COST ACTION BIONECA

WG5 - Heart Diseases

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Definition of Heart Failure

1. A condition in which the heart is unable to pump blood at an adequate rate or in adequate volume

2. Cessation of heartbeat : Death

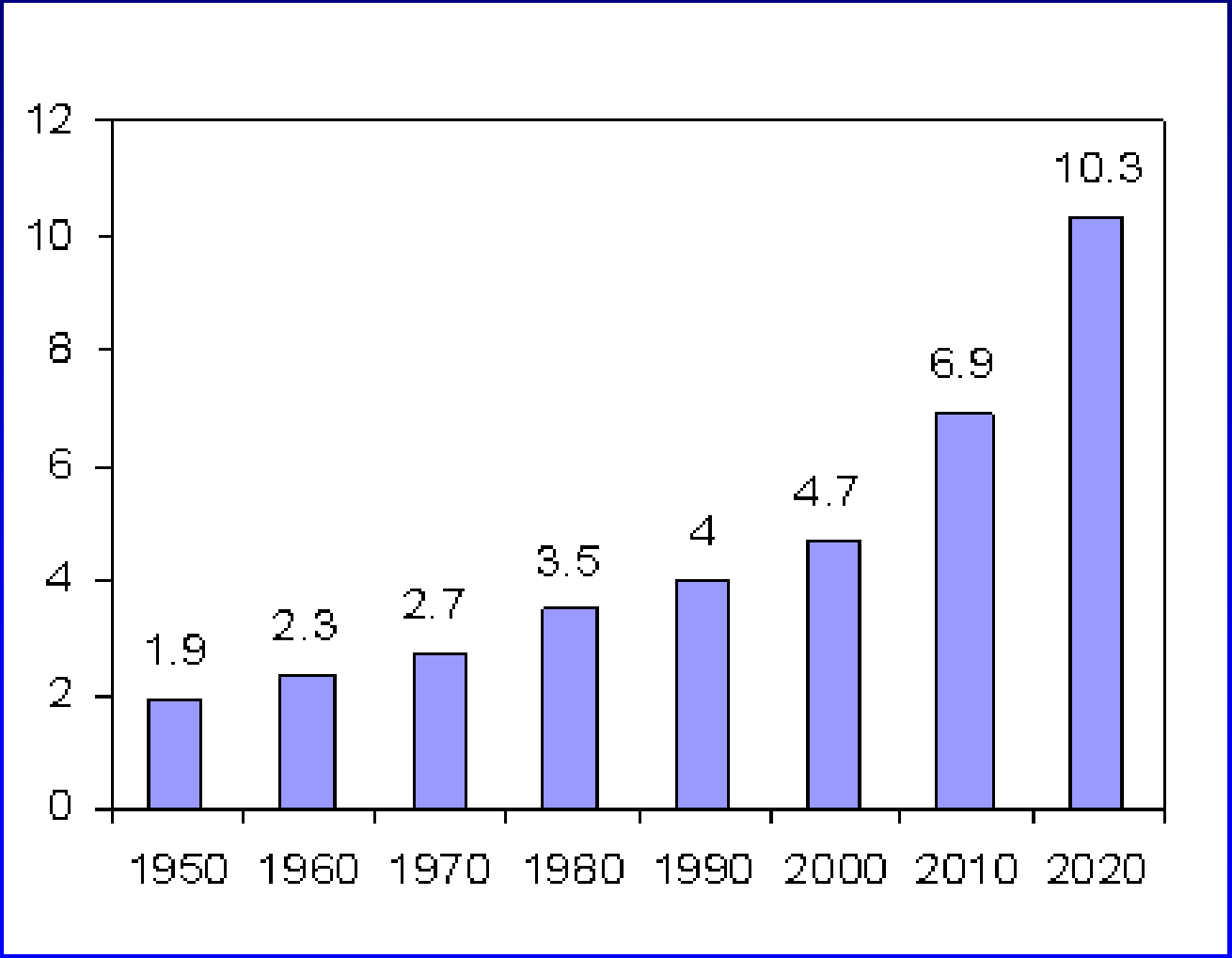
HEART FAILURE IN EUROPE

Total population 750 millions

- Around 14 million people in Europe have heart failure and its incidence is increasing (expected 30 million in 2020)
- 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

(total population: 320 millions)



ETIOLOGY OF HEART FAILURE

- CORONARY ARTERIOSCLEROSIS
- MYOCARDIAL INFARCTION
- CARDIOMYOPATHIES ischemic & non-ischemic : idiopathic, viral, toxic, trypanosomic
- HEART VALVE DISEASES
- CONGENITAL CARDIAC DISEASES

Heart Failure (HF) treatments

- Current medical and surgical treatments can help alleviate the symptoms of HF, they do not restore contractile function to injured myocardium

- Emerging biological (cell transplantation) and mechanical therapies (assist devices) show promise for post-MI repair, but functional benefits appear modest

- Clearly, there is an urgent need to develop novel treatment strategies for post-MI repair of the heart

RISK FACTORS FOR CARDIOVASCULAR DISEASES

- ARTERIAL HYPERTENSION
- STRESS
- DIABETES
- HYPERCHOLESTEROLEMIA
- OBESITY
- SEDENTARY LIFE
- TOBACCO
- GENETIC - FAMILIAL
- ALCOHOL - TOXINS

WG5 PLANS

- **Increase the incorporation of BIONECA members interested in cardiac biology, physiology and pathology.**

- **Interdisciplinary cooperation with emerging technologies : Extracellular Vesicles (ECVs).**

  Neuropatch for Pain and Cancer therapy.

  Vitriorgans Bank - Longevity & Cryopreservation.

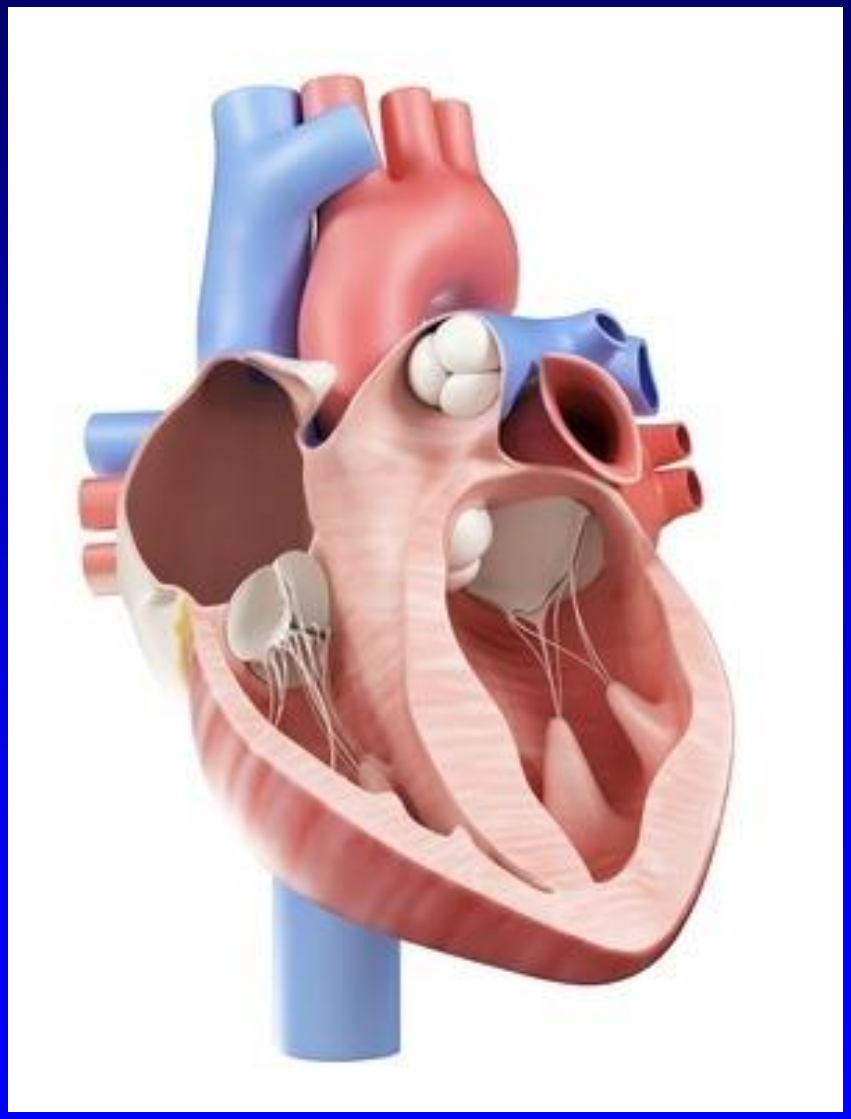
  Risks of Cardiac Device Hacking: pacemakers, defibrilators, vulnerable remote-monitoring networks, artificial heart.

