Bioengineered grafts for the infarcted heart

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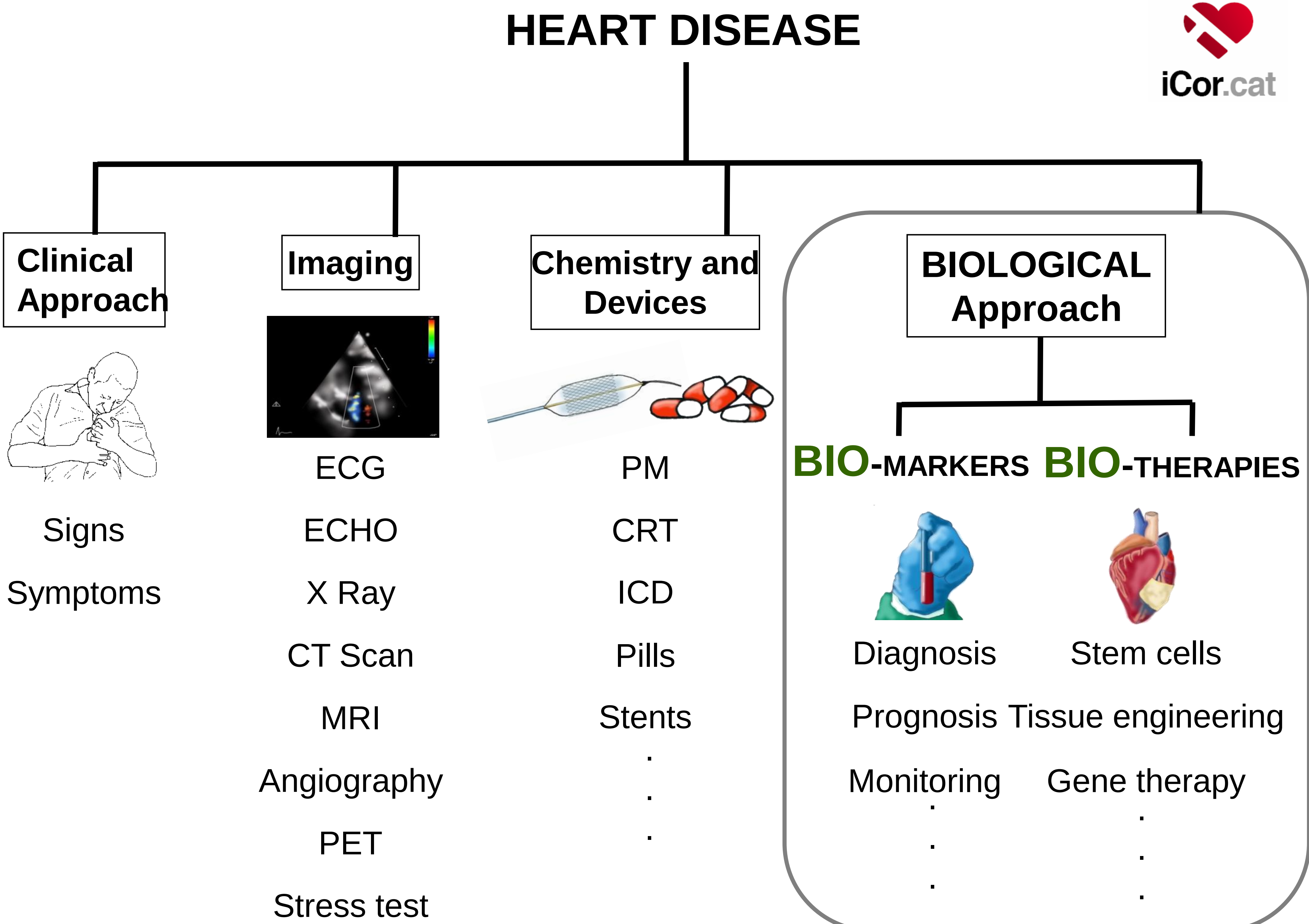
Badalona, Spain


HEART DISEASE
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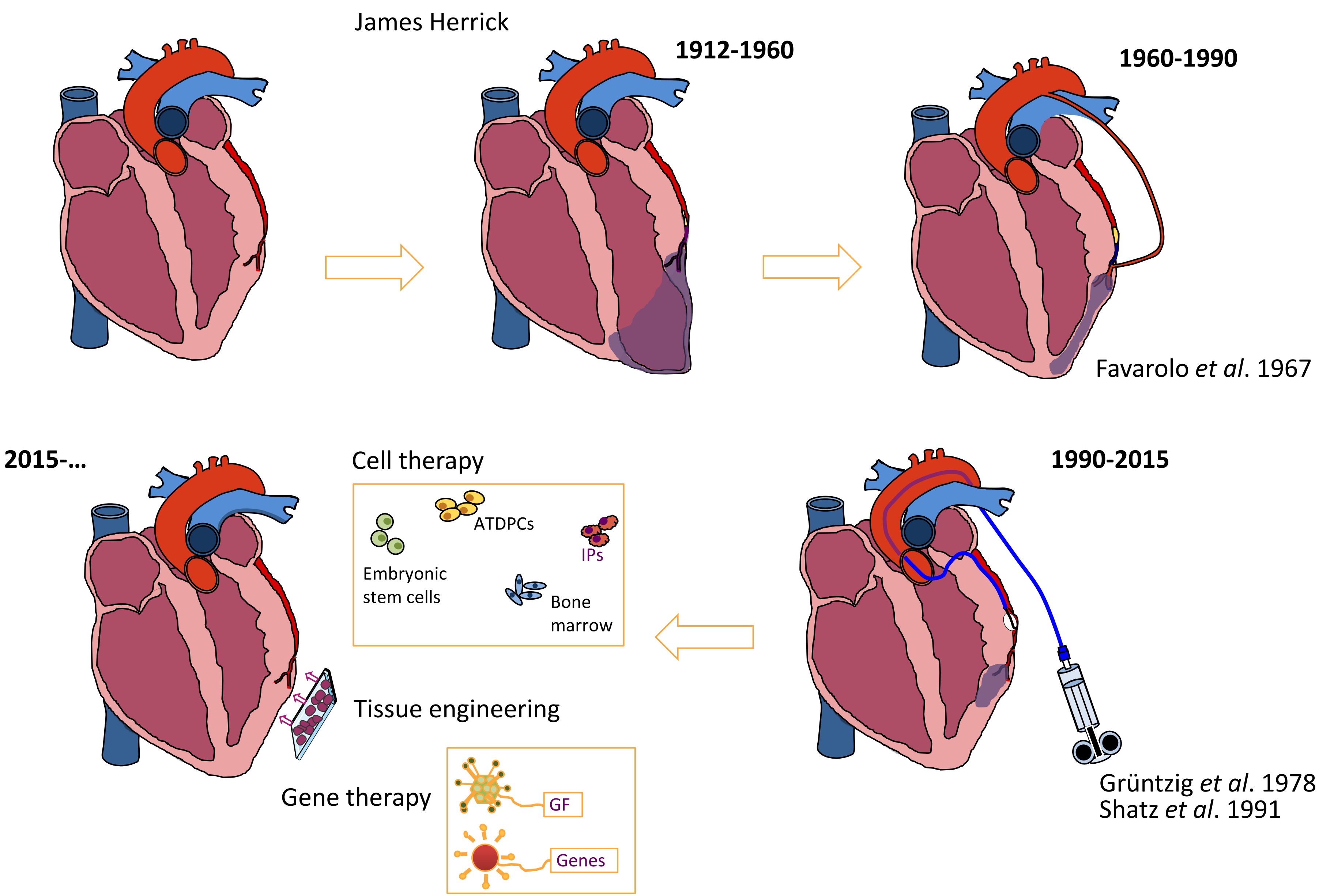
Clinical Approach
Imaging
Chemistry and Devices
BIOLOGICAL Approach
BIO-MARKERS
BIO-THERAPIES
Signs
Symptoms
ECG
ECHO
X Ray
CT Scan
MRI
Angiography
PET
Stress test
PM
CRT
ICD
Pills
Stents
Diagnosis
Prognosis
Monitoring
Stem cells
Tissue engineering
Gene therapy

Myocardial Infarct

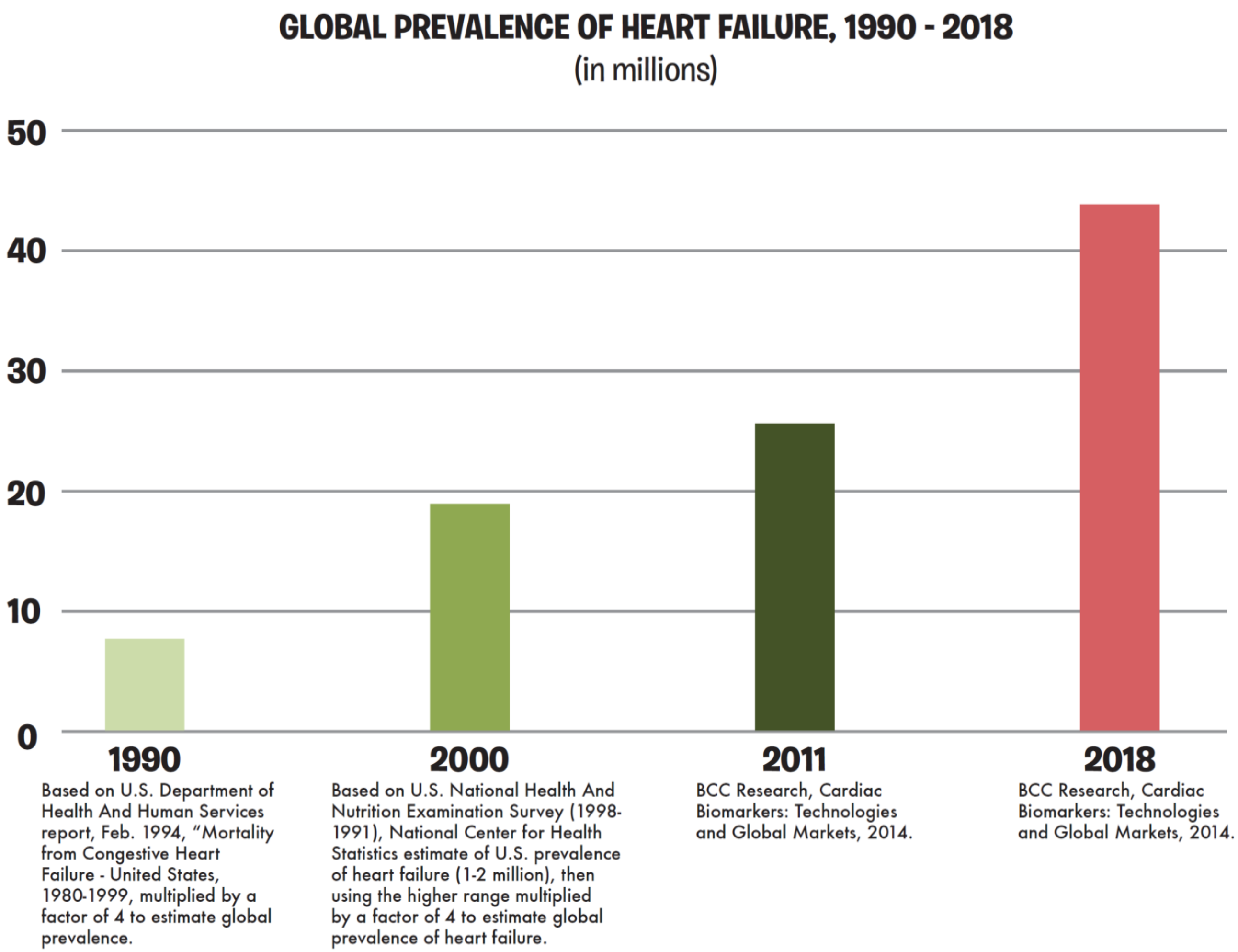


Gálvez-Montón *et al*. E Heart J. 2012.

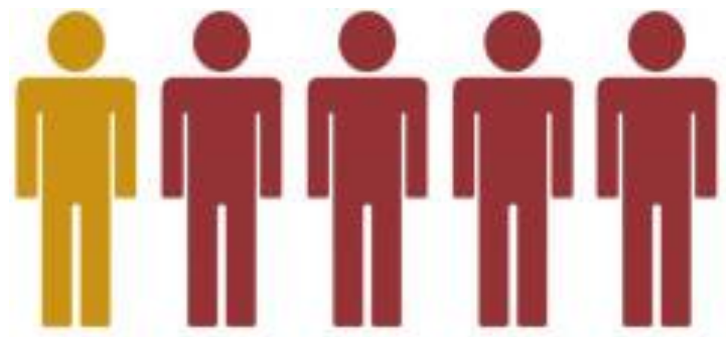
HF prevalence

	%	CI 95%	CI 95%
Men	7.8	5.5	10.0
Women	6.4	4.7	8.0
45-54 yrs	1.7	0.1	3.3
55-64 yrs	4.1	2.1	6.1
65-74 yrs	6.1	3.9	8.4
➢74 yrs	18.7	13.9	23.4
Total	**7.0**	**5.6**	**8.3**

HF Epidemic… in the WORLD



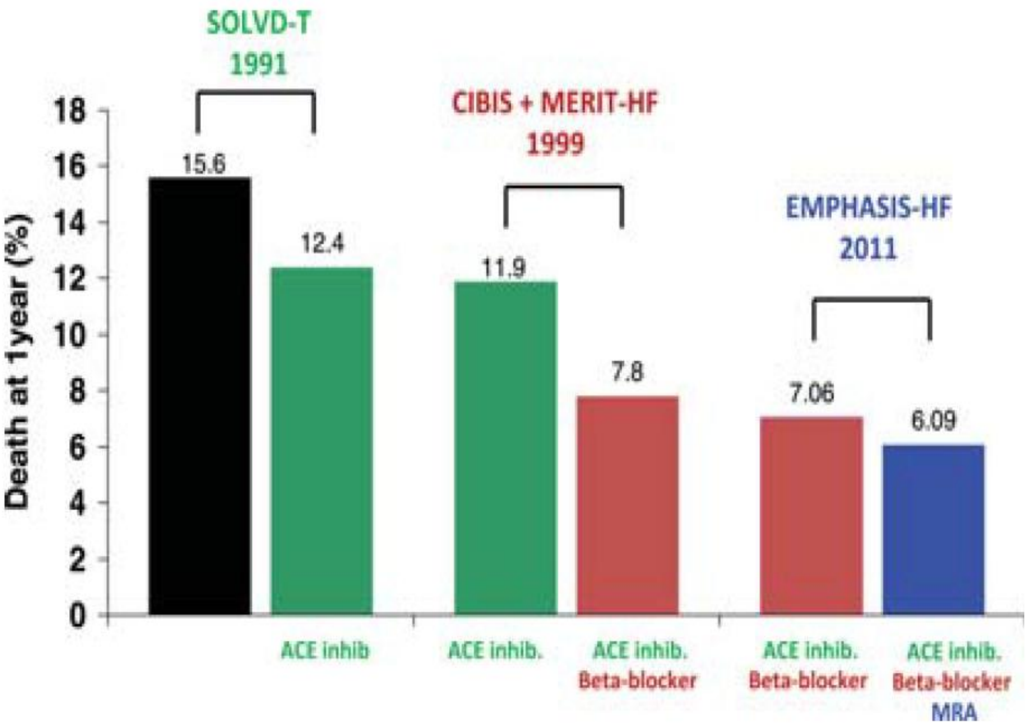
…. In US and Western Europe



1 in 5 individuals > 40 years will develop HF

HF unmet needs?

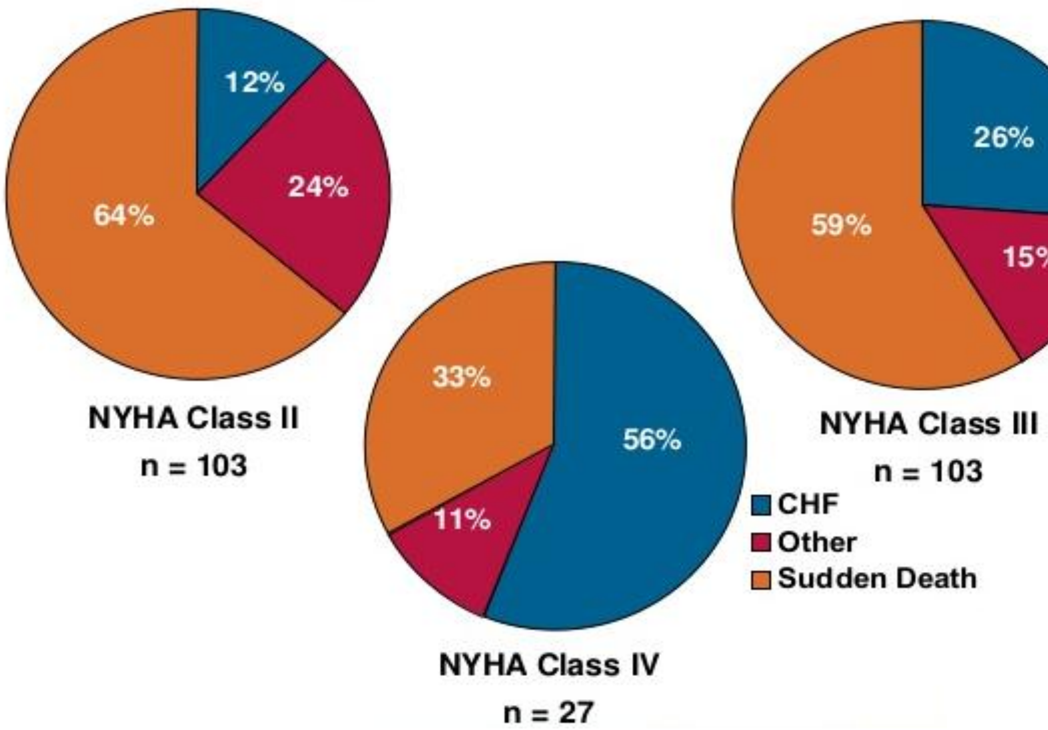
1. Excessive mortality despite neurohormonal blockade



HF progresses and mortality remains high despite optimal neurohormonal blockade

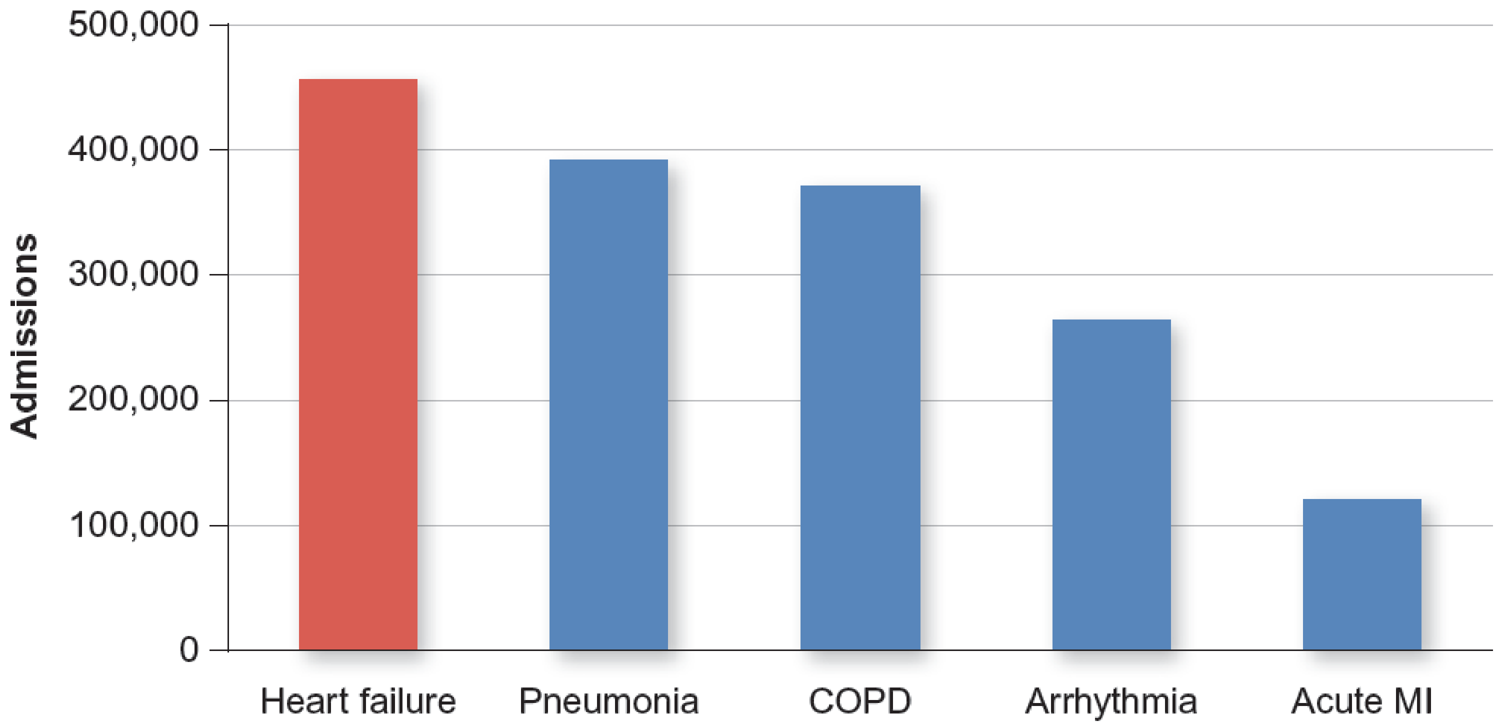
McMurray. Eur J Heart Fail. 2011;13:929–36

2. Sudden death accounts for 50% of HF mortality



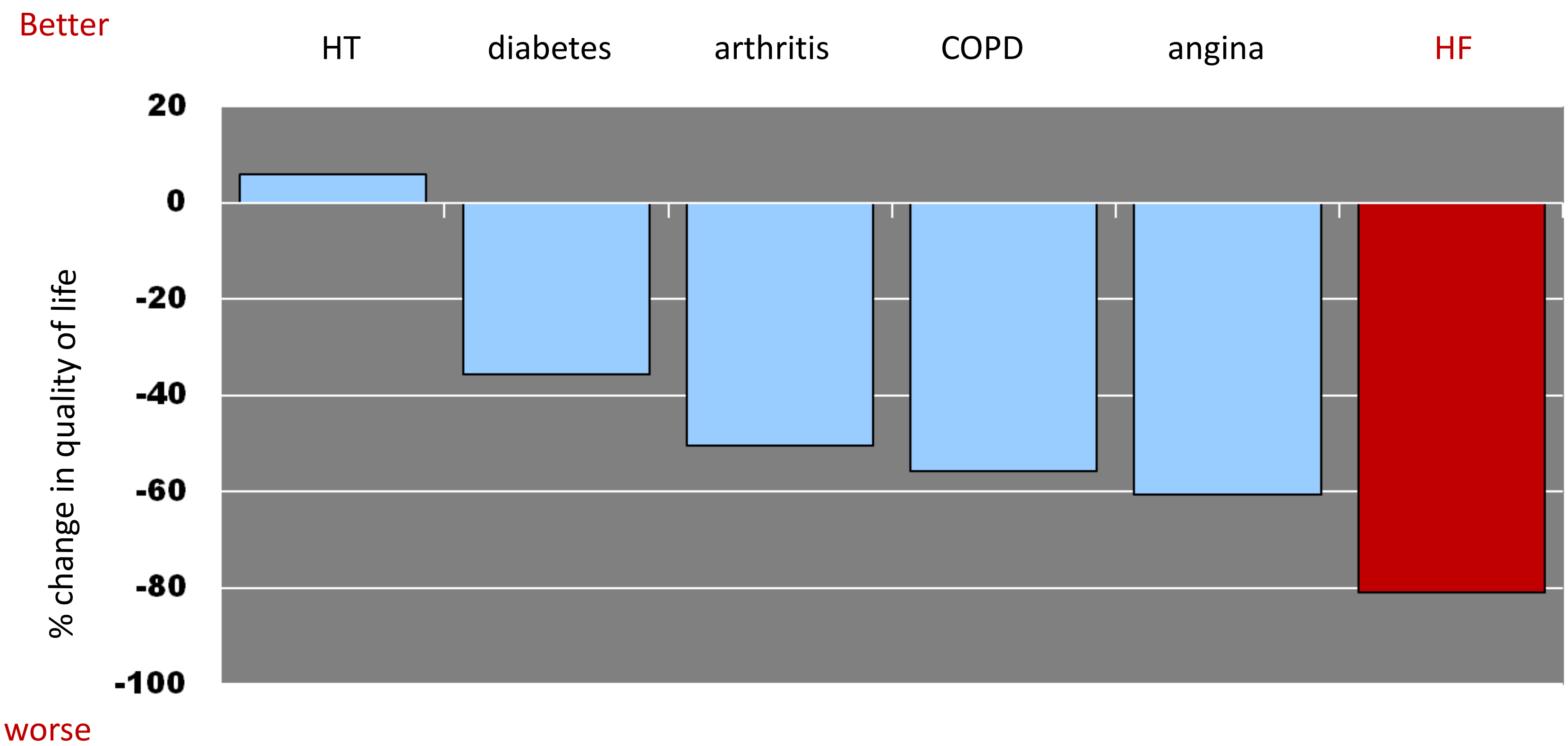
MERIT-HF Study Group. Lancet. 1999;353:2001-7

3. Too many HF admissions and readmissions



Centers for Medicare & Medicaid Services. Medicare Provider Utilization and Payment Data: Inpatient. 2013

