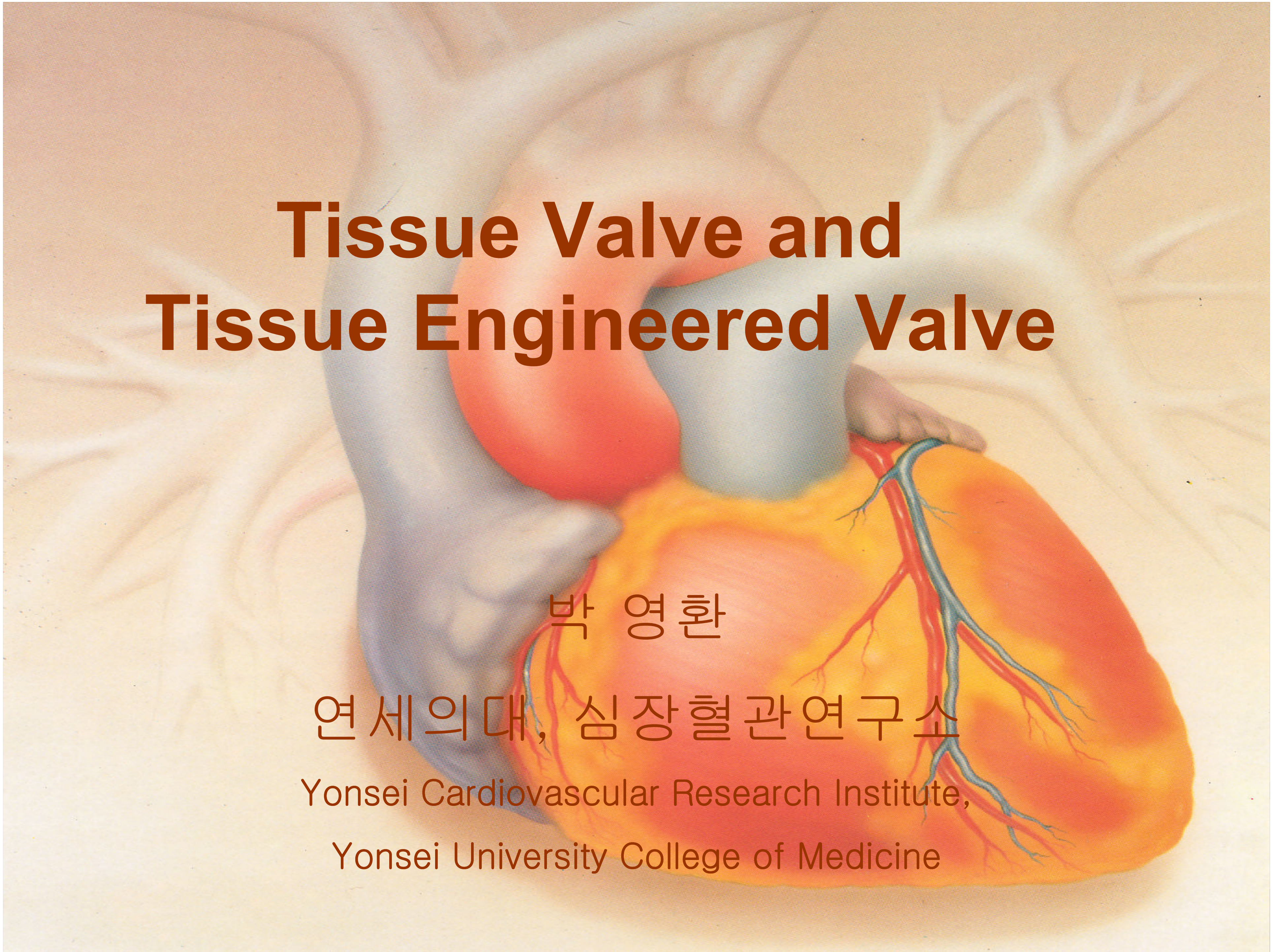
# Tissue Valve and Tissue Engineered Valve



박 영환

연세의대, 심장혈관연구소

Yonsei Cardiovascular Research Institute,

Yonsei University College of Medicine

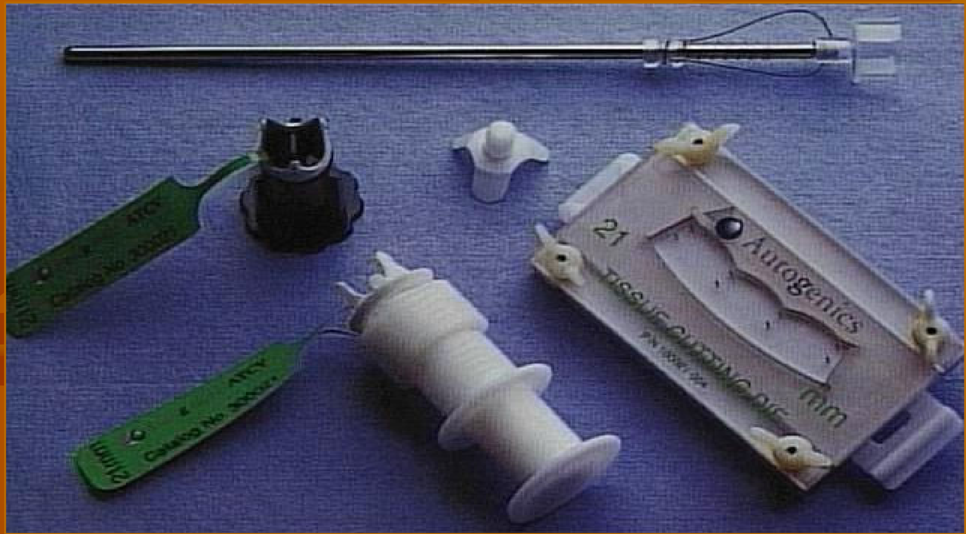
# Heart Valve Replacement

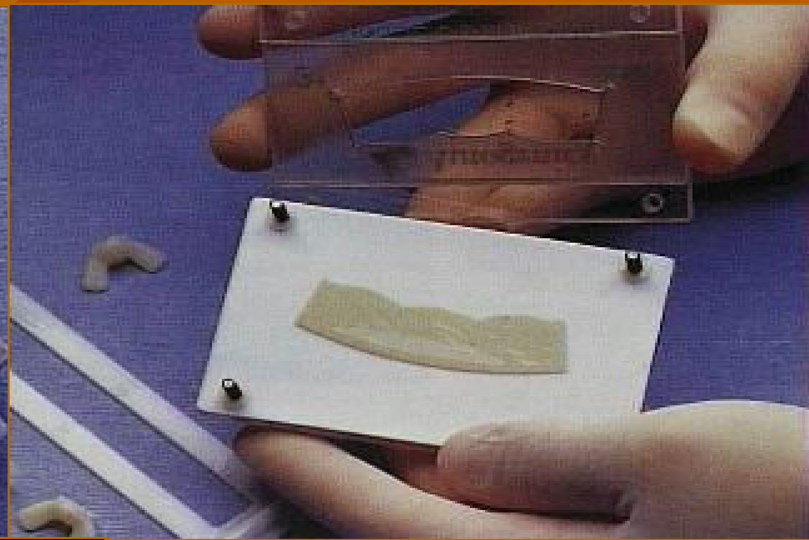
- 85,000 USA
- 2,000 Korea
- 285,000 Worldwide

# Modification of Glutaraldehyde Treatment

- Zero pressure fixation
- Photo fixation
- Anticalcification treatment (toludene)
- Prolonged irrigation
- Other kinds of buffer solution

Autogenics



Autologous Pericardial
Glutaraldehyde Treated
Artificial Valve

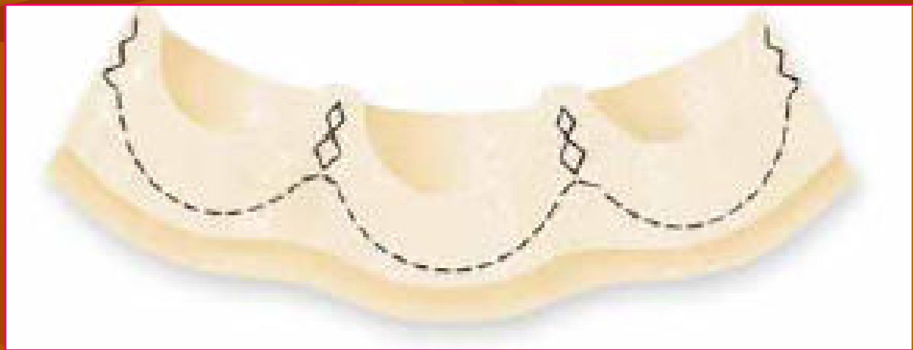
# Bovine Pericardial Prosthesis

MITROFLOW

**Mitroflow Synergy**

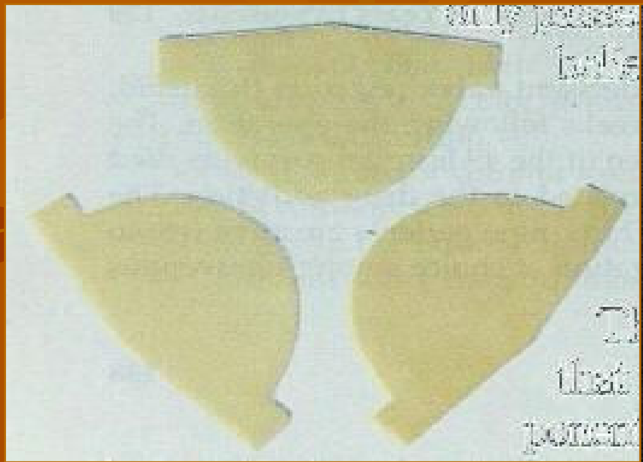
BRAILE BIOMÉDICA

# Soprano Pericardial Bioprosthesis



SORIN BIOMEDICAL

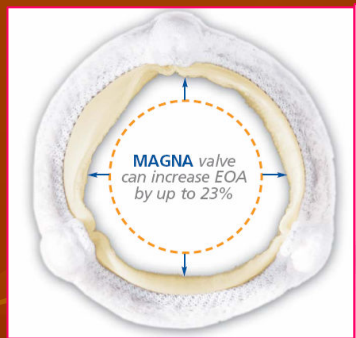
# The Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis



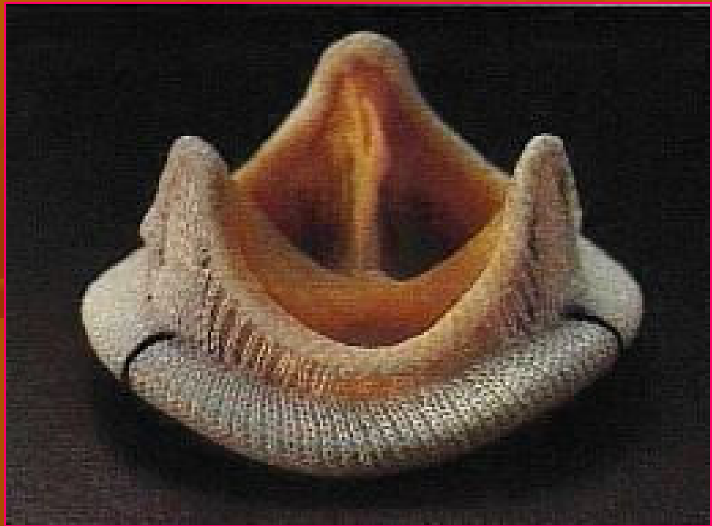

Baxter

Elgiloy wireform (nickel-cobalt alloy), support ring, polyester sewing ring, pericardial leaflet tissue, silicone sewing ring insert.

**Magna**



# Porcine Aortic Valve Prosthesis(I)



**Carpentier Edwards**
**Porcine Valve Bioprostheses**

Edwards

**Biocor Valve**

ST. JUDE MEDICAL
*Enhancing the Quality of Life.*

**Synergy**
**by SulzerCarbomedics**

# Porcine Aortic Valve Prosthesis (II)

Hancock

Medtronic


Toludene

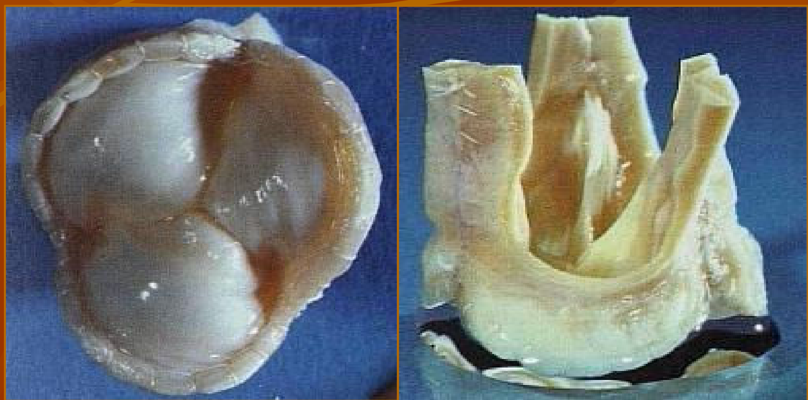
Hancock II

Mosaic

# Stentless Valve

**Stentless Freestyle® Valve**

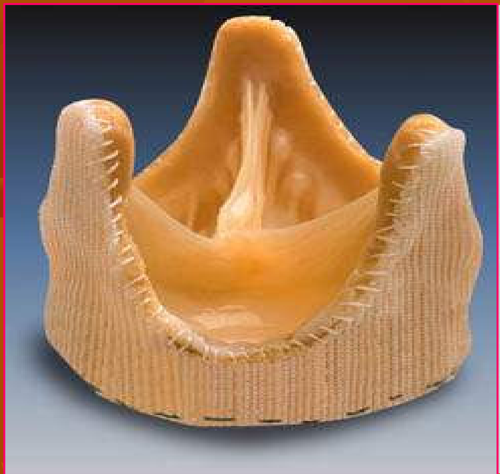
Medtronic



**Cryolife-O'Brien valve**

CryoLife,® Inc.

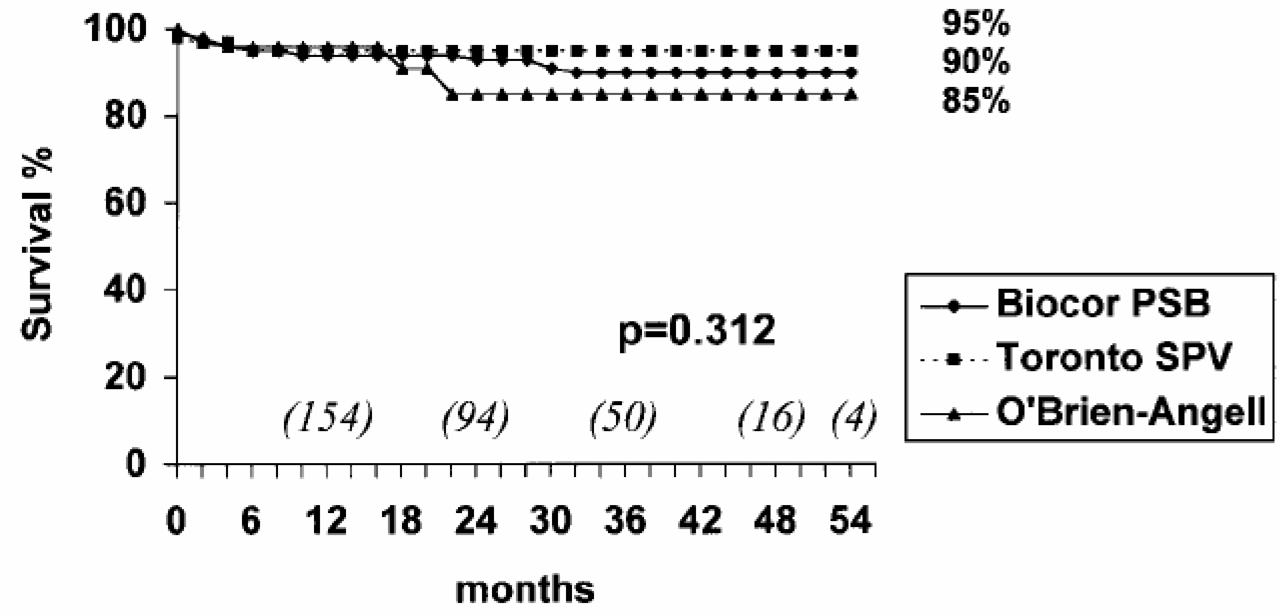
# Stentless Valve (II)



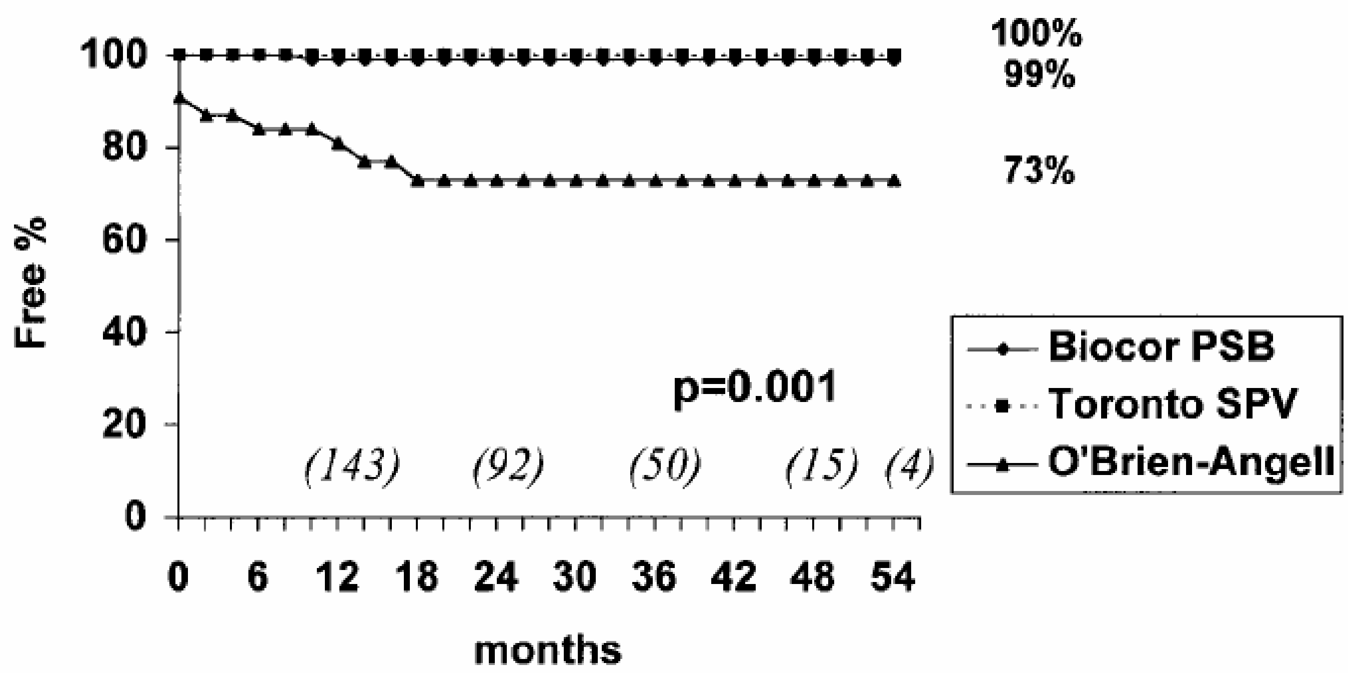

The Toronto SPV valve

ST. JUDE MEDICAL
*Enhancing the Quality of Life.*

Freedom Solo by Sorin group
Two bovine pericarial sheet

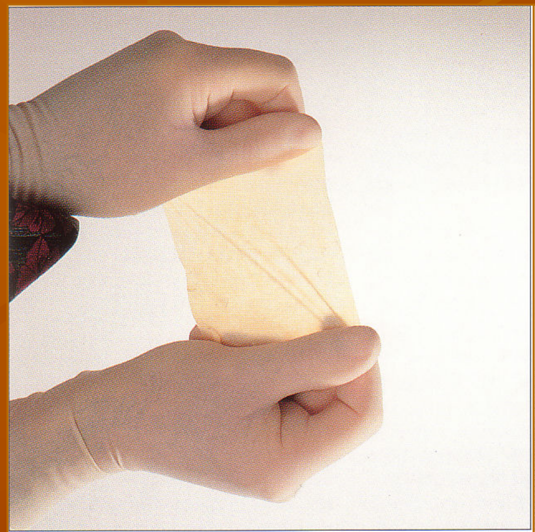


100
80
60
40
20
0
Survival %
95%
90%
85%
Biocor PSB
Toronto SPV
O'Brien-Angell
p=0.312
(154)
(94)
(50)
(16)
(4)
0
6
12
18
24
30
36
42
48
54
months

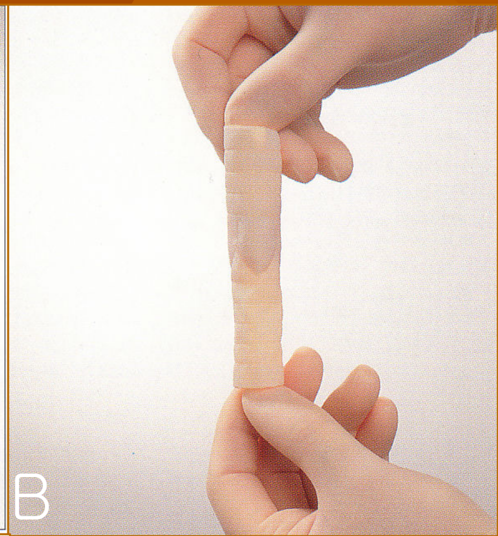



100
80
60
40
20
0
Free %
100%
99%
73%
Biocor PSB
Toronto SPV
O'Brien-Angell
p=0.001
(143)
(92)
(50)
(15)
(4)
0
6
12
18
24
30
36
42
48
54
months

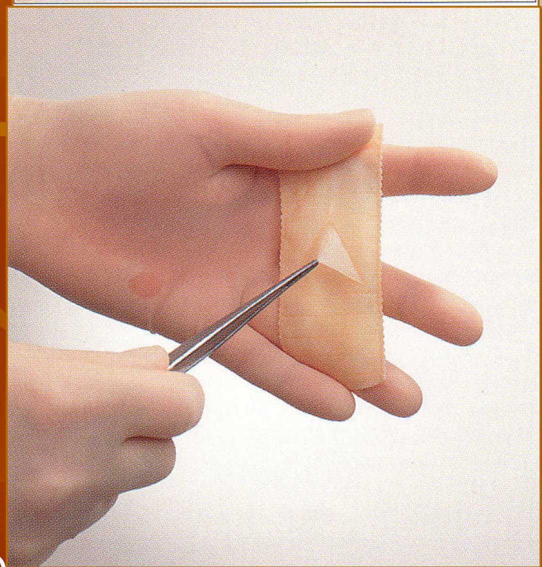
# Tissue Valved Conduit



A



B

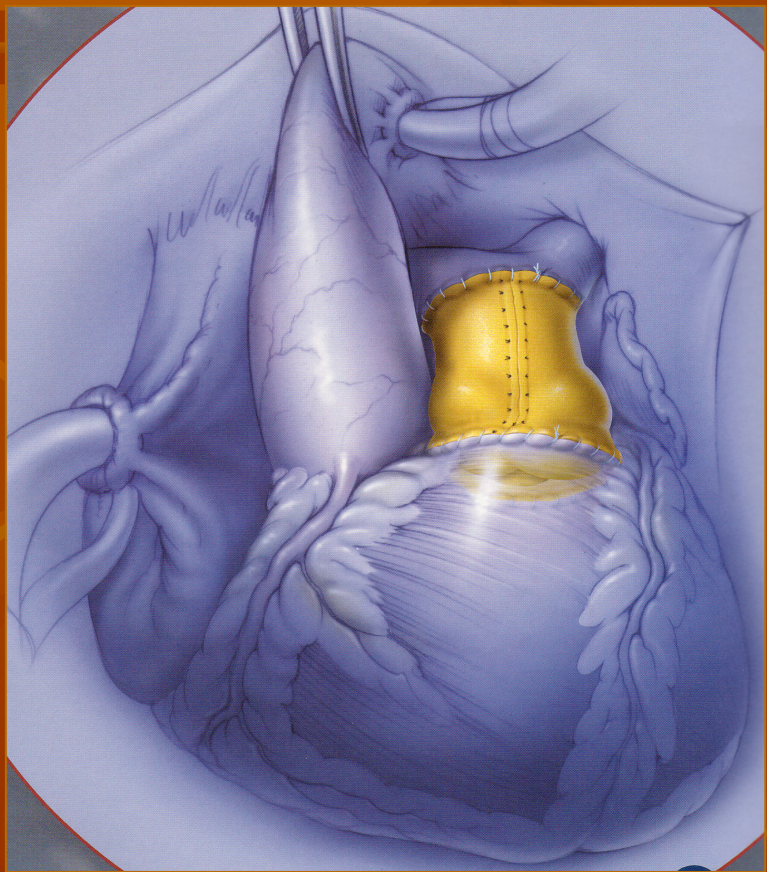


C

A. Pericardial Patch
B. Valved Conduit
C. Monocusp RVOT Patch

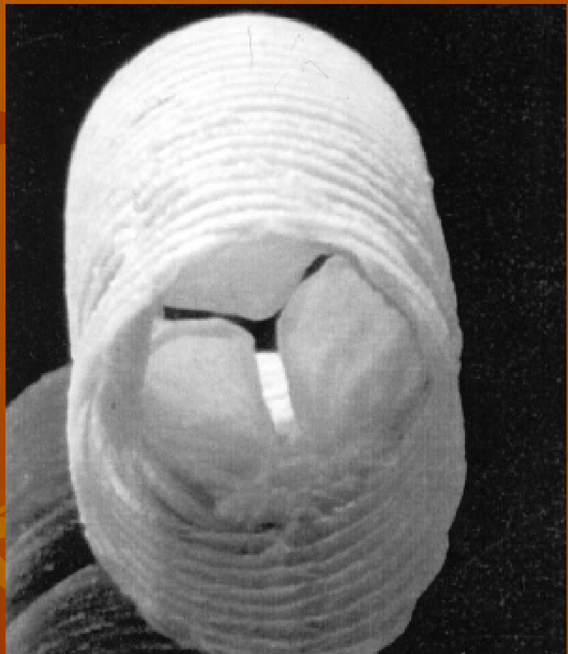
# Synergraft
glutaraldehyde treated
porcine pulmonic valve

# Contegra
glutaraldehyde treated
bovine jugular vein conduit



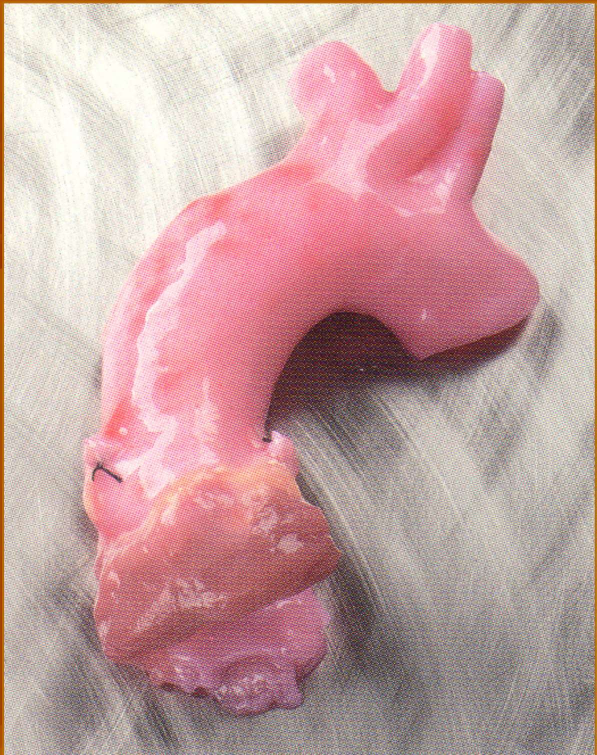
# Composite Stentless Porcine Valved Conduit

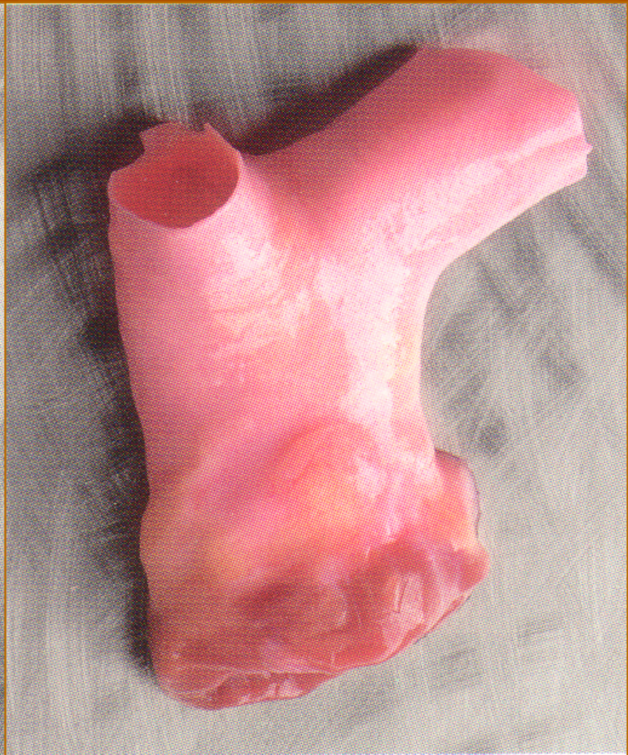
**Bovine Pericardium LabCor**

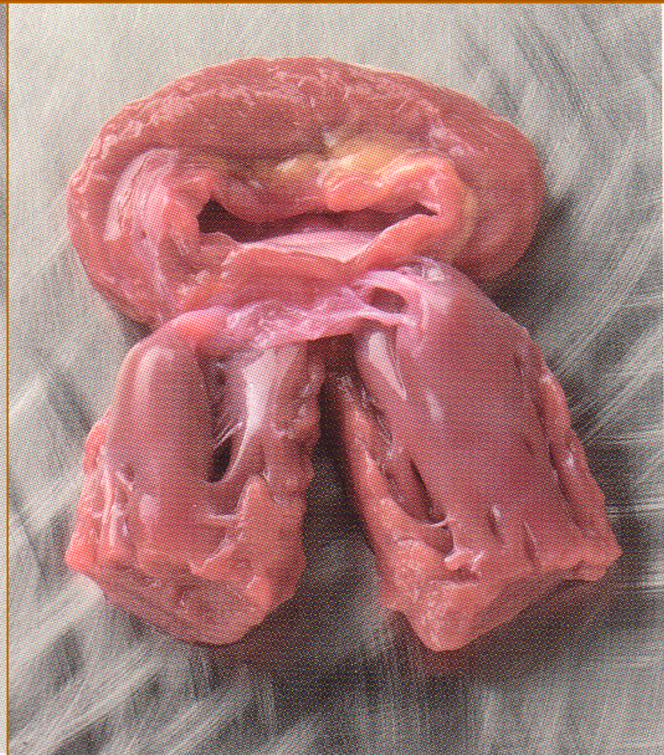


**Woven Dacron Medtronic**

# Cardiac Homografts





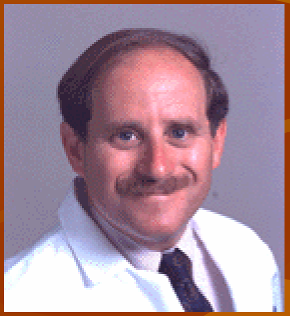


**Aortic Homograft** **Pulmonic Homograft** **Mitral Homograft**

# Problems with Tissue Valve

- Glutaraldehyde fixation – mineralizaiton
- Topical fixation of cell remnants – primary nucleation site for calcium deposition
- Lack of ECM turn over and/or remodeling – mechanical fatigue

*“Tissue engineering requires an understanding of the relationships of structure to function in normal and pathological tissues”*



**Frederick Shoen**
**Cardiac Pathology**
**Brigham and Women’s Hospital**

# Tissue Engineering of Heart Valve

- Valve anatomy
- Physiology
- Development
- Remodeling
- Response to injury
- Substitution

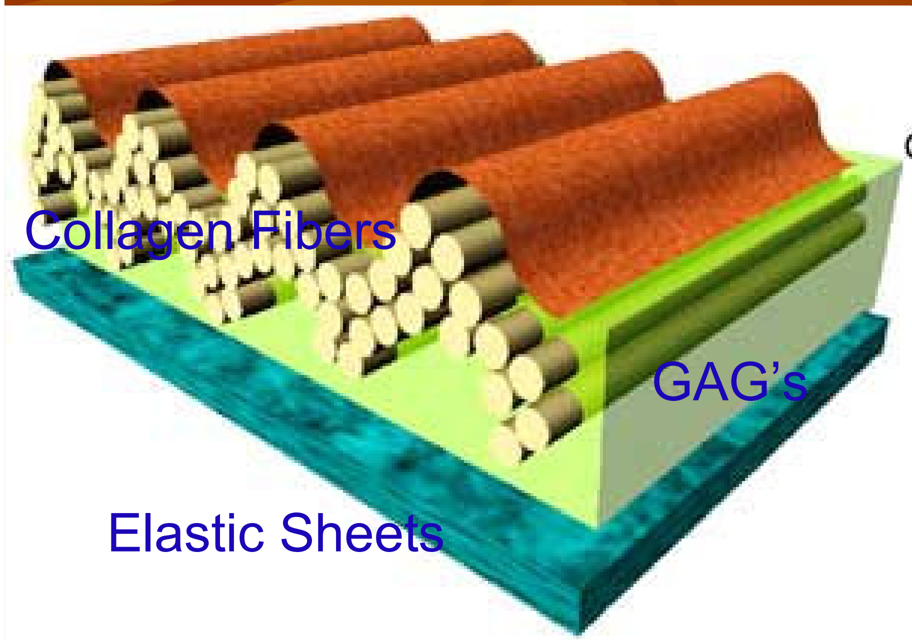
# Goal of Heart Valve Tissue Engineering

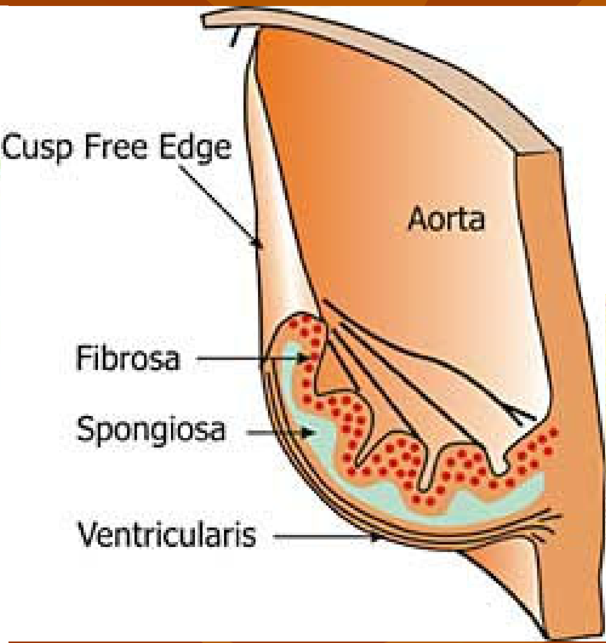
- Functions well hemodynamically
- Repairs ongoing tissue damage
- Long term durability
- Growth potential

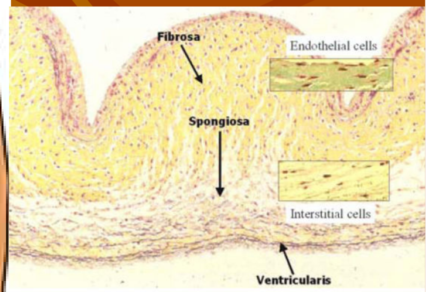
**Similar to the natural heart valve !**

# Functional Structure of Heart Valve

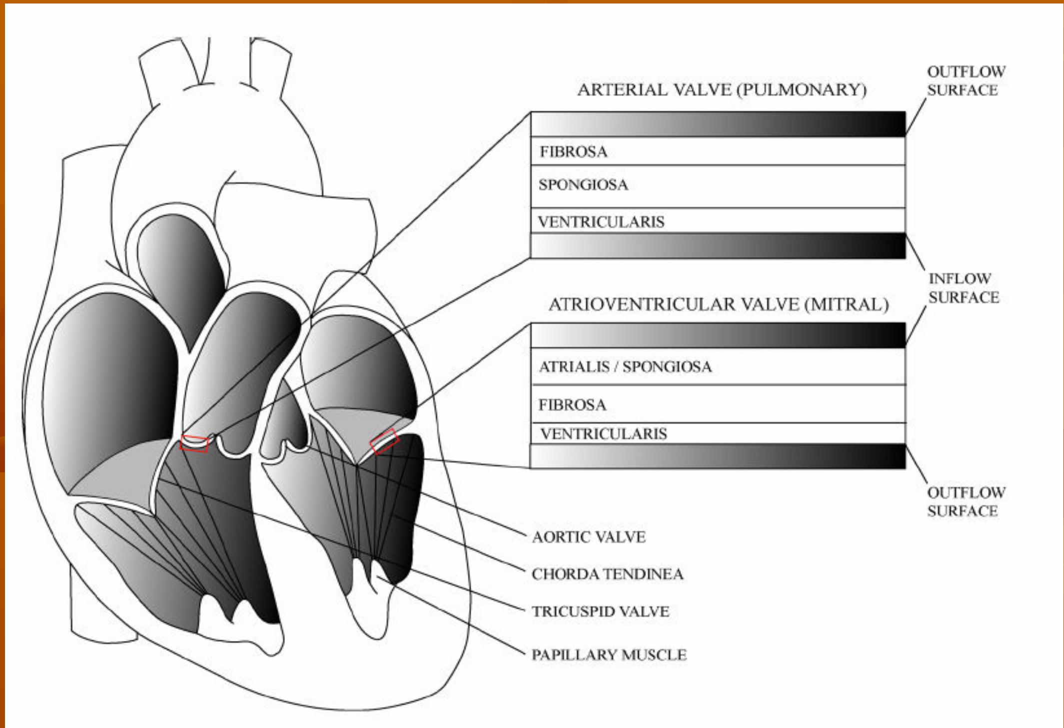
- Cusps are three well defined cellular tissue layer

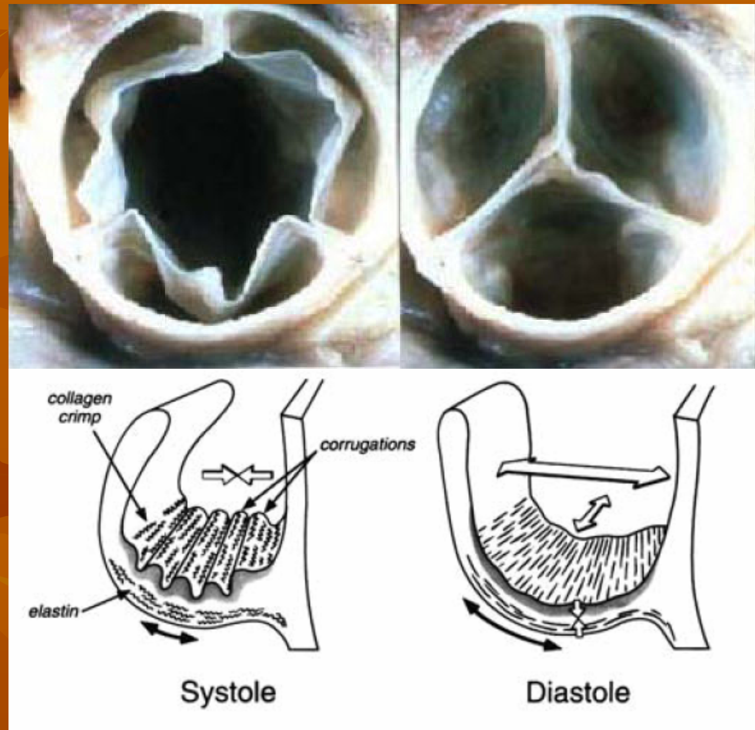



- Valvular endothelial cells (VEC)
- Valvular interstitial cells (VIC)

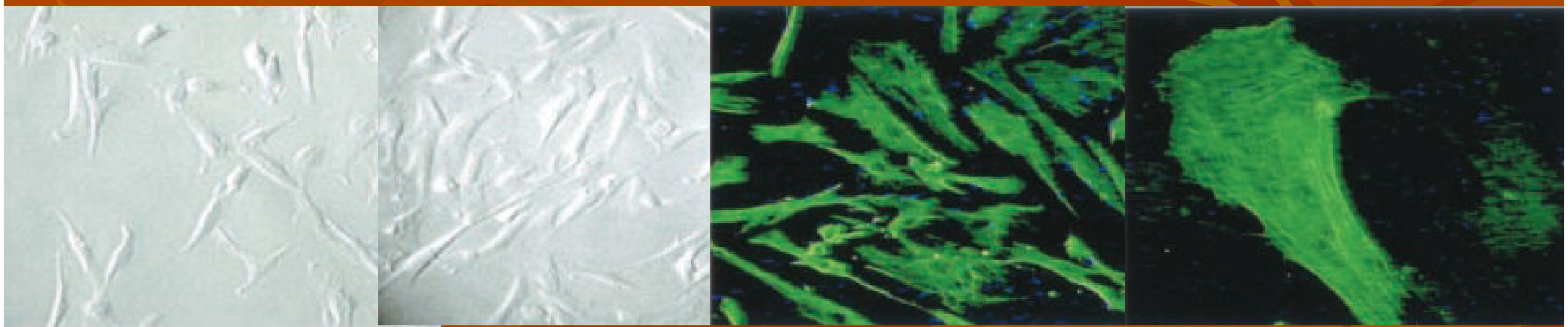



| **Valve layer** | **Main ECM component** | **Function** |
|---|---|---|
| (Atrialis) | (Elastin) | (Recoil of AV valves during closure) |
| Fibrosa | Collagen | Tensile strength |
| Spongiosa | Proteoglycans | Formation of hydrated lattice<br>Resistance against compressive forces |
| Ventricularis | Elastin | Retention of corrugated collagen structure in aortic valve<br>Recoil of arterial valves during closure |

# Tissue Engineering Concept(I)

- Autologous available stem cell source
  - endothelial progenitor cells(EPC)
  - mesenchymal stem cells (MSC)

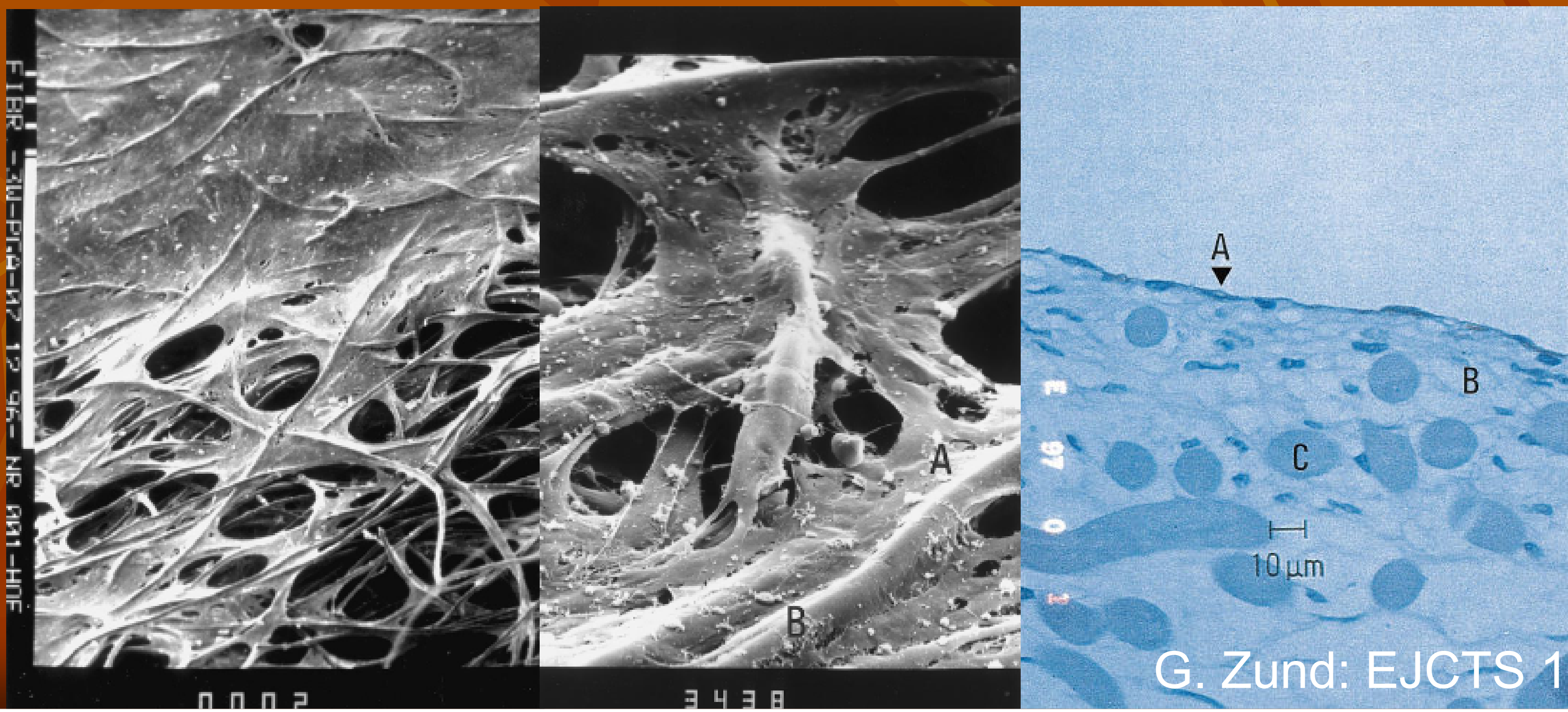


72 hours | 10-14 days | ASMA | Vimentin

S. Hoerstrup: Circulation 2002

# Tissue Engineering Concept(II)

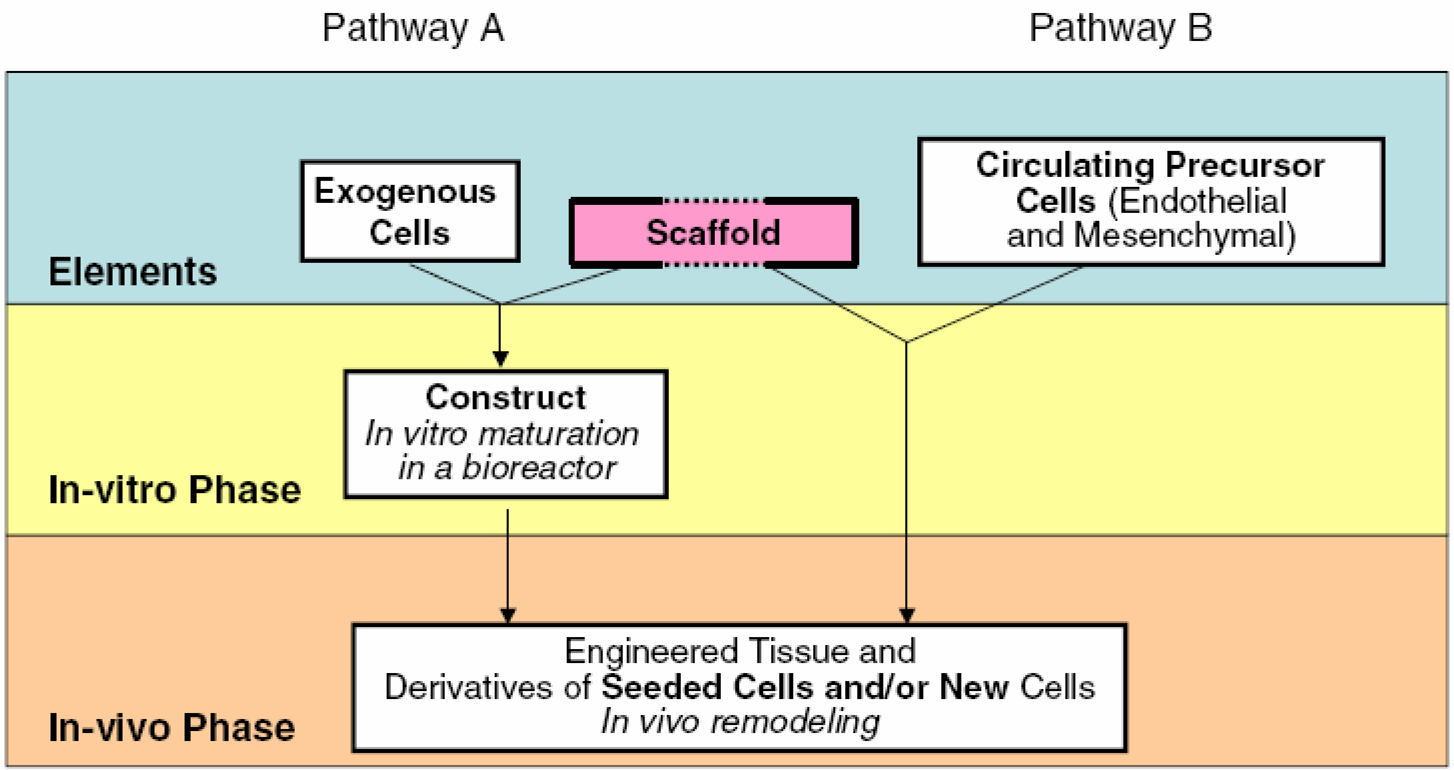
- In vitro phase generating the desired structure using bioreactor
- In vivo using a decellularized or synthetic scaffold and repopulation with cells – inflammatory damage and failure in human



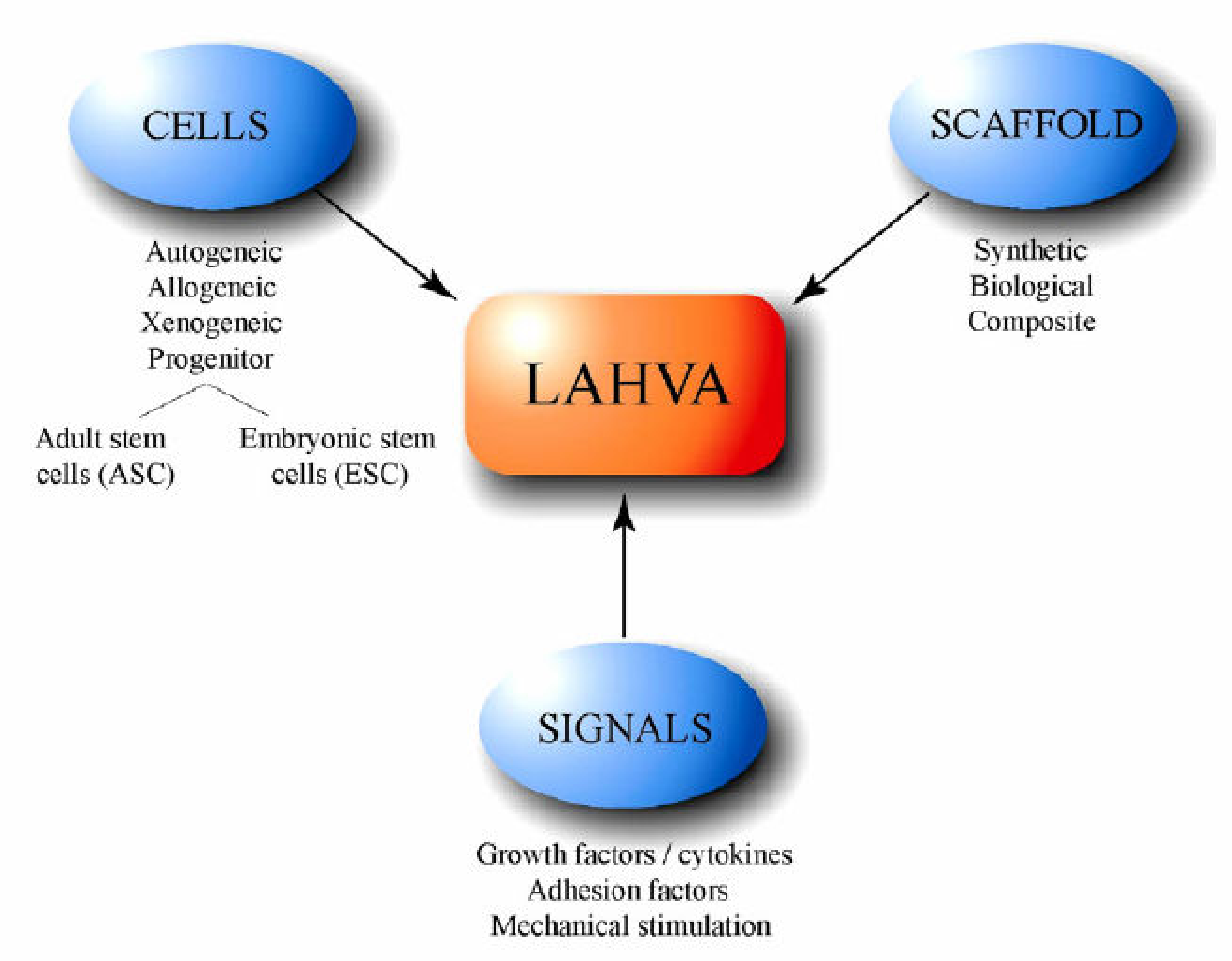

G. Zund: EJCTS 1998

# Tissue Engineering Heart Valve Fate

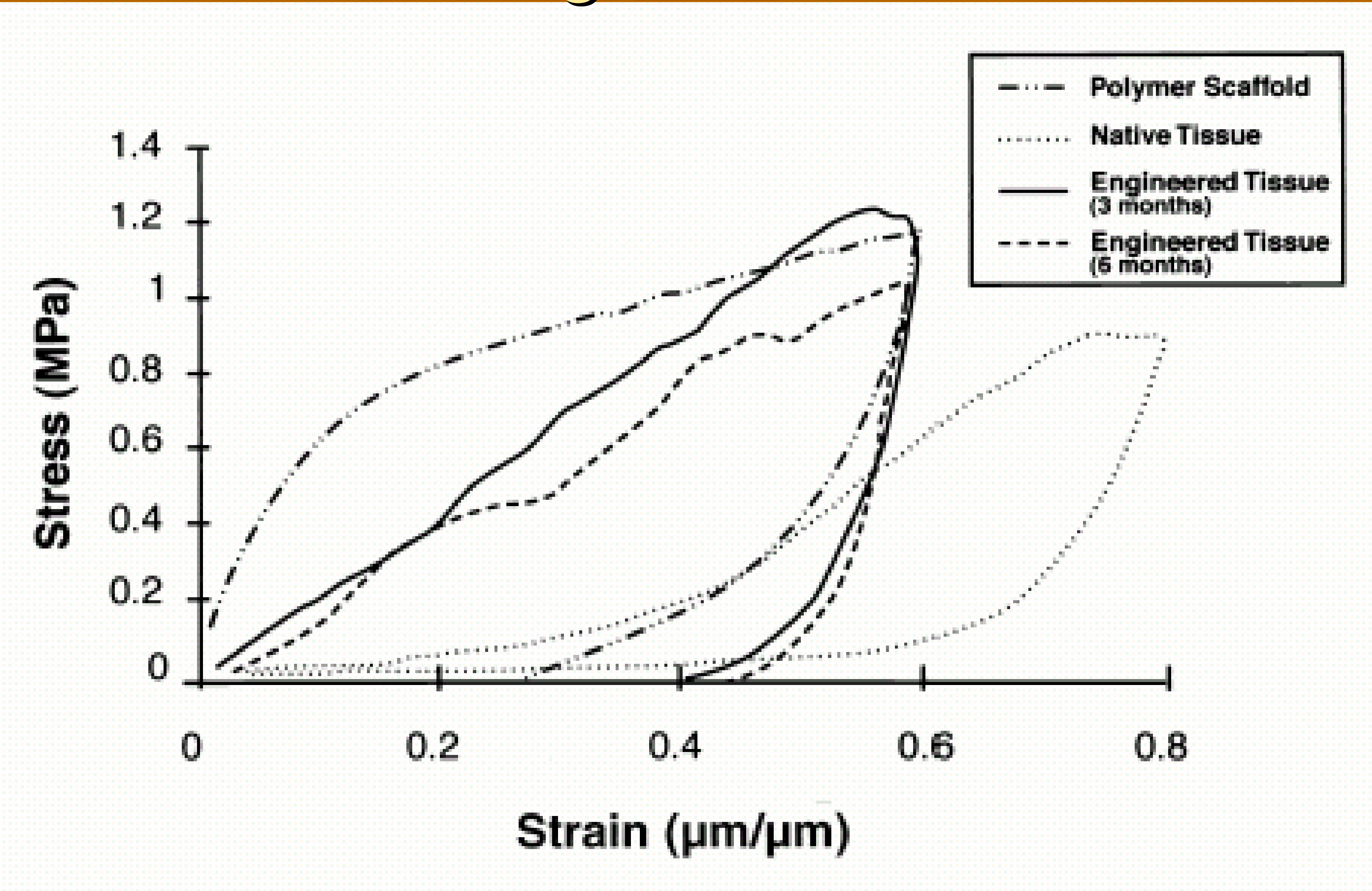
- Cell adhesion, proliferation, sorting and differentiation
- ECM production,organization
- Degradation of the scaffold
- Remodeling and potential growth of the tissue




| **Pathway A: Conventional Paradigm** | **Pathway B: Modified Paradigm** |
|---|---|
| •Combine appropriate cells and scaffold<br>•Grow valve in-vitro in a bioreactor that provides mechanical and metabolic support<br>•Implant in anatomic site in-vivo | •Implant appropriate scaffold in-vivo<br>•Enhance release, targeted recruitment, adhesion, migration, proliferation, differentiation, and function of desired cell populations<br>•Avoid unwanted recruitment |


CELLS
Autogeneic
Allogeneic
Xenogeneic
Progenitor
Adult stem cells (ASC)
Embryonic stem cells (ESC)
SCAFFOLD
Synthetic
Biological
Composite
LAHVA
SIGNALS
Growth factors / cytokines
Adhesion factors
Mechanical stimulation

# The Strain-Stress Curve of Tissue Engineered Graft



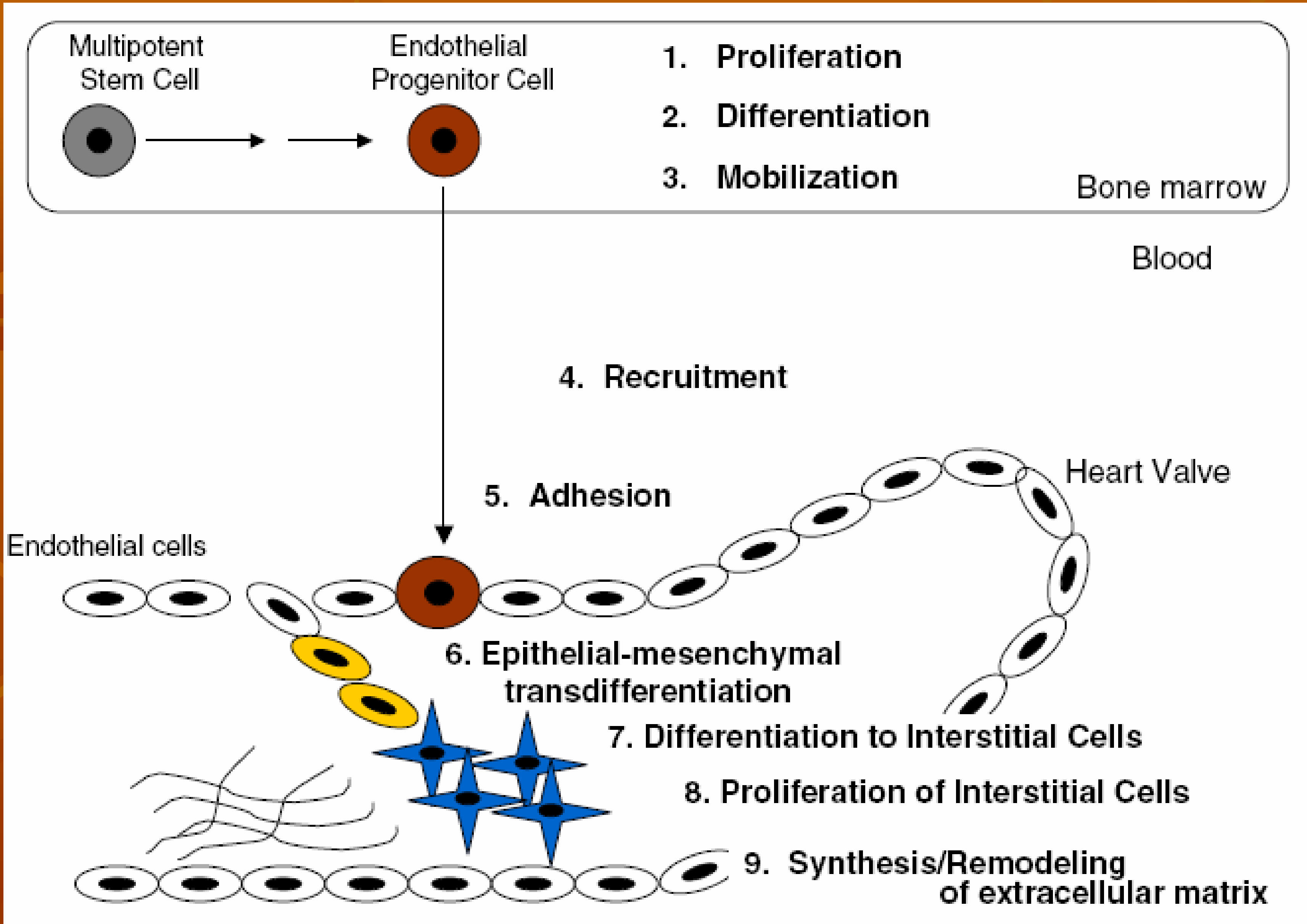

D. Shun-Tim: Annals of Thoracic Surgery 1999

# Cell Source (I)

- Ovine femoral artery and PGLA + PGA scaffold (Shinoka,1995)-sacrifice
- Dermal fibroblasts(Shinoka,1997)
- Human saphenous vein(Schnell, 2001)
- Carotid artery (Stock 2000)-sacrifice
- Autogenous umbilical cord cell (Kadner, 2002)-mixed, Wharton's jelly myofibroblast, umbilical cord artery or vein

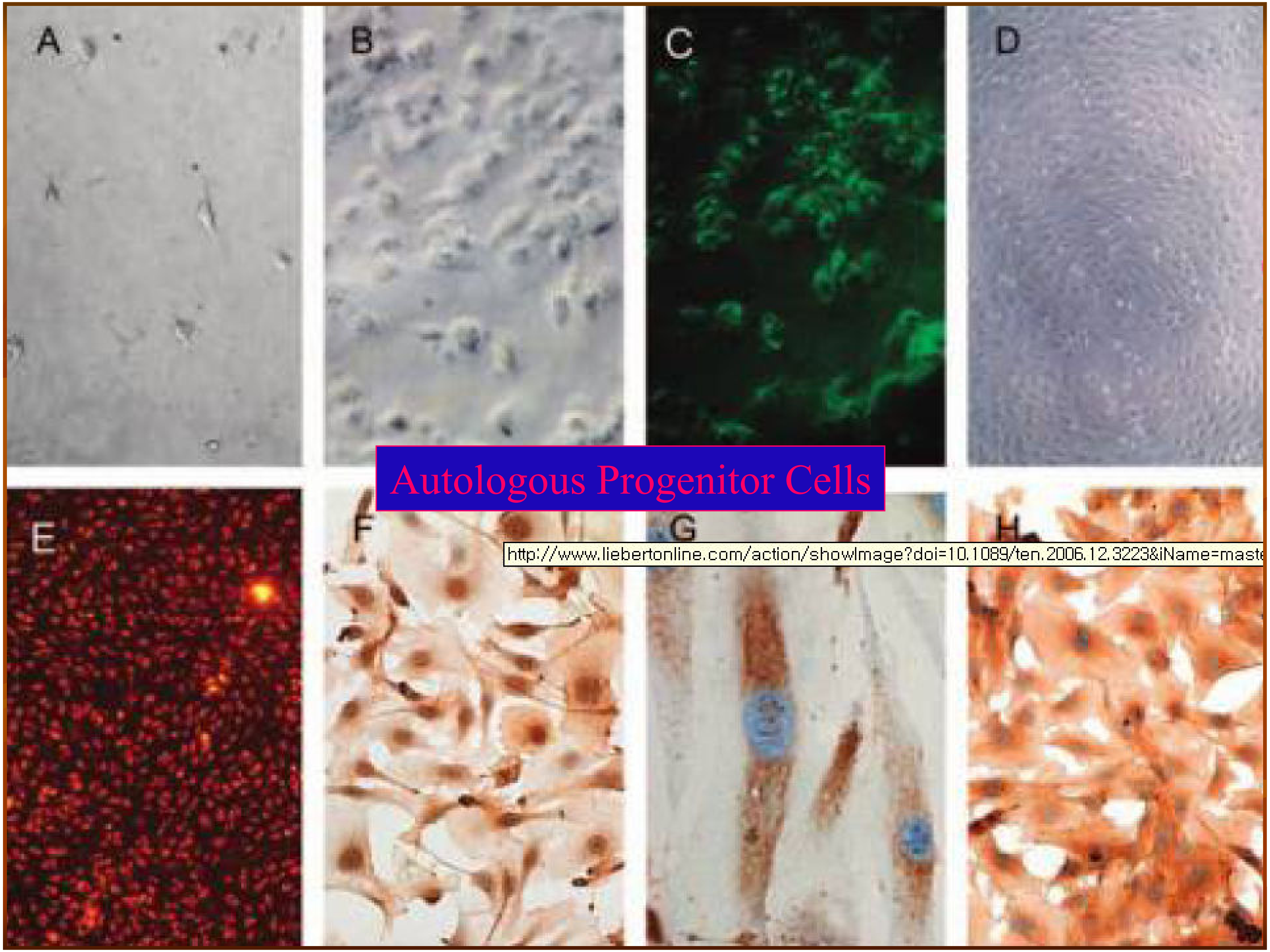
# Cell Source (II)

- Mesenchymal stem cell(MSC); adult bone marrow (Kadner, 2002) – remain differentiation in vivo
- VICs and VECs themselves (Maish, 2003) – leaflet biopsy – not enough cells
- Circulating endothelial and smooth muscle progenitor cells (Rafii, 2000, Simper, 2002)

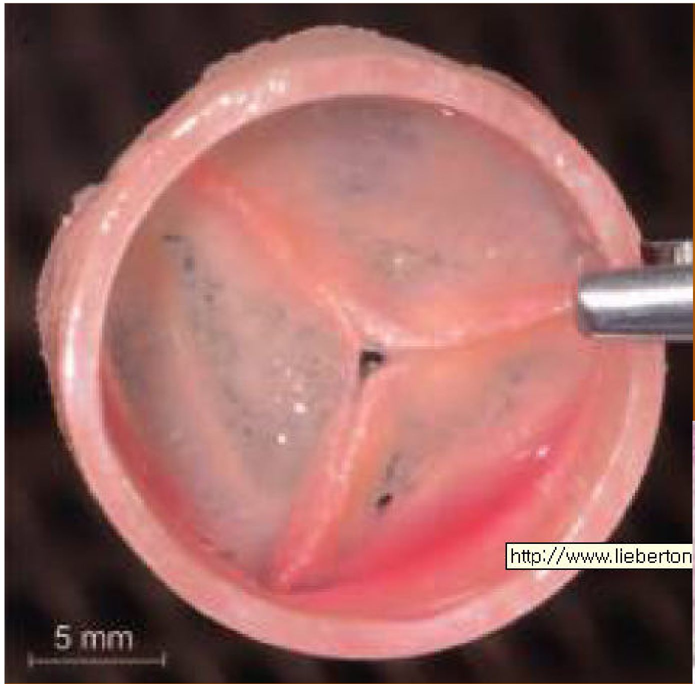


Multipotent Stem Cell
Endothelial Progenitor Cell
1. Proliferation
2. Differentiation
3. Mobilization
Bone marrow
Blood
4. Recruitment
5. Adhesion
Heart Valve
Endothelial cells
6. Epithelial-mesenchymal transdifferentiation
7. Differentiation to Interstitial Cells
8. Proliferation of Interstitial Cells
9. Synthesis/Remodeling of extracellular matrix

# Autologous Progenitor Cells

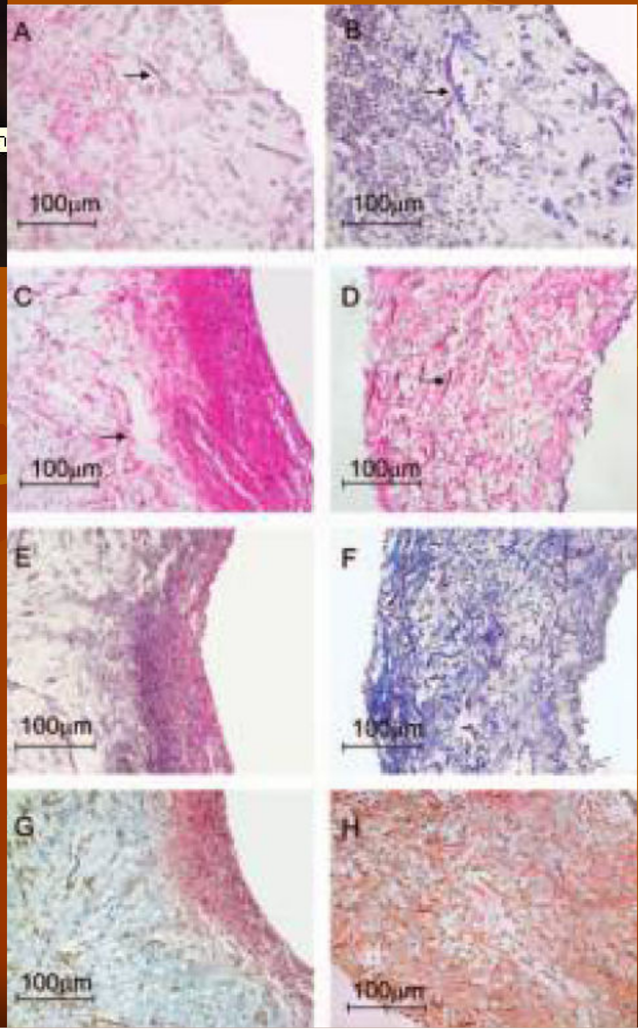


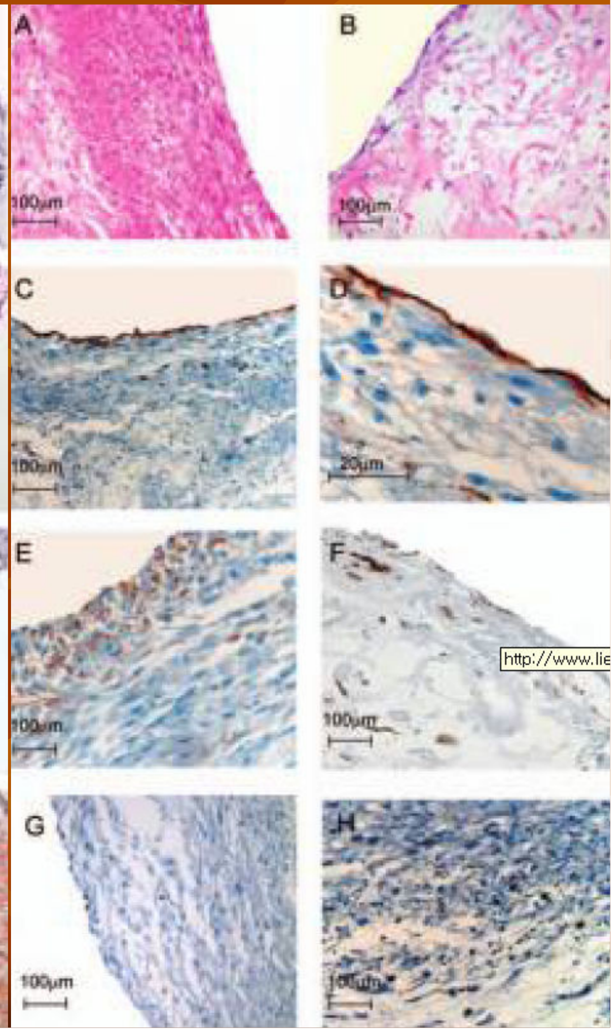

http://www.liebertonline.com/action/showImage?doi=10.1089/ten.2006.12.3223&iName=maste

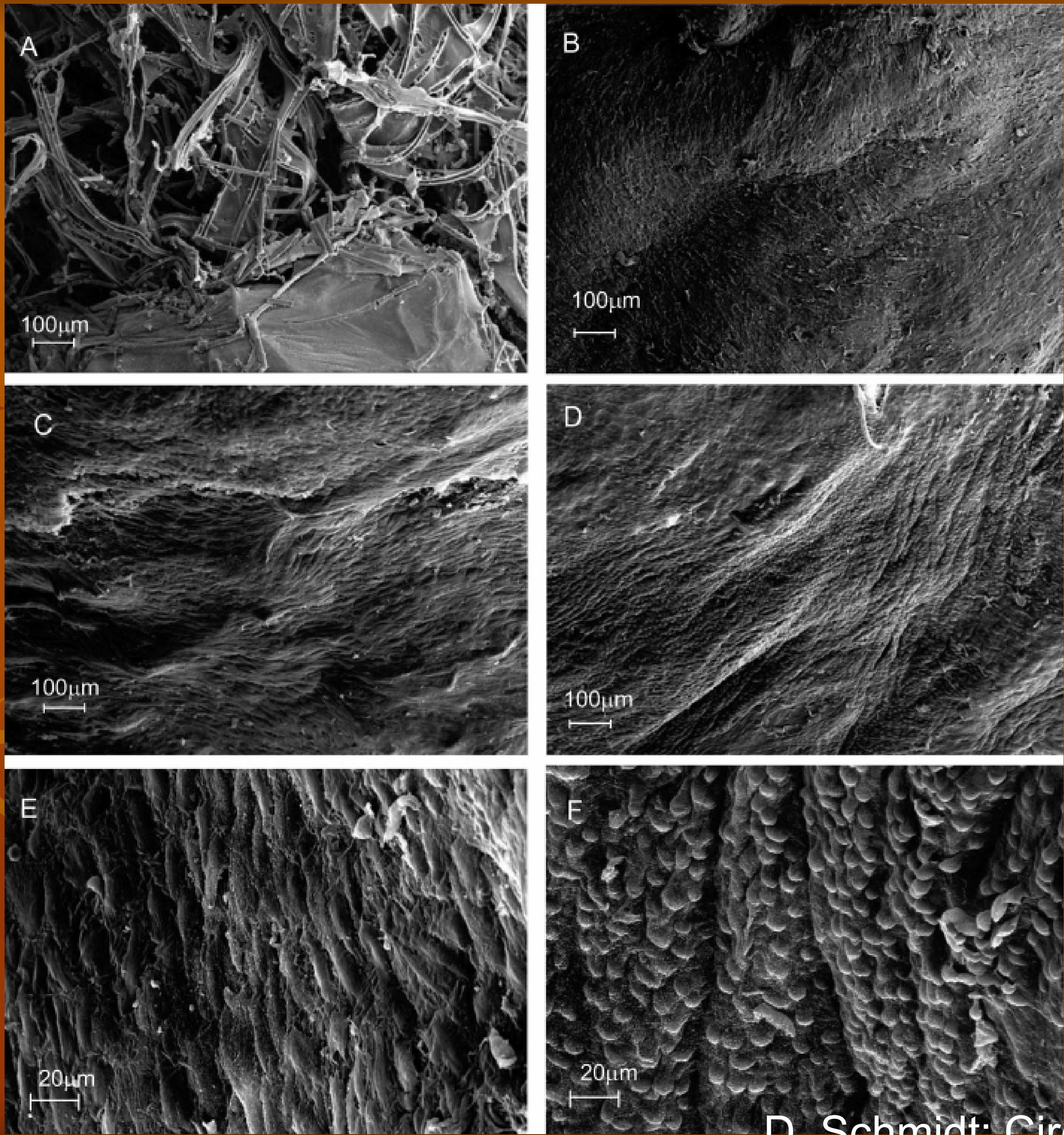



PGA mesh with P4BH coating leaflet
Human Wharton's Jelly-derived myofibroblasts
Human umbilical cord blood-derived EPCs

D. Schmidt: Tissue Engineering 2006





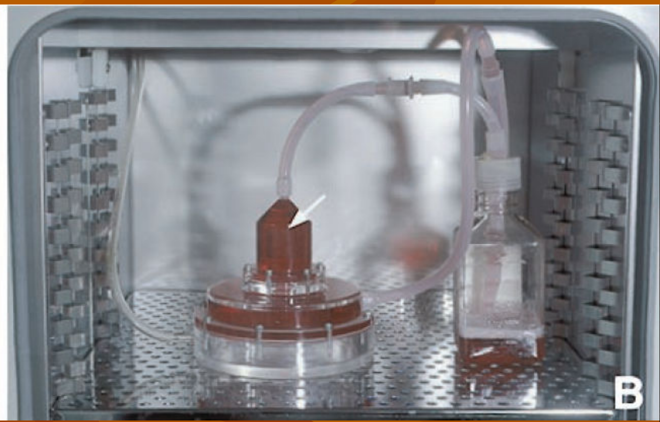

D. Schmidt: Circulation 2006

# Scaffold
# (Synthetic biodegradable polymer)

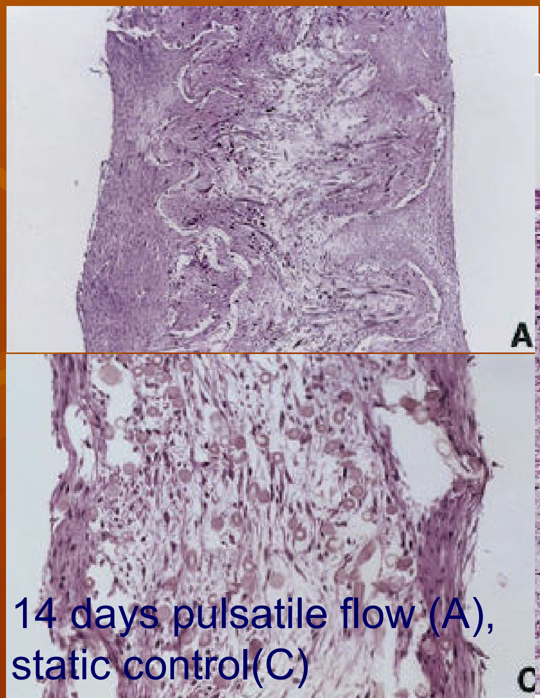
- PGLA woven mesh sandwiched between two non-woven PGA mesh sheets (Mayer, 1995) – too immalleable
- Polyhydroxyoctanoate(PHO) (Stock, 2000)

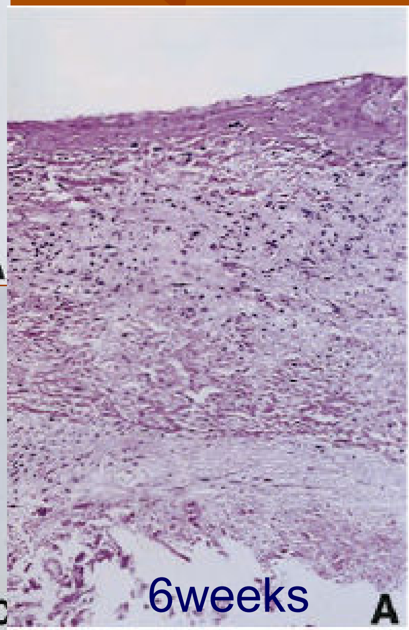
  Conduit wall: non porous PHO film(240 μm), Two layers of non-woven PGA felt(1 mm), Monolayer of porous PHO(120μm) – low pressure pulmonary position
- Porous PHO scaffold; thermal processing (Sodian, 2000) – devoid of elastin
- PGA coated with a thin layer of poly-4-hydroxybutyrate(P4HB) – a flexible, thermoplastic (Hoerstrup, 2000) –welding technique, bioreactor ; partial endothelial cell coverage

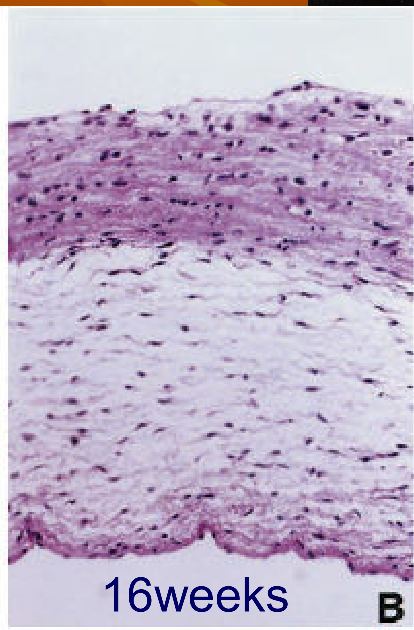
Pulse duplicator system(Bioreactor) consisting of 2 principal Chambers seperated by silicone diaphragm.



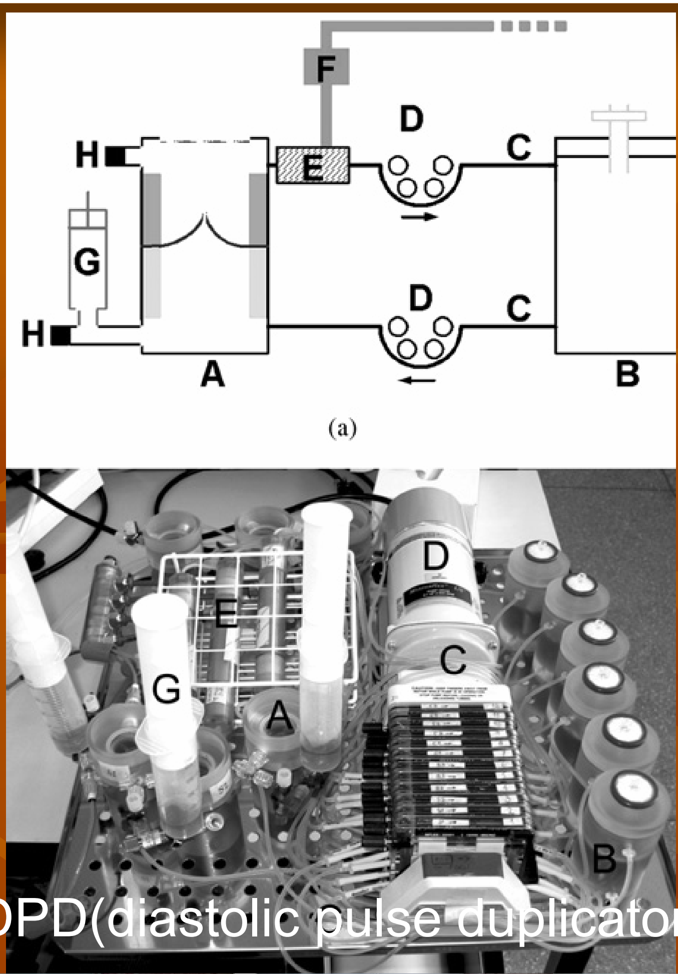


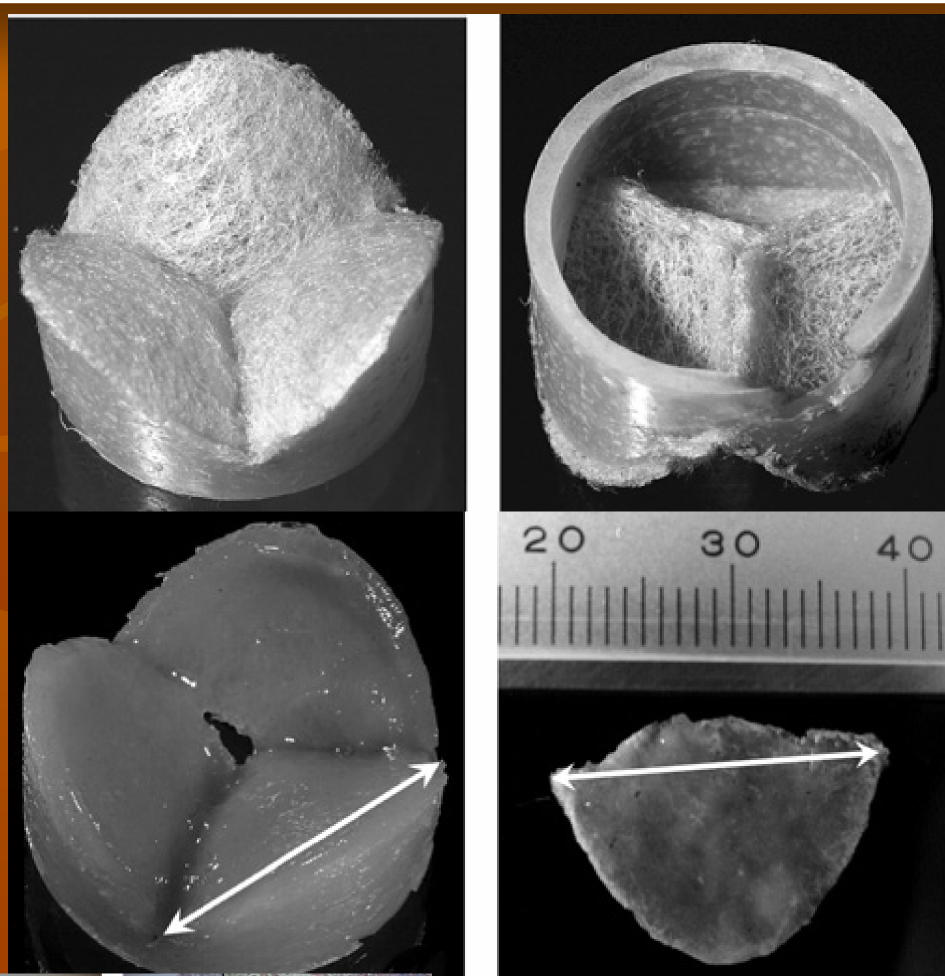



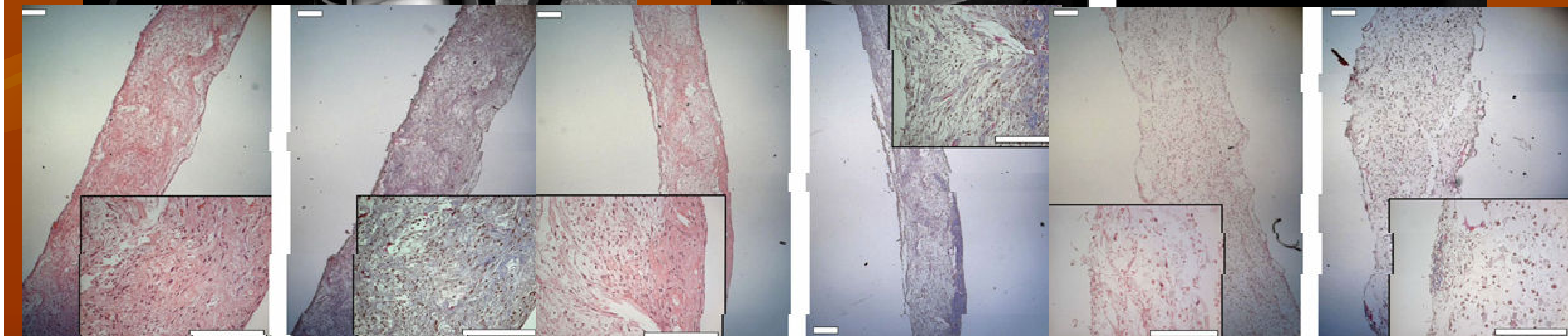





S. Hoerstrup: Circulatoin 2000



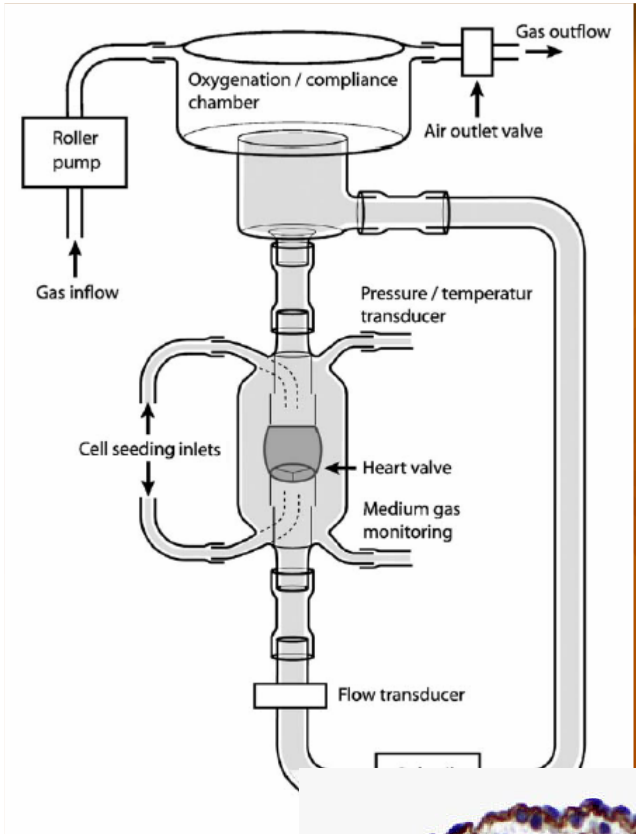



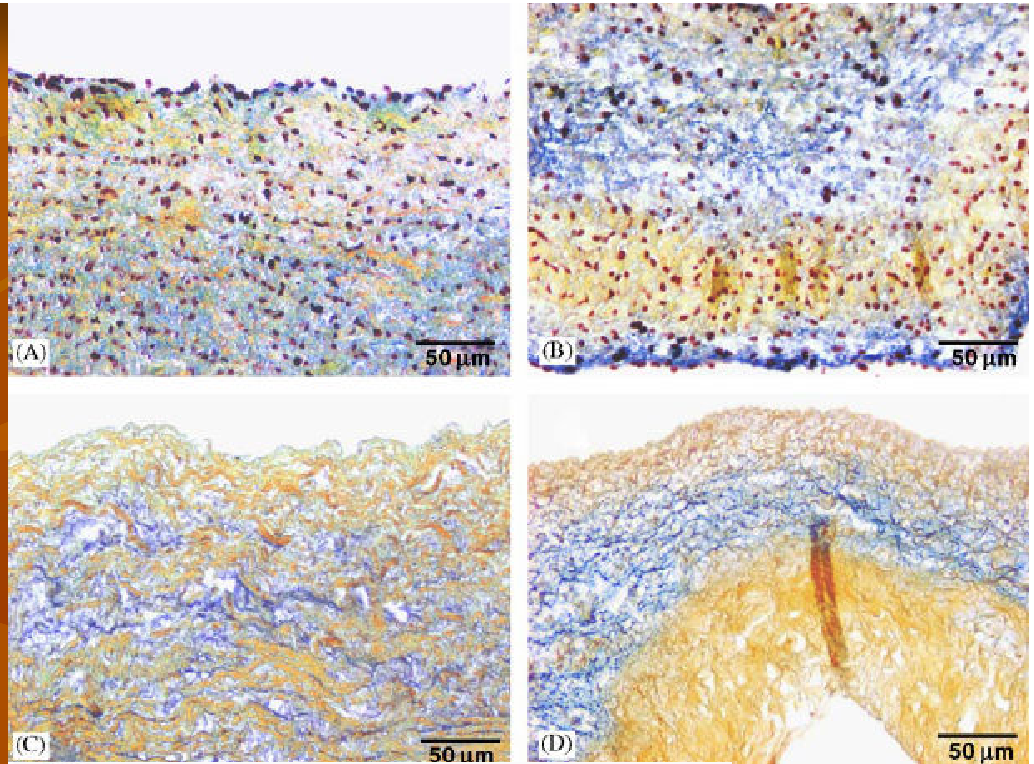



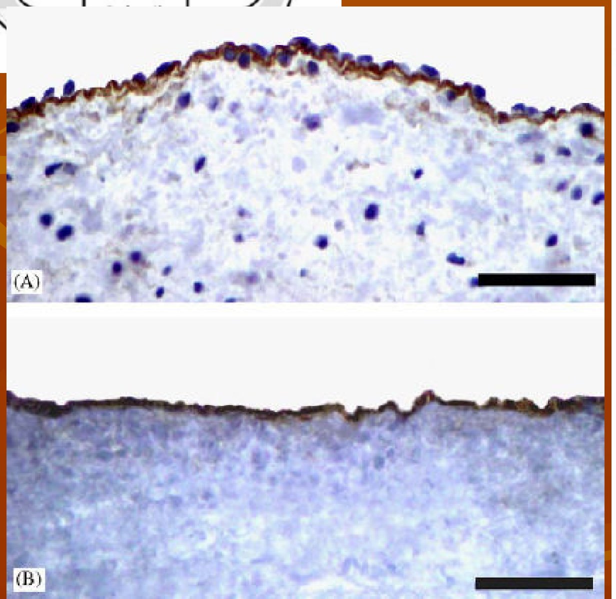
A. Mol: Ann Biomed Eng 2005

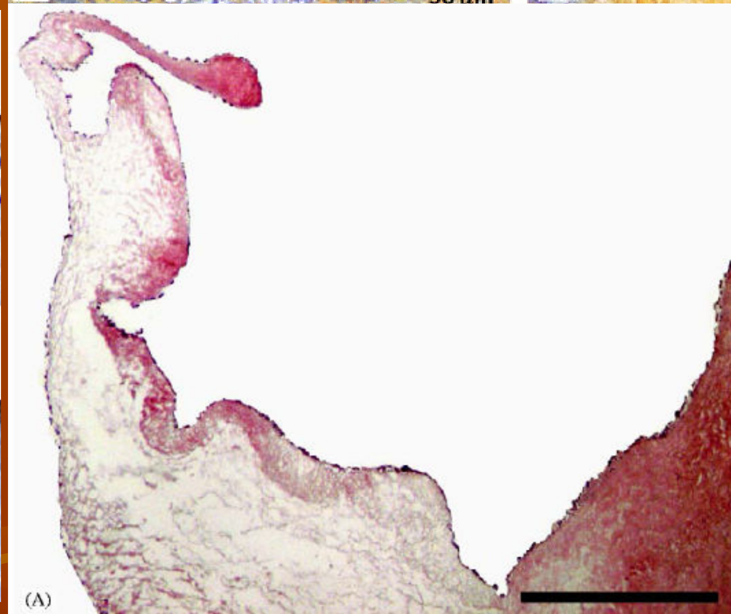
# Scaffold (Decellular Tissue)

- Decellularising with detergent(triton X-100) and enzymes(DNAse, RNAse) –removes cell membranes, nucleic acids, lipids, cytoplasmic structures, soluble matrix molecules, retaining the collagen and elastin ECM (Wilson, 1995) –patial endothelialization, partial VIC infiltration
- Reseeding of accullularised porcine aortic valve with human endothelial cells (Bader, 1998) –cellular remnants
- Carotid artery myofibroblast and endothelial cell seeding sequentially (Bader, 2000) – calcification and inflammatory reaction
- Synergraft by cryolife (O'Brien, 1999) ; decellularized porcine aortic valve - strong inflammatory response in human
- Unknown ideal heart valve decellularising agent
- Possible toxicity

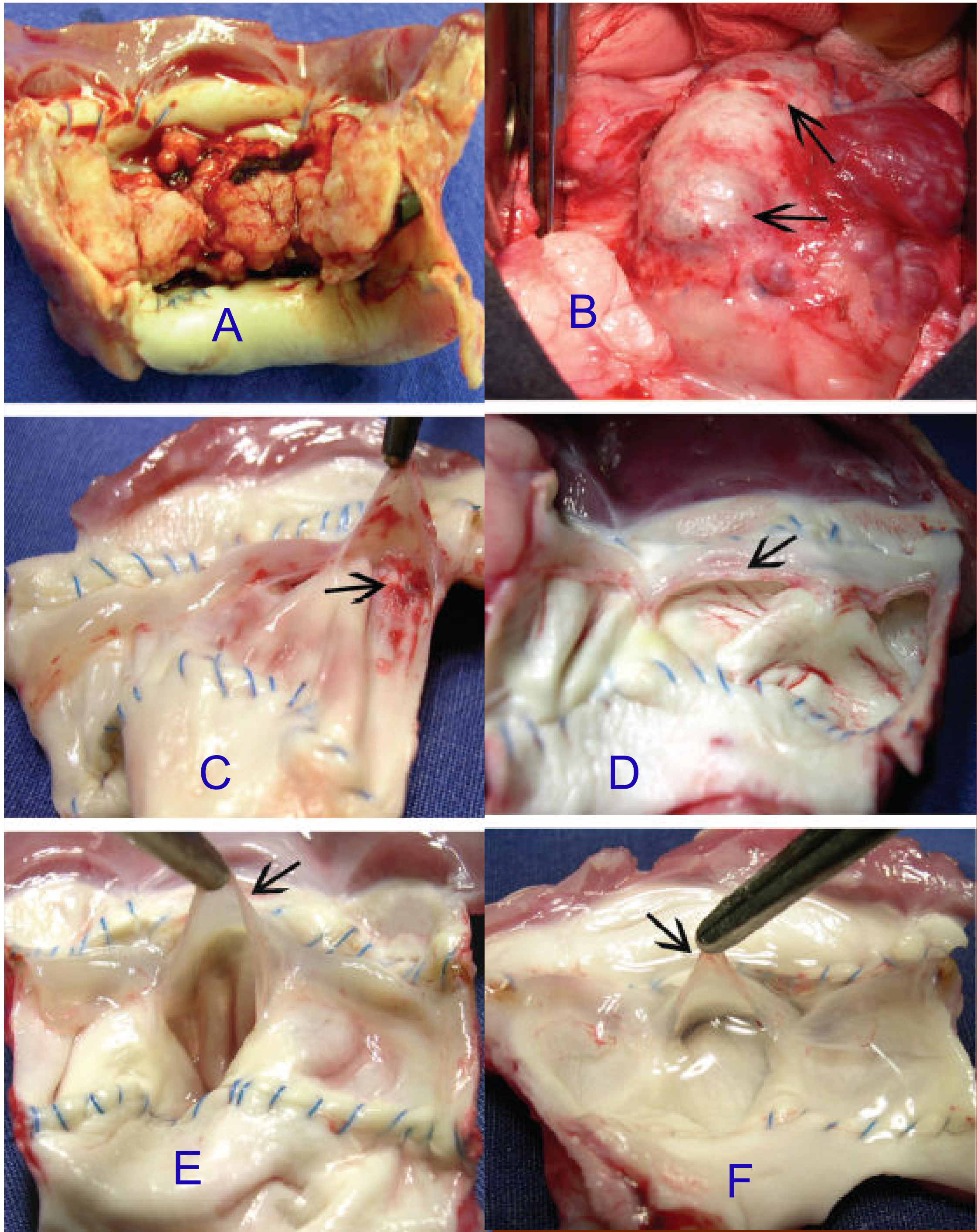



A. Lichtenberg: Biomaterials 2006




A:EPV
infective endocarditis 39days
B: EPV, good shape 3 months

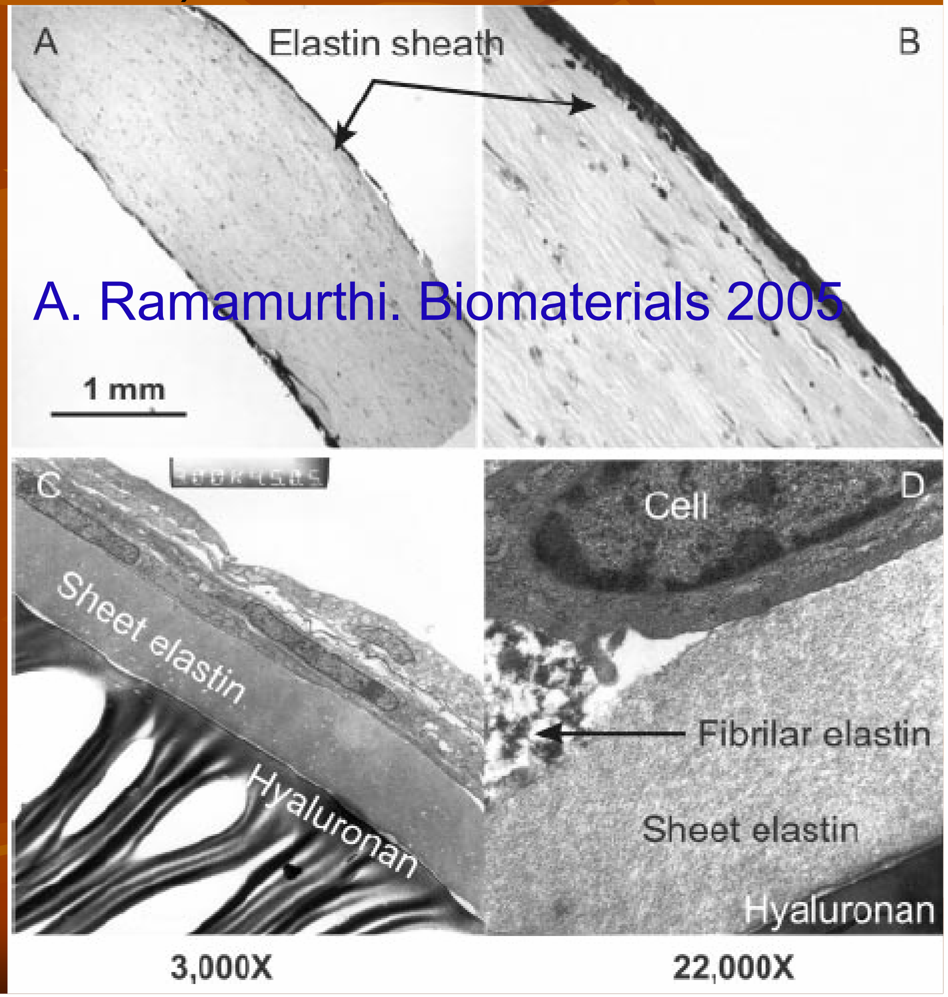
C:DPV
Thrombotic formations 3 months
D: DPV
leaflet sclerosis 3 months

E:EPV
Translucent leaflets 1 months
F: EPV 3 months

A. Lichtenberg: Circulation 2006

# Scaffold (Natural Biodegradable Polymeric)

- Acellