Artificial organs

From bioinert implants to tissue engineering and 3D organ printing

Cardiovascular (CV) diseases

- Main cause of death in industrialized countries. Among three major causes globally
- In USA 5 millions deaths annually caused by CV diseases. Economical consequences are more than 33 billion $ annually (statistics 2007).
- In Europe more than 4 millions deaths annually (1,9 in EC) 47% (40%) of total due to CV diseases. Annual cost in EC 196 billion Euro (statistics 2012).
- Surgical therapy of CV circulation in coronary and peripheral arteries corresponds in 600.000 patients/year in USA using arterial and venous auto implantation.
- In Greece a need of more than 5.000 surgical treatments annually for CV diseases

The Need For Organs Today

-110.000 people in United States in need of organ according to organdonor.gov
-In 2019 39.718 patients received organ while 20 each day die from a lack of ones
-Kidneys, hearts, livers, lungs are most needed organs

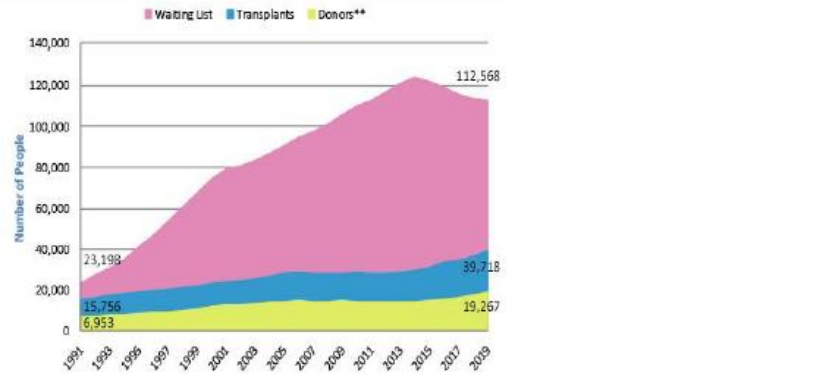
Statistics at a Glance

112,000+
Number of men, women and children on the national transplant waiting list as of March 2020.

39,718
transplants were performed in 2019.[2]

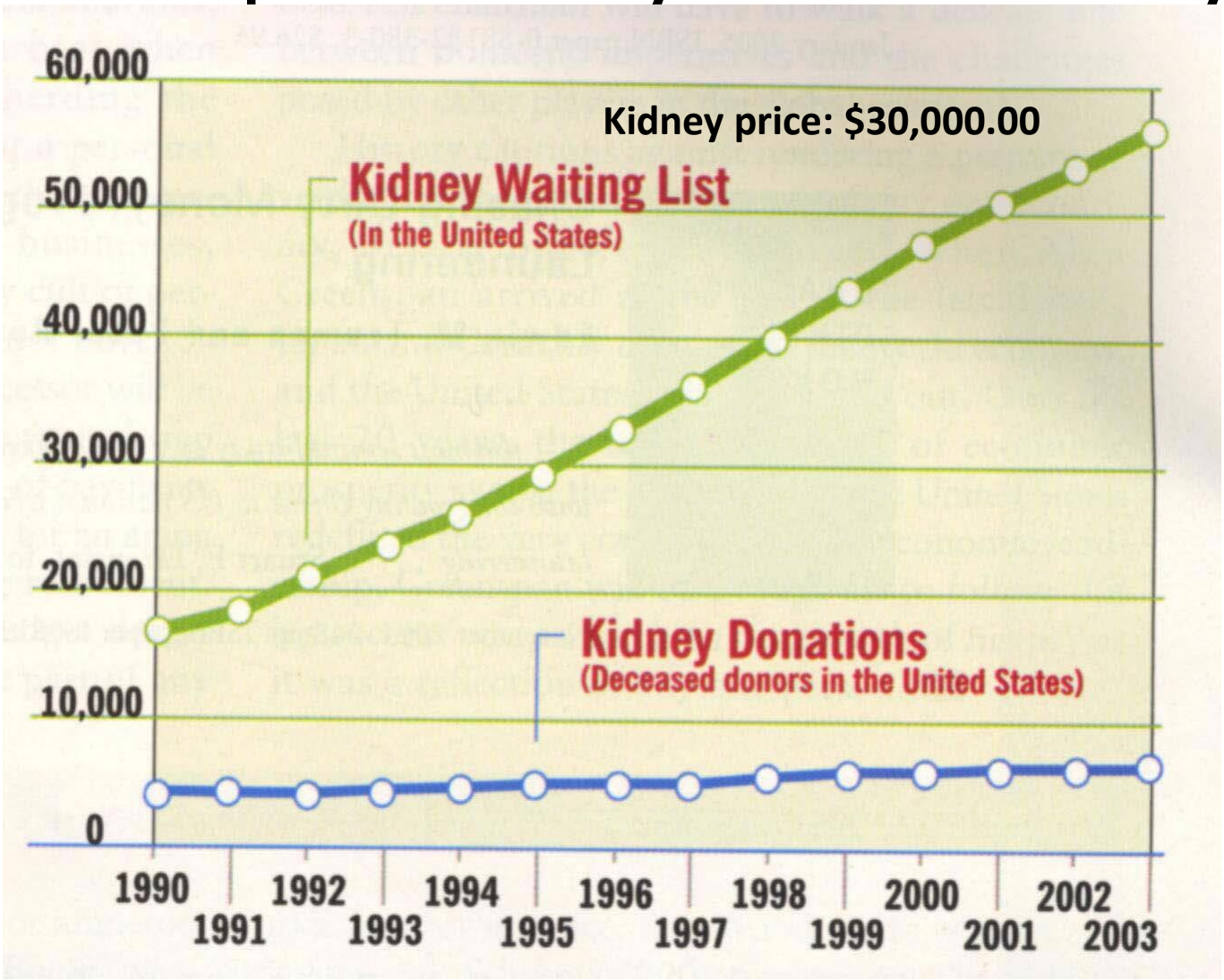
20
people die each day waiting for an organ transplant.

Each year, the number of people on the waiting list continues to be much larger than both the number of donors and transplants, which grow slowly.



http://www.organdonor.gov/about/data.html

Example:Kidney insufficiency



Common implants in use

Today, for the surgical therapy of CV diseases a lot of different implant technology are used:

- Artificial metallic, ceramic or polymeric implants
- Living autotransplanted or homotransplanted grafts
- Biochemically treated implants of biological origin (Allo-Xeno grafts).

For cardiac valve, myocardial or cardiovascular treatment bioinert materials are used, which do not enhance cell infiltration inside, so the possibility of autorepair or tissue regeneration is not possible.

- Use of cytotoxic drugs for immunological reasons result in mid and long term structural deterioration of implant materials.
- Additionally, the lack of remodeling in bioinert implants make them unable to , so they are not sufficient for implantation in children and young patients.
- **In conclusion, tissue engineering prospects as a fully permanents solution for the treatment of CV diseases**

Strategic technologies on implants/ organs

- Bioinert implants
- Bioactive implants
- TE implants
- Regenerative therapies
- Biohybrid organs
- Complete TE organs
- 3D organ printing - personalizedmedicine.

Bioinert implants

"Permanent" artificial structures for functional restore of patients.