4 … and poor quality of life



McMurray J. Eur Heart J 1998; 19 (supp. P): P9

Heart Transplant in Spain

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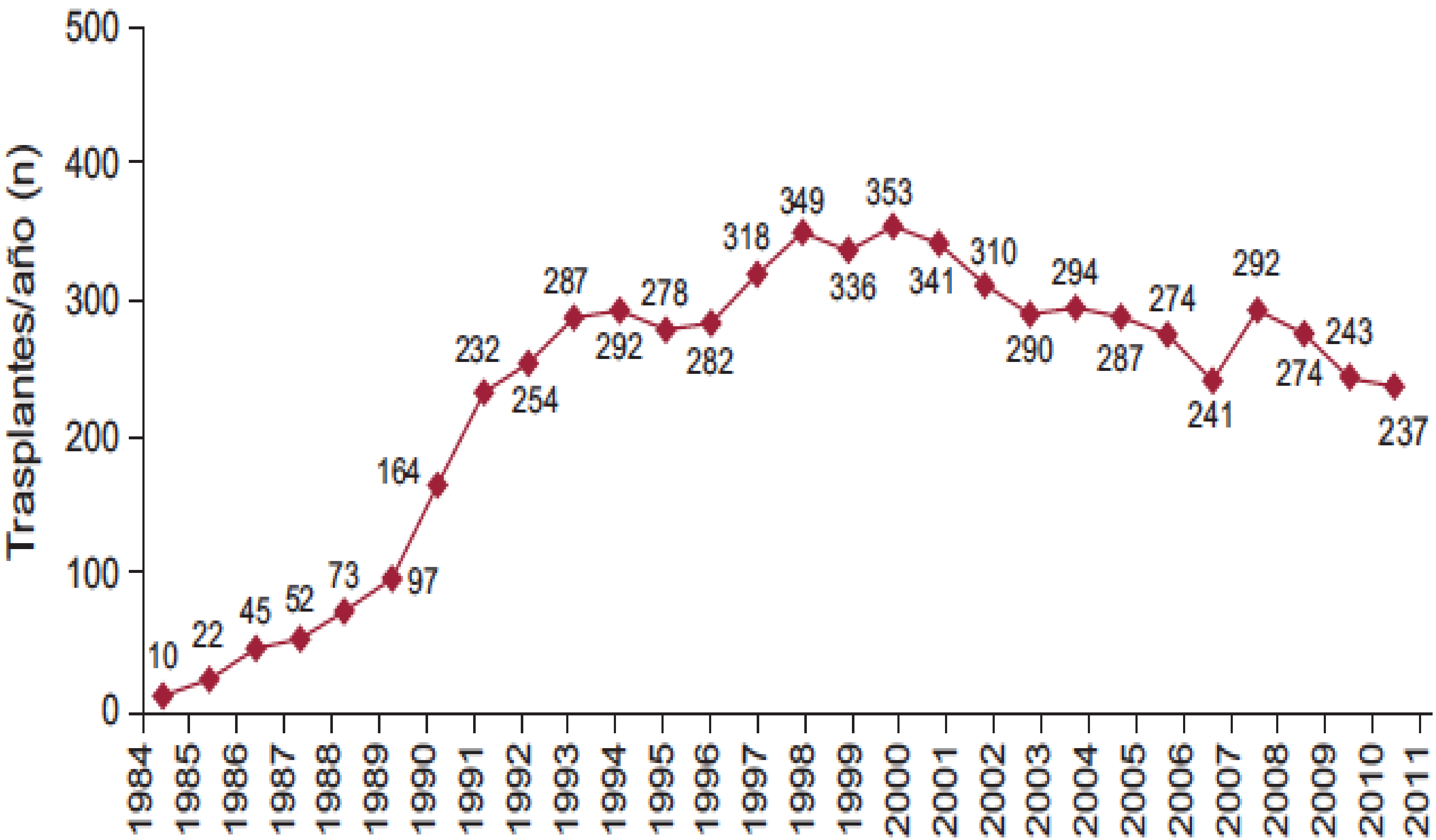
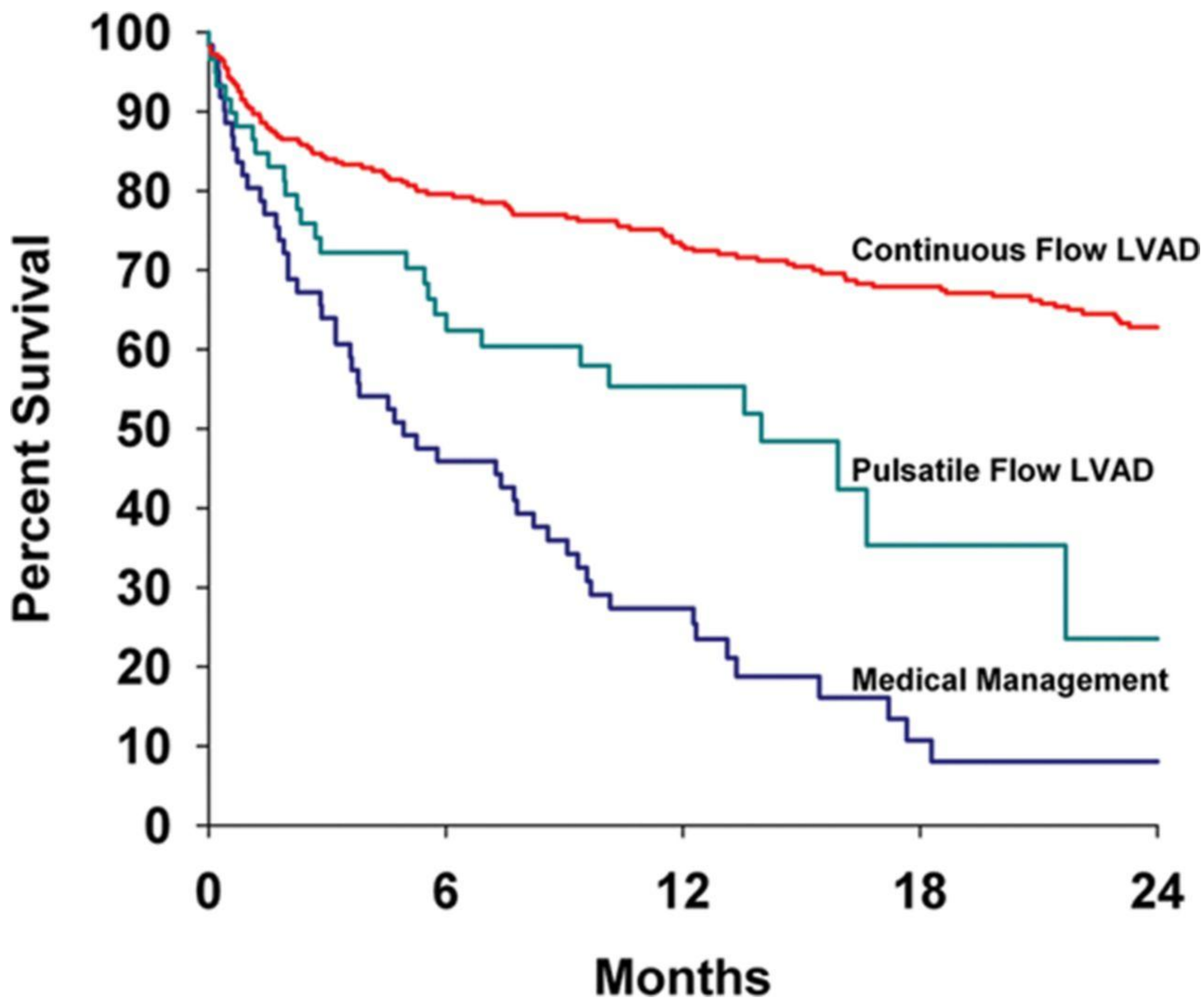


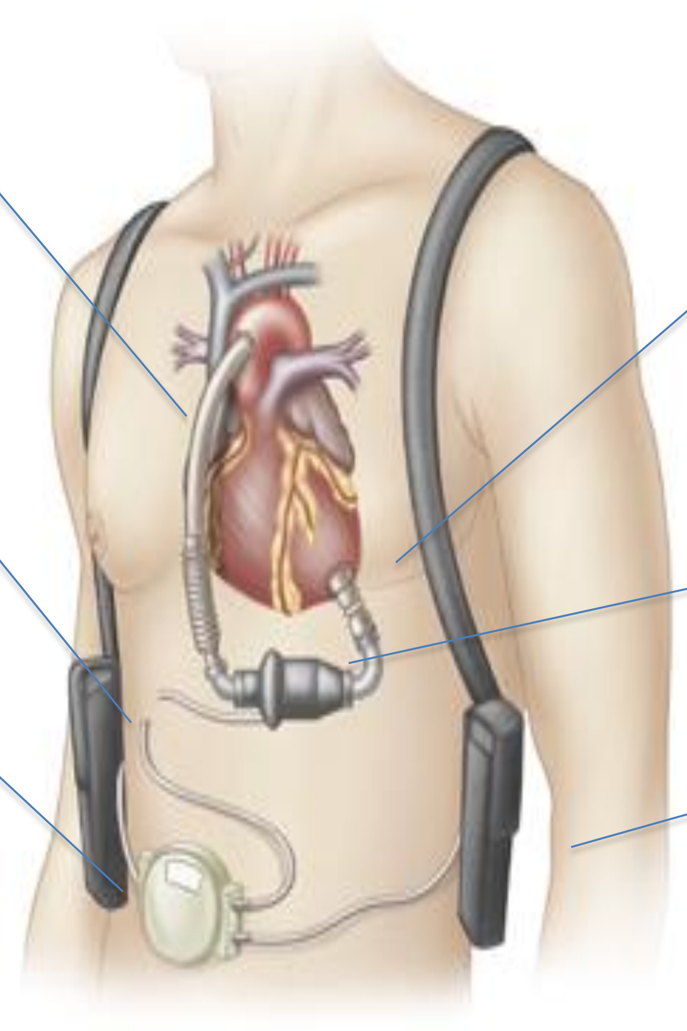
Figura 1. Número de trasplantes por año.

Survival in advanced HF - LVADs



Miller L W et al. Circulation. 2013;127:743-748

Potential Device Complications



Costs of VAD

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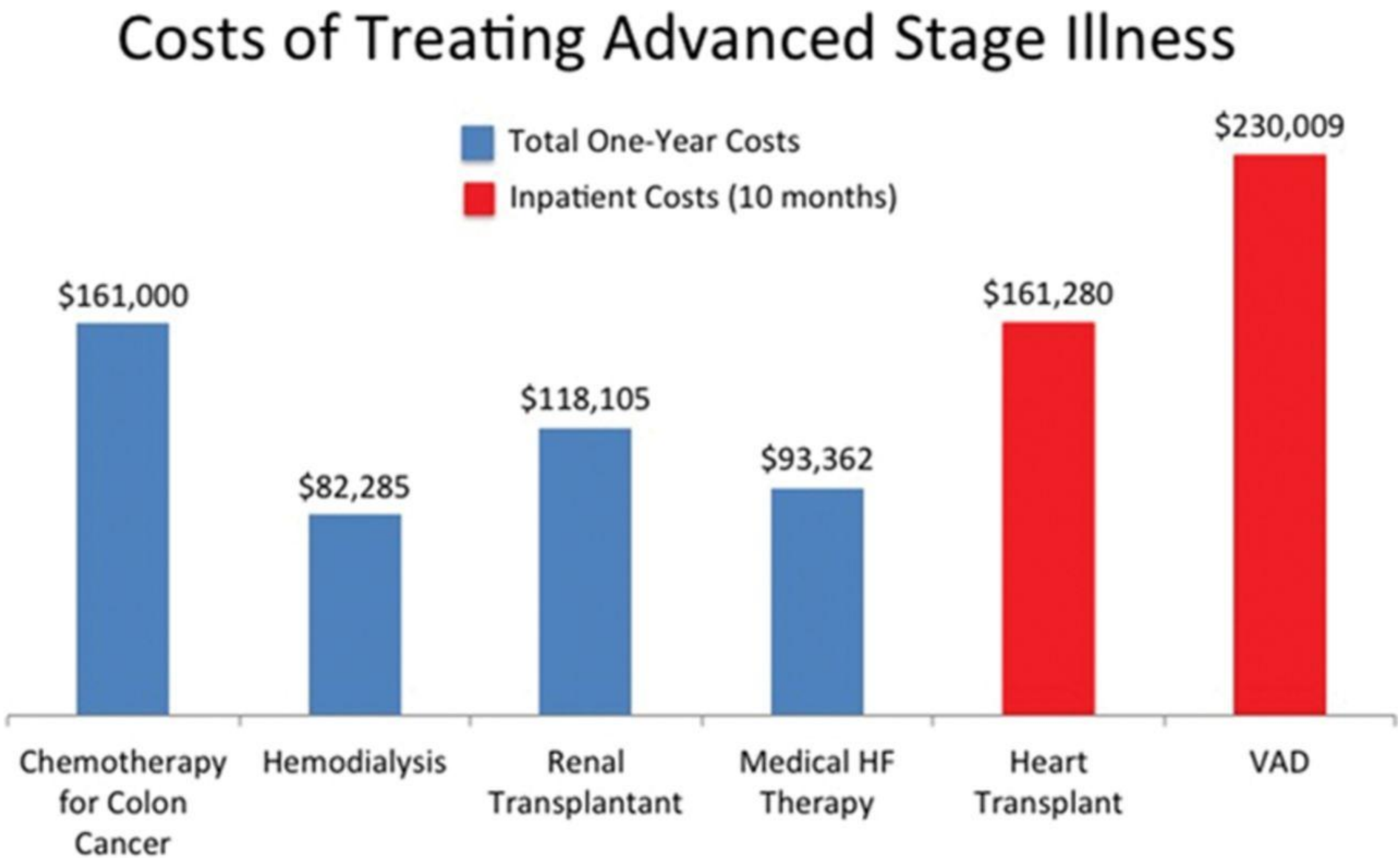
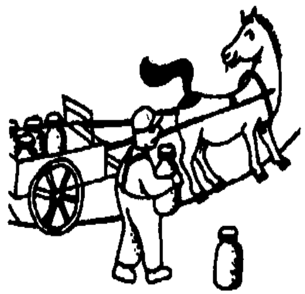


Miller L W et al. Circulation. 2013;127:743-748

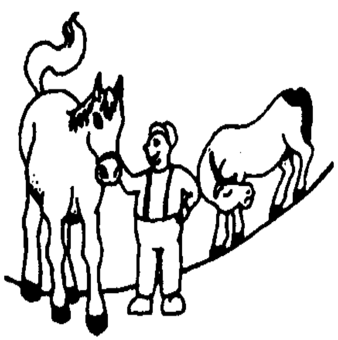
Addressing Heart Failure in 2017

WHIP THE HORSE

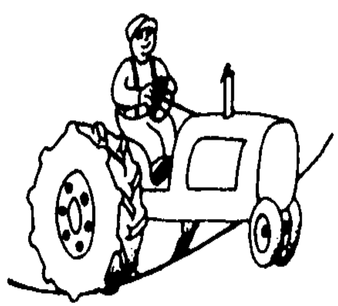


UNLOAD THE WAGON

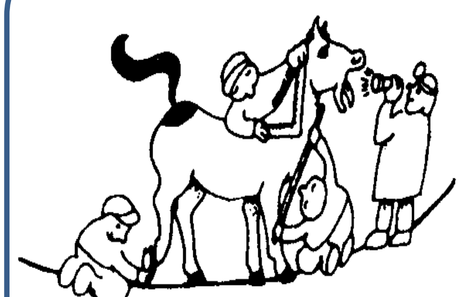
SLOW THE HORSE



GET A NEW HORSE



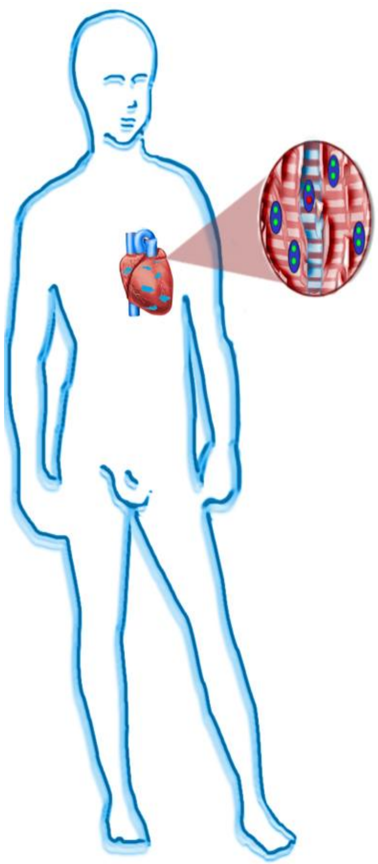
GET A TRACTOR



HEAL THE HORSE

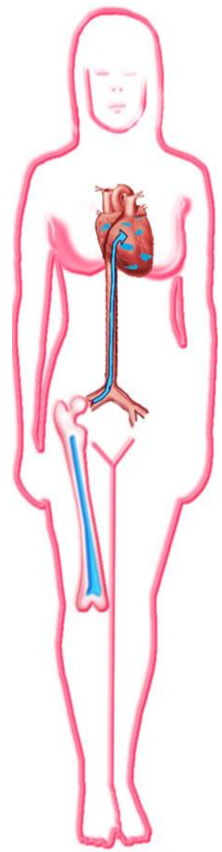
Katz AM
Heart Failure

Human heart regenerative capacity



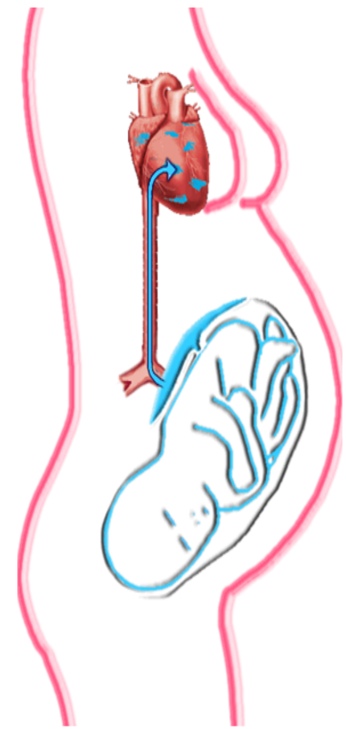
Post-HT Chimerism

Bayes-Genis et al.
Cardiovasc Res 2002;404-10



Post-BMT Chimerism

Bayes-Genis et al.
Eur J Heart Fail 2004;6:399



Fetal Microchimerism

Bayes-Genis et al.
J Heart Lung Transplant 2005;24:2179

Bayes-Genis et al. Nature CPCM 2007;1:40

Real Situation

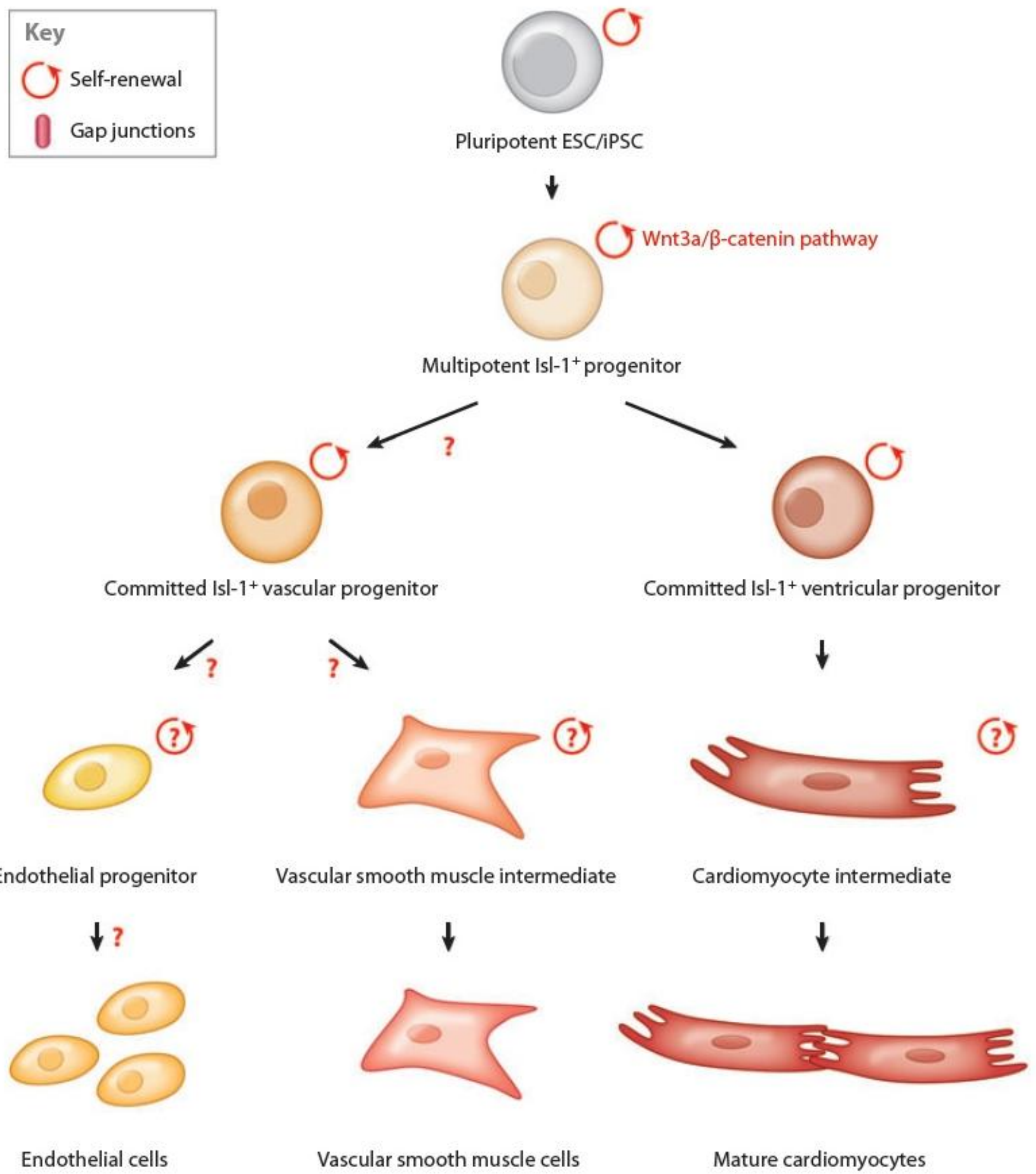
Cell loss and myocyte proliferation are part of the heart normal homeostasis

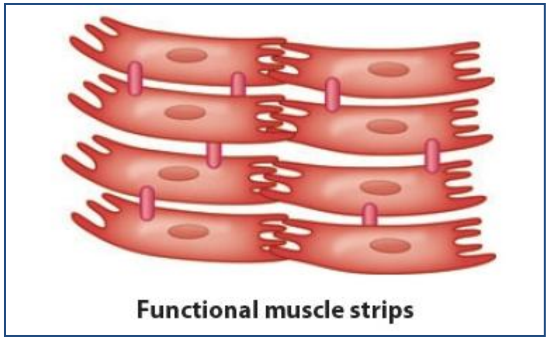
- *The human heart has limited ability fo autoregeneration*
- *Cell therapy and tissue engineering may emerge as efficient and safe therapies in addition to current treatment.*

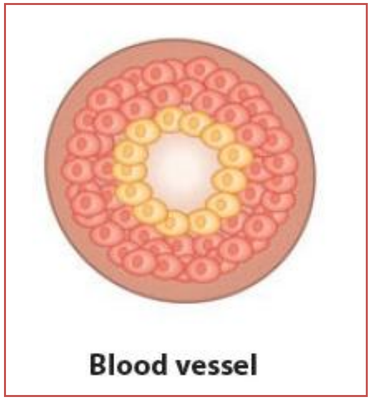
Cardiac regeneration therapy (Cell Therapy)

- I.C. delivery of BMC or CPC
  - Randomized clinical trials after AMI
    - BOOST — Lancet 2004;364:141-48
    - Janssens et al. — Lancet 2006;367:113-21
    - ASTAMI — NEJM 2006;355:1199-209
    - REPAIR-AMI — NEJM 2006;355:1210-21
  - Randomized clinical trials in chronic IHD
    - TOPCARE-CHD — NEJM 2006;355;1222-32
- Intramyocardial myoblast delivery
    - MAGIC — On hold
- Stem cell mobilization with cytokines (G-CSF)
    - REVIVAL-2 — JAMA 2006;295:1003-10

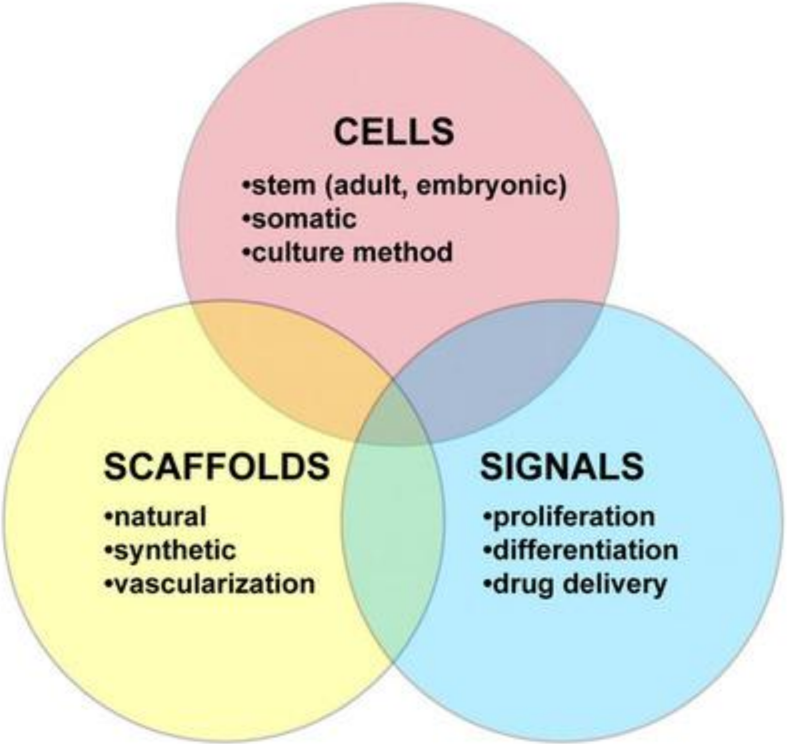
Pathways to regenerate cardiac muscle and blood cells