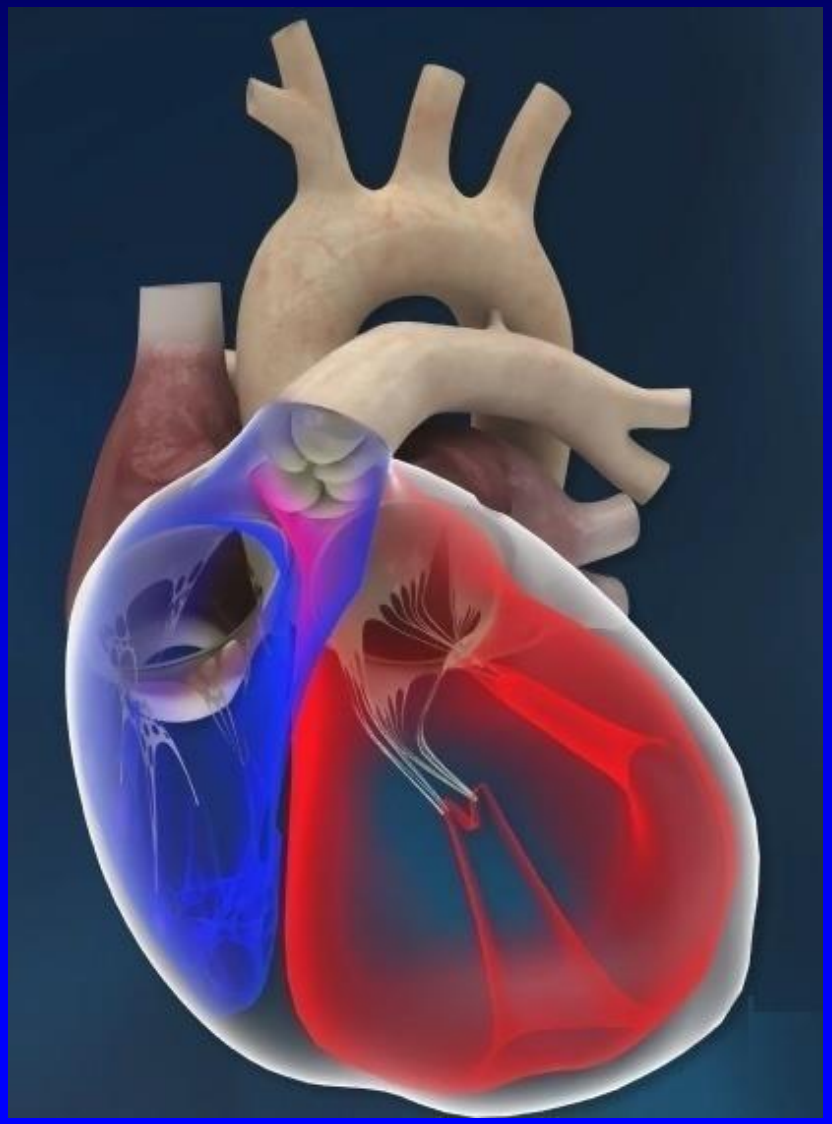
VENTRICULAR REMODELING IN CHRONIC HEART FAILURE

- Cardiomyopathy induces geometric remodeling of ventricular cavities, which change from a natural elliptical (conical) shape to a spherical shape

- Ventricular chamber dilatation and spherical deformation are important causes of morbidity and mortality of patients with congestive heart failure

Spherical Shape in Heart Failure





HEART FAILURE THERAPY

PHARMACOLOGICAL THERAPY

EXERCISE TRAINING for CARDIAC REHABILITATION

CARDIAC PACING for RESYNCHRONIZATION

CORONARY ARTERY BYPASS GRAFT (CABG)

VENTRICULAR CONSTRAINT, REDUCTION, RECONSTRUCTION

CARDIOMYOPLASTY, AORTOMYOPLASTY

CELLULAR CARDIOMYOPLASTY, ARTIFICIAL MYOCARDIUM

HEART TRANSPLANTATION

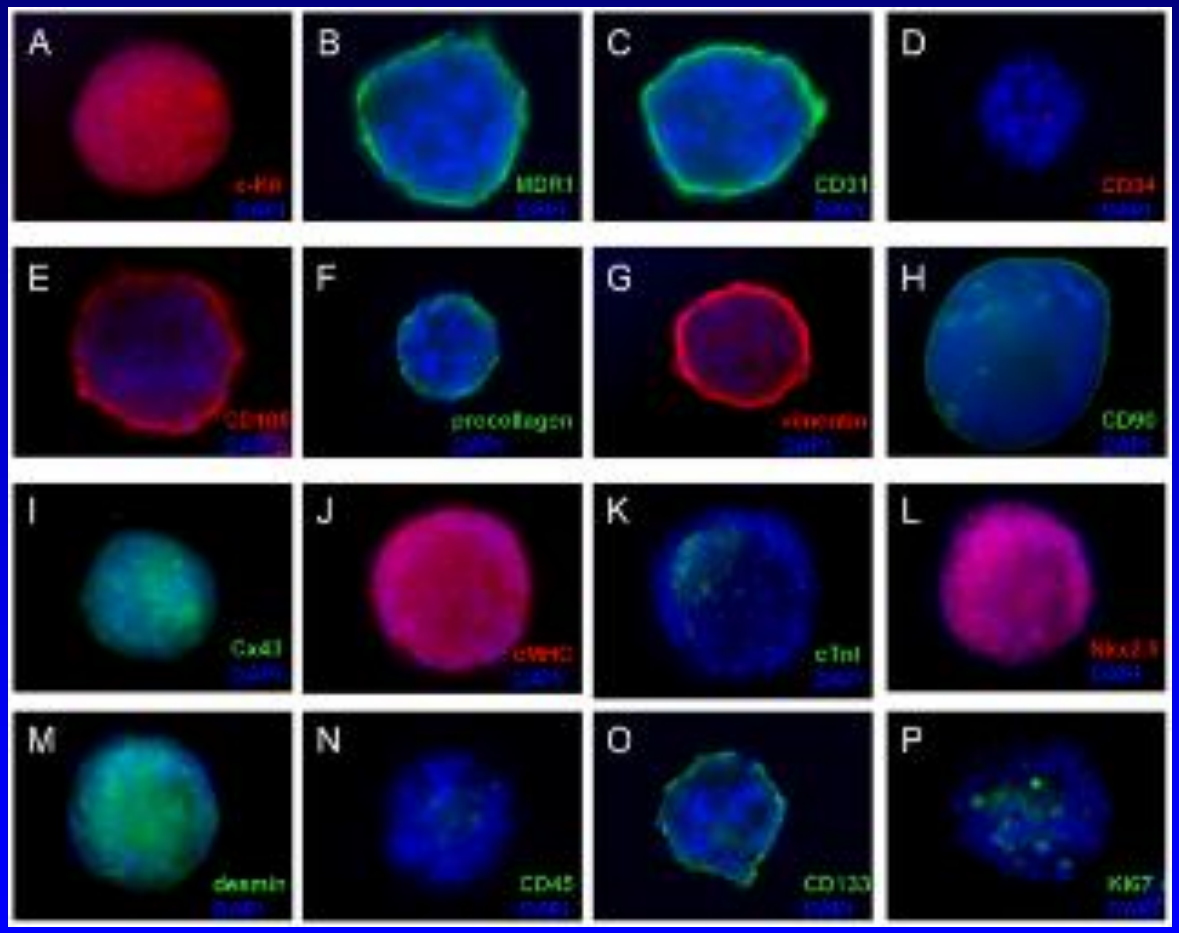
MECHANICAL ASSIST DEVICES, ARTIFICIAL HEART

CELLS FOR MYOCARDIAL REGENERATION

- Cardiospheres
- Adipose tissue mesenchyml stem cells
- Bone marrow mesenchymal cells
- Bone marrow mononuclear cells
- Umbilical cord cells
- Embryonic cells (pluripotents)
- Induced Pluripotent Stem Cells (iPSCs)
- Skeletal myoblasts
- Mesothelial cells (from epiploon)
- Human amniotic fluid stem cells
- Extracellular Vesicles, Exosomes

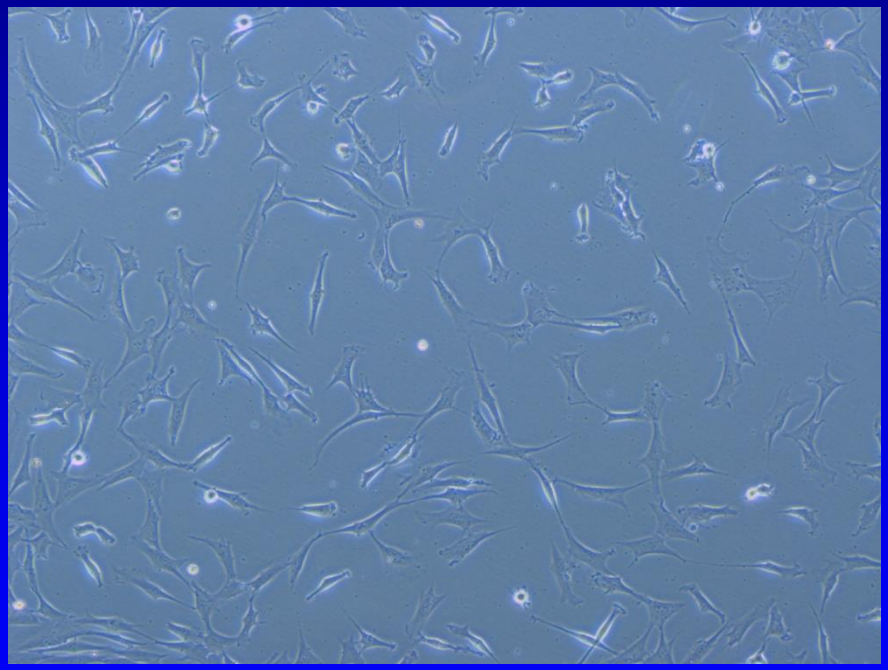
ORGANOIDS

3D Cardiosphere immunostained for 16 different cardiac-related antigens



Adipose Derived Mesenchymal Stem Cells

Isolated from Liposuction



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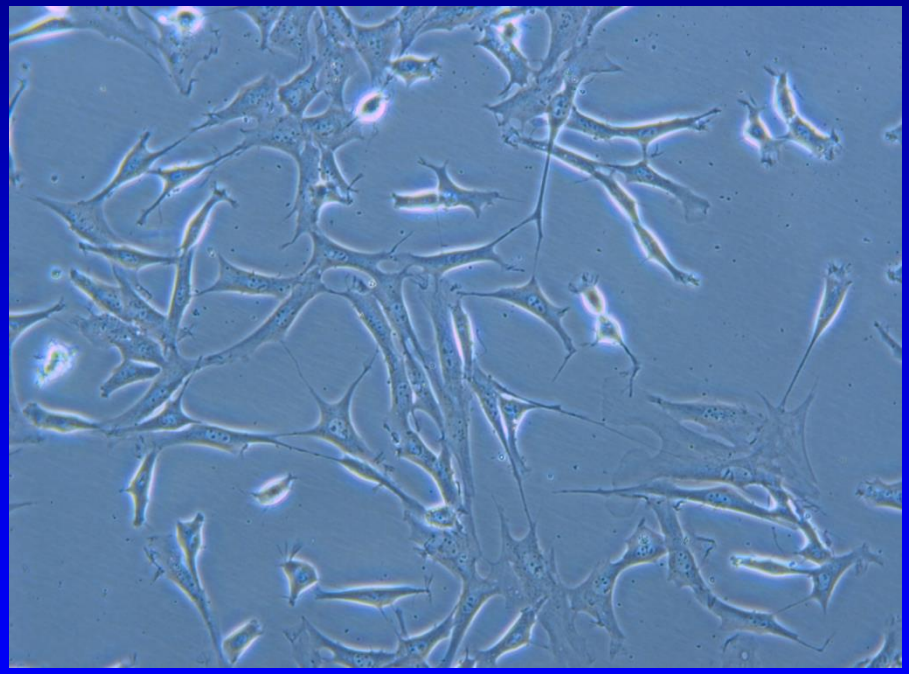