- Heart valves (biological - mechanical)
- Pacemakers- Defibrillators
- Artificial vascular implants
- Stents
- Ventricular assist devices (Left/Right ventricle)
- Total Artificial Heart (TAH)

➢ Restricted longevity

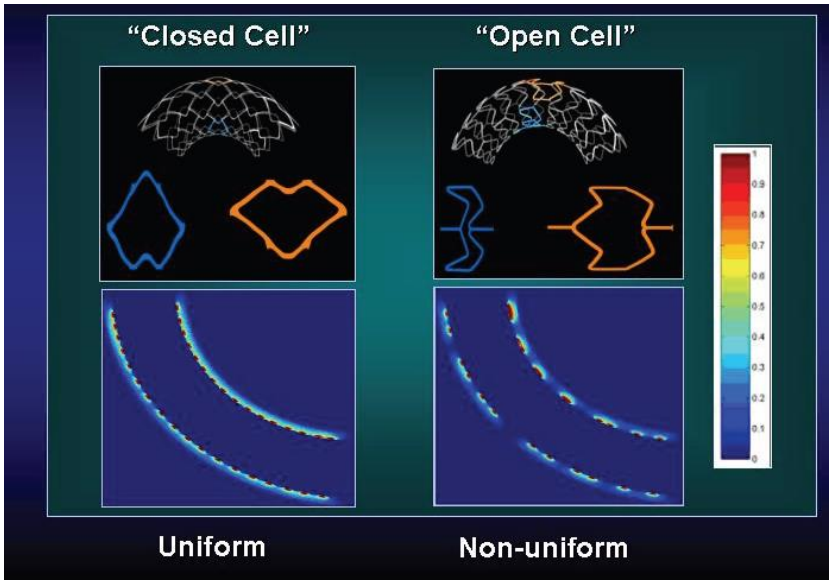
➢ Malfunctions

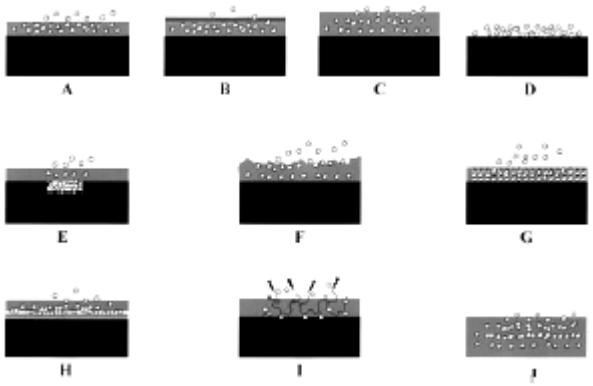
➢ Side effects

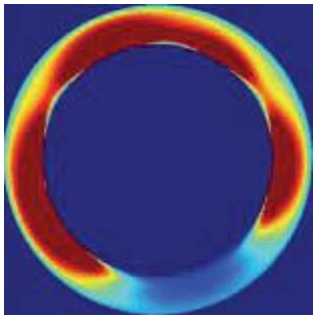
Bioactive implants

Structures using materials able to stimulate biological and biochemical reactions ***in vivo***

- Bioceramics (bones, teethes)
- Drug eluted stents liberating drugs inhibitors of vascular restenosis
- Results in better hosting ability, however remaining BIOINERT







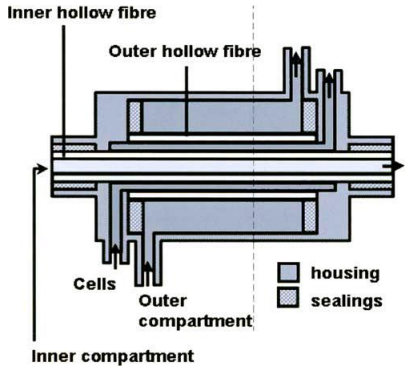
Htay and Liu,*Vascular Health and Risk Management 2005:1(4)*

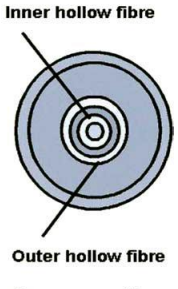
Biohybrid organs

- **Hybrid structures from permanent artificial materials with bioinert/biodegradable parts**
- **Stimulation/triggering of biological/biochemical reactions *in vivo* aiming in integration (anatomical/functional) of implant in patients' organization.**
- Artificial Liver – Pancreas
- Connective channels
- THE INERT MATERIAL PART REMAINS WITH RISK OF LONG – TERM OF COMPLICATIONS

Hollow fiber technology for haemofiltration

U Patras

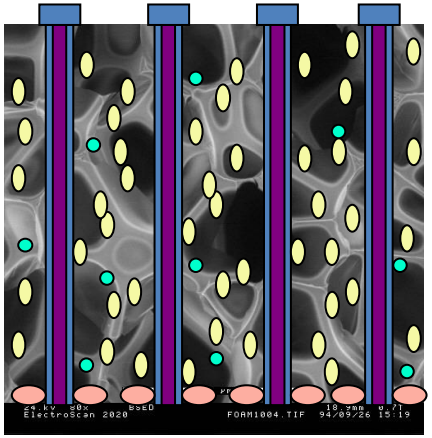




STRP 13811 - **VascuPlug**

Bioreactive composite scaffold design for improved vascular connexion of tissue-engineered products

U-Patras



Regenerative Therapies

- **Feed (minimally invasive placement or injected)of biological gel constructs** in diseased regions enriched with cells, growth factors, differentiation agents etc
- **Incubation period (in vivo)** for biological environment response for cell integration, proliferation, differentiation and tissue regeneration
- Current pilot clinical applications in articular cartilage diseases and cardiology (cartilage and myocadiac tissue regeneration)

Tissue Engineering

- Implantation of a temporal construction (scaffold) with double target:

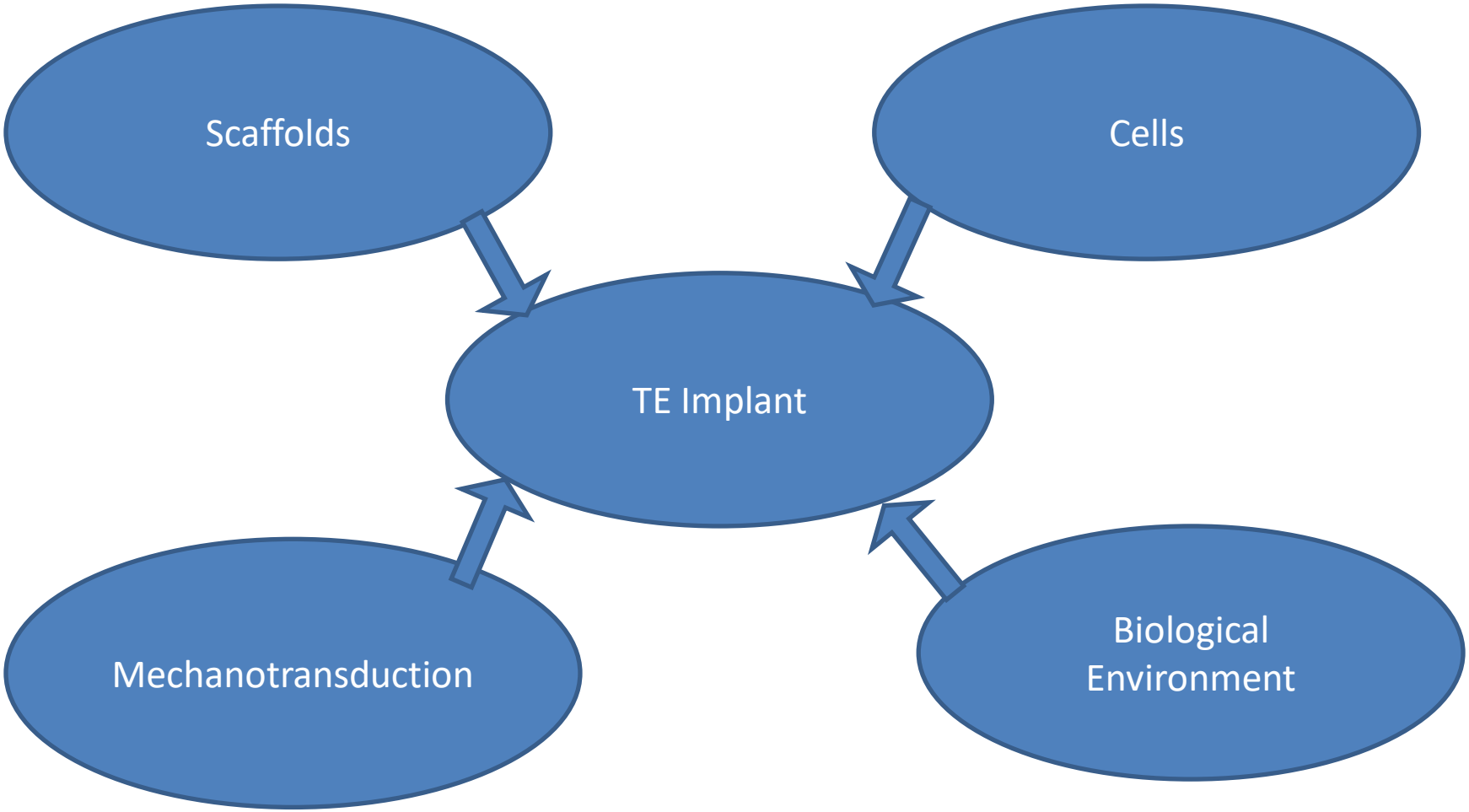
1. To restore a near physiological function, replacing the pathological organ or tissue (for a certain time period)
2. To secure full biological response with host environment enhancing the procedure for tissue regeneration inside the scaffold structured as a full living organ
3. To be biodegraded in the meantime with a rate similar to the growth of new living tissue (not a lack of structure, not tissue overgrowth.