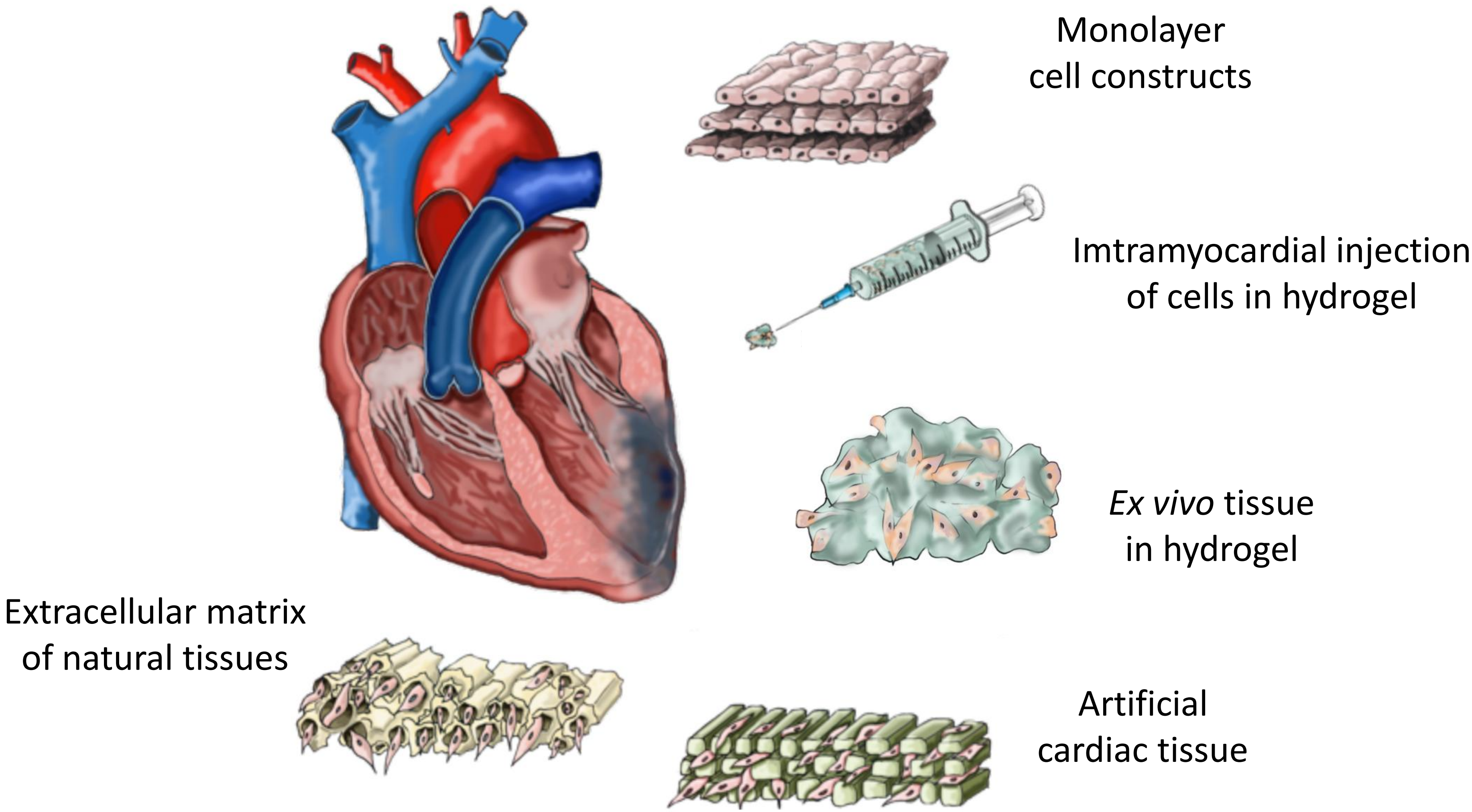
Cardiac tissue engineering



General biomaterial approaches to treatment of MI:

- LV restraints
- Cardiac patches
- Injectable approaches

Cardiac tissue engineering



Gálvez-Montón *et al*. Rev Esp Cardiol. 2013

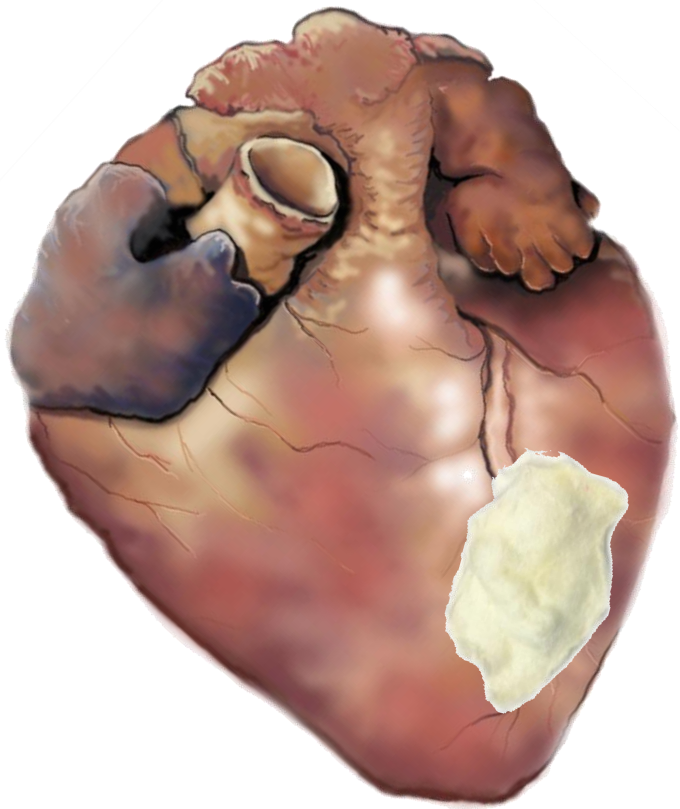
Scaffolds

Natural scaffolds

- Fibrin
- Alginate
- Chitosan
- Collagen

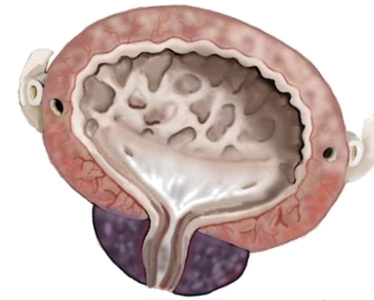
Synthetic scaffolds

- PEG
- PLA
- PCL
- PLGA
- Polyglicolic acid



Extracellular matrix scaffolds

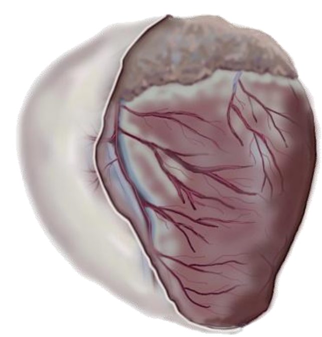
Urine Bladder



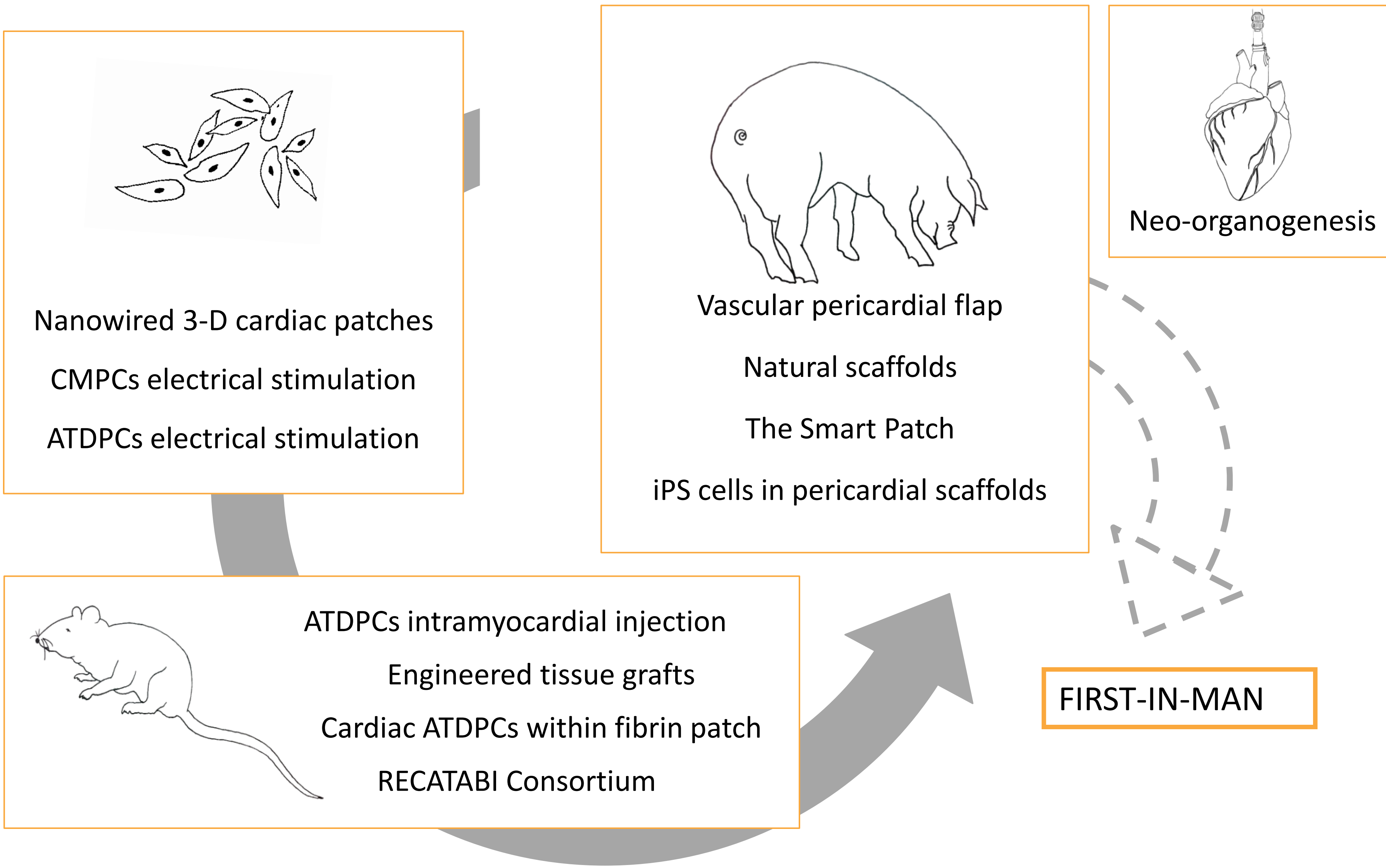
Small Intestinal Submucosa

Pericardium

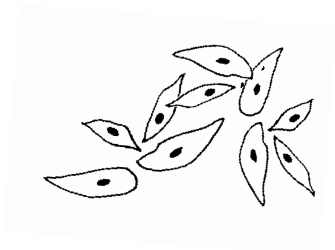
Myocardium



Experimental approaches



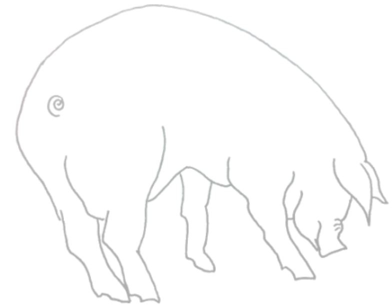
Experimental approaches



Nanowired 3-D cardiac patches

CMPCs electrical stimulation

ATDPCs electrical stimulation



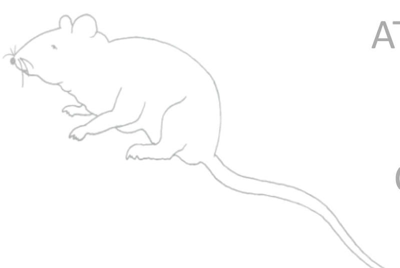
Vascular pericardial flap

Natural scaffolds

The Smart Patch

iPS cells in pericardial scaffolds

Neo-organogenesis



ATDPCs intramyocardial injection

Engineered tissue grafts

Cardiac ATDPCs within fibrin patch

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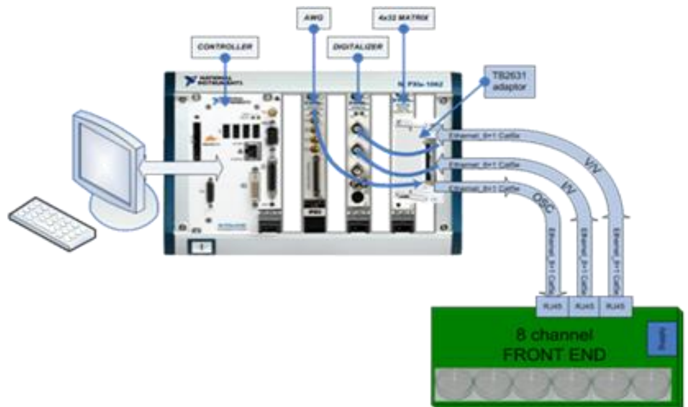
FIRST-IN-MAN

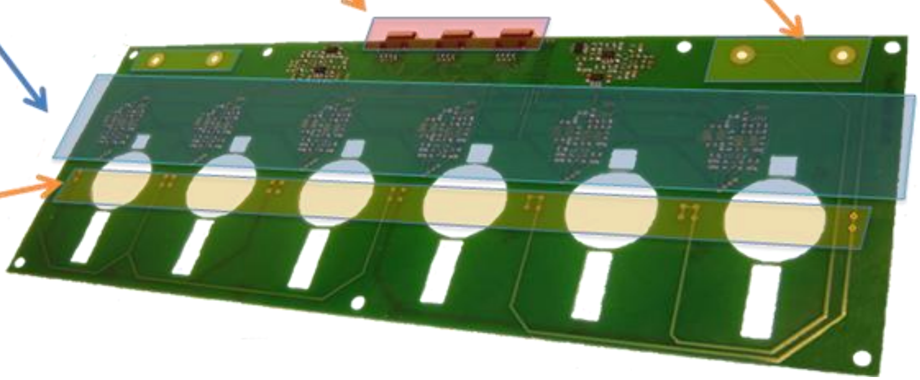
Electro-mechanical stimulation



3 x EIS Connector + power supply

Electrical Stimulation Connector

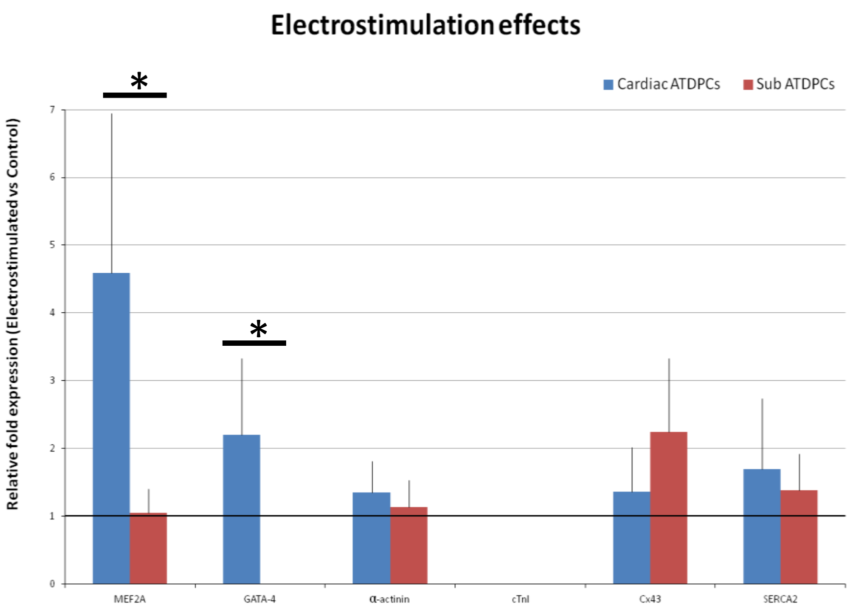
6 x FrontEnd + 2 ref. channels



Electrical Stimulation Connector

ATDPCs electrical stimulation

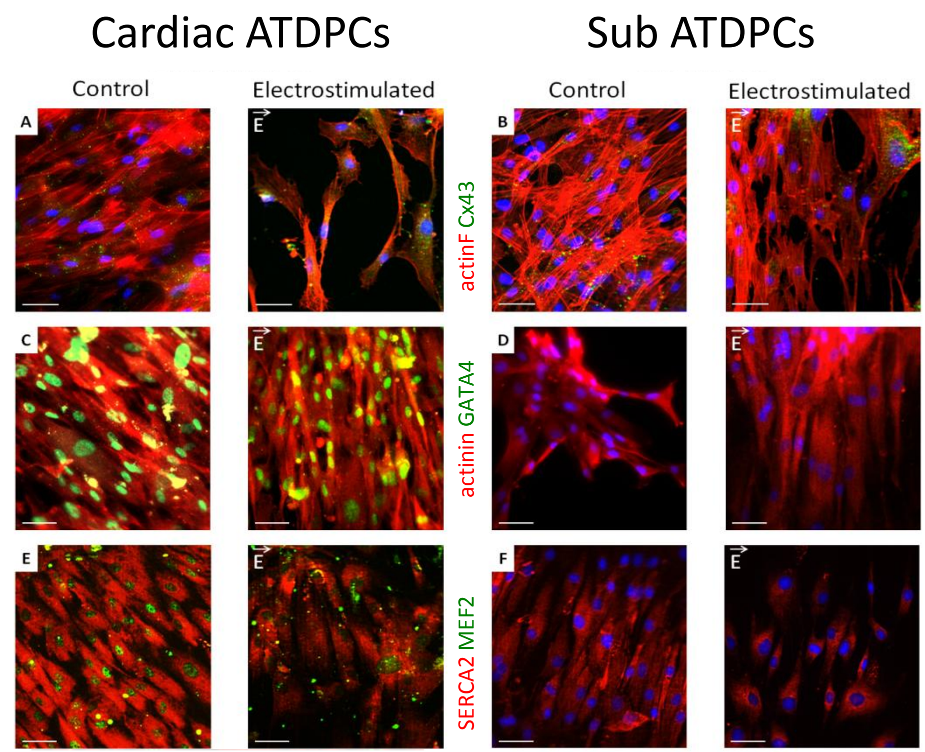
Electrostimulation on ATDPCs:



Transcription factors

Contractile apparatus

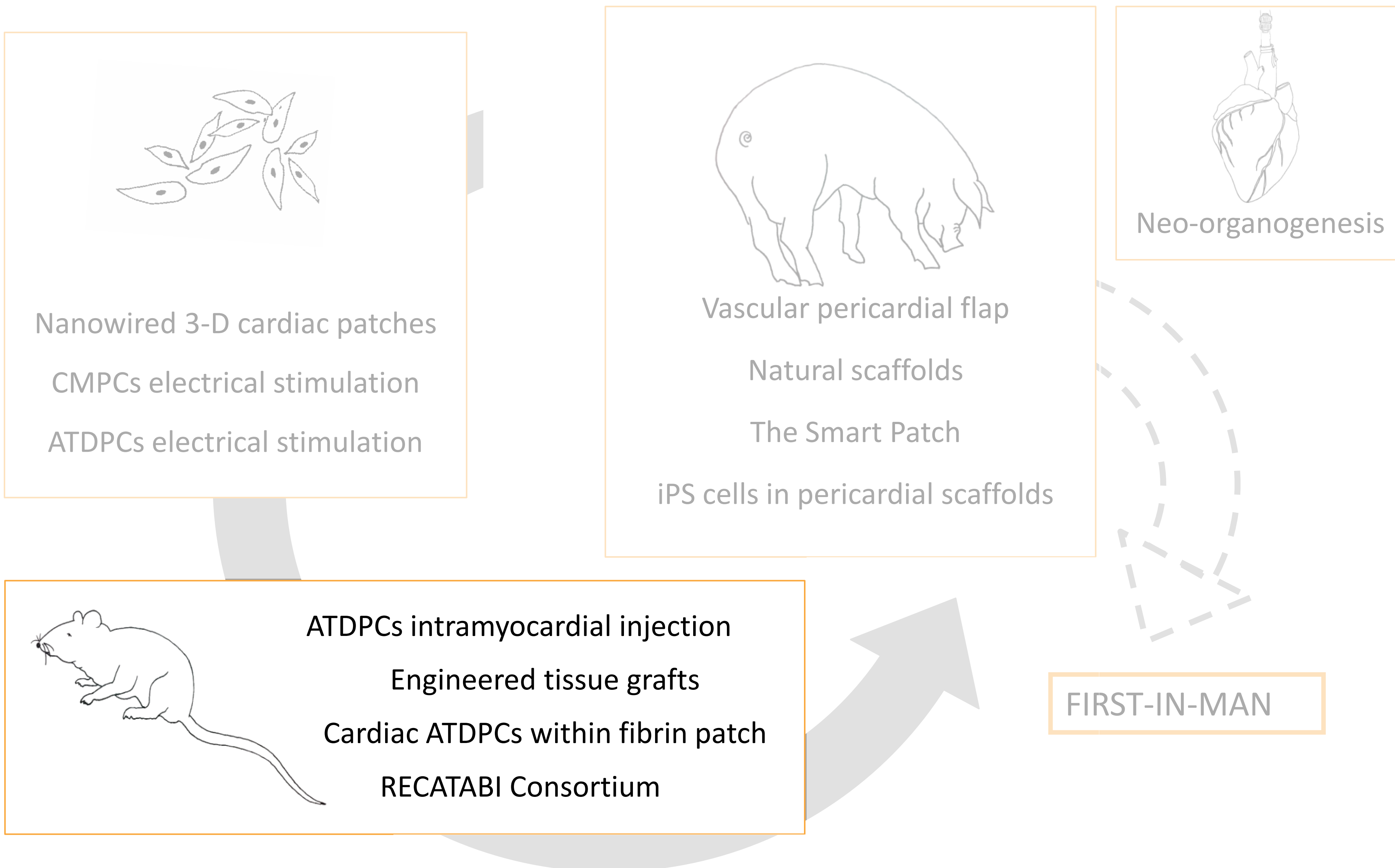
Cell connections/ calcium handling

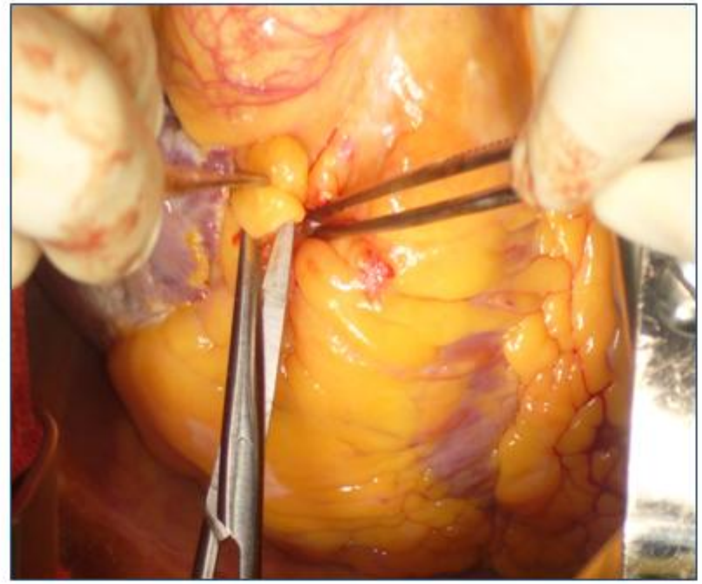


$\vec{E}$ = electric field direction

Llucià-Valldeperas *et al.*, *J Tissue Eng Regen Med*, 2013.

