

M_HH

Herz-, Thorax-, Transplantations-
und Gefäßchirurgie

Clinical applications of scientific and/or technological innovations

Axel Haverich, Hannover



MIT SICHERHEIT.

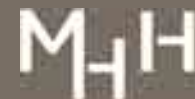
The Environment in Medicine:

Patients

Doctors

Health Insurance

Industrie



Herz-, Thorax-, Transplantations-
und Gefäßchirurgie

PART 1:

The need of the environment

Medical knowledge doubles every 10 years?
Are we twice as healthy in 10 years from now?

Ambient pressure

- Patients suffering from suboptimal and recurrent interventions
- Increasing patients` demands on health care providers
- Limited availability of grafts and/or implants
- Economic results (Insurance vs Industrie)

Handling the ambient hypertension

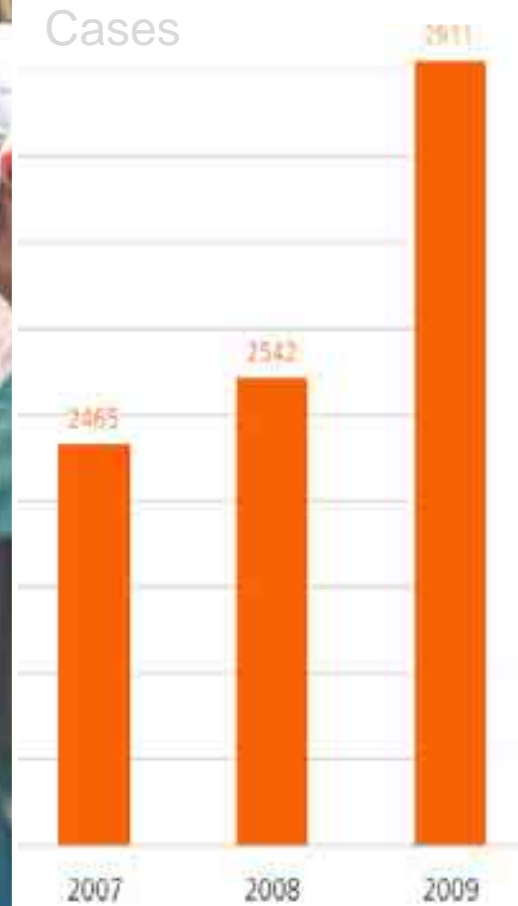
- Innovation



- Precision



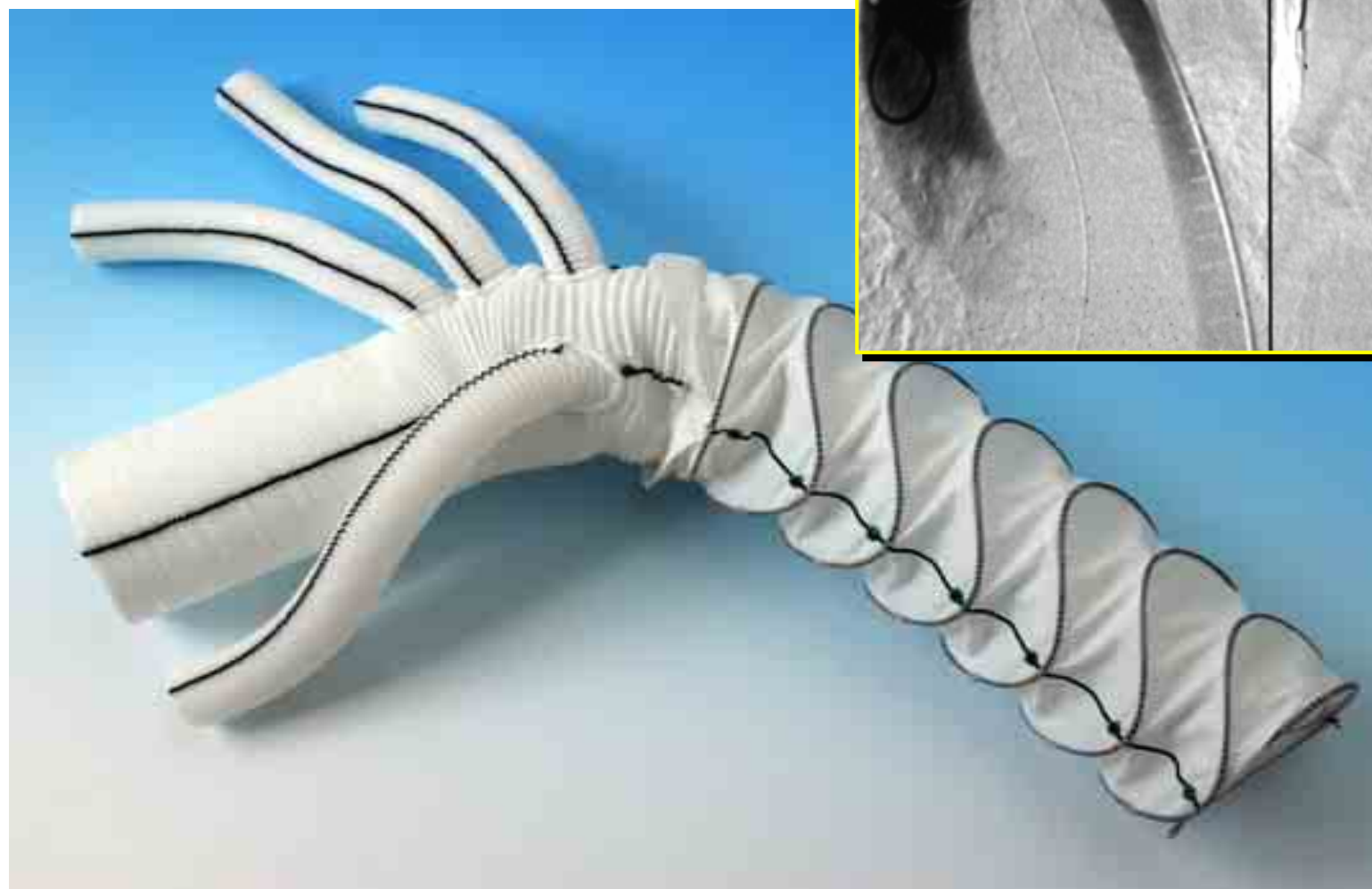
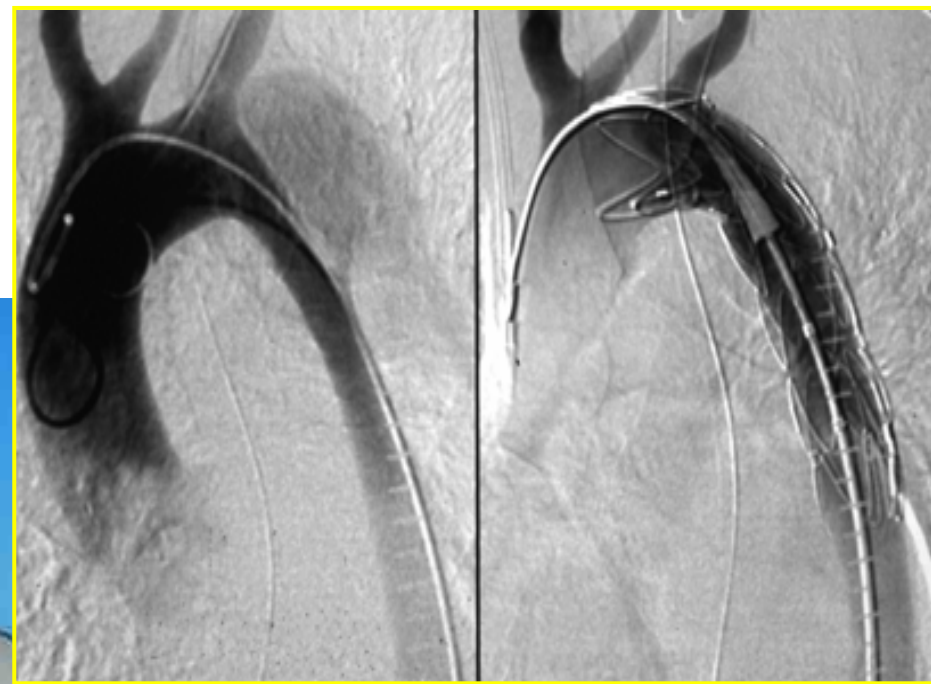
- Sustainability



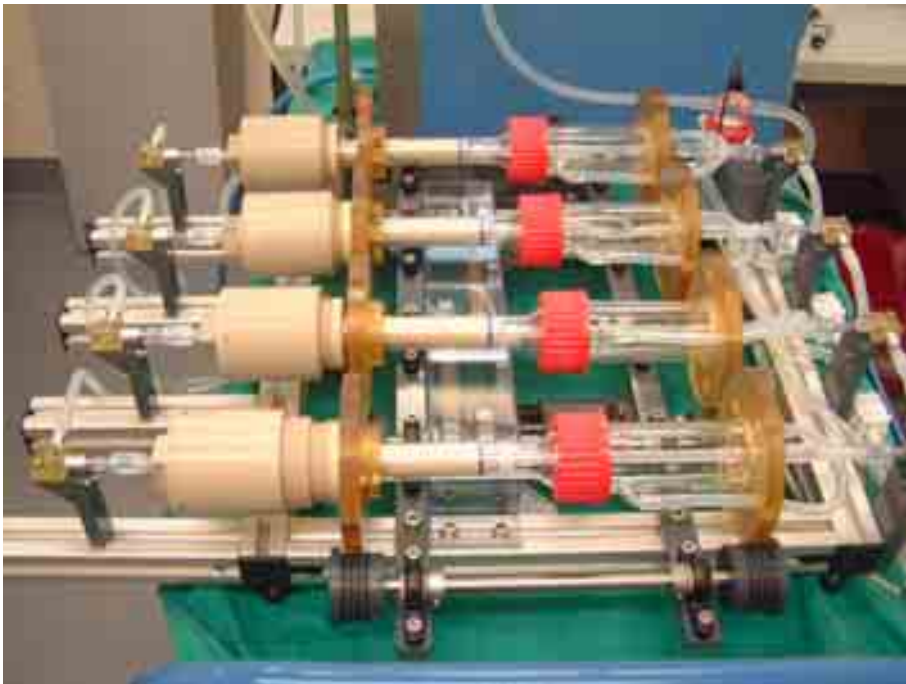
Innovation:

Determined to invent

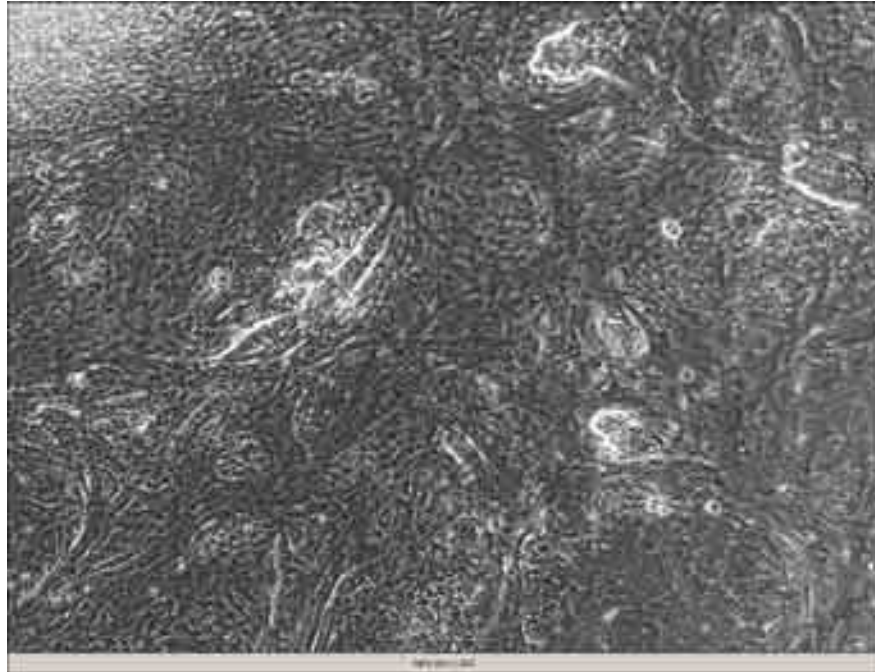
Vaskutek/Haverich Hybrid Aortic Prosthesis



Innovation: Bioartificial Dialysis Shunt



Innovation: Functional cardiomyocytes from human induced pluripotent stem (iPS) cells, e.g.



Innovation: Mini-ECMO-Circuit, Cell Seeded



Innovation: Tissue engineering of heart valves



Handling the ambient hypertension

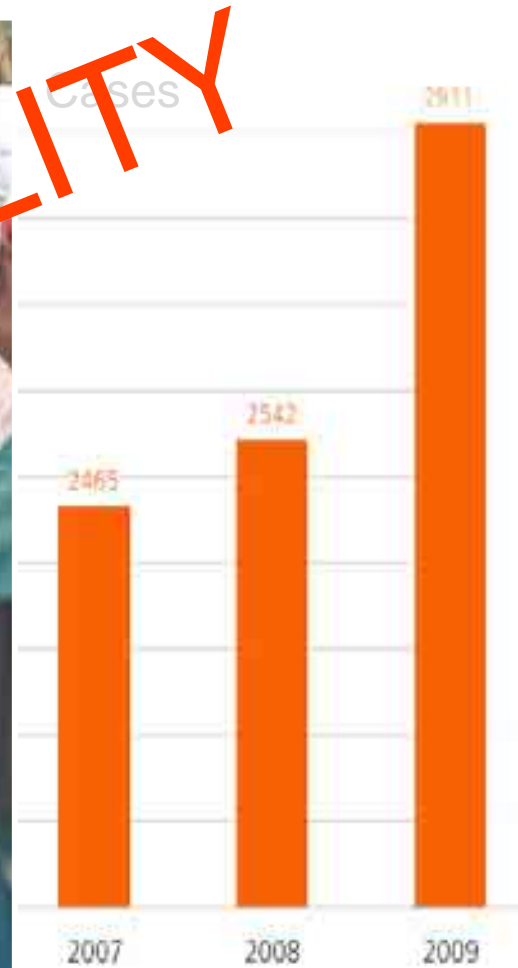
- Innovation



- Precision



- Sustainability



BIOCOMPATIBILITY

Precision:

Handle with care



Herz-, Thorax-, Transplantations-
und Gefäßchirurgie

Precision:

