7FP-EU Project RECATABI
(Regeneration of Cardiac Tissue Assisted by Bioactive Implants)

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Heart Attack

- Blood clot
- Artery
- Cholesterol plaque
- Coronary arteries
- Healthy muscle
- Dying muscle

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HEART FAILURE IN EUROPE

• Heart failure is the single biggest reason for acute hospital admission.

• Around 30 million people in Europe have heart failure and its incidence is increasing.

• More people are living to an old age, and more are surviving a heart attack but with damage to the heart.
PREVALENCE of HEART FAILURE in USA
DAVID

Michelangelo

McDonald’s
HEART FAILURE THERAPY

- PHARMACOLOGICAL THERAPY
- EXERCISE TRAINING for CARDIAC REHABILITATION
- CARDIAC PACING for RESYNCHRONIZATION
- VENTRICULAR CONTAINMENT & REDUCTION
- HEART TRANSPLANTATION
- MECHANICAL ASSIST DEVICES, ARTIFICIAL HEART
- ANGIOPGENIC GROWTH FACTORS, GENE THERAPY
- CARDIOMYOPLASTY, AORTOMYOPLASTY
- CELLULAR CARDIOMYOPLASTY, ARTIFICIAL MYOCARDIUM
INDICATIONS FOR STEM CELL THERAPY IN CARDIOLOGY

• LEFT or RIGHT VENTRICULAR INFARCTION

• DILATED CARDIOMYOPATHY & CHAGAS DISEASE

  Injections in left coronary 60% cells, right coronary 40%
Stem Cell Transplantation in affected zones

- RCA
- LCX
- Balloon catheter
- LAD
- Cell flow into the infarcted area
- Migration into the central necrosis
- Border zone
- Syringe containing adult stem cells
CELL THERAPY FOR MYOCARDIAL REGENERATION

**RATIONALE**

CARDIOMYOCYTE PROLIFERATION AFTER MYOCARDIAL INJURY IS LOW

MIGRATION OF STEM CELLS FROM EXTRACARDIAC SOURCE IS LIMITED

STEM CELL TRANSPLANTATION CAN BE USED FOR MYOCARDIAL REGENERATION
CELLS FOR MYOCARDIAL REGENERATION

- Skeletal myoblasts
- Bone marrow mononuclear cells
- Bone marrow mesenchymal cells
- Adipose tissue mesenchymal cells
- Mesothelial cells (from omentum)
- Umbilical cord cells
- Embryonic cells (pluripotents)
- Cardiospheres
Bone marrow or adipose tissue derived mesenchymal stem cells
CELLULAR CMP
MECHANISMS OF ACTION

- Cellular plasticity:
  trans de-differentiation and/or re-differentiation
- Pluripotency
- Fusion with resident cells (Chimerization)
- Paracrine secretion
- Inflammation modulation
Limitations of Cellular Cardiomyoplasty

- Cell bio-retention and engraftment within scar tissue is low
- Mortality of implanted cells in ischemic myocardium is high
- In ischemic heart disease the extracellular matrix is pathologically modified
Rationale for cardiac tissue engineering

Develop a platform for myocardial and extracellular matrix regeneration, i.e.

Cellular cardiomyoplasty + Collagen scaffold grafting
COMPONENTS OF EXTRACELLULAR MATRIX IN HUMAN HEART

Collagen Type I (80%): Structural support, myocyte shape and alignment

Collagen Type III (10%): Role in transduction of myocyte shortening into overall ventricular ejection
CELL NICHE & HOMING

LV Extracellular Matrix

ml : muscular lacunae
cl : capillary lacunae
s : struts
EXTRACELLULAR MATRIX IN ISCHEMIC HEART DISEASE

Collagen Type I: Decreases from 80% to 40%

Collagen Type III: Increases from 10% to 35%

RESULTS: Ventricular remodeling, Dilatation, Systolic and diastolic dysfunctions
COLLAGEN TYPE I MATRIX (Pangen 2, France)
lyophilised, bovine collagen, 5 x 7 x 0.6 cm
BIOARTIFICIAL MYOCARDIUM
« MAGNUM » Clinical Trial

Myocardial Assistance by Grafting a New bioartificial Upgraded Myocardium
Myocardial Assistance by Grafting a New Bioartificial Upgraded Myocardium (MAGNUM Trial): Clinical Feasibility Study

Juan C. Chachques, MD, PhD, Jorge C. Trainini, MD, PhD, Noemi Lago, MD, Miguel Cortes-Morichetti, MD, Olivier Schussler, MD, and Alain Carpentier, MD, PhD

Department of Cardiovascular Surgery, Pompidou Hospital, Paris, France; and Departments of Cardiology and Cardiovascular Surgery, Avellaneda Hospital, Buenos Aires, Argentine

**Background.** Cell transplantation for the regeneration of ischemic myocardium is limited by poor graft viability and low cell retention. In ischemic cardiomyopathy, the extracellular matrix is deeply altered; therefore, it could be important to associate a procedure aiming at regenerating myocardial cells and restoring the extracellular matrix function. We evaluated the feasibility and safety of intracardiac cell therapy associated with a cell-seeded collagen scaffold grafted onto infarcted ventricles.

**Methods.** In 20 consecutive patients presenting with left ventricular postischemic myocardial scars and indication for coronary artery bypass graft surgery, bone marrow cells were implanted during surgery. In the last 10 patients, we added a collagen matrix seeded with bone marrow cells, placed onto the scar.