Experimental approaches





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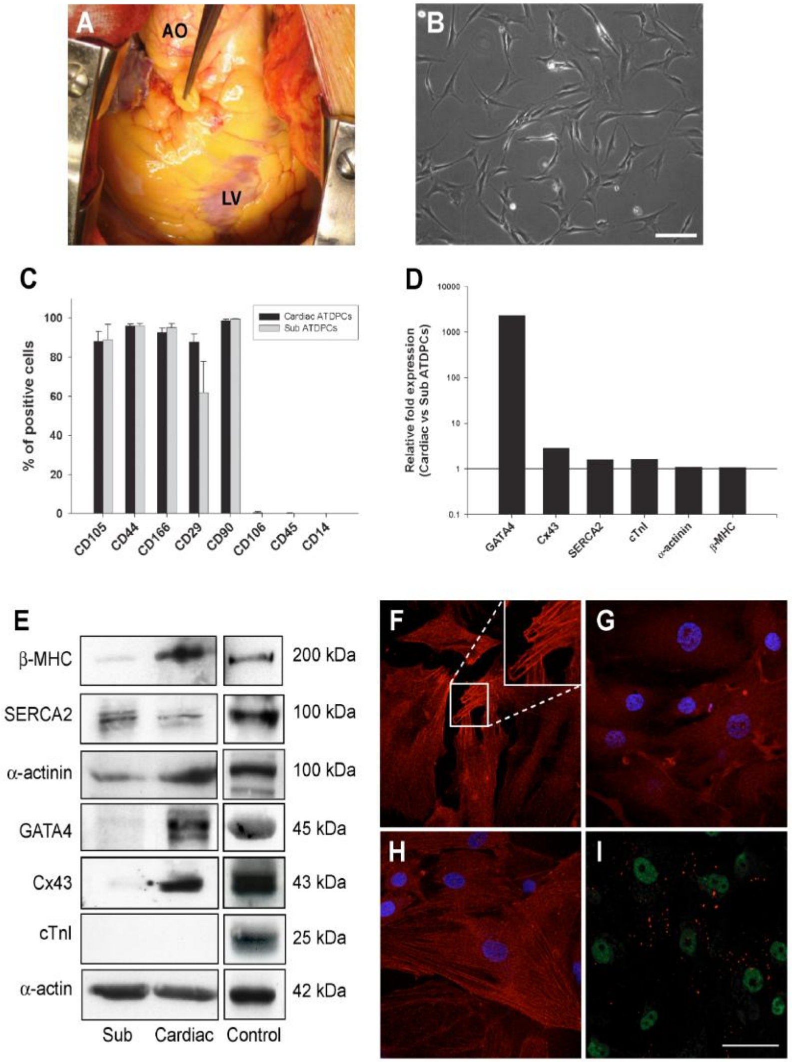
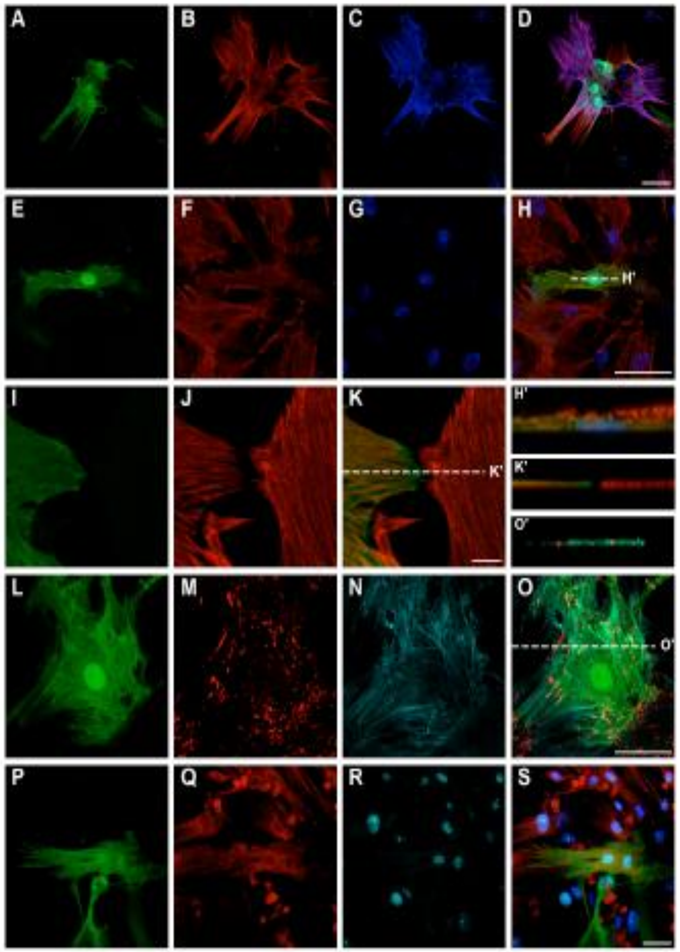
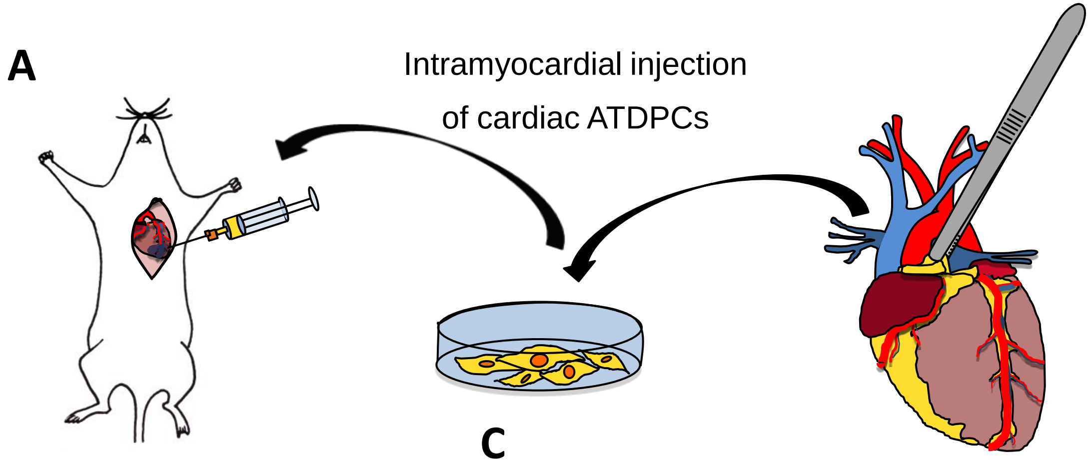
Cardiac adipose tissue derived progenitor cells



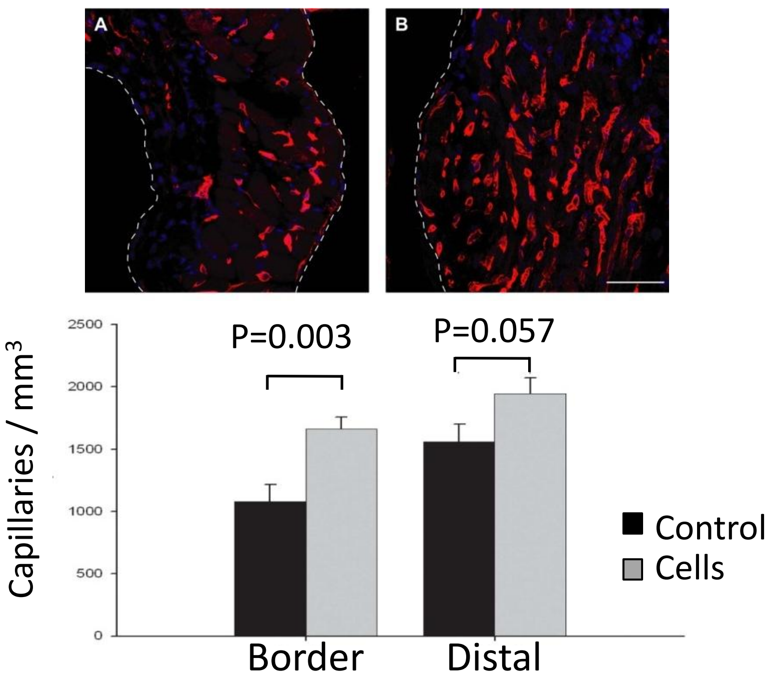


A Bayes-Genis et al. J Mol Cell Cardiol 2010

Intramyocardial injection of ATDPCs



B



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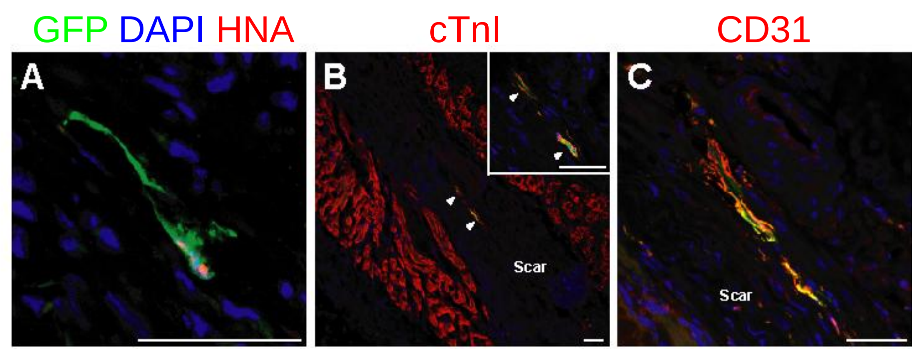
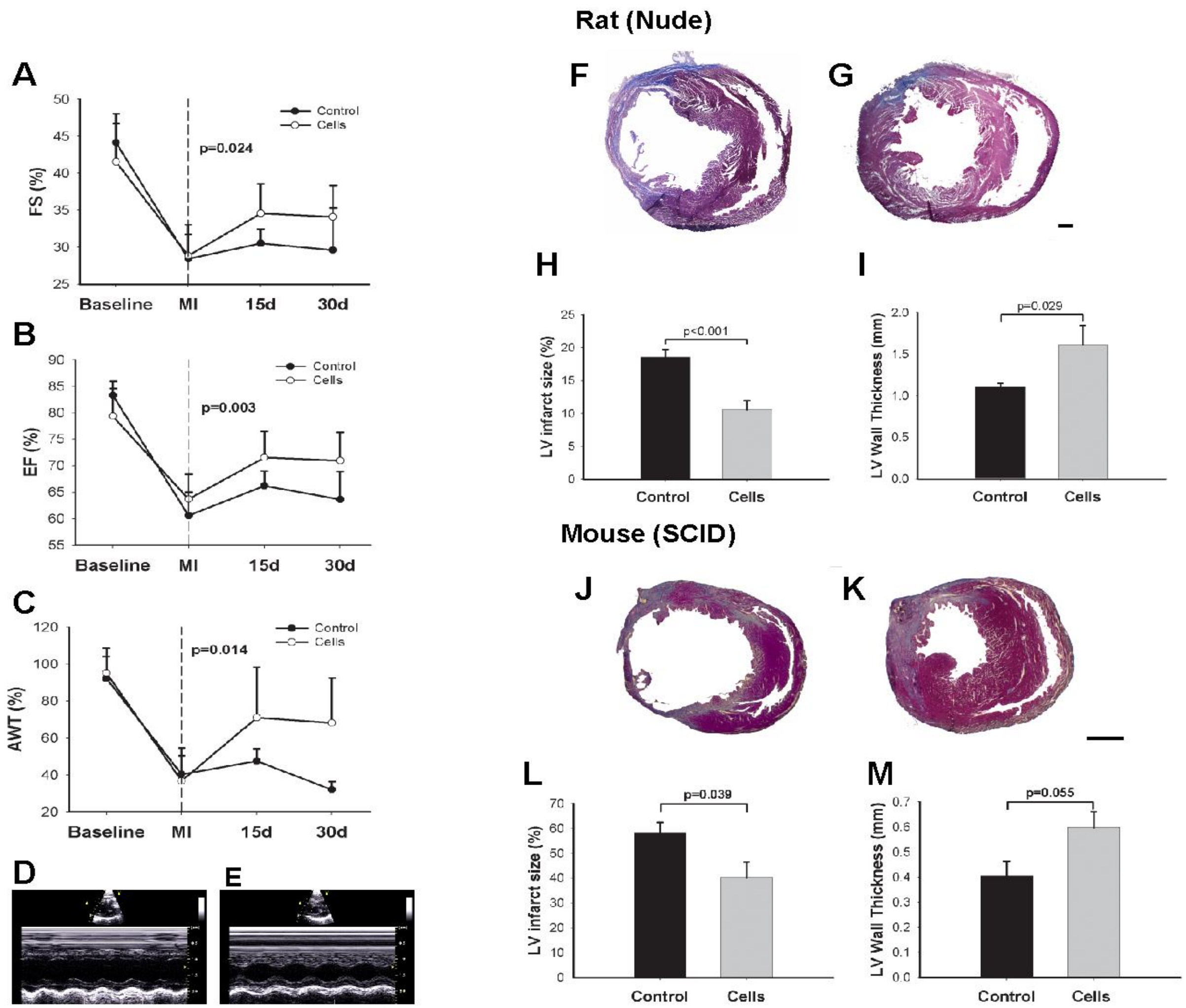


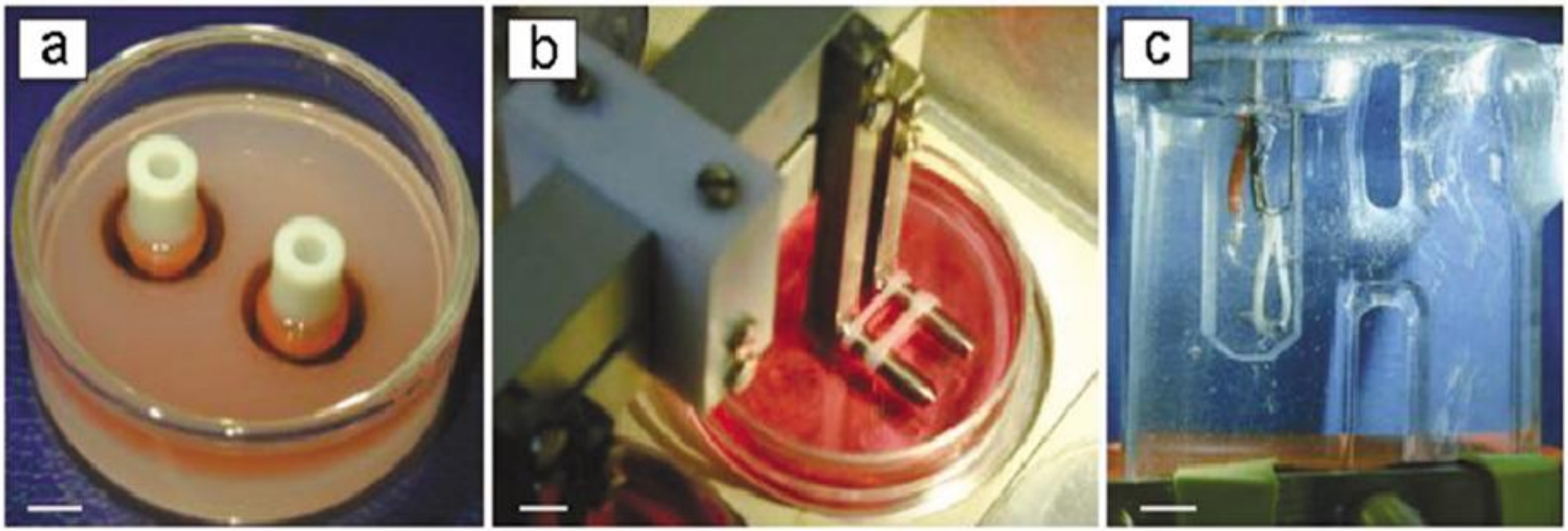
Bayes-Genis A *et al. J Mol Cell Cardiol* 2010

Intramyocardial injection of ATDPCs



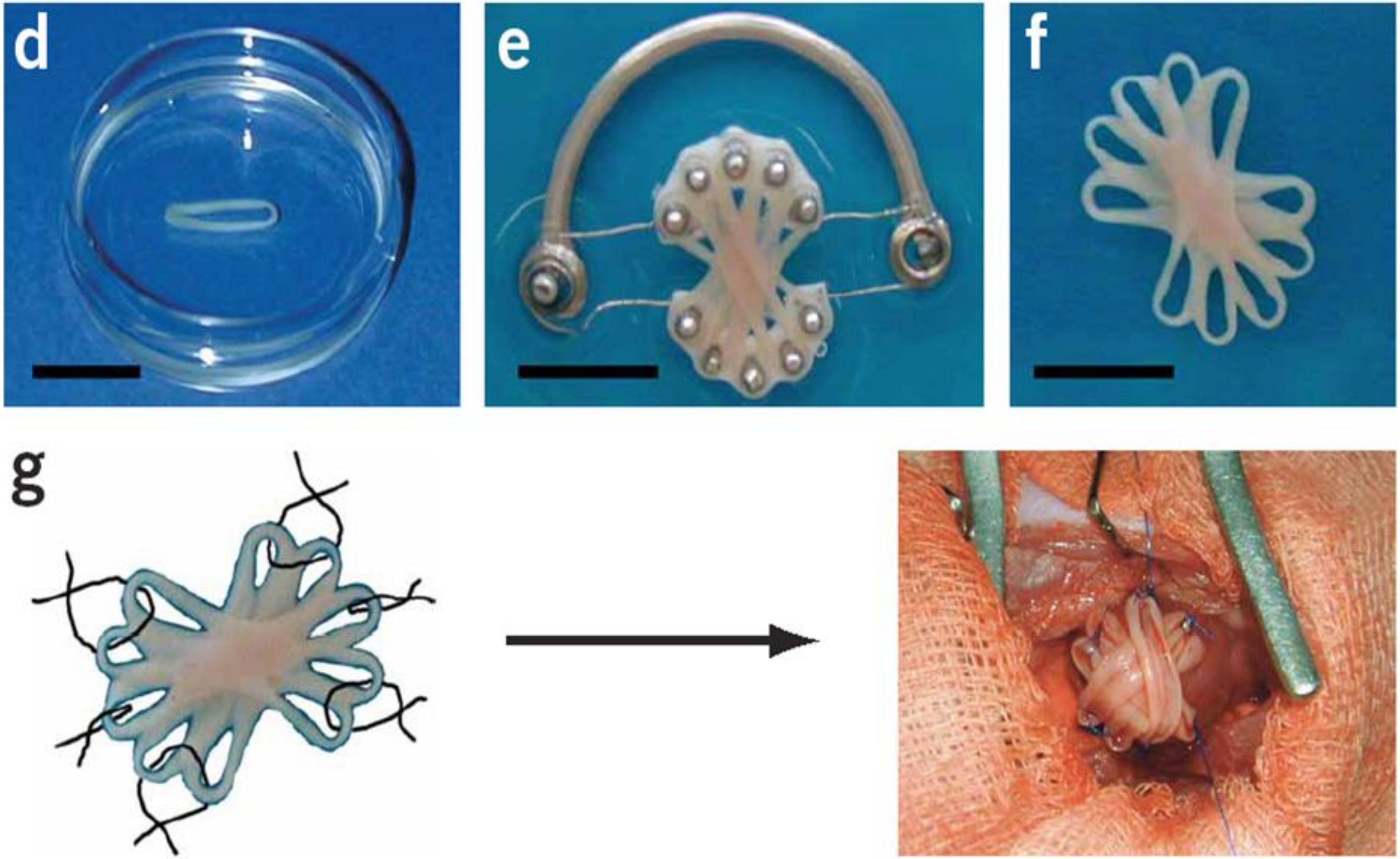
Bayes-Genis A *et al. J Mol Cell Cardiol* 2010

Engineered heart tissue: T Eschenhagen



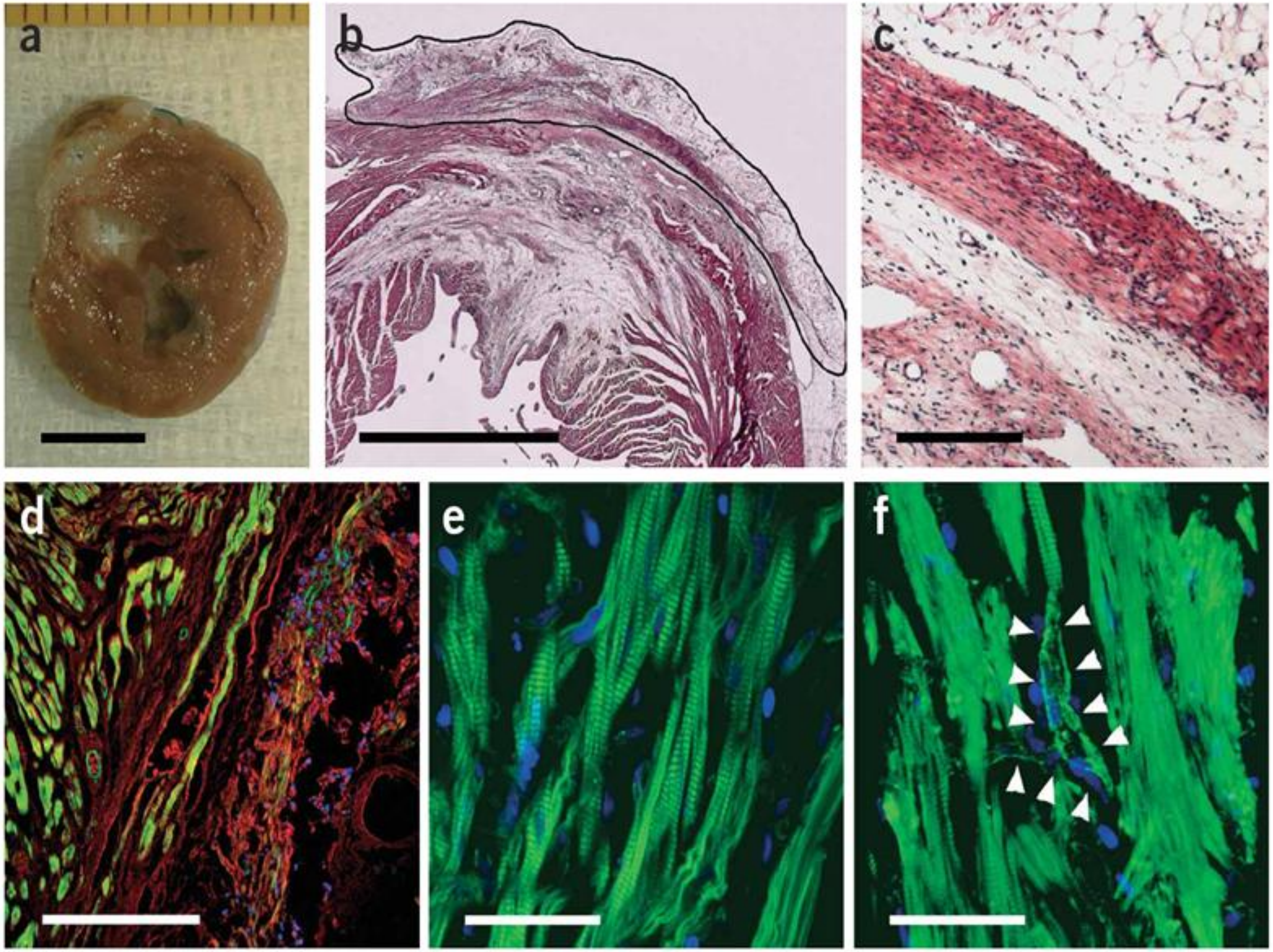
Zimmermann WH at al. Cardiovasc Res 2006;71:419

Engineered tissue grafts



Zimmermann WH et al. Nat Med 2006.

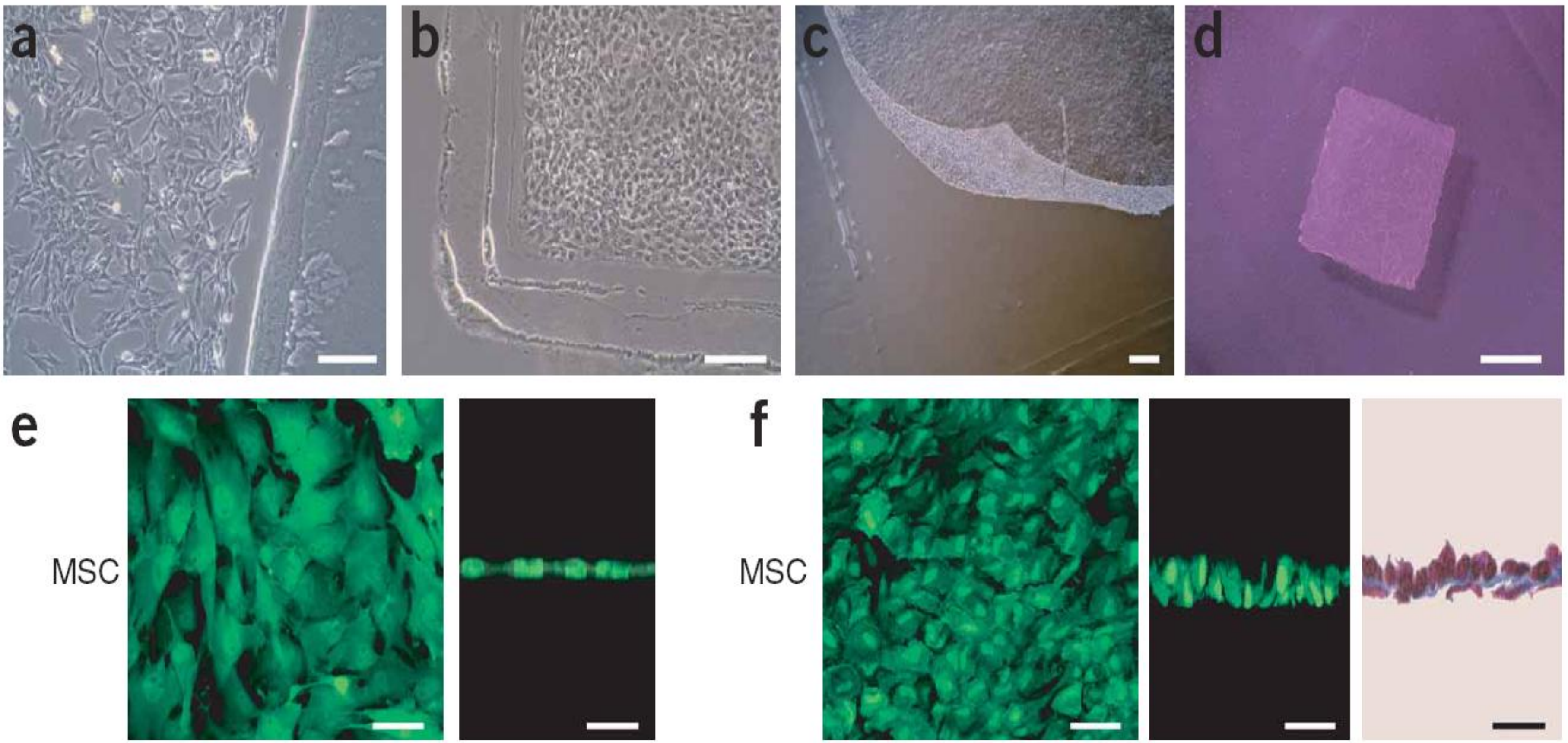
Engineered tissue grafts



Zimmermann WH *et al*. *Nat Med* 2006.

