CARDIAC REGENERATION IN ISCHAEMIC CARDIOMYOPATHY

THE PARACRINE REGENERATIVE EFFECT OF APOSEC

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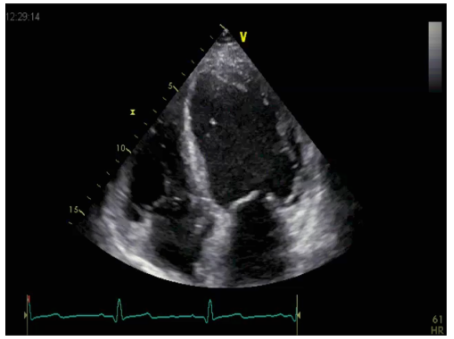
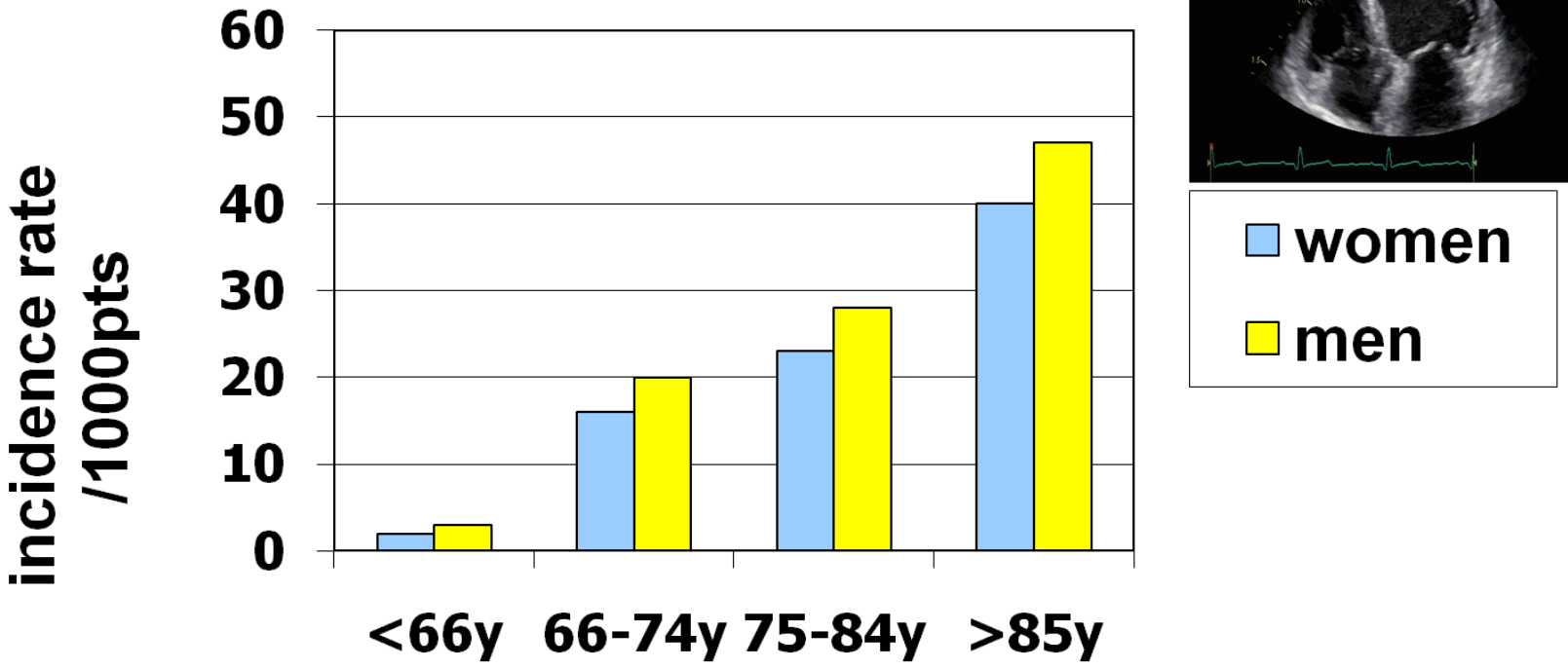
Declaration

No conflict of interest.

Heart failure





AMI triggers a series of cellular and molecular changes leading to apoptosis, necrosis, and hypertrophy of cardiomyocytes; impaired neovascularization; interstitial fibrosis and inflammation; reduced contractility; and pathological remodeling.

McCollough et al., JACC 2002.

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Cell-based cardiac regeneration

- stem or progenitor cells hold the promise of tissue regeneration for decades
  - rescue ischemic myocyte damage
  - enhance vascular density
  - rebuild injured myocardium

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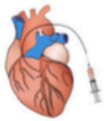
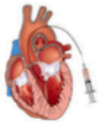
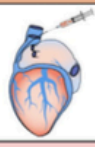
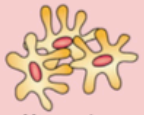
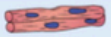
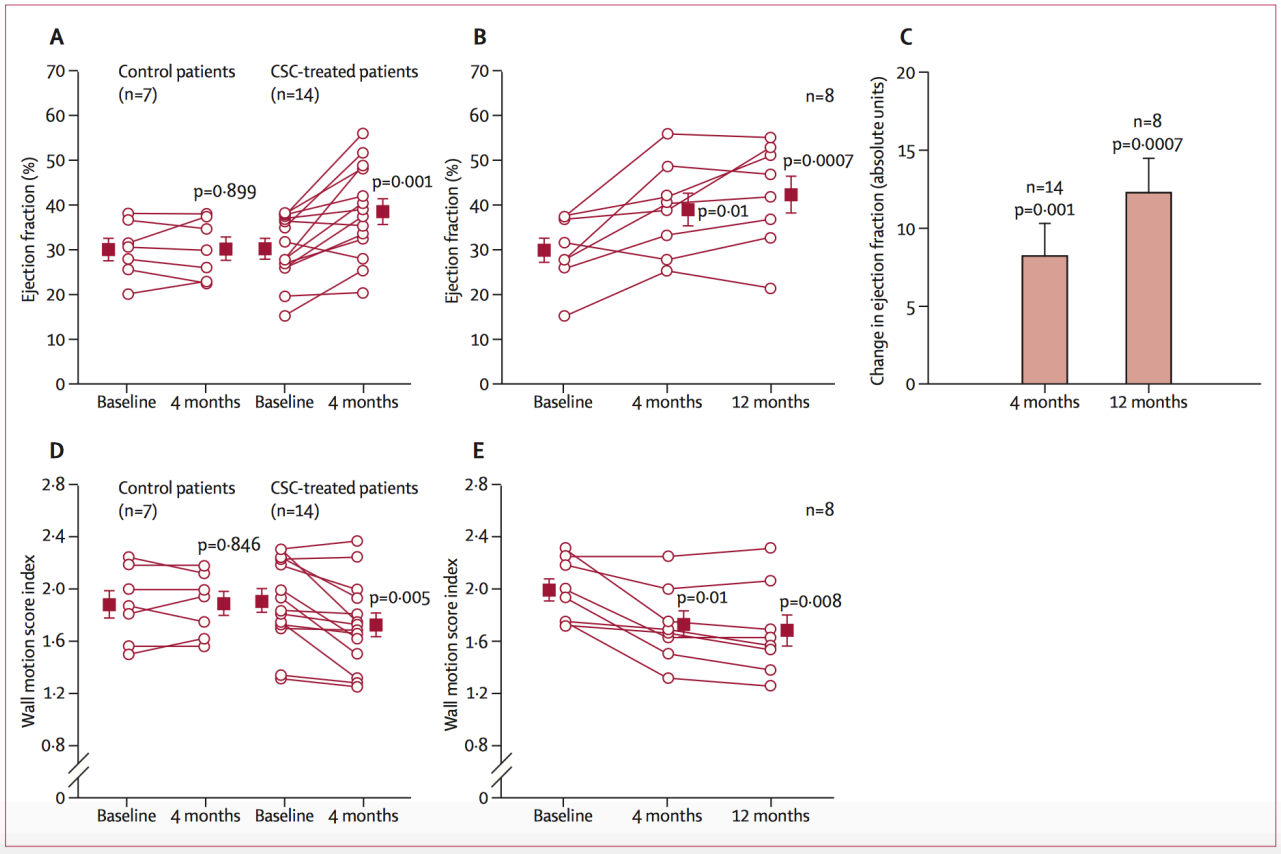
Stem cell origin/ percutaneous delivery route		Intracoronary	Percutaneous intramyocardial	Coronary sinus
				
BM-origin SC	 Mononuclear	Strauer et al [21], Topcare-AMI [11], Repair-AMI [63], BOOST [64], TCT-STAMI [65], ASTAMI [66], FINCELL [67], DanCell-CHF [68], BONAMI [69], CELLWAVE [70], HEBE [71], LATE TIME [72], MySTAR [73]	PROTECT-CAD [74], MYSTAR [73]	NA
	CD 34	REGENT [31]	Losordo et al [75]	NA
	CD 133	Bartunek et al [26], COMPARE AMI [76]	NA	NA
	 Mesenchymal	Chen et al [77], RELIEF [37] (ongoing)	POSEIDON [40], MSC-HF [78], TAC—HFT [38]	NA
 Adipose-derived stem cells		ADVANCE [79], APOLLO [47]	PRECISE [48]	NA
 Endometrial regenerative cells			NA	RECOVER-ERC [50] (ongoing)
 Circulating peripheral blood endothelial progenitor cells G-CSF mobilized		Choi et al [60], Li et al [24], MAGIC [25], TOPCARE-AMI [27], TOPCARE-CHD [30]	NA	NA
 Multipotent Cardiac Stem cells		SCIPIO [55]	NA	NA
 Cardiosphere-derived cells		CADUCEUS [56], ALLSTAR [57] (ongoing)	NA	NA
 Myoblasts		NA	CauSMIC [81], Smits et al [11]	NA
 Phenotypically modified		NA	C-CURE [82]	NA
 Allogenic		NA	POSEIDON [40]	NA

Pavo et al., J Mol Cell Cardiol. 2014.

Cardiac derived stem cells (CDCs)

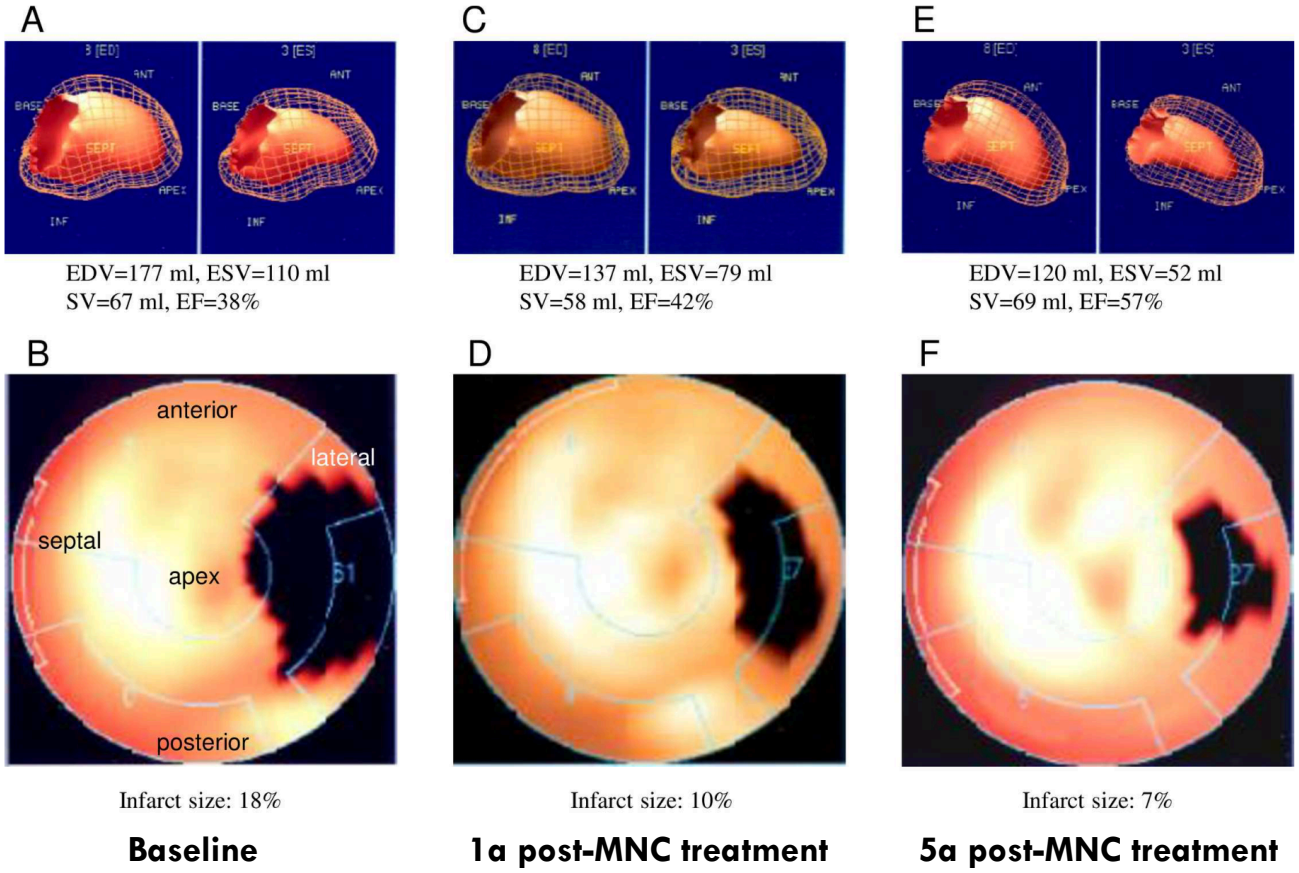
- **SCIPIO** (Stem Cell Infusion in Patients with Ischemic cardiOmyopathy) in patients undergoing CABG (intracoronnary infusion 4 months after surgery)



Bolli R. et al., Lancet 2011.

Mononuclear stem cells (MNCs)

- **MYSTAR** (Combined (Percutane- ous Intramyocardial and Intracoronary) Application of Autologous Bone Marrow Mononuclear Cells Post Myocardial Infarction)



Gyöngyösi M. et al., Nat Clin Pract Cardiovasc Med. 2009 and PLOS One 2015.

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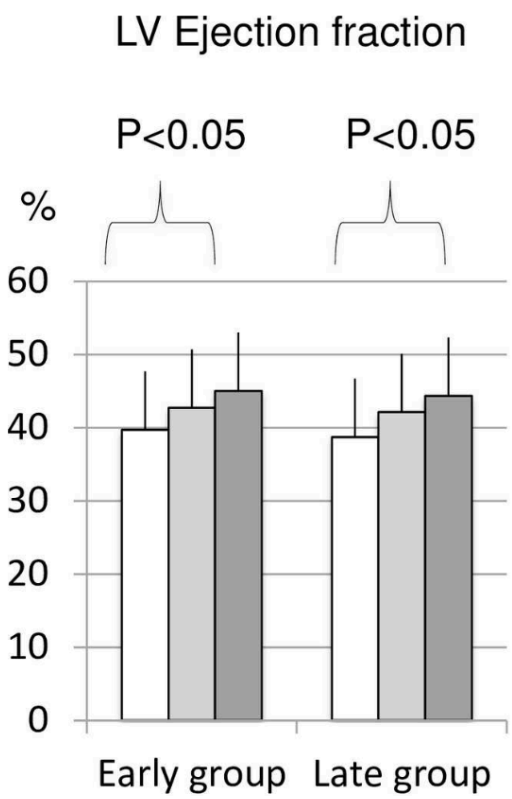
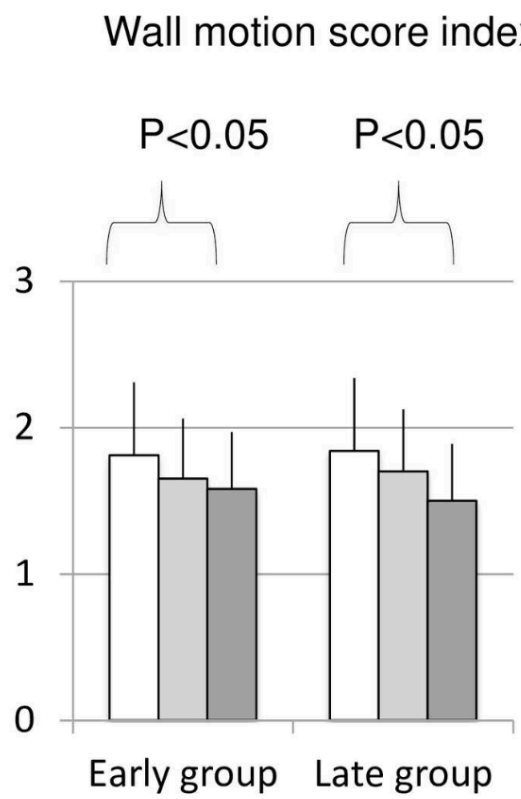
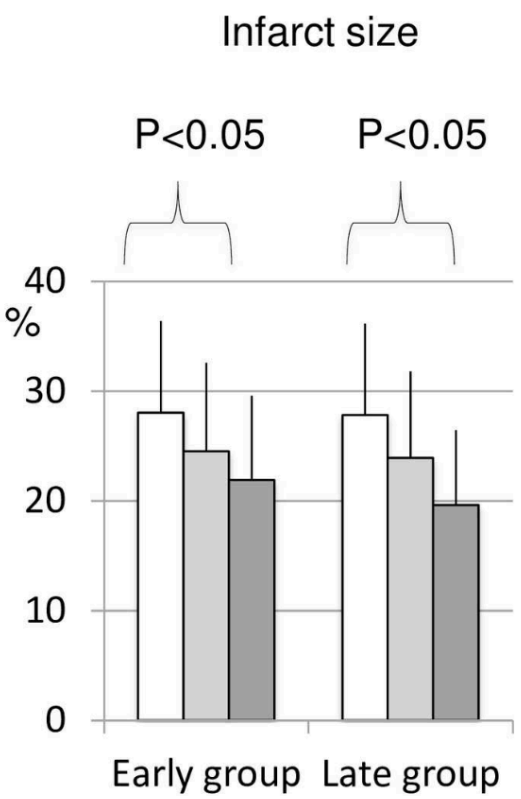


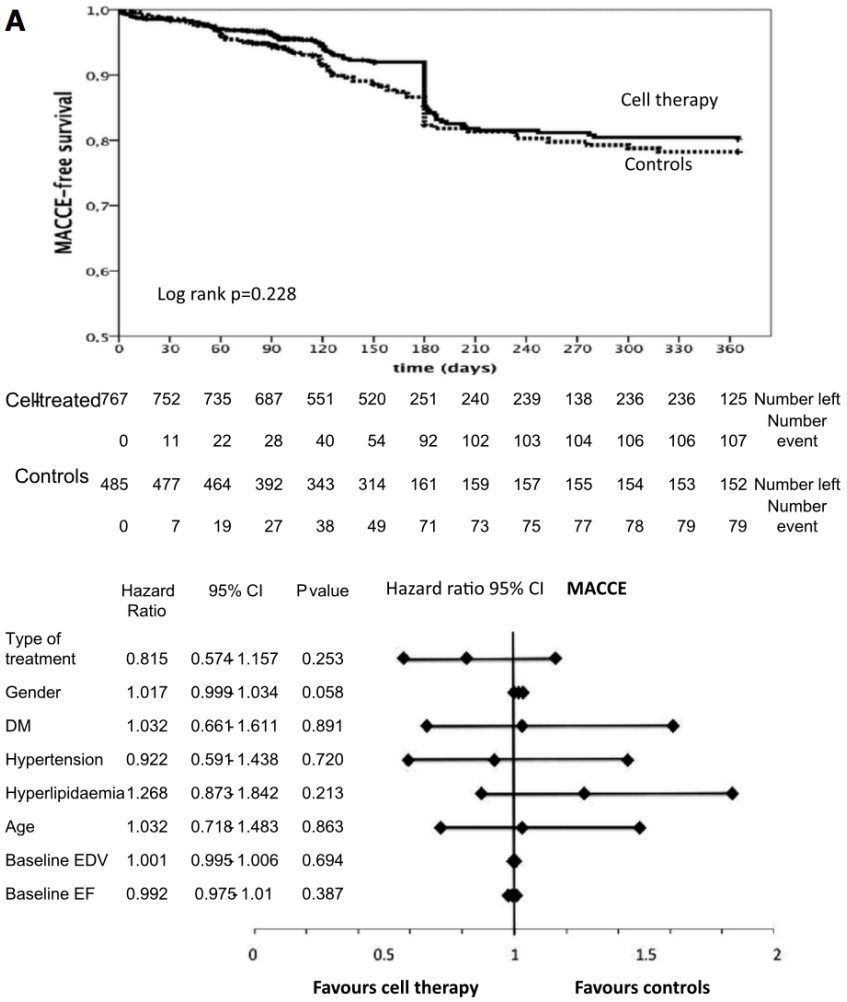




Gyöngyösi M. et al., Nat Clin Pract Cardiovasc Med. 2009 and PLOS One 2015.

Meta-analysis MACCE

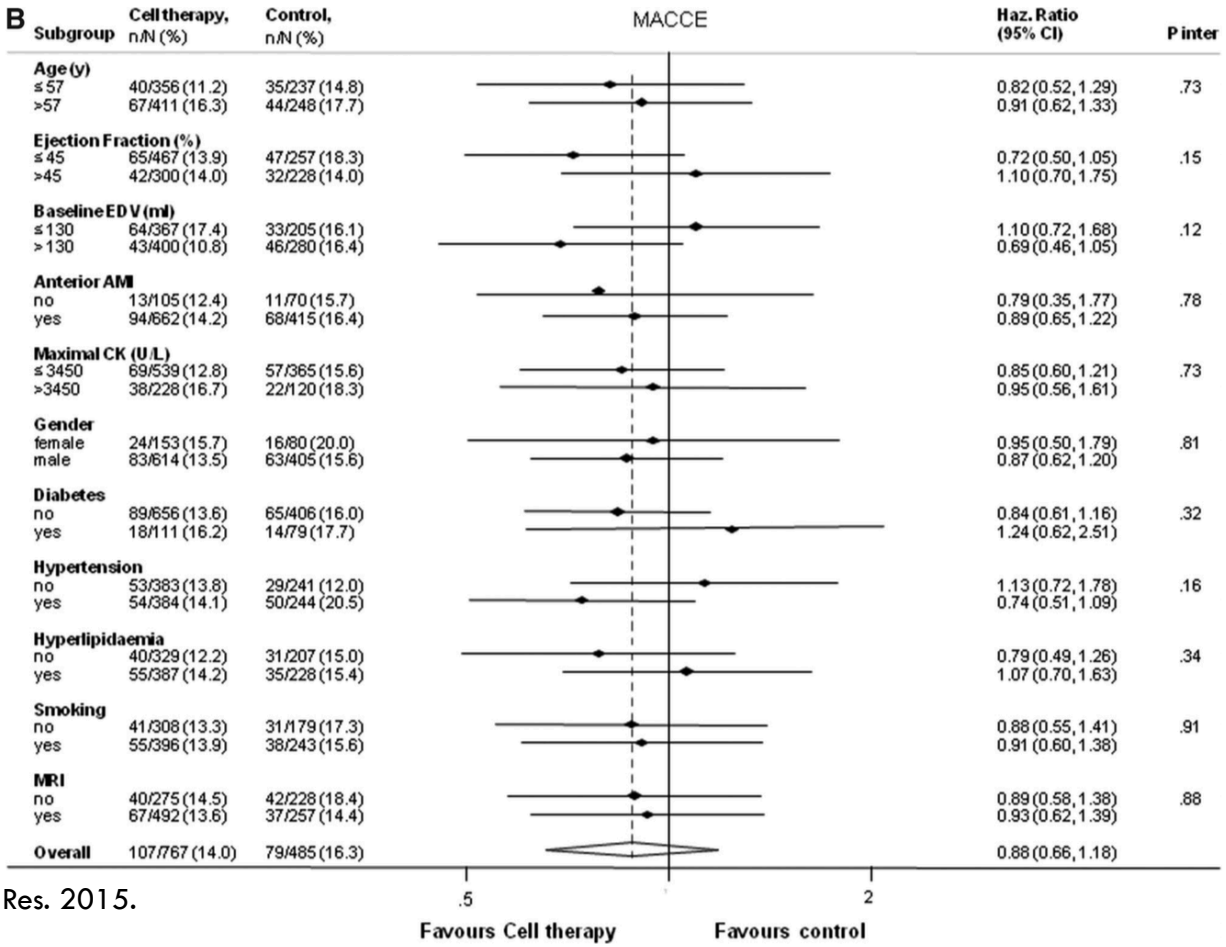
- **ACCRUE** (Meta-Analysis of Cell-based CaRdiac stUdiEs in Patients With Acute Myocardial Infarction)



Gyöngyösi M. et al., Circ Res. 2015.

Meta-analysis subgroups MACCE

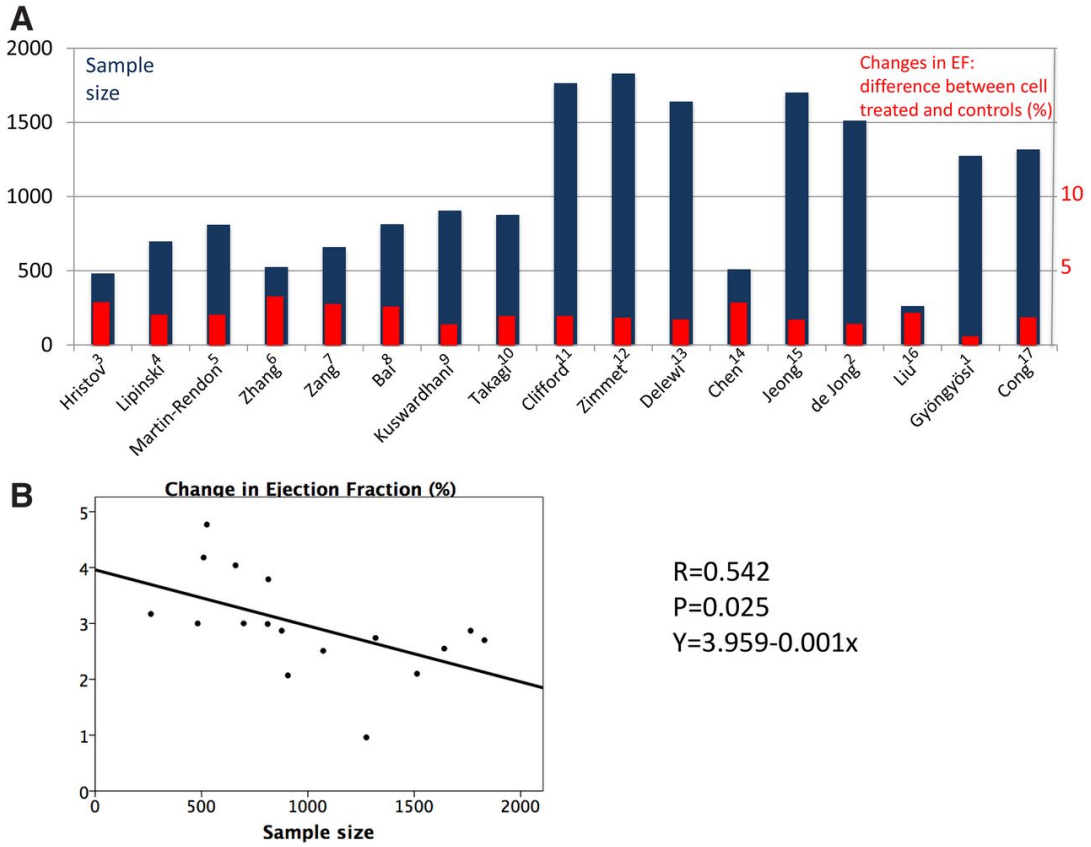
- **ACCRUE** (Meta-Analysis of Cell-based CaRdiac stUdiEs in Patients With Acute Myocardial Infarction)



Gyöngyösi M. et al., Circ Res. 2015.

Meta-analyses of cell-based therapies

Association between sample size and observed change in LVEF.



R=0.542
P=0.025
Y=3.959-0.001x

Gyöngyösi M. et al., Circ Res. 2016.

Bami – ongoing phase III study

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

  - This is a multinational, multicentre, randomised open-label, controlled, parallel-group phase III study. Its aim is to demonstrate that a single intracoronary infusion of autologous bone marrow-derived mononuclear cells is safe and reduces all-cause mortality in patients with reduced left ventricular ejection fraction(</=45%) after successful reperfusion for acute myocardial infarction when compared to a control group of patients undergoing best medical care.

This study is currently recruiting participants. (see **Contacts and Locations**)

Verified June 2016 by Queen Mary University of London

Sponsor:
Queen Mary University of London

Information provided by (Responsible Party):
Anthony Mathur, Barts & The London NHS Trust

ClinicalTrials.gov Identifier:
NCT01569178

First received: March 30, 2012
Last updated: June 10, 2016
Last verified: June 2016
History of Changes

Lack of breakthrough in clinical trials

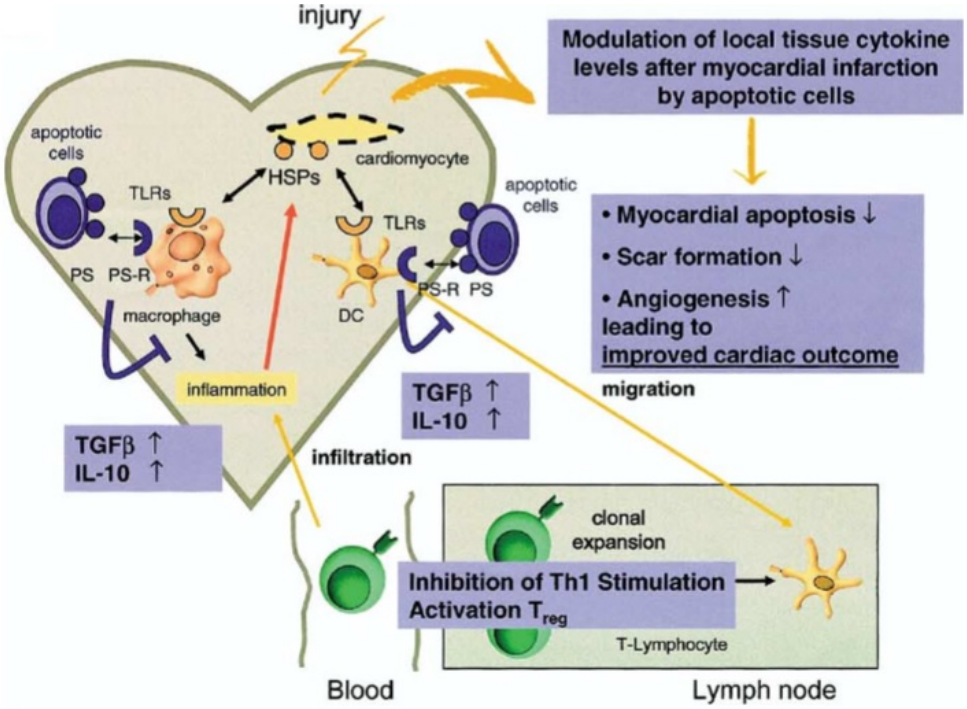
- Major discrepancies to pre-clinical trials
  - Differences in the AMI model (open vs closed chest)
  - Delivery route
  - Origin of implanted cells
  - Number of cells respective to body weight

- Does cell differentiation into cardiomyocytes really work?
- Do the administered cells stay in the myocardium, does homing really work?

Despite some promising pre-clinical results there is a lack of breakthrough in clinical trials.

The dying stem cell hypothesis

apoptosis of transplanted cells modulates local tissue reactions

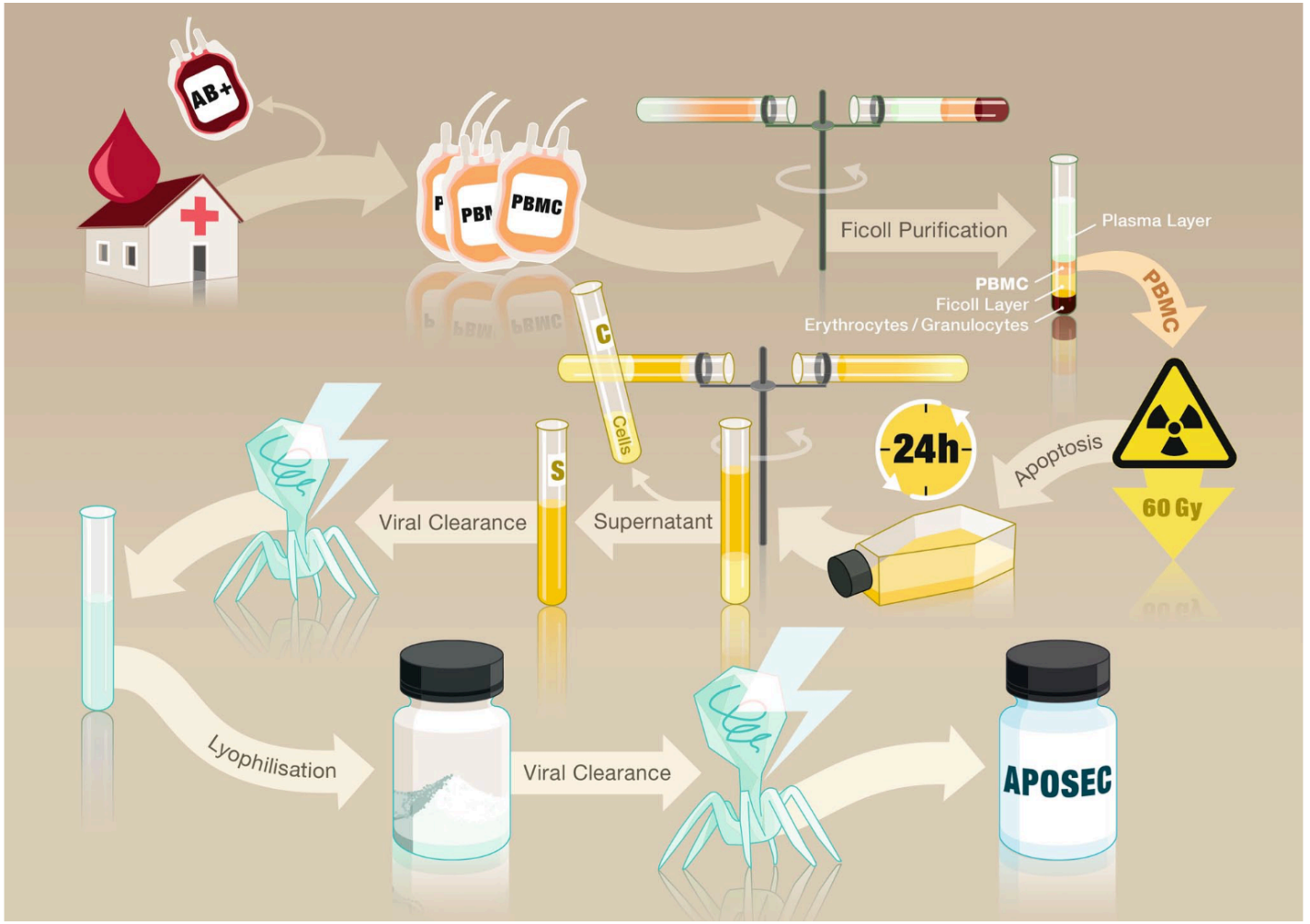


Local paracrine signaling of the transplanted living or apoptotic cells is supposed to be responsible for the benefit of cell transplantation.

Thum T. et al., JACC 2005.

APOSEC

- **APOSEC** (= APOptotic cell SECretoma)



APOSEC

Soluble factors (ng/ml) 25×10^6	Viable PBMC	Apoptotic PBMC	
IL-8	10.49 ± 3.53	18.01 ± 2.87	✦
GRO-alpha	2.06 ± 1.58	3.95 ± 0.93	
ENA-78	34.89 ± 16.33	108.86 ± 27.88	✦
MCP-1	0.27 ± 0.00	0.27 ± 0.00	
RANTES	37.63 ± 2.72	51.58 ± 4.44	
HMGB1	33.57 ± 6.45	20.51 ± 3.62	
MMP9	29.46 ± 8.29	19.35 ± 5.34	
sICAM-1	7.43 ± 0.85	9.40 ± 1.29	✦
$VEGF_{165}$	0.82 ± 0.34	4.39 ± 1.22	✦
MIF	13.24 ± 0.85	58.99 ± 1.17	✦
PAI-1	49.60 ± 9.04	45.86 ± 1.43	
IL-16	0.84 ± 0.31	5.25 ± 0.52	✦
IL-1ra	2.16 ± 0.96	6.43 ± 1.33	✦
IL-10	0.05 ± 0.01	0.06 ± 0.01	
IGF-I	0.03 ± 0.02	0.03 ± 0.03	
HGF	0.69 ± 0.19	0.79 ± 0.19	
FGF-2	0.59 ± 0.01	0.55 ± 0.02	
TGF-β	0.21 ± 0.07	0.39 ± 0.09	
SDF-1	0.22 ± 0.03	0.12 ± 0.04	
G-CSF	0.00 ± 0.00	0.00 ± 0.00	
GM-CSF	0.07 ± 0.02	0.08 ± 0.02	

=CXCL8, induces chemotaxis for neutrophils, promotes angiogenesis

=CXCL5, protective role in atherosclerosis, induces chemotaxis

leukocyte transmigration
angiogenesis
inflammatory cytokine

modulator of T cell activation
antagonist for IL-1α, IL-1β (proinflammatory cytokines)

Mediators of the paracrine effect.

Lichtenauer M. et al., Basic Res Cardiol. 2011.

APOSEC

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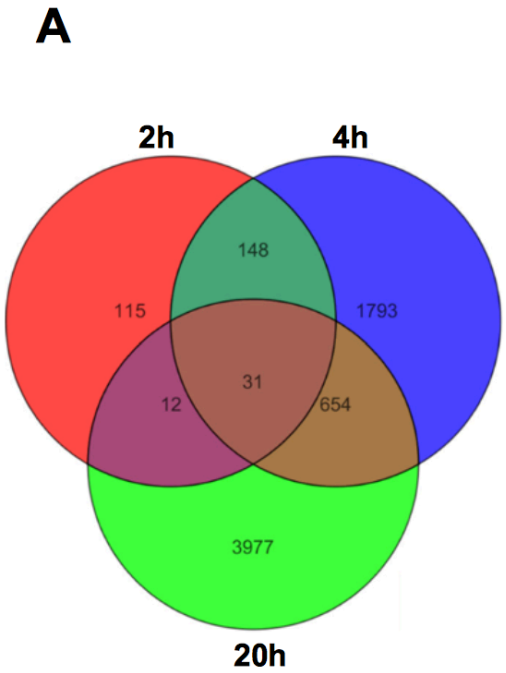
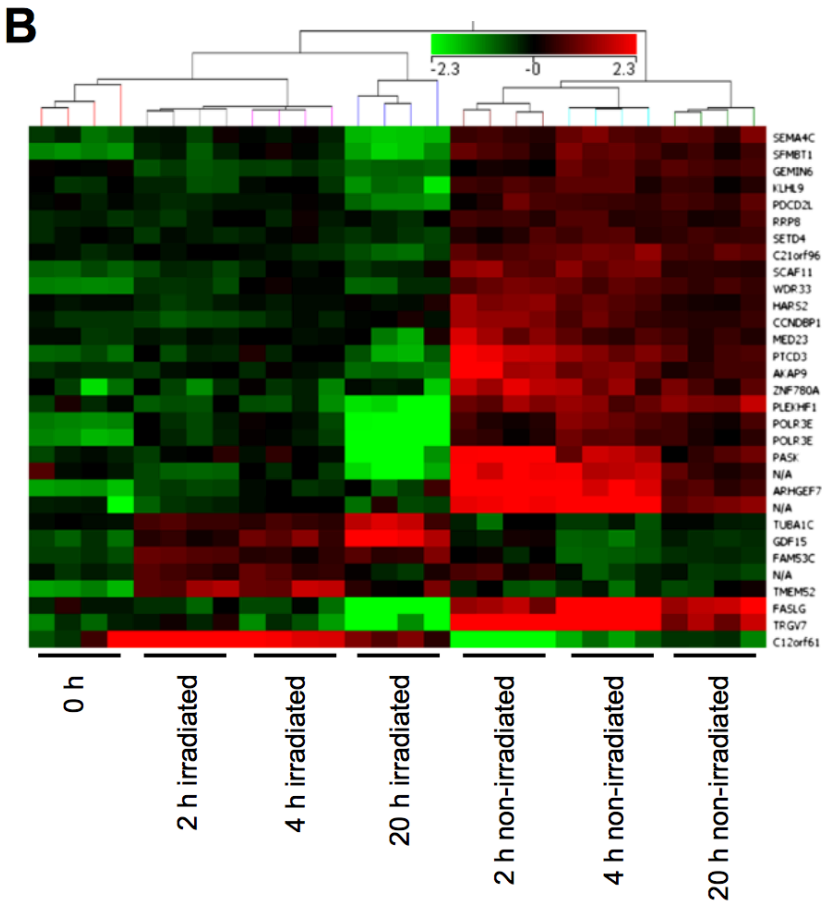
Transcriptomics after irradiation of PBMC.





Beer L. et al., BMC Genomics 2014.

APOSEC

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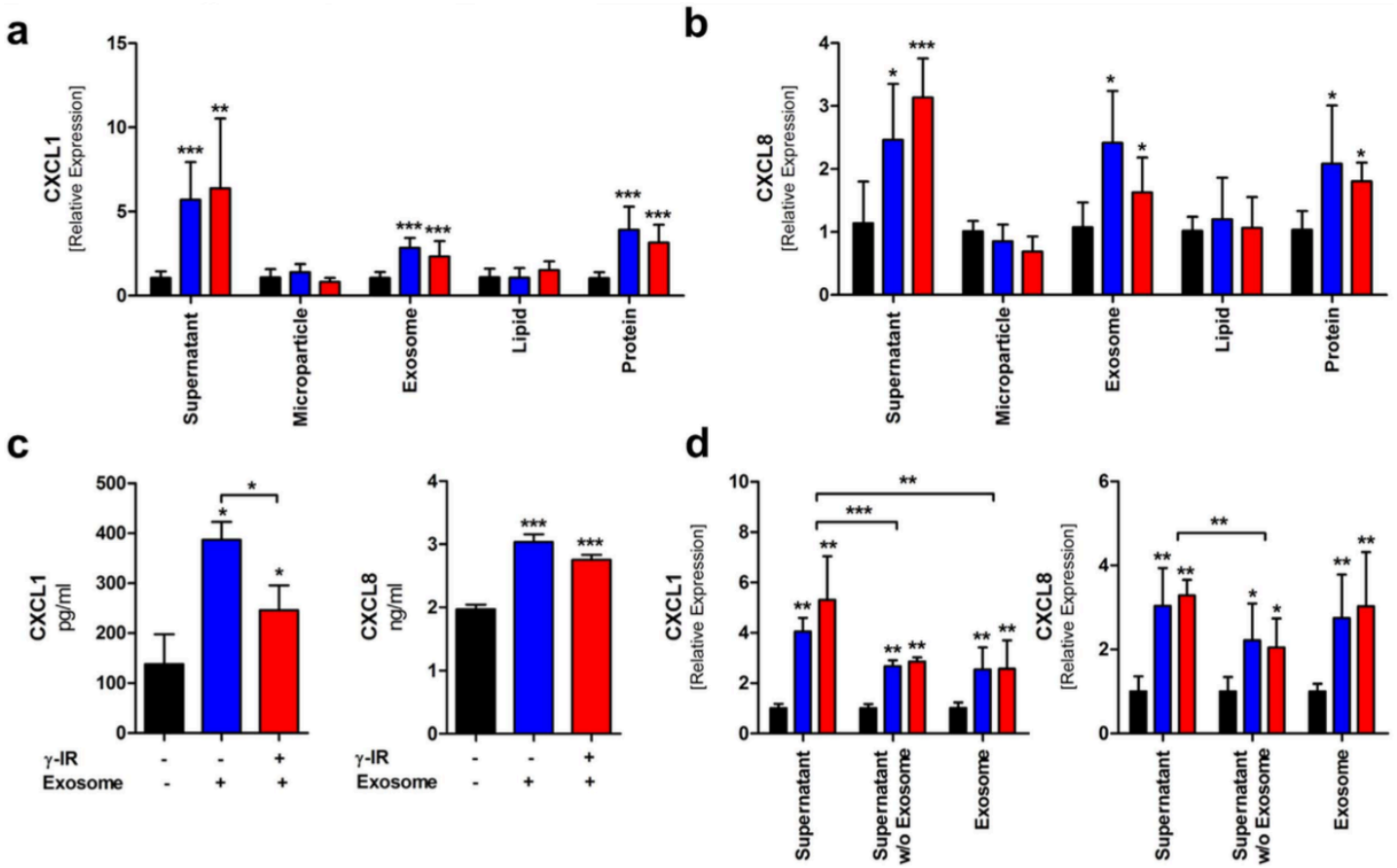
Effect of different subfractions of APOSEC.



Beer L. et al., Sci Rep 2015.

APOSEC

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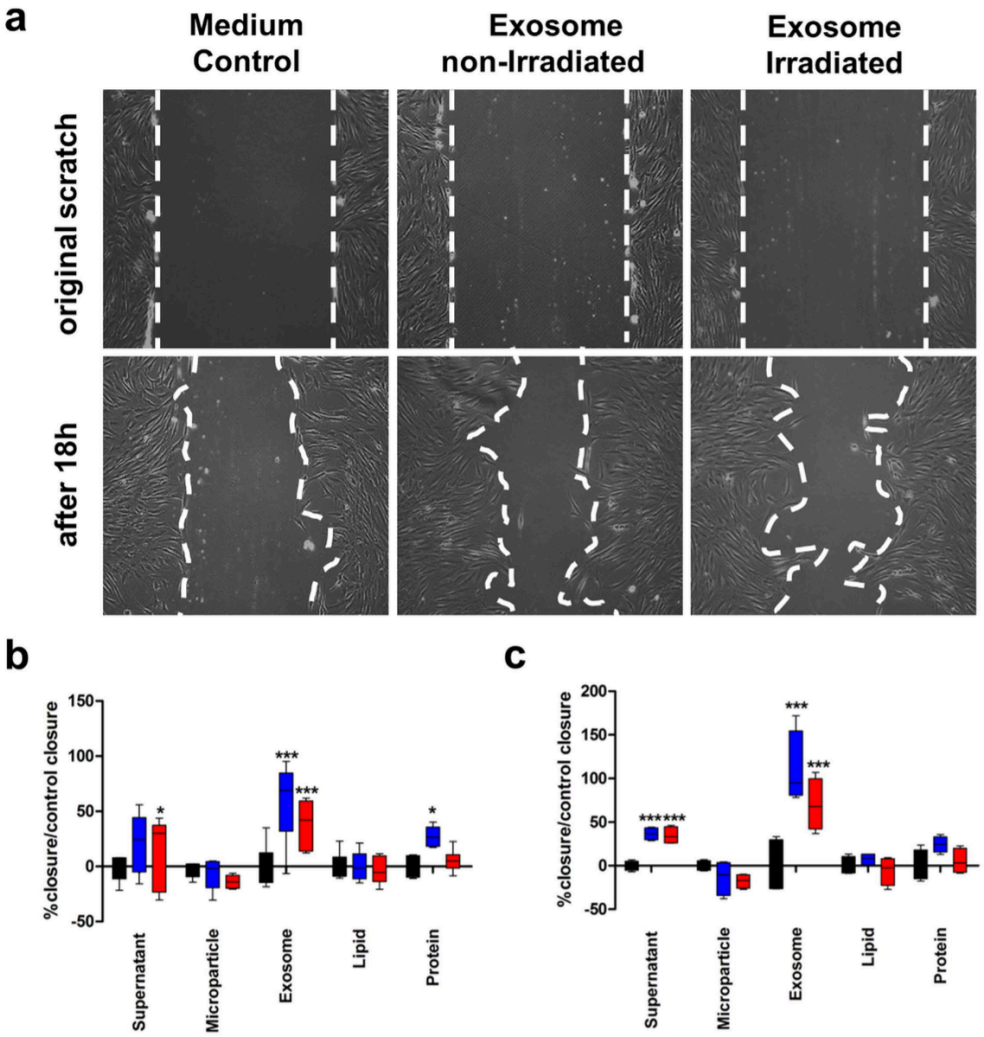
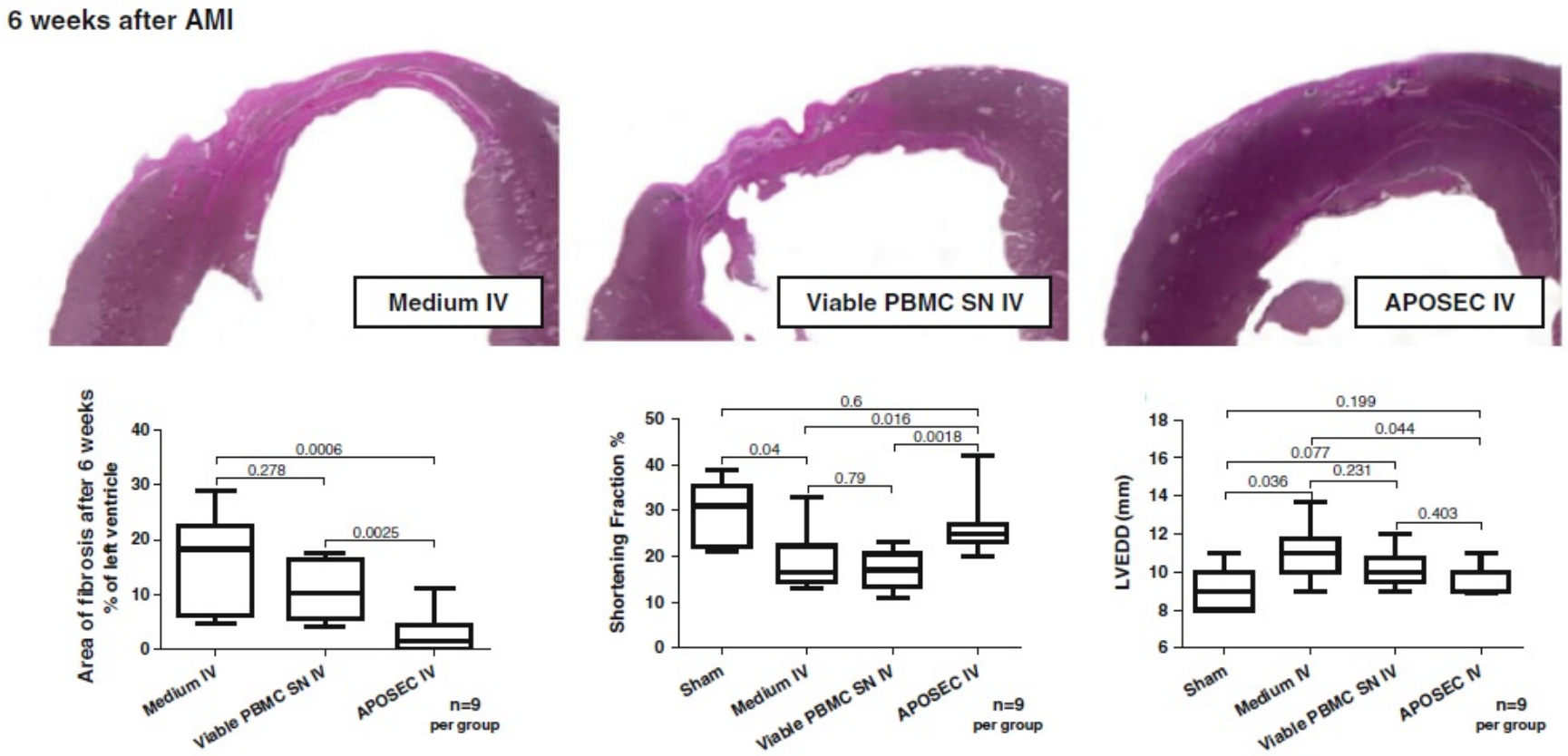
Fibroblast migration.



Beer L. et al., Sci Rep 2015.

APOSEC

Intravenous application of APOSEC, viable PBMC or medium right after the onset of myocardial ischemia through ligation of the LAD



Lichtenauer M. et al., Basic Res Cardiol. 2011.

APOSEC

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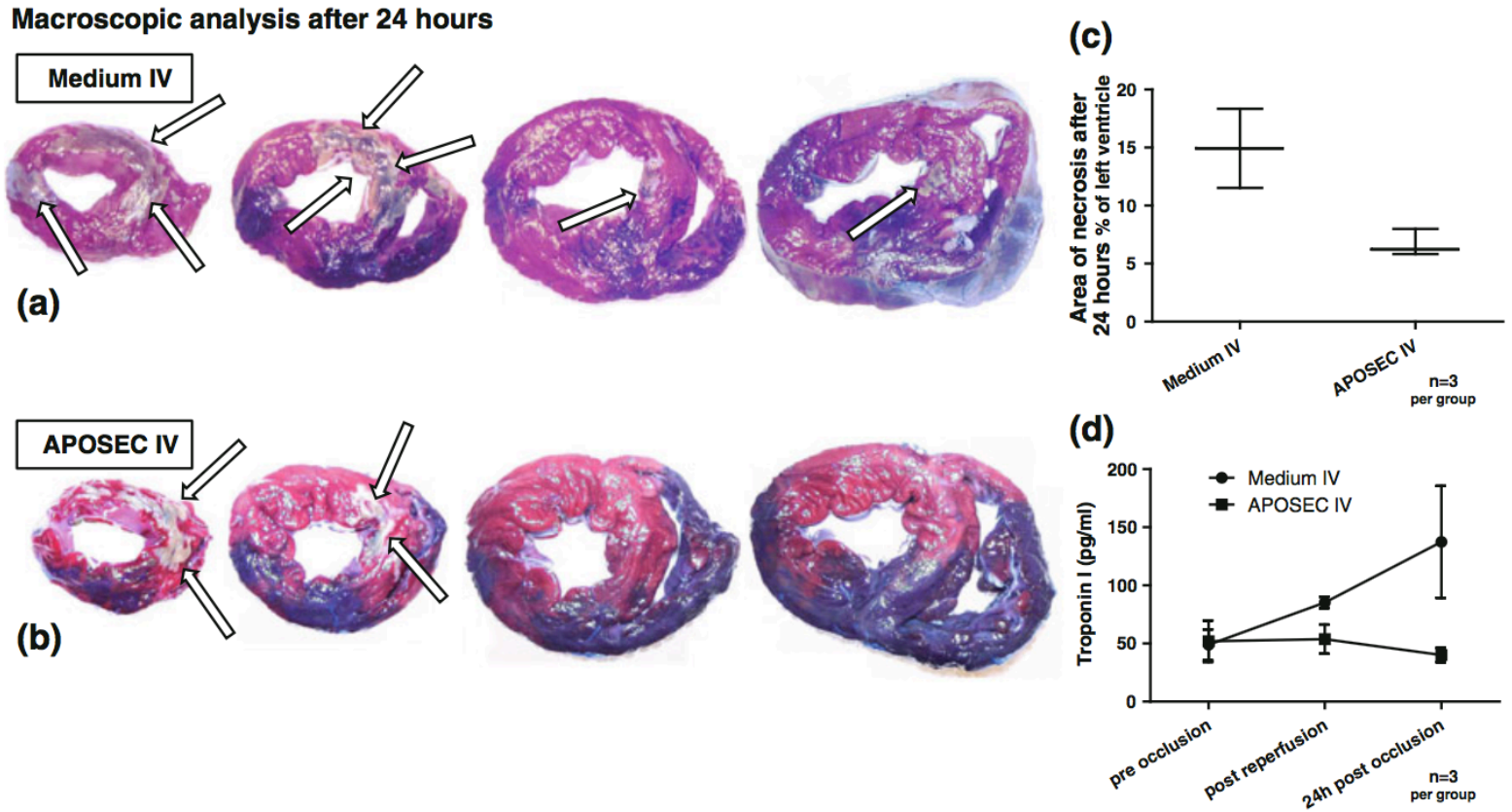
Intravenous application of low-, high-dose APOSEC or medium 40min after the onset of the 90min ischemia in porcine-reperfused AMI



Lichtenauer M. et al., Basic Res Cardiol. 2011.

APOSEC

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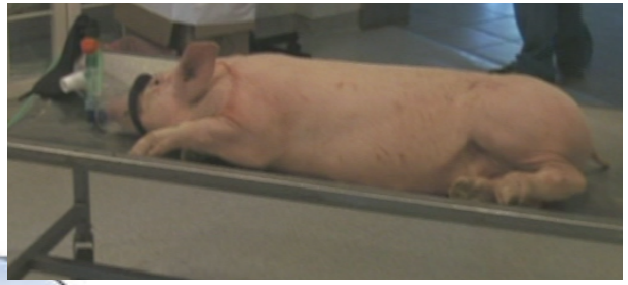
Intravenous application of low- and high-dose APOSEC 40min after the onset of the 90min ischemia in porcine AMI

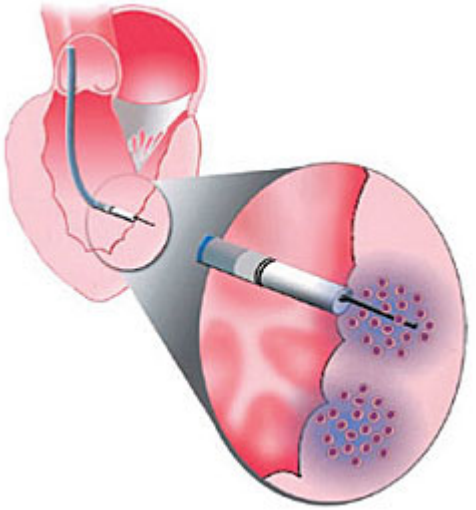
Cardiac MRI data

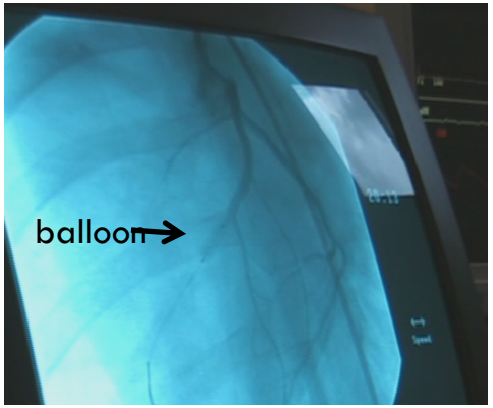
	Parameters	Medium control ($n = 8$)	250×10^6 apoptotic PBMC (low-dose APOSEC, $n = 7$)	1×10^9 apoptotic PBMC (high-dose APOSEC, $n = 7$)
After 3 days	Weight (kg)	31.86 ± 9.1	30.86 ± 1.6 ns	33.33 ± 1.3 ns
	Age (days)	90 ± 0	90 ± 0 ns	90 ± 0 ns
	LVEDV (ml)	67.59 ± 2.7	64.19 ± 5.4 ns	63.73 ± 1.6 ns
	LVESV(ml)	38.42 ± 2.5	35.96 ± 3.0 ns	33.93 ± 2.1 ns
	LVSV (ml)	29.17 ± 1.3	28.23 ± 3.2 ns	29.77 ± 1.8 ns
	LVEF (%)	43.38 ± 1.9	43.63 ± 2.8 ns	46.65 ± 2.9 ns
	HR/min	111 ± 6	109 ± 5 ns	111 ± 13 ns
	CO (l/min)	3.24 ± 0.1	3.03 ± 0.3 ns	3.28 ± 0.3 ns
	CI (l/min/m^2)	3.64 ± 0.1	3.59 ± 0.4 ns	3.82 ± 0.4 ns
	Infarct %	18.17 ± 1.7	14.01 ± 1.9 ns	8.66 ± 1.5**
After 30 days	Weight (kg)	39.43 ± 0.5	37.00 ± 1.9 ns	48.83 ± 0.7***
	Age (days)	120 ± 0	120 ± 0 ns	120 ± 0 ns
	LVEDV (ml)	54.74 ± 4.1	53.43 ± 3.2 ns	65.99 ± 3.5 ns
		32.93 ± 4.0	31.89 ± 2.9 ns	
	LVSV (ml)	21.84 ± 1.8	21.54 ± 1.9 ns	37.29 ± 1.7***
	LVEF (%)	40.54 ± 3.6	40.64 ± 3.2 ns	57.05 ± 3.3**
	HR/min	114 ± 7	108 ± 7 ns	107 ± 5 ns
	CO (l/min)	2.44 ± 0.1	2.28 ± 0.1 ns	3.98 ± 0.2***
	CI (l/min/m^2)	2.46 ± 0.1	2.40 ± 0.1 ns	3.51 ± 0.2***
	Infarct %	12.60 ± 1.3	11.50 ± 1.5 ns	6.92 ± 1.4*

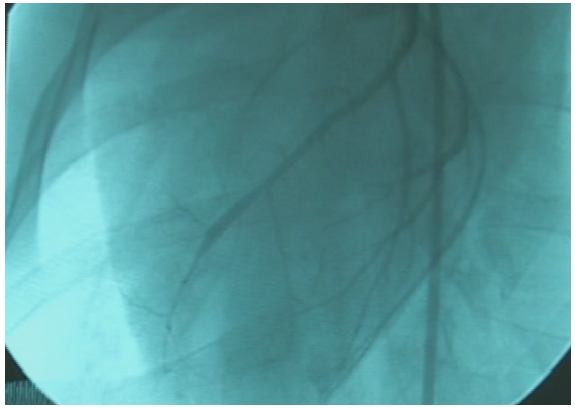
Lichtenauer M. et al., Basic Res Cardiol. 2011.

Porcine AMI-model and the NOGA system









Similar to primary PCI in humans with ST-segment elevation myocardial infarction.

AIMS

- Comparing the performance of the NOGA system with cardiac MRI in their ability to determine infarction size and infarction transmurality – is the NOGA system a valid tool to guide intramyocardial regenerative substance delivery?

- Assessing the efficacy and safety of percutaneous intramyocardial delivery of APOSEC in a clinically relevant porcine model of chronic left ventricular dysfunction in response to myocardial infarction

- Investigation of the effects of APOSEC on haemodynamic function and gene expression profile in chronic left ventricular dysfunction

to **validate the diagnostic value of** a percutaneous intramyocardial navigation system (**NOGA**)

OPEN ACCESS Freely available online

PLOS ONE

Comparison of NOGA Endocardial Mapping and Cardiac Magnetic Resonance Imaging for Determining Infarct Size and Infarct Transmurality for Intramyocardial Injection Therapy Using Experimental Data

Noemi Pavo[1], Andras Jakab[2], Maximilian Y. Emmert[3,4,5], Georg Strebinger[1], Petra Wolint[3,4,5], Matthias Zimmermann[6], Hendrik Jan Ankersmit[6,7], Simon P. Hoerstrup[3,4,5], Gerald Maurer[1], Mariann Gyöngyösi[1]*

Study design

- 60 domestic pigs with closed chest reperfused AMI
- 60 days later (after the development of chronic LV dysfunction) cMRI and NOGA-mapping were performed and compared

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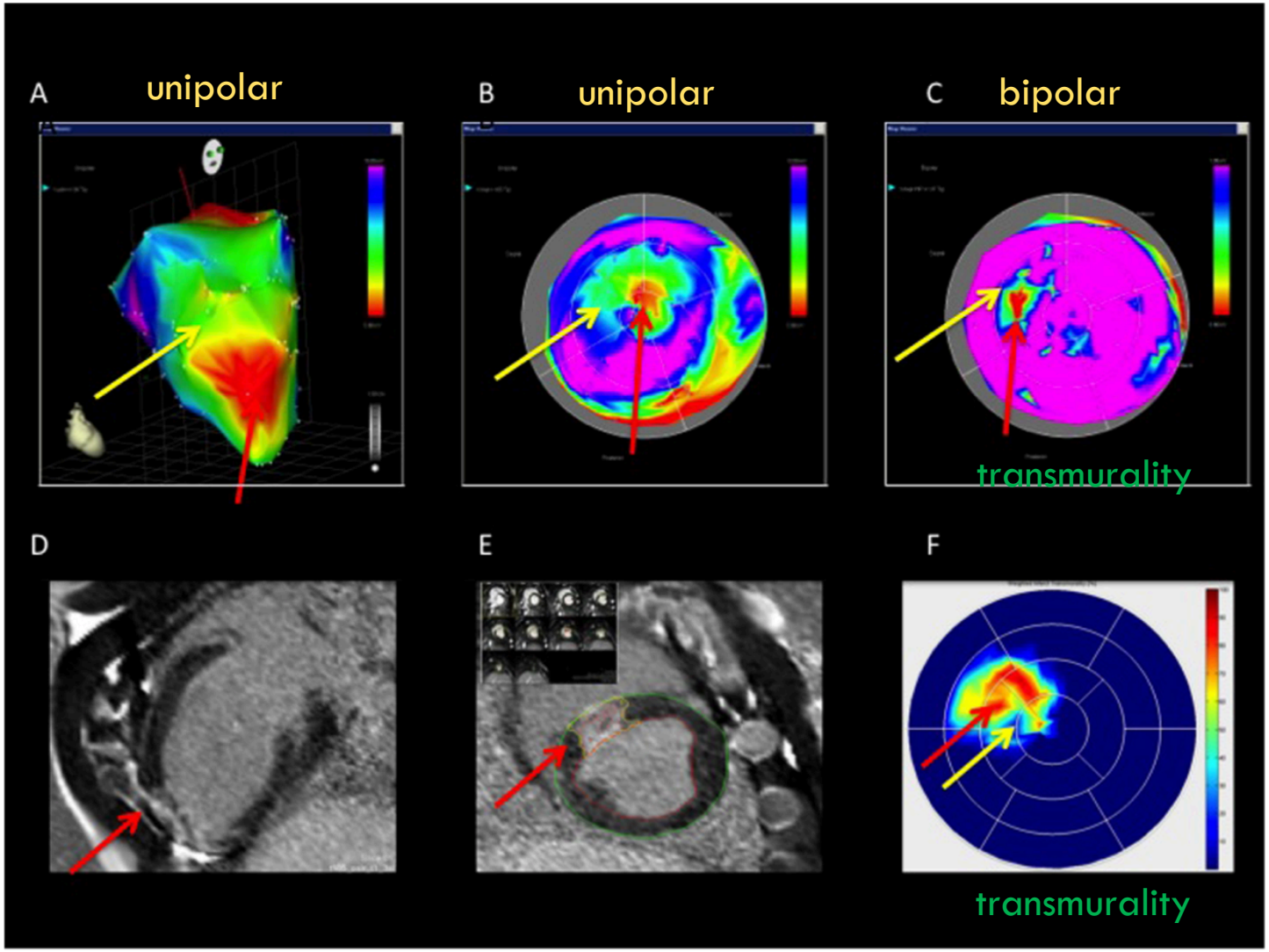
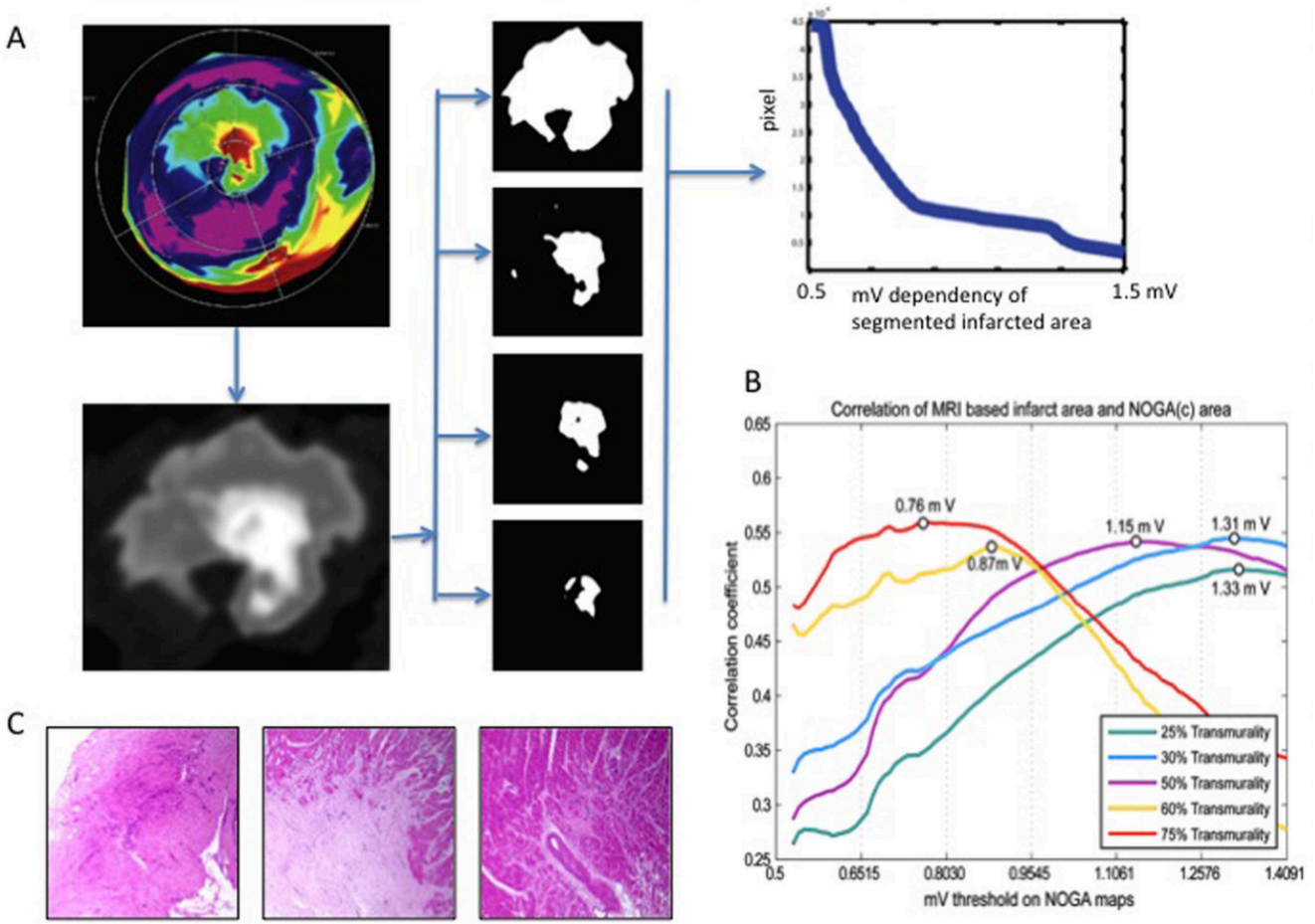
Example of NOGA and cMRI in chronic infarction



cMRI derived values for transmurality

Determintion of NOGA bipolar voltage values for infarct transmurality based on cMRI values



NOGA bipolar voltage:	**<0.8 mV**	**0.8–1.9 mV**	**>1.9 mV**
cMRI transmurality:	**>75%**	**50%**	**<25%**

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NOGA cut-off values

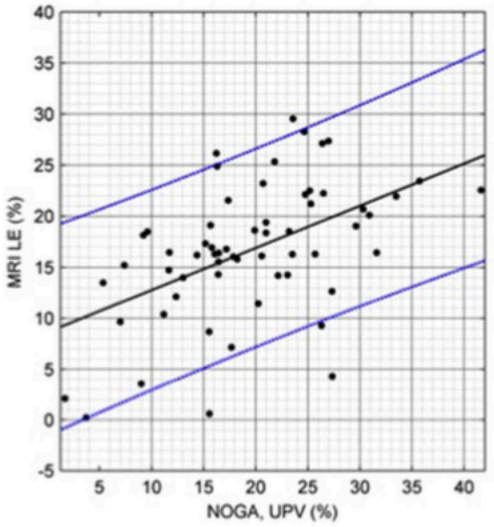
Cut-off value	Color on the NOGA map	Definition
Unipolar voltage map		
>15 mV	Blue, violet	Normal tissue
5–15 mV	Yellow, green	Border zone of infarction
<5 mV	Red	Area of myocardial infarction
Bipolar voltage map		
>1.9 mV	Blue, violet	Normal tissue
0.8–1.9 mV	Yellow, green	Non-transmural infarction
<0.8 mV	Red	Transmural infarction

Correlation infarct size

Infarct size

Unipolar voltage polar map – cMRI-LE

A

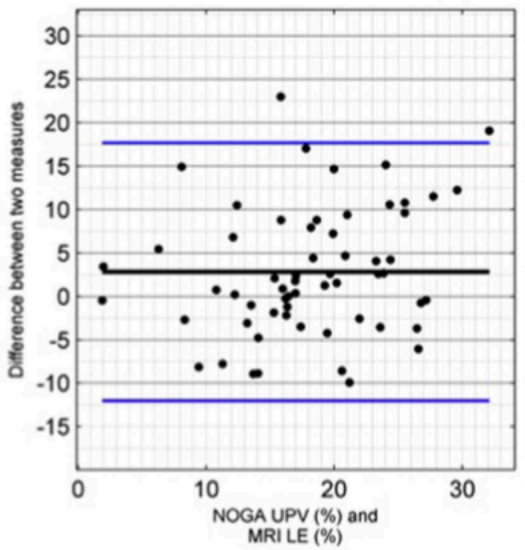


R = 0.504

P <0.001

Y = 8.63 + 0.41x

B



Mean of differences = 2.82 %

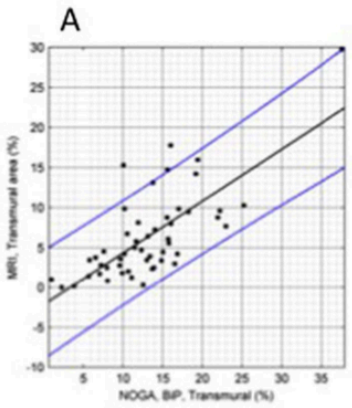
1SD = 7.43 %

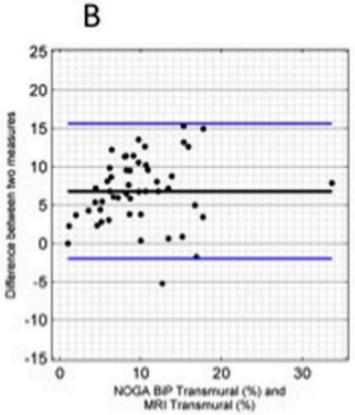
Correlation transmural and non-transmural infarction

Size of transmural and non-transmural infarction
NOGA bipolar polar maps – cMRI-LE transmurality polar maps

Transmural infarction

R = 0.727
P < 0.001
Y = -2.18 + 0.65x

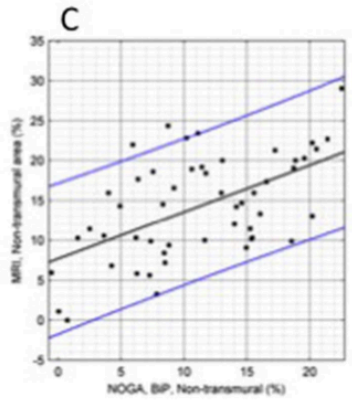


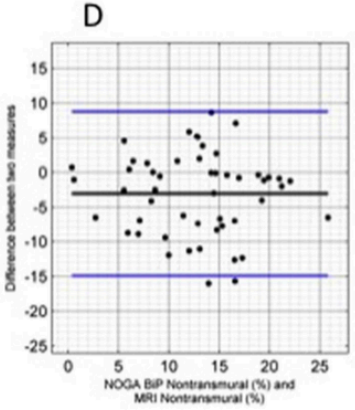


Mean of differences = 6.81 %
1SD = 4.39 %

Non-transmural infarction

R = 0.555
P < 0.001
Y = 7.68 + 0.59x





Mean of differences = -3.04 %
1SD = 5.92 %

Summary

- NOGA mapping showed good concordance with the off-line gold standard, cMRI-LE imaging
- NOGA mapping may be useful in patients with contraindications for cMRI who require targeted intramyocardial regenerative therapy

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regenerative and cardioprotective effects of APOSEC in a translational model of ischemic cardiomyopathy using gene expression analysis

Contents lists available at ScienceDirect

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Long-acting beneficial effect of percutaneously intramyocardially delivered secretome of apoptotic peripheral blood cells on porcine chronic ischemic left ventricular dysfunction

Noemi Pavo [a], Matthias Zimmermann [b], Dietmar Pils [c], Michael Mildner [d], Zsolt Petrási [e], Örs Petneházy [e], János Fuzik [a], András Jakab [f], Christian Gabriel [g], Wolfgang Sipos [h], Gerald Maurer [a], Mariann Gyöngyösi [a,1], Hendrik Jan Ankersmit [b,i,*,1]

Study design

Day 0
Closed chest reperfused AMI
Haemodynamics measurements

↓

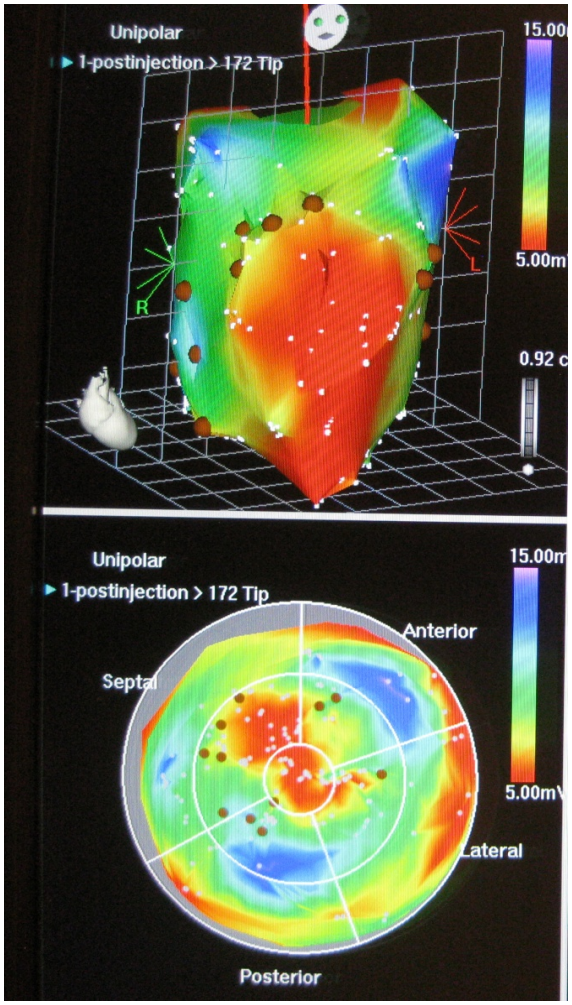
Day 3
Cardiac MRI
LV function
Late enhancement

↓

Day 30
Percutaneous intramyocardial injection of APOSEC or Medium

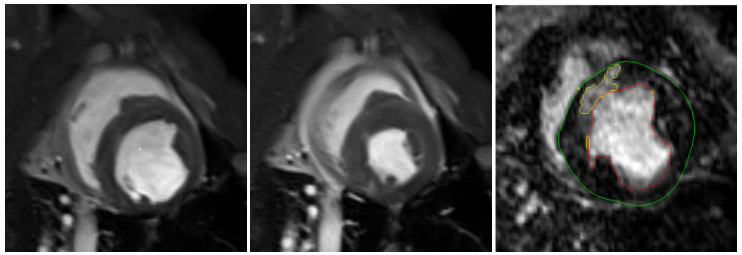
↓

Day 60
Cardiac MRI
LV function
Late enhancement
Control angiography
Haemodynamic measurements



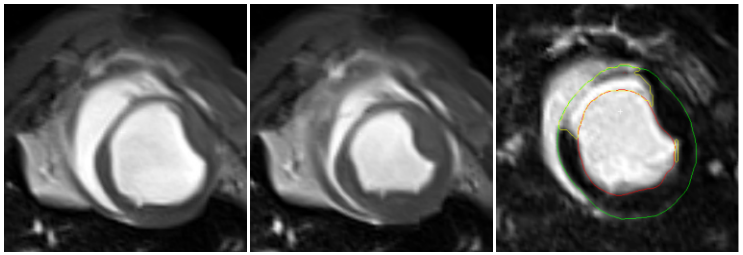
MRI and NOGA example

APOSEC



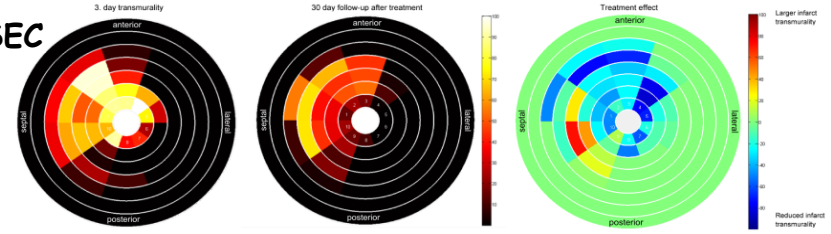
FUP EDV FUP ESV FUP LE

Medium

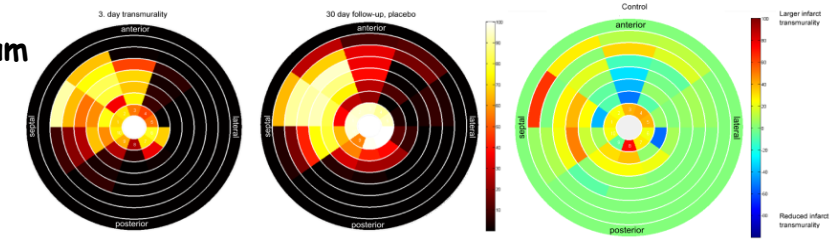


FUP EDV FUP ESV FUP LE

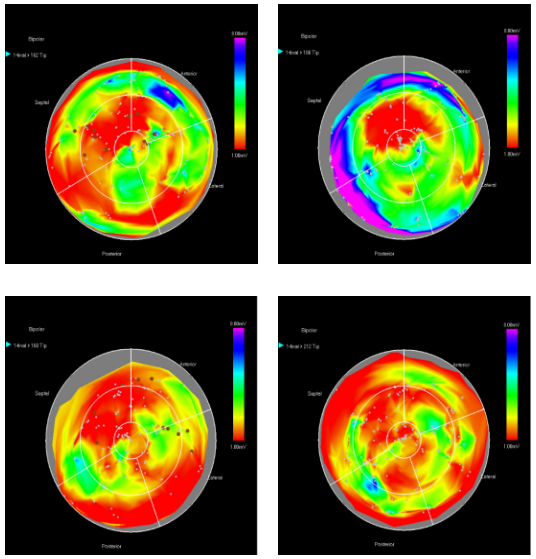
APOSEC



Medium



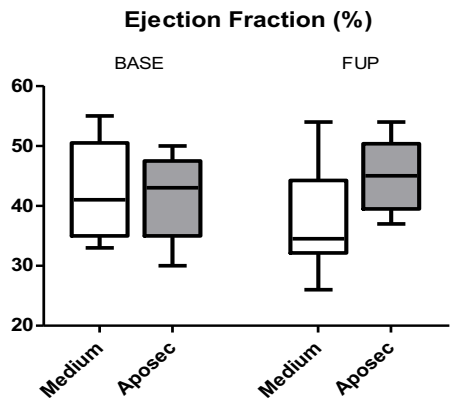
Baseline injection FUP Difference between baseline and FUP



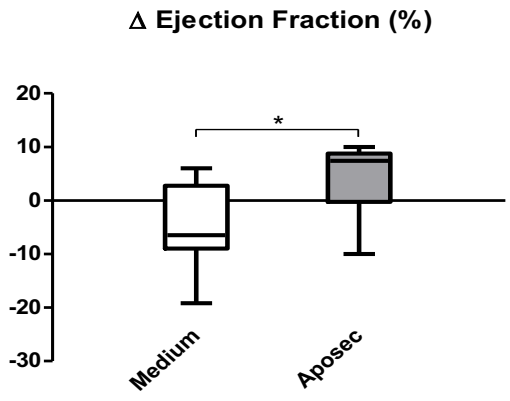
Baseline injection FUP

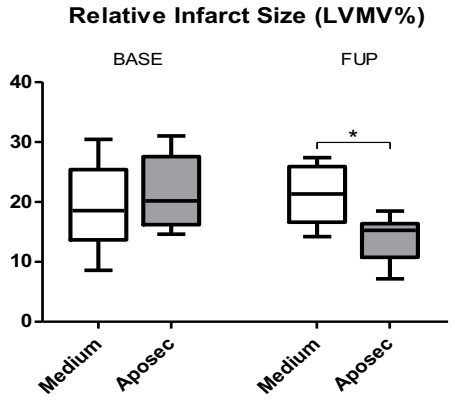
Segmental infarct transmurality is reduced in the FUP images of an APOSEC-treated pig, while slight enlargement of the infarct area is seen in a medium solution-treated pig.

MRI and hemodynamic results

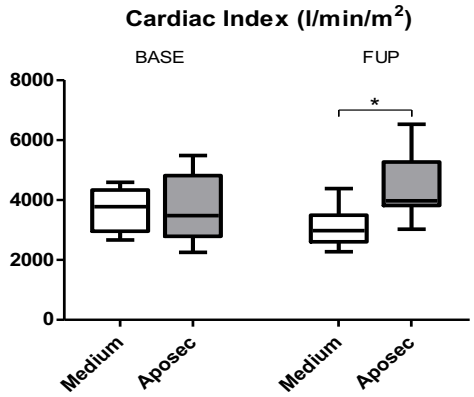


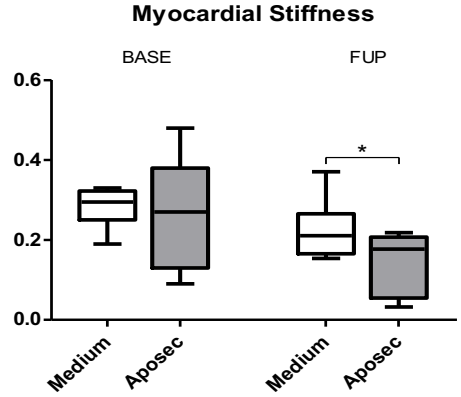
37.4+/-8.0 vs. 45.4+/-5.9 %; p = 0.052

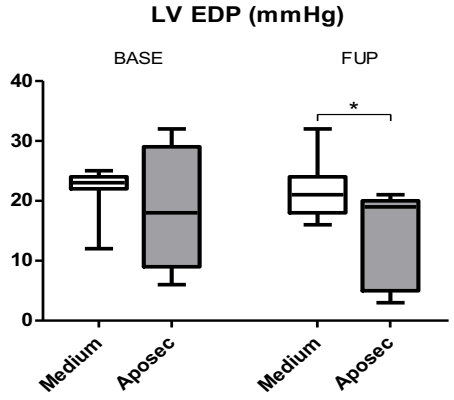




21.58+/-2.09 vs.13.92+/-1.34 %; p < 0.05



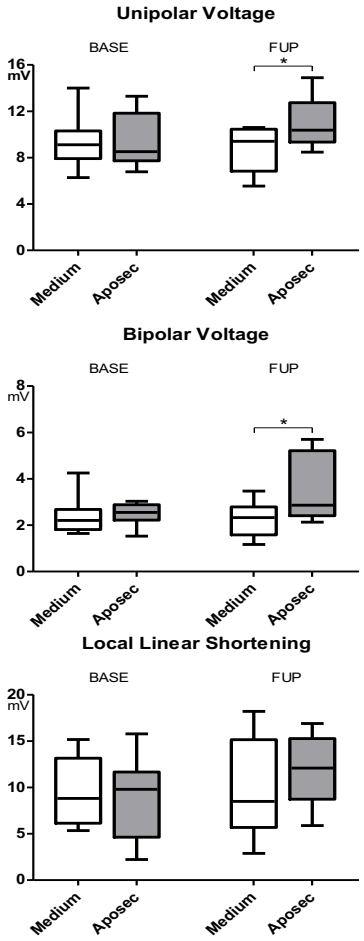




3.07+/-2.35 vs.4.40+/-3.94 l/min/m2; p < 0.05

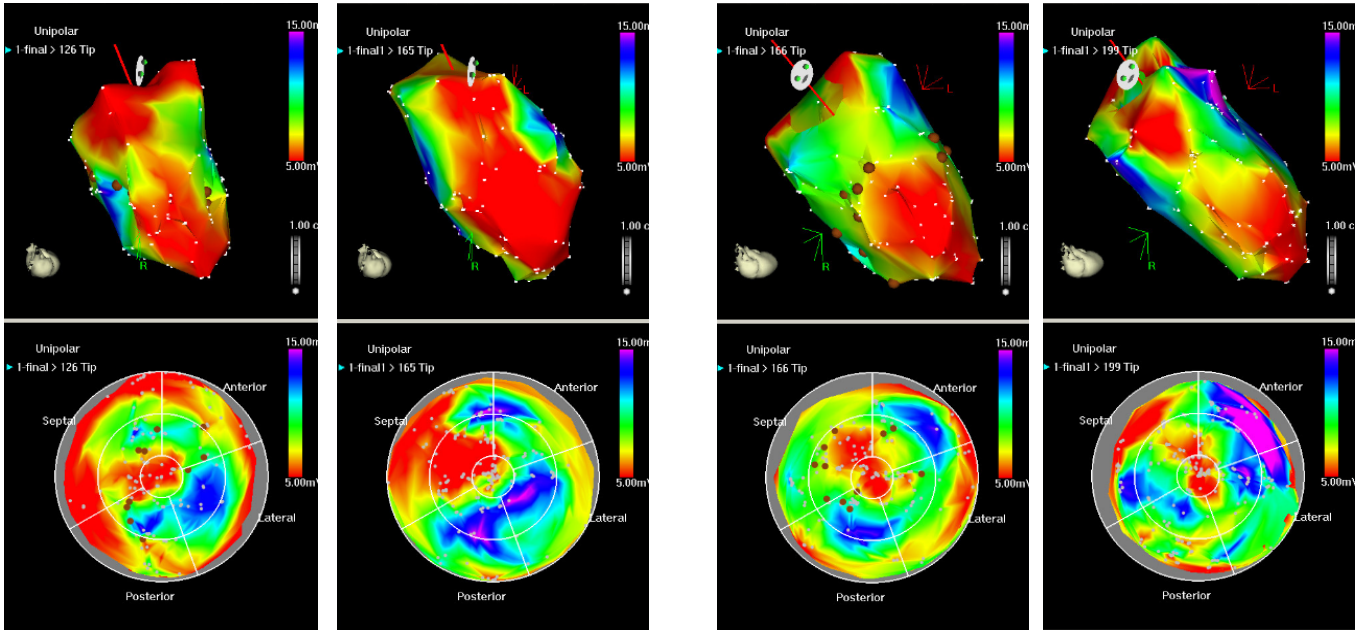
APOSEC-treated animals had significantly smaller infarcts, a significantly higher cardiac index and showed a trend towards a higher EF.

NOGA results



Unipolar voltage maps of a control (medium solution-treated) animal

Unipolar voltage maps of an Aposec-treated animal



Baseline with injections

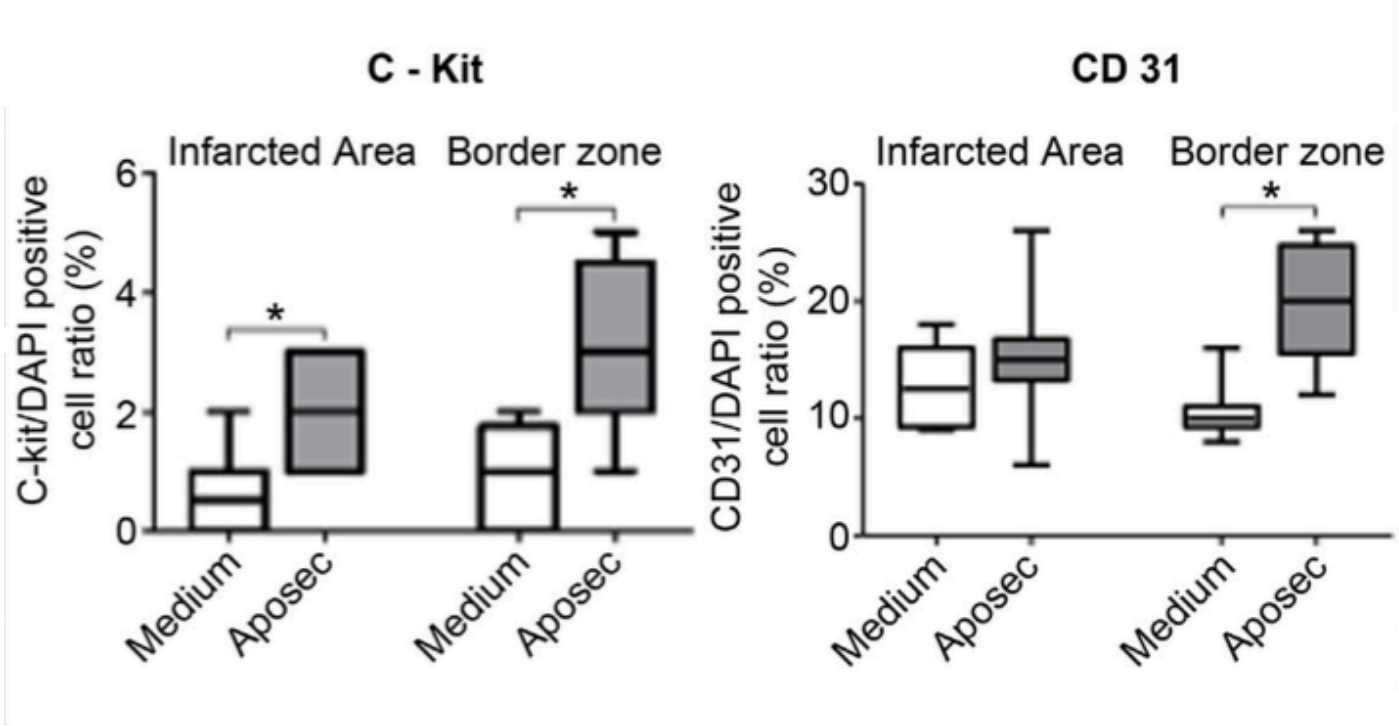
FUP

Baseline with injections

FUP

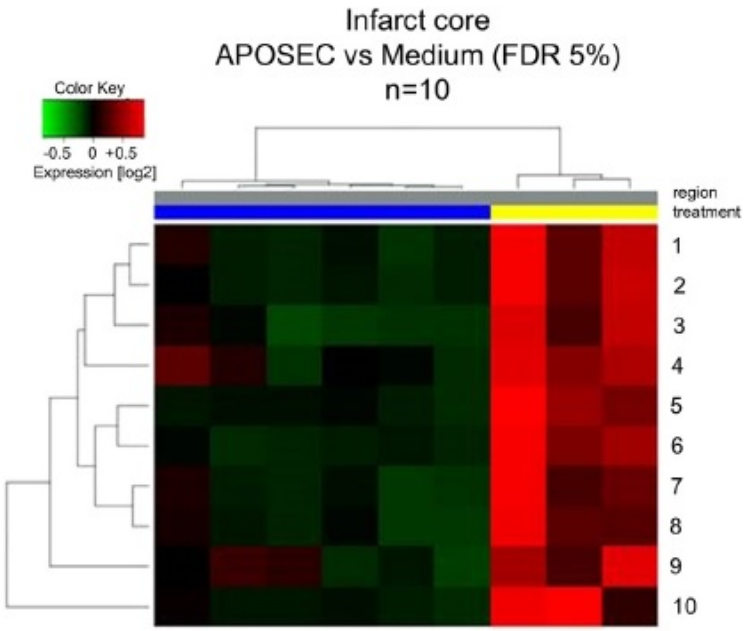
The APOSEC group had significantly higher unipolar voltage values (viability) and bipolar voltage (index of infarct transmurality) values. The infarcted area was visibly smaller at FUP in the APOSEC-pigs, indicating that ventricular remodeling was reduced.

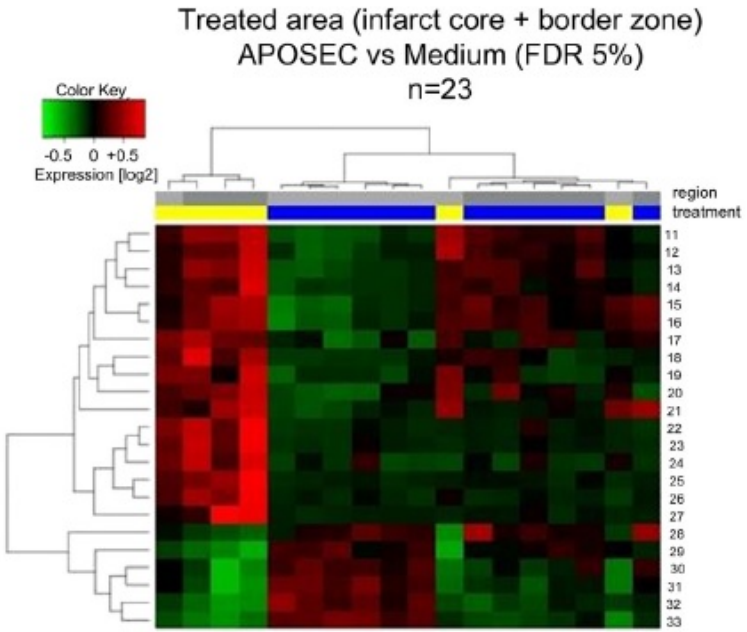
Histologic findings



APOSEC-treated pigs show a higher density of CD31+ and CD117+ cells both in infarct core and border areas, indicating enhanced level of microvascularization and homing of endogenous c-kitþ cardiac stem cells.

Gene expression analysis





FDR=5%

2 – CD209
4 – claudin3
7 – arachidonate 15-lipoxygenase

REGION: normal, border zone, infarct core

TREATMENT: treated, control

17 – caspase-1
20 – TNF-ligand member 13b
26 – uroplakin1B
31 – claudin3
32 – similar to S100-A2

Microarray analysis revealed 10 genes with significantly altered expression in the infarcted zone and 23 in the treated area at an FDR of 5%.

Systematic name	Log fold changes	Adjusted *P* value	Name of gene	Regulation in APOSEC group
Infarct core *FDR5%*				
NM_001129972	−1.426	0.029	CD209 molecule	Down
NM_213931	−3.367	0.038	Arachidonate 15-lipoxygenase	Down
ENSSSCT00000010283	−0.675	<0.001	Similar to LOC513955 protein	Down
NM_001160075	−0.798	<0.001	Claudin 3	Down
ENSSSCT00000013027	−2.047	0.005	n.i.	Down
NM_001123212	−1.081	0.001	Uroplakin 1B	Down
TC533994	−1.573	0.043	n.i.	Down
ENSSSCT00000008105	−1.249	0.016	Epididymal secretory protein	Down
XM_001927650	−0.847	0.002	Similar to trichohyalin	Down
Combined treated areas *FDR5%*				
NM_214162	−1.887	0.029	Caspase 1-apoptosis-related cysteine peptidase (interleukin 1-beta-convertase)	Down
NM_001097498	−0.753	0.015	Tumor necrosis factor (ligand) superfamily member 13b	Down
ENSSSCT00000010283	−0.815	0.003	Similar to LOC513955 protein	Down
NM_001160075	−0.949	0.005	Claudin 3	Down
ENSSSCT00000013346	−1.18	0.007	Similar to uncharacterized protein CXorf21 homolog	Down
NM_001123212	−1.287	0.01	Uroplakin 1B	Down
ENSSSCT00000011046	−1.623	0.014	Similar to stromal cell-derived factor 2-like protein 1 precursor (SDF2-like protein 1) (PWP1-interacting protein 8)	Down
ENSSSCT00000007208	−2.936	0.015	Similar to Protein S100-A2 (S100 calcium-binding protein A2) (Protein S-100L)	Down
ENSSSCT00000008105	−1.249	0.016	Epididymal secretory protein	Down
XM_001927650	−0.908	0.022	Similar to trichohyalin	Down
NM_213931	−3.367	0.038	Arachidonate 15-lipoxygenase	Down
TC520240	−1.61	0.047	n.i.	Down
ENSSSCT00000013027	−2.617	0.013	n.i.	Down
AK233548	−1.097	0.015	n.i.	Down
ENSSSCT00000011046	−1.297	0.015	n.i.	Down
AK230687	−2.509	0.015	n.i.	Down
ENSSSCT00000011934	−1.895	0.016	n.i.	Down
A_72_P409998	0.929	0.007	n.i.	Up
TC601625	1.154	0.013	n.i.	Up
TC591961	0.592	0.015	n.i.	Up
TC540937	2.522	0.015	n.i.	Up
TC526711	3.032	0.029	n.i.	Up
AK232497	2.857	0.04	n.i.	Up
Combined treated areas FDR between 5% and 10%				
NM_214037	−1.42	0.093	Ameloblastin	Down
DQ845172	−1.5	0.097	Beta-2-microglobulin	Down
NM_213990	−1.51	0.093	C-type lectin domain family 5, member A	Down
NM_213776	−1.26	0.093	CD2 molecule	Down
NM_214155	−1.18	0.093	CD247 molecule	Down
NM_001008691	−3.35	0.093	Chemokine (C-X-C motif) ligand 10	Down
NM_001114289	−3.97	0.097	Chemokine (C-X-C motif) ligand 9	Down
NM_001003924	−1.89	0.093	Complement component 1, q subcomponent, A-chain	Down
NM_214153	−1.32	0.093	Ectonucleoside triphosphate diphosphohydrolase 1	Down
NM_214000	−0.95	0.008	Haptoglobin	Down
NM_213813	−2.46	0.063	Killer cell lectin-like receptor subfamily K, member 1	Down
NM_001097415	−0.81	0.089	Lymphocyte antigen 86	Down
NM_001113706	−1.64	0.093	MHC class II DR-alpha	Down
NM_213811	−2.36	0.076	Scavenger receptor for phosphatidylserine and oxidized low density lipoprotein	Down
ENSSSCT00000007803	−1.72	0.081	Similar to cystatin F	Down
AK232017	−2.63	0.097	Similar to signaling threshold-regulating transmembrane adapter 1 precursor (suppression-inducing transmembrane adapter 1) (SHP2-interacting transmembrane adapter protein) (gp30/40)	Down
NM_001001632	−1.45	0.08	Tropomyosin 3	Down
NM_213883	3.05	0.063	Insulin-like growth factor 2 (somatomedin A)	Up
NM_001134346	1.41	0.093	Kruppel-like factor 11	Up
NM_001025222	1.39	0.097	Myozenin 1	Up
ENSSSCT00000007708	0.92	0.093	Prion protein	Up
ENSSSCT00000011141	1.01	0.093	Similar to glyceronephosphate O-acyltransferase	Up
AY609888	0.67	0.081	Similar to NAD(P) dependent steroid dehydrogenase-like	Up
AY609888	0.78	0.097	Similar to NAD(P) dependent steroid dehydrogenase-like	Up

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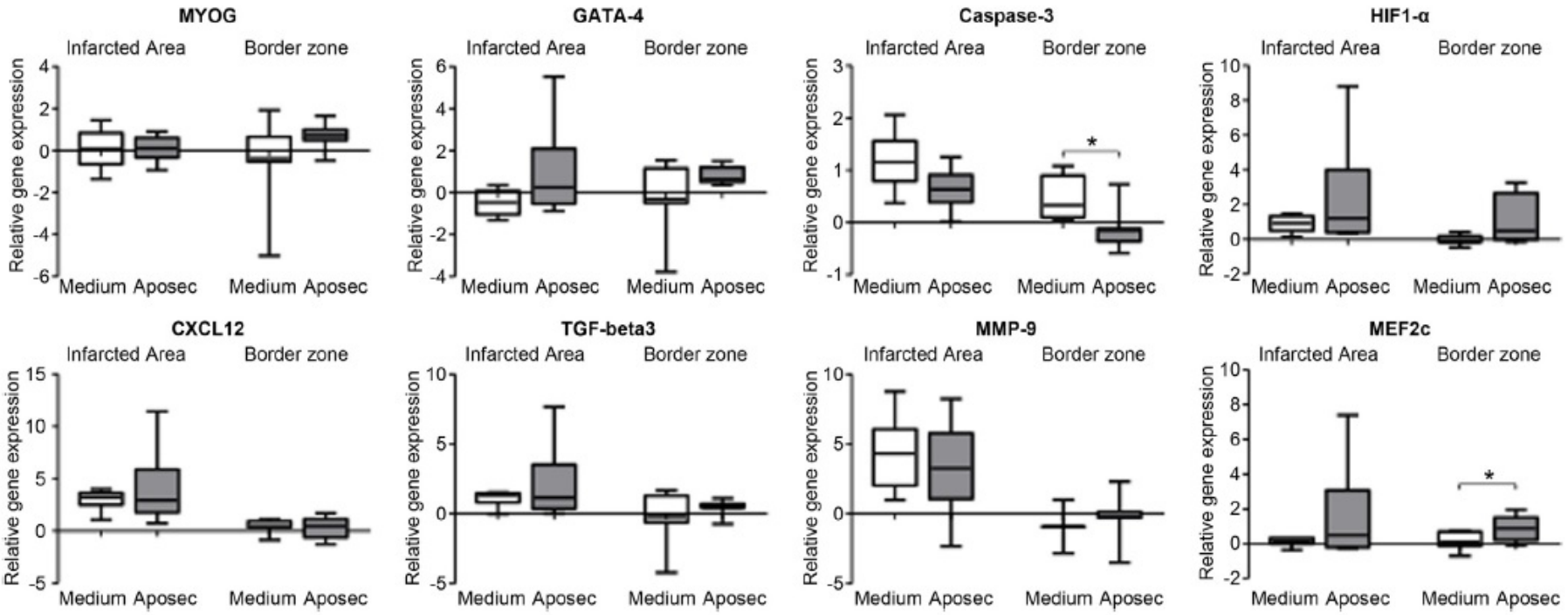
FDR=10%

RT-PCR



Significant overexpression of the cardiac myogenesis and vascular development gene, myocyte-specific enhancer factor 2C (MEF2c), and repression of the apoptosis regulator caspase-3 and a trend towards higher expression of GATA-4 were found.

Summary

1. The presented large animal models of not only acute but chronic myocardial ischemia studies demonstrate the beneficial effects of paracrine factors (as a cell-free therapy) in myocardial regeneration.

2. In chronic myocardial ischemic LV dysfunction APOSEC injection was associated with reduction in infarct size and significant increase in CO accompanied by improvement in contractile function.

3. Gene profiling analysis of the APOSEC-treated myocardial areas revealed downregulation of inflammatory and apoptotic genes.

4. Post-hoc validation of gene expression by RT-PCR showed higher levels of expression of Mefc2 and a robust downregulation of apoptosis regulator, caspase-3.

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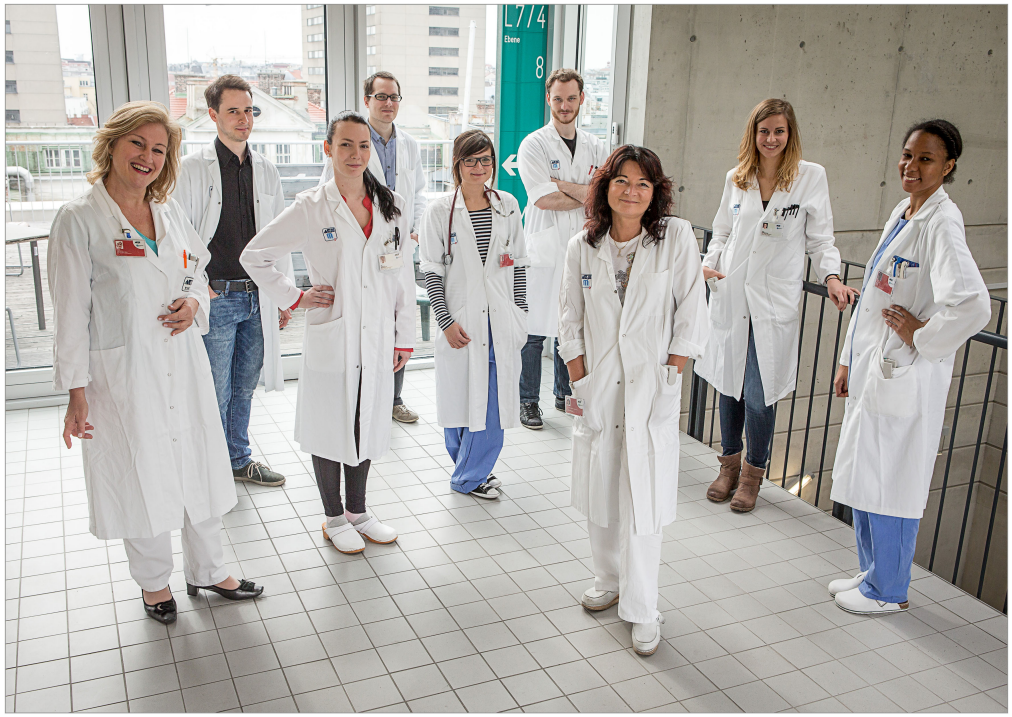
Acknowledgments

ÖKG
Österreichische Kardiologische Gesellschaft



Christian Doppler Forschungsgesellschaft

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Thank you for your attention!