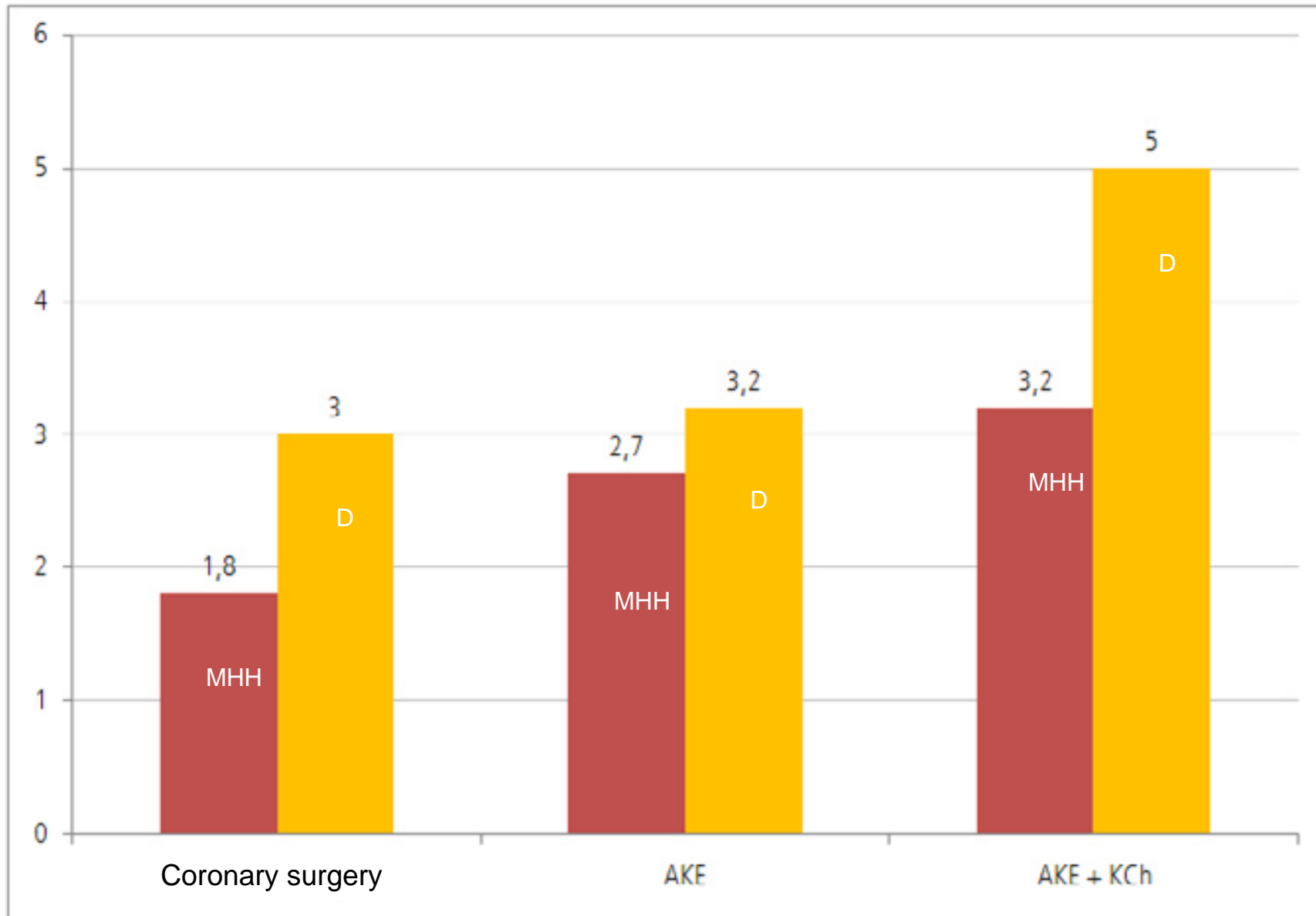
Handle with care

Surgical Precision
Technological Precision

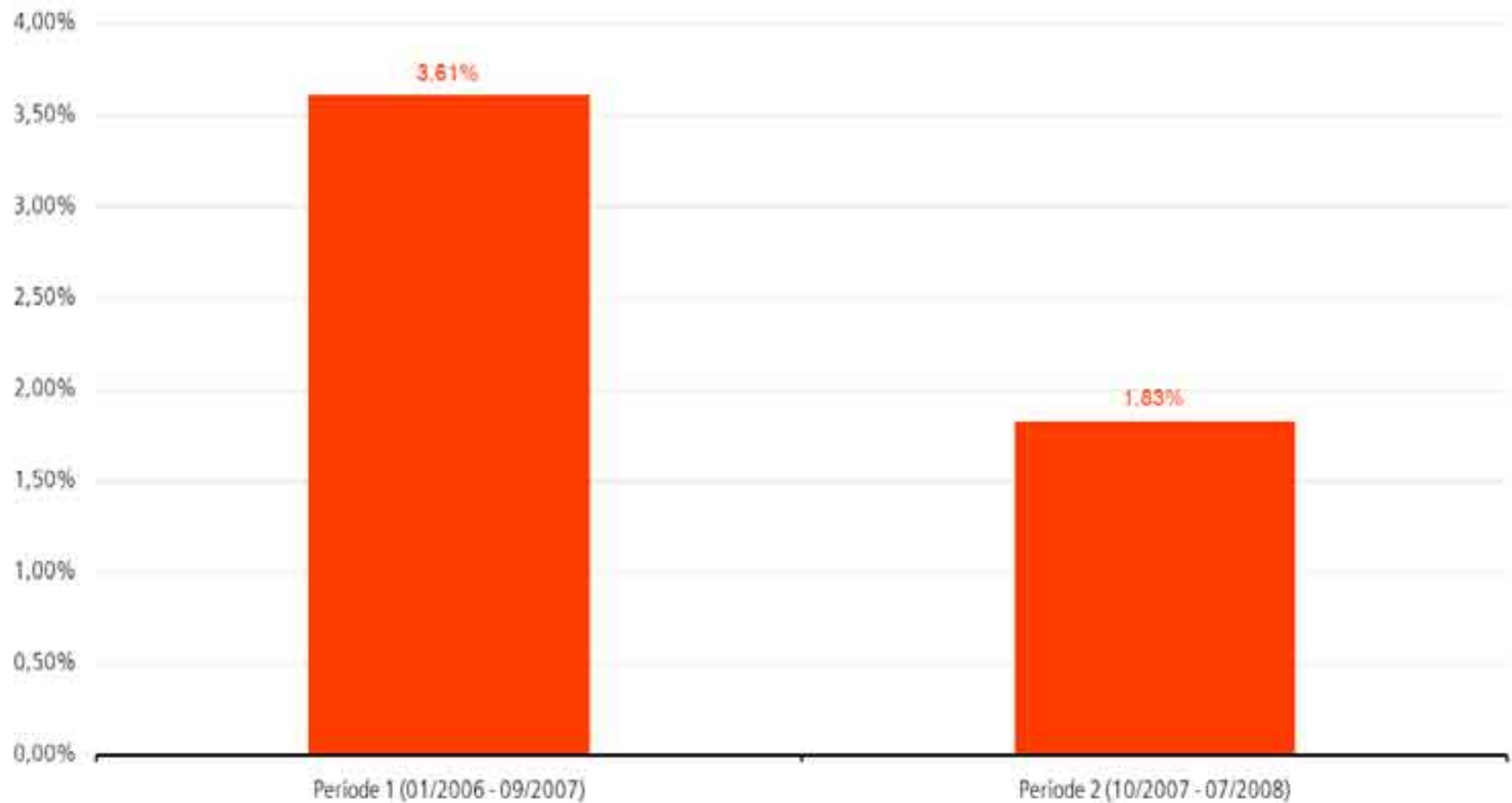


Herz-, Thorax-, Transplantations-
und Gefäßchirurgie

Precision: Risk adjusted in-hospital-mortality (log.KCH/AKL-Score)



Precision: Incidence of sternal wound infections



Precision:

Handle with care

Surgical Precision
Technological Precision



Herz-, Thorax-, Transplantations-
und Gefäßchirurgie

Sonderforschungsbereich-TRANSREGIO 37

„Micro- and Nanosystem-Technology in Medicin – Biofunctionalisation“

Hannover – Aachen – Rostock

Speaker: Prof. Dr. med. A. Haverich
Thorax-, Herz- Gefäßchirurgie
Medizinische Hochschule Hannover



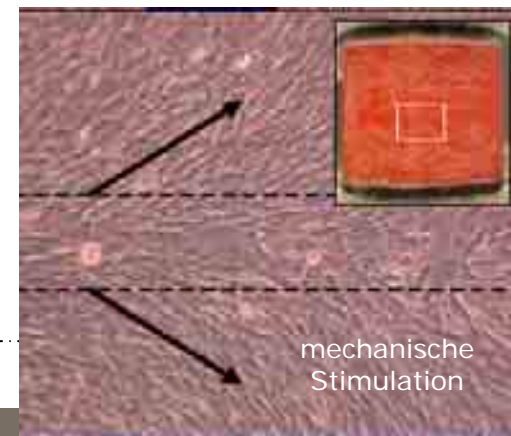
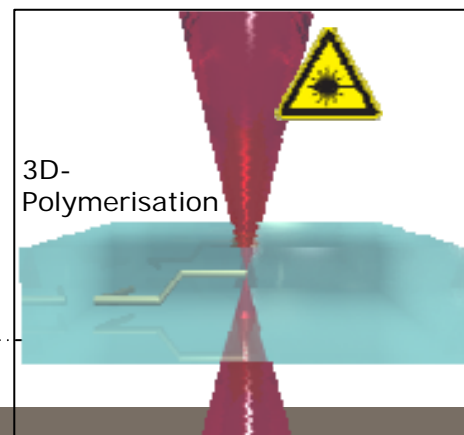
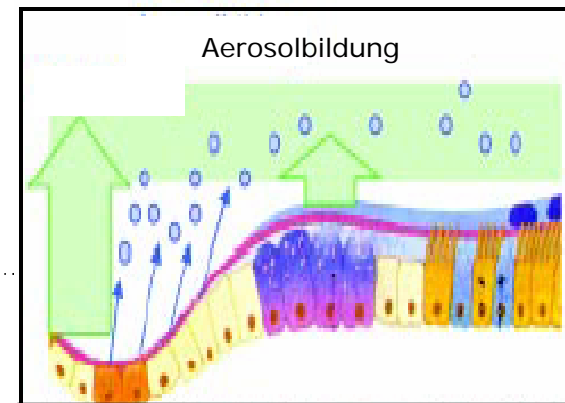
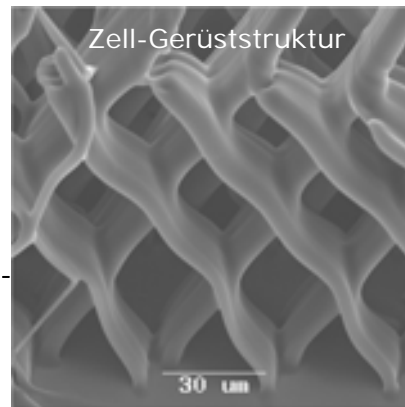
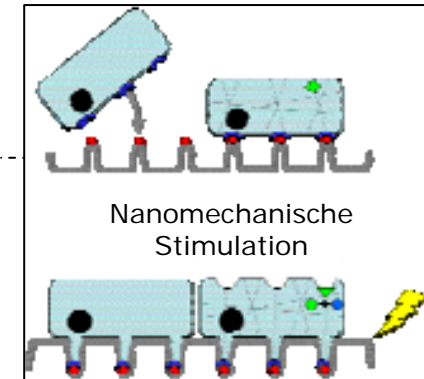
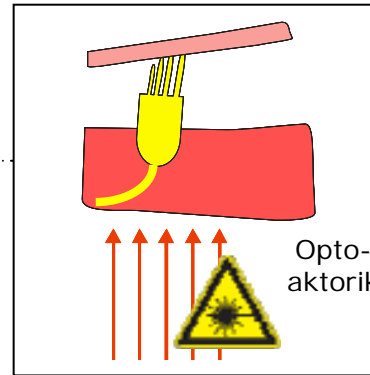
Größenordnung

nm

μm

mm

Physik

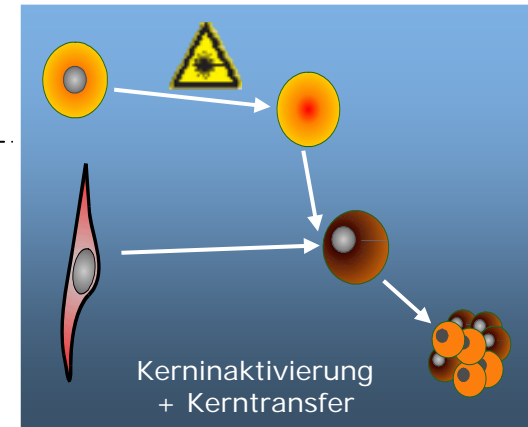


MHH

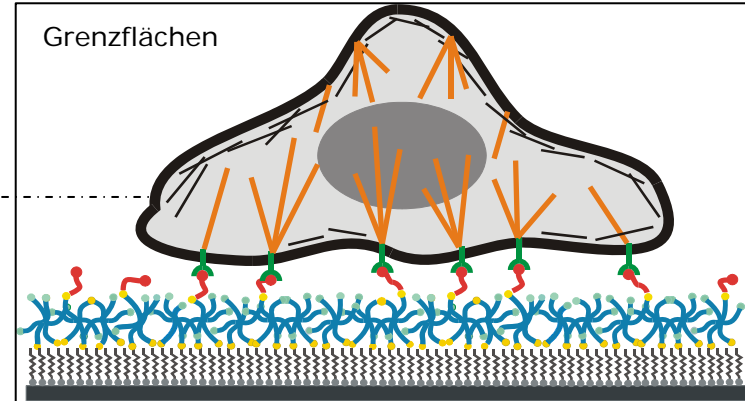
Herz-, Thorax-, Transplantations-
und Gefäßchirurgie

Größenordnung

nm

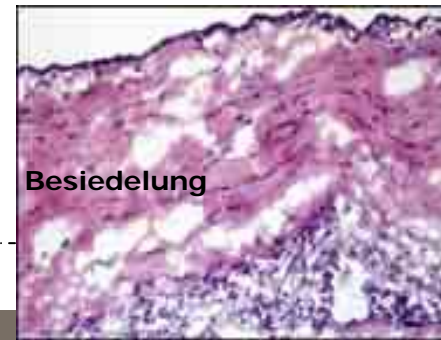
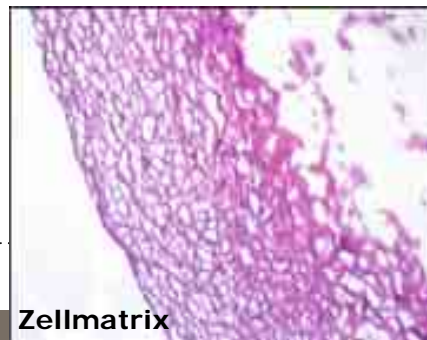


μm



Biologie/
Chemie

mm



MHH

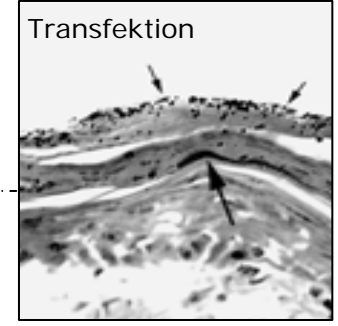
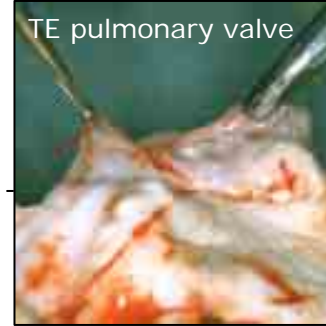
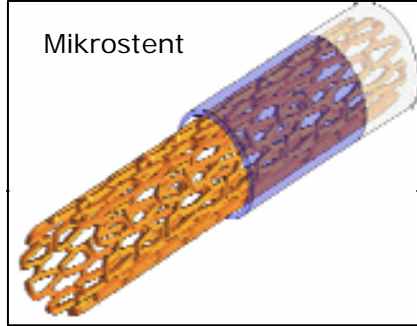
Herz-, Thorax-, Transplantations-
und Gefäßchirurgie