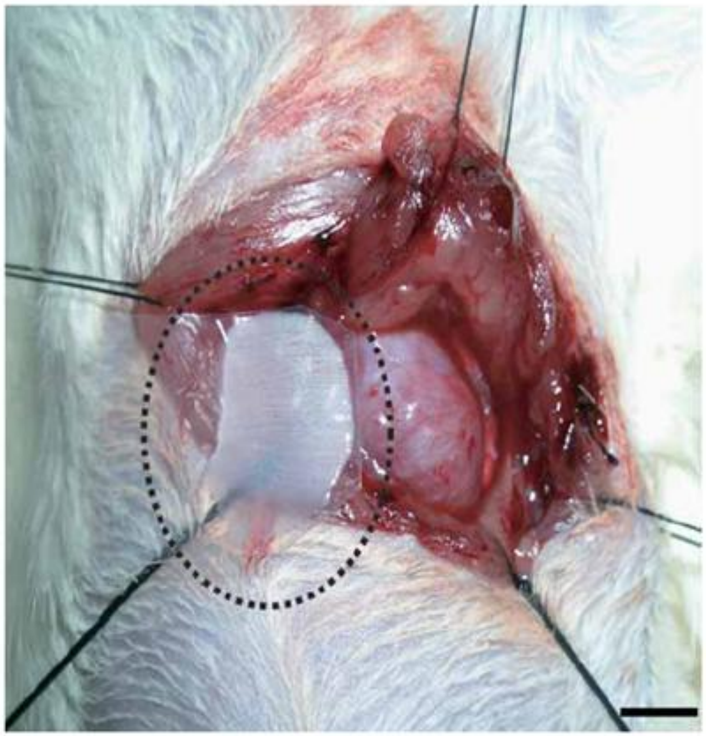
Tissue Engineering for heart muscle: Idezo Mori

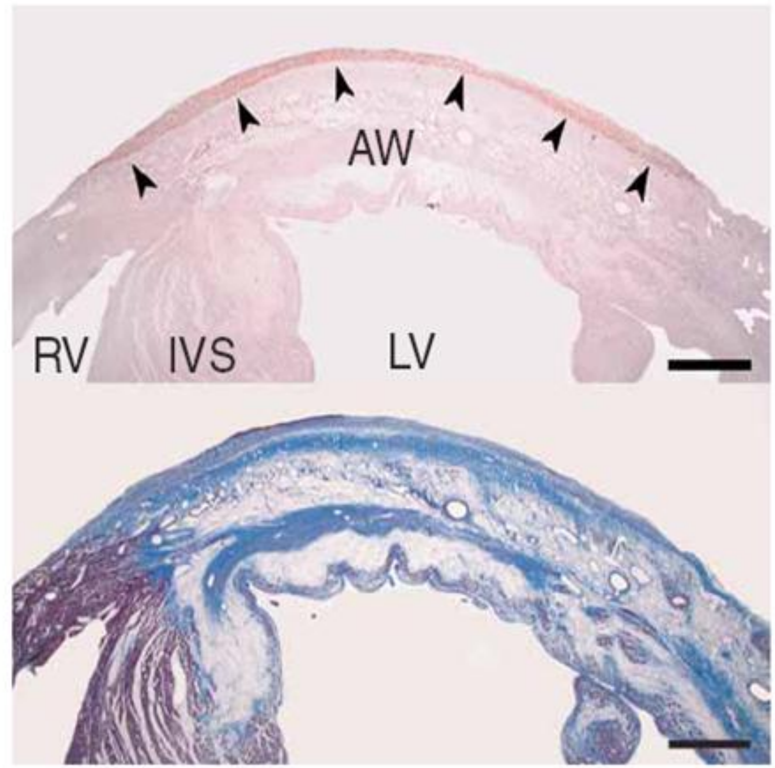
Monolayered mesenchymal stem cells



Miyahara Y et al. Nat Med 2006;12:459

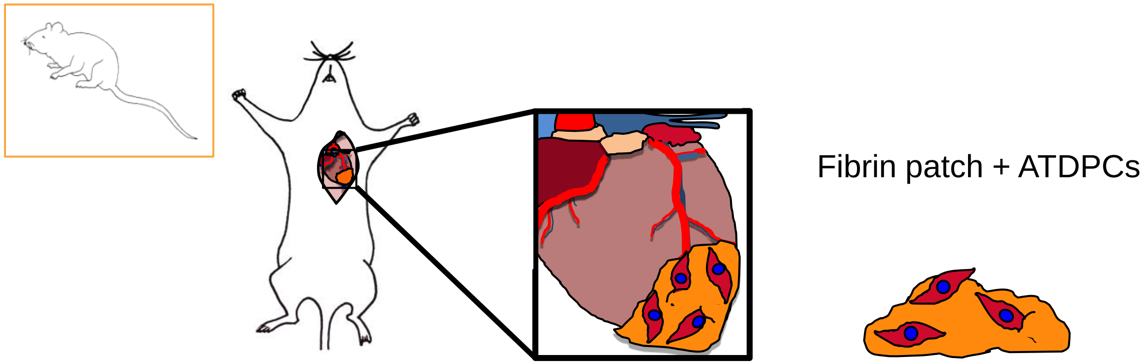
Monolayered mesenchymal stem cells



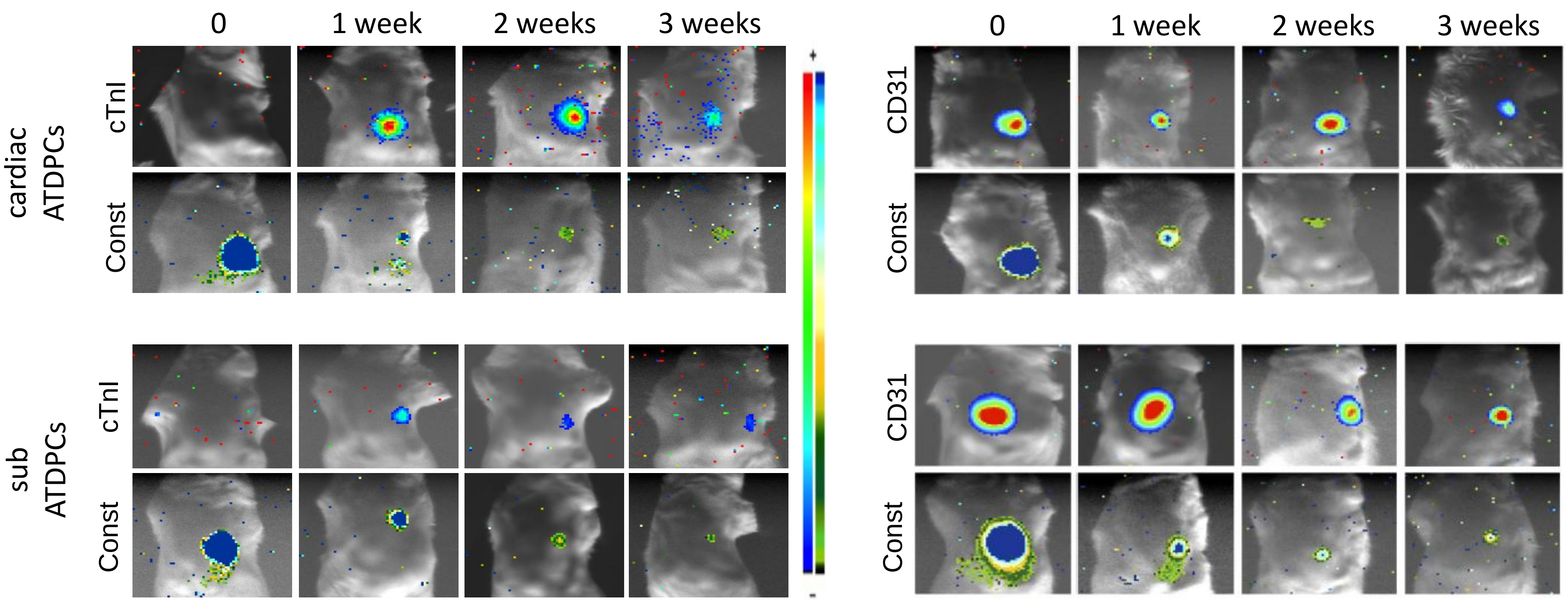


Miyahara Y et al. Nat Med 2006; 12:459

Implantation of cardiac ATDPCs through a fibrin patch



To monitor (BLI) cTnI and CD31 expression of cardiac ATDPCs delivered through a fibrin patch



Bagó JR *et al. Int J Cardiol.* 2013

RECATABI consortium, 7FP EU

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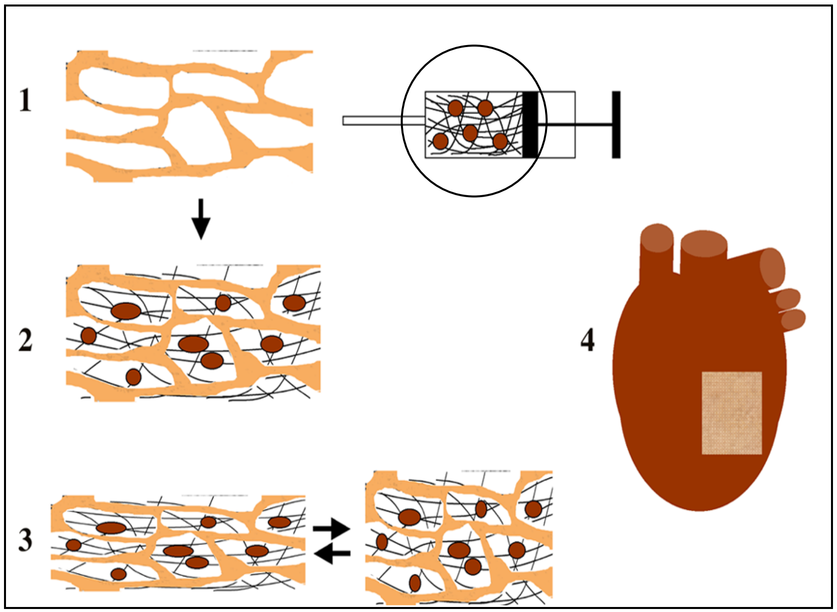
NMP-2008-2.3-1 Advanced implants and bioactive materials for critical organs



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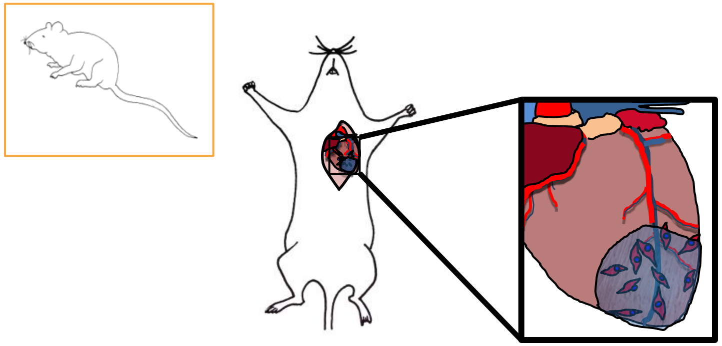
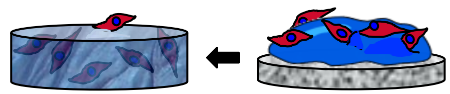
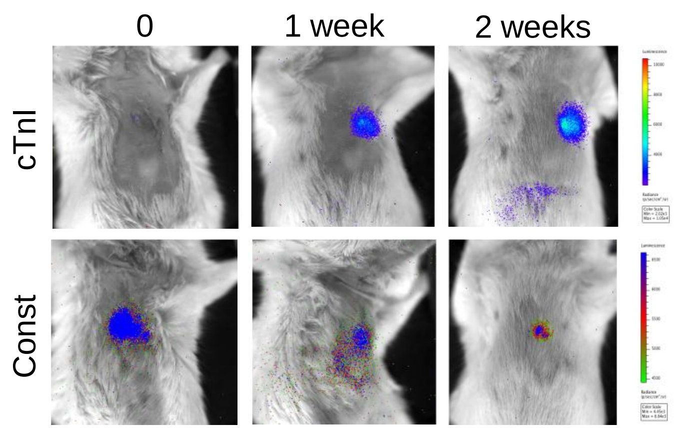


PCLMA membrane +
peptide hydrogel +
ATDPCs

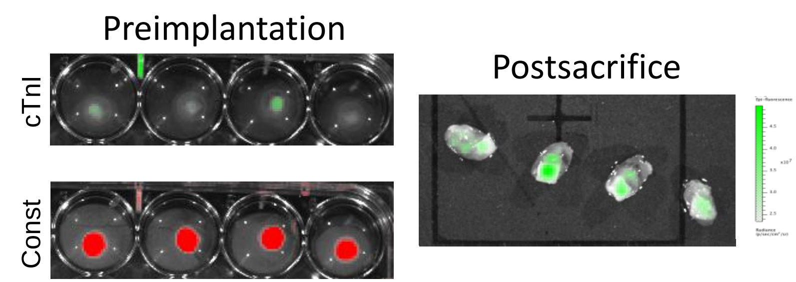


To create a scaffold delivering ATDPCs in the mouse model of myocardial infarction

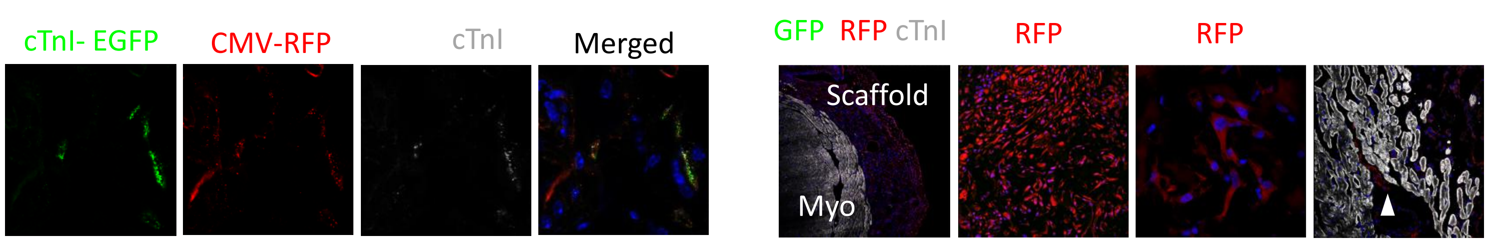
BLI



Fluorescence



De novo expression of cTnI



Soler-Botija C *et al.* Am J Transl Res. 2014

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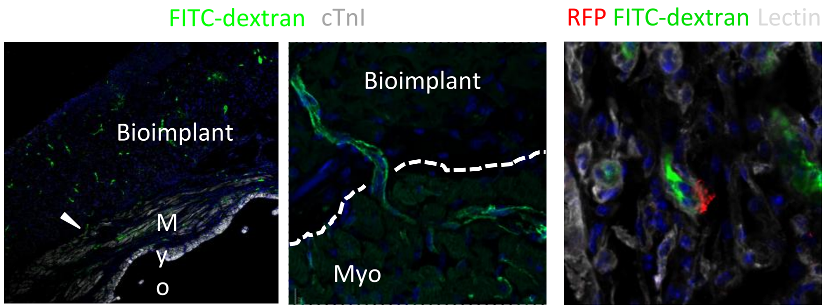
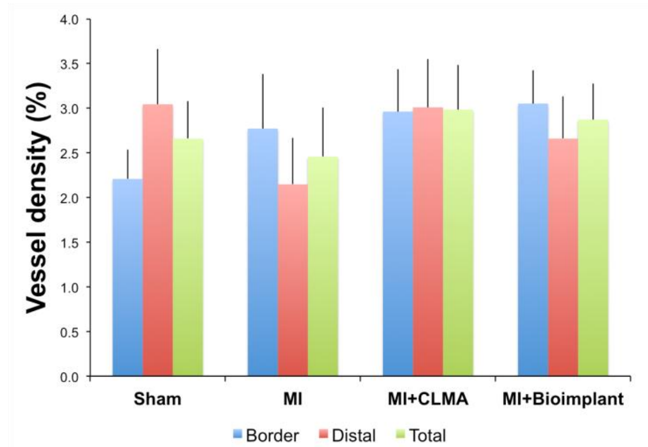
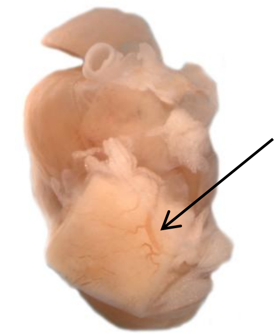
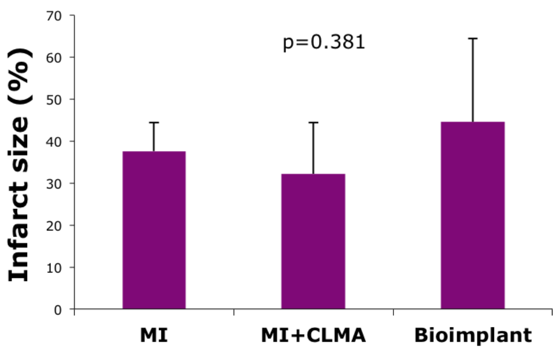
Bioimplant vascularization



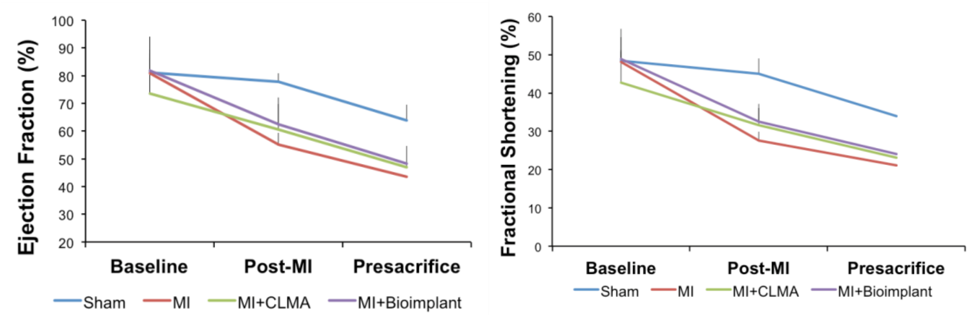




Morphometry

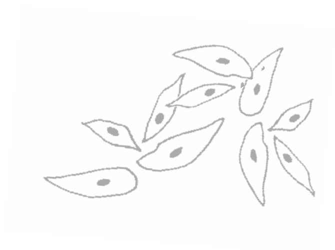


Cardiac Function



Soler-Botija C *et al.* Am J Transl Res. 2014

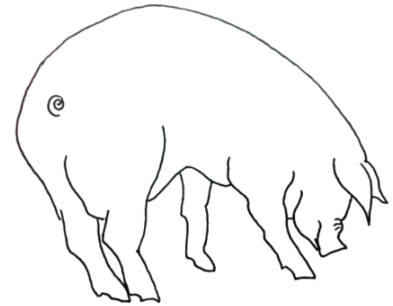
Experimental approaches



Nanowired 3-D cardiac patches

CMPCs electrical stimulation

ATDPCs electrical stimulation



Vascular pericardial flap

Natural scaffolds

The Smart Patch

iPS cells in pericardial scaffolds

Neo-organogenesis

ATDPCs intramyocardial injection

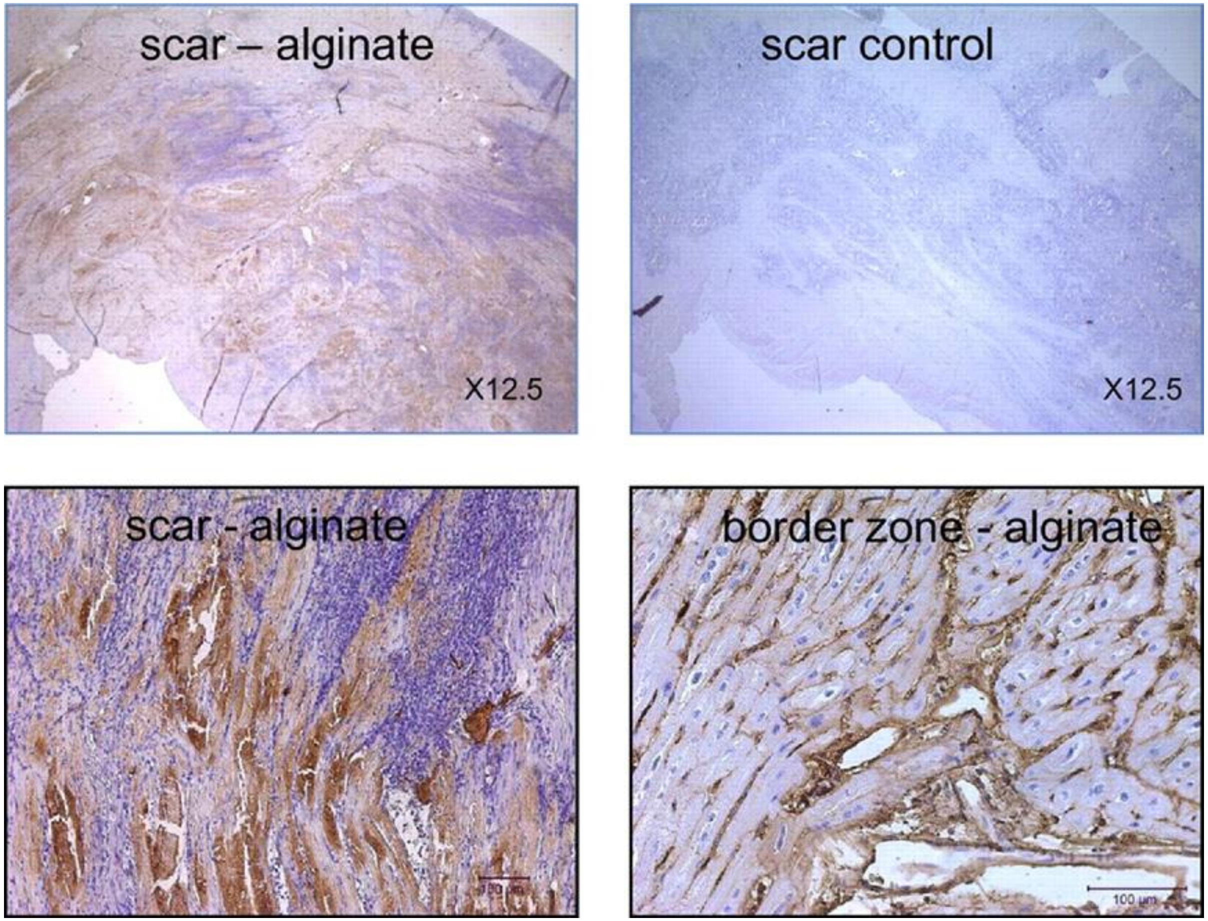
Engineered tissue grafts

Cardiac ATDPCs within fibrin patch

RECATABI Consortium

FIRST-IN-MAN

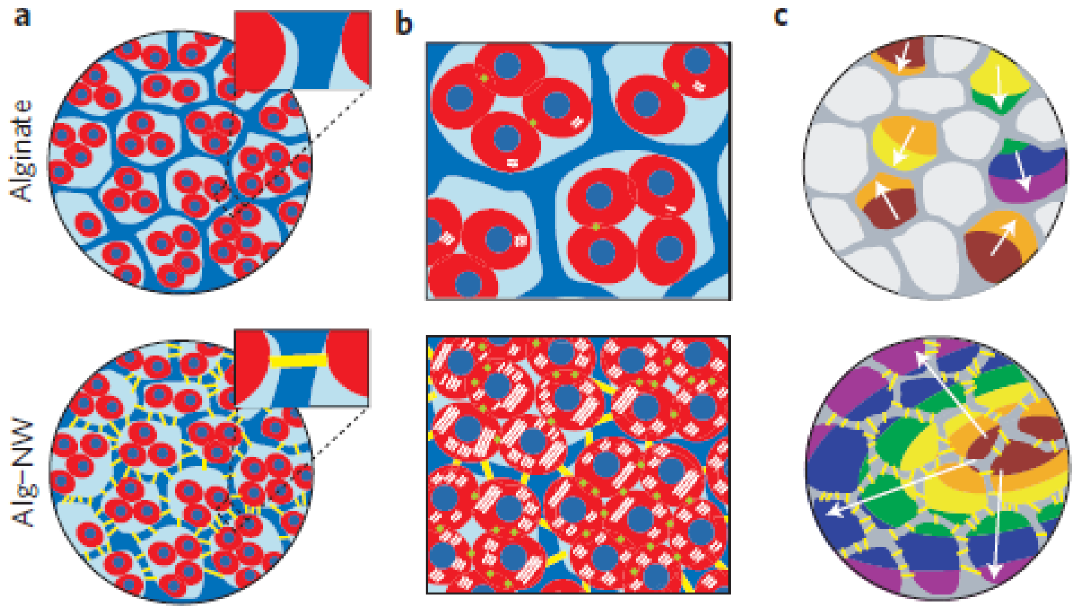
Alginate hydrogel reverses LV remodeling: J Leor



Swine model post-MI: preservation of LV area + incraesed scar thickness

Leor J et al. JACC 2009; 54:1014-23.

