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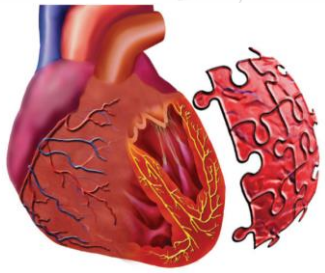
Cell implantation after myocardial infarction:

a 10 years experience from the ICREC laboratory

BANFF-SCT Joint Scientific Meeting 2017

Barcelona, 29th March



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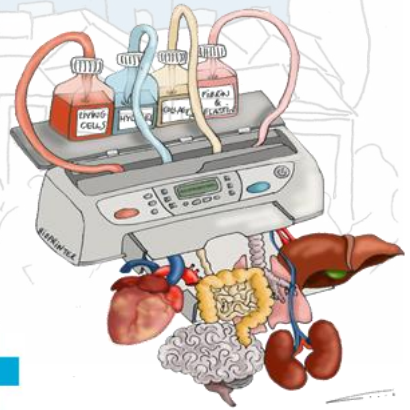
ADVANCE (CAT)
Accelerating Development of Advanced Therapies in Catalonia

No competing interests exist
in relation to this presentation



IGTP · ICREC Insuficiència Cardíaca Regeneració Cardíaca · UAB

“You never fail until you stop trying.” — Albert Einstein

“All men dream: but not equally. Those who dream by night in the dusty recesses of their minds wake in the day to find that it was vanity: but the dreamers of the day are dangerous men, for they may act their dreams with open eyes, to make it possible. This I did.” — Thomas Edward Lawrence

The ICREC laboratory: aim

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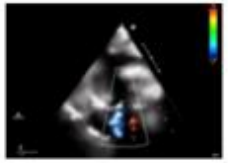
HEART DISEASE

Clinical Approach

Signs

Symptoms

Imaging



ECG

ECHO

X Ray

CT Scan

MRI

Angiography

PET

Stress test

Chemistry and Devices

PM

CRT

ICD

Pills

Stents

. . .

BIOLOGICAL Approach

BIO-MARKERS

Diagnosis

Prognosis

Monitoring

. . .

BIO-THERAPIES

Stem cells

Tissue engineering

Gene therapy

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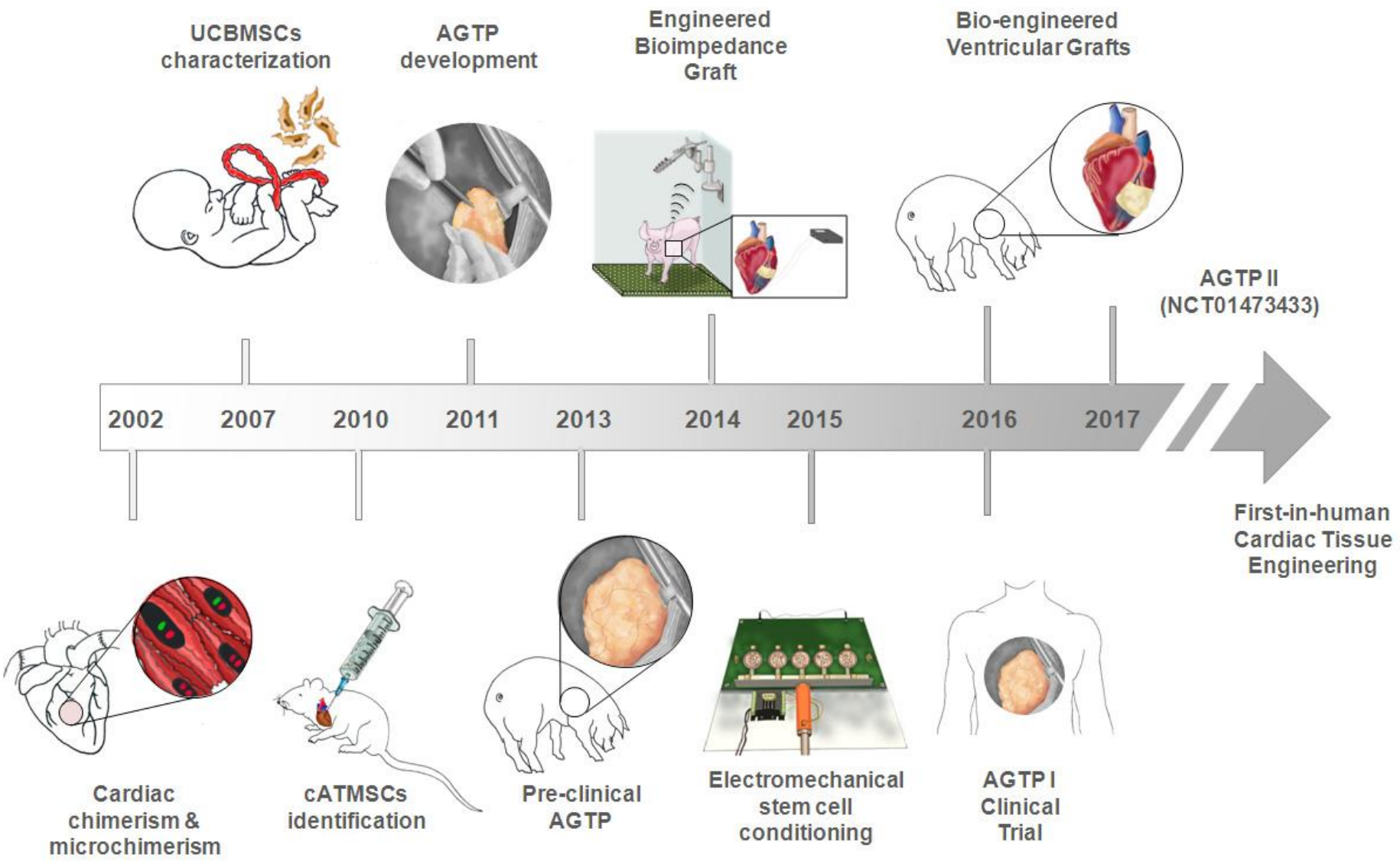
The ICREC laboratory: milestones in biotherapies



Source: ICREC, unpublished

What are we facing? What are we looking for?

before therapy

after therapy

Myocardial infarction

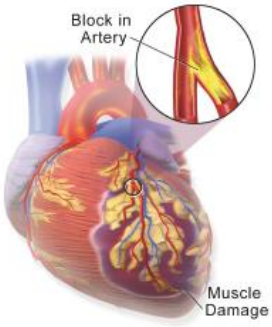
• Myocardial infarction is caused by coronary artery occlusion provoking irreversible myocardial ischemia, loss of cardiomyocytes and formation of a non-contractile fibrous scar. It may induce ventricular remodeling and lead to heart failure

• The human heart has a limited regenerative capacity thus, cardiac function is only fully re-established after heart transplantation. This option, however, is extremely restricted by limit number of donors and graft rejection

• First evidences of myocardial regeneration were seen in rodents (1060s), in amphibia (1974) and, finally, in zebrafish (2002)

• Several findings changed the old dogma describing the human heart as a terminally differentiated organ:

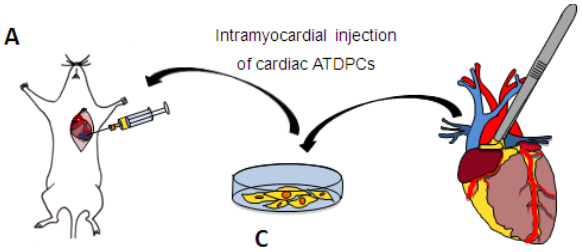
- resident cardiac stem cells in the heart
- cardiomyocyte DNA synthesis
- cardiac chimerism phenomena



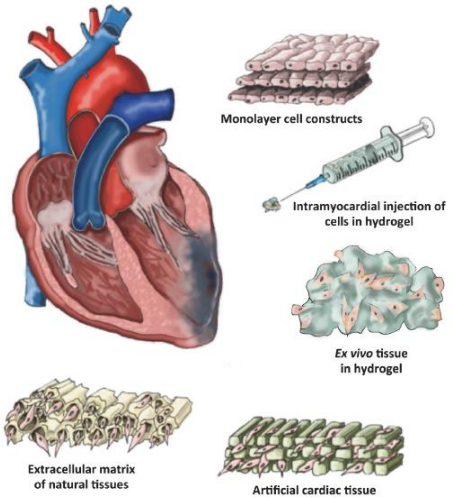
Myocardial Infarction. Image obtained from the Medical Institution.