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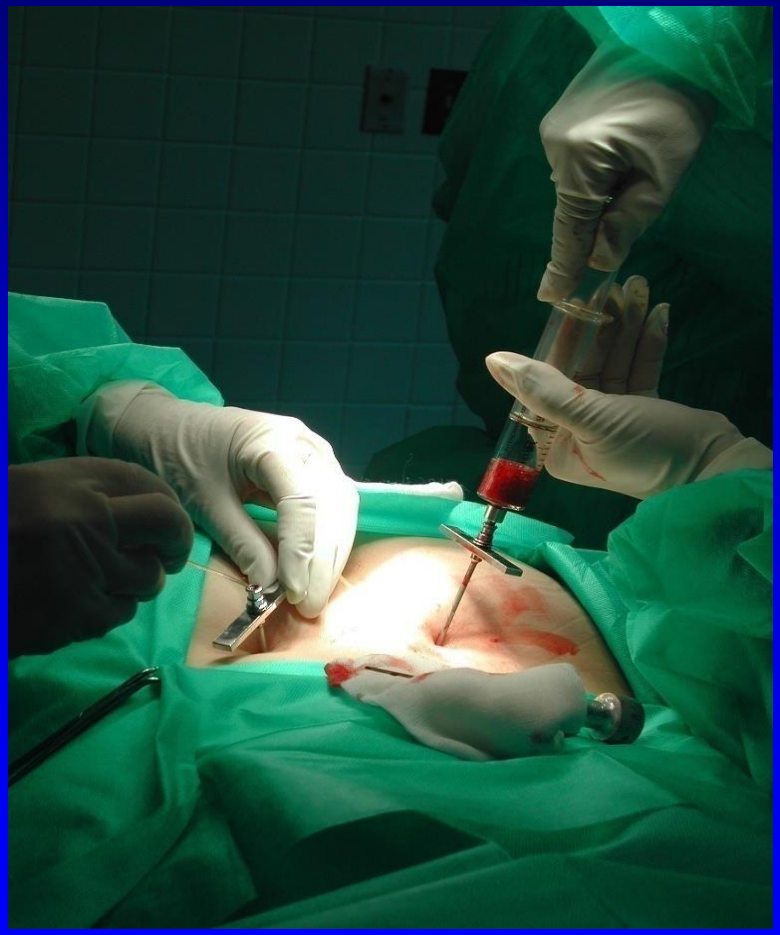
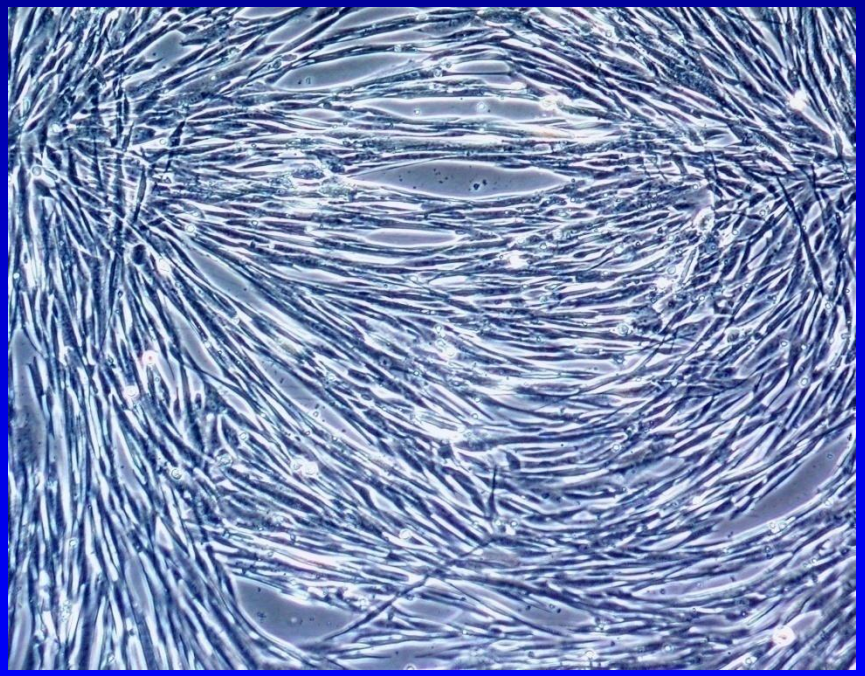
BONE MARROW ASPIRATION