Therapie
+
Diagnostik

nm

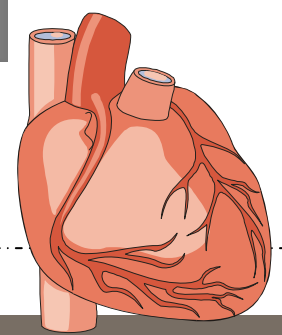


μm



Medizin

mm



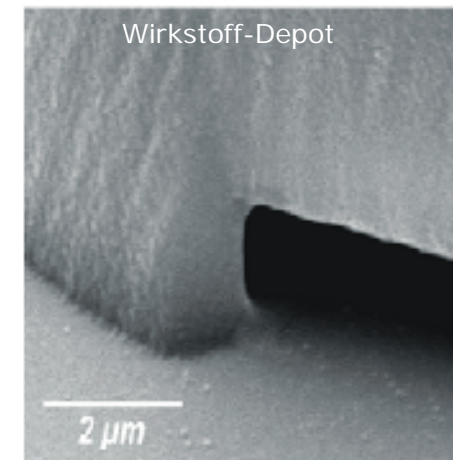
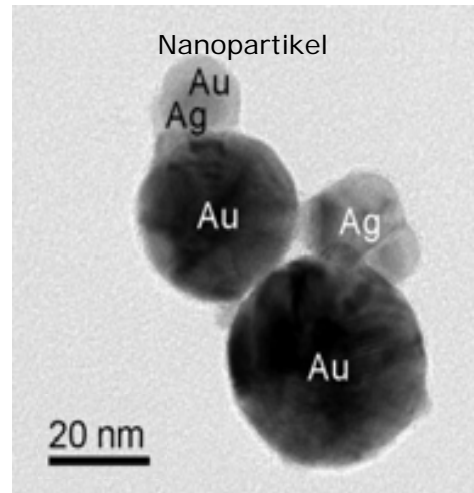
Organsysteme



MTH

Herz-, Thorax-, Transplantations-
und Gefäßchirurgie

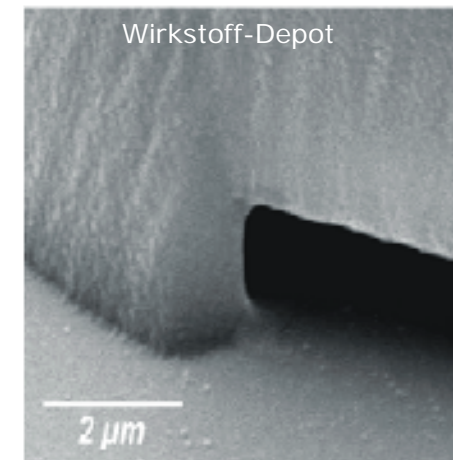
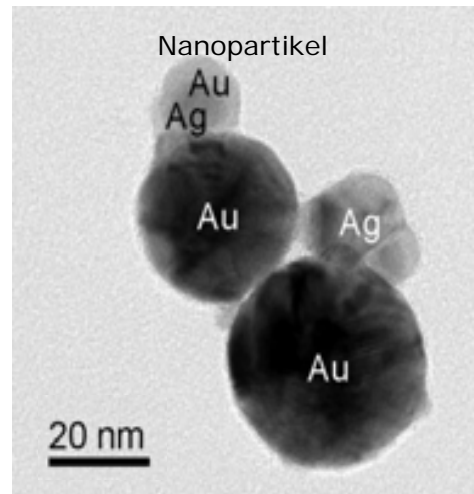
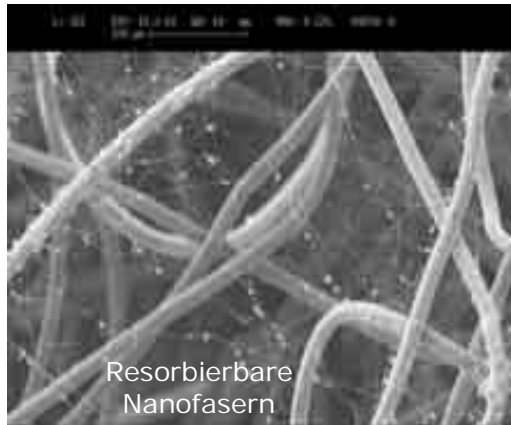
Precision: Use of Micro- and Nanostructures



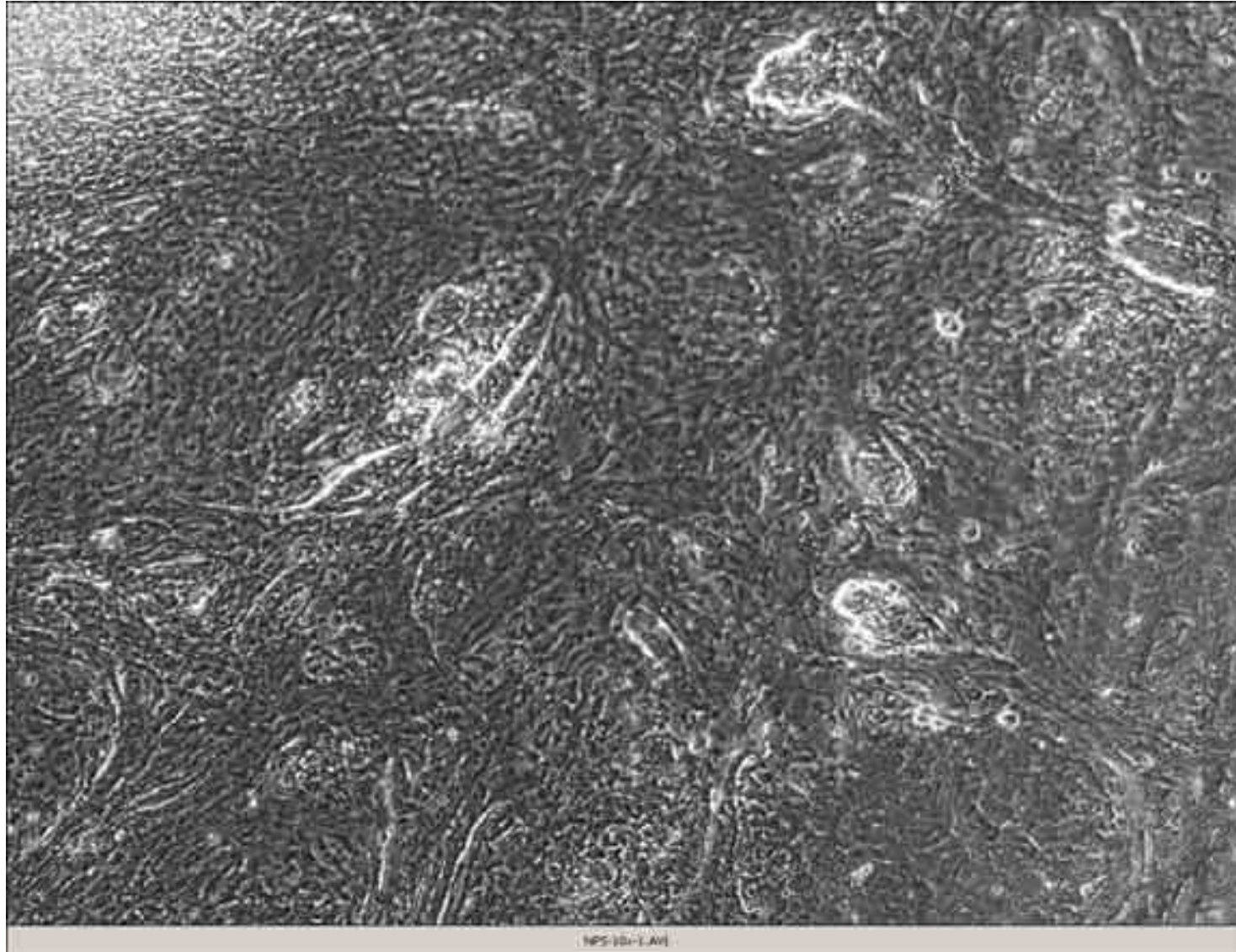
Innovation: Mini-ECMO-Circuit, Cell Seeded



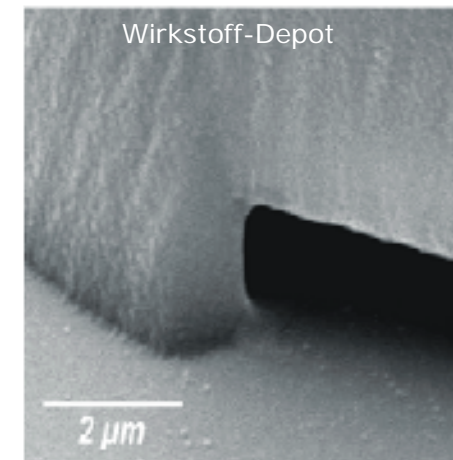
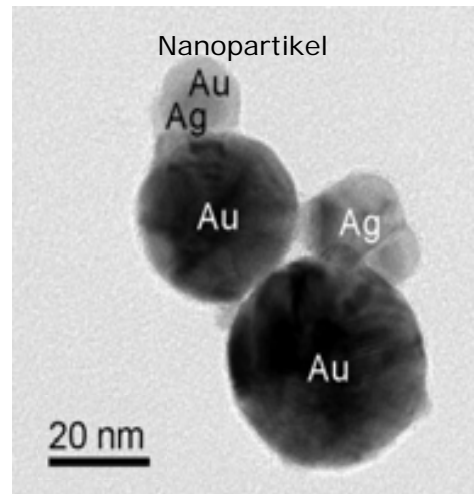
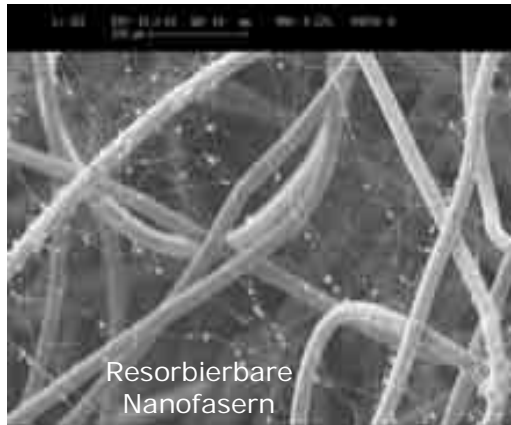
Precision: Use of Micro- and Nanostructures



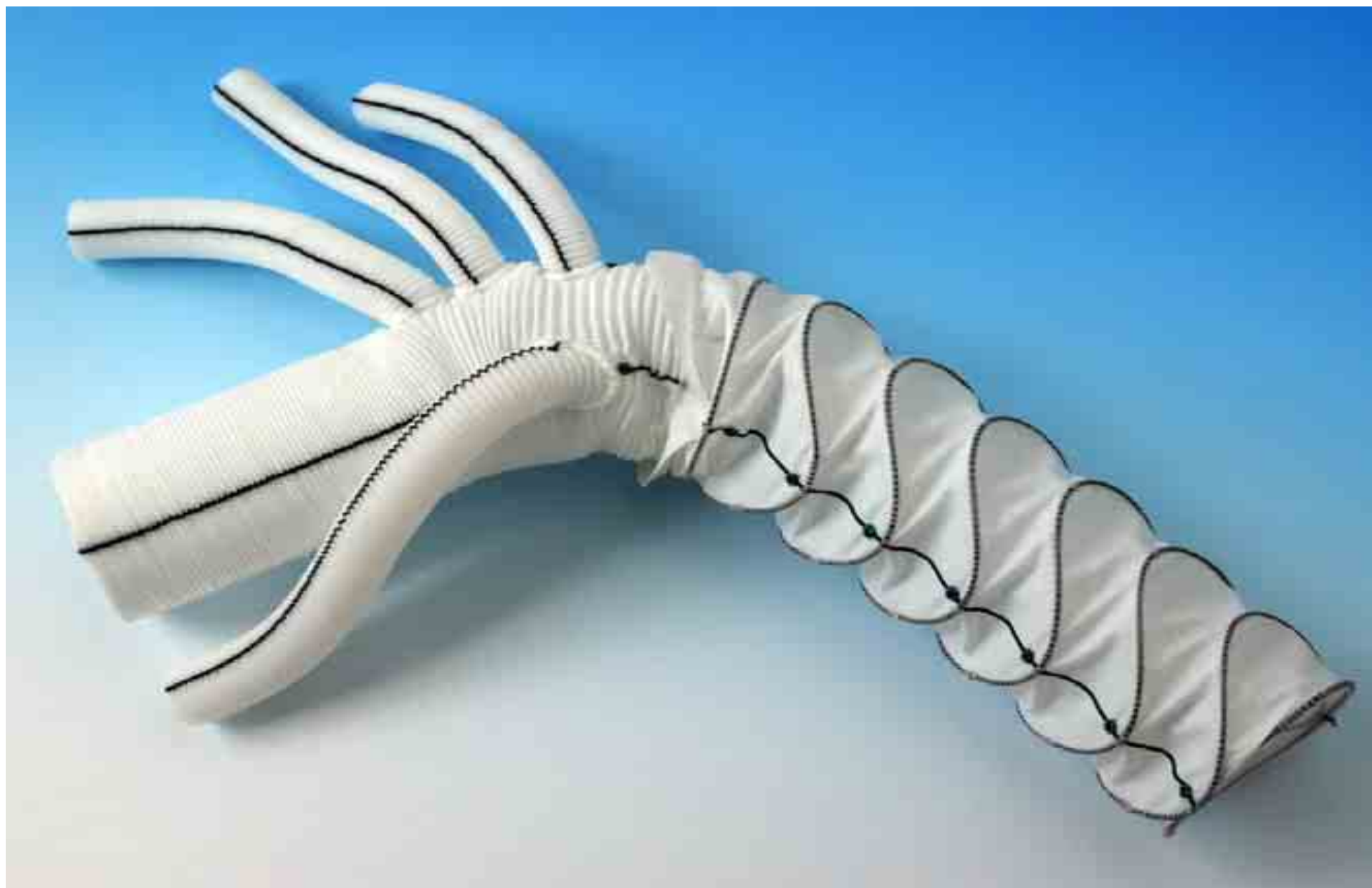
Innovation: Functional cardiomyocytes from human induced pluripotent stem (iPS) cells, e.g.