Cardiovascular research: efforts

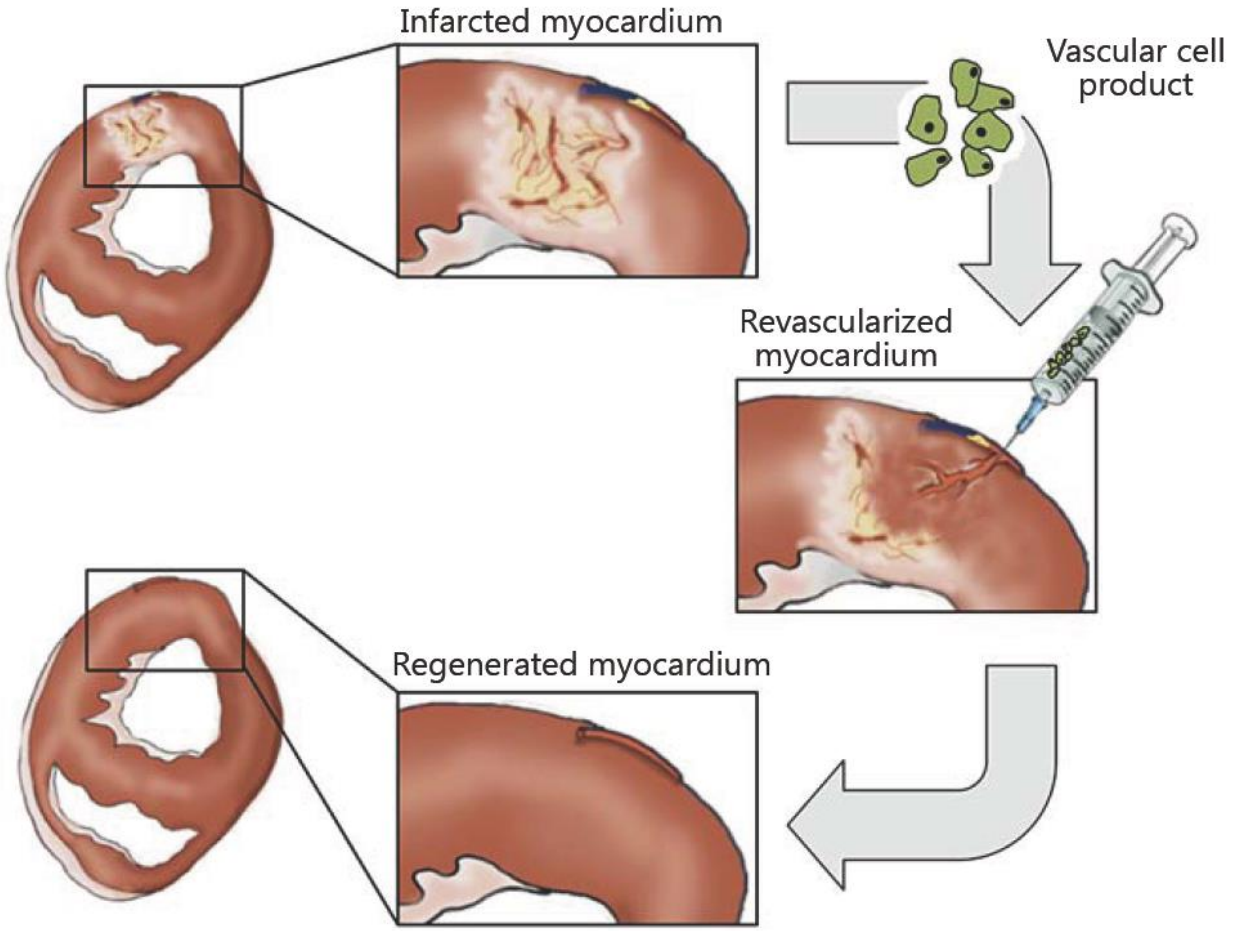
- Cellular cardiomyoplasty



- Cardiac tissue enginnering

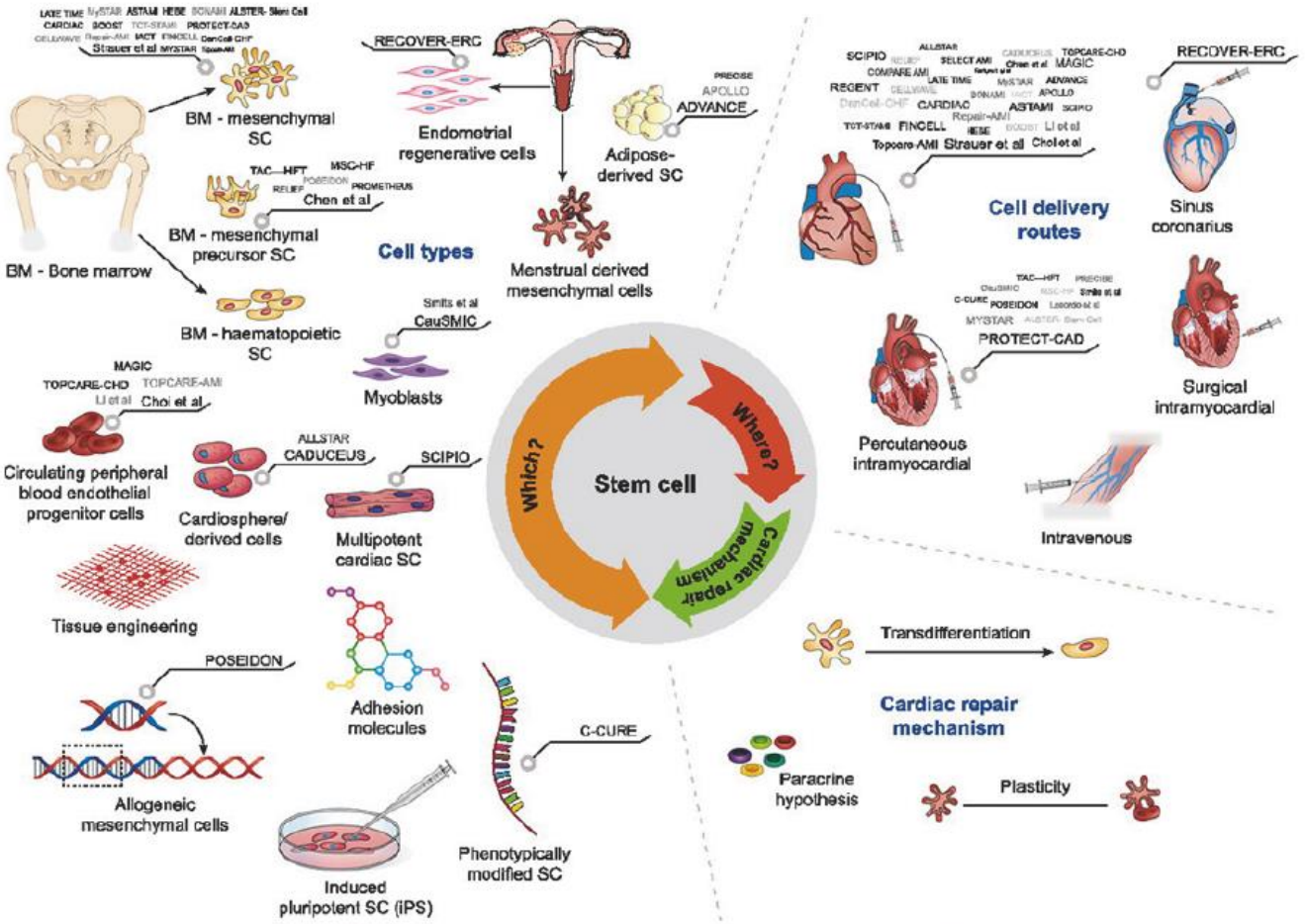


Cell therapy: basis and objectives



Roura et al. J Vasc Res. **2013**;50(4):304-23

Cell therapy: a myriad of cellular actors



Cellular cardiomyoplasty strategies. From Pavo *et al*, 2014.

Cell therapy: clinical results

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- Cumulative clinical evidence (mostly using bone marrow cells) indicates that cell therapy modestly improves cardiac function following myocardial infarction (MI)

Table 2. Summary of major BMMNC-based clinical trials in acute and chronic MI

Study/references	Condition	n	Cell type	Delivery method	Safety[1]	Outcomes
Hamano et al. [134]	CMI	5	BMMNC	IC	+	Increased coronary perfusion (3/5)
Strauer et al. [135]	AMI	10	BMMNC (2.1% CD34+)	IC	+	Improved LVEF and contractility, reduced infarct size at 6 months
TOPCARE-AMI [136–138]	AMI	35/51	CPC/BMMNC	IC	+	Similar results for both cell types: improved LVEF and local contractility, reduced infarct size at 4–12 months
Fernández-Avilés et al. [139]	AMI	20	BMMNC (1% CD34+)	IC	+	Improved LVEF and regional contractility, reduced end systolic volume
Stamm et al. [140]	AMI	12	CPC (CD133+)	IM	+	Increased perfusion, motility and wall thickness
Tse et al. [141]	CMI	8	BMMNC	IM	+	Increased motility and wall thickness
BOOST [142]	CMI	30	BMMNC	IC	+	Improved LVEF at 6 months, no difference at 18 months, improved LV function and increased regional contractility
ASTAMI [143]	AMI	49	BMMNC	IC	+	No effect on global LVEF at 6 months
REPAIR-AMI1 [144, 145]	AMI	200	BMMNC	IC	+	Improved EF and reduced infarct size at 4 months
Janssens et al. [146]	AMI	67	BMMNC	IC	+	Reduced infarct size, improved regional systolic function but no augment recovery of global LV function
FINCELL trial [147–149]	AMI	80	BMMNC	IC	+	Increased global LVEF at 6 months
MYSTAR [150]	AMI	60	BMMNC	IM	+	Reduced infarct size, increased myocardial viability and global EF
Hu et al. [151]	CMI	60	BMMNC	CABG	+	Increased LVEF, LV end-systolic volume index and wall motion index score at 6 months
BONAMI [152]	AMI	101	BMMNC	IC	+	Increased myocardial viability at 3 months
TIME [153–155]	AMI	120	BMMNC	IC	+	Similar results for both timing of cell delivery groups: no significant effects on regional and global LV function

CMI = Chronic MI; AMI = acute MI; IC = intracoronary; IM = intramyocardial; CABG = coronary artery bypass graft; EF = ejection fraction; LV = left ventricular; LVEF = left ventricular ejection fraction.

[1] No adverse events, including arrhythmias, calcifications and teratoma formation, were detected.

Roura et al. J Vasc Res. **2013**;50(4):304-23

Cell therapy: the discovery of a new stem cell source

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- Novel cell sources with increased potential to repair injured tissue have been sought

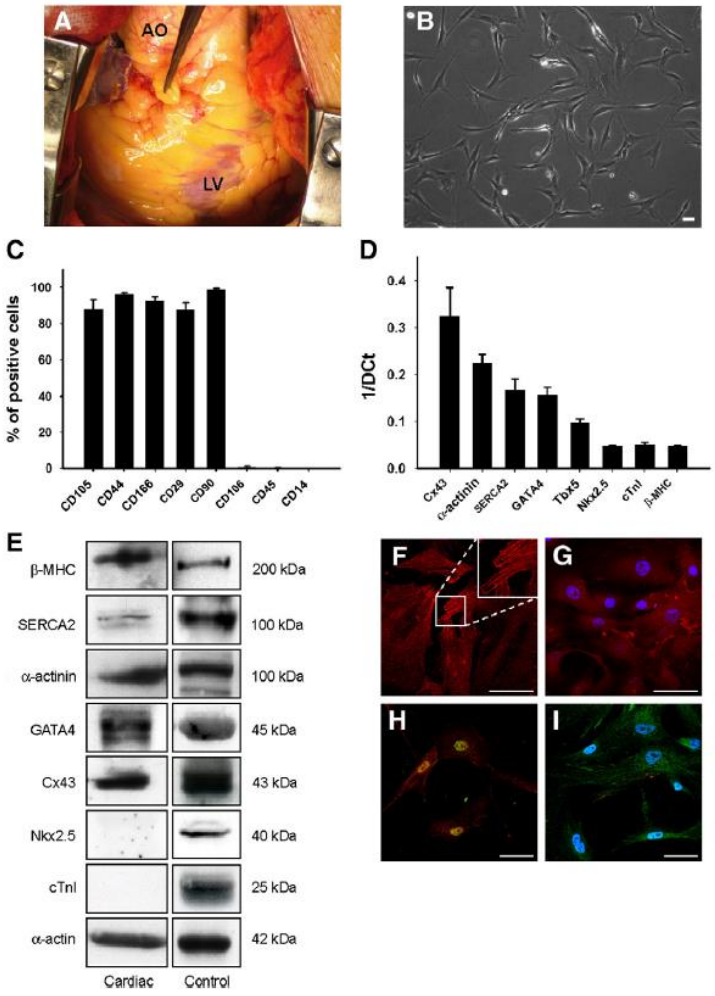
- We identified and characterized a progenitor cell population from biopsies of human adult cardiac adipose tissue (cardiac ATDPCs)

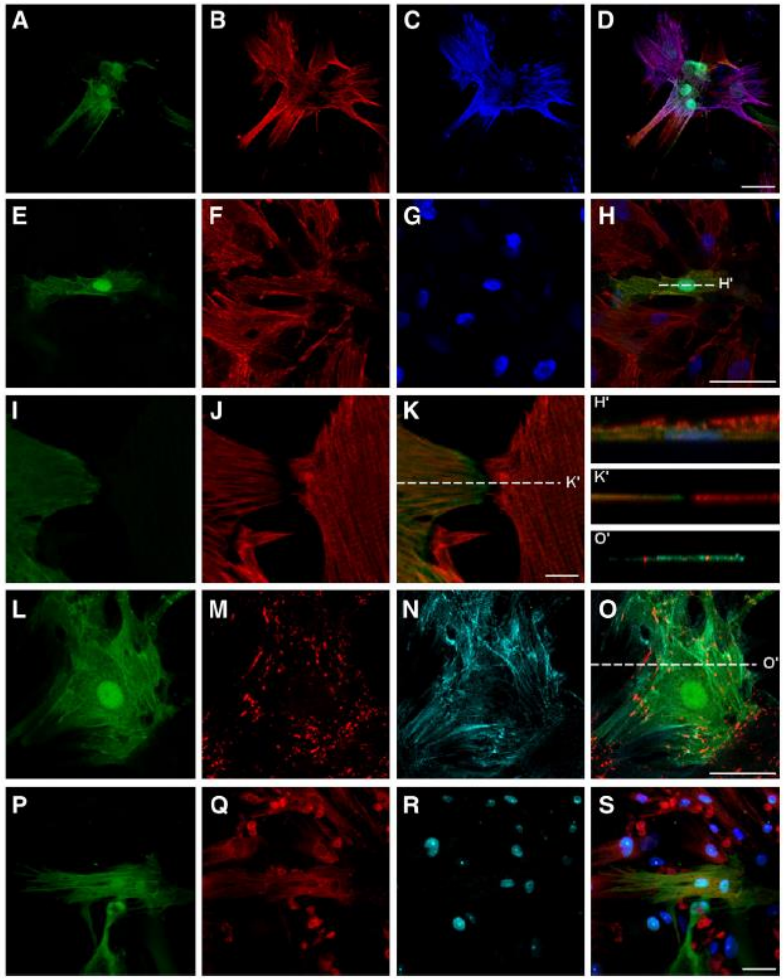
- Cardiac ATDPCs show a MSC-like marker profile and immunosupressive capacity

- Remarkably, cardiac ATDPCs have an inherent cardiac-like phenotype and were able to express *de novo* myocardial and endothelial markers in vitro but not to differentiate into adipocytes

- Following *in vivo* implantation, cardiac ATDPCs improves cardiac function and diminishes scar size after MI