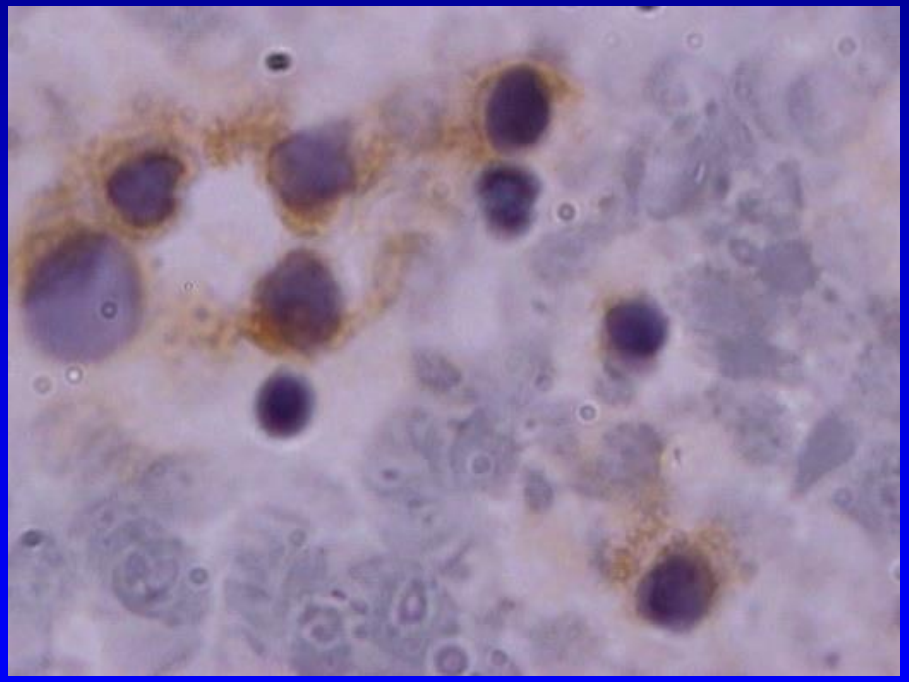


SKELETAL MUSCLE BIOPSY & MYOBLAST CULTURE

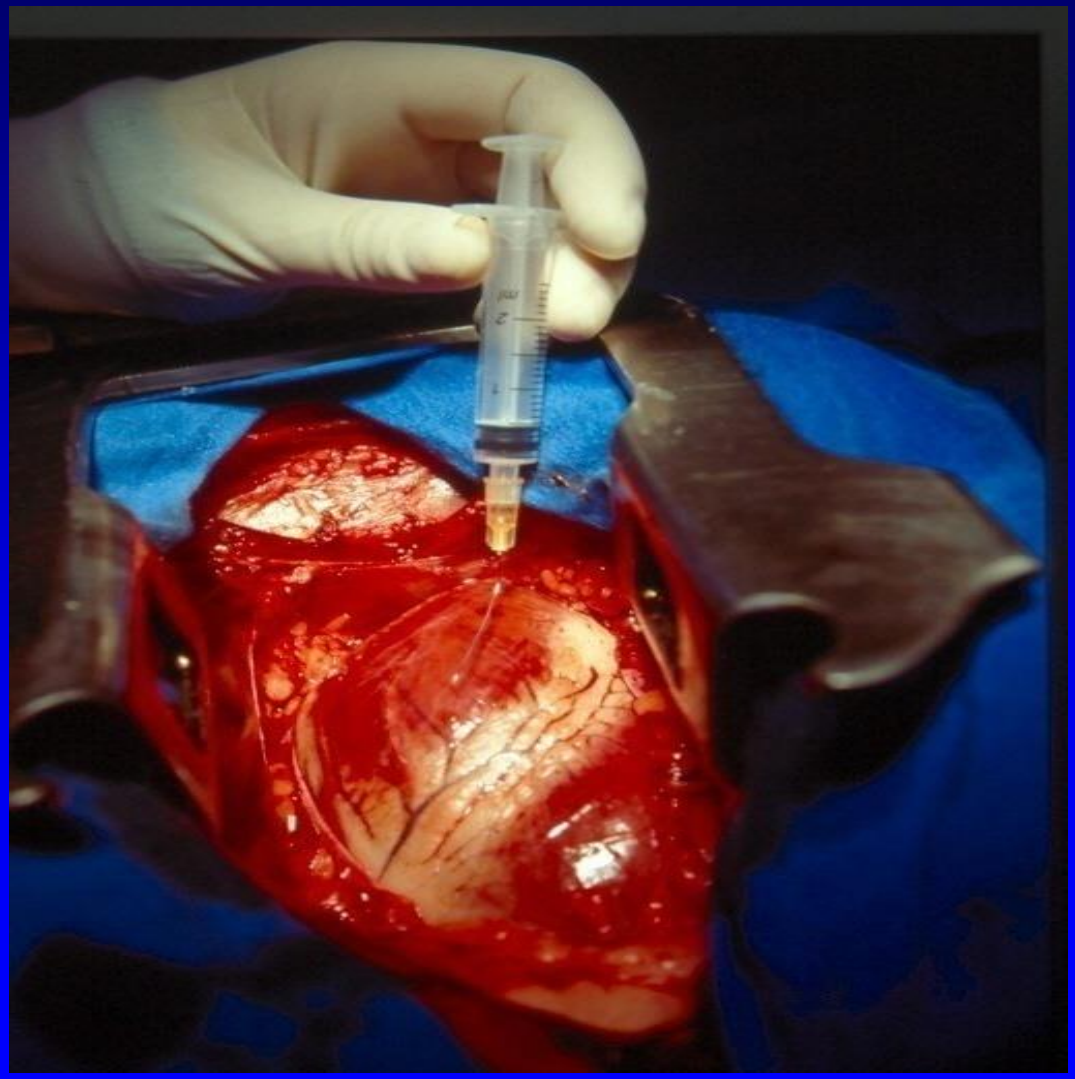
Skeletal myoblasts



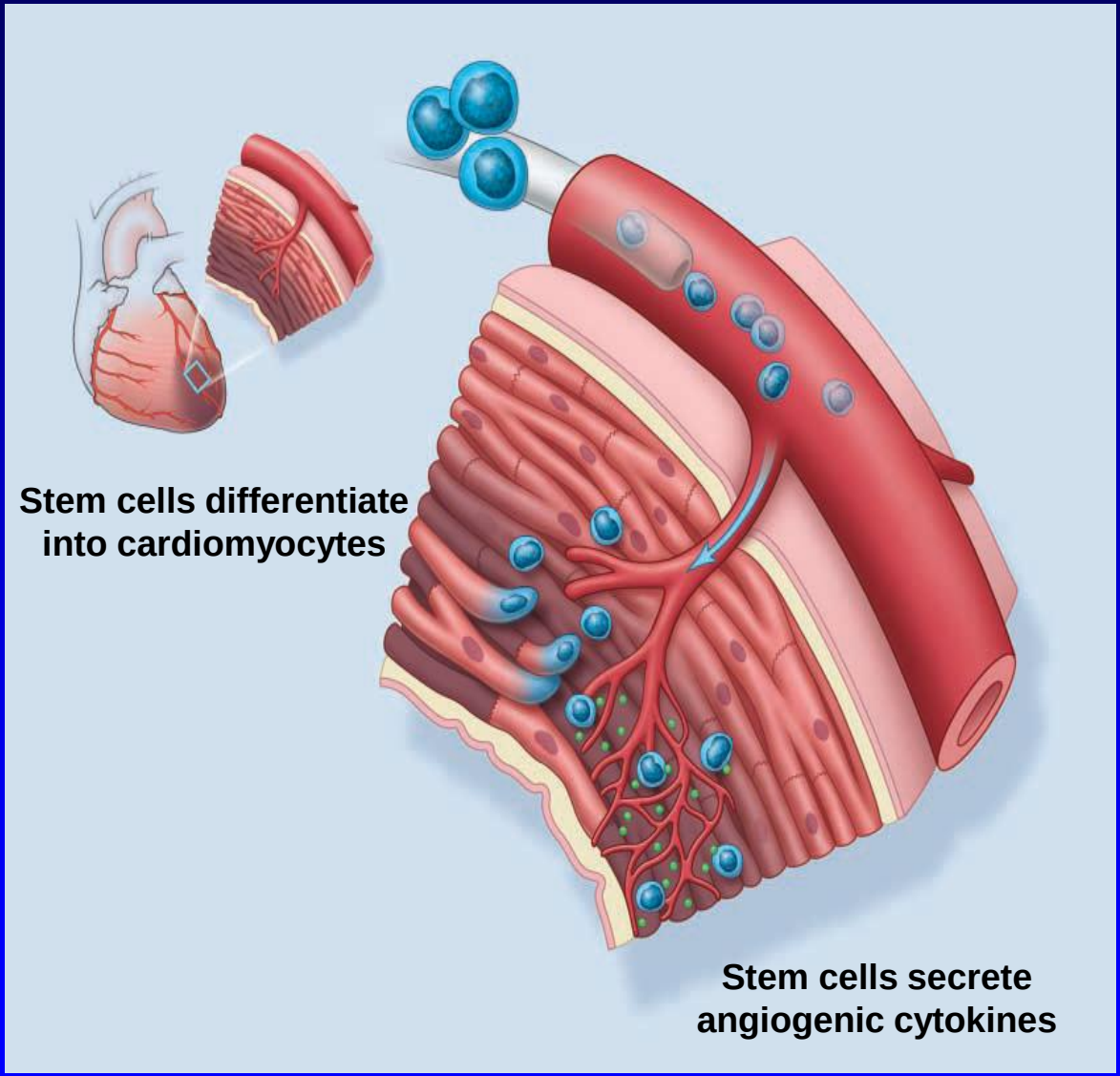
Bone marrow cells



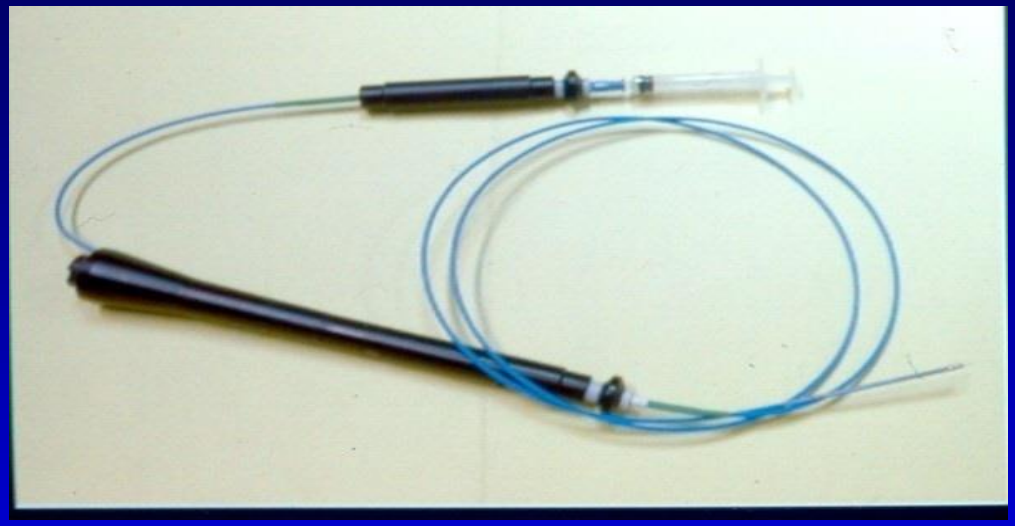
SURGICAL CELL IMPLANTATION



Intracoronary Stem Cell Therapy

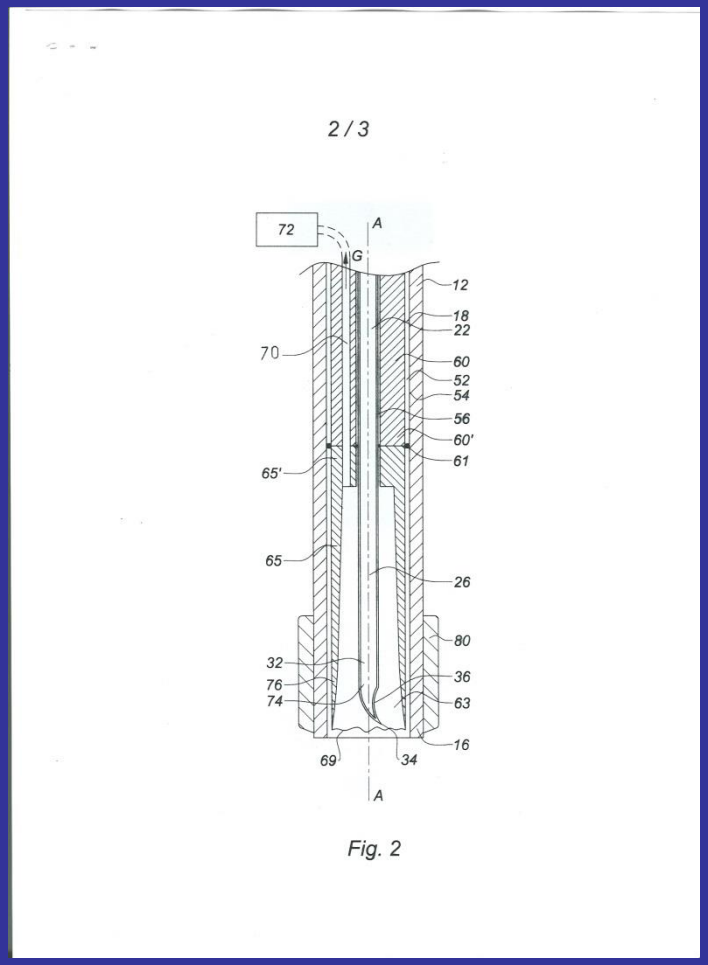


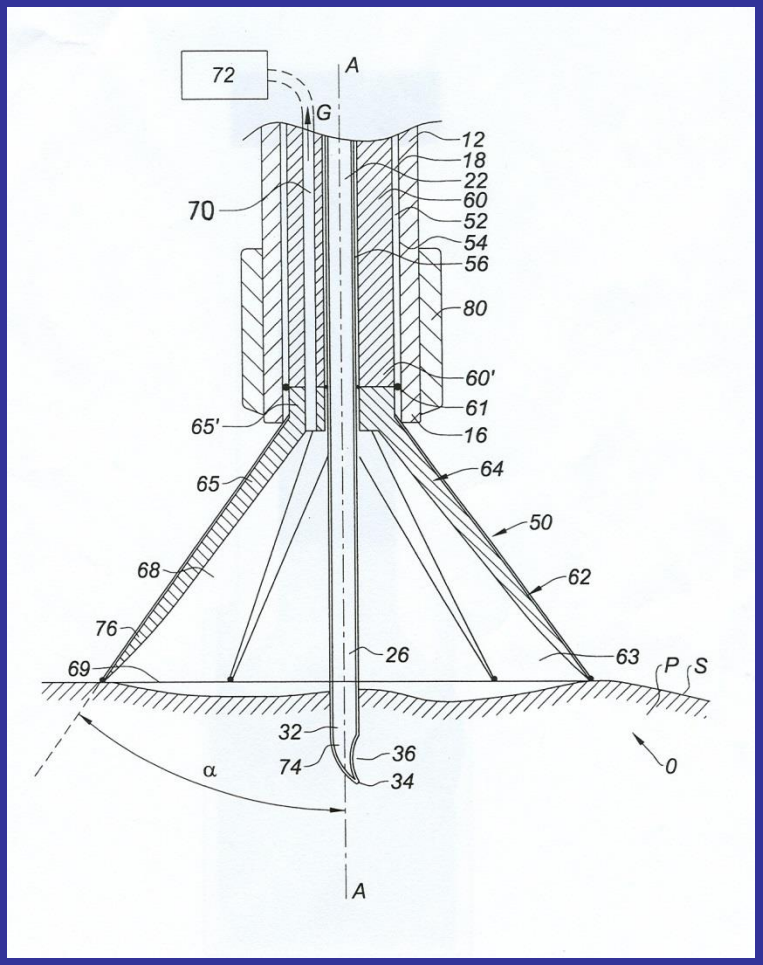
CATHETER FOR ENDOVENTRICULAR CELL DELIVERY



CATHETER - ELECTRODE

stabilizing by vacuum the infarct area