Precision: Use of Micro- and Nanostructures



Vaskutek/Haverich Hybrid Aortic Prosthesis

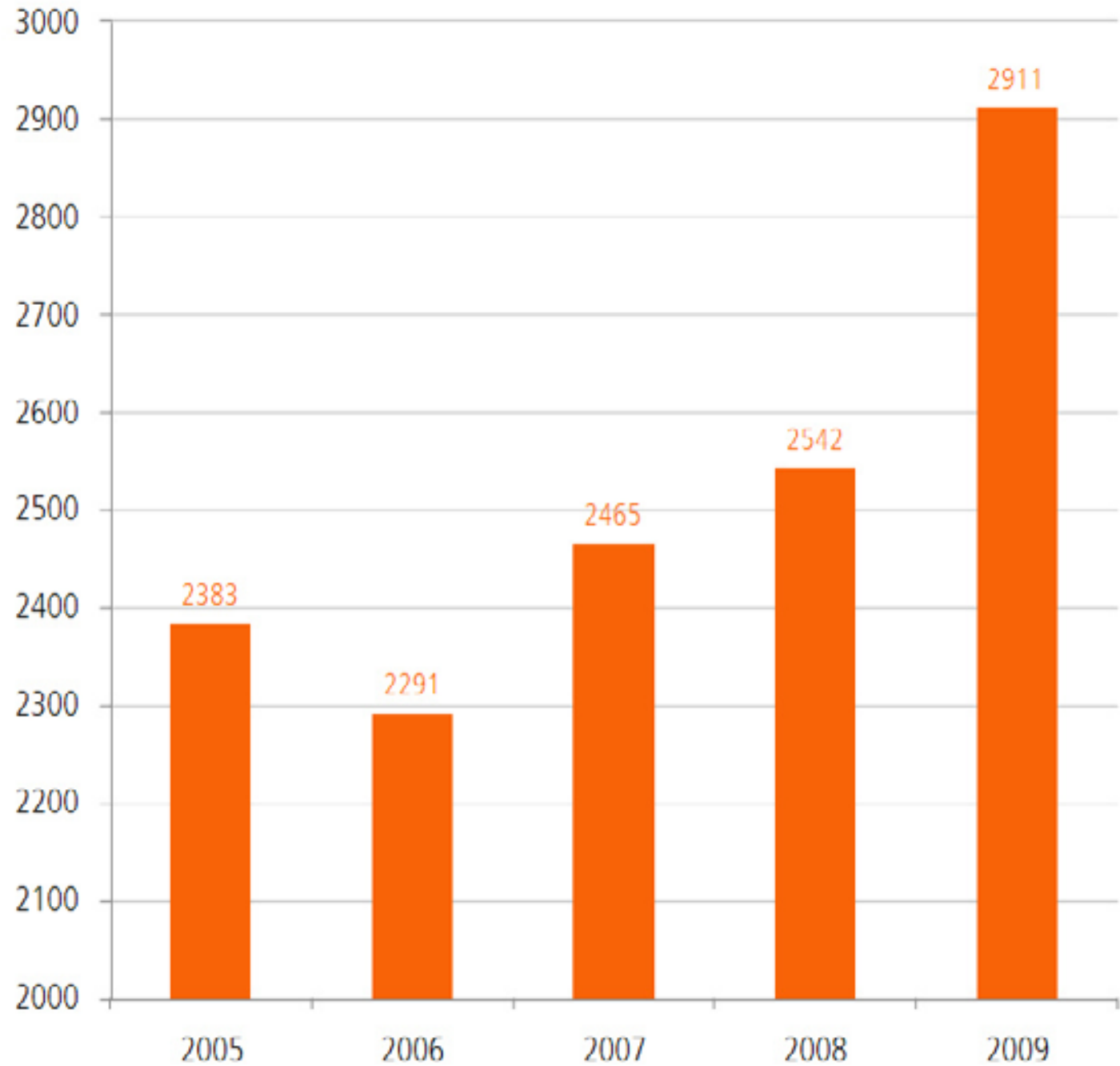


Sustainability:

Meeting the requirements

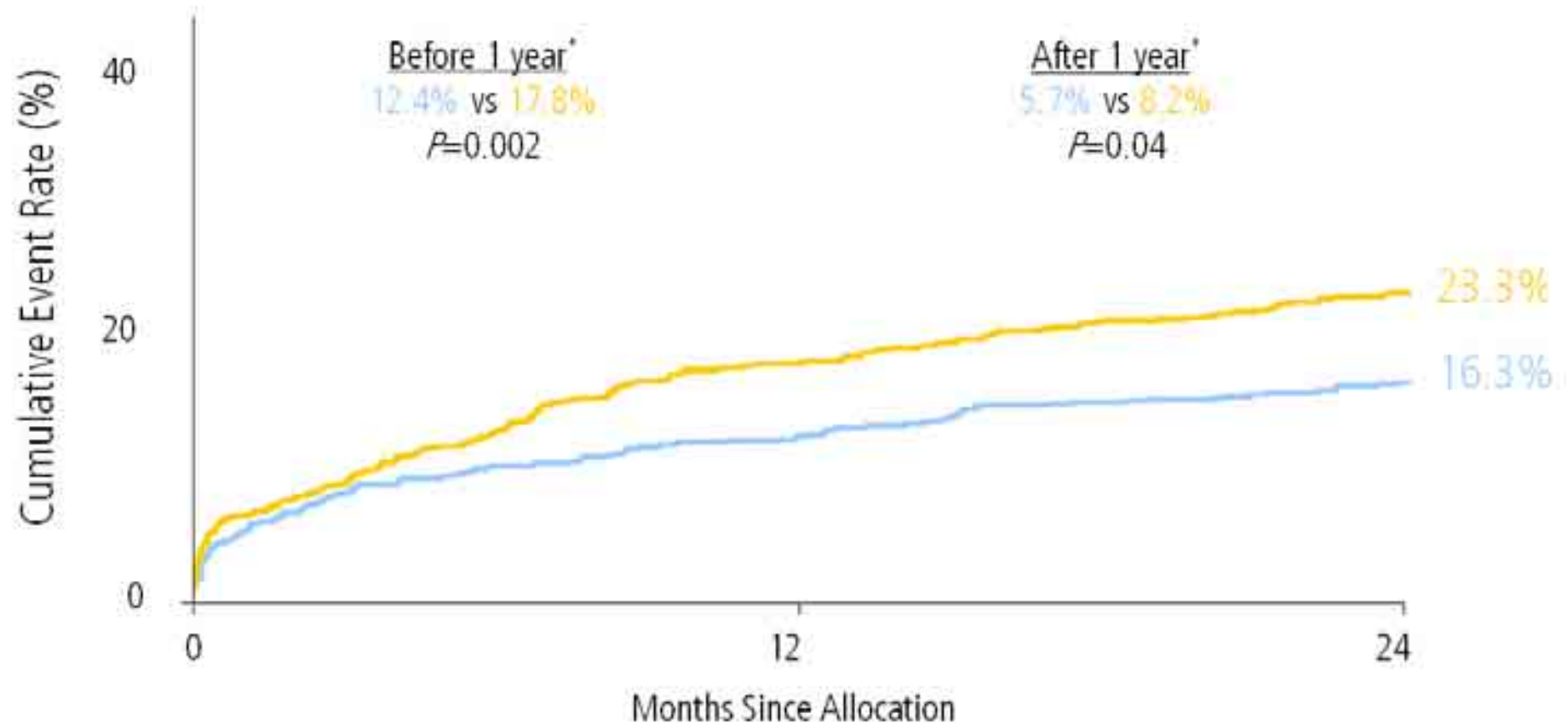
Sustainability?

Number of cases p.a.



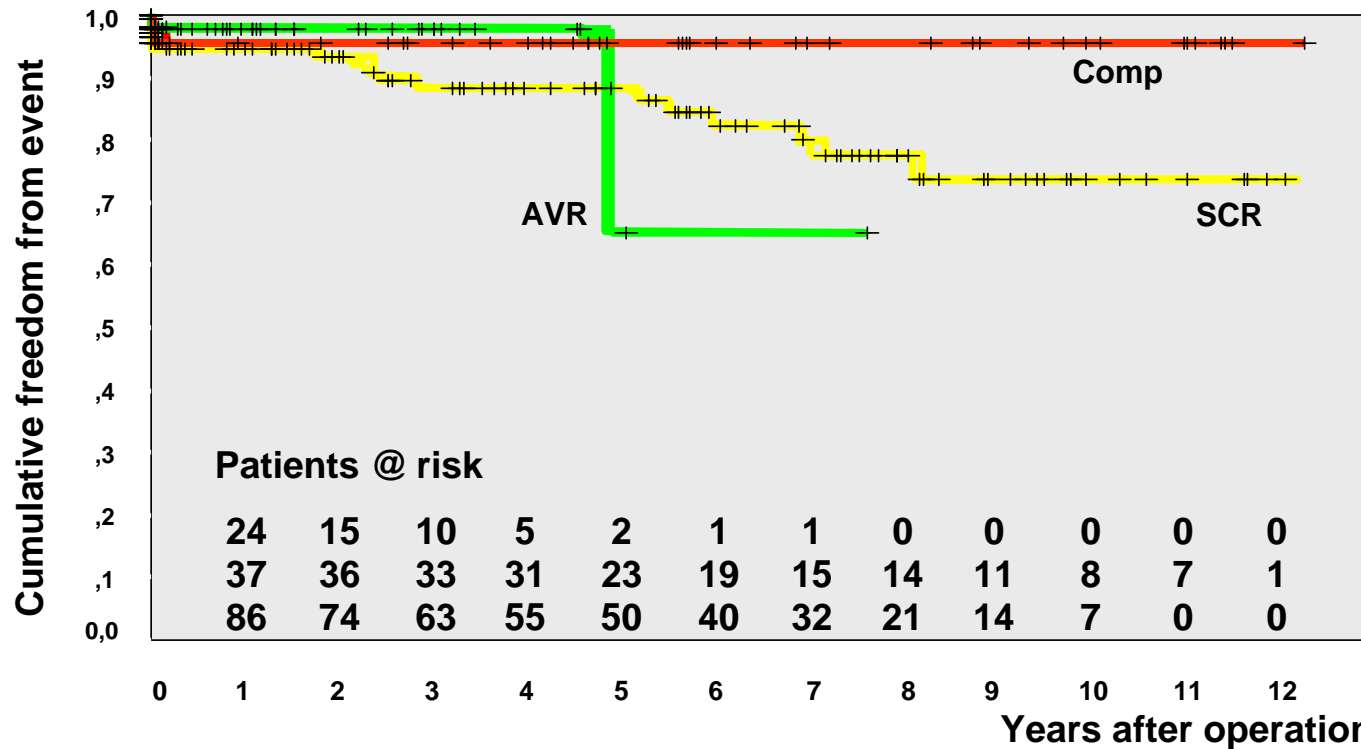
Sustainability? MACCE to 2 Years. CABG vs TAXUS

■ CABG (N=897) ■ TAXUS (N=903) P=0.0003



Cumulative KM Event Rate \pm 1.5 SE; log-rank P value;*Binary rates

Reoperation for Valvular Morbidity



actuarial freedom @

	AVR	Comp	SCR
3 year	89 ± 5	96 ± 3	88 ± 3
5 years	65 ± 27	96 ± 3	88 ± 3
10 years	-	96 ± 3	74 ± 6

log rank p=0.092

Handling the ambient hypertension

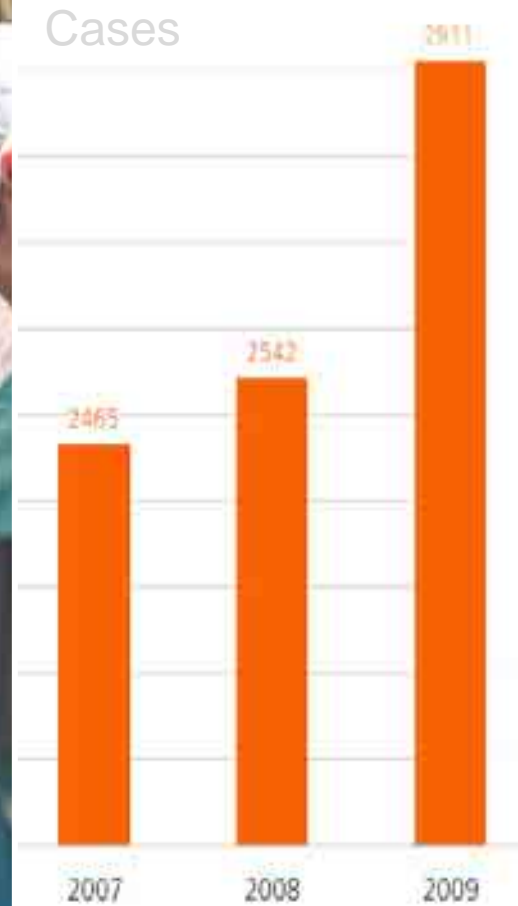
- Innovation



- Precision



- Sustainability



PART 2a:

Innovations to impact the environment

“From idea to clinical application”



Herz-, Thorax-, Transplantations-
und Gefäßchirurgie

Ideal heart valve prosthesis

Mechanical valve
★ ★

Biological (xenogeneic) valve
★ ★ ★

Homograft - Klappe
★ ★ ★ ★

Tissue Engineered heart valve
Ideal Valve-Prosthesis ?

durable

non-immunogenic

non-thrombogenous

normal hemodynamics

capable to grow

resistant to infections

non-hemolytic

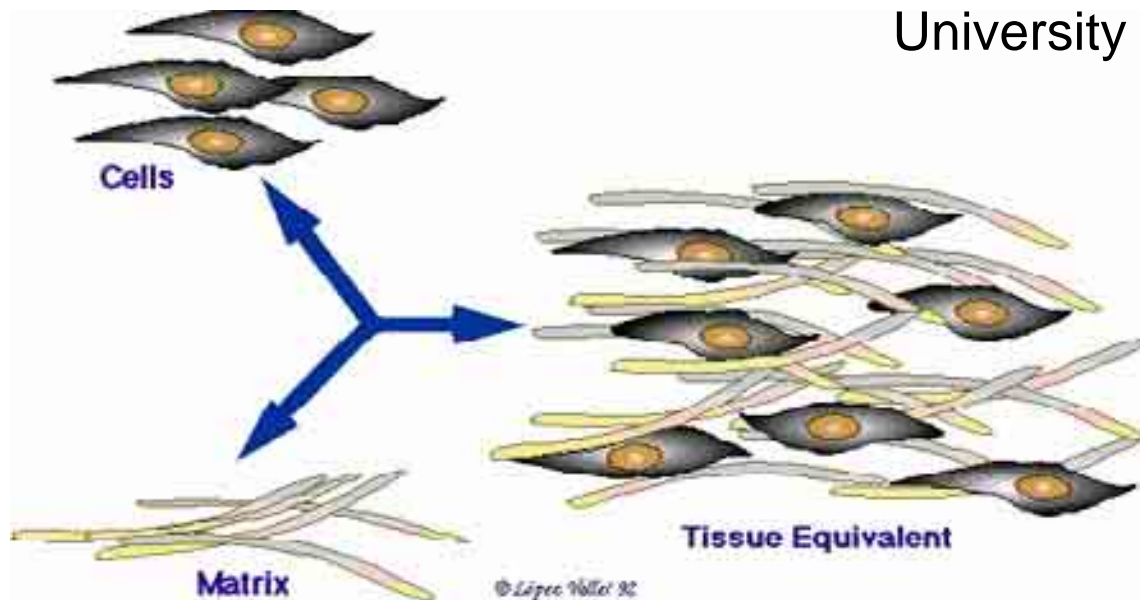
Concept of Tissue Engineering

Biological matrices

- Dr. A. Haverich, Hannover Medical School, Germany
- Dr. M. Yacoub, Imperial College London, Harefield, UK

Biodegradable matrices

- Dr. J. Meyer, Dr. Vacanti, Children's Hospital Boston, USA
- Dr. T. Shinoka, Tokyo Women's Medical University, Japan
- Dr. S. Hoerstrup, University Hospital Zurich, Switzerland



Role of decellularization for clinical application



Complete removal of immunogenic cells from collagen matrix

Optimal maintenance of

- 3D-matrix-structure
- mechanical stability

Methods of decellularization

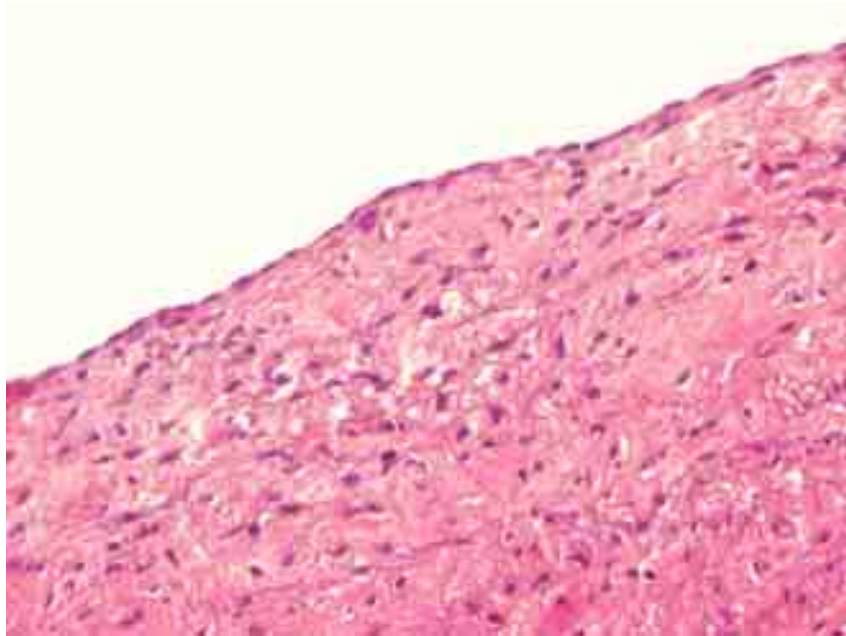
Enzymatic

- Trypsin/ EDTA

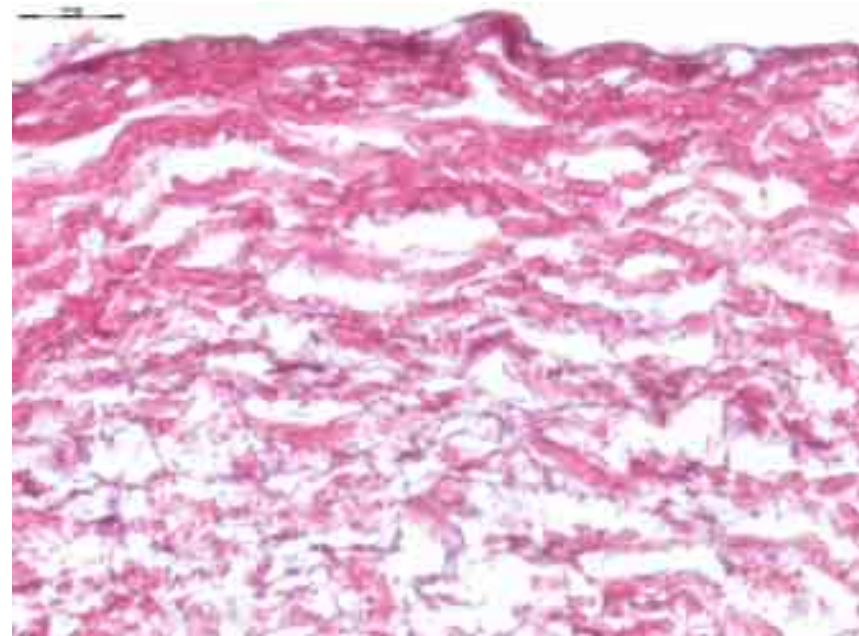
Detergent based

- Sodium-dodecyl-sulfate (SDS) 1%
- Sodium-deoxycholate (SD) 1%
- SD + SDS (“Hannover” Method)

NSD Decell. ovine, PA-wall, PHE staining, x400

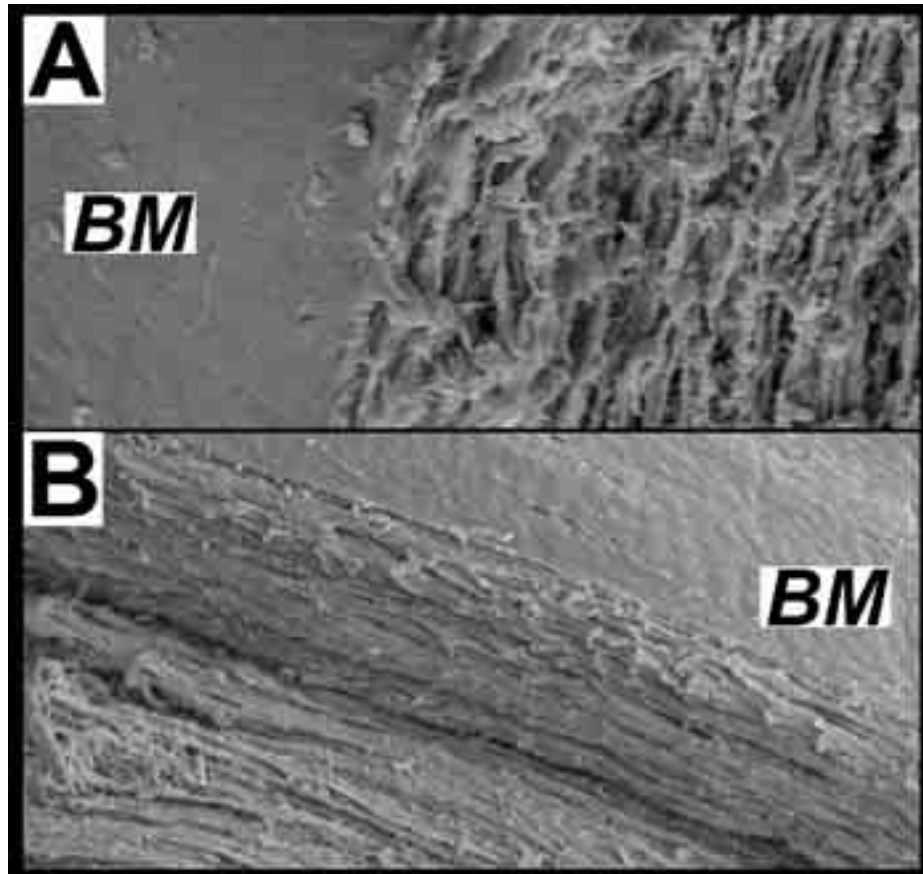


Native



Decellularized

Scanning electron microscopy



- Decellularization by SD + SDS
- Maintenance of basal lamina

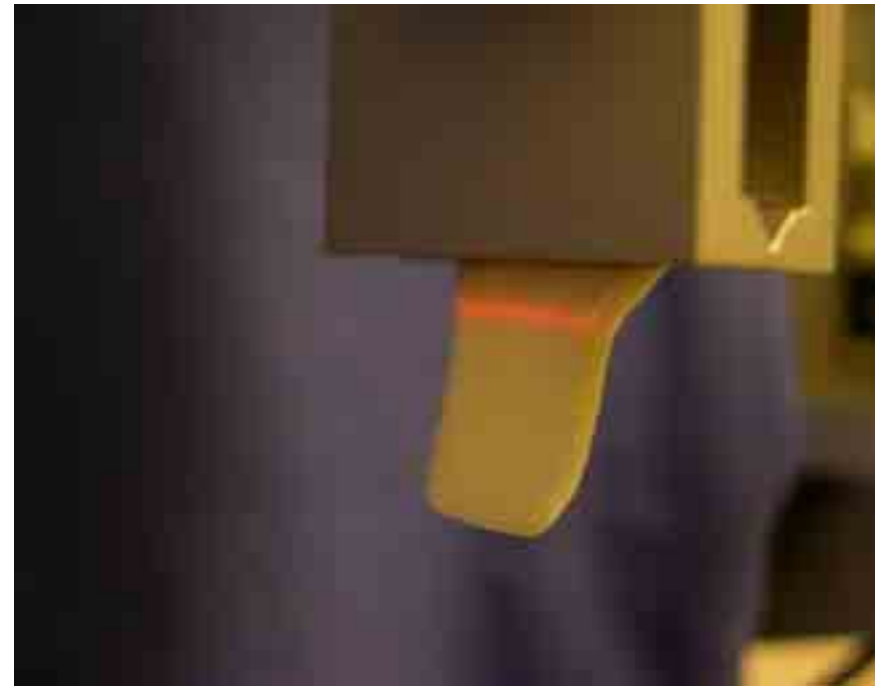
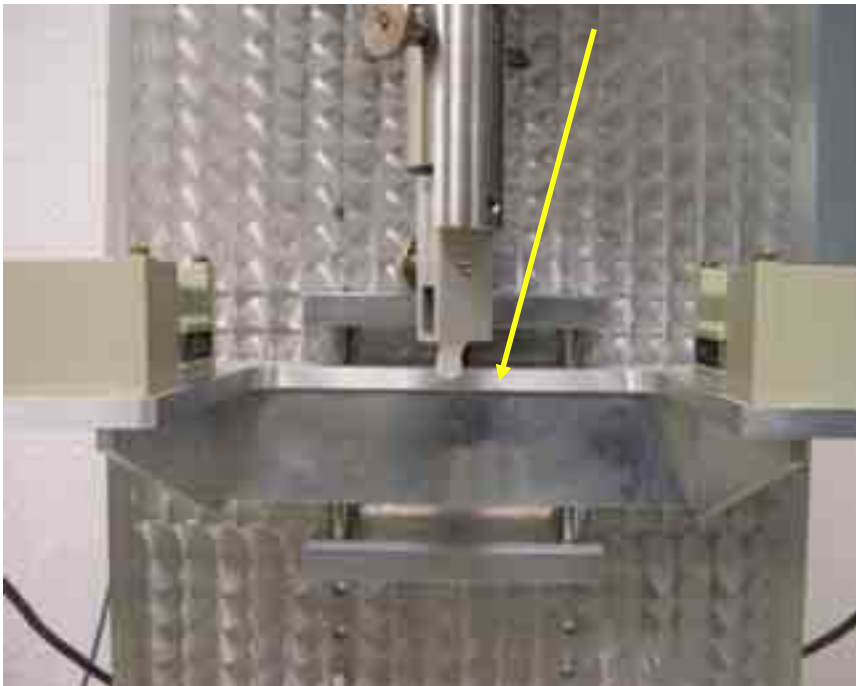
Biomechanical tests



Tudorache I, Cebotari S, Sturz G, et al. Tissue Engineering of Heart Valves: Biomechanical and Morphological Properties of Decellularized Heart Valves. *The Journal of Heart Valve Disease* 2007;16:567-574

Biomechanical Tests. Profile – Surface assessment

No-Touch Laser-Micrometer



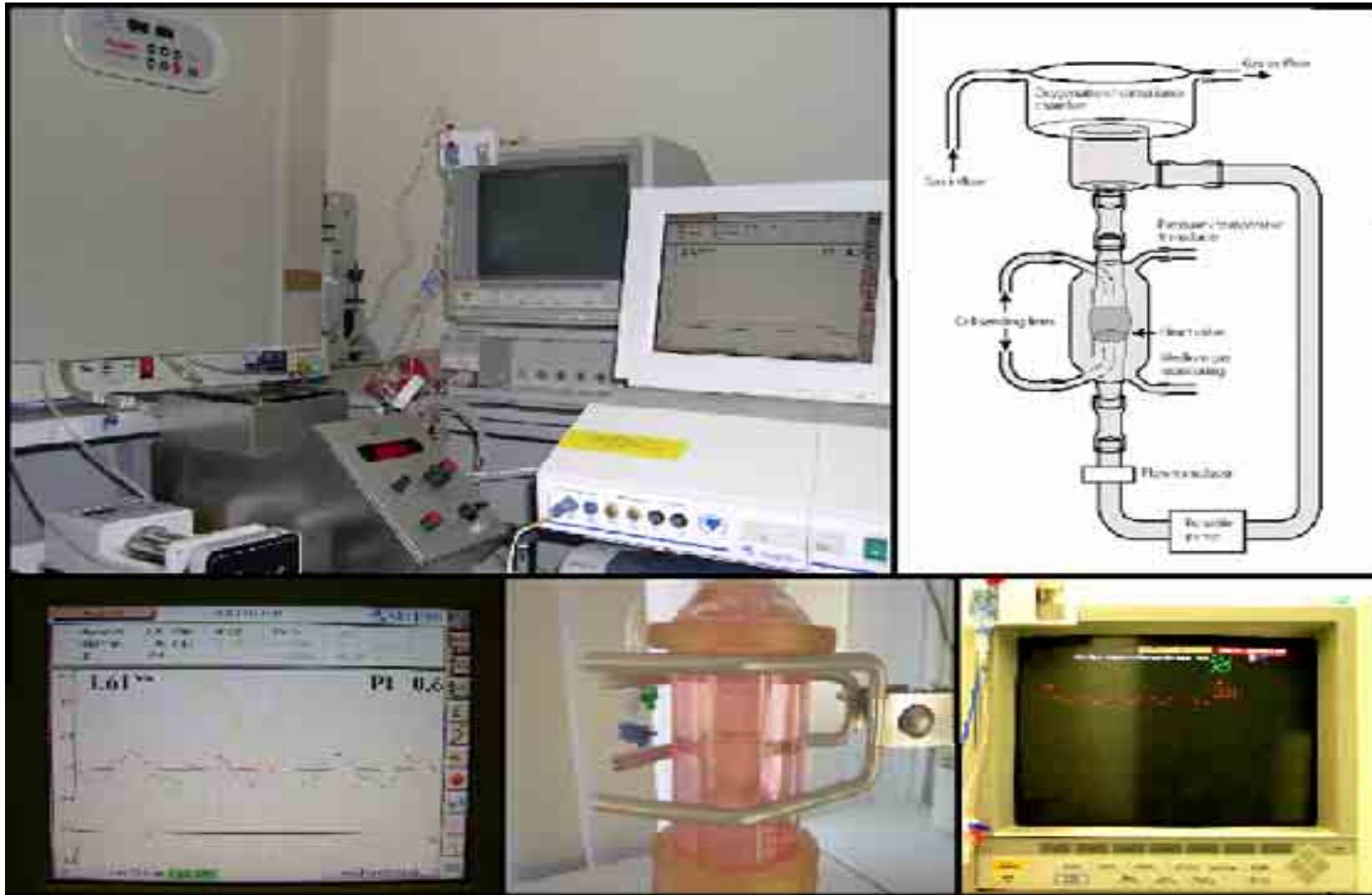
Tudorache I, Cebotari S, Sturz G, et al. Tissue Engineering of Heart Valves: Biomechanical and Morphological Properties of Decellularized Heart Valves. *The Journal of Heart Valve Disease* 2007;16:567-574

Biomechanical tests



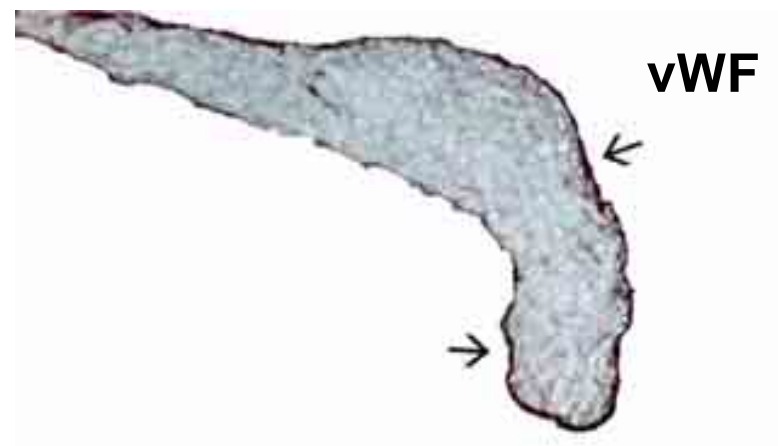
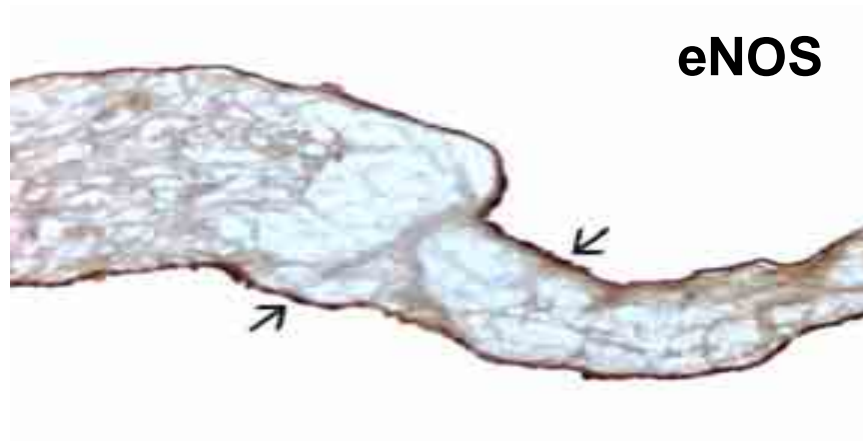
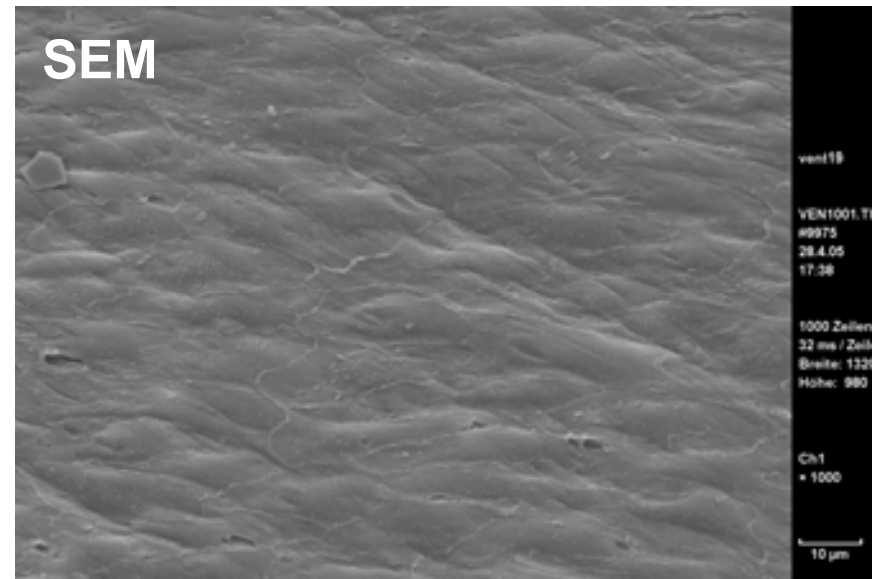
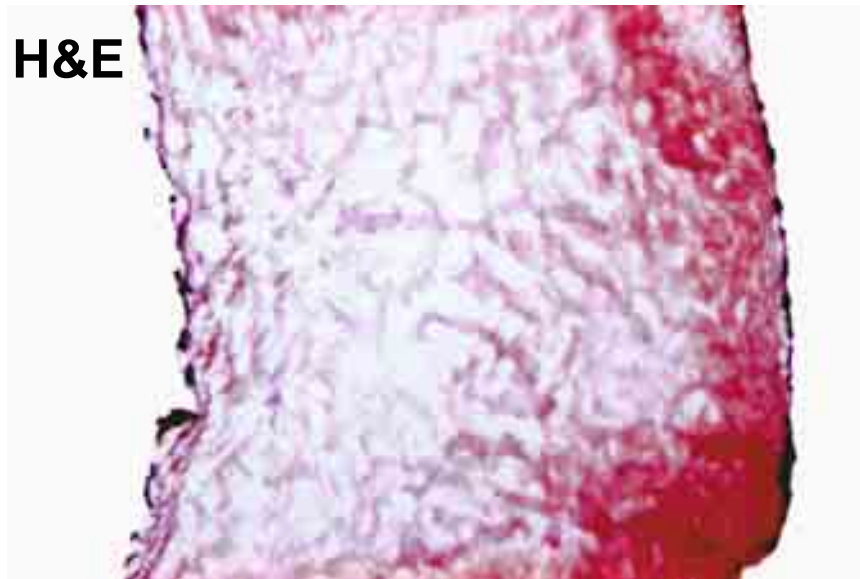
Distensibility (0.1mm/s)

Re-Seeding: Bioreactor system



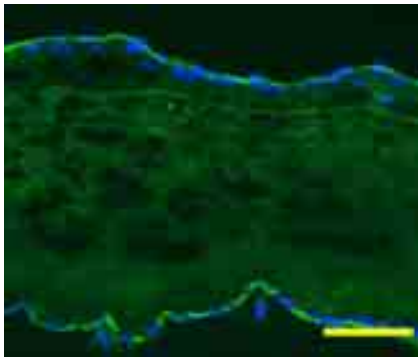
Lichtenberg A, Tudorache I, Cebotari S, et al. In vitro re-endothelialization of detergent decellularized heart valves under simulated physiological dynamic conditions. *Biomaterials*. 2006 Aug;27(23):4221-9.

Results: Dynamic re-endothelialization

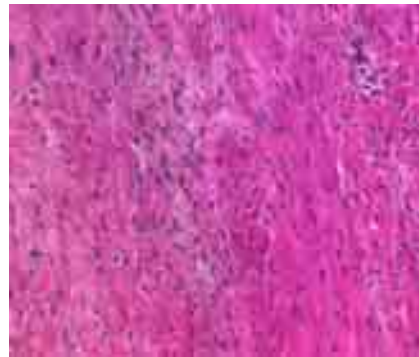


Preclinical results: TE heart valves after implantation in young sheep

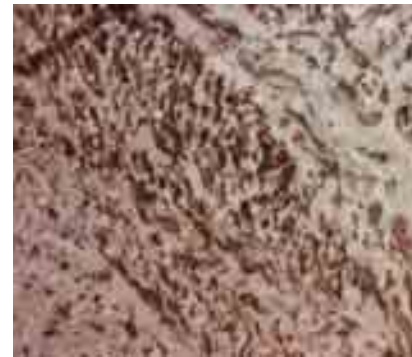
- Complete re-endothelialization of grafts after 1 month following implantation
- Physiologic in vivo remodelling of grafts by host`s cells



eNOs Färbung einer
rebesiedelten PK
1 Monat nach Implantation



H&E Färbung



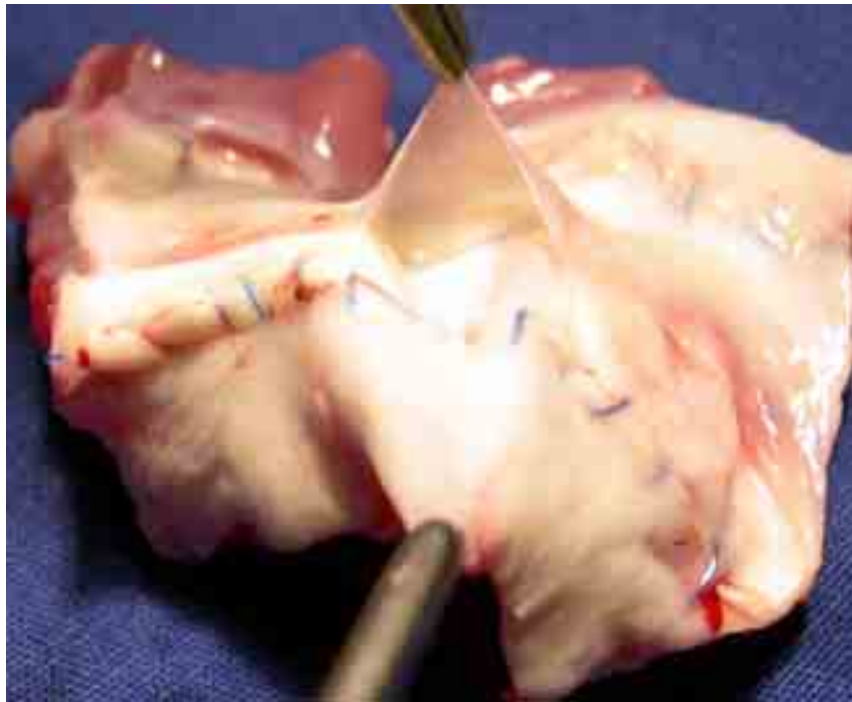
α – Aktin Färbung



Prokollagen Färbung

Results after 6 month of implantation: Re-seeding

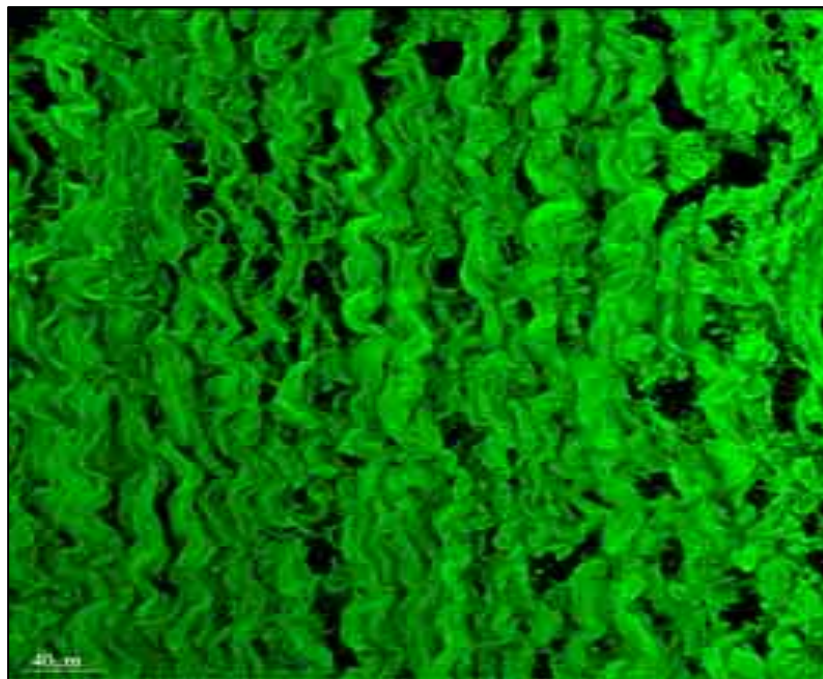
Decellularized heart valve



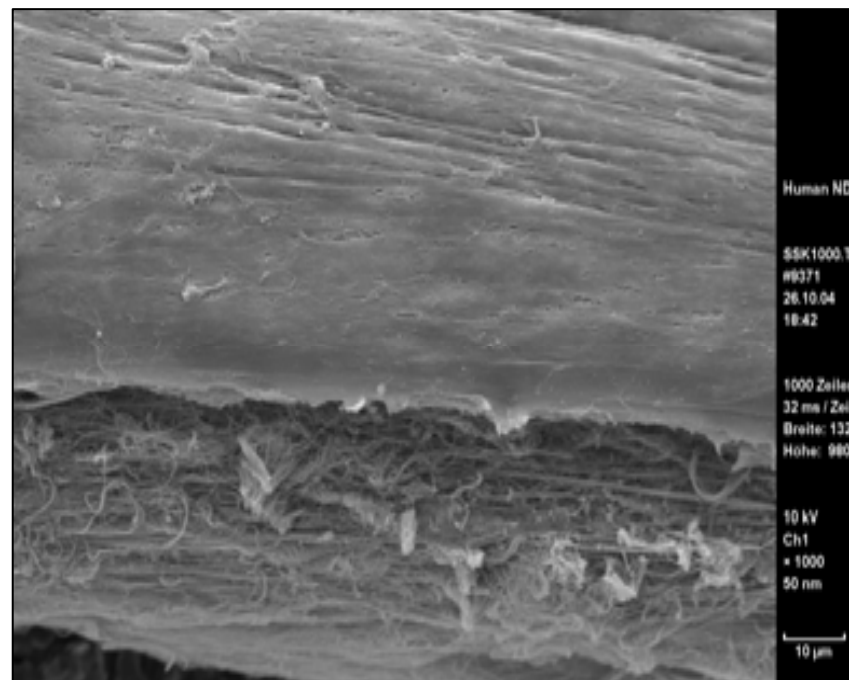
Re-endothelialized heart valve



Structure of human collagen heart valve matrix after decellularization



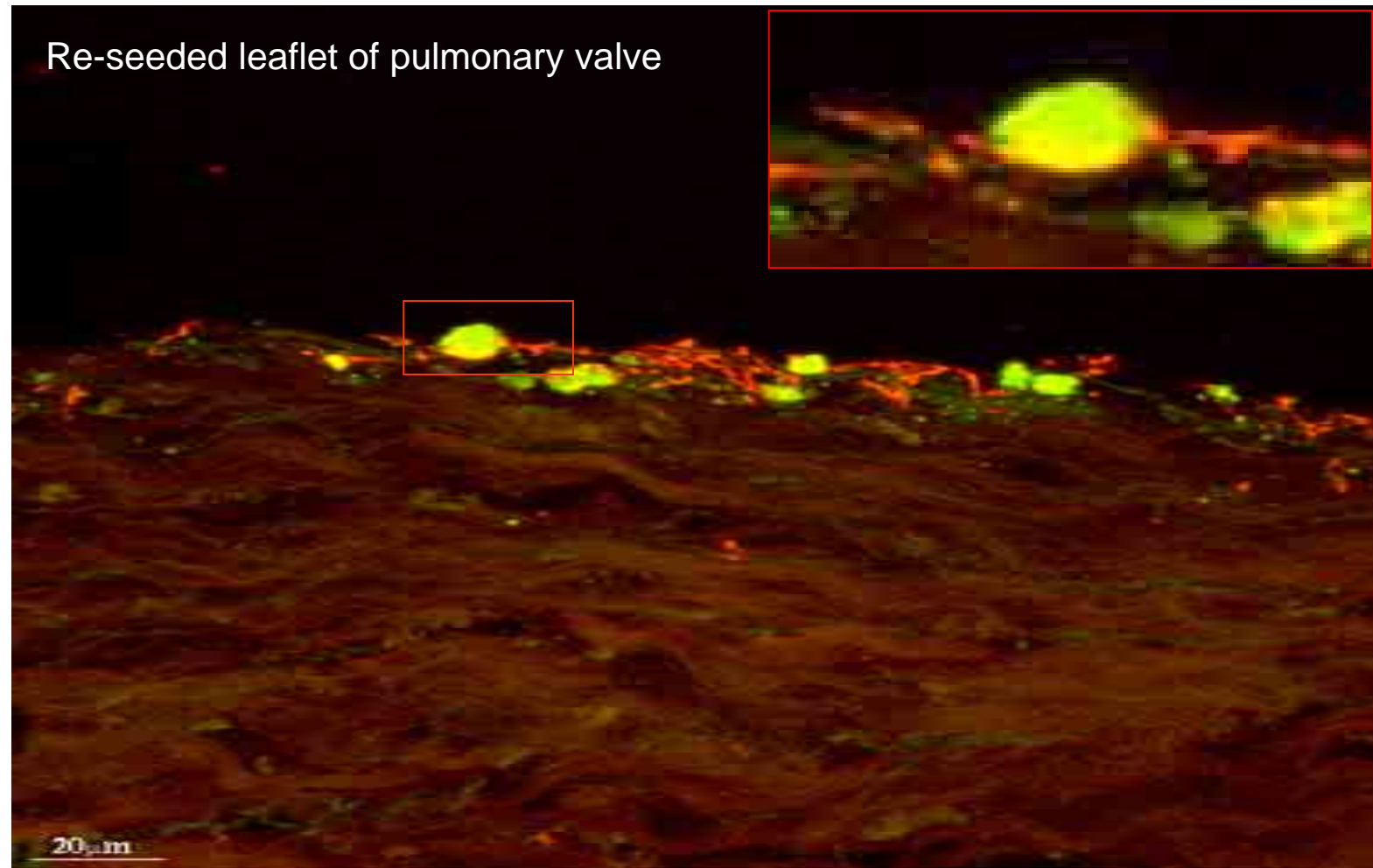
Coll I staining, Confocal microscopy



Scanning electron microscopy

Cebotari S, Mertsching H, Kallenbach K, et al. Construction of autologous human heart valves based on an acellular allograft matrix. *Circulation*. 2002 Sep 24;106(12 Suppl 1):I63-I68.

Re-seeding of acellular heart valves with human endothelial cells (CD31 staining)

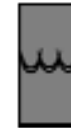


Cebotari S, Mertsching H, Kallenbach K, et al. Construction of autologous human heart valves based on an acellular allograft matrix. *Circulation*. 2002 Sep 24;106(12 Suppl 1):I63-I68.

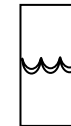
First results of clinical application of TE heart valves

Implantations

Conduits : 2 re-seeded



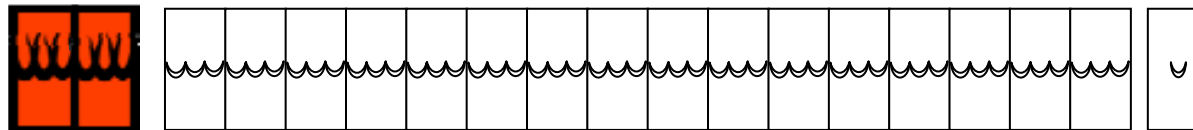
16 decellularized homografts

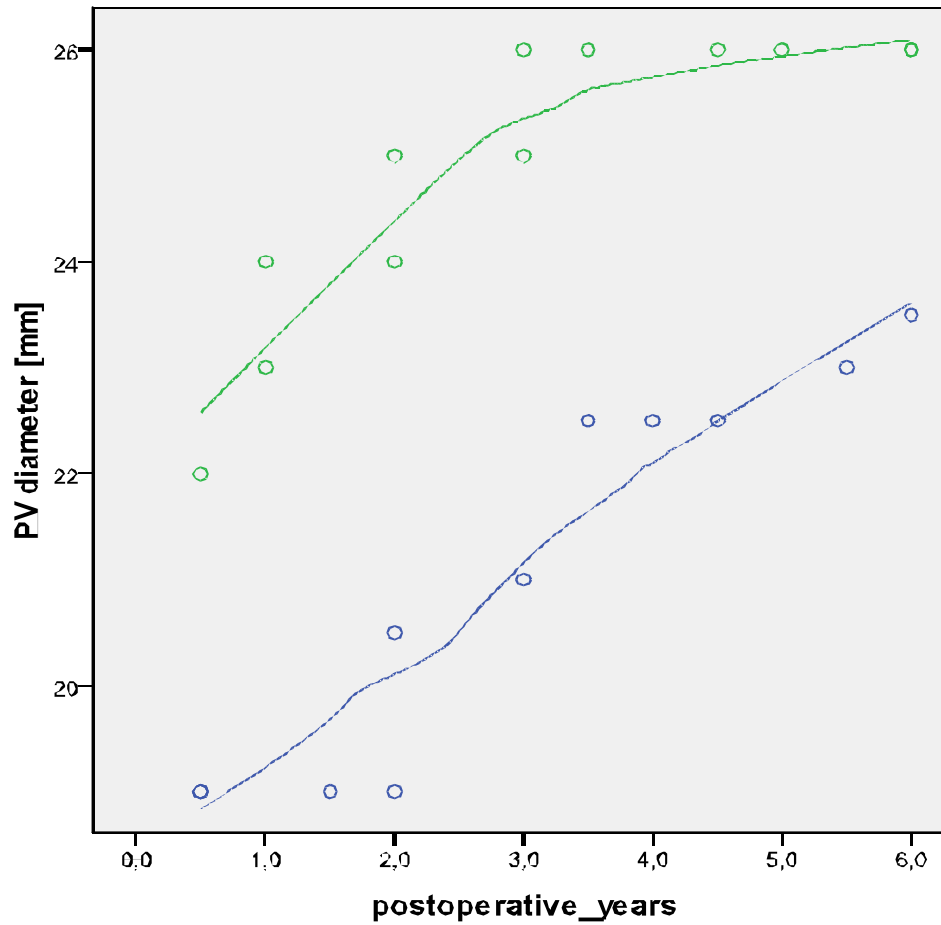


1 decellularized monocusp



Technique: Standard (median sternotomy, conventional ECC)



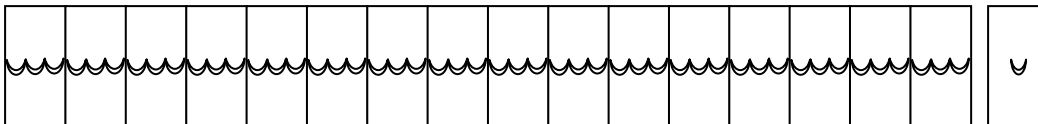


female, 13
years

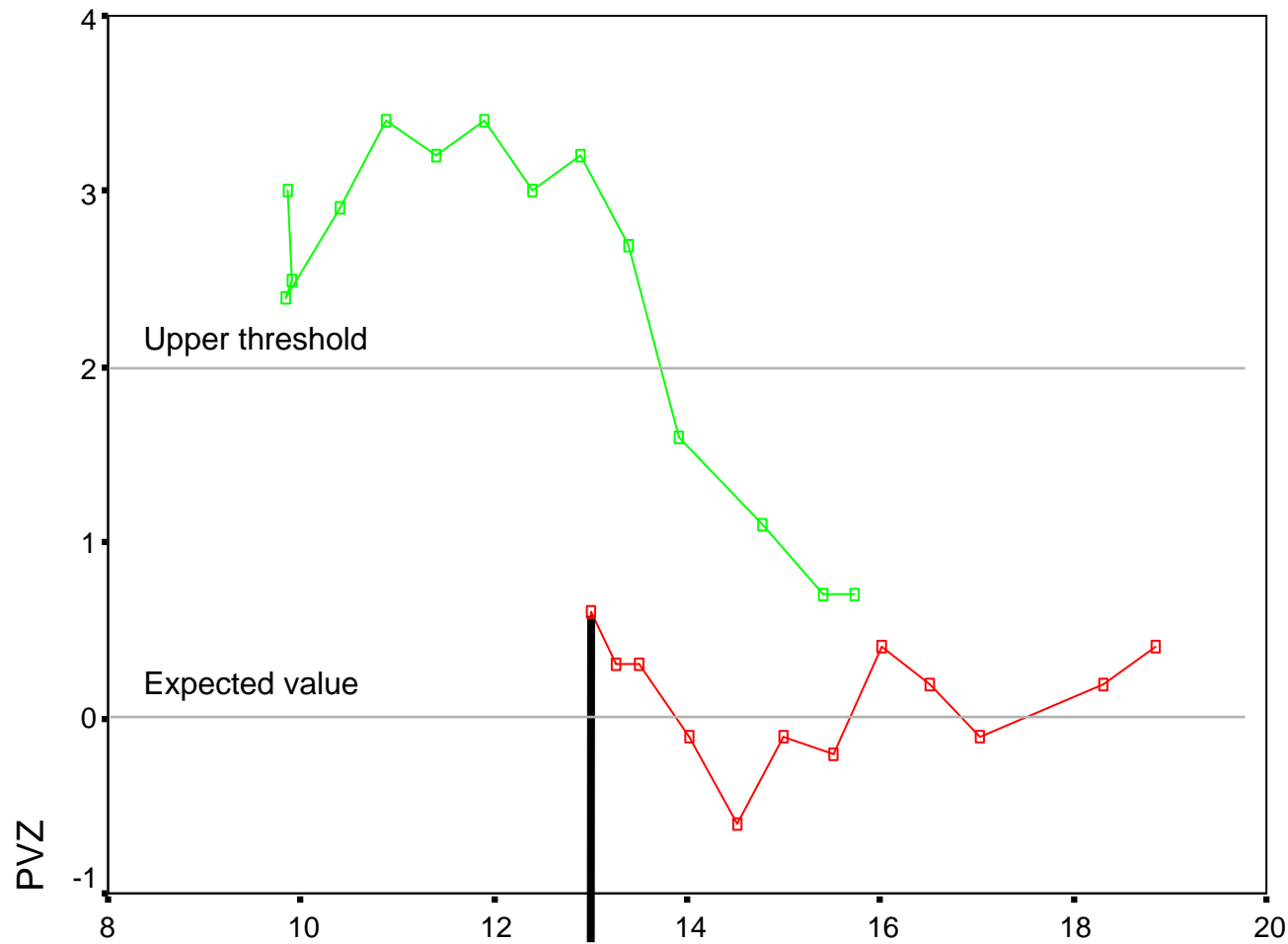
male, 10
years

PV diameter

(2 re-seeded
homografts)



Z-value-development



PV diameter

(2 re-seeded
homografts)

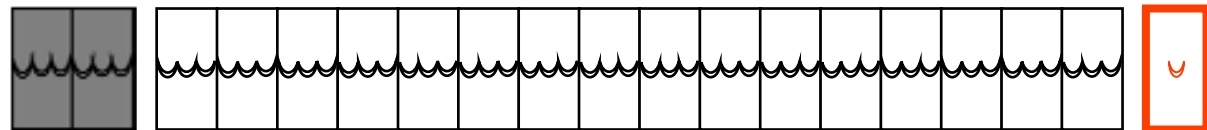
AGEATEXAM

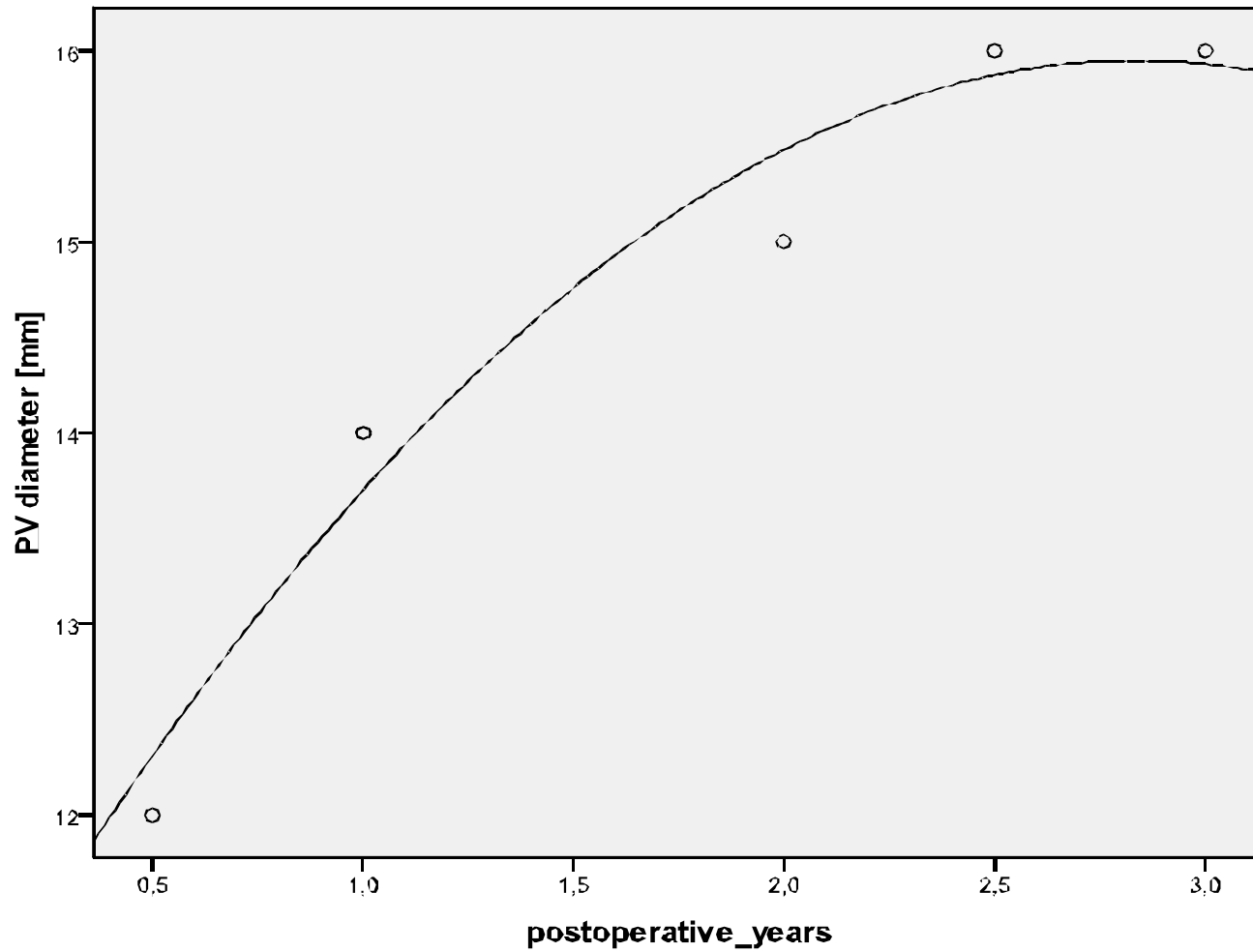
MTH

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Follow-up (1 monocusp)

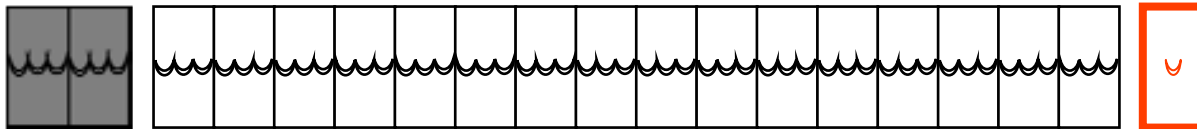
Follow-up: 2.7 years
Examinations: 6



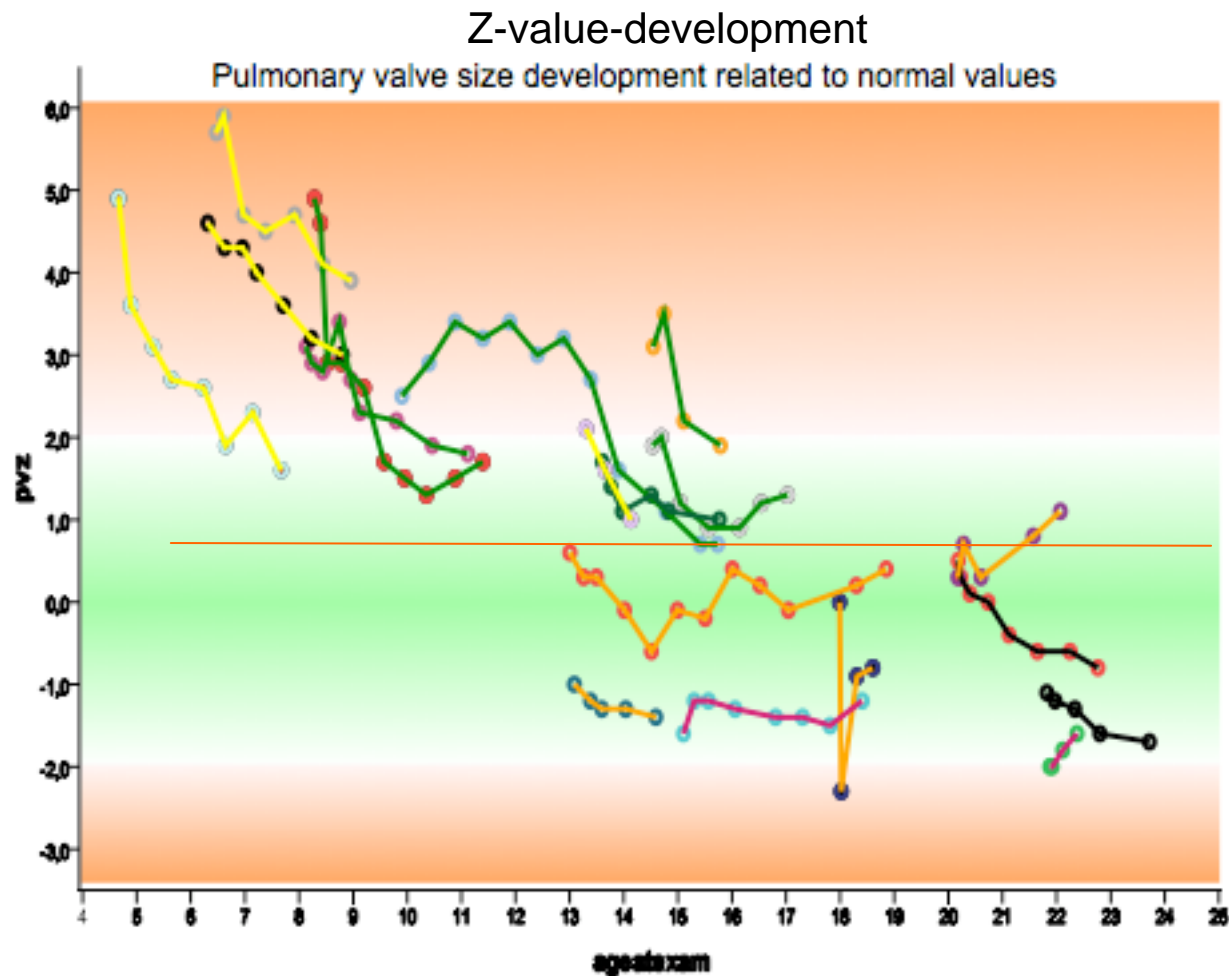


PV diameter

(1 Monocusp)



PV diameter (16 decellularized homografts)



4 approaching normal values

6 reached normal values and stayed there

4 stayed close to normal values

2 grew up to normal values

Conclusion

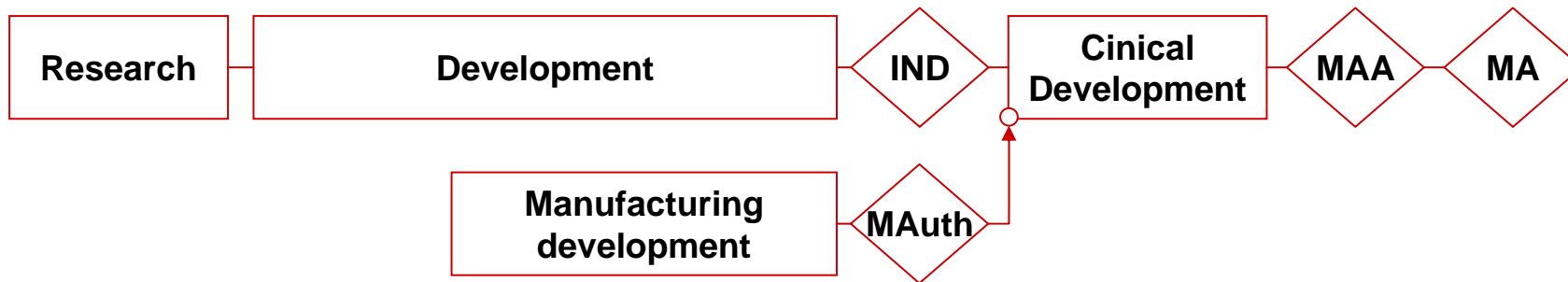
Tissue engineering by decellularization

- is a feasible and safe **INNOVATION**
- **PRECISION** manufacturing for adaptive-physiologic growth
- 100% functional grafts at 7.5 years **Sustainability**

PART 2b:

Roadmap from idea to marketing authorization

Development chart



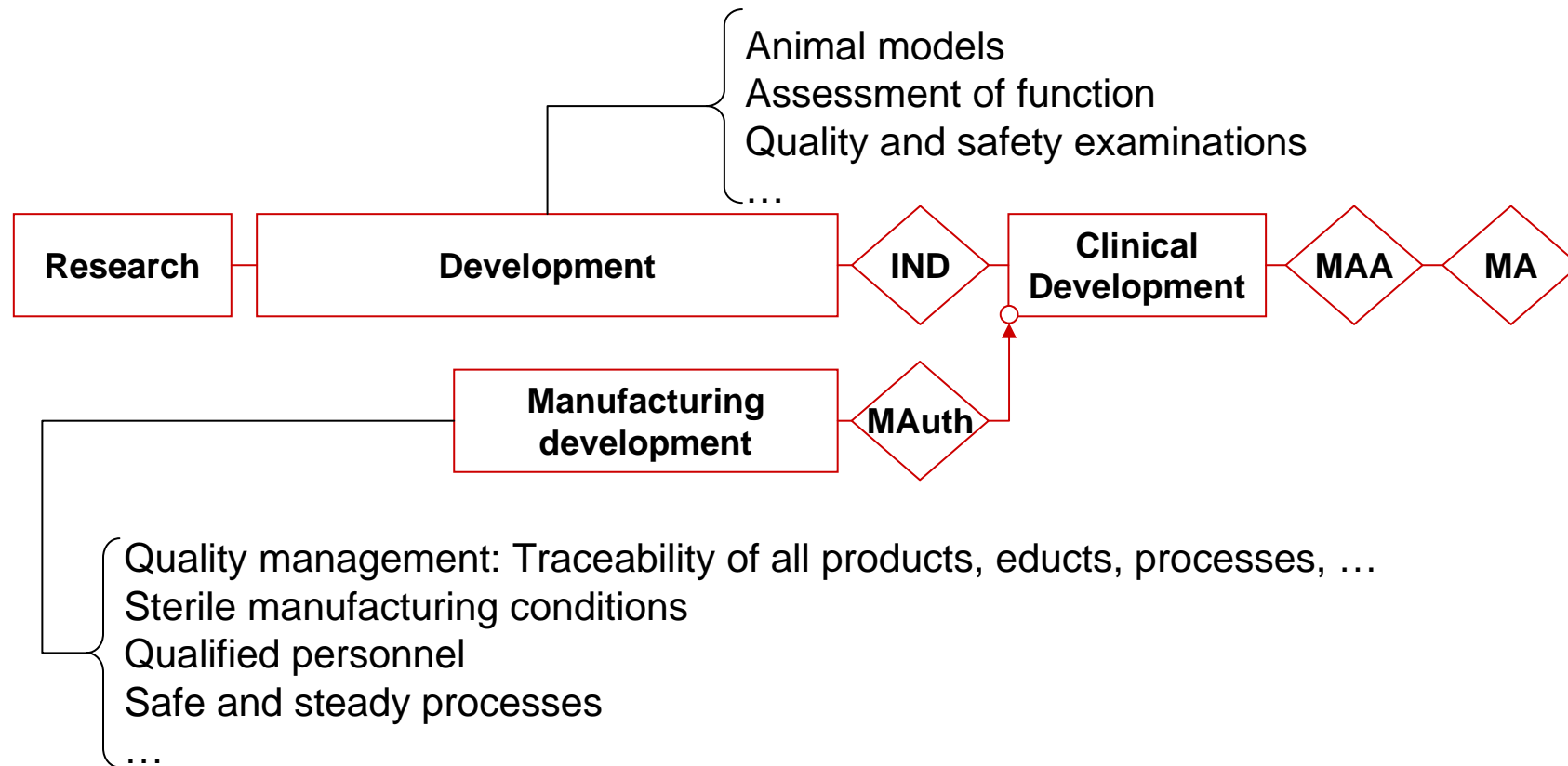
IND: Investigational New Drug Application

MAA: Marketing Authorization Application

MA: Marketing Authorization

MAuth: Manufacturing Authorization

Development Chart



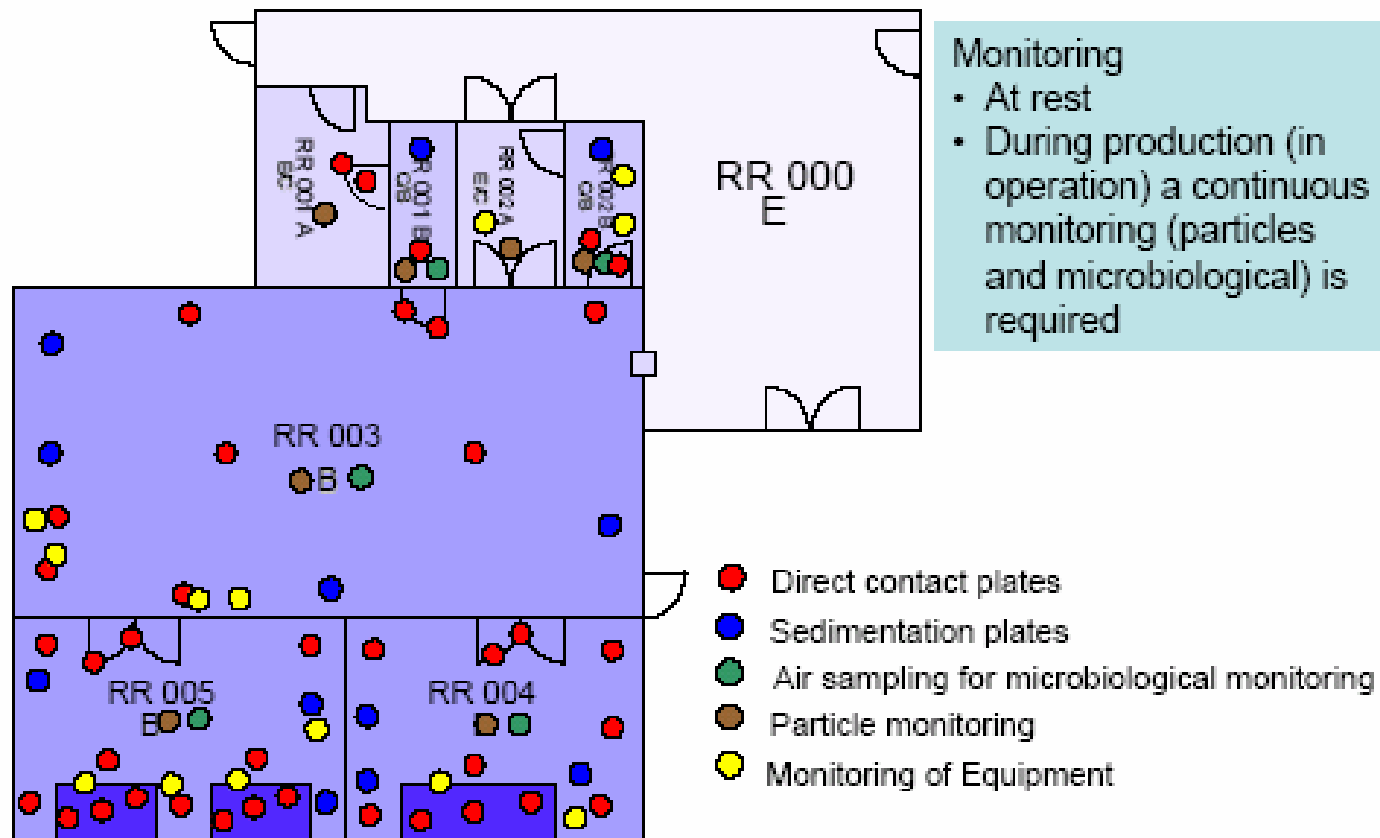
EMA/CHMP/410869/2006

- 4.1 RISK ANALYSIS
- 4.2 QUALITY AND MANUFACTURING ASPECTS
 - 4.2.1 Starting and raw materials
 - 4.2.2 Manufacturing process
 - 4.2.3 Characterisation
 - 4.2.4 Quality control
 - 4.2.5 Validation of the manufacturing process
 - 4.2.6 Development Pharmaceuticals
 - 4.2.7 Traceability
 - 4.2.8 Comparability
- 4.3 NON-CLINICAL DEVELOPMENT
 - 4.3.1. Pharmacology
 - 4.3.2. Toxicology
- 4.4 CLINICAL DEVELOPMENT
 - 4.4.1 General aspects
 - 4.4.2 Pharmacodynamics
 - 4.4.3 Pharmacokinetics
 - 4.4.4 Dose finding studies
 - 4.4.5 Clinical Efficacy
 - 4.4.6 Clinical Safety
 - 4.4.7 Pharmacovigilance and Risk Management Plan

Example of a GMP-facility

Monitoring of Clean Room

Concept of CellMed AG



„Conventional“ studies

- Phase I: Compatibility of agents, absorption in human body, kinetics;
- Phase II: Effectiveness, improvement of dose, short term adverse effects
- Phase III: Proof of effectiveness and compatibility
- Phase IV: Therapeutic application of approved drug: risk-benefit analysis

G. Migliaccio, Istituto Superiore di Sanità, Rome:

Pivotal or first in man studies

- While a deviation from the progression from Phase I to III is acceptable, it should be justified
- In the impossibility to have a strong animal model, it might be necessary to perform limited pivotal or first-in-man studies to identify a biological activity and a potency assays in order to define a dose.

Properties of „surgiceuticals“



Issue	Drugs	Devices	Surgiceuticals
Delivery	Oral/IV/IM	Usually Implanted or tool used in surgical procedure	Implanted G2
Marginal cost/ treatment	Low	Low-medium	High
Clinical Trials	Extensive, but well defined	Variable	Extensive, Unique & Challenging
Regulation	Well defined	Well Defined	Evolving

Summary (Tissue-engineered Implants, ?Nano?)

- Approval of tissue for therapeutic application similar to „conventional“ drugs
- Legal basis: Common Technical Document + guidelines (ICH, EMEA, FDA, BfArM/PEI, Pharmakopoe);
- Individual approval procedures and deviation from conventional mode allowed due to special properties of therapeutic tissues

Clinical applications of scientific and/or technological innovations

The Environment in Medicine:

Patients

Doctors

Health Insurance

Industrie



Herz-, Thorax-, Transplantations-
und Gefäßchirurgie

Handling the ambient hypertension

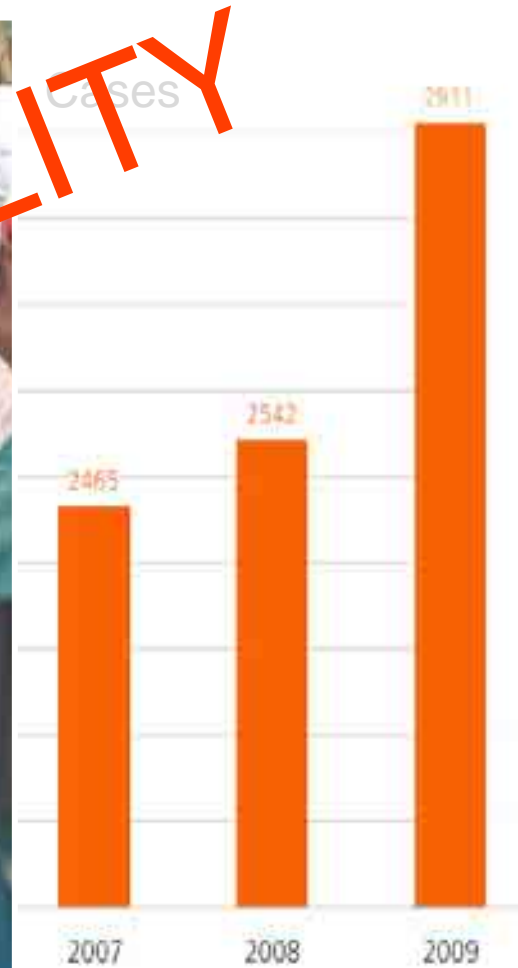
- Innovation



- Precision



- Sustainability



BIOCOMPATIBILITY