Nanowired 3-D cardiac patches



Alginate + Gold nanowires

Better alignement

Synchronous contraction

Higher levels of muscle contraction and electrical coupling proteins

Dvir T *et al. Nature Nanotech* 2011

Myocardial matrix hydrogel: Karen Christman

Catheter-deliverable hydrogel dereived from decellularized ventricular extracellular matrix

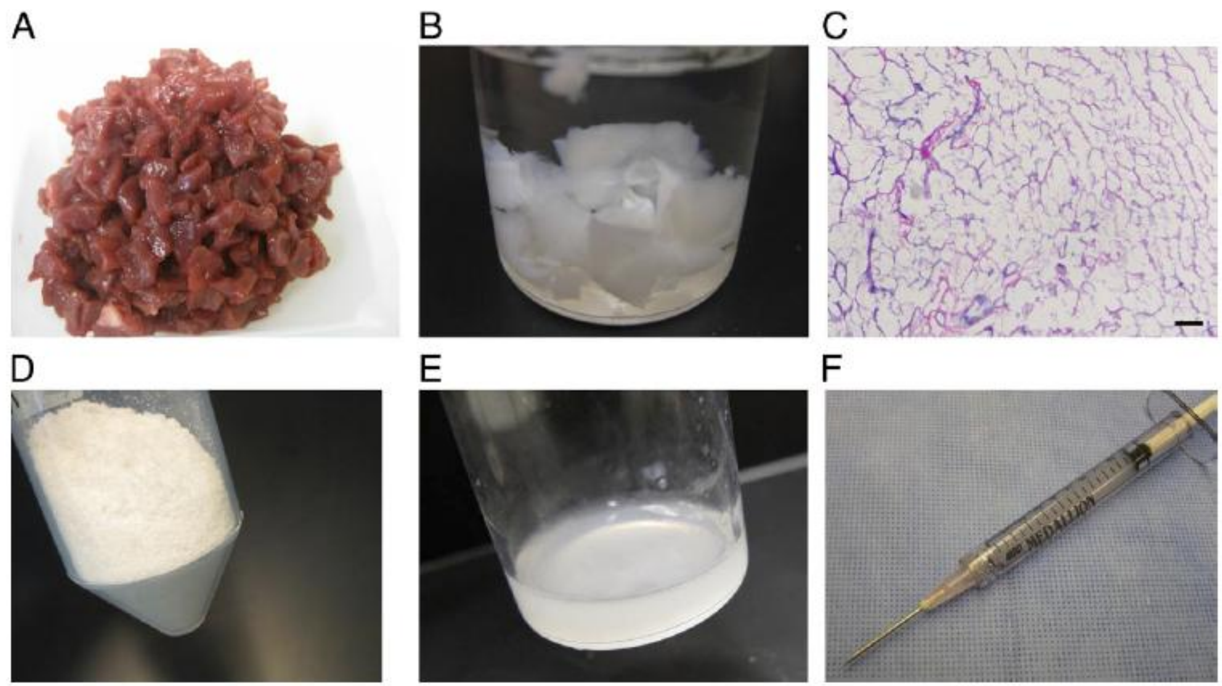


Figure 1 **Myocardial Matrix Fabrication**

(A) Porcine ventricular myocardium is sliced and then **(B)** decellularized using sodium dodecyl sulfate. **(C)** Hematoxylin and eosin staining of a histological section reveals cellular removal. The decellularized extracellular matrix is then milled into a fine powder **(D)** and then solubilized through enzymatic digestion **(E)**, which allows for injection via syringe and a 27-gauge needle **(F)**.

Singelyn JM et al. JACC 2012: 59;751-63.

Gelled myocardial matrix within healthy myocardium

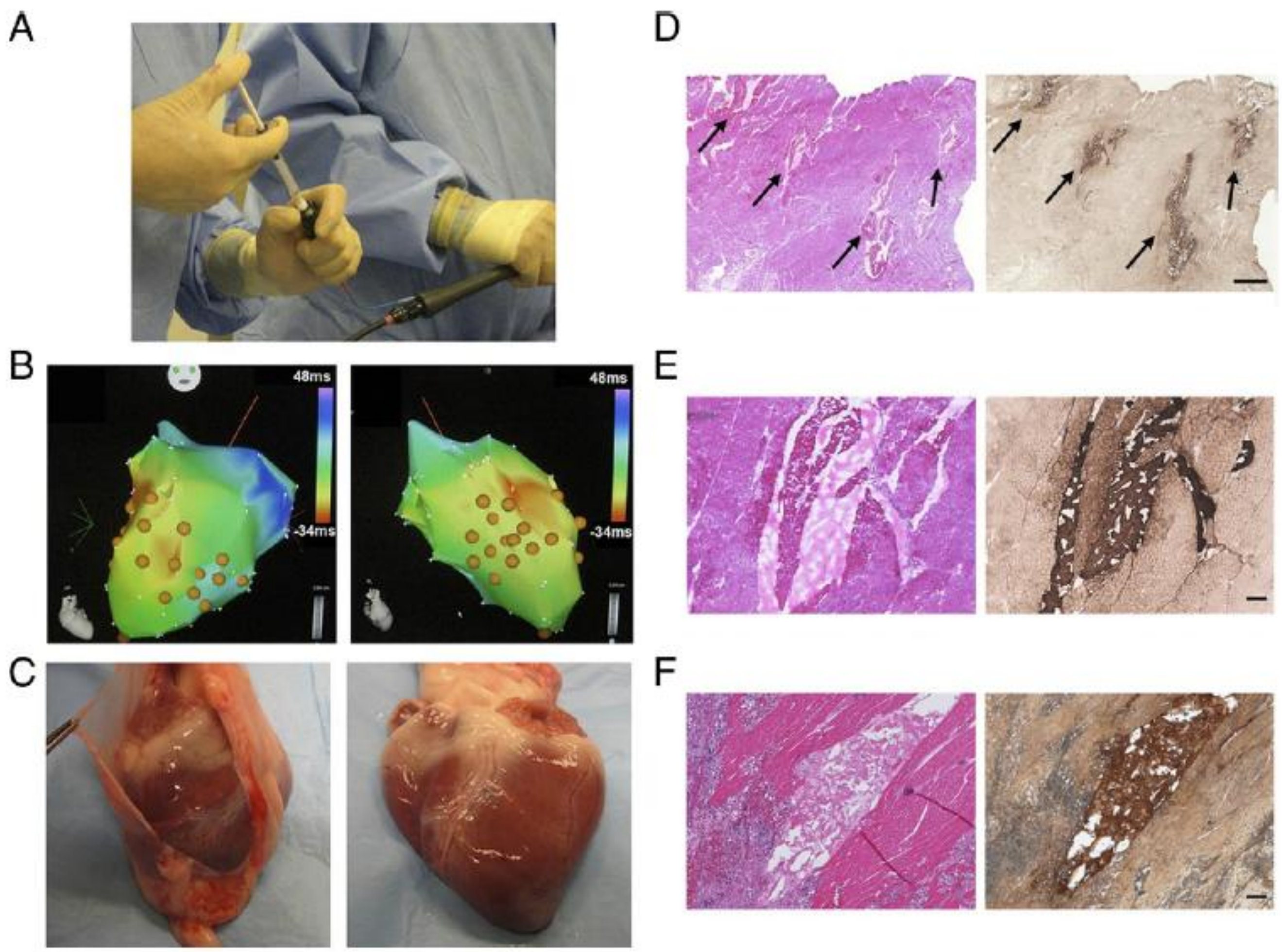
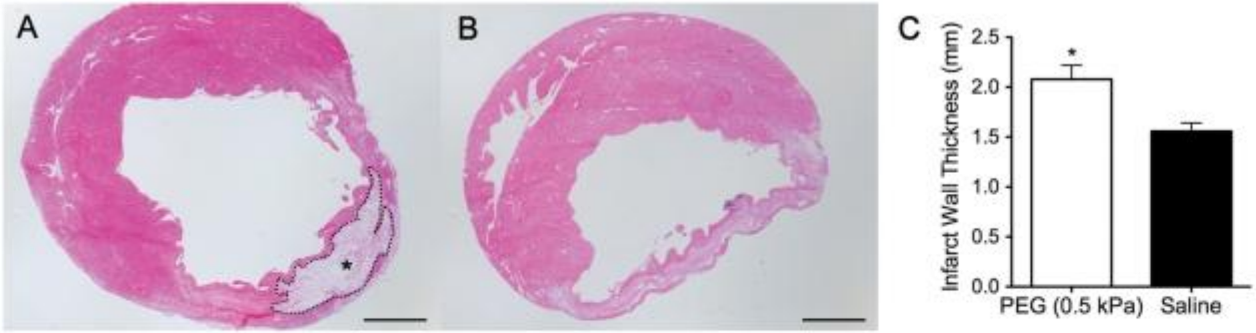
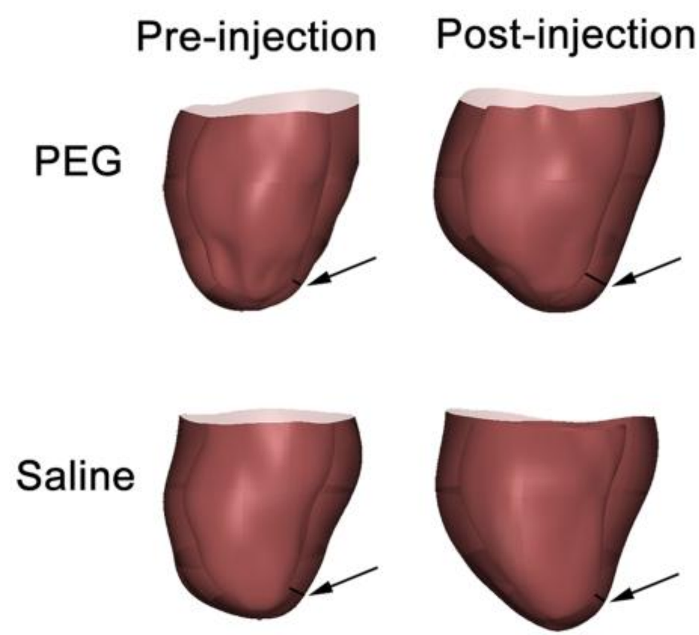


Figure 5 Percutaneous Transendocardial Delivery of Myocardial Matrix Hydrogel

Biomaterial alone may not be sufficient !!



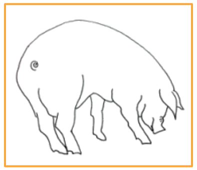
PEG hydrogel Saline

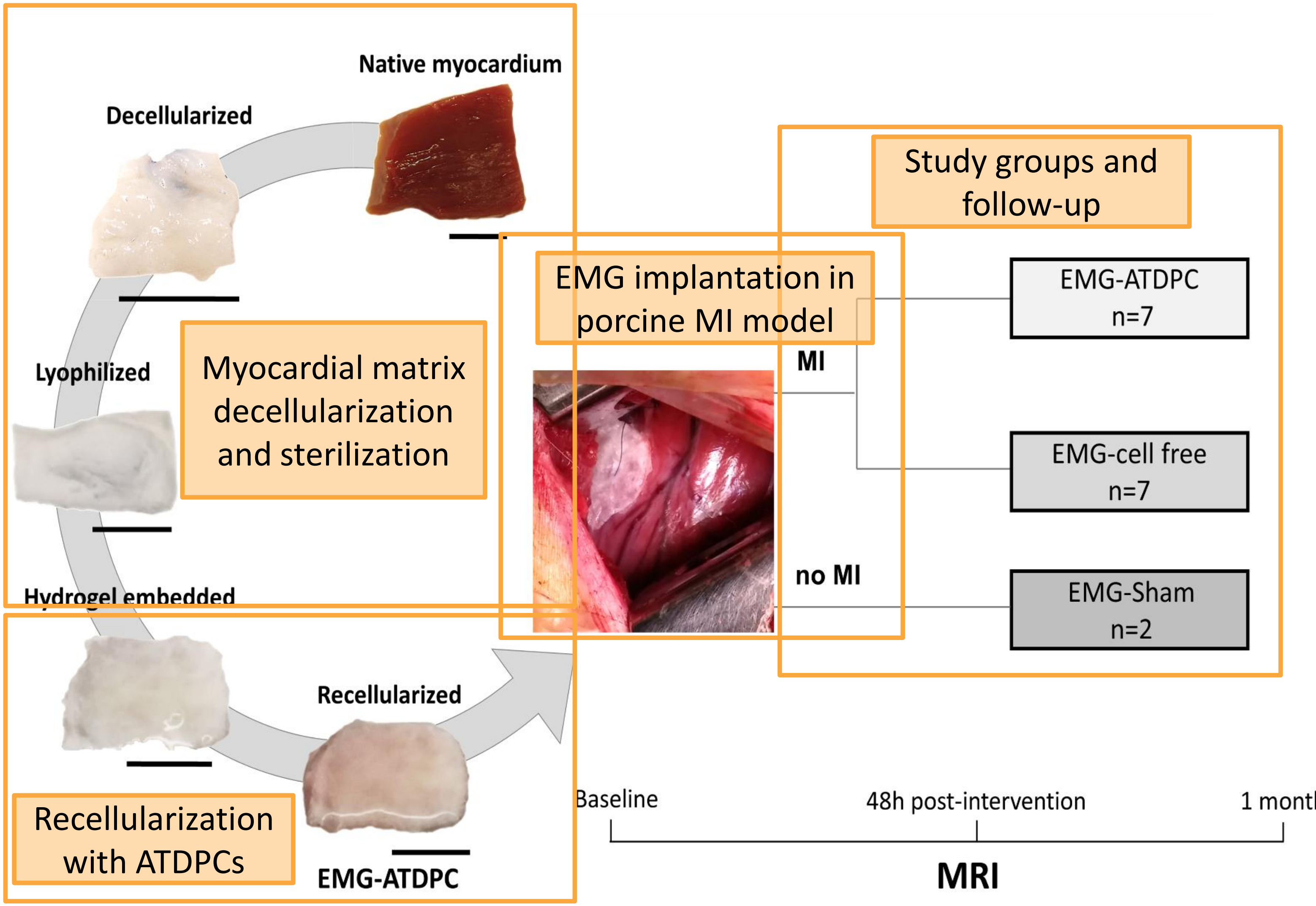


Increased infarct wall thickness by a bio-inert material is insufficient to prevent negative left ventricular Remodeling after myocardial infarction.

Rane AA et al. PLoS One 2011;6(6):e21571

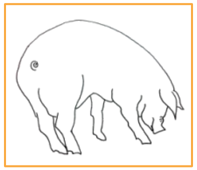
EMG Patch (I)



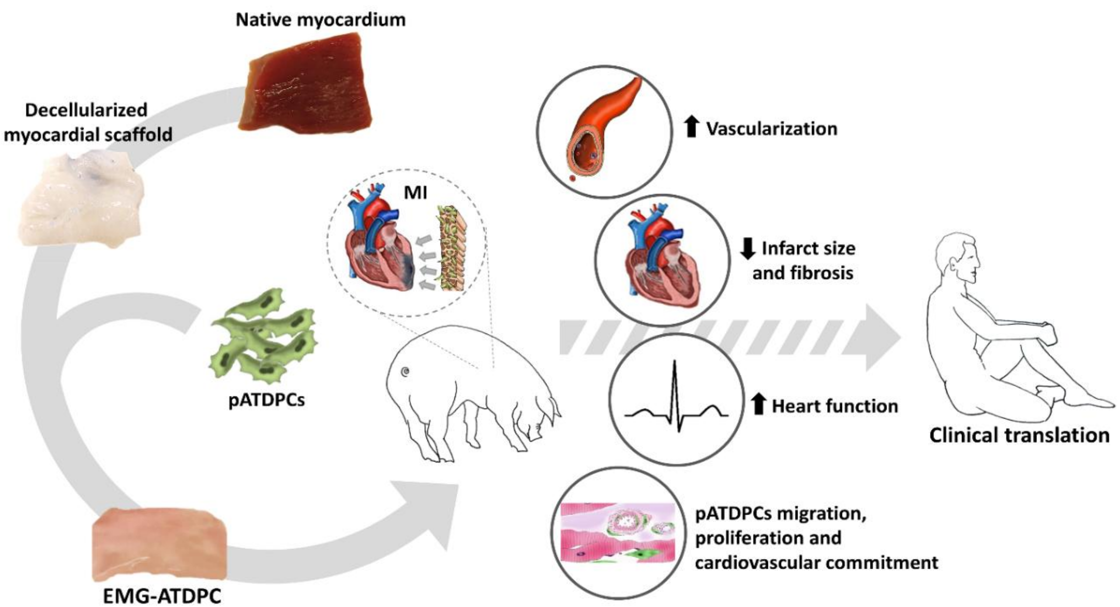


Native myocardium
Decellularized
Lyophilized
Hydrogel embedded
Recellularized
EMG-ATDPC
Myocardial matrix decellularization and sterilization
Recellularization with ATDPCs
EMG implantation in porcine MI model
MI
no MI
Study groups and follow-up
EMG-ATDPC n=7
EMG-cell free n=7
EMG-Sham n=2
Baseline
48h post-intervention
1 month
MRI

EMG Patch (III)



30 days EMG-ATDPC post-implantation:



- Vascularization increase
- Cardiac function enhancement
- Fibrotic progression limitation
- Infarct size diminution
- ATDPCs: migration and cardiovascular-like phenotype

The EMG-ATDPC engraftment led to beneficial effects regarding cardiac recovery in swine pre-clinic MI model. In turn, this should ease its future clinical translation

the "smart patch" concept

iCor.cat

Biological membrane: decellularized human pericardium

NanoGold: nanometric gold particles

Smart Patch

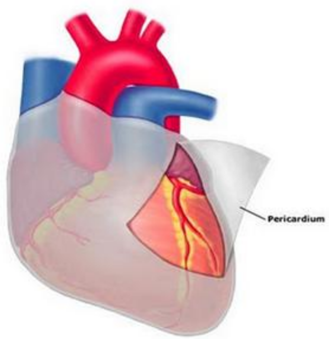
Peptide hidrogel: RAD16-I

Platinum microelectrodes + implantable electronic system

Mesenchymal stem cells: ATDSC

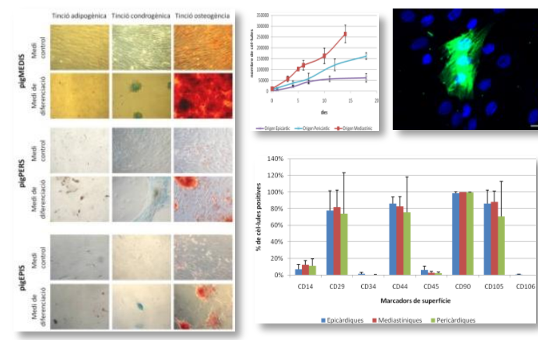
The next generation: the “smart patch” concept

Bio-membrane



Human pericardium= fibrous membrane made up of 2 layers that surounds the heart and great vessels .

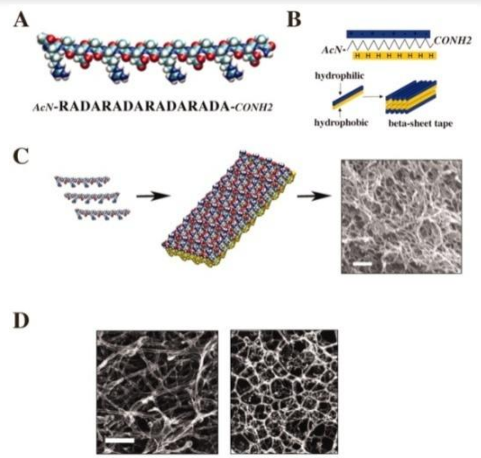
Cardiac ATDSC



MSCs derived from porcine cardiac adipose tissue

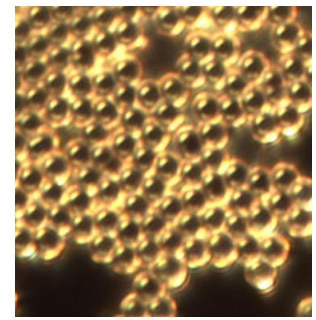
The next generation: the “smart patch” concept

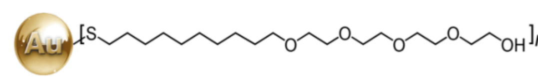
Peptide Hydrogel



RAD16-I = *PuraMatrix*™
Spontaneously autoassembly nanopeptide, forming a molecular network with nanometric pores. Encapsulation of $2 \cdot 10^6$ cells in 400 μL of hydrogel

NanoGold





NanoGold = colloidal solution of gold nanoparticles applied on the electrodes to improve electrical current through the patch

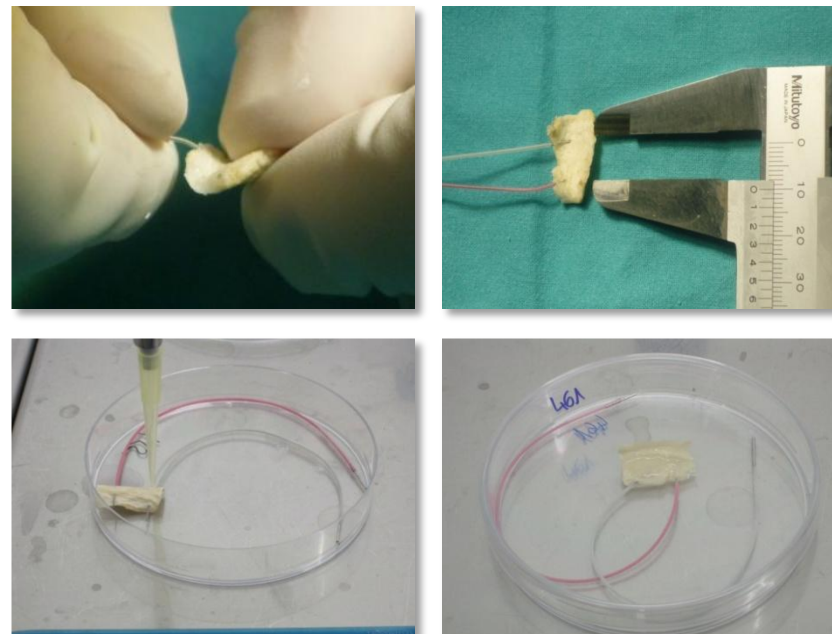
The next generation: the “smart patch” concept

iCor.cat

Microelectrodes + implantable electronic system

Equipment of 35mm x 38mm x 8mm with battery with autonomy for 1 month, performing a measurement every 10 minutes

“The Smart Patch”



The next generation: the “smart patch” concept

Experimental design

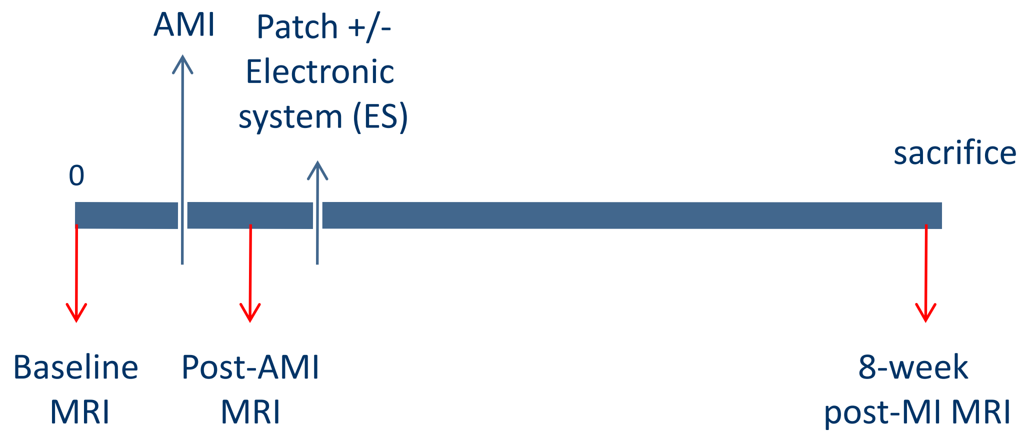
♀ *Landrace X Large White* (30 kg)