LIMITS OF CELLULAR CARDIOMYOPLASTY

- Results of cardiac cell therapy show low cell engraftment and low bio-retention
- Myocardial tissue engineering represents a cell delivery platform replacing extracellular matrix

IN VITRO & IN VIVO

TISSUE ENGINEERING

“ the body as a living bioreactor ”

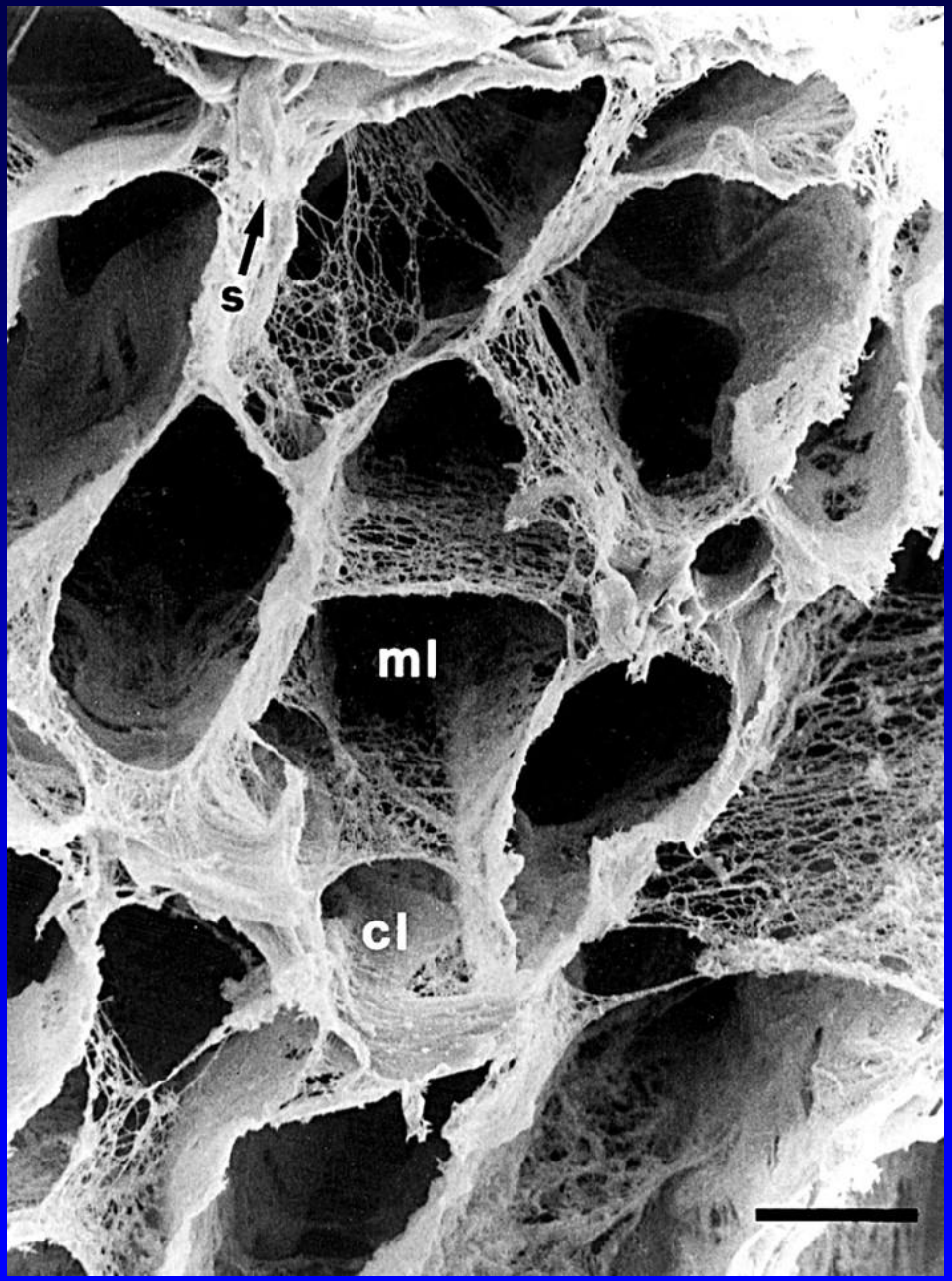
Cardiopatch - Rationale

- Biomimetic extracellular matrix
- Porous nanomaterial for safe cell homing
- Cellular niches with hydrogel, alginates, peptides.
- Nanoreservoirs:

  angiogenic growth factors and antiapoptotic products

Benefits

Long term local treatment with bioactive products



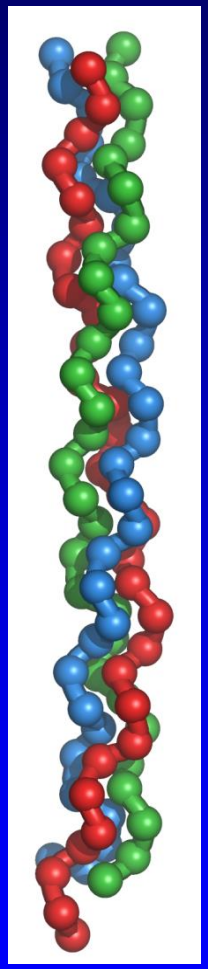
Heart extracellular matrix

Cell niche + cell homing

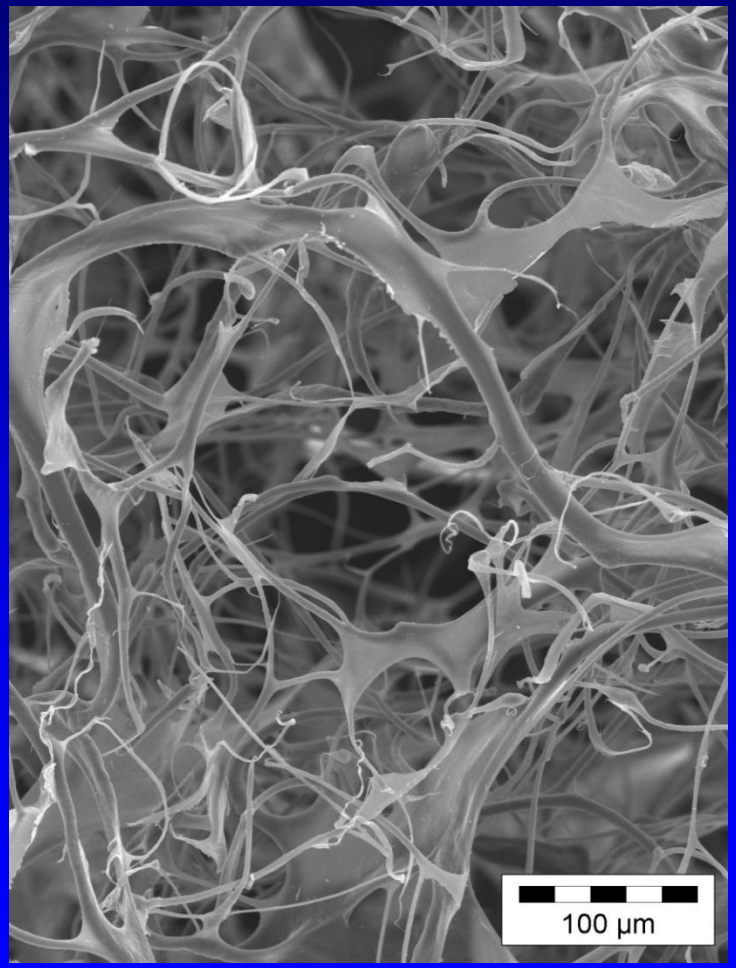
ml : muscular lacunae

cl : capillary lacunae

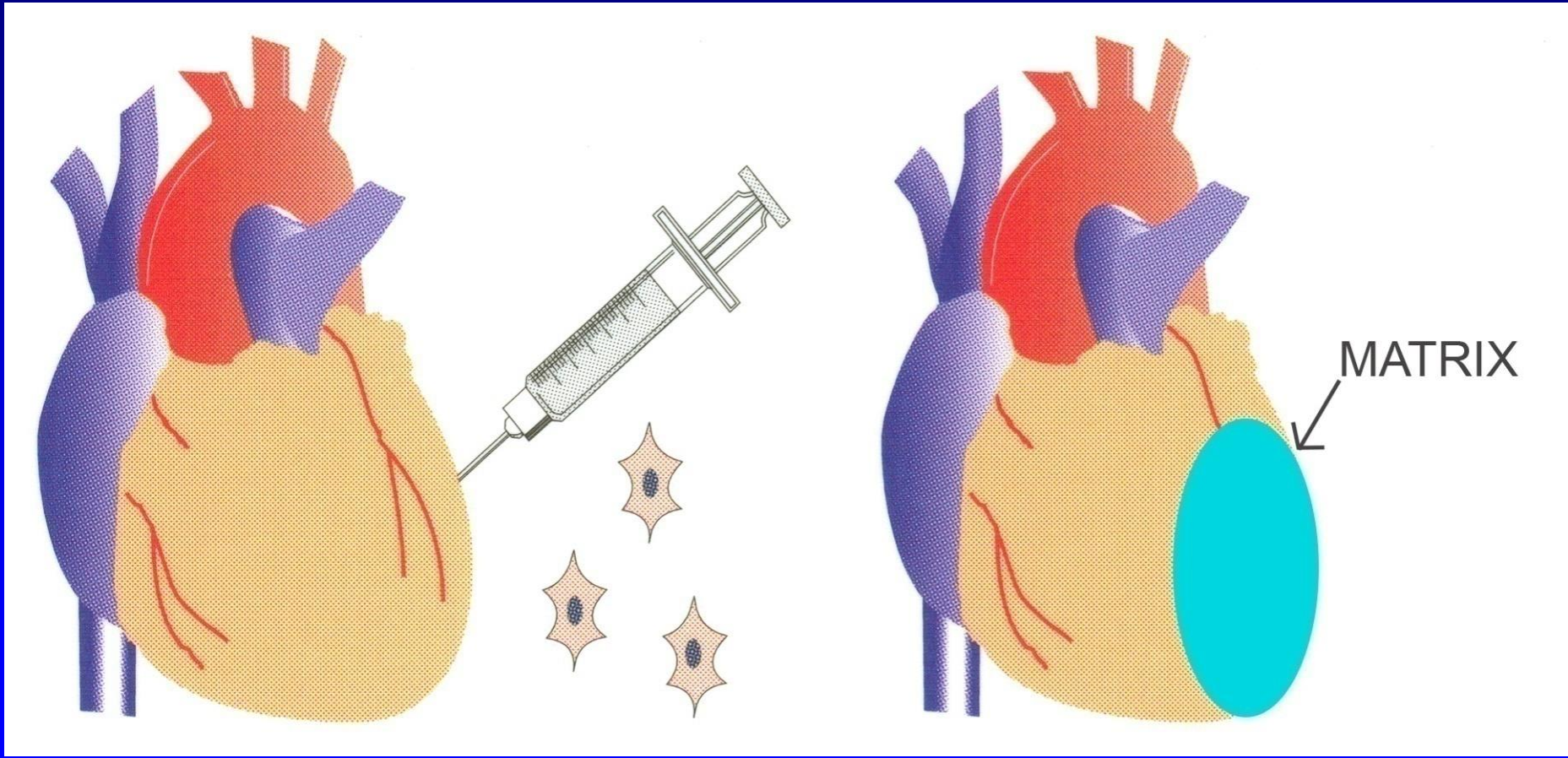
COLLAGEN TYPE I MATRIX (Pangen 2, France)
lyophilised, bovine collagen, 5 x 7 x 0.6 cm



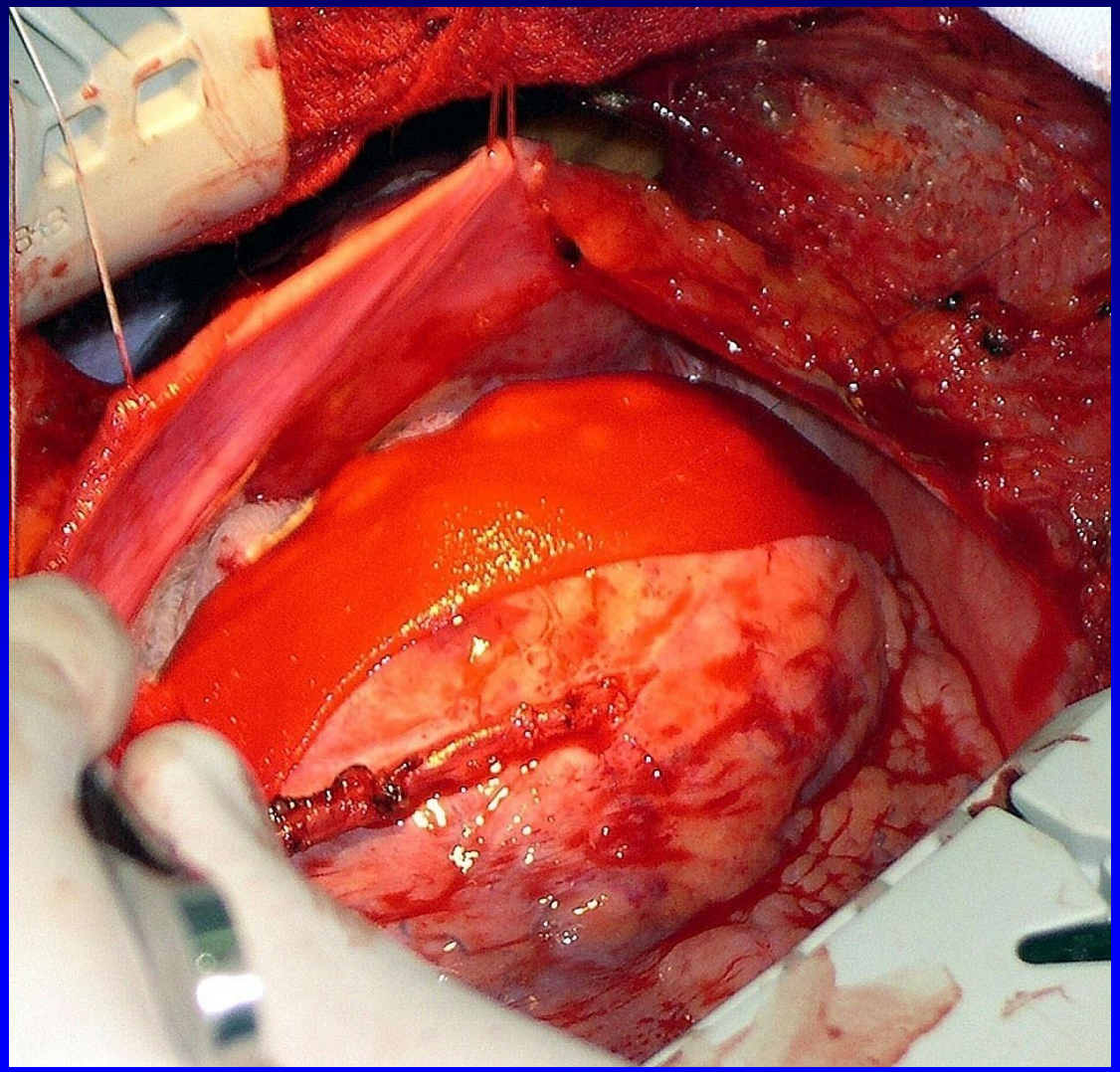
Collagen
triple helix



Stem cell injections + Collagen matrix with cells



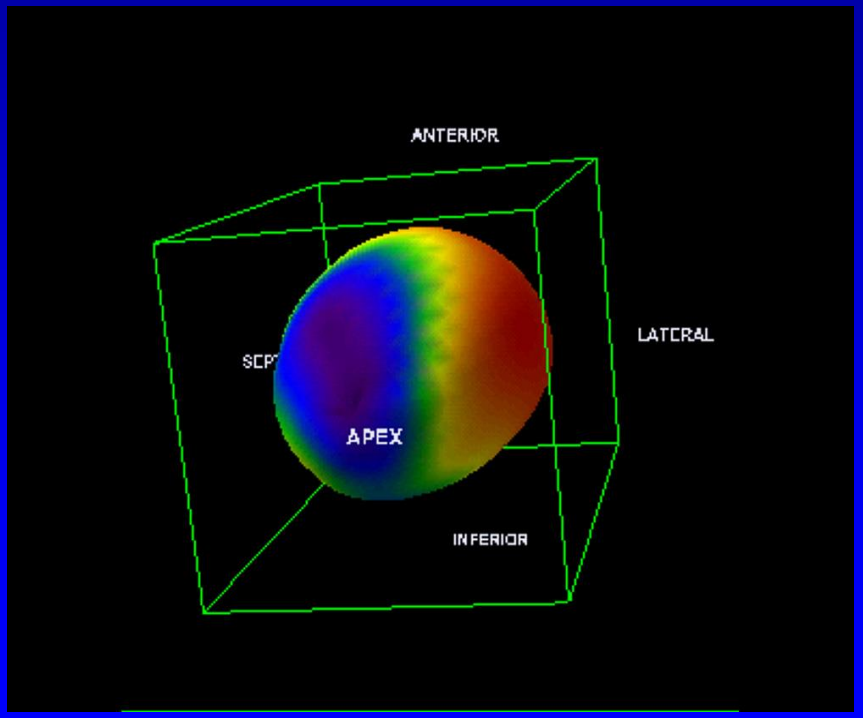
Collagen scaffold implantation in patients