Cardiac ATDPCs: baseline and induced traits

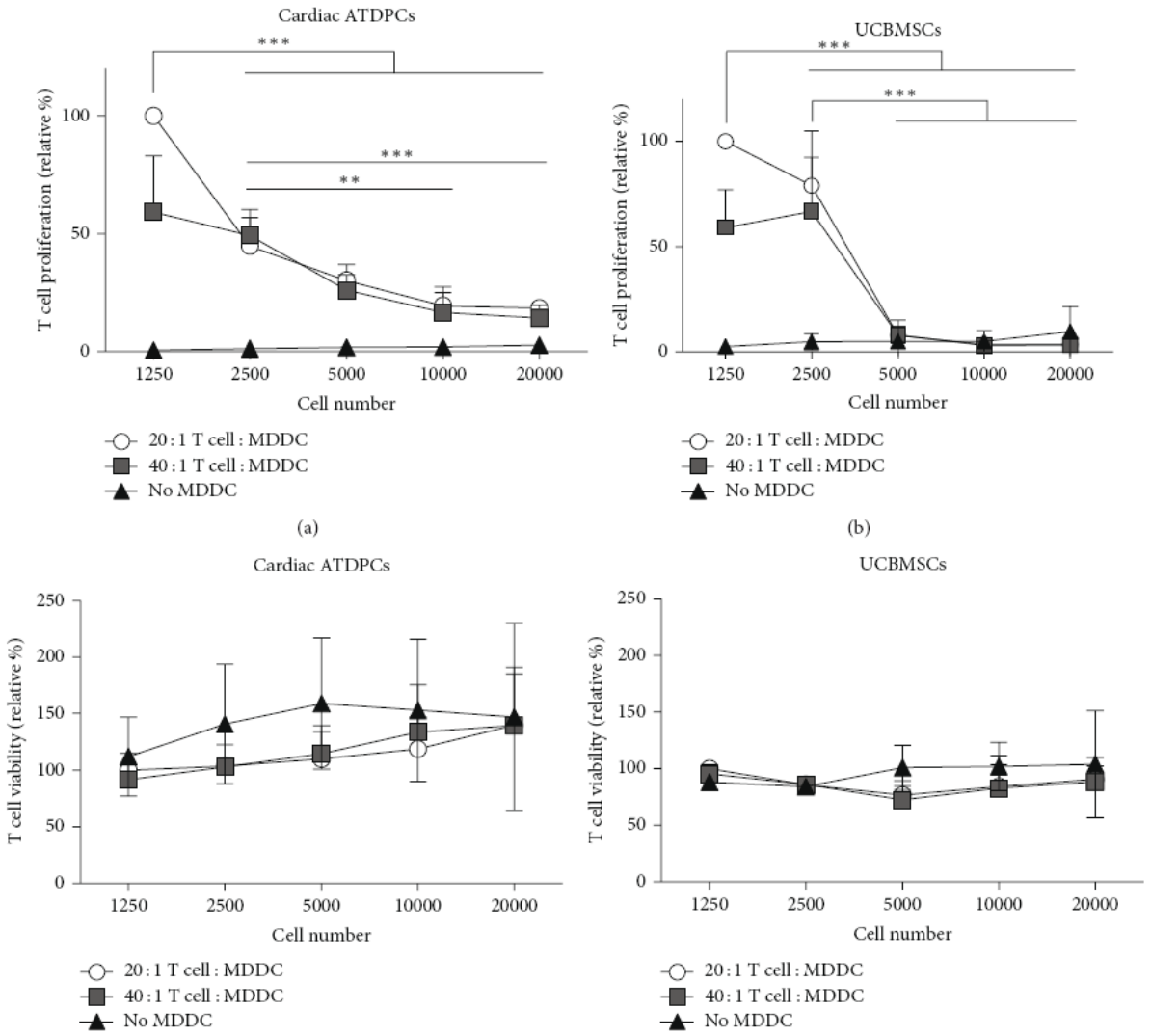




Coculture with neonatal rat cardiomyocytes

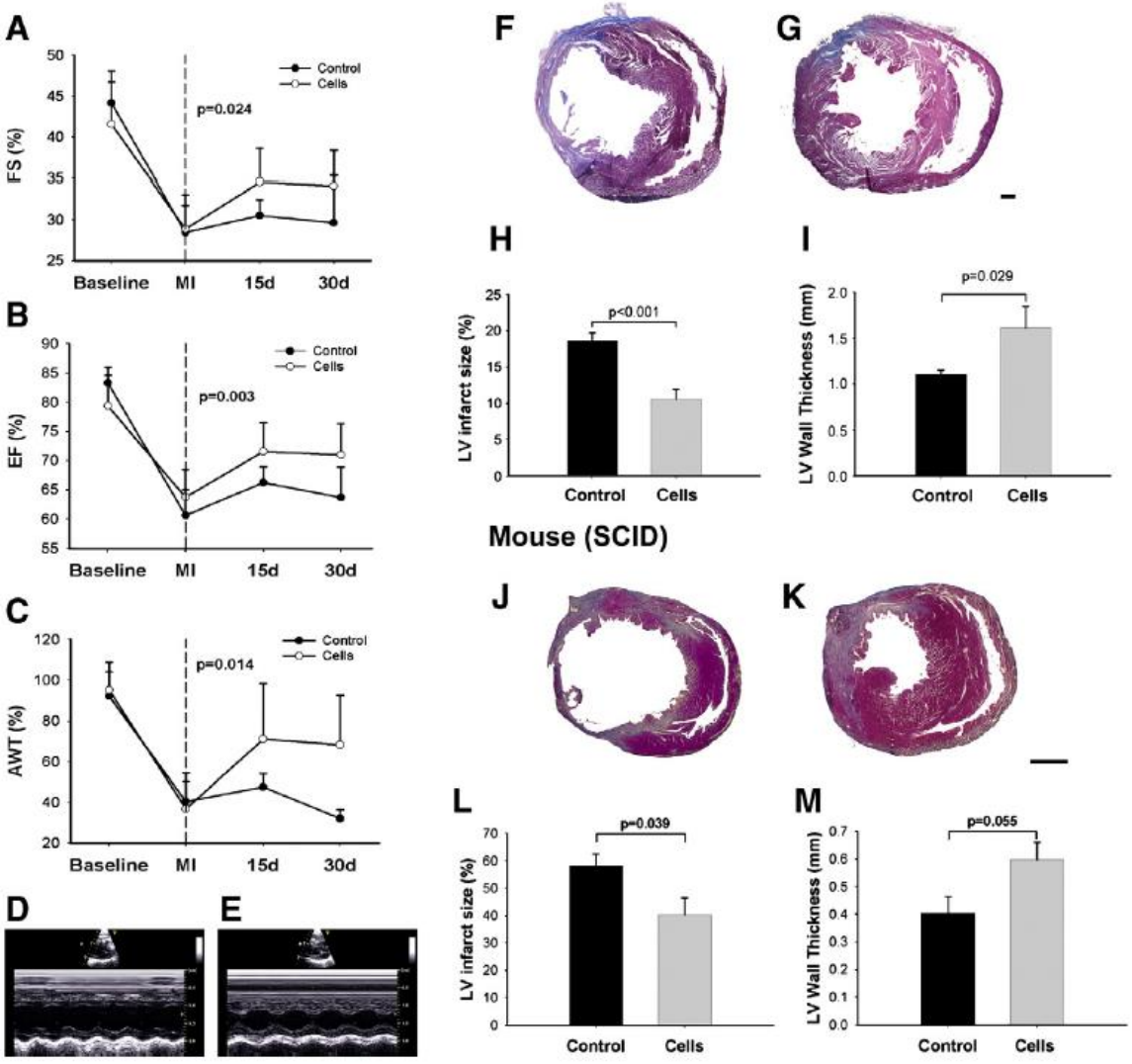
Bayes et al. J Mol Cell Cardiol. **2010** Nov;49(5):771-80

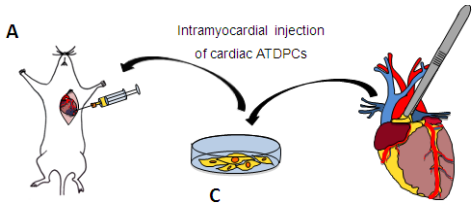
Cardiac ATDPCs: immunomodulatory potential



Perea-Gil et al. Biomed Res Int. **2015**;**2015**:439808

Cardiac ATDPCs: *in vivo* transplantation





Bayes et al. J Mol Cell Cardiol. **2010** Nov;49(5):771-80

UCBMSCs: vascular potential

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• To date, the acquisition of properties related to vascular growth has been reported for distinct cell sources, including mesenchymal stem cells (MSCs)

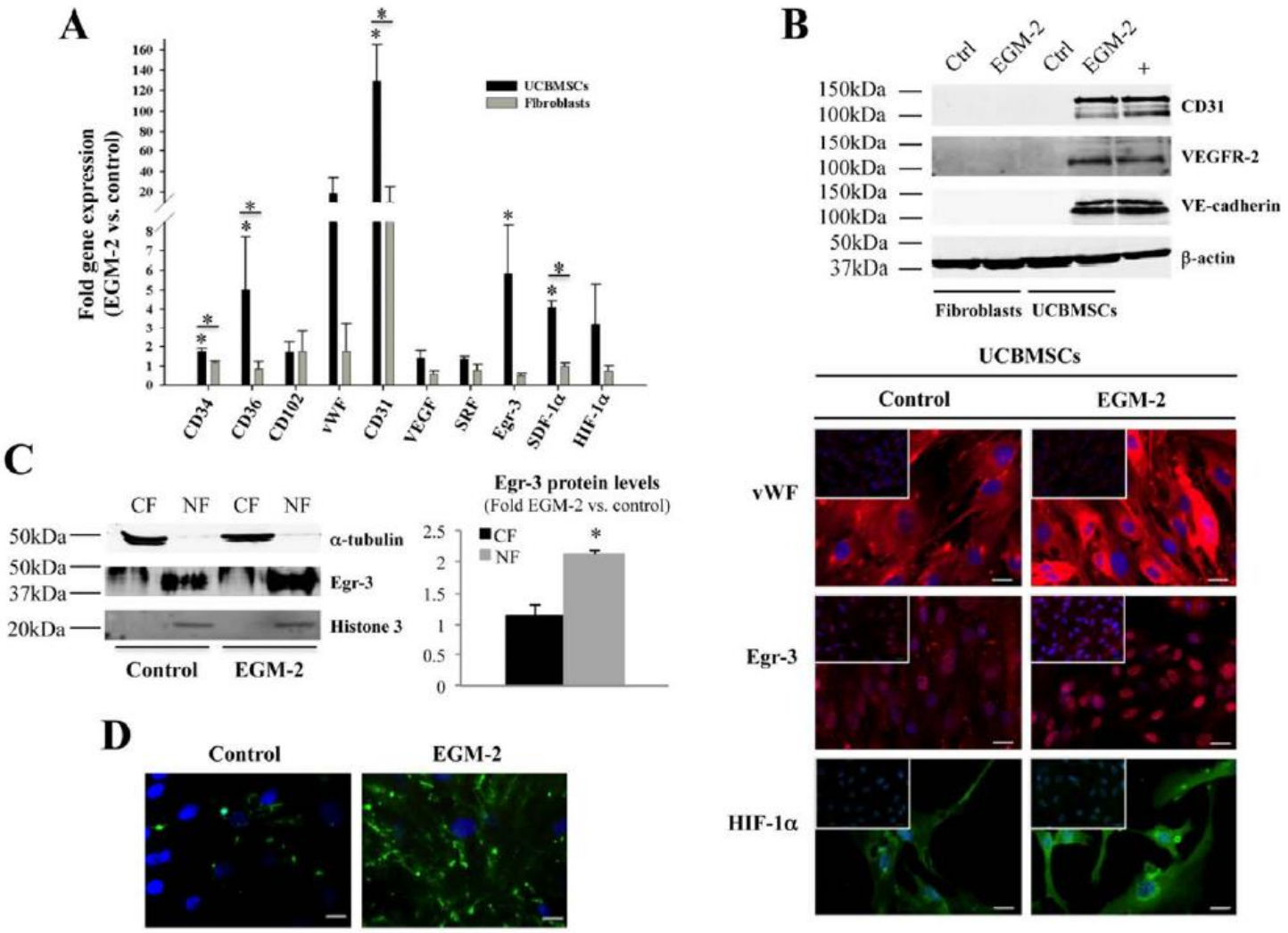
• MSCs comprise a population of multipotent progenitor cells derived from distinct human tissues (bone marrow, adipose tissue, umbilical cord blood, Wharton's Jelly..)

• *In vitro*, UCBMSCs acquire new endothelial cell markers, increased Ac-LDL uptake, migratory/invasive capacity and self-organization into tube-like structures in Matrigel assays (vasculogenesis)

• Of note, following *in vivo* subcutaneous injection with Matrigel, UCBMSCs actively participate in the formation of new microvasculature connected with the host circulatory system

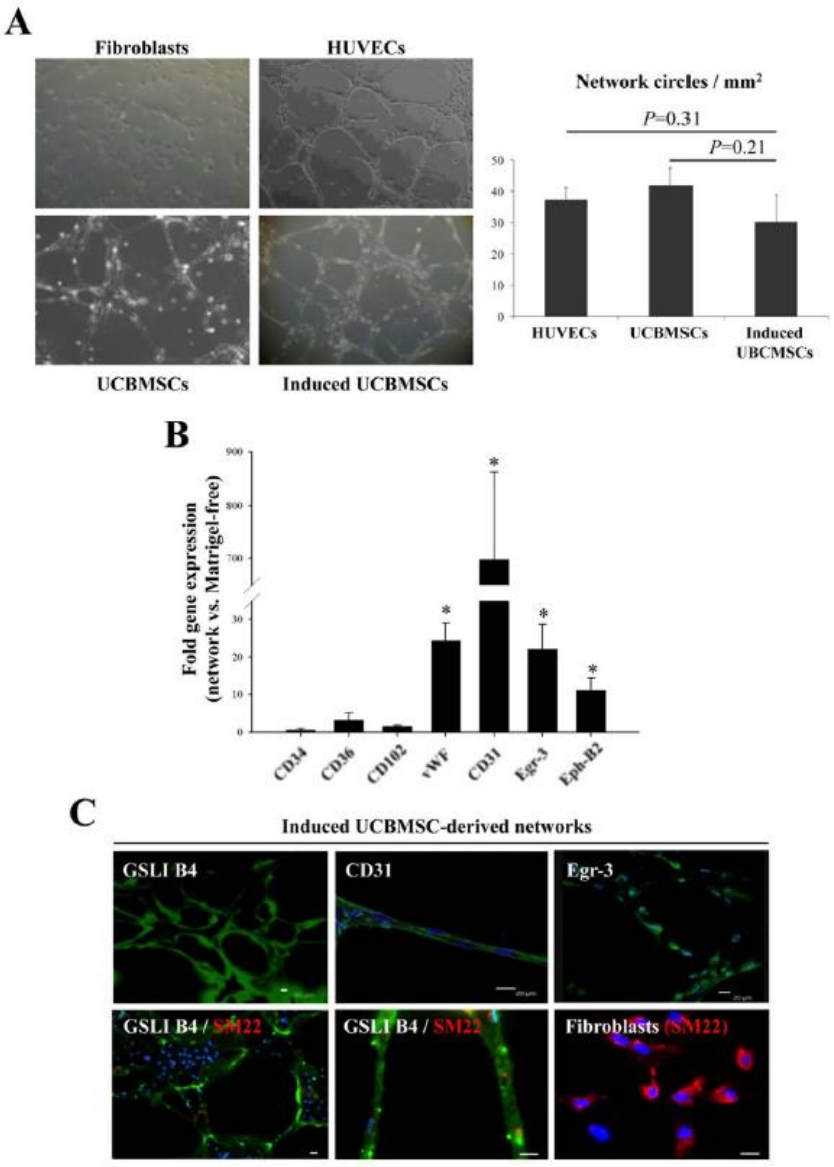
• By using a fibrin patch, UCBMSCs survive 4 weeks above infarcted myocardium, reduce infarct size (3-fold) and increase vessel-occupied area (2-fold)