Tissue Engineering

Steps in production of a fully implantable TE implant:

1. Design and production of a biodegradable scaffold.
2. Enrichment with proper biochemical factors/drags e.t.c. for enhancements of cytocompatibility - protection from inappropriate pathophysiology.
3. Optionally creation *in vitro* of a **cell-scaffold construct** and cell culture in **bioreactors**.
4. Packaging-storage-logistics from production line to the final clinical use.

Strategic of production for TE implants



Step1: Scaffold design/construction

- Data from Physiology, Anatomy & Histology of natural organ.
- Decision 1 Therapy: Regenerative Medicine or TE?
- Decision 2 if TE, material: Synthetic or decellularized scaffold?
- Decision 3 Strategic: One (*in vivo)* or 2 *(in vitro & in vivo)* step implantation?

Decision 1

- Regenerative Medicine

Production of injectable gel or membranous patch from biodegradable polymer enriched with medium, cells, growth factors etc.

- TE Scafolds

Strategic design: scaffold type, anatomical/physiological data

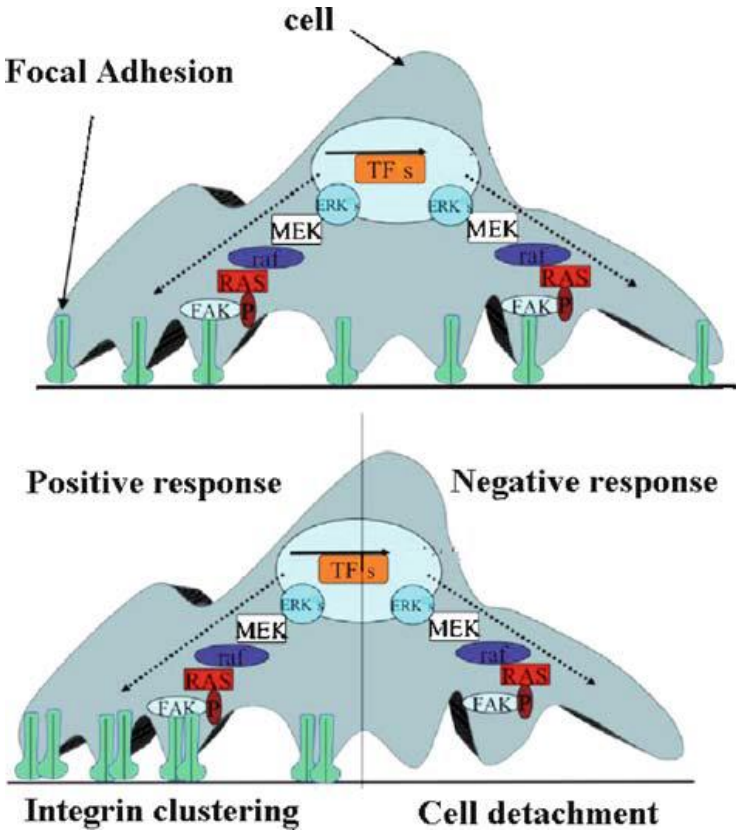
Decisions 2 & 3

Decision 2^A material
Use of decellularized scaffold

- ✓ Selection of Animal Tissue: Anatomical & histological compatibility
- ✓ Decellularization protocol: Efficiency, structural integrity of ECM, time, economy
- ✓ Material/scaffold Characterization: International standards for medical implants (where possible)

- ✓ **Testing of toxicity, biocompatibility, cytocompatibility** International standards for medical implants (where possible)
- ✓ Recellularization, differentiation, cell function, bioreactor (?)
- ✓ **Feedback:** Need of biofunctionalization, repeat of recellularization

- ✓ Animal experiments (ectopic – orthotopic placement)
- ✓ Application-Approval of clinical trial studies
- ✓ Application-Approval of clinical use



tecas | Tissue Engineering Solutions for Cardiovascular Surgery
Marie Curie Initial Training Network

SEVENTH FRAMEWORK PROGRAMME
MARIE CURIE ACTIONS

Marie Curie ITN 2013-2017

TE Implants for cardiovascular surgery

- TE Heart valve, blood vessels and patches.
- Use of biological decellularized implants and patients' blood components
- Test in bioreactors and animal studies.

Medizinische Hochschule Hannover

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UNIVERSITY OF PATRAS

RWTH AACHEN UNIVERSITY

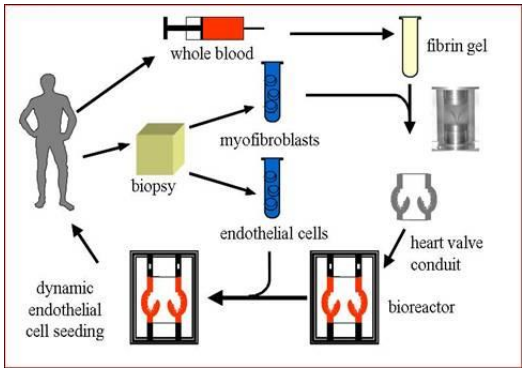
TU/e Technische Universiteit Eindhoven University of Technology

Università degli Studi di Padova

corlife

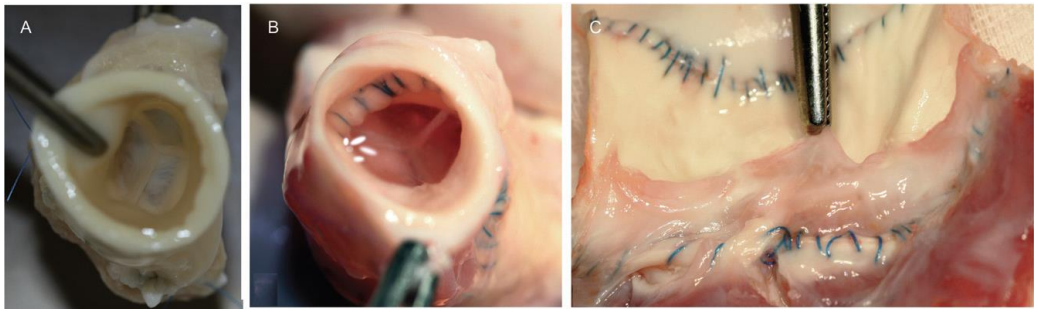
TE natural implants

- Dcell scaffolds of biological origin
- Functional, time predictable behavior lost
- Able to host, proliferate, differentiate and function of cells for tissue regeneration
- *In vitro step function in bioreactors*

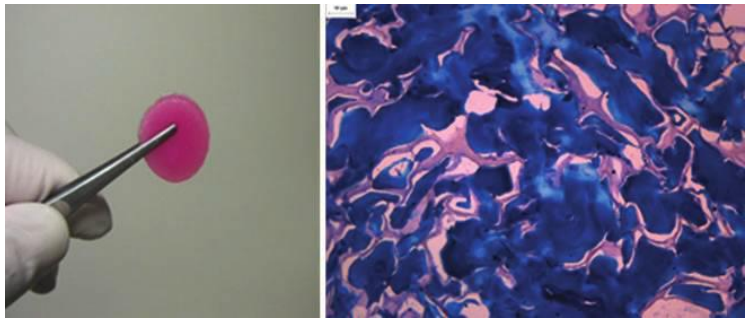


Aachen: The concept of fibrin scaffolds for TEHV

U Patras: TE Pericardial patches



Padova: TRICOL (TEHV): Before and 15 months after implantation (VP).