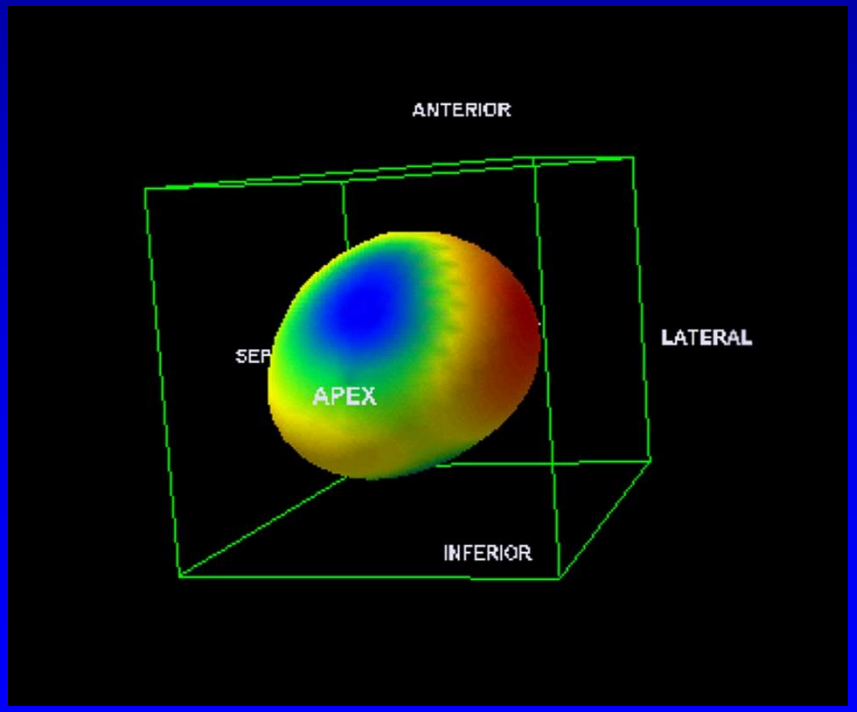
Cellular CMP + Matrix

Radioisotopic SPECT studies

Preop



12 Months



Cardiac Tissue Enginering: 1st World Clinical Trial

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

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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 intrainfarct 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.

(Ann Thorac Surg 2008;85:901–8)

COLLAGEN SCAFFOLD DRAWBACKS

The main disadvantages of collagen scaffolds are the low mechanical characteristics of the materials and the fast bioresorption rate

BIOMIMETIC DEVELOPMENTS

Elastomeric porous scaffolds to create extracellular matrix associated with hydrogels (alginates from marine algae, nanoscale peptides)

RECATABI PROJECT 2010-2014

European Union (France + Germany + Spain)