UCBMSCs: pre-clinical results



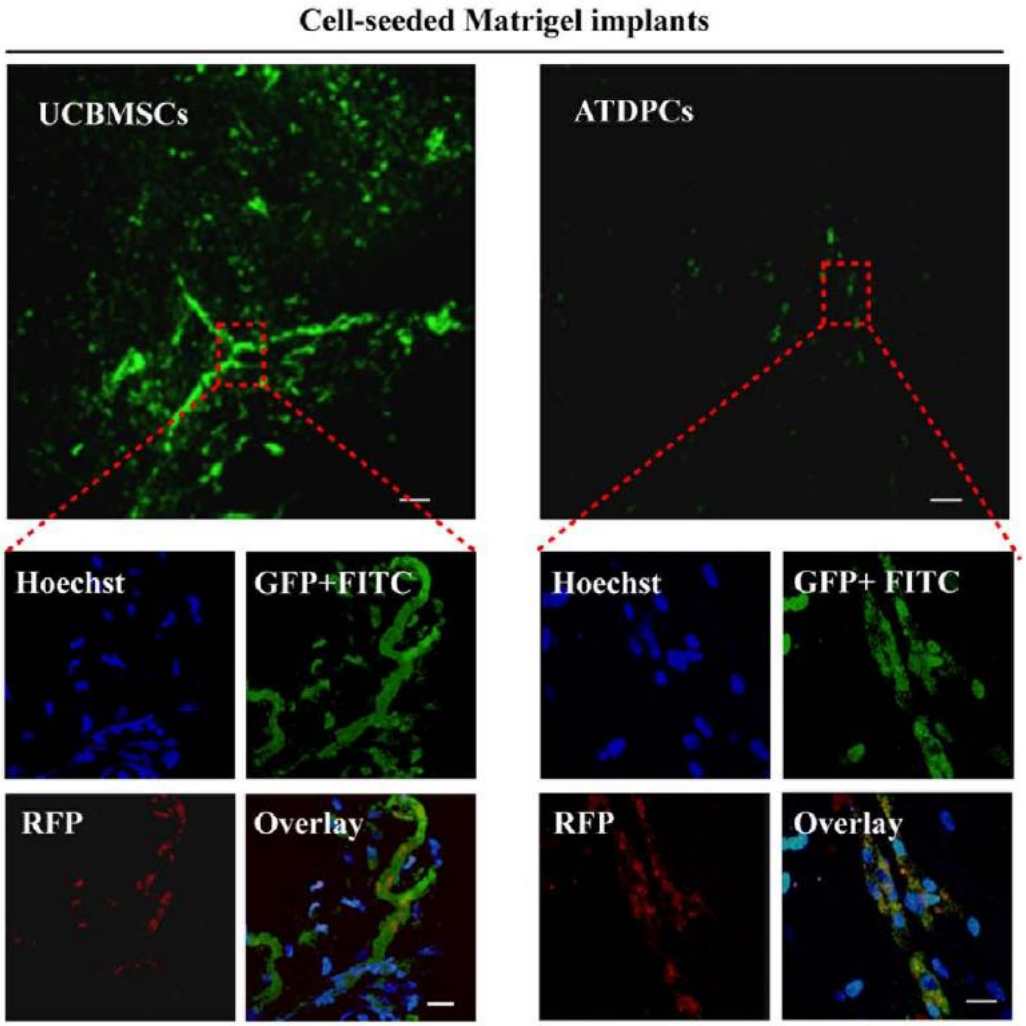
Roura et al. PLoS One. 2012;7(11):e49447

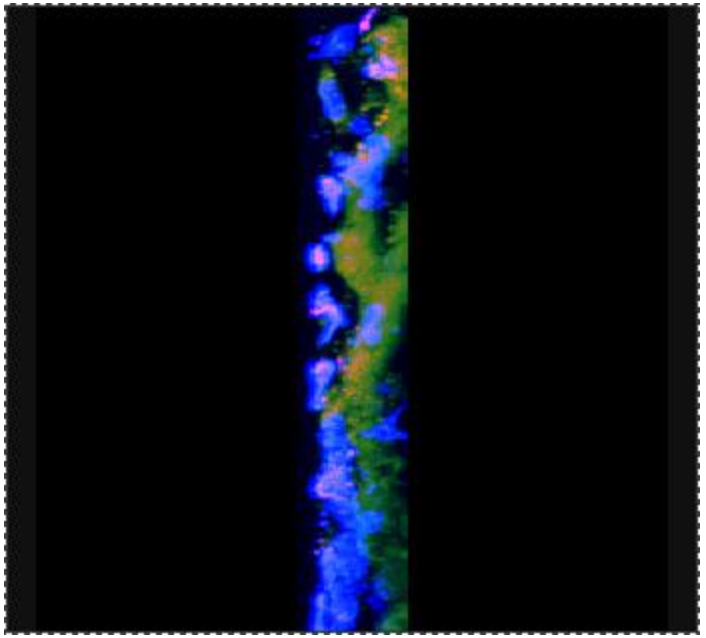
UCBMSCs: pre-clinical results



Roura et al. PLoS One. 2012;7(11):e49447

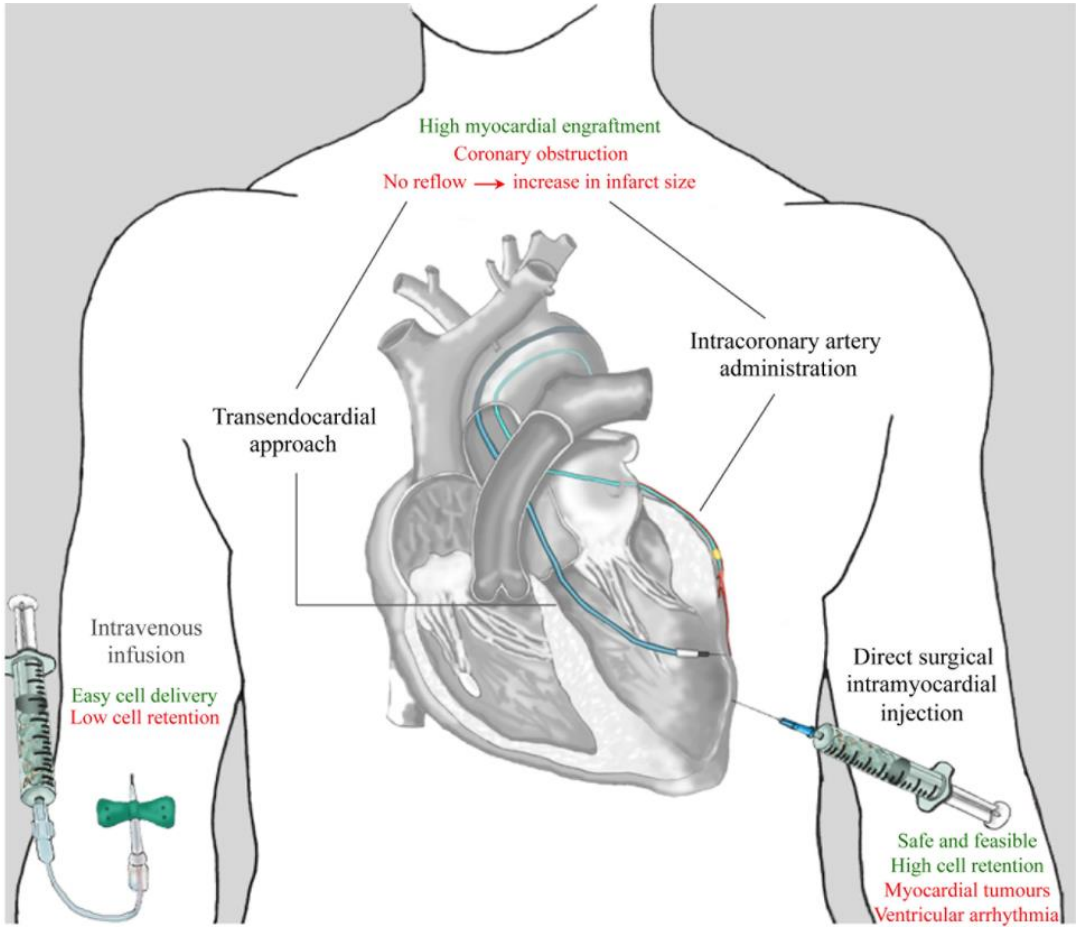
UCBMSCs: pre-clinical results





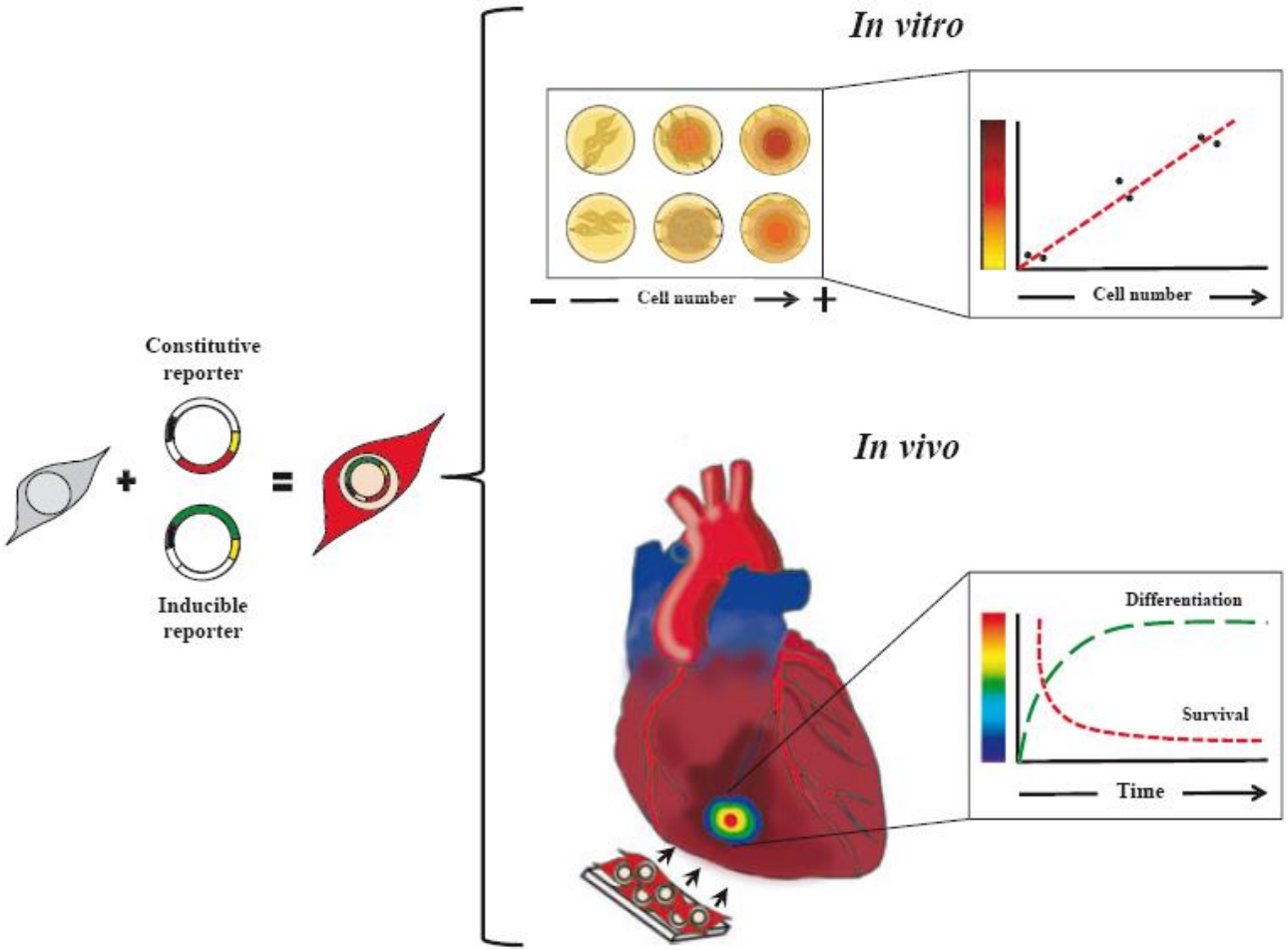
Roura et al. PLoS One. 2012;7(11):e49447

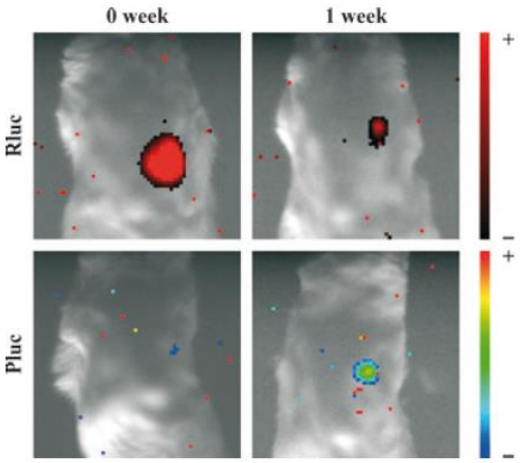
Biodistribution and cardiac cell delivery: a limitation



Roura et al. J Tissue Eng Regen Med. 2016 Apr 6

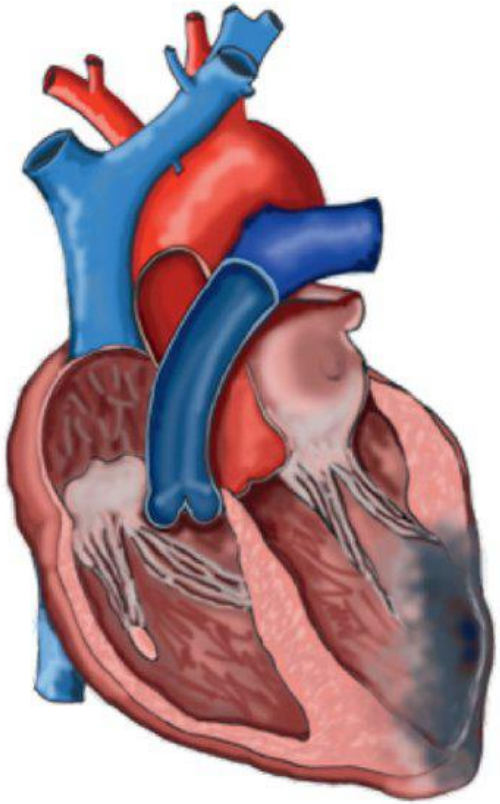
Cell tracking system: bioluminescence

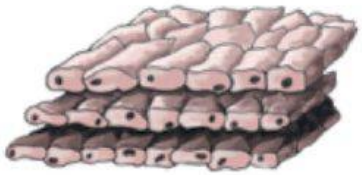




Roura et al. J Cell Mol Med. 2013 Jun;17(6):693-703.