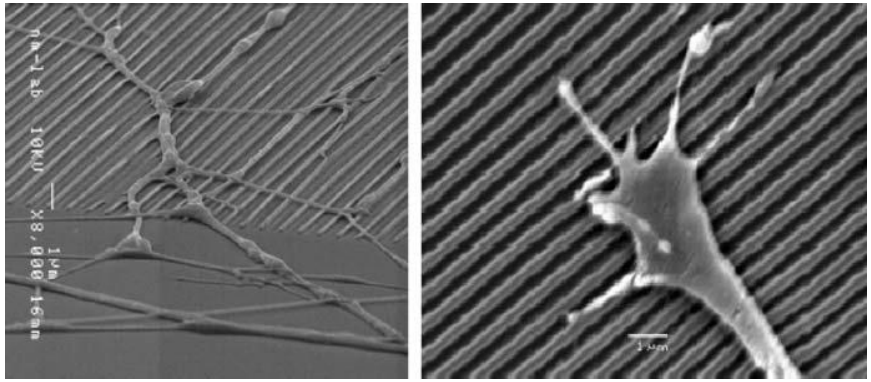


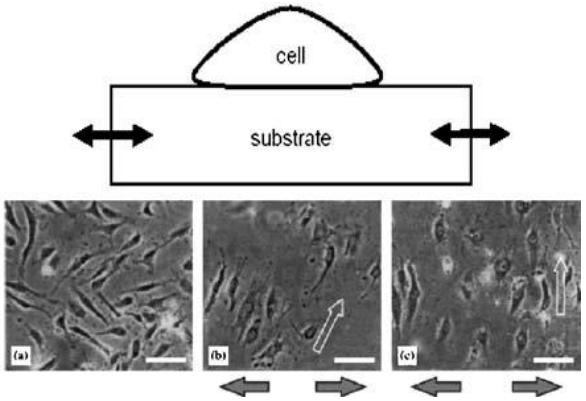
Leeds-MHH: Stem cell differentiation in collagen sponges under mechanical loading

D-Cell heart valves: Bioreactor design Upatras team (Cr. D'Alessandro)

Decision 2^B material
Use of synthetic scaffolds

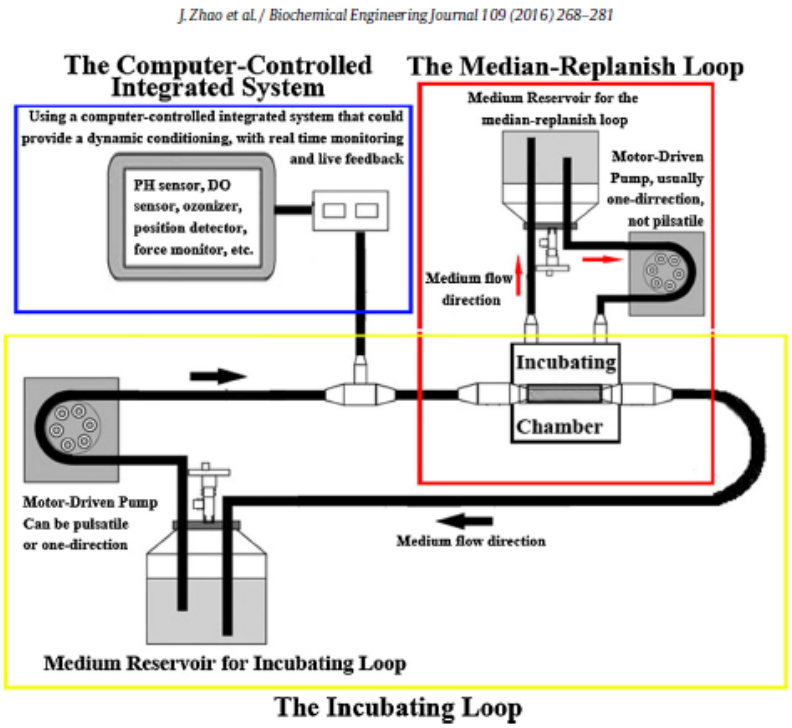
- ✓ Selection of Biomaterial (Design, selection of polymer/s, methodology)
- ✓ Mechanical-biodegradation testing *in vitro*
- ✓ Toxicity, biocompatibility, cytocompatibility testing
- ✓ Cell spread/infiltration, cell functional testing in static cell culture & dynamic (bioreactors)
- ✓ Feedback: need of Functionalization or not?
- ✓ Animal experiments

