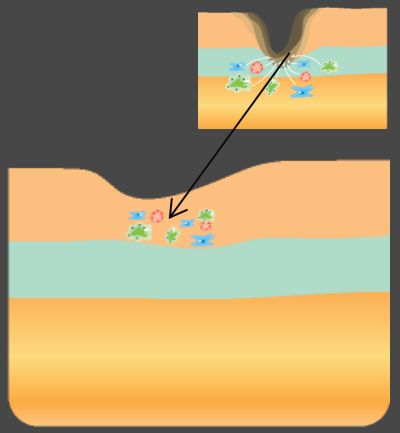
Anti-apoptosis

SFRP-2
SFRP-1
Tβ4
HGF
IGF-1
LIF

Anti-inflammation

IL-6
IL-11

Anti-Scarring(Fibrolysis)

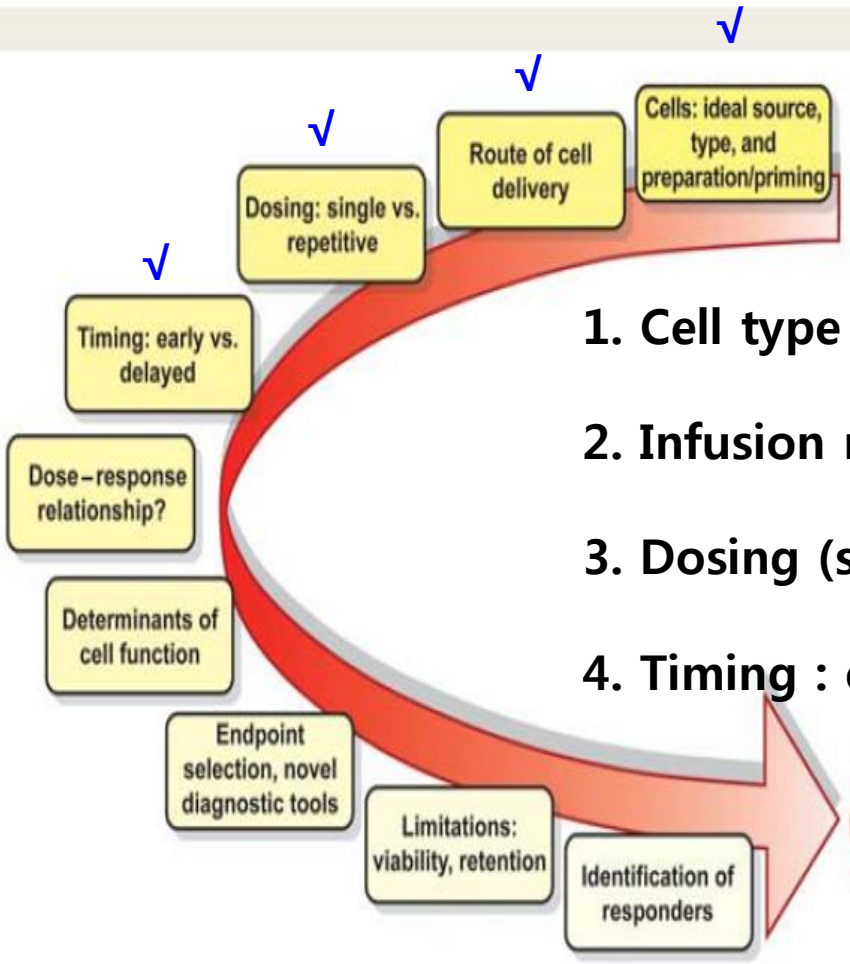


Tβ4
FGF-2
MMP-1
MMP-2
MMP-9
TIMP-1
TIMP-2
CTGF

Advantages & challenges of SC Types for Cardiac Repair

Cell Types	Advantage	Challenges
BMC	Many experience	- Conflicting results describing functional benefit
MSC	Immunoprivileged	Large diameter of cells limits transplantation
Cardiac-derived Cells	Simple isolation and expansion process	Autologous cells requiring expansion
Skeletal Myoblasts	Minimally invasive tissue harvest	Arrhythmia concerns
iPS cell	Patient's specific	-No safety (tetatoma) & efficacy data from clinical trial

Considerations for Future SC therapy in Ischemic heart Disease



1. Cell type 과 조작 범위
2. Infusion route
3. Dosing (single vs. repertitive)
4. Timing : early vs. delayed

Source: Tongers et al. Eur Heart J 32: 1197-1206, 2011

Clinical Experience (STEMI-Rose study using Hearticellgram-*AMI*)

Study title		A randomized, open-label, multicenter trial for the safety and efficacy of intracoronary autologous mesenchymal stem cell transplantation in patients with acute myocardial infarction (Phase II/III)
Investigational product		Hearticellgram-*AMI* (Autologous BM-derived MSCs)
Sponsor		Pharmicell Co., Ltd.
Infusion route/dose		Intracoronary / 1 x 10^6 cells/kg (single)
Enrollment & F/U period		80 (Control: 40, MSC: 40) / 6 months
Institution		**Severance Hospital,** Wonju Christian Hospital, Inha University Hospital, Ilsan Paik Hospital
Outcome measures	**Efficacy**	**Primary endponit** - Changes in global LVEF by SPECT **Secondary endpoint** - Changes in LVEDV, LVESV, Wall Motion Score Index, MACE
	Safety	- Adverse event, Lab test, Vital sign, Physical exam., 12-lead EKG, Chest X-ray

Clinical Experience (STEMI-Rose study using Hearticellgram-*AMI*

■ Final product release criteria of Hearticellgram-*AMI*

Test items		Test method	Acceptance criteria/specification
Sterility (bacterial & fungal testing)		Culture method (14 days)	Negative
Mycoplasma		Culture method (28 days)	Negative
Adventitious agent testing (in vitro viral testing)		Culture method (CPE & Had) (14 days)	Negative
Identity	Morphology	Microscopy	Adherent spindle-shaped cells
	Surface marker (positive)	FACS analysis (CD105 , CD73)	≥ 85%
	Cardiomyocytic differentiation	Immunostaining	Positive for cardiomyocyte-specific protein
Purity		FACS analysis (CD 14, CD34, CD45)	≤ 3%
Endotoxin		LAL test	≤ 0.5 EU/mL
Potency		Paracrine secretion (ELISA)	Secretion of cytokine or growth factor involved in angiogenesis
Viability		Microscopy (trypan blue staining)	≥ 70%
Cell number/dose		Microscopy (trypan blue staining)	4.5 -5.5 x 10^6/mL

Clinical Experience (STEMI-Rose study using Hearticellgram-*AMI*)

Variables	MSC group (n=30)	Control group (n=29)	p value
Age, year	53.9 ± 10.5	54.2 ± 7.6	0.955
Men, n(%)	27 (90.0)	26 (89.7)	1.000
Risk f			
Hyp			1.000
Diab			0.360
Cere			1.000
Smo			0.785
Killip			0.220
Coron			
1 ves			0.719
2 ves			
3 ves			
Locati			
Left			0.694
Left			
Righ			
Medic			
Aspi			1.000
Clop			1.000
Cilo			0.748
Beta			1.000
ACE			1.000
Stati			1.000
Vital s			
Initi			0.490
Initi			0.732
Sympt			0.775
≤ 2 hours	5 (19.2)	3 (12.0)	
2 - 6 hours	16 (61.5)	17 (68.0)	
> 6 hours	5 (19.2)	5 (20.0)	
Primary PCI, n(%)	26 (86.7)	25 (89.3)	0.621

Safety results

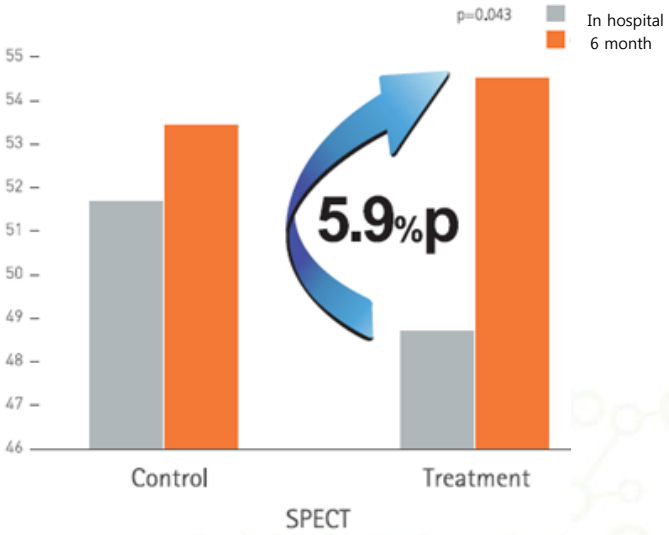
→ No MACE or cell-related serious adverse events

→ No immediate or delayed toxicity related to MSC infusion

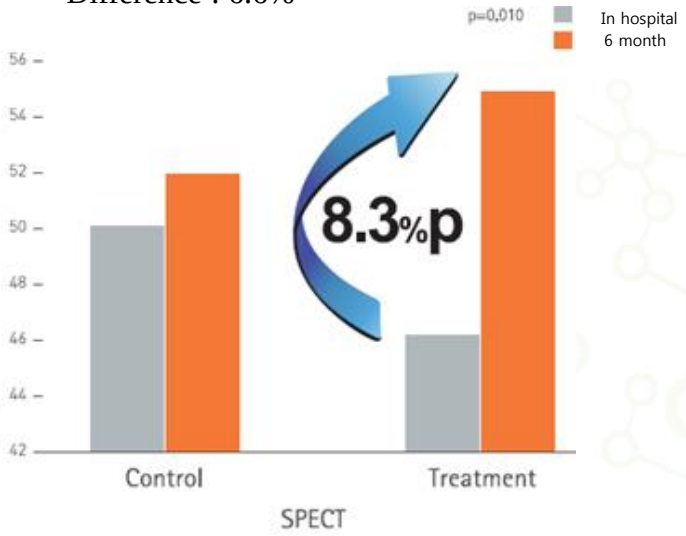
■ Patient demographics & baseline date

Clinical Experience (STEMI-Rose study using Hearticellgram-*AMI*)

Efficacy evaluation : Primary Endpoint
LVEF (%)
Difference : 4.3%



Subgroup analysis (S2B≤ 6 hours)
LVEF (%)
Difference : 6.6%



	SPECT		MRI	
	MSC (n=30)	Control (n=29)	MSC (n=10)	Control (n=7)
	Mean±SD		Mean±SD	
After enrollment	49.03±11.70	52.17±9.11	46.06±15.20	54.89±9.61
After 180 days	54.97±11.79	53.93±10.04	51.28±13.60	54.63±10.27
Change	5.93±8.46	1.76±6.94	5.22±7.60	-0.26±0.89
Change between two groups (95% CI)	**4.18±7.75** (0.13, 8.22)		**5.48±5.92** (-0.74, 11.69)	
p-value	<0.05		<0.05	

KJT M/73 #5829503

C.C: D.O.E

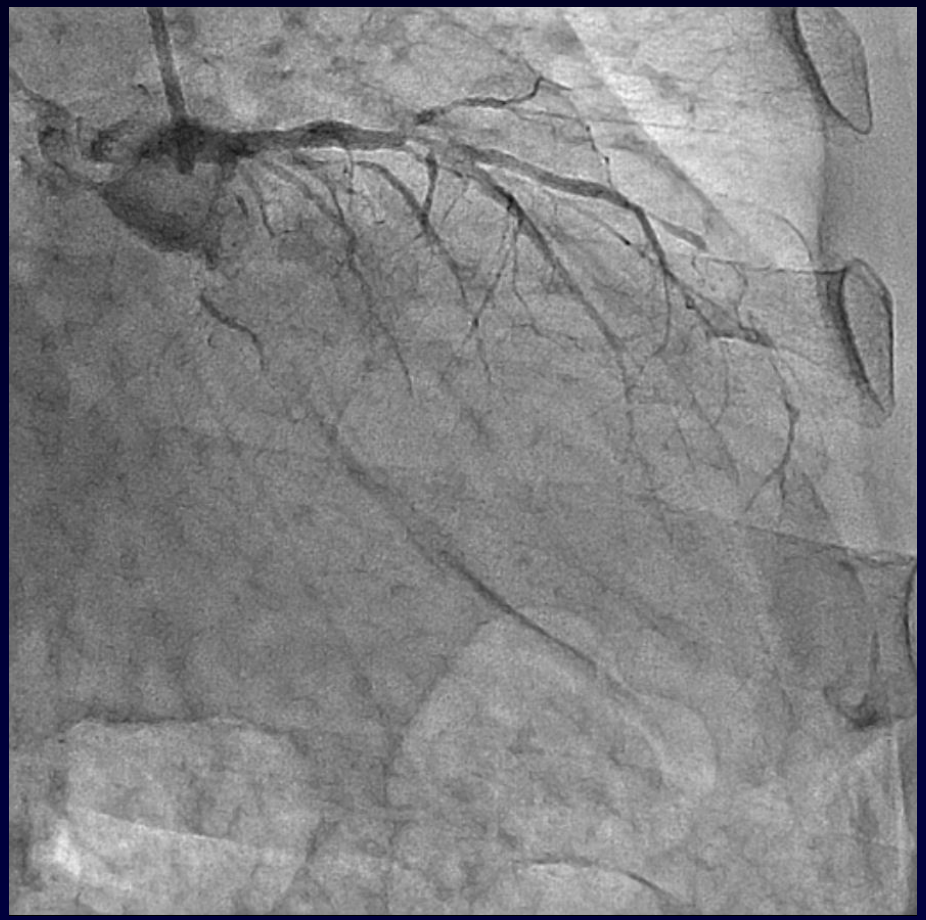
P/Hx:

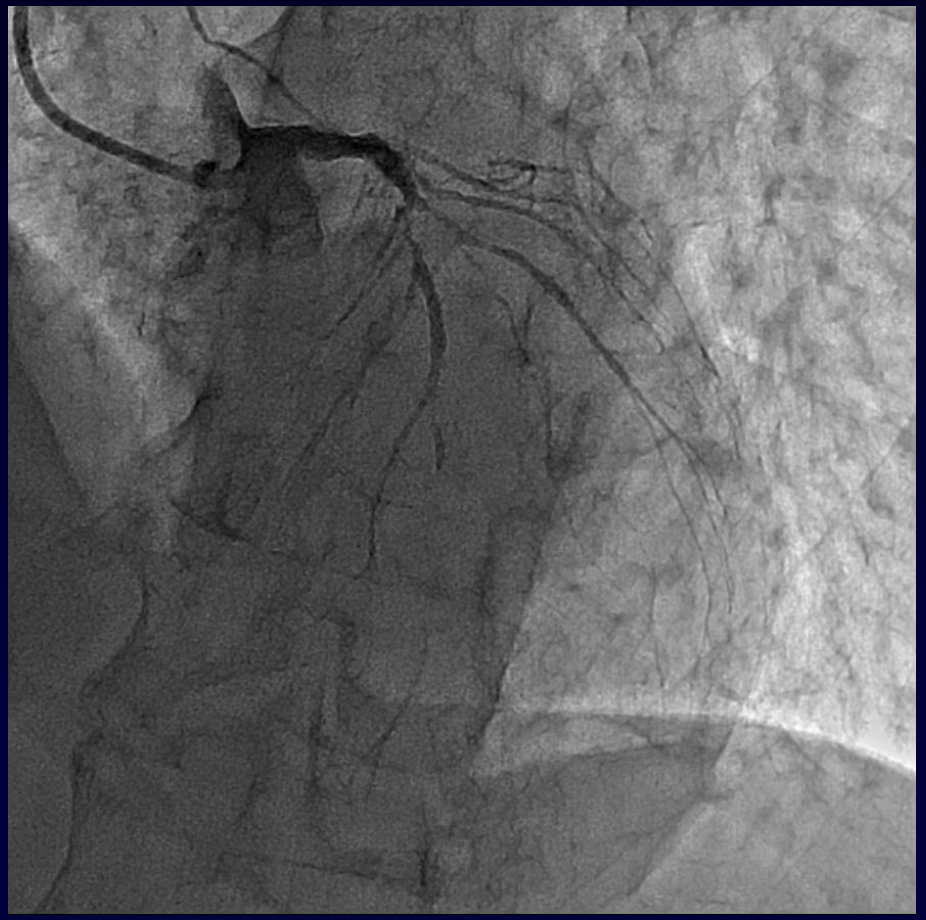
- DM/Hypertension (+/+)
- MI (2002)
- Ischemic DCMP
- CVA (2008)

Laboratory findings

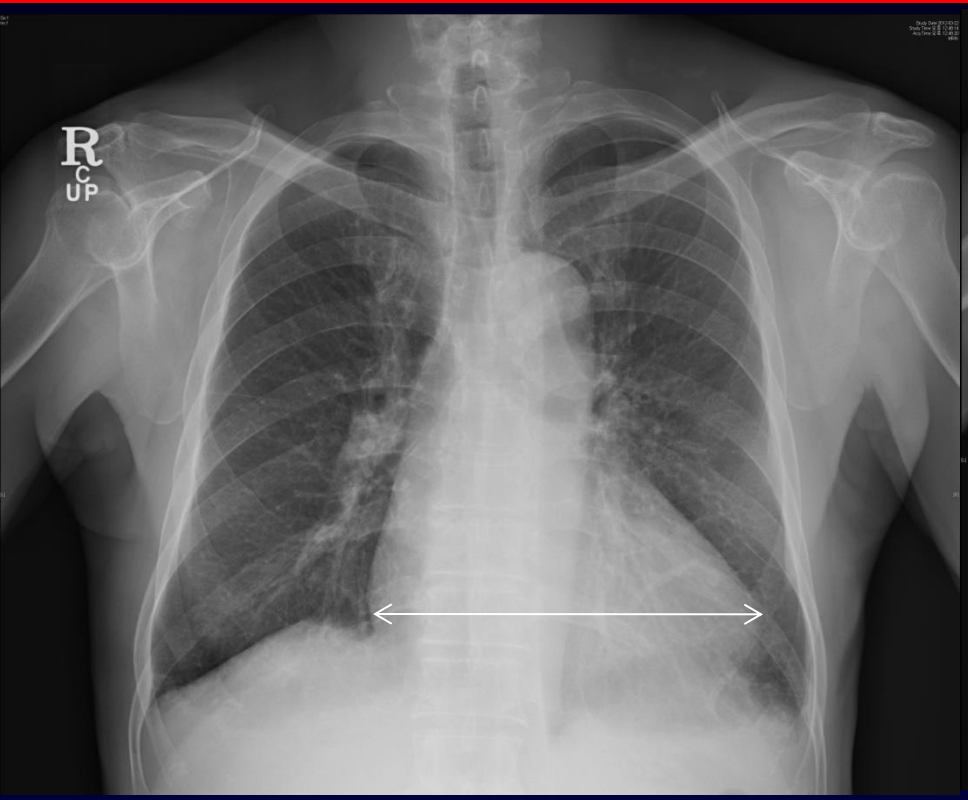
- BUN/Cr 27.6/1.75
- T-chol/LDL/HDL/TG 155/83/61/116

Coronary angiography

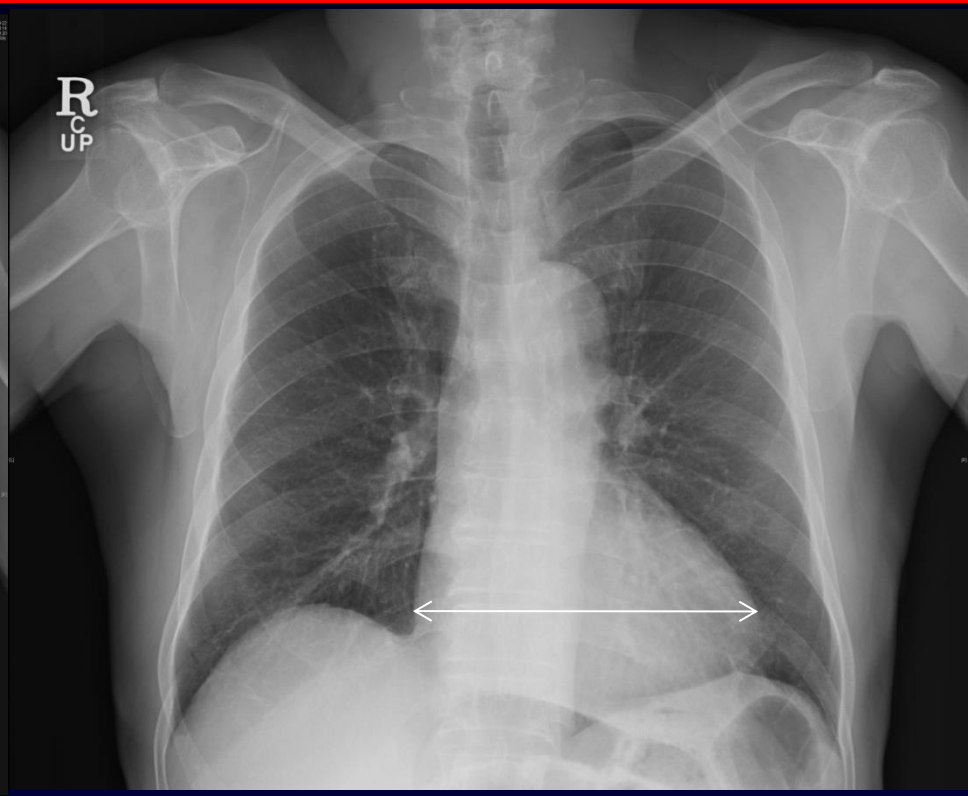




흉부 X 선 사진



시술 전

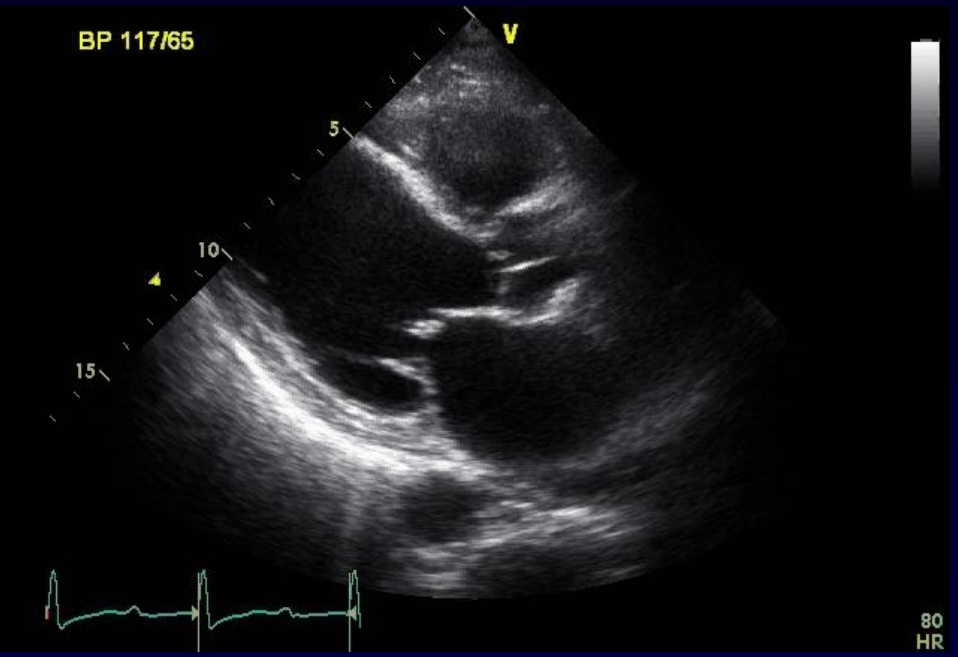


시술 3개월 후

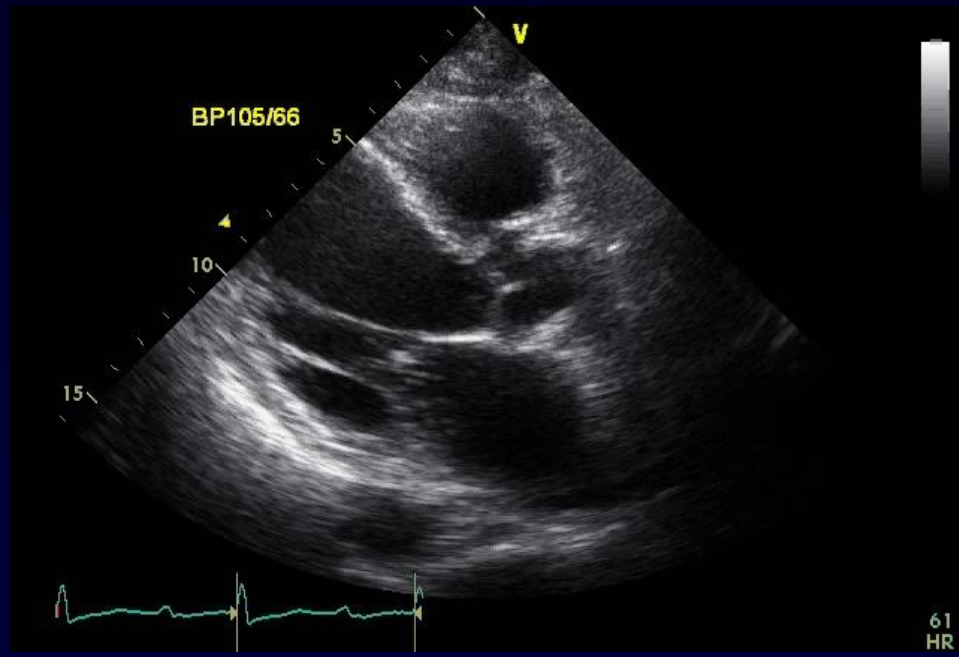
심 흉곽 비가 55%에서 50% 로 감소

심장 초음파 영상

시술 전



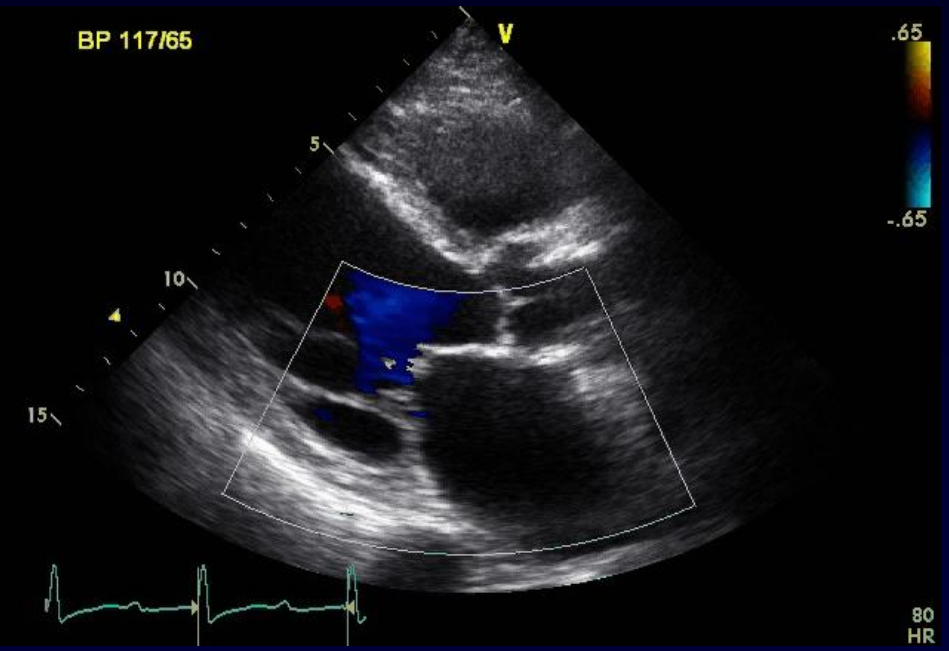
시술 3개월 후



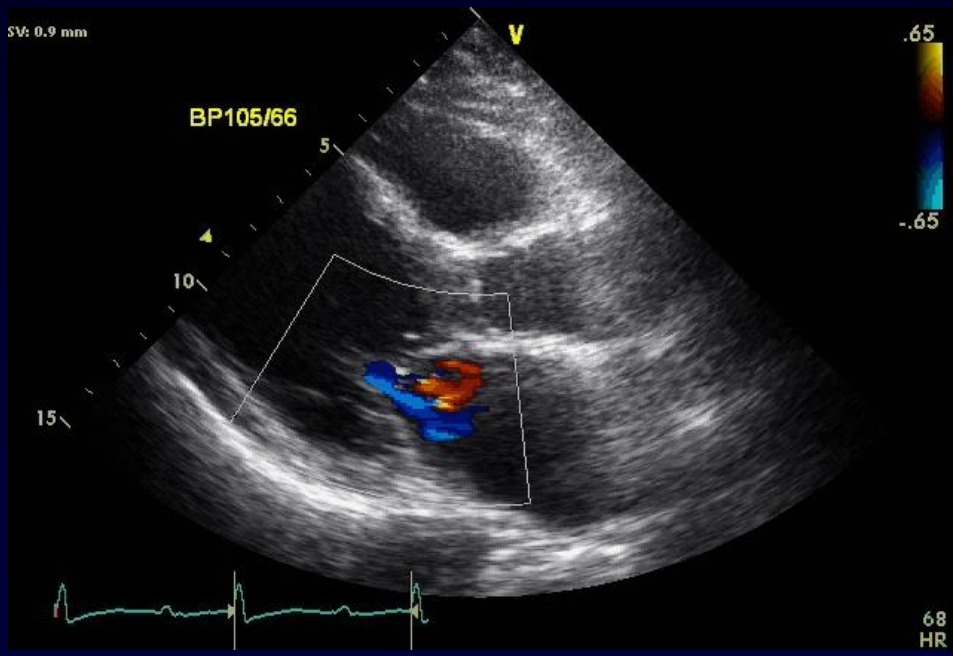
심장의 내경이 61mm에서 57mm로 감소하고
좌심실 수축 기능이 26%에서 35%로 상승함

심장 초음파 영상

시술 전



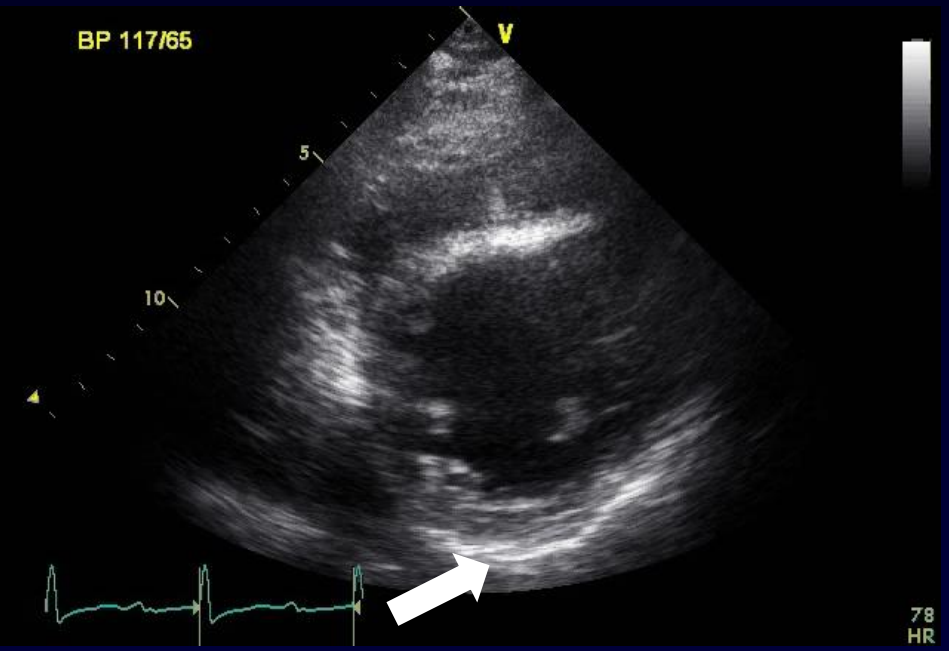
시술 3개월 후



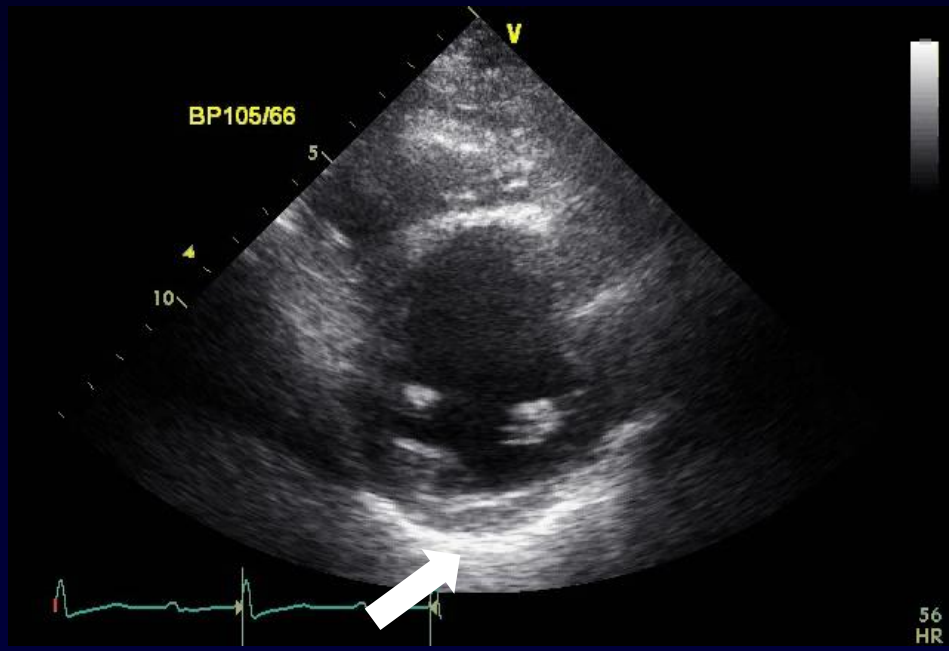
심장 내경 감소와 수축기능 호전으로
허혈로 인해 발생한 판막의 역류가 감소 됨

심장 초음파 영상

시술 전



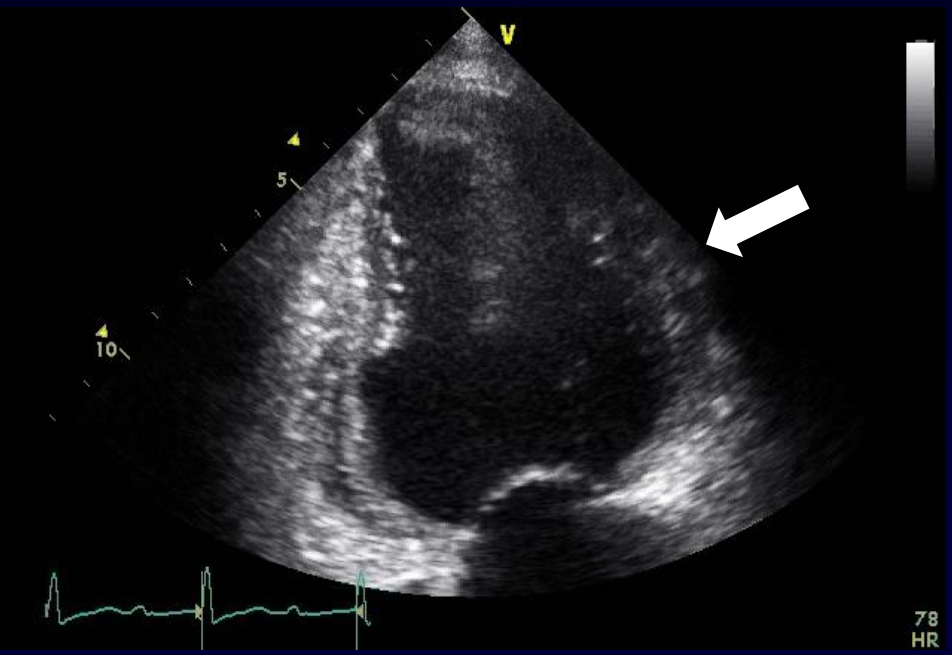
시술 3개월 후



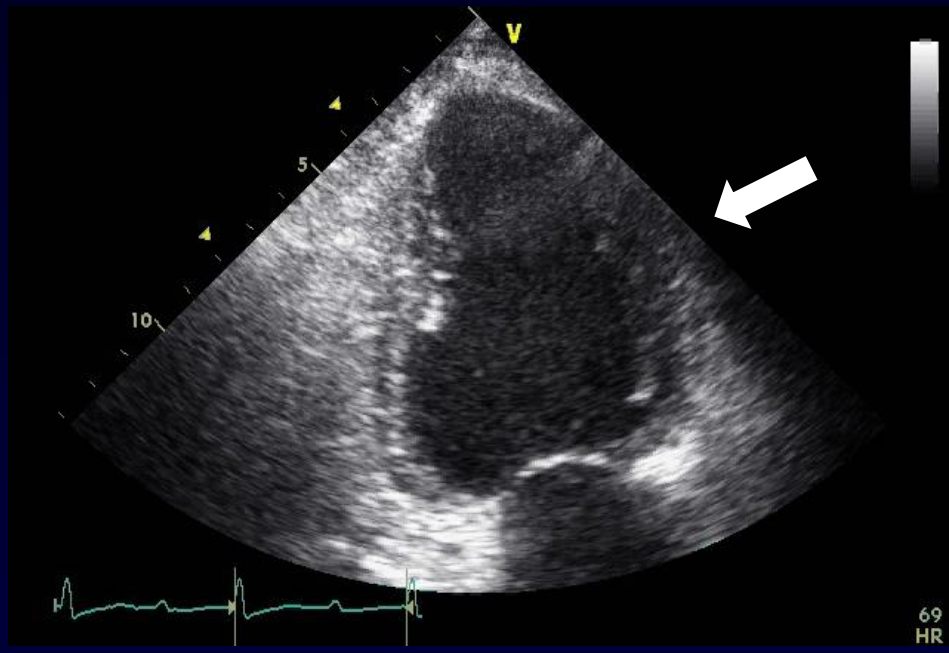
심장 후벽의 국소운동 장애의 호전

심장 초음파 영상

시술 전



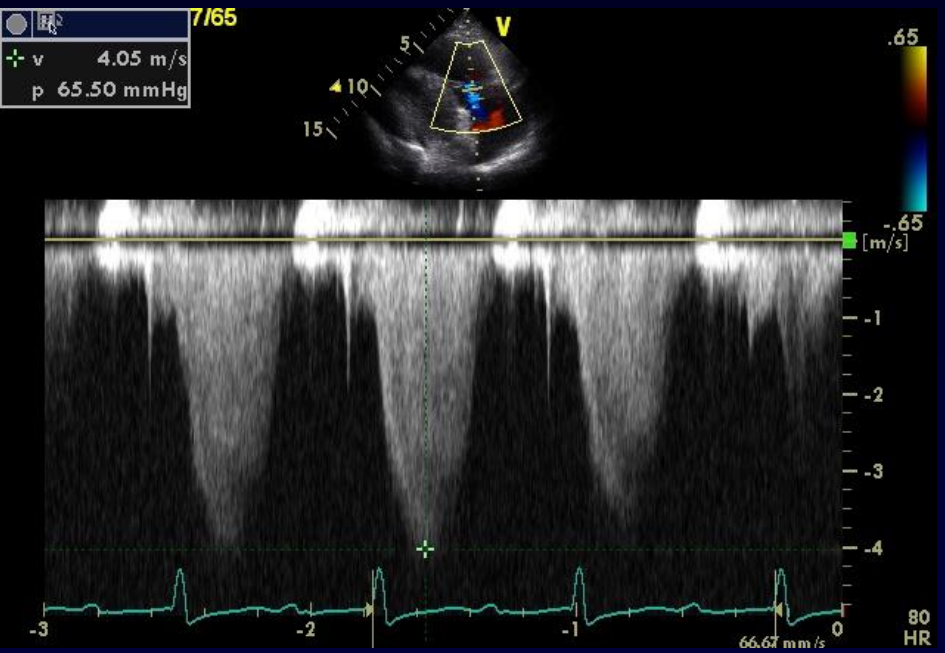
시술 3개월 후



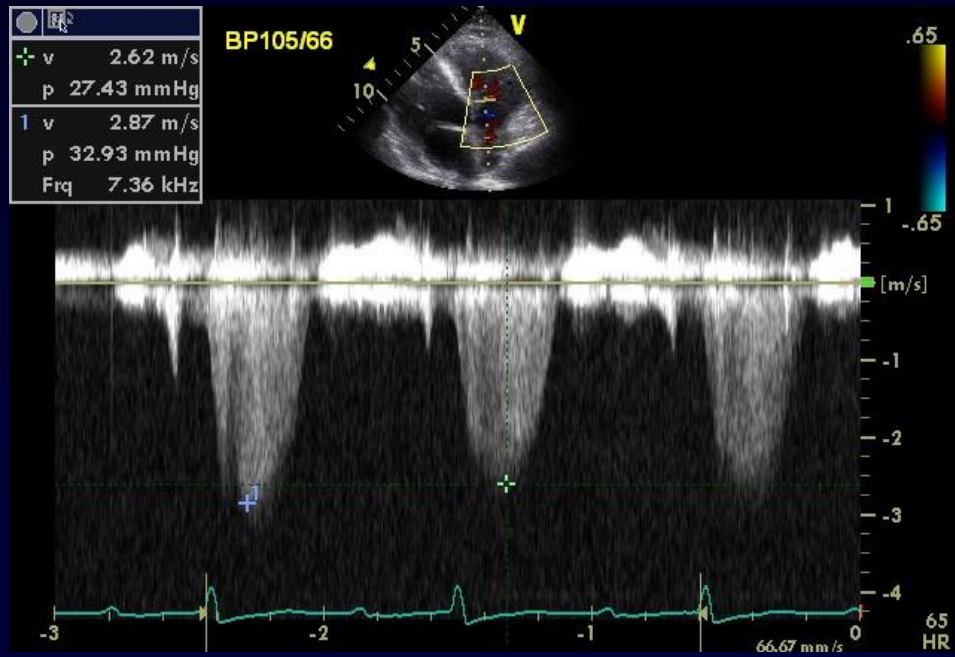
심장 전벽의 국소운동 장애의 호전 및
좌심실 수축력의 전반적 호전

심장 초음파 영상

시술 전



시술 3개월 후



좌심실 부전으로 발생한 **폐동맥 고혈압**이
시술 후 **호전** 됨

줄기세포 치료

1. 심장 내경의 감소 및 심장의 수축기능 호전

2. 국소벽 운동장애의 호전

3. 판막 역류의 호전

4. 폐동맥 고혈압의 호전

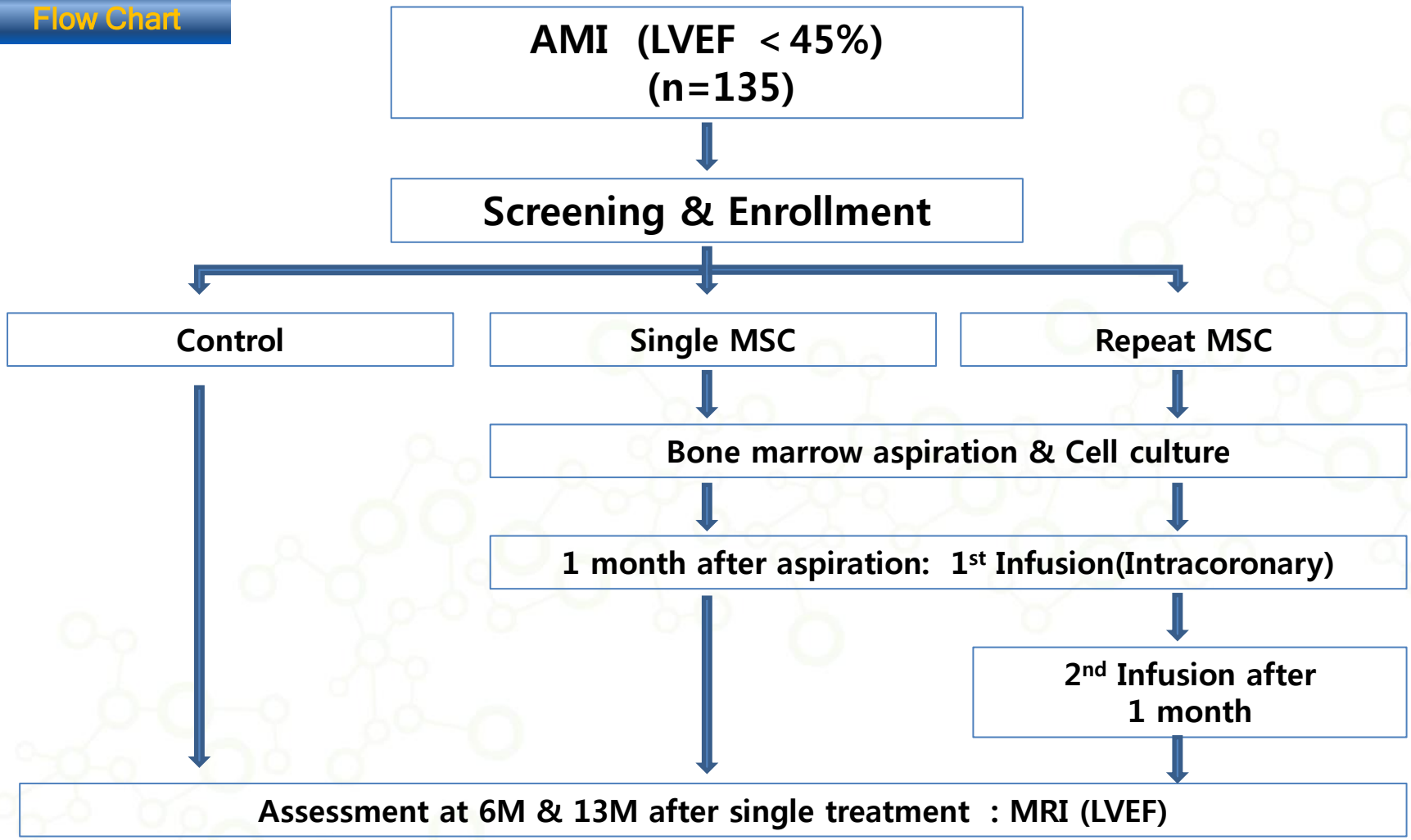
➔ 환자의 임상 증상 호전 및 운동 능력 향상

Ongoing study (RELIEF study, repeated Hearticellgram-*AMI*

Study title		**RELIEF (A Randomized,Open labEled, muLticenter Trial for Safety and Efficacy of Intracoronary Adult Human Mesenchymal stEm Cells Acute Myocardial inFarction)** [ClinicalTrials.gov Identifier: NCT01652209]
Investigational product		Hearticellgram-*AMI* (Autologous BM-derived MSCs)
Sponsor		Pharmicell Co., Ltd.
Infusion route/dose		Intracoronary / ~ 1 x 10^6 cells/kg (single & twice)
Enrollment & F/U period		135 (Control: 45, 1 dose: 45, 2 dose: 45)/ 13 months
Institution		More than eight institutions including Severance Hospital
Outcome measures	**Efficacy**	**Primary endponit** - LVEF measured 13 months after the cell treatment (MRI measurement) **Secondary endpoint** - Changes in Infract size, LVEDV, LVESV, Wall Motion Score Index, MACE, NT-proBNP
	Safety	- Adverse event, Lab test, Vital sign, Physical exam., 12-lead EKG, Chest X-ray

Ongoing study (RELIEF study, repeated Hearticellgram-*AMI*)

Flow Chart



Ongoing study (RELIEF study, repeated HearticellgramⓇ-*AMI*)

A Randomized,Open labEled, muLticenter Trial for Safety and Efficacy of Intracoronary Adult Human Mesenchymal stEm Cells Acute Myocardial inFarction

This study is not yet open for participant recruitment.

Verified April 2013 by Pharmicell Co., Ltd.

Sponsor:
Pharmicell Co., Ltd.

Information provided by (Responsible Party):
Pharmicell Co., Ltd.

ClinicalTrials.gov Identifier:
NCT01652209

First received: July 25, 2012
Last updated: April 4, 2013
Last verified: April 2013
History of Changes


Thank you
for your attention!

Advantages of MSC for Cardiac Repair(ESC vs iPSC vs MSC)

	ESC	iPSC	MSC
Differentiation capability			
Cardiomyocyte	Possible	Possible	Possible
EC	Possible	Possible	Possible
SMC	Possible	Possible	Possible
Other cell types	Possible	Possible	Possible
Cell source	Limit	Diverse	Diverse
Immune rejection response	Exists	Exists	No exist if autologous
Functionally and electrically synchro-nized after transplantation	Possible	Possible	Possible
Paracrine effect	Exists	Exists	Exists
Isolation markers	Diverse	Diverse	Diverse
Isolation purity	Extremely low	Extremely low	Low
In vitro amplification capability	Limit	Limit	Limit
Teratoma generation	Possible	Possible	No
Remarks	Ethical Problems	Using viral vectors	-

ESC, embryonic stem cells; iPSC, induced pluripotent stem cells; BMSC, bone-marrow derived stem cells; MB, myoblasts; CSC, cardiac stem cells; EC, endothelial cells; SMC, smooth muscle cells.

MSC는…

-Cell source가 다양
-자가에서 면역 거부 반응이 없음

-윤리적 문제 없음
-Teratoma 없음

(Circ J 2012; 76: 1307 –1312)

Advantages of MSC (ESC vs iPSC vs MSC)

<줄기세포 종류별 논문 발표 주요 국가('11)>

순위	성체 줄기세포		배아 줄기세포		역분화 줄기세포	
	국가명	논문 수	국가명	논문 수	국가명	논문 수
1	미국	3,305	미국	874	미국	310
2	중국	1,402	중국	222	일본	105
3	독일	813	영국	188	중국	81
4	일본	699	일본	187	독일	52
5	영국	575	독일	165	스페인	31
6	이탈리아	511	캐나다	102	캐나다	30
7	프랑스	420	한국	96	영국	29
8	한국	391	프랑스	76	한국	26
9	캐나다	328	호주	75	호주	24
10	스페인	275	네덜란드	68	싱가폴	22
	세계 합계('11)	9,052	세계 합계('11)	2,038	세계 합계('11)	645
	세계 합계('10)	8,970	세계 합계('10)	2,107	세계 합계('10)	420
	세계 합계('09)	8,132	세계 합계('09)	1,827	세계 합계('09)	202

※ 검색기간: 2011. 1. 1 ~ 2011. 12. 31
※ 출처: 생명공학정책연구센터

성체 줄기세포 분야의 논문이 9,052건으로 가장 많은 비중(77.1%)을 차지

Advantages of MSC (ESC vs iPSC vs MSC)

<줄기세포 종류별 주요국 특허 현황('10~'11)>

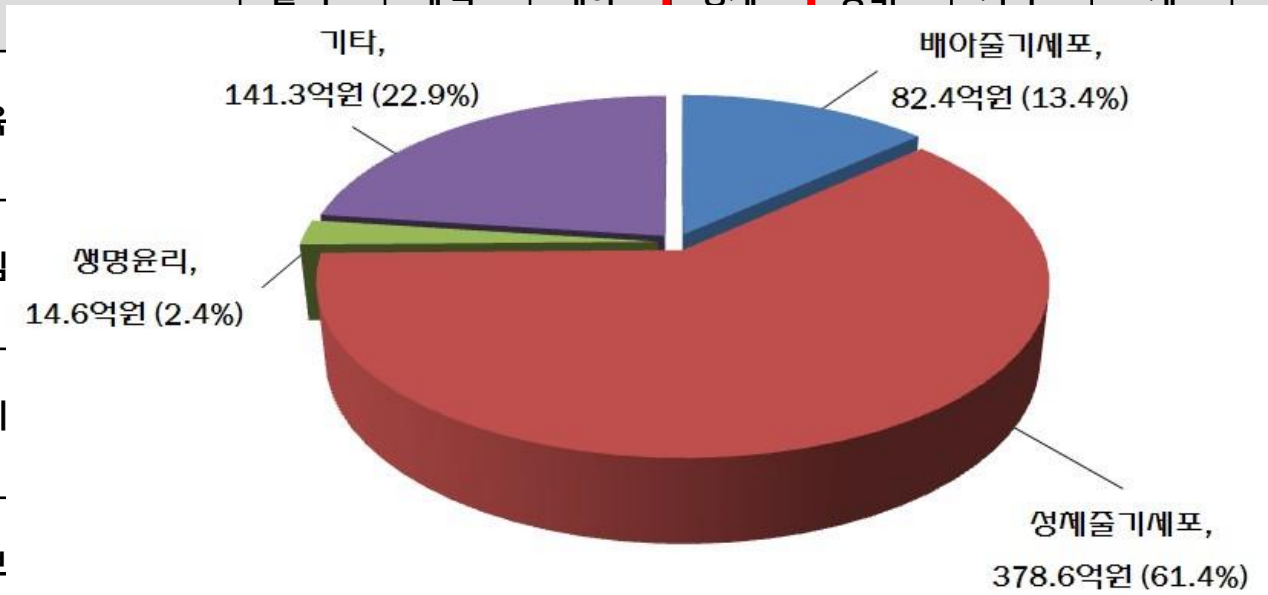
순위	성체 줄기세포		배아 줄기세포		역분화 줄기세포	
	국가명	특허 수	국가명	특허 수	국가명	특허 수
1	미국	1,189	미국	423	미국	262
2	EU	110	EU	40	일본	27
3	일본	83	일본	28	EU	20
4	한국	65	영국	22	한국	9
5	영국	37	한국	21	영국	8
6	독일	23	독일	6	중국	4
7	호주	16	호주	6	싱가폴	3
8	핀란드	13	핀란드	5	핀란드	2
9	스페인	13	독일	5	호주	2
10	인도	12	중국	4	독일	1
	세계 합계	1,640	세계 합계	586	세계 합계	340

※ 검색기간: 2010. 1. 1 ~ 2011. 12. 31 (특허공개는 통상 18개월이 걸려 검색기간을 2년으로 설정함)
※ 검색 도메인: 미국/유럽 공개 및 등록, PCT/일본영문 공개
※ 출처: 생명공학정책연구센터

Advantages of MSC

<2011년 정부 부처별 줄기세포 투자실적>

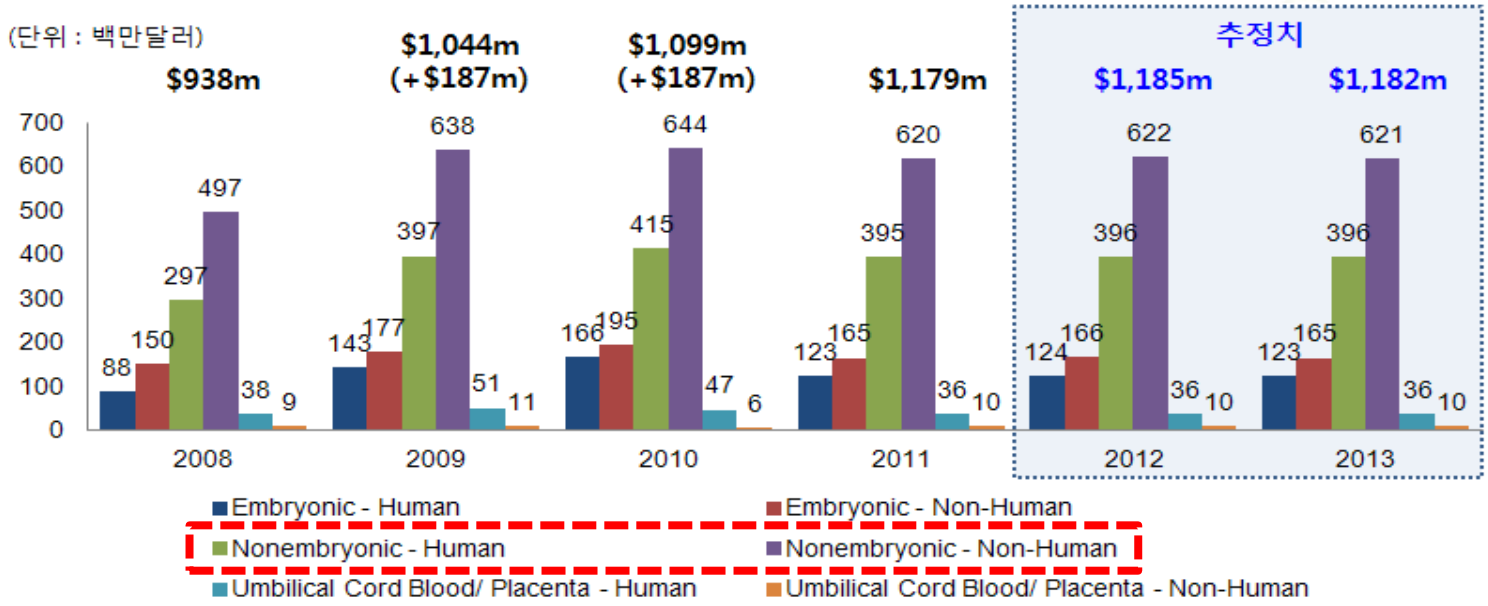
구 분	'10년 투자 실적	'11년 투자 계획	'11년 투자실적					증감율 (%)
			배아	성체	생명	기타	계	
교육								21.8
농림								7.6
지								0
보								8.7
계	53,071	59,750	8,243	37,864	1,455	14,133	61,695	16.2



※ 출처: 교육과학기술부, 농림수산부, 지식경제부, 보건복지부 "2012년도 줄기세포 연구시행계획"

Advantages of MSC

<미국 NIH의 줄기세포 분야별 투자('08~'13)>



* '09, '10년에는 ARRA(美 경기부양책)의 일환으로 각각 $187m 추가 지원
* 줄기세포 분야별 일부 중복으로 분야별 합계는 총액과 다름

※ 출처 : NIH, 생명공학정책연구센터 재구성

- 비배아줄기세포(Non-embryonic stem cell)에 가장 많은 지원이 이루어지고 있음.
- 주로 신약개발에 활용 가능한 줄기세포, 줄기세포 성장 플랫폼 등을 대상으로 지원.

Advantages of MSC for Cardiac Repair(ESC vs iPSC vs MSC)

Table: MSC clinical trials in MI, chronic ischemia, and heart failure.

Group	Condition	Dose(cells)	Follow up (months)	Results
Chen et al. [2004]	Acute MI	8-10 × 10^9 (IC)	3	↑Myocardial perfusion,↑ LVEF, and↓LV chamber
Katritsis et				re index viability ility
Mohyeddin [2007]				ct and↑
Osiris therap [2005]	Acute MI	(IV)	6	↑ n and↓ arrhythmic events
Hare et al. [2009]	Acute MI	0.5, 1.6, and 5 × 10^6 (IV)	3	↑LVEF and↓ventricular arrhythmia
Williams et al. [2011]	Chronic ischemic cardiomyopathy secondary to MI	10 repeated injections of 0.5mL of cell suspension (TESI)	3-12	↓Cardiac remodeling,↓ ESV and EDV, and↑ regional contractility
Bartunek et al. [2011] (C-CURE)	Heart failure secondary to ischemic cardiomyopathy	6-12 × 10^8 (EMG)	6	↑LVEF and↓ESV and EDV

MSC clinical trial for Heart disease

- MSC를 이용한 심장질환 치료의 임상 연구는 다양하게 진행되어왔음

- 현재도 지속적으로 수많은 심장관련 질환 치료를 위해 MSC를 활용하여 다양한 clinical trial이 Ongoing 중임

-ESC : No clinical studies for Heart disease
-iPS : Preclinical research stages

다양한 Clincal Trial로 환자의 심장 질환 치료의 Safety & Efficacy 에 대해 수많은 검증을 MSC를 통해 확인

Table. Ongoing Clinical Trials using MSCs in ischemic heart diseases (www.clinicaltrials.com)

Trial Name or Sponsor	Phase	Source	Route	Endpoint	Patient (N)	Condition
RELIEF/Pharmicell Co., Ltd	3	BM(Auto) [Hearticellgram]	Intracoronary	LVEF	135	Acute Myocardial Infarction
Angioblast Systems	2	BM(Allo)	Transendocardial	Safety	60	Heart Failure
Stempeuti						ion
Osins The						on
ESTIMATI						on
National						ardiomyopathy
AHEPA Uni				Viability		yopathy
RIMECARD/ Universidad Los Andes	1/2	UCB(Allo)	Intravenous	LVEF	30	Dilated Cardiomyopathy
Helsinki University	2	BM(Auto)	Intramyocardial	LVEF	60	Heart Failure
ESTIMATION Study	3	BM(Auto)	Endocardial	LV Systolic Volume	50	Acute Myocardial Infarction
The POSEIDON-DCM Study	1/2	BM(Auto&Allo)	Transendocardial	Serious Adverse Event	36	Nonischemic Dilated Cardiomyopathy
National University of Malaysia	2	BM(Auto)	Intracoronary	LVEF	80	Ischemic Dilated Cardiomyopathy
Rigshopitalet	1/2	BM(Auto)	Intramyocardial	LV Function	60	Congestive Heart Failure
AHEPA University Hospital	2/3	BM(Allo)	Intramyocardial	LVEF	30	Ischemic Dilated Cardiomyopathy
University Hospital, Toulouse	1/2	BM(Auto)	Transendocardial	Safety	10	Chronic Myocardial Ischemia

Ongoing MSC clinical trial for Heart disease