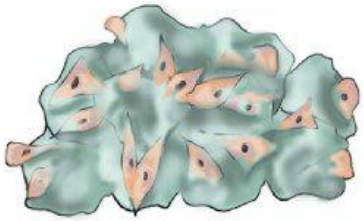
Cardiac tissue engineering: novel approaches of cell delivery



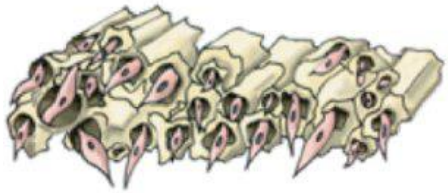


Monolayer cell consturcts

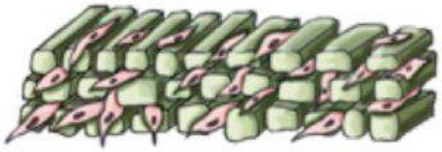
Intramyocardial injection
of cells in hydrogel



Ex vivo tissue
in hydrogel



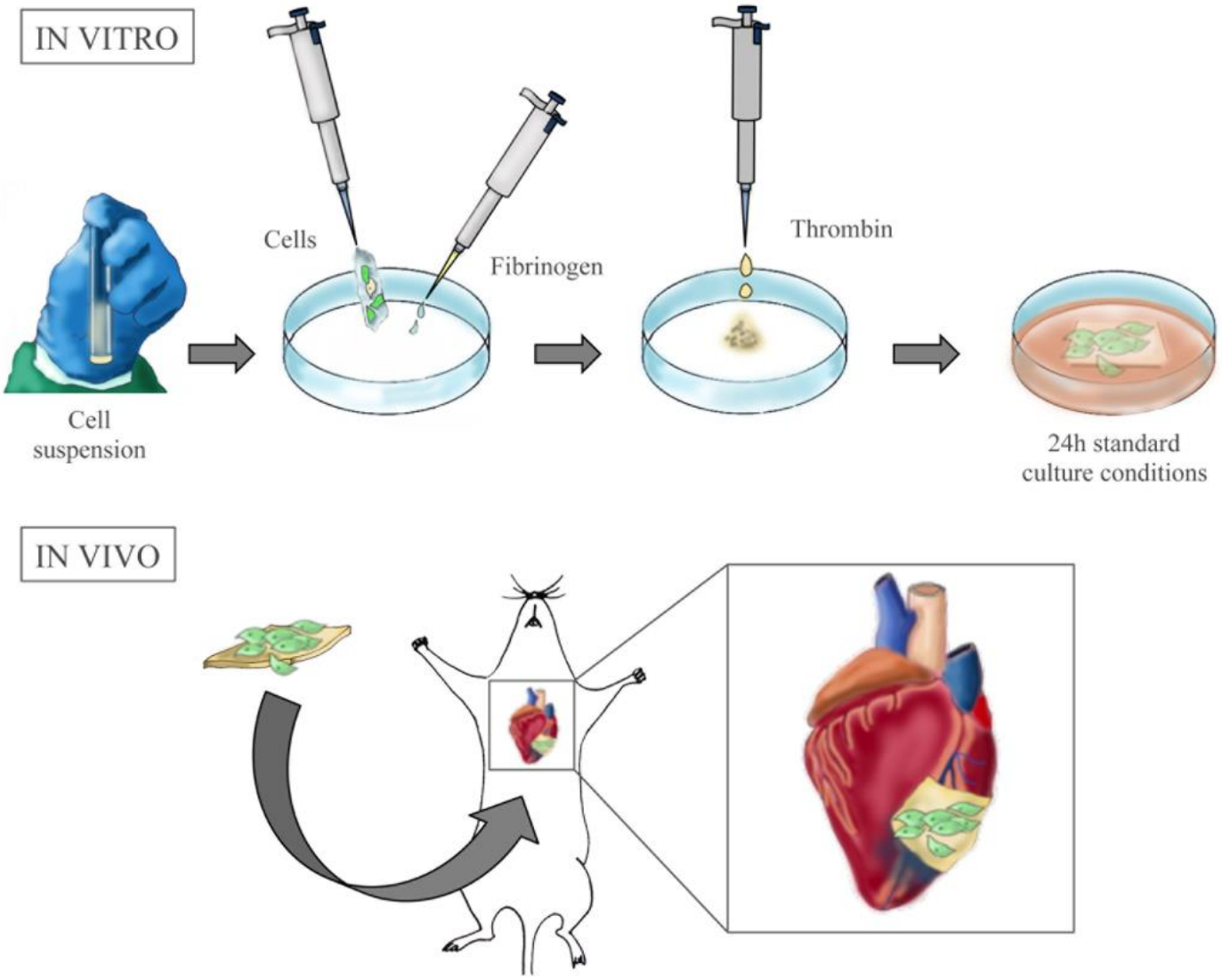
Extracellular matrix
of natural tissues



Artificial cardiac tissue

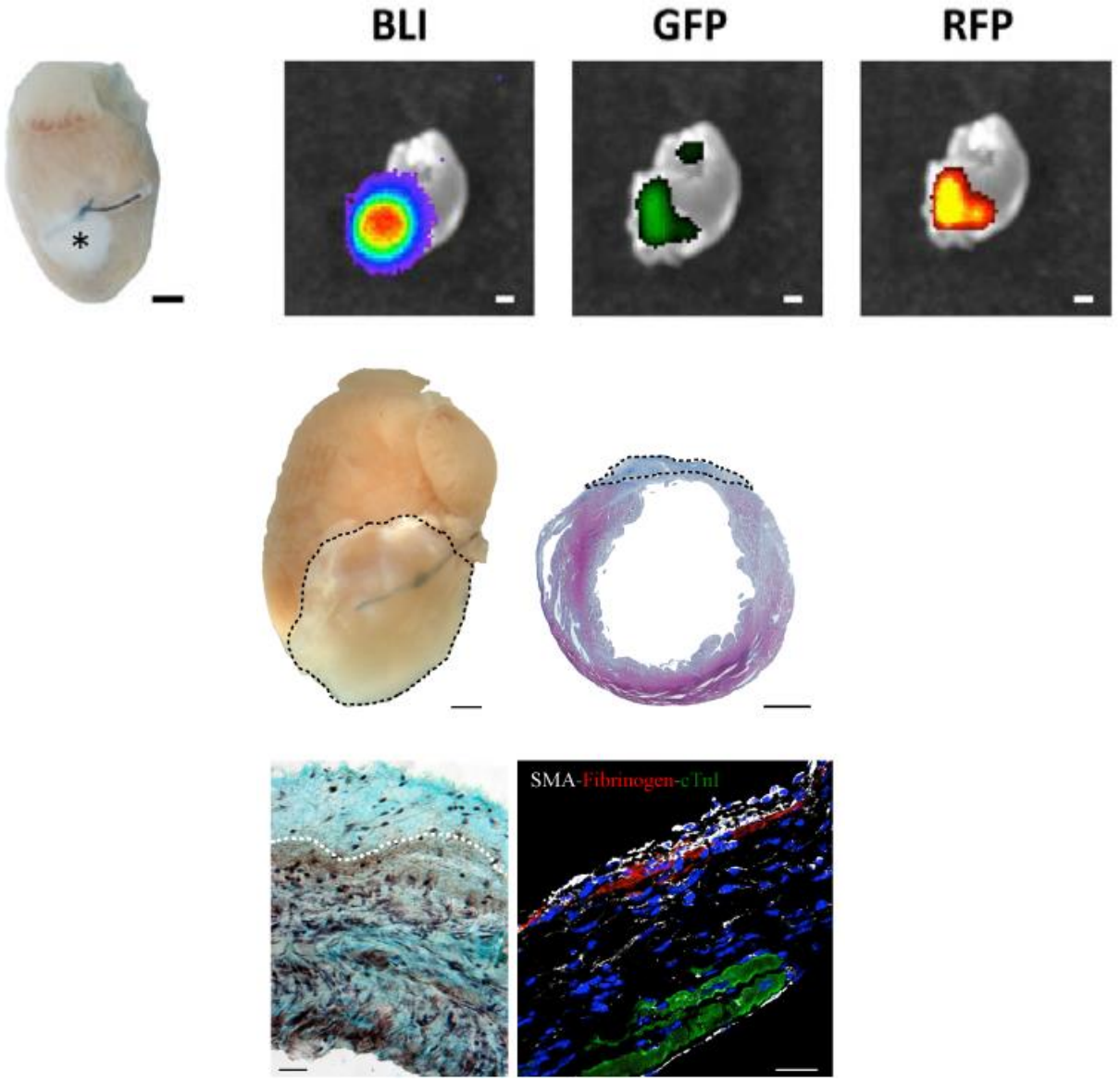
Gálvez-Montón et al. Rev Esp Cardiol (Engl Ed). 2013 May;66(5):391-9

Cell delivery system: fibrin patches



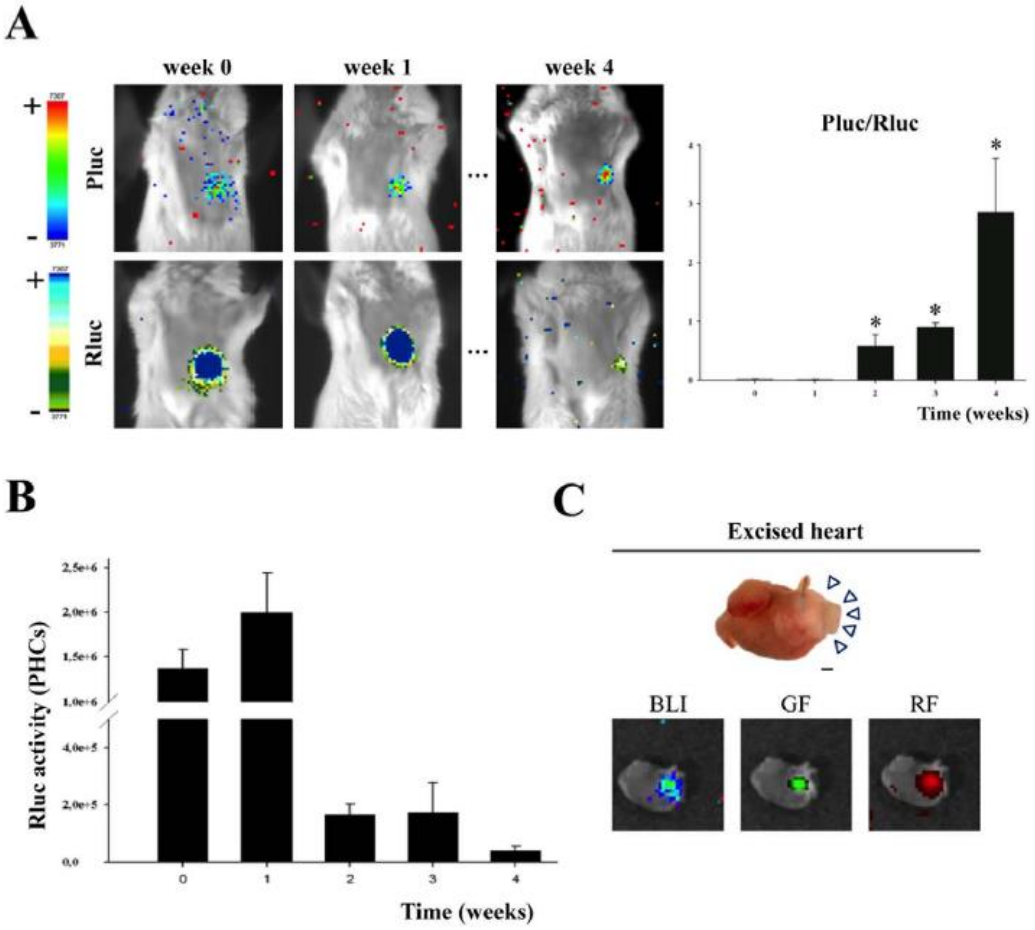
Roura et al. J Tissue Eng Regen Med. 2016 Apr 6

Cell delivery system: fibrin patches



Roura et al. J Tissue Eng Regen Med. 2016 Apr 6

UCBMSCs: pre-clinical results



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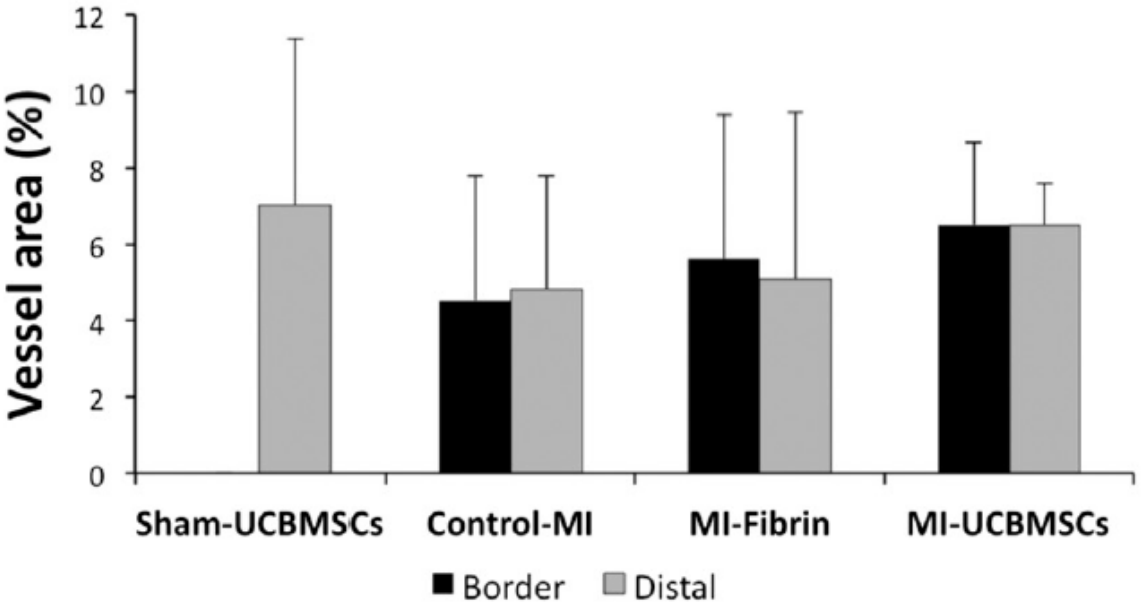

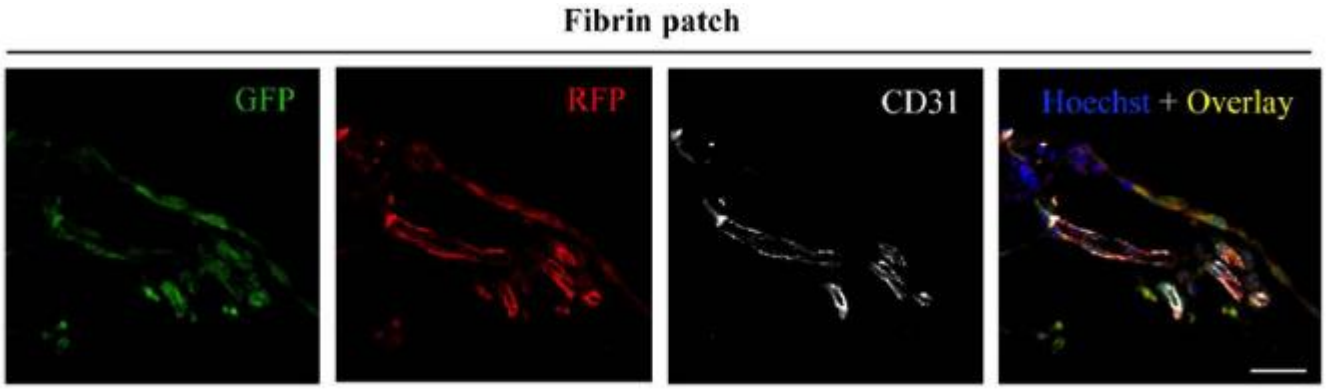

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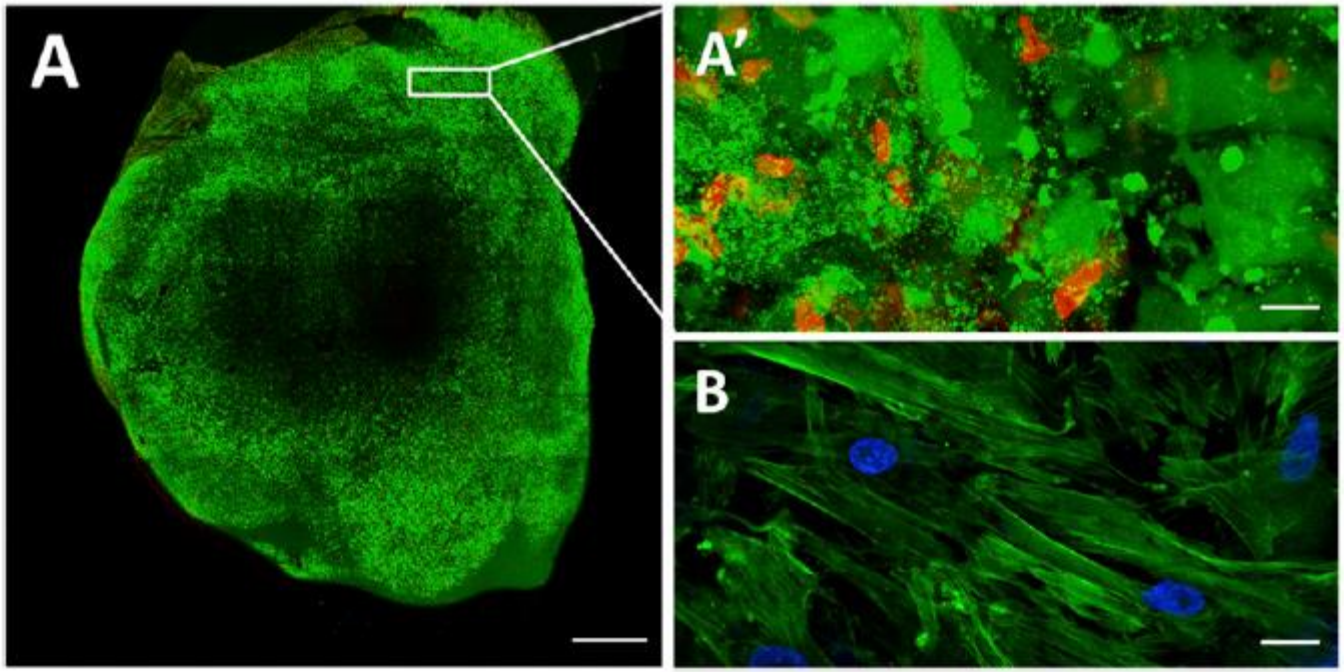
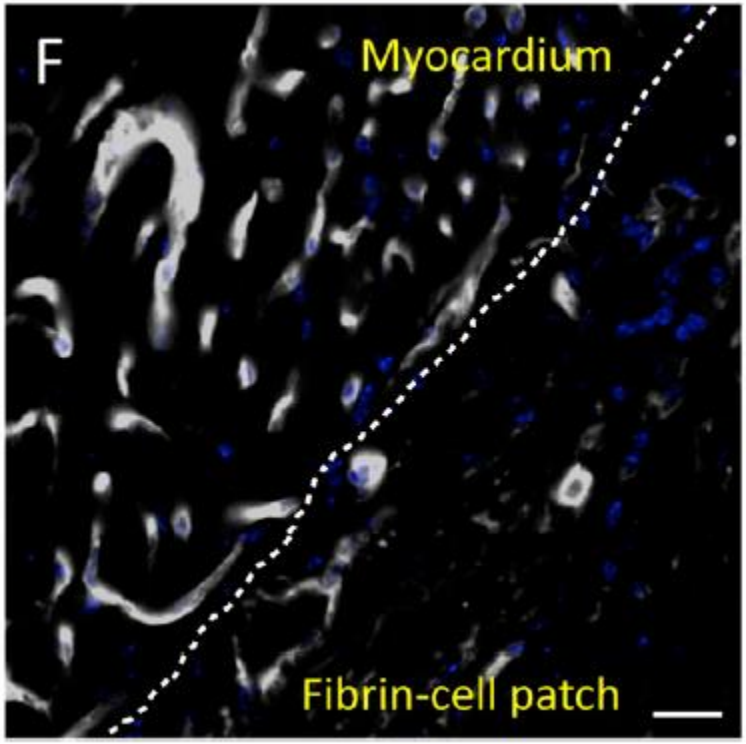
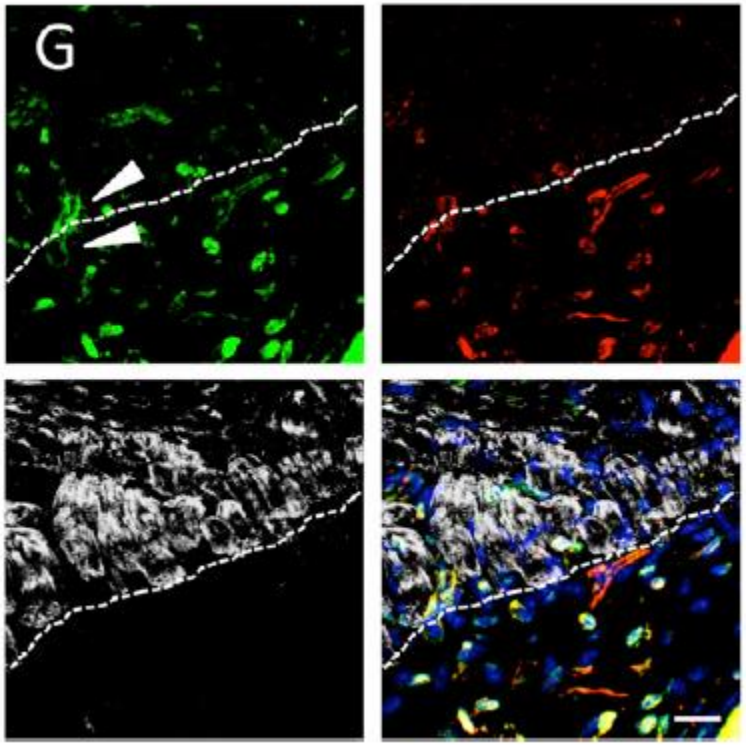


Roura et al. Stem Cells Transl Med. 2015 Aug;4(8):956-66

UCBMSCs: pre-clinical results





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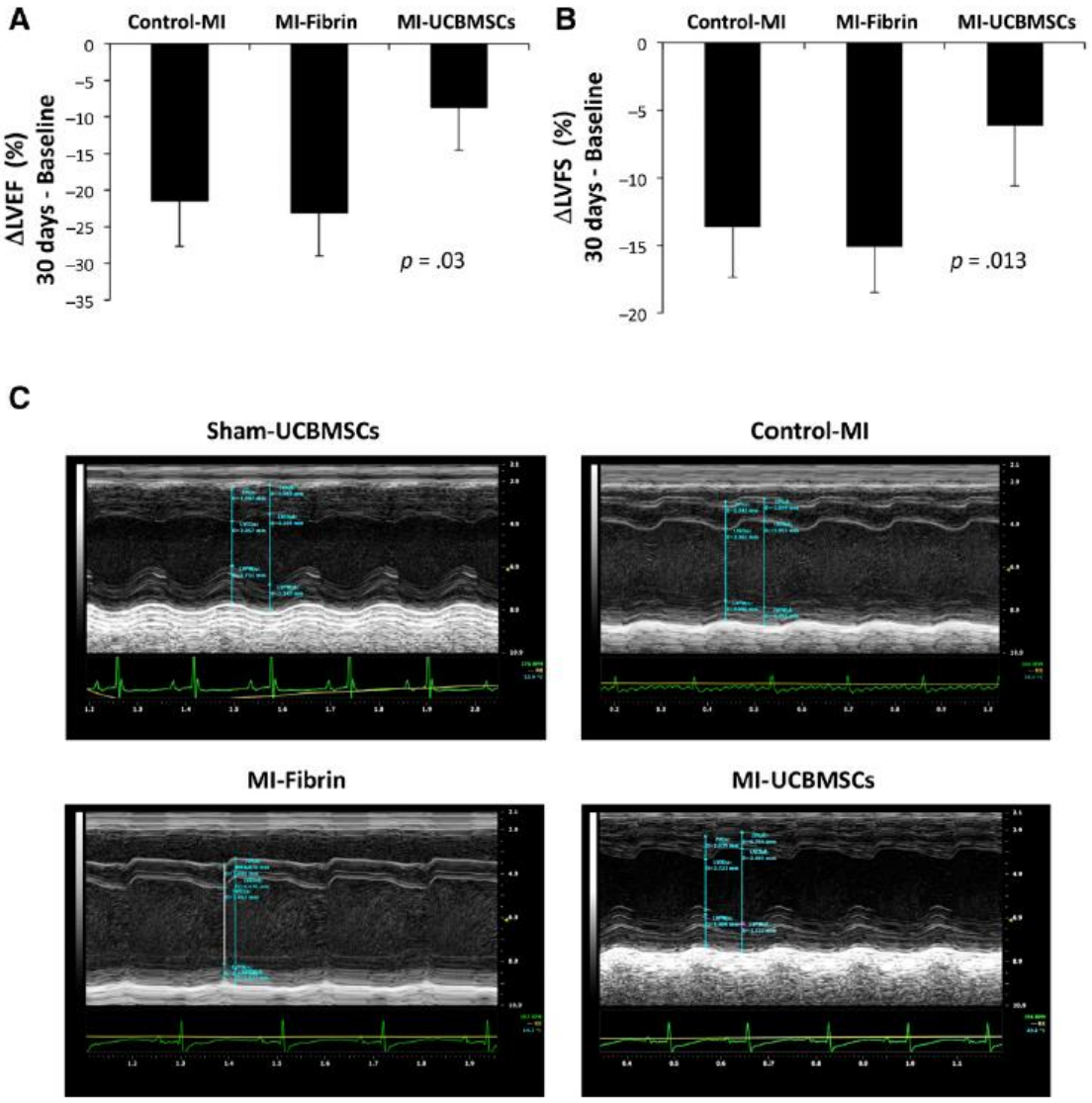

Roura et al. Stem Cells Transl Med. 2015 Aug;4(8):956-66

Electromechanical stimulation: as a pre-conditioning approach

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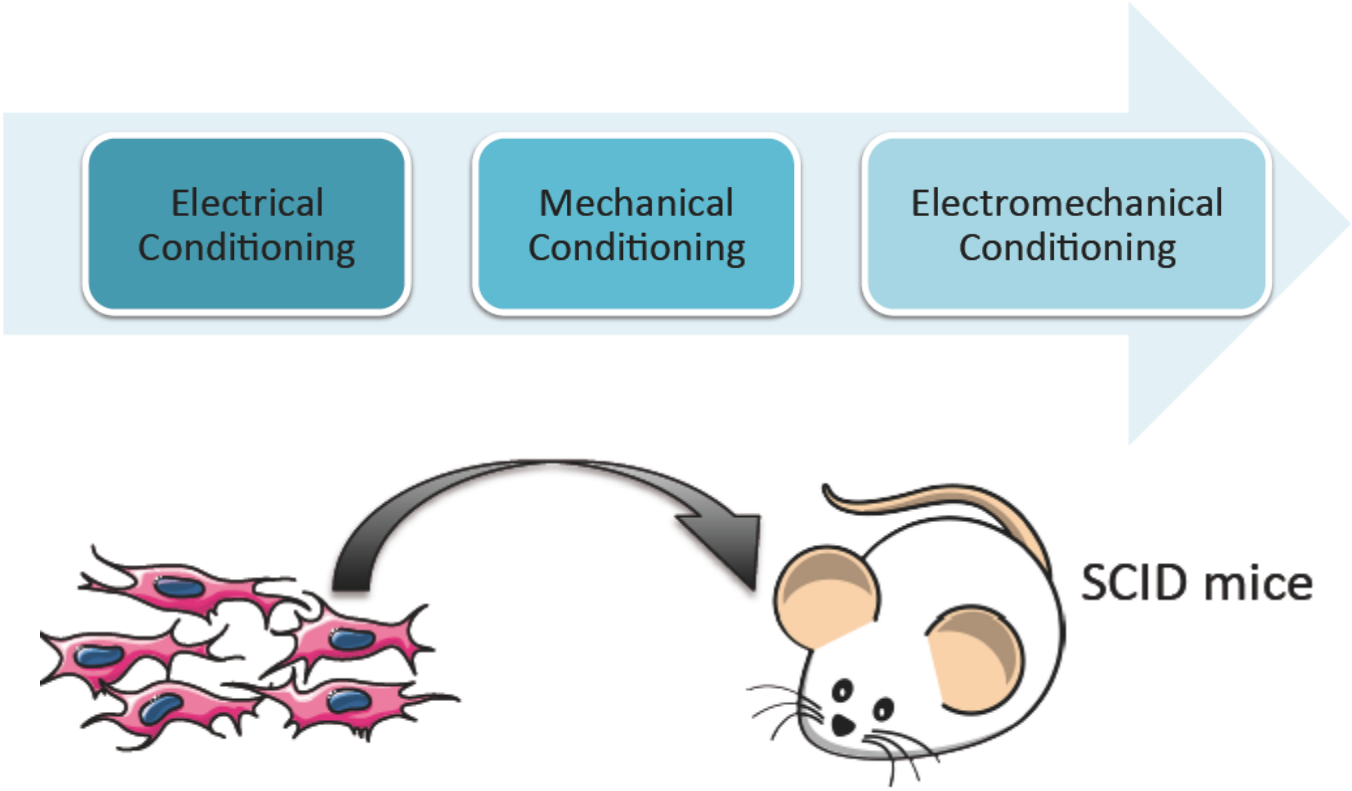
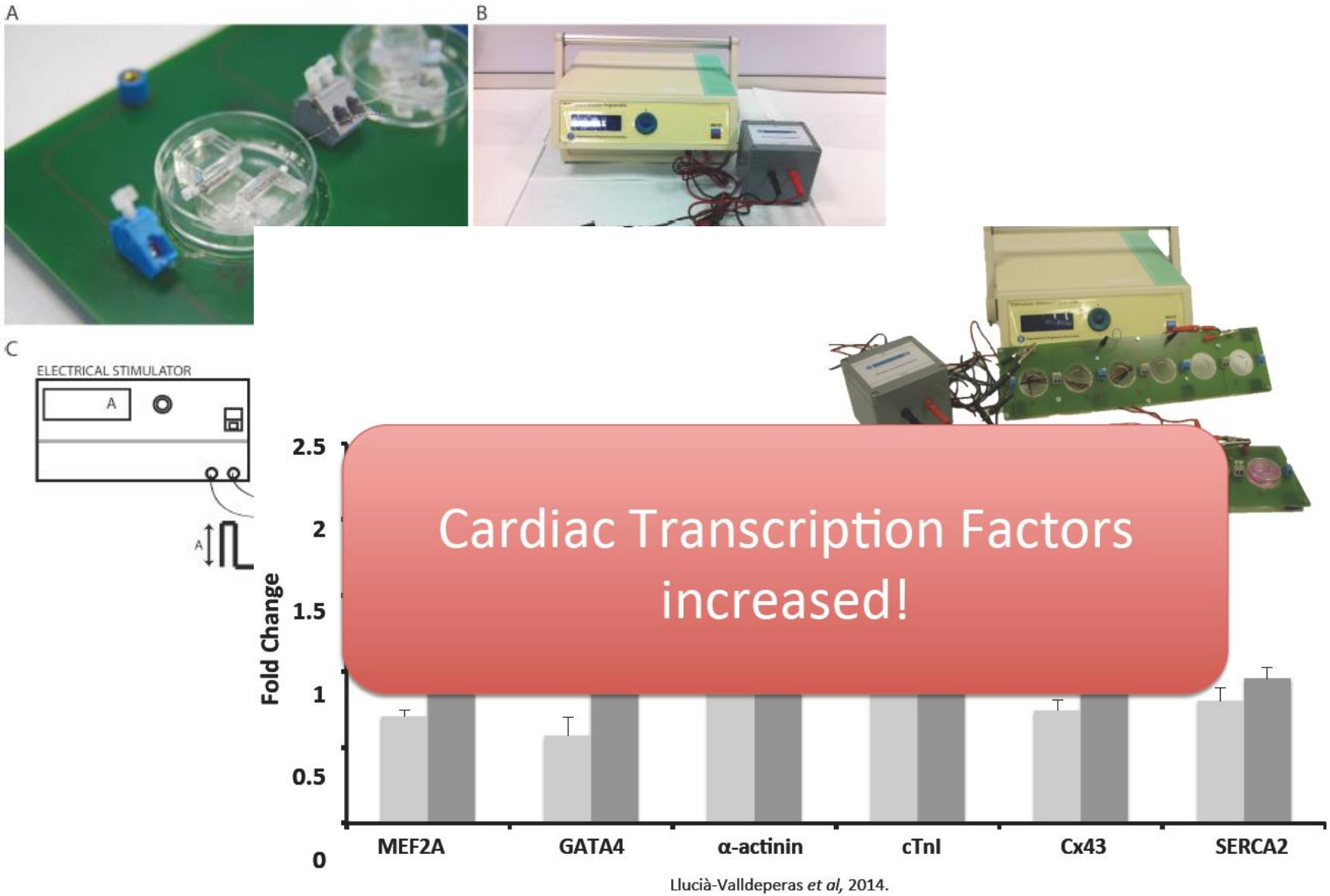
• *In vitro* individual or combined synchronous electromechanical stimuli mimicking the cardiac environment, could mature or induce cardiac differentiation on therapeutic cells to benefit further retention and integration into the myocardium



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)
(19) World Intellectual Property Organization
International Bureau
(43) International Publication Date
19 December 2013 (19.12.2013)
WIPO | PCT
(10) International Publication Number
WO 2013/185818 A1

IGTP Health Research Institute Germans Trias i Pujol

Electrical conditioning: *ad-hoc* device and results



Llucià-Valldeperas et al. Stem Cell Res Ther. 2014 Aug 4;5(4):93

Mechanical conditioning: *ad-hoc* device and results

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A

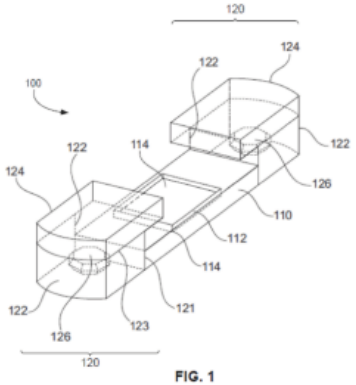
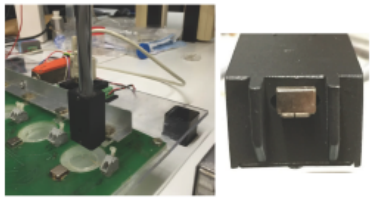


FIG. 1

B



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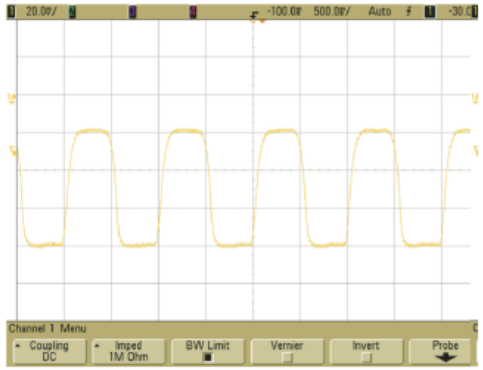

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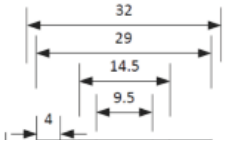


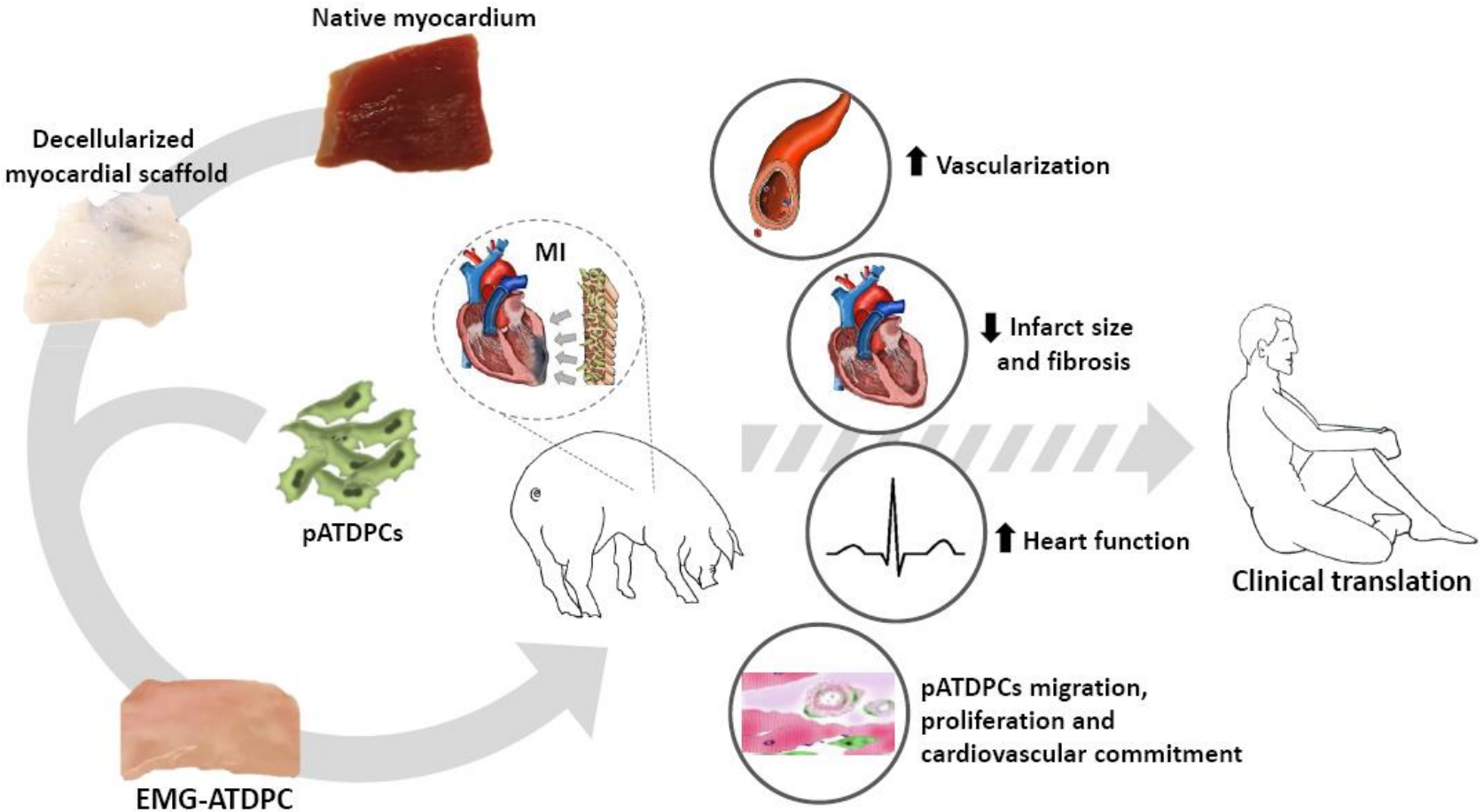
D

	Sample	Tbx5	MEF2A	GATA-4	α-actinin	Cx43	SERCA2	β-MyHC	cTnI
Vertical	cardiac ATDPCs Con	0.003 ± 0.001	0.089 ± 0.018	0.428 ± 0.196	2.445 ± 1.089	0.705 ± 0.253	0.397 ± 0.237	0.095 ± 0.049	0.693 ± 0.555
	cardiac ATDPCs M								0.964 ± 0.620
	Ratio cardiac A								1.391
	P-value Con *vs*								0.940
Horizontal	cardiac ATDPC								$5.1 \cdot 10^{-6} \pm 2.0 \cdot 10^{-6}$
	cardiac ATDPC								$1.4 \cdot 10^{-5} \pm 1.9 \cdot 10^{-6}$
	Ratio cardiac A								2.672
	P-value Con *vs*								*0.044
Smooth	cardiac ATDPC								$7.64 \cdot 10^{-6} \pm 5.09 \cdot 10^{-6}$
	cardiac ATDPCs								$1.18 \cdot 10^{-5} \pm 1.15 \cdot 10^{-5}$
	Ratio cardiac ATDPCs	1.716	1.537	1.326	0.891	1.151	1.390	1.182	1.547
	P-value Con *vs* MS	0.217	0.404	0.312	**0.001	0.817	0.198	0.848	0.662

Cardiac Transcription Factors and Structural genes upregulated!

ICREC: several future research lines

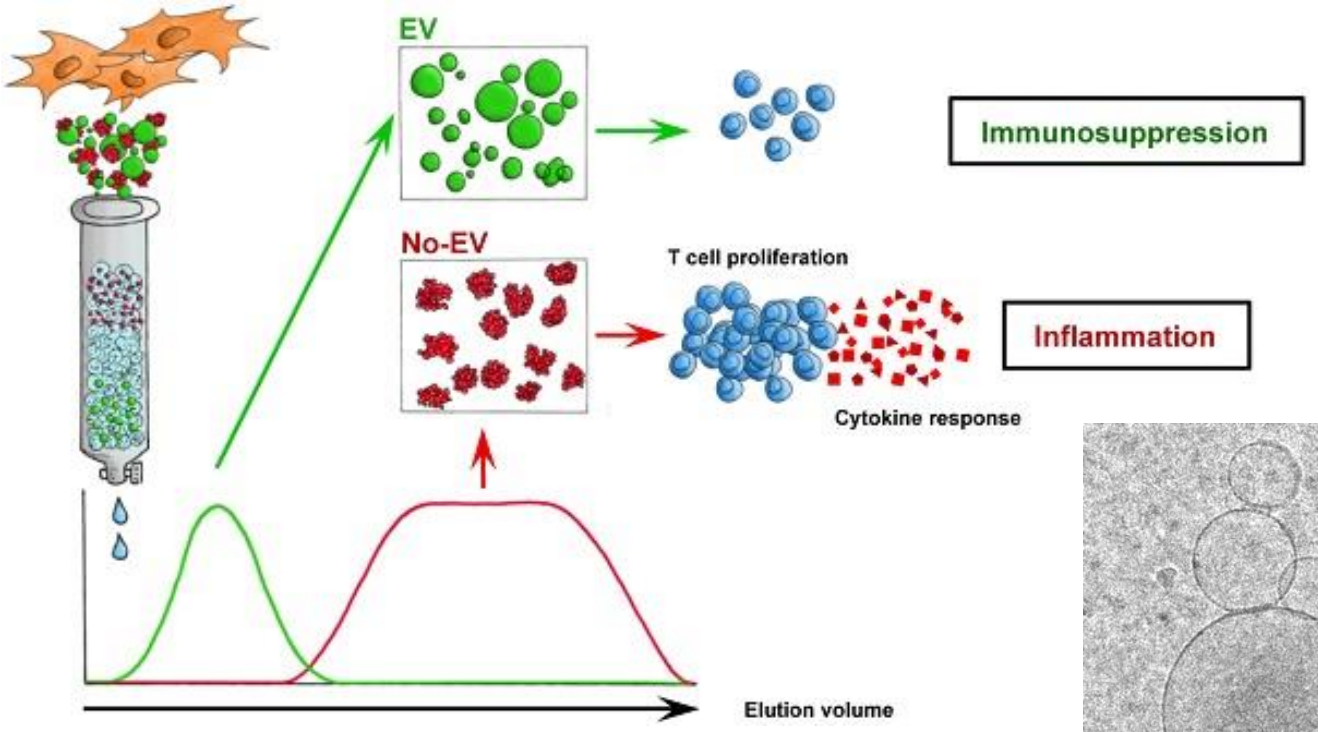
- Translation of Allogeneic Bioengineered Myocardial/Pericardial Grafts into Clinics

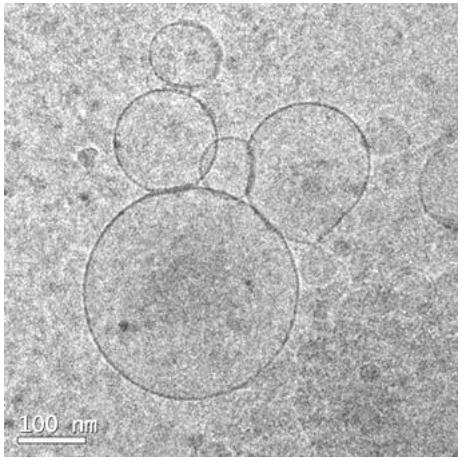


Perea-Gil et al. JACC: Basic to Translational Medicine. 2016. 10.1016/j.jacbts.2016.06.005

ICREC: future research lines

- Analysis of MSC-induced Immunomodulation using well-purified Size Exclusion Chromatography-Extracellular Vesicles or exosomes (EVs)

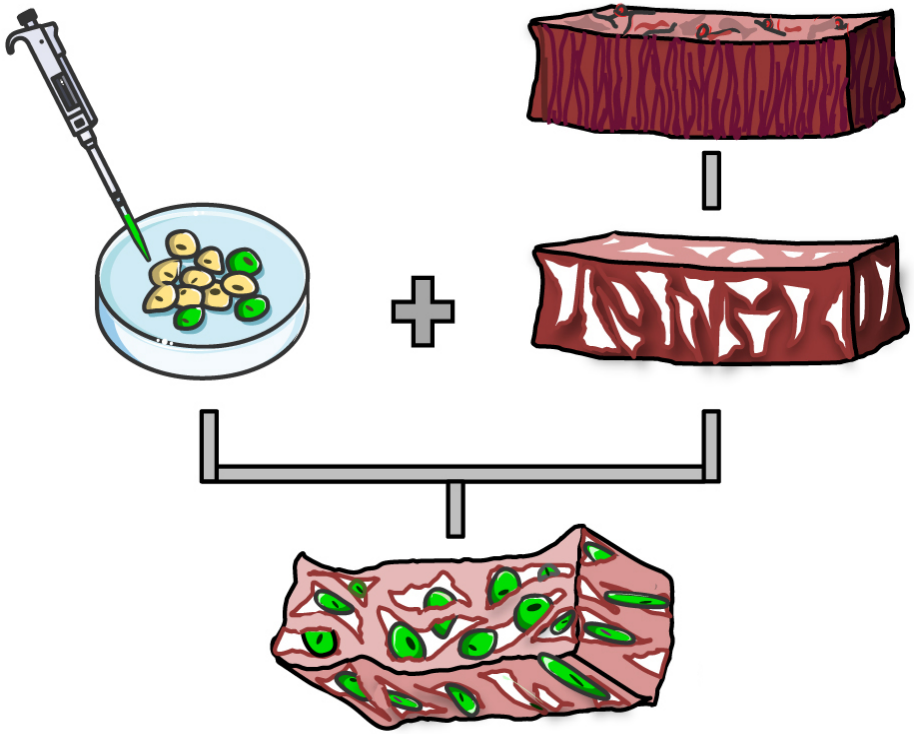




Roura et al. Theranostics. 2017 Jan 1;7(2):270-284

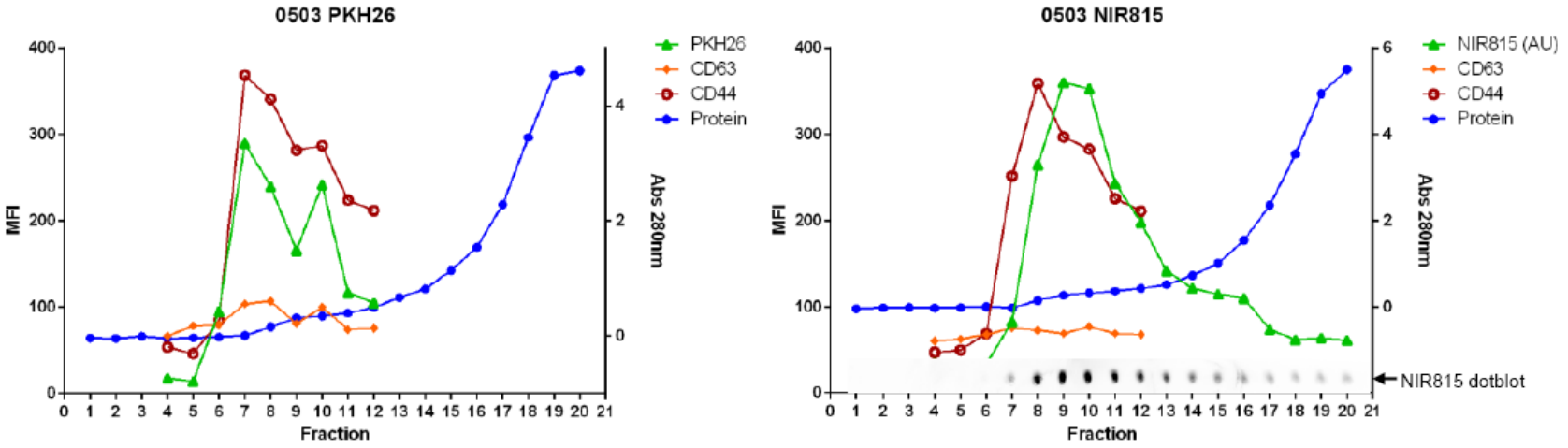
ICREC: future research lines

- Is possible to increase regeneration outcomes by implantation of engineered scaffolds enriched with EVs?



ICREC: future research lines

- Set up of EV-enriched scaffolds to be implanted in a porcine MI model



‘Take-home messages’

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• Cardiovascular diseases are the first cause of death worldwide with >17 million deaths in 2012

• Cellular cardiomyoplasty and cardiac tissue engineering mostly focus current efforts to enhance heart regenerative capacity

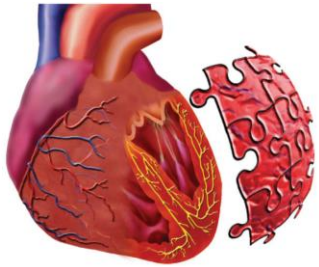
• Both cardiac ATDPCs and UCBMSCs represent useful stem cell populations with numerous pre-clinical evidences in treating post-infarcted myocardium

• Since cardiac cells are constantly submitted to physical stimuli from the cardiac environment, electrical and mechanical stimuli to monolayer stem cell cultures pre-commits them to the cardiomyogenic lineage and against the hostile cardiac milieu

• Among others, the clinical translation of allogeneic bioengineered implantable biografts and the exploitation of the immunomodulatory/regenerative potential of MSC-EVs represent novel striking research lines in the aim of treating cardiovascular diseases

“There are no impossible dreams...” — Antoni Gaudi

“… such as that envisioning the repair of broken heart” — ICREC Res Lab.



ICREC staff, funding and collaborations

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ADVANCE (CAT)
Accelerating Development of Advanced Therapies in Catalonia

ICREC Research program

(Insuficiència Cardíaca i REgeneració Cardíaca)

www.icor.cat/investigacio/grups-d-investigacio/en-insuficiencia-cardiaca-i-regeneracio-icrec

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UN ECOSISTEMA DE SALUT INNOVADOR I COMPETITIU A CATALUNYA

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Thank you!!

Fundació Bancària "la Caixa"

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