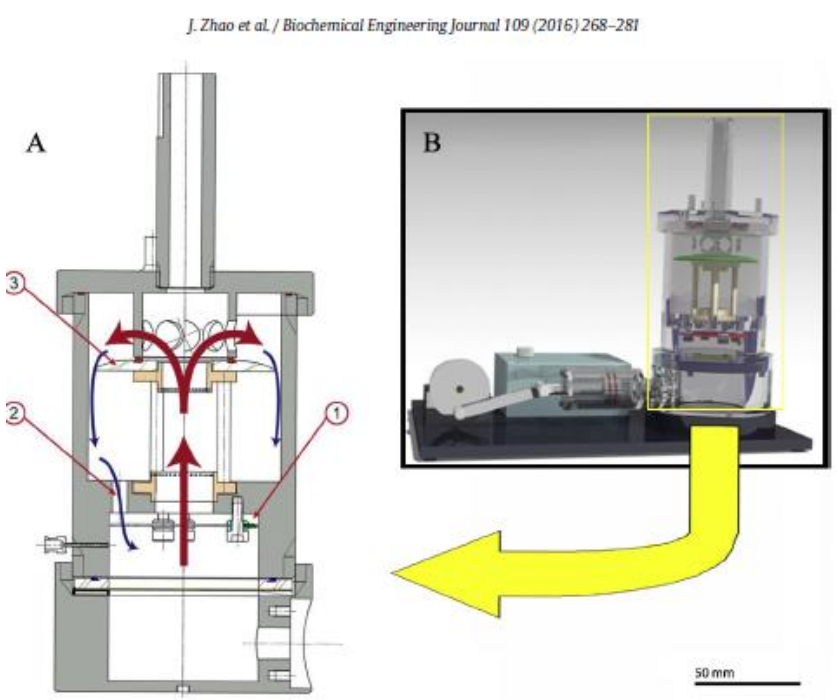




Bioreactors

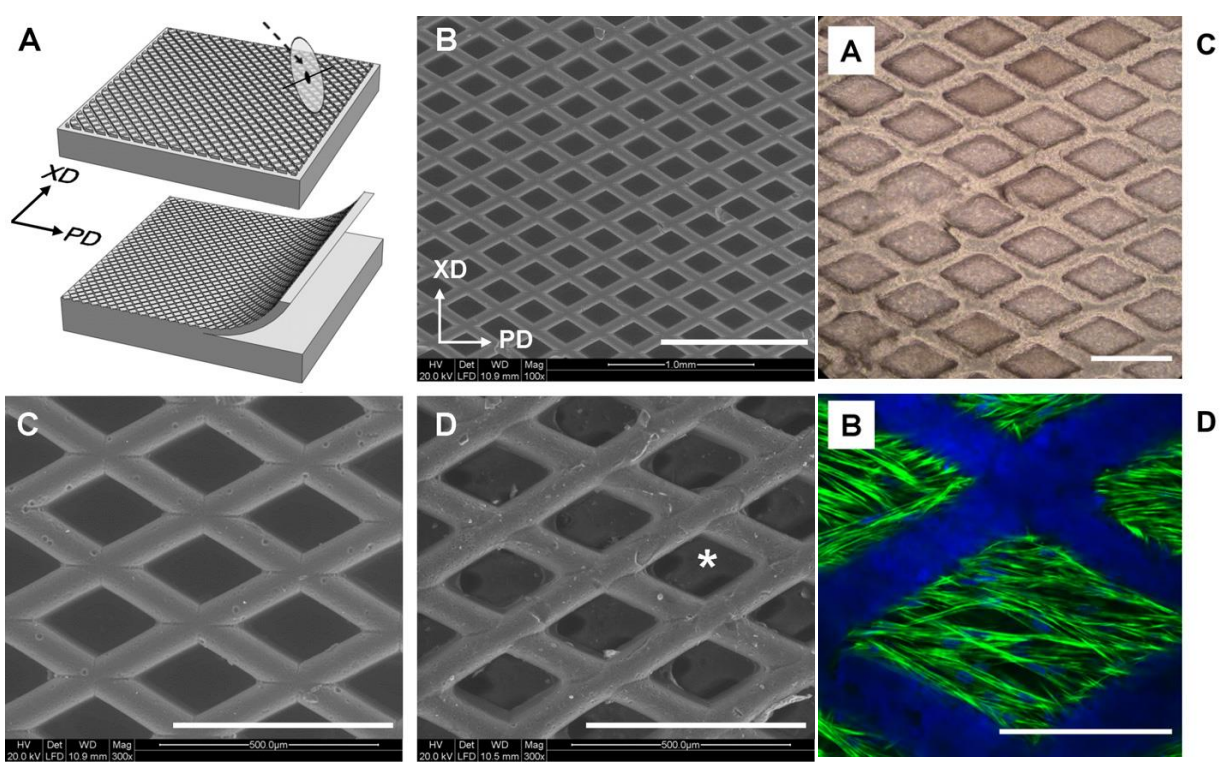
- Designs for inducing mechanotransduction in cell/biomaterial constructs
- Incubator conditions (Temperature, CO2, Humidity control
- Mechanical stimulation of constructs
- May be electrical stimulation (nervous, muscle constructs)

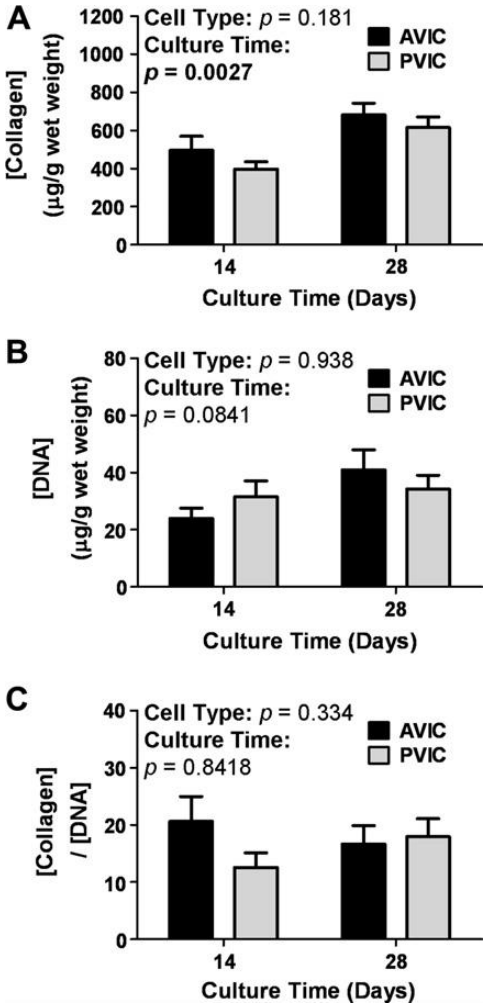




Valvular bioreactor in our Lab

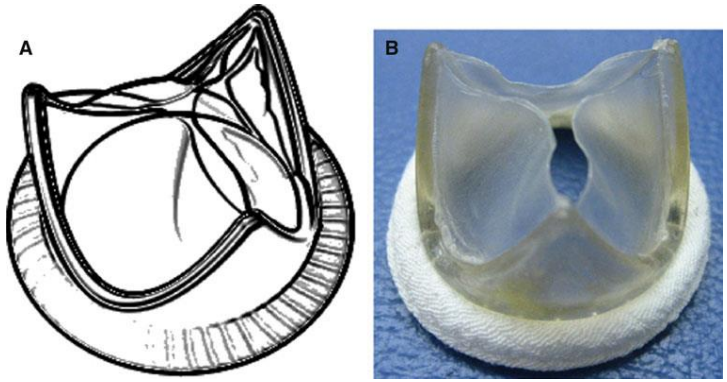
Example1



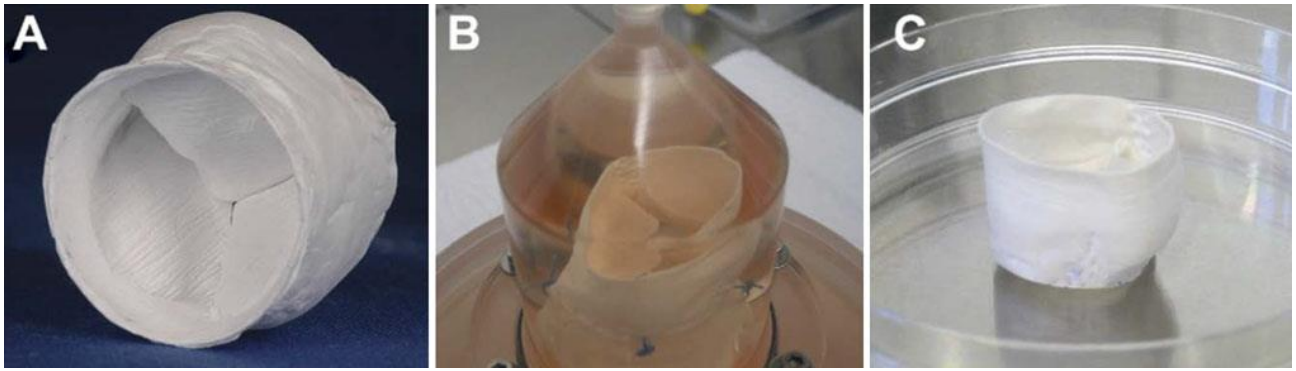


Valvular interstitial cell seeded poly(glycerol sebacate) scaffolds: Toward a biomimetic in vitro model for heart valve tissue engineering