Regeneration of Cardiac Tissue Assisted by Bioactive Implants

ELASTOMERS

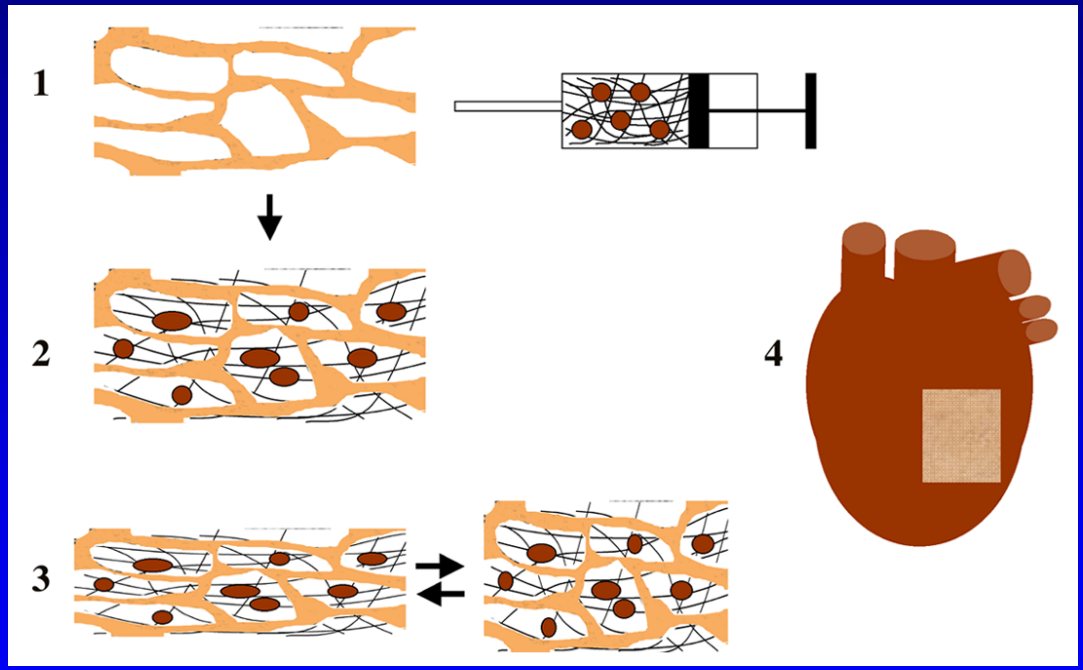
+

Self - assembling

PEPTIDES *

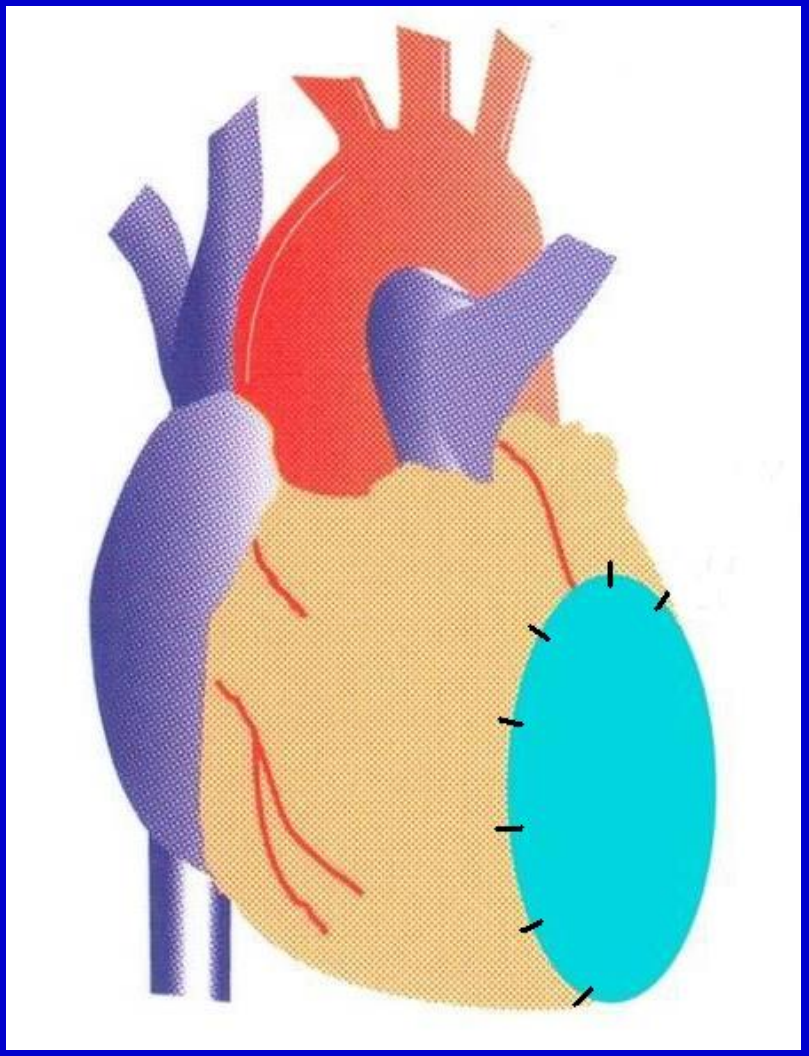
+

STEM CELLS

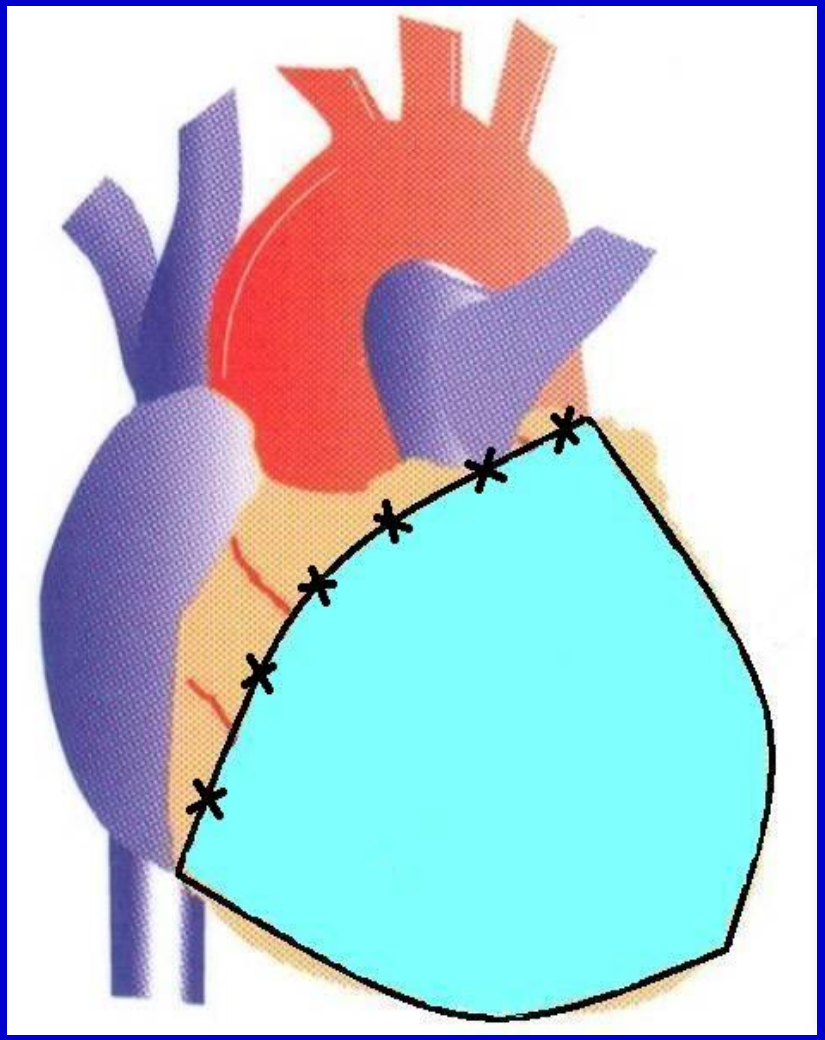


*** Puramatrix: nanoparticles smaller than 100 nm**

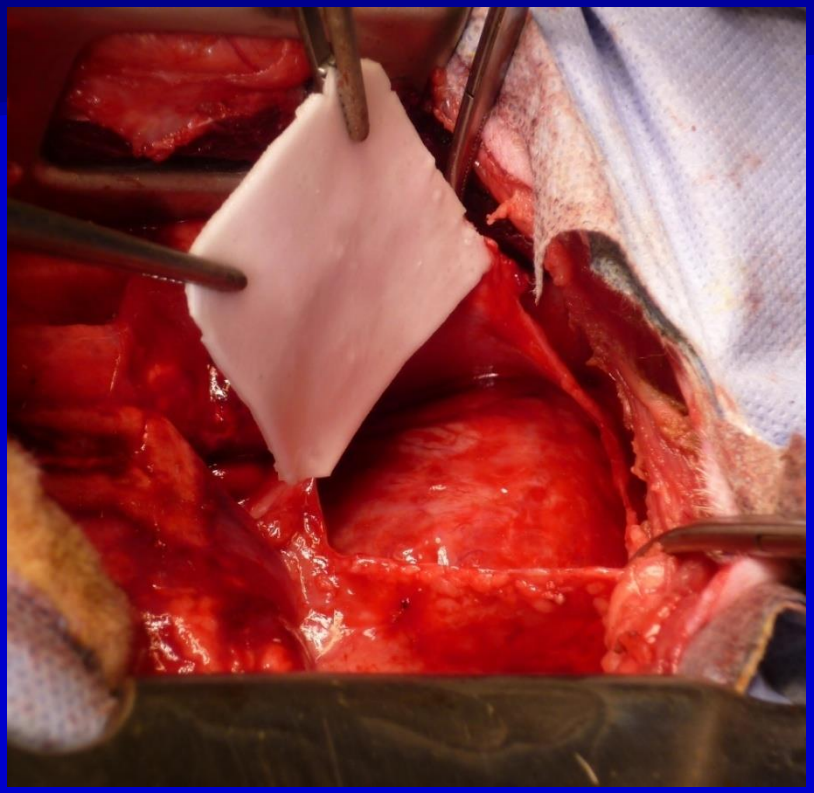
Cardiopatch

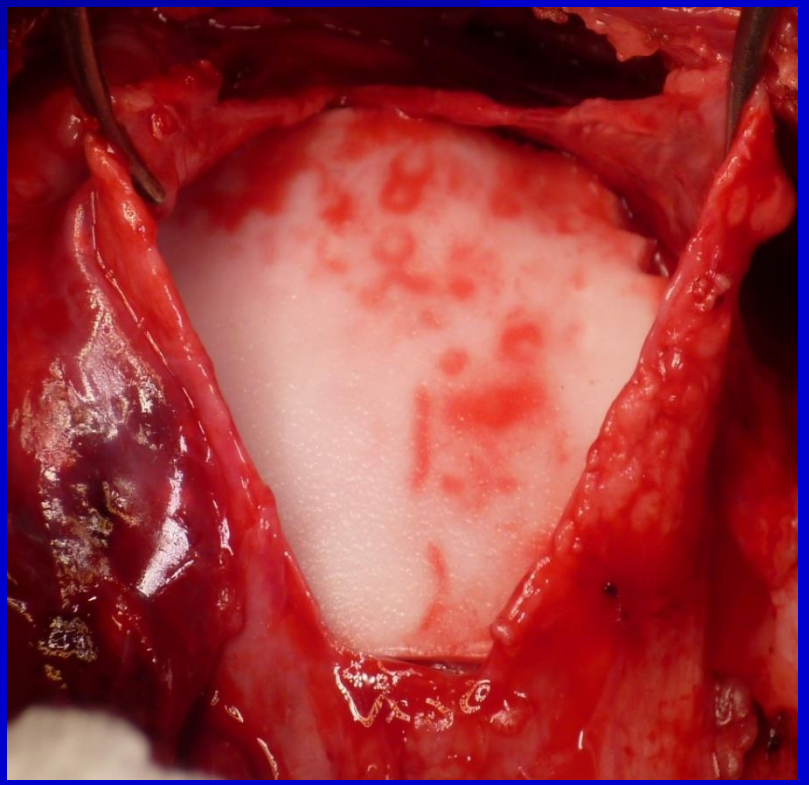


Ventricular Wrap Bioprosthesis



ELASTOMERIC SCAFFOLDS

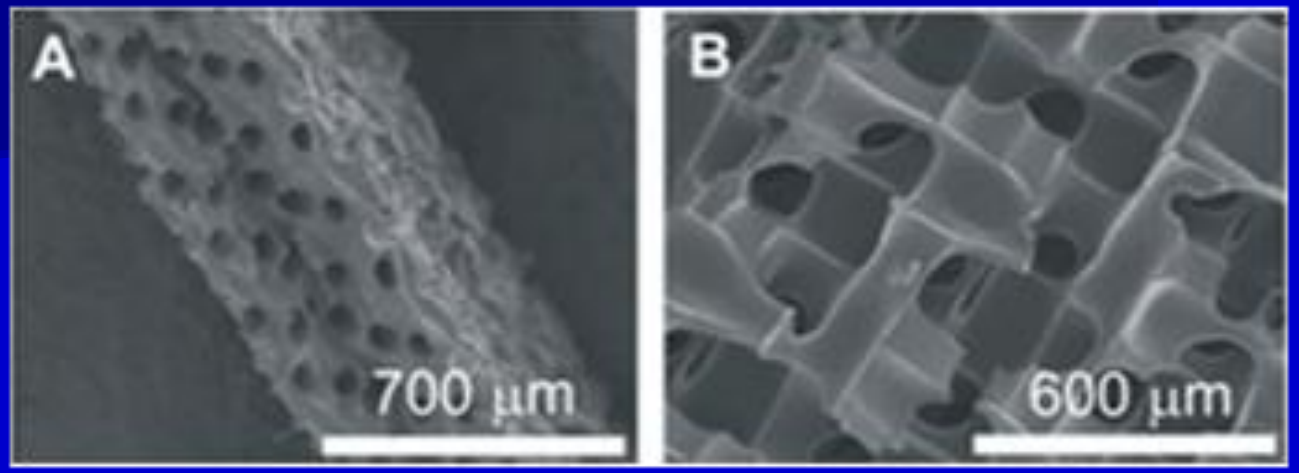




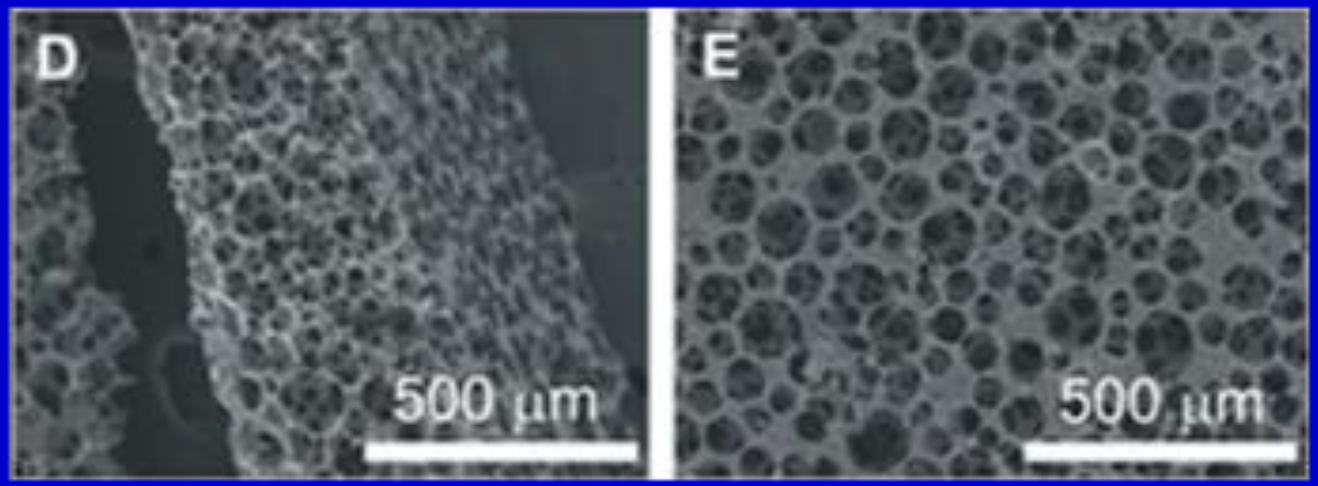
Non-degradable polymer: Poly Ethyl Acrylate (PEA)

Partially degradable: Polycaprolactone (PCL)

PEA scaffolds with cylindrical orthogonal pores



PCL scaffolds with spherical pores



Biohybrid Scaffolds for Bioartificial Myocardium

Clinical Translation

The goal of Bioartificial Myocardium is to reduce the risk of heart failure progression and the indication for heart transplantation