**Results.** There was no mortality and any related adverse events (follow-up 10 ± 3.5 months). New York Heart Association functional class improved in both groups from 2.3 ± 0.5 to 1.3 ± 0.5 (matrix, p = 0.0002) versus 2.4 ± 0.5 to 1.5 ± 0.5 (no matrix, p = 0.001). Left ventricular end-diastolic volume evolved from 142.4 ± 24.5 mL to 112.9 ± 27.3 mL (matrix, p = 0.02) versus 138.9 ± 36.1 mL to 148.7 ± 41 mL (no matrix, p = 0.57), left ventricular filling deceleration time improved significantly in the matrix group from 162 ± 7 ms to 198 ± 9 ms (p = 0.01) versus the no-matrix group (from 159 ± 5 ms to 167 ± 8 ms, p = 0.07). Scar area thickness progressed from 6 ± 1.4 to 9 mm ± 1.1 mm (matrix, p = 0.005) versus 5 ± 1.5 mm to 6 ± 0.8 mm (no matrix, p = 0.09). Ejection fraction improved in both groups, from 25.3% ± 7.3% to 32% ± 5.4% (matrix, p = 0.03) versus 27.2% ± 6.9% to 34.6% ± 7.3% (no matrix, p = 0.031).

**Conclusions.** This tissue-engineered approach is feasible and safe and appears to improve the efficiency of cellular cardiomyoplasty. The cell-seeded collagen matrix increases the thickness of the infarct scar with viable tissue and helps to normalize cardiac wall stress in injured regions, thus limiting ventricular remodeling and improving diastolic function.

MAGNUM CLINICAL TRIAL
INCLUSION CRITERIA

• LV POSTISCHEMIC MYOCARDIAL SCAR

• LV EJECTION FRACTION < 40 %
Cellular CMP + Cell Seeded Matrix
BONE MARROW ASPIRATION
MATRIX CELL SEEDING

Orbital Shaker: 10 min at 160 RPM
Cell-Matrix Implantation
MAGNUM Clinical Trial

RESULTS

Functional Outcomes: 1 year follow-up
LV Ejection Fraction (%)

Echocardiographic Study

Baseline
End FU

$p = 0.04$
LV End Diastolic Volume (mL)

Echocardiographic Study

Baseline

End FU

$p = 0.03$
LV Filling Deceleration Time (ms)

DIASTOLIC FUNCTION

Echocardiography

Baseline

End FU

p = 0.01
Echocardiographic Study

Scar Area Thickness (mm)

$\text{Baseline}$  $\text{End FU}$

$p = 0.005$
Cellular CMP + Matrix

Radioisotopic SPECT sestamibi studies

Preoperation 12 Months
CONCLUSIONS

- REDUCES THE SIZE AND FIBROSIS OF INFARCT SCARS
- MINIMIZES GLOBAL VENTRICULAR DILATATION
- INCREASES MYOCARDIAL WALL THICKNESS
- INDUCES MODULATION OF EXTRACELLULAR MATRIX
RECOMMENDATIONS

Research & development of cell preconditioning:
Hypoxia (5 %) during cell cultures
*In-vitro* cell electrostimulation

Periodically repeated cell injections if necessary

Association of Tissue Engineering technologies
# Regeneration of Cardiac Tissue Assisted by Bioactive Implants

**RECATABI**

NMP-2008-2.3-1 Advanced implants and bioactive materials for critical organs  
(FP7-NMP-2008-SMALL-2; Small Collaborative Project)

**Proposal No: Stage 1 CP-FP 229239-1**

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RECATA BI Consortia

Project Coordinator: Prof. Carlos E. Semino, IQS-URL, Spain

**Smart Nanomaterials**

Prof. Nicole zur Nieden, Fraunhofer Institute, Leipzig, Germany

**Cell biomechanics, Bioreactors**

Prof. Manuel Monleon, Politécnico de Valencia, Spain

**Smart elastomeric Materials**

Prof. Juan Carlos Chachques, Cardio-Monde, France

**Cardiac surgeon - Big animal model**

Prof. Antoni Bayes-Genis, Hospital Sant Pau, Barcelona, Spain

**Cardiac surgeon - Small animal model**

Dr. Philippe Jenny, CREASPINE Inc., France

**Industrial Partner - Exploitation, Commercialization**
RECATA.BI basic platform
A prototypic synthetic extracellular matrix

- Molecular designed material
- Chemically defined
- Synthetic process
- Highly similarity to natural ECMs
  - Structure: nano-scale fibers
  - Self-assembling process
  - Biologically permissive
  - Non-competition with natural ECM
  - Biodegradable
- Mechanical properties for soft tissues
- Modification control Building up properties
- Transient scaffold
- Injecting biological material
Generic peptide sequence

8-16 amino-acids

\[
\text{AcN-} \overset{+}{\begin{array}{cccccccc} & + & - & + & - & + & - & + & - \\ H & H & H & H & H & H & H & H & H \\
\end{array}} \text{CONH}_2
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RAD16-I: PuraMatrix (BD)

\[
\text{AcN-RADARADARADARADA-CONH}_2
\]

\[
\text{H H H H H H H H H H}
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R=Arg; A=Ala; D=Asp. acid
AcN- CONH₂

H H H H H H H H H H H

Hydrophobic

Hydrophilic

\( \beta \)-sheet tape: a single molecule thick

“Self-assembling”

A generic peptide scaffold network

Peptide nanofibers = 10-20 nm
Scaffold pore size = 50-200 nm
Peptide Scaffold allows cell cluster formation

Nanofiber = “Clear gels”
“RAD16-I nanofibers”

• Genové et al, 2005
Micro-Elastomeric Scaffold
(biome mechanics)
+
Nanometric Scaffold
(cell network, signaling)
RECATABI Group

Mar
Cris
Núria
Tere
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