Examples 2 & 3

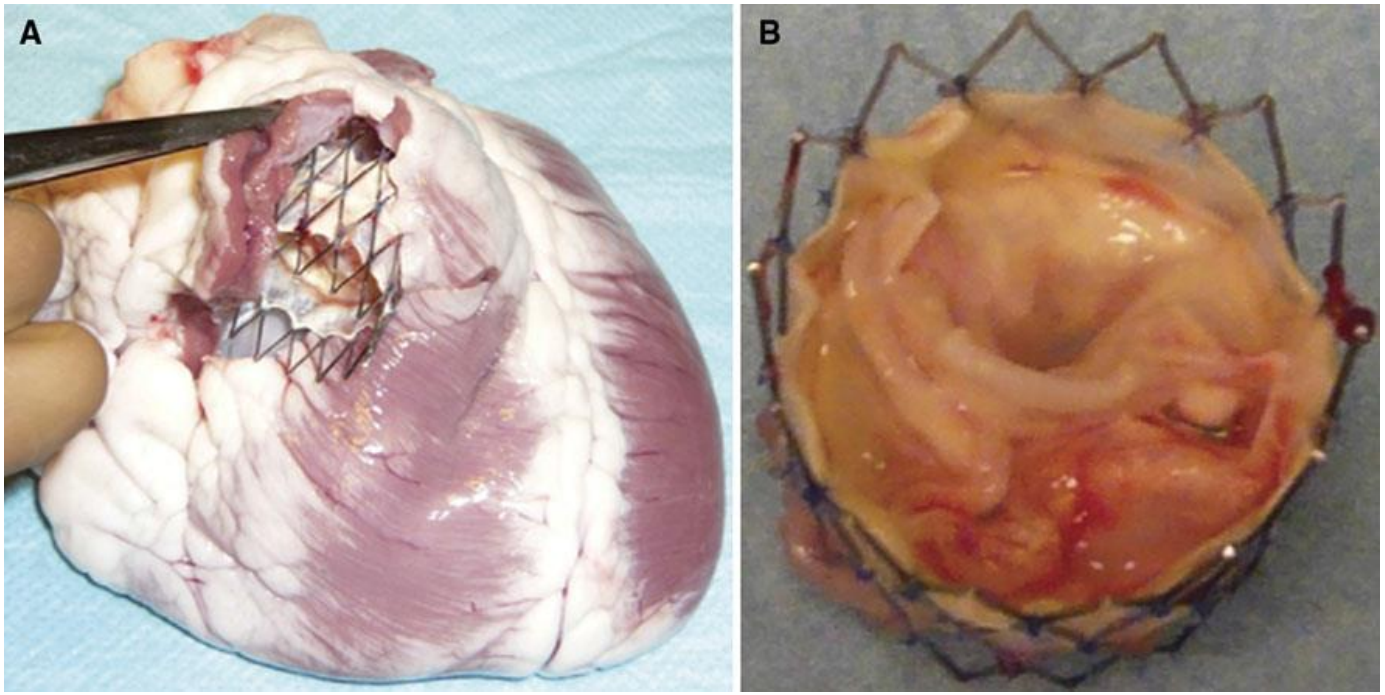


Trileaflet nanocomposite (POSS-PCU)-based tissue engineered heart valve (UCL design). Complex leaflet design on Dacron suture ring ensures high performance and durability



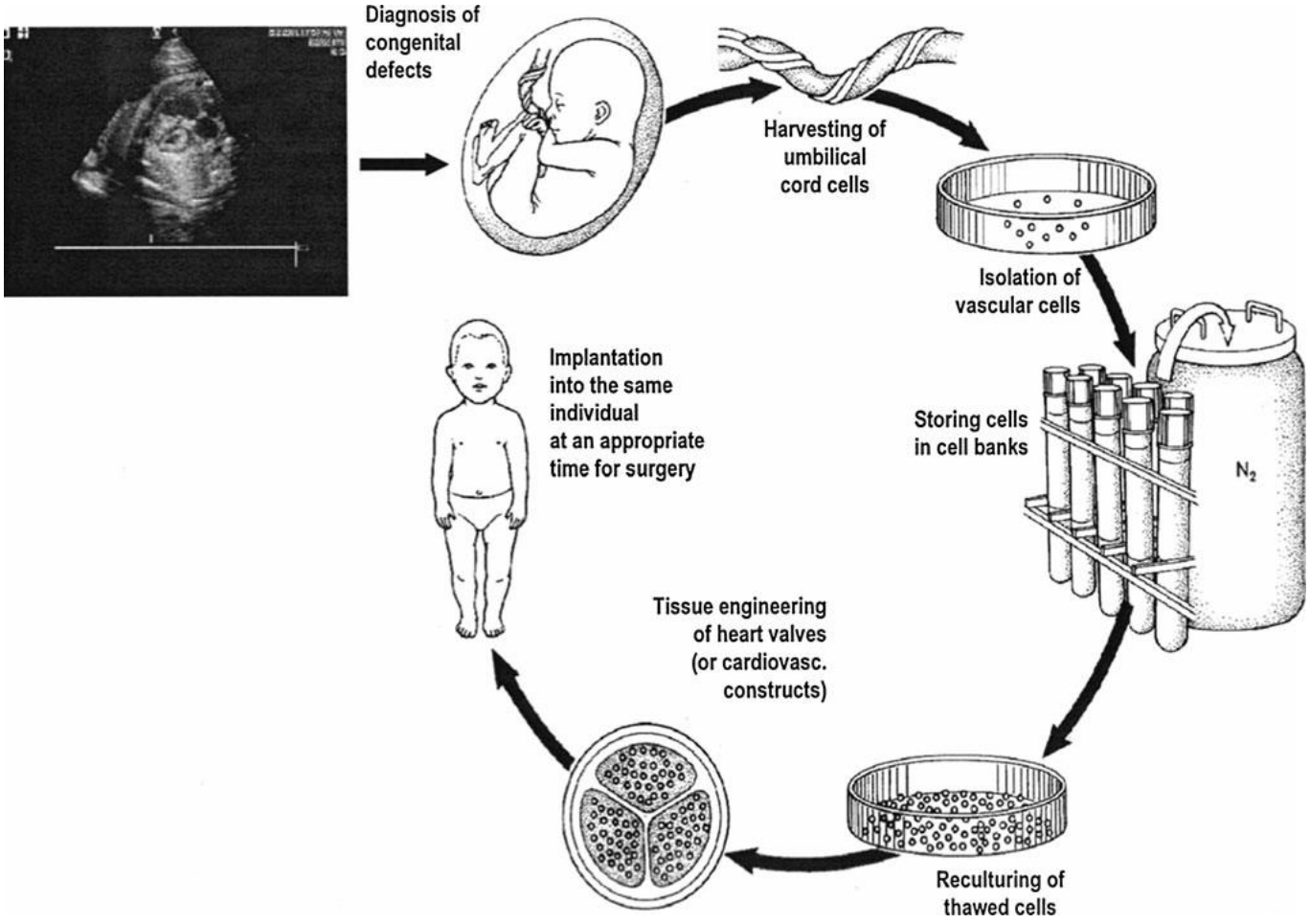
A. Polymeric scaffold. B.Tissue-engineered heart valve in bioreactor. C. Maturation of the heart valve in semi-open position of the bioreactor. Reprinted with permission from Sodian R, Lueders C,Kraemer L et al. (2006) Tissue engineering of autologous human heart valves using cryopreserved vascular umbilical cord cells. Ann Thorac Surg 81:2207–2216

Example 4



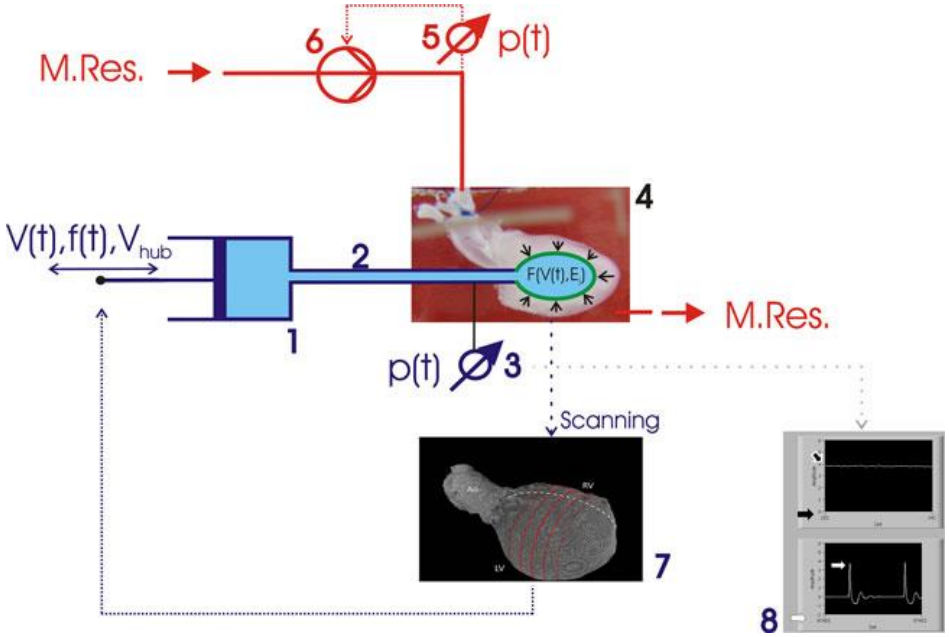
Tissue-engineered pulmonary valve on stent. Optimal positioning of stent (A) and macroscopic analysis of the tissue engineering leaflets showed smooth surfaces with no thrombus formation (B). Reprinted with permission from Lutter G, Metzner A, Jahnke T, Bombien R, Boldt J, Iino K, Cremer J (2010) Percutaneous tissue engineered pulmonary valved stent implantation. Ann Thorac Surg 89:259–264

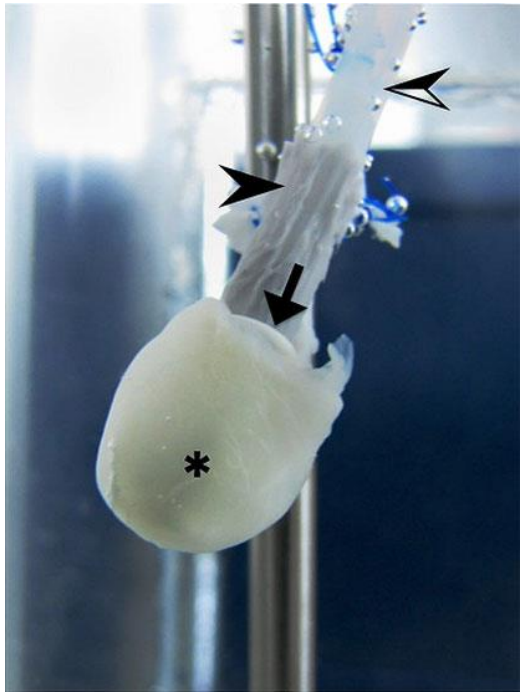
The cells: Basic idea



Total TE organs

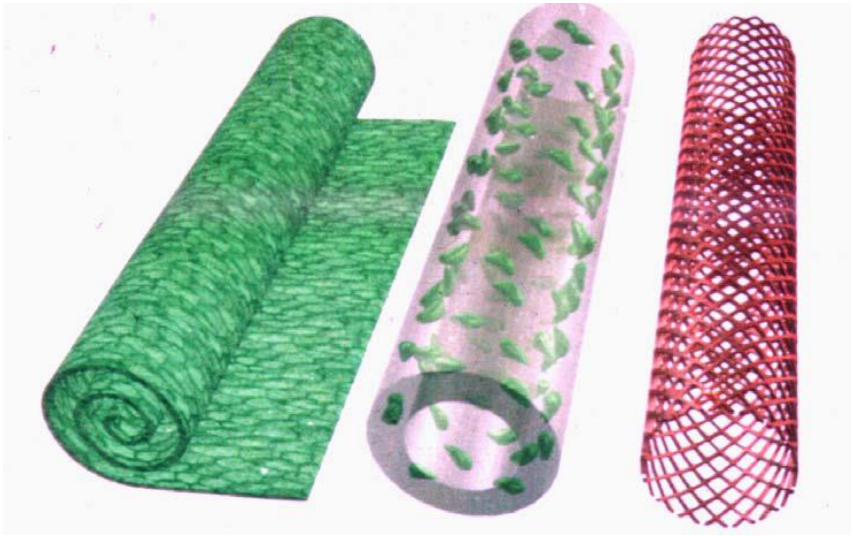
Bioreactor for whole-heart cultivation under controlled 3D biomechanical stimulation. Decellularized rat heart.





J. Hülsmann *et al.* J Artif Organs, April 2013

3D Organ printing



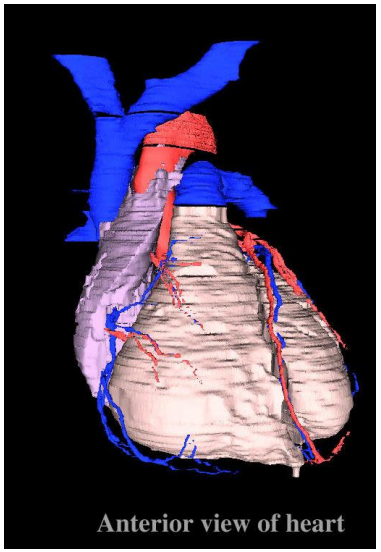
Technologies

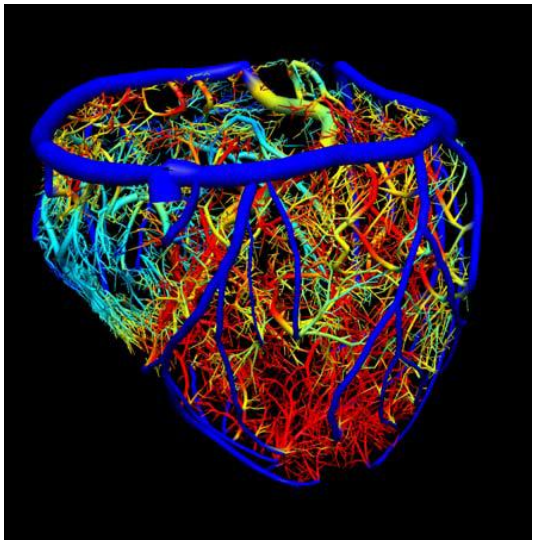
- **1. Rolling**
- **2. Embedding**
- **3. Seeding**

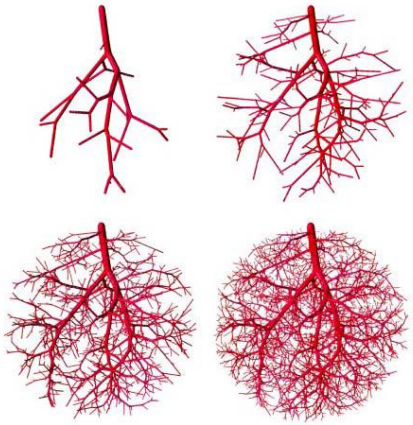
The steps

Three Main Steps in Organ Printing Technology.

1. **Preprocessing(CAD, blueprints, preconditioning).**
2. Processing(actual printing, solidification)
3. Postprocessing(perfusion,post-conditioning,accelerated tissue maturation)







The steps

Three Main Steps in Organ Printing Technology.

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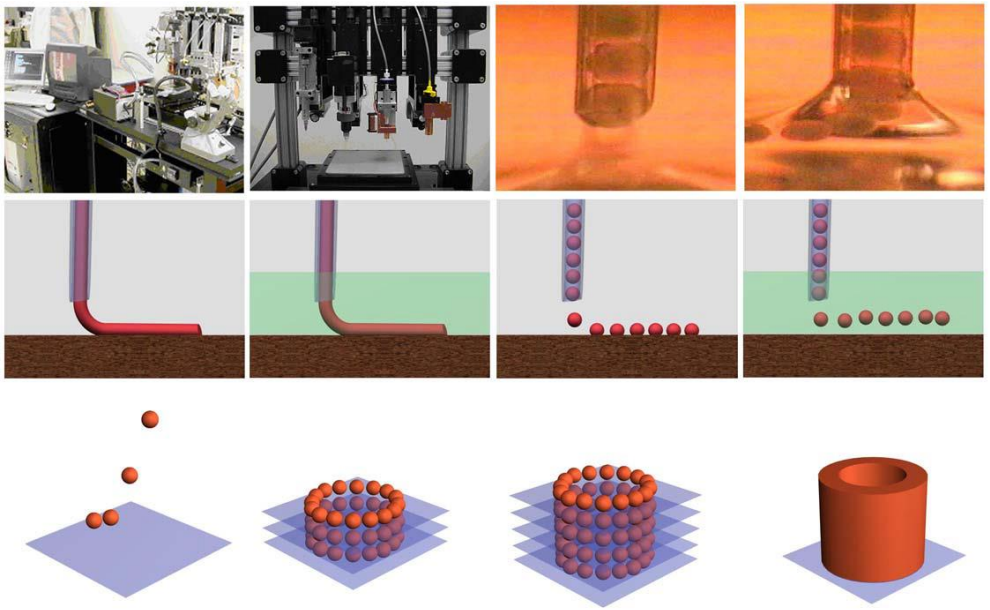
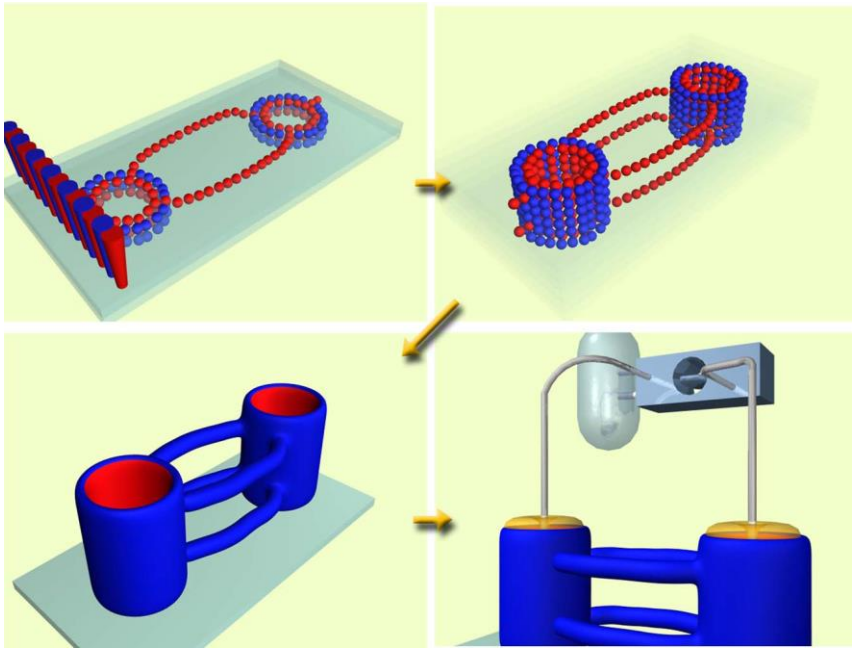
The key point: Bioink

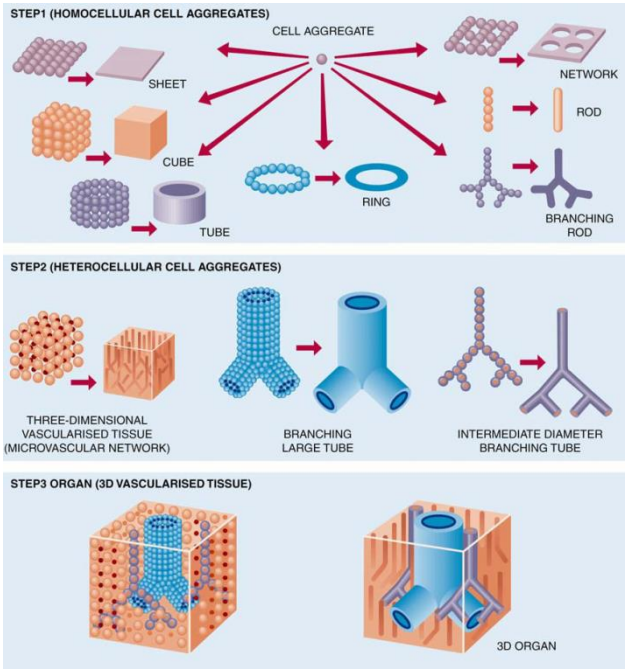


Modeling of Printed Vascular Unit
Sometimes modeling is not a bad idea...



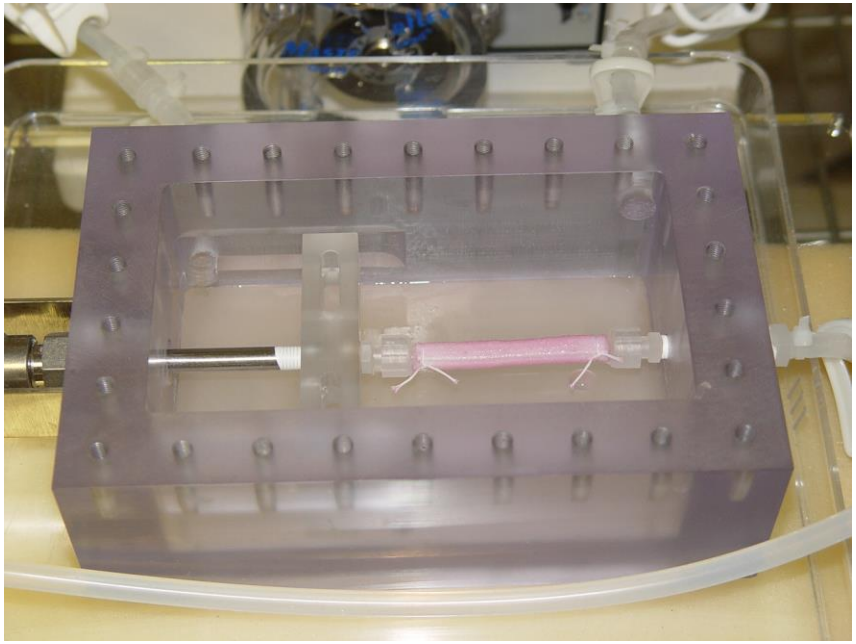
The future: Total TE Organs
3D organ printing – personalized medicine.

- 3D anatomical imaging/modelling CT/CAD
- 3D design level by level
- Synthesis of biodegradable polymeric materials
- Preparation of “Bioinks” from cells and relevant biochemical entities (e.g. growth factors, nutritients…)
- Level by level porous micro/nanocontruction of scaffold (rapid prototyping – 3D printing)
- Nano/micro printing of bioink in predetermined positions in each level)
- Full integration of the construction
- Early function – cell culture in bioreactors
- Implantation of construct

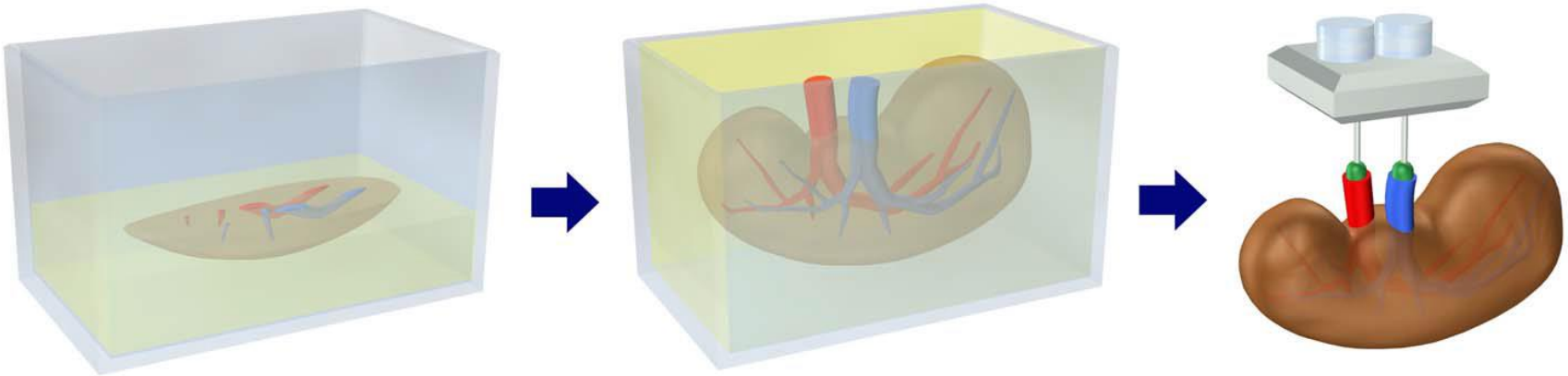


From
Vladimir Mironov MD, PhD
MUSC Bioprinting Center
Medical University of South Carolina, Charleston, USA

Perfusion Bioreactor



Organ Printing Technology



- Printing of living organs will be another pioneering step in the history of science, technology and civilization

Is it just another concept?
How far from clinical practice?