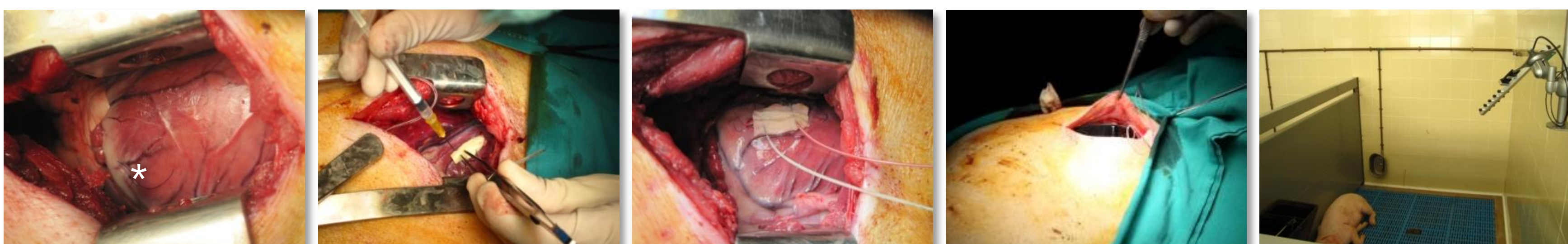
n=2 control (AMI + patch)

n=5 control (AMI + patch) + ES

n=5 treatment (AMI + patch + cells)

n=5 treatment (AMI + patch + cells) + ES

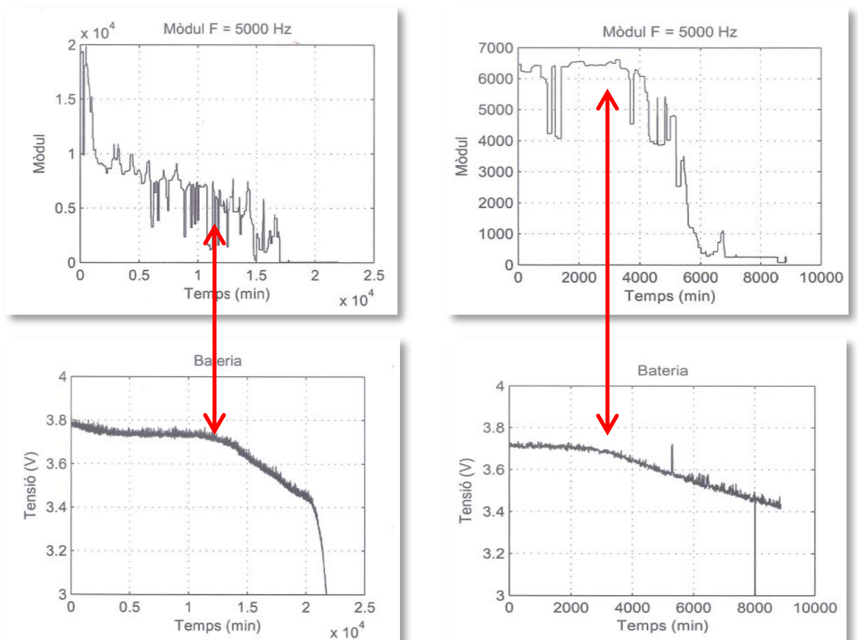




the “smart patch” concept

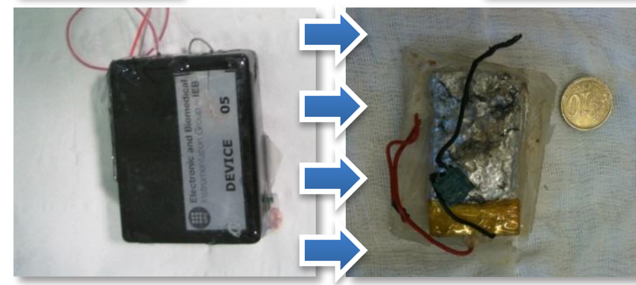
iCor.cat

Patch NO cells | **Patch + cells**



Problems

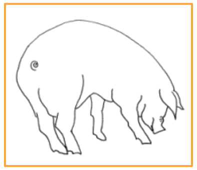
Before | **After**

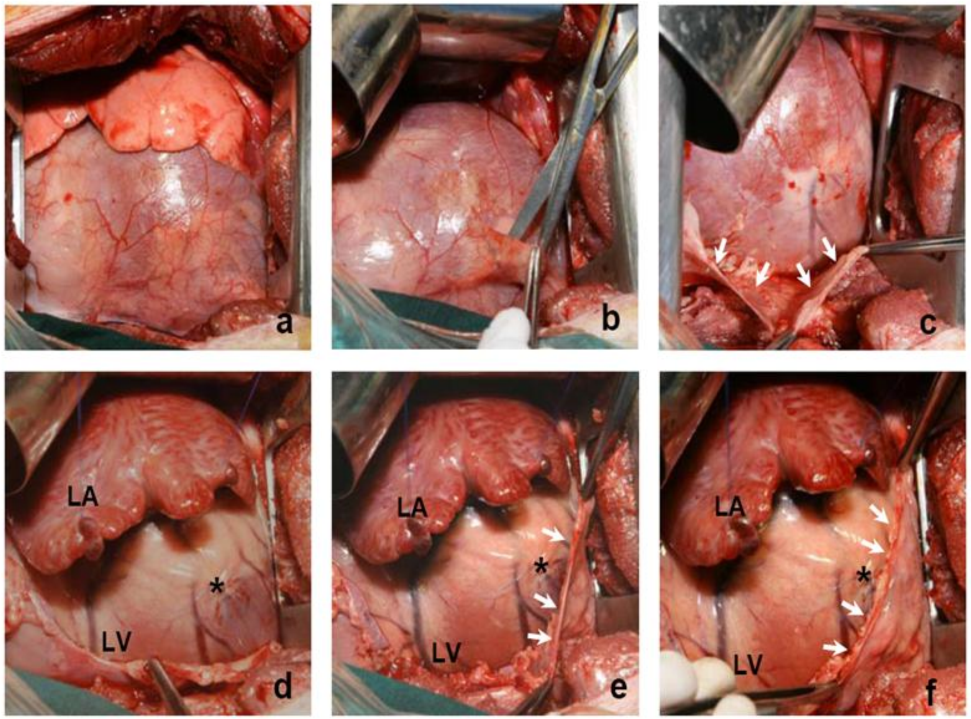


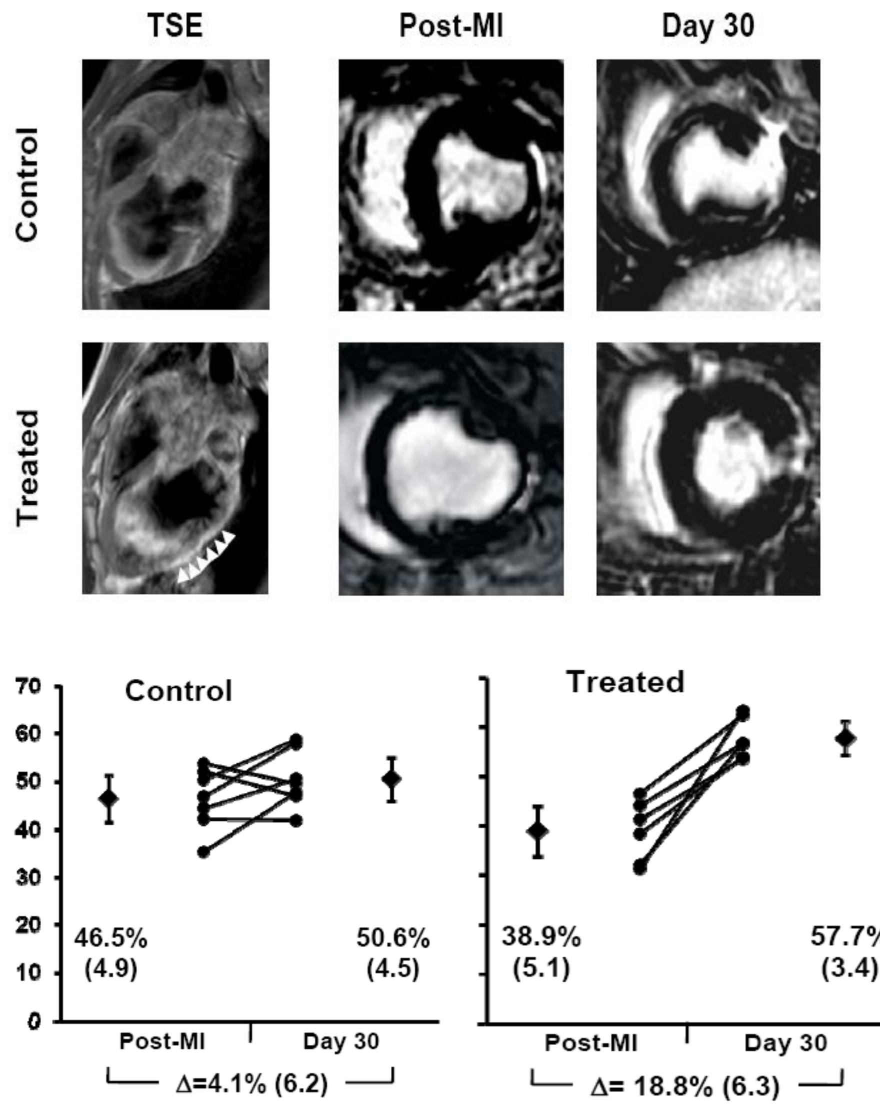
First impedance measurmenents to monitor regeneration *in vivo* to date

Work in progress…………

Vascular pericardial flap

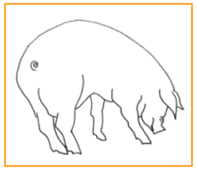


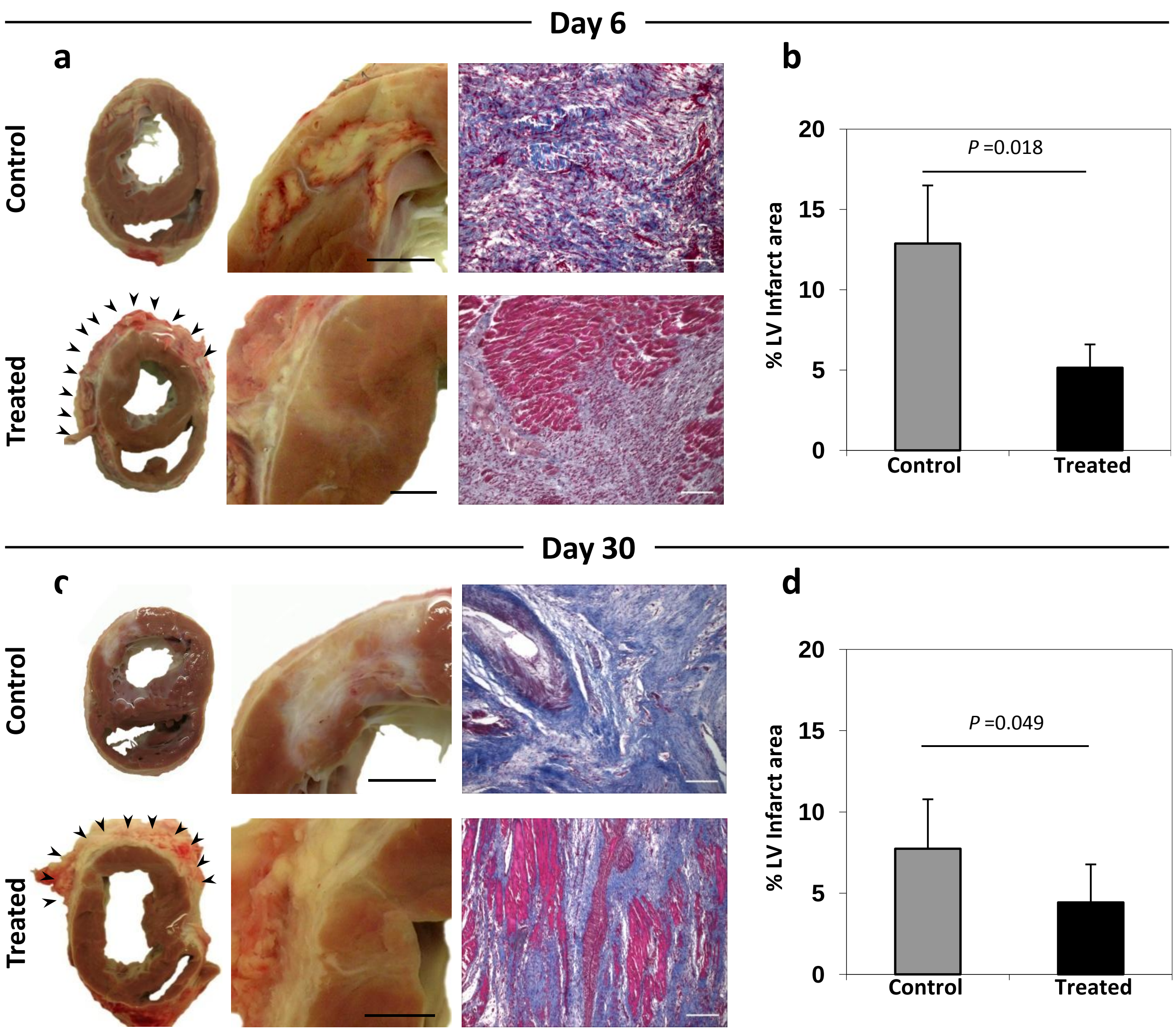




Gálvez-Montón C *et al. Cardiovasc Res.* 2011

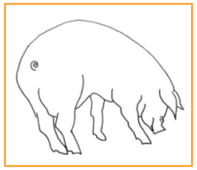
Vascular pericardial flap

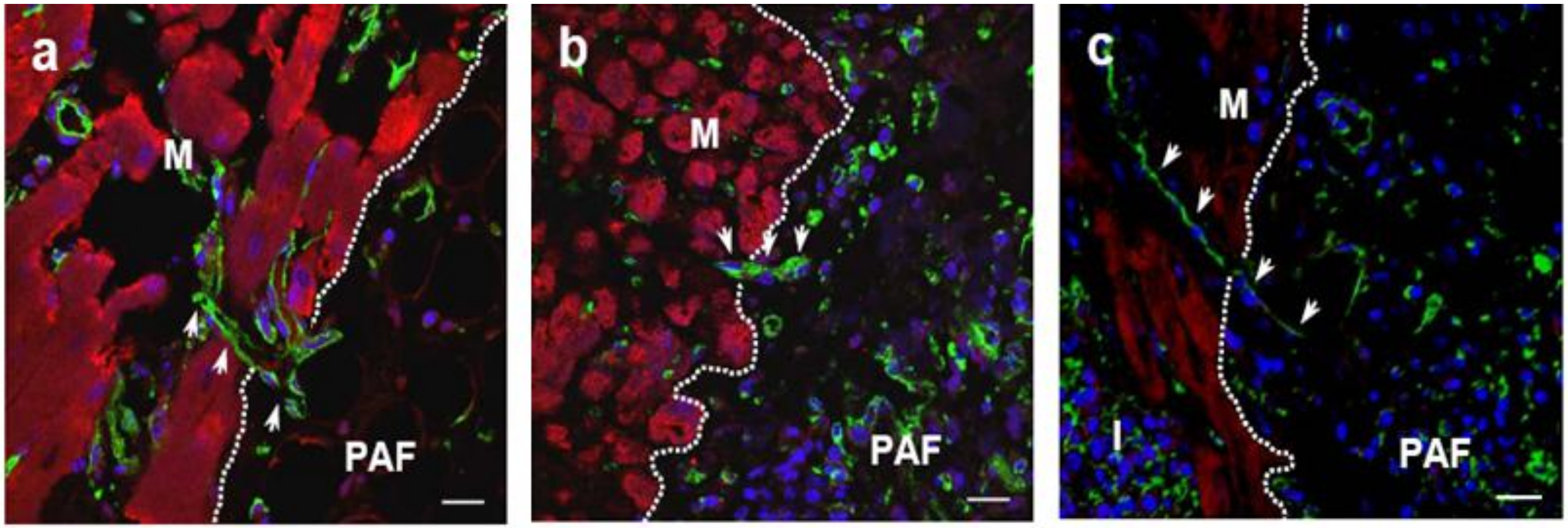




Gálvez-Montón C *et al. Cardiovasc Res.* 2011

Vascular pericardial flap



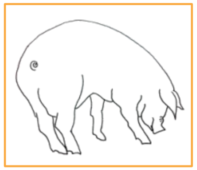


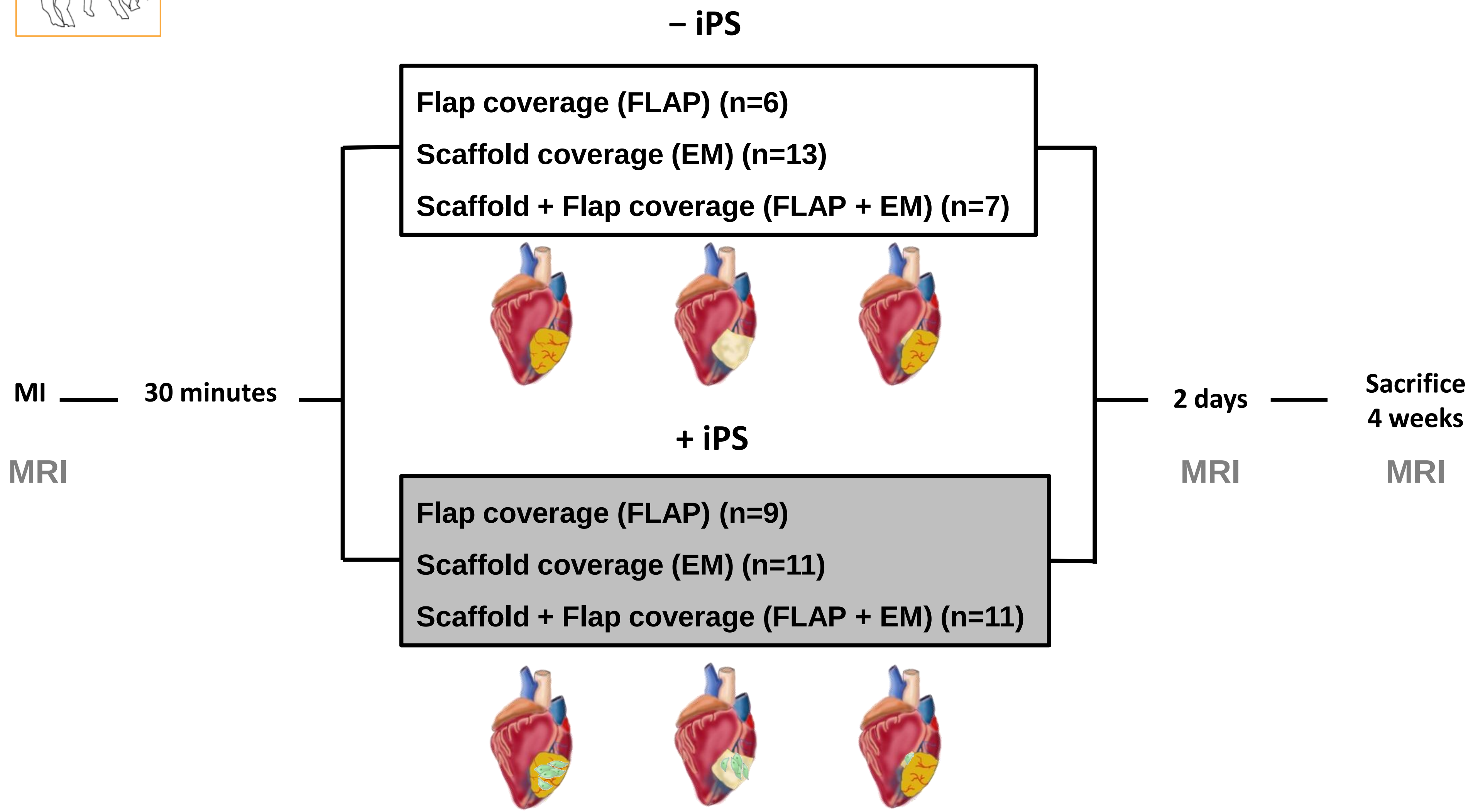
Clinical Trial ongoing

1. NO ethical issues
2. NO technical complications
3. NO economic issues

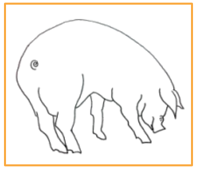
Gálvez-Montón C *et al. Cardiovasc Res.* 2011

iPS cells in pericardial scaffolds



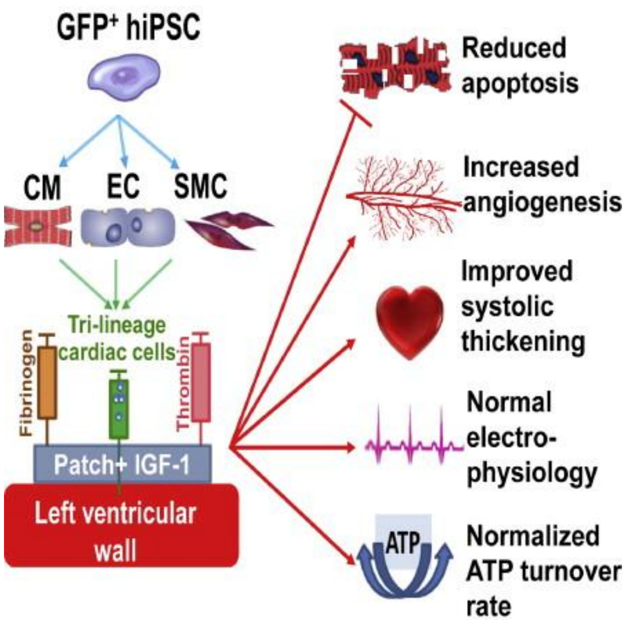


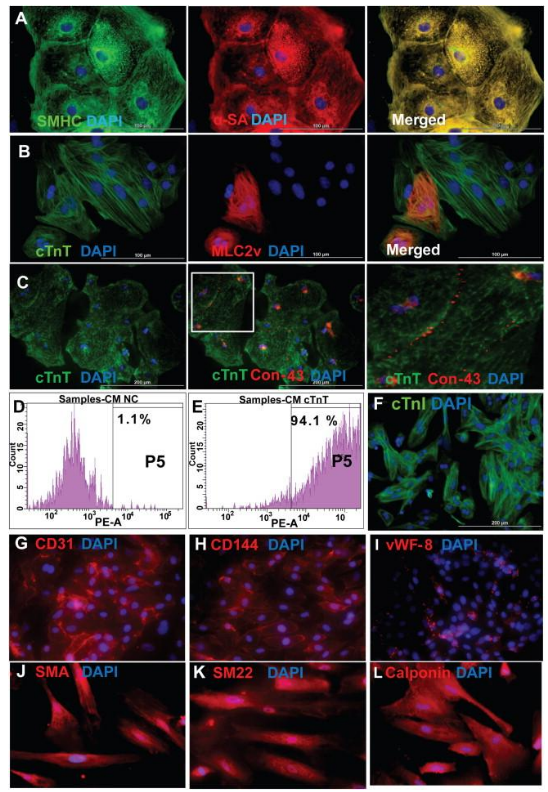
Differentiated iPS



Fibrin scaffold + human iPS

Pigs with ischemia/reperfusion with 1 month of follow up





Cardiac function improvement

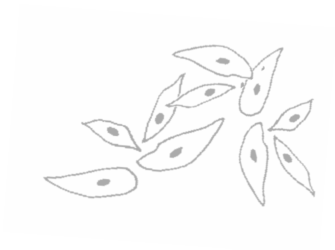
Differentiation of hiPSCs into Cardiac-Lineage CMs, ECs, and SMCs

No arrhythmias

Less apoptosis

Lei Y *et al.* Cell Stem Cell. 2014

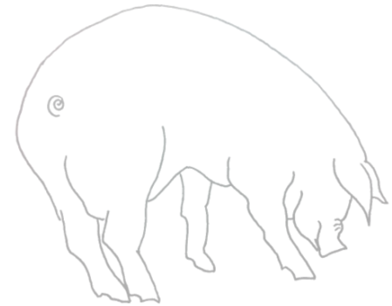
Experimental approaches



Nanowired 3-D cardiac patches

CMPCs electrical stimulation

ATDPCs electrical stimulation



Vascular pericardial flap

Natural scaffolds

The Smart Patch

iPS cells in pericardial scaffolds

Neo-organogenesis

ATDPCs intramyocardial injection

Engineered tissue grafts

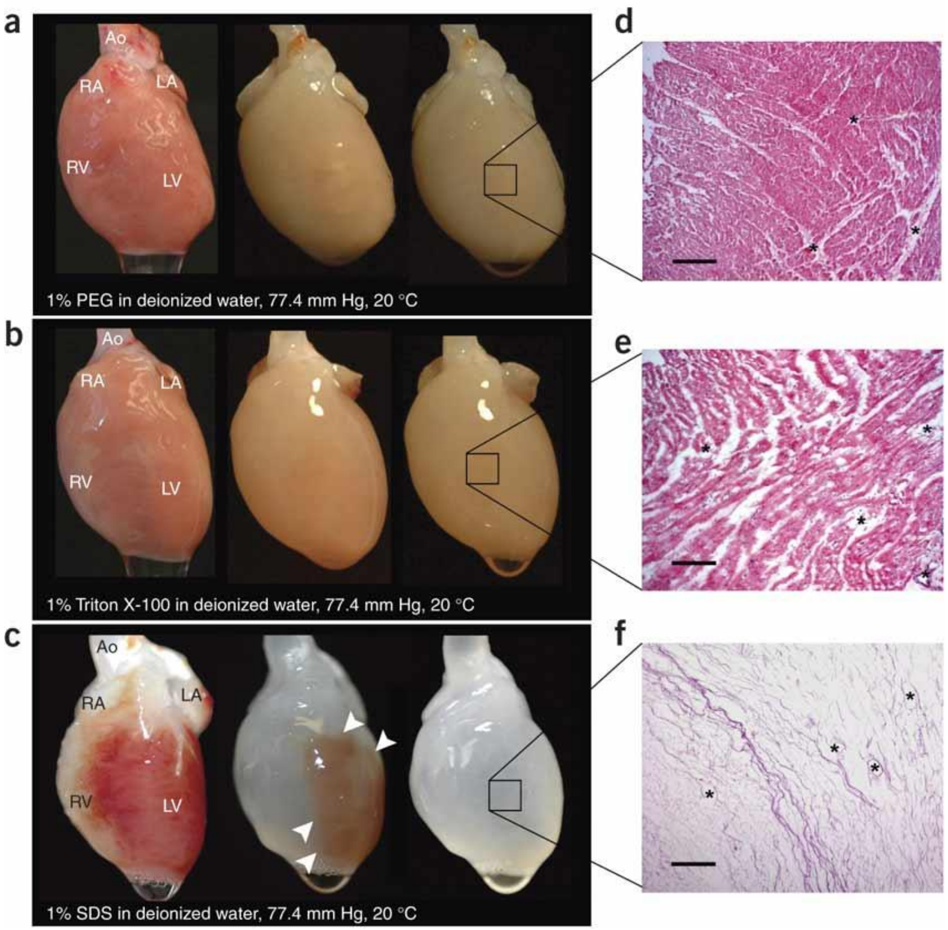
Cardiac ATDPCs within fibrin patch

RECATABI Consortium

FIRST-IN-MAN

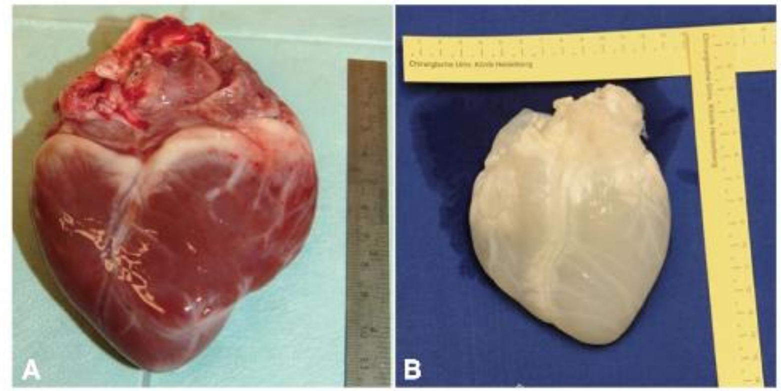
Tissue Engineering for heart muscle

Murine heart

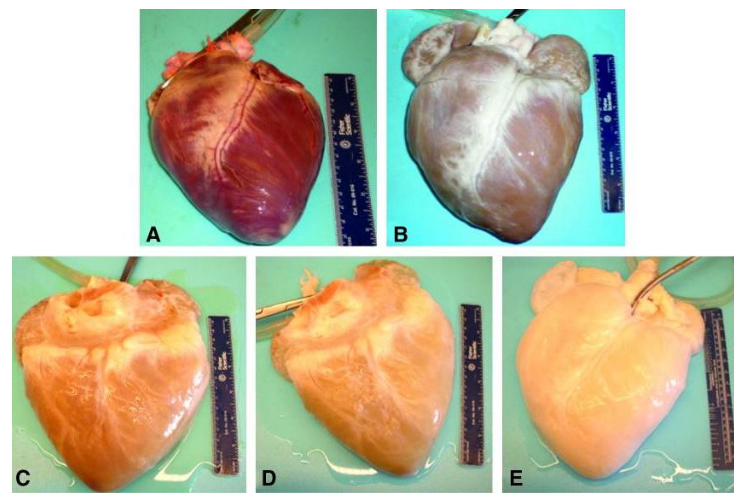


Ott HC *et al. Nat Med.* 2008

Swine heart

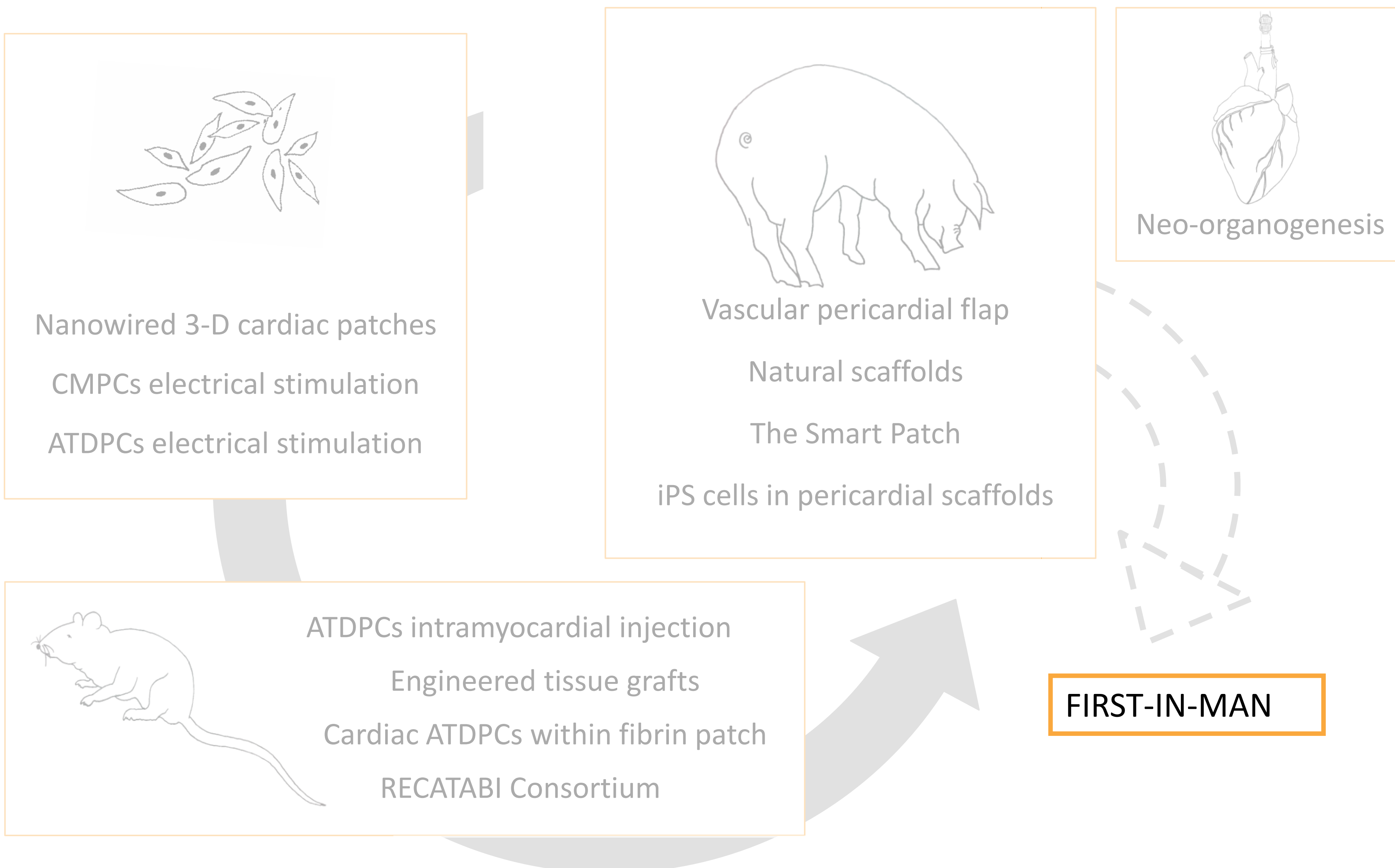


Weymann A *et al.* Circ J 2011



Wainwright JM et al. Tissue Eng Part C Methods 2010

Experimental approaches



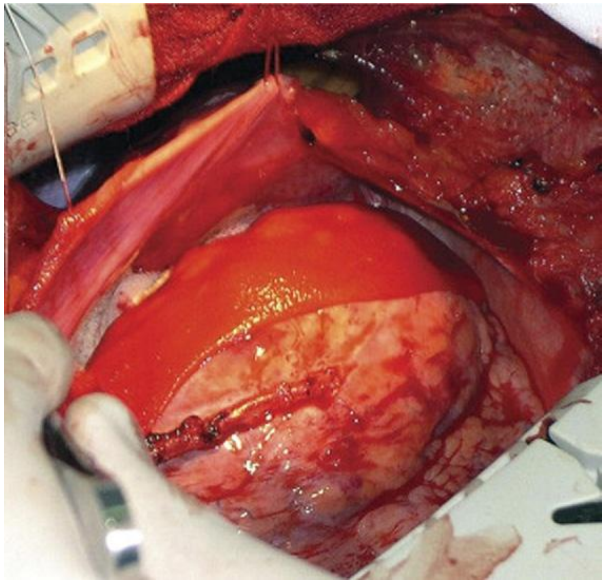
Clinical Trials

FIRST-IN-MAN

MAGNUM Trial

Phase I clinical trial: JC Chachques

Demonstration of safety + efficacy of a
bone marrow cell-seeded collagen matrix patch



Benefit in LVED volume and scar thickness in treated patients

Chachques *JC et al*. Ann Thorac Surg. 2008

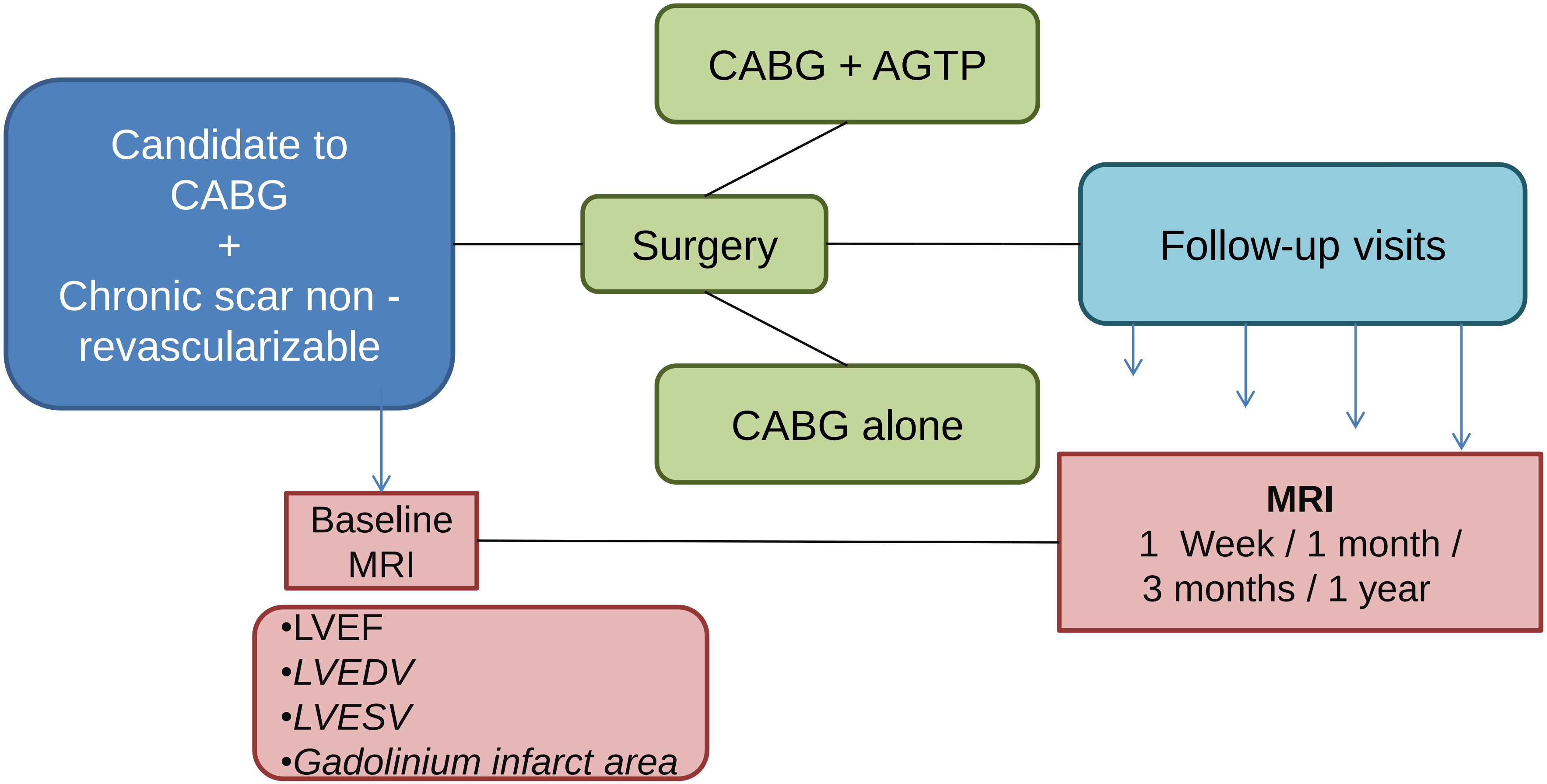
Clinical Trials

FIRST-IN-MAN

AGTP-I Trial

Phase I clinical trial: A Bayes-Genis

Demonstration of safety + efficacy of a pericardial adipose flap transposition

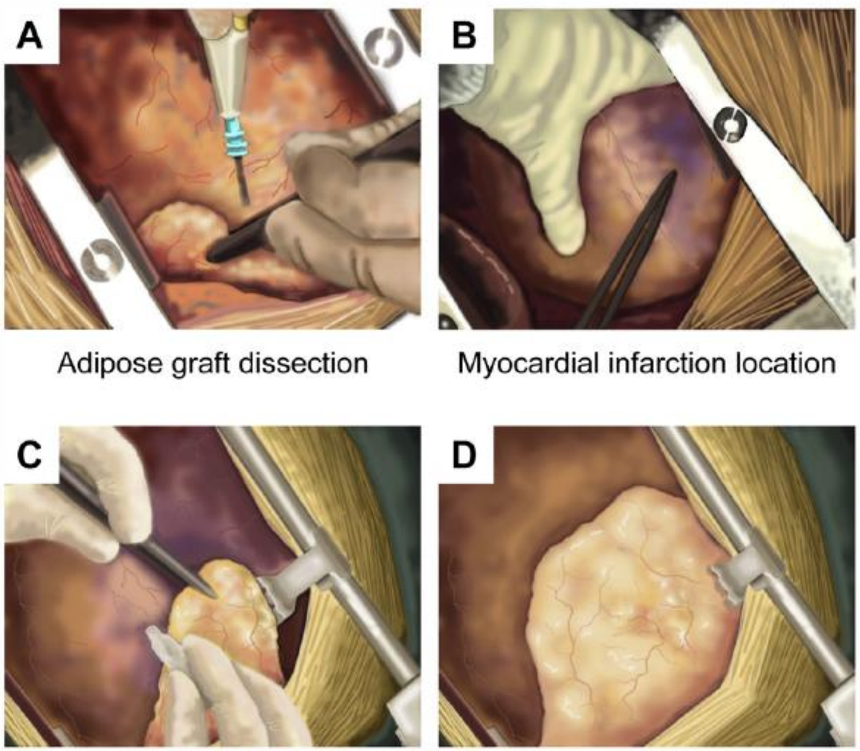


AGTP-1

Research Paper

First-in-man Safety and Efficacy of the Adipose Graft Transposition Procedure (AGTP) in Patients With a Myocardial Scar

Antoni Bayes-Genis [a,b,c,*], Paloma Gastelurrutia [c], Maria-Luisa Cámara [d], Albert Teis [a,e], Josep Lupón [a,b], Cinta Llibre [a], Elisabet Zamora [a], Xavier Alomar [e], Xavier Ruyra [d], Santiago Roura [c,f], Ana Revilla [g], José Alberto San Román [g], Carolina Gálvez-Montón [c]



Adipose graft dissection

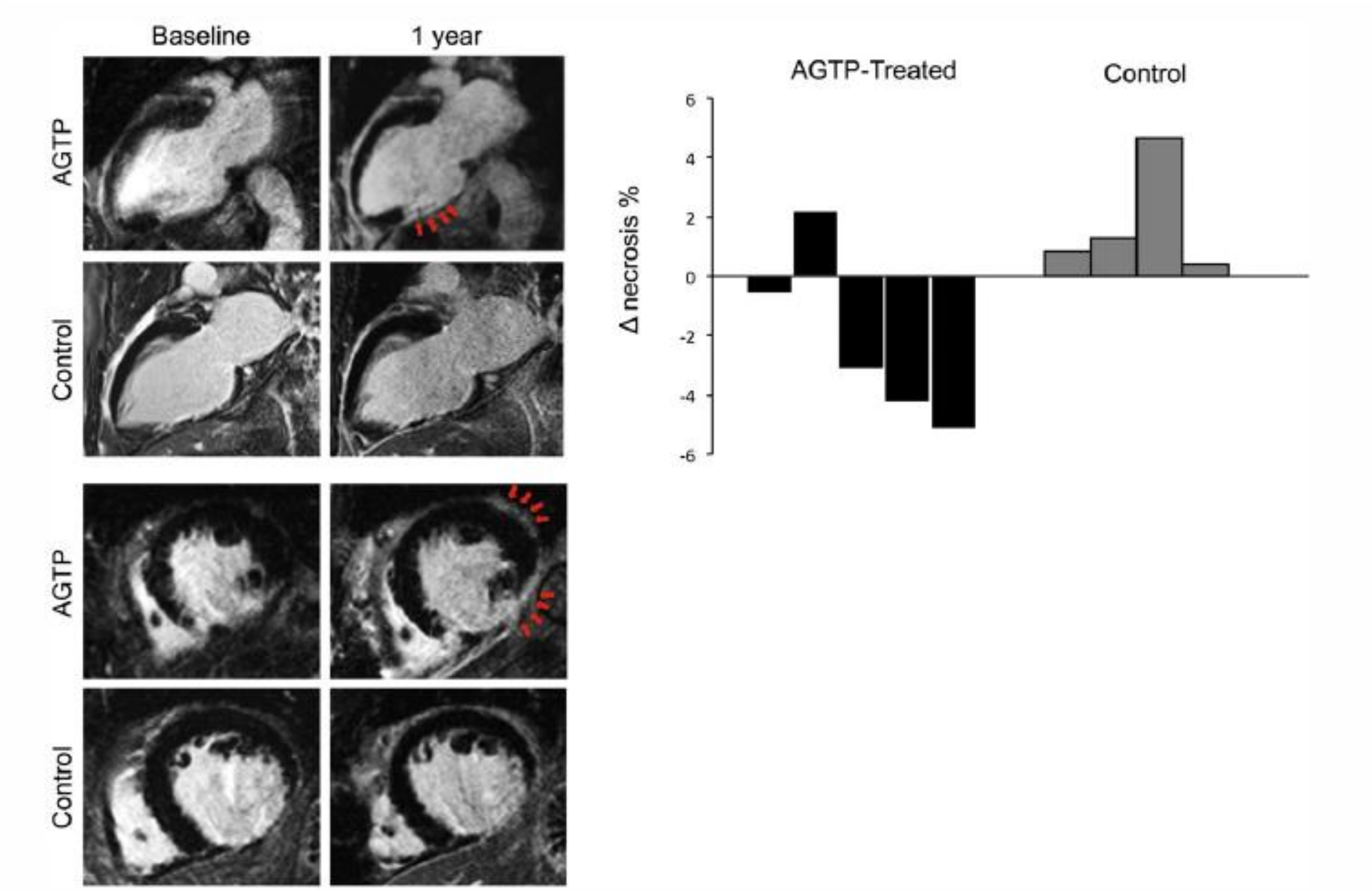
Myocardial infarction location

Adipose graft adhesion

Result

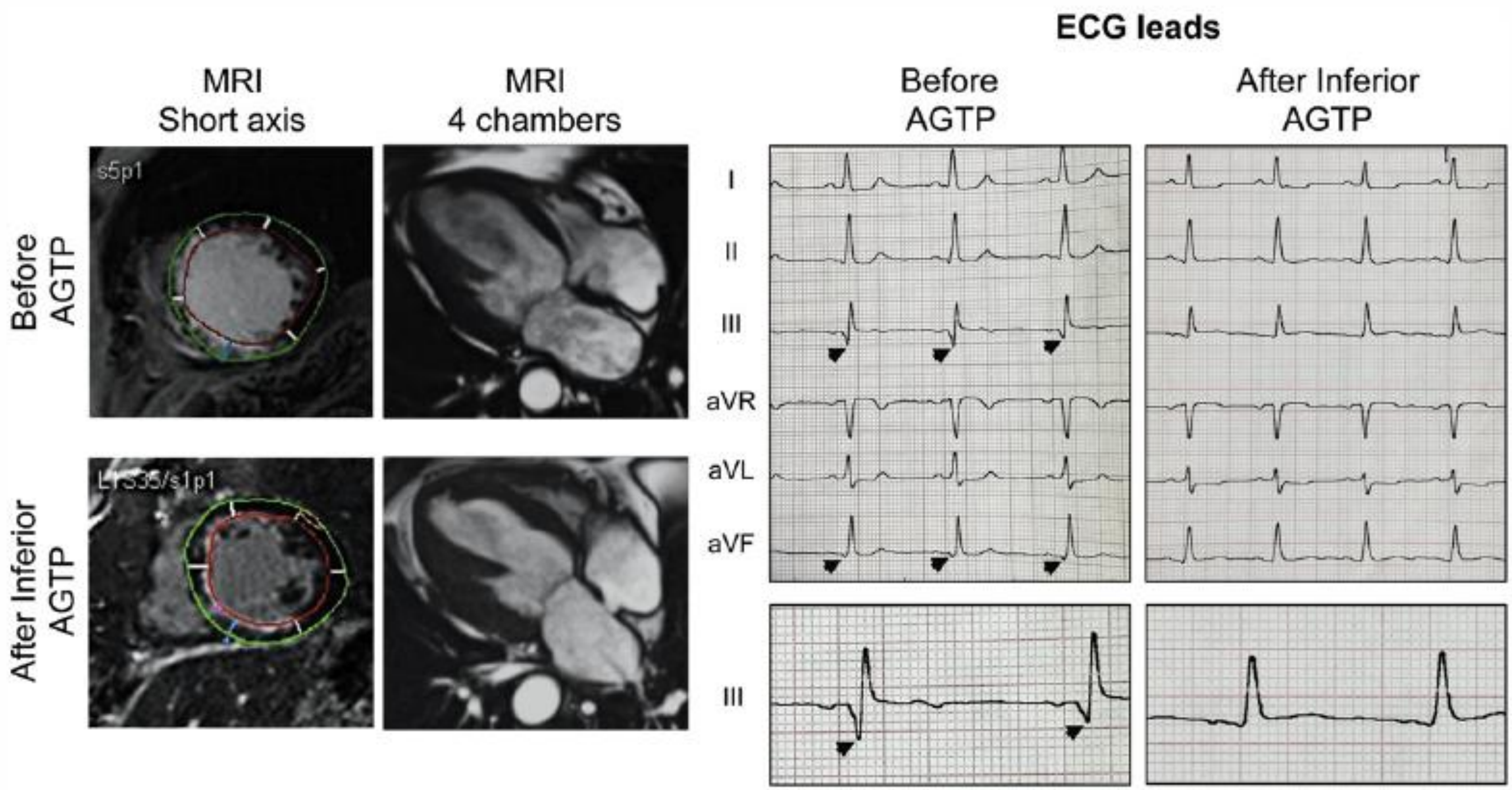
Bayes-Genis A *et al. EBioMedicine.* 2016

AGTP-1



Bayes-Genis A *et al. EBioMedicine.* 2016

AGTP-1



Bayes-Genis A *et al. EBioMedicine.* 2016

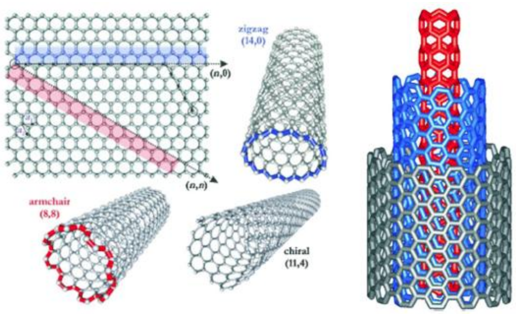
Perspectives

Carbon nanotube scaffolds

Biochemical and mechanical scaffold improvement

Porous structures mimicking natural collagen fibers

- Cell adhesion
- Cell adhesion
- Cell proliferation



Hopley EL *et al*. Biotechnol Avd. 2014.

Cell electrospinning

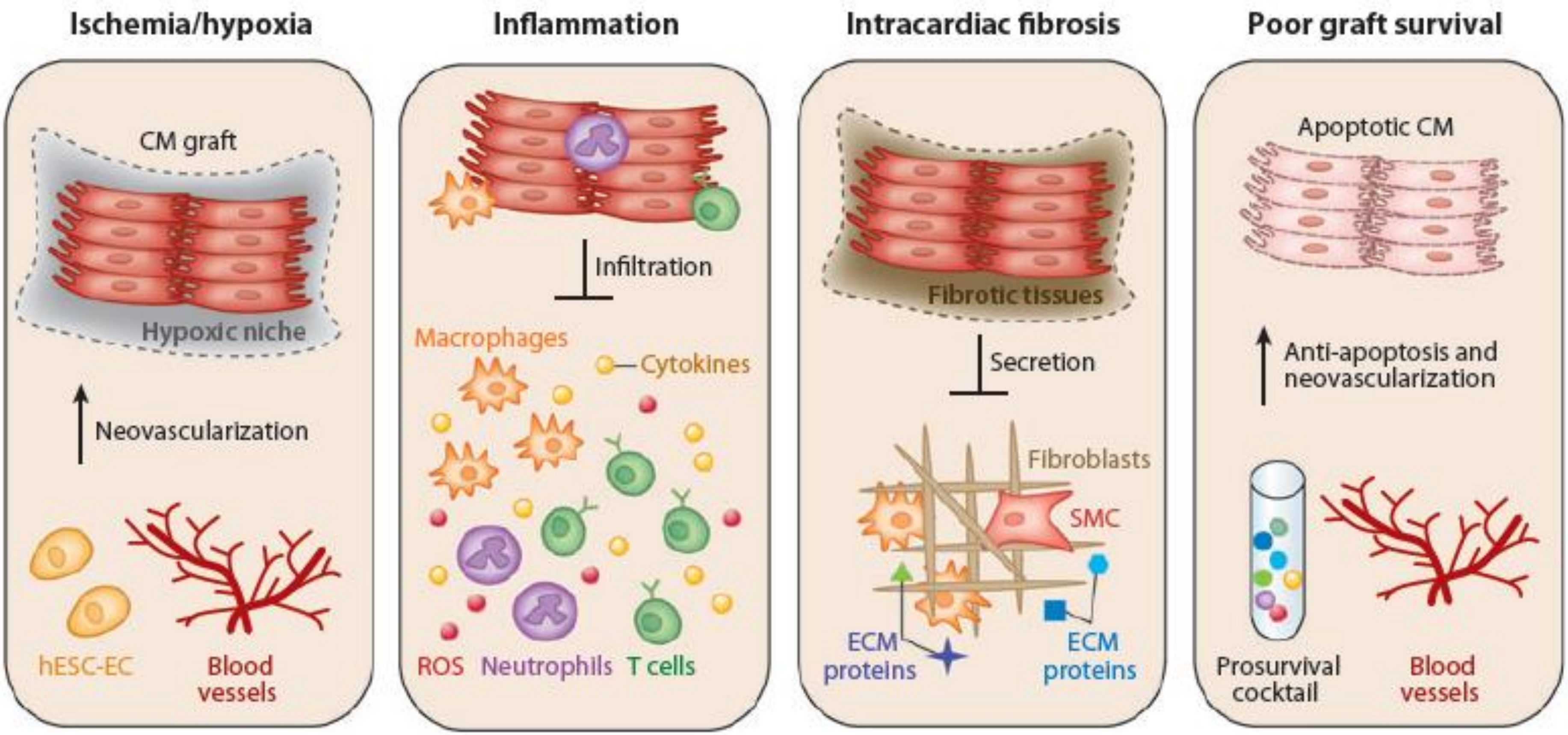
Small and large quantity of cells generating cell-laden fibers and scaffolds

Generation of true architectures having 3D features

To cross-stitch the architecture during the forming stage

Ehler E *et al*. Anlayst. 2014.

Major barriers to cardiac regeneration



Acknowledgements

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Thank you for your attention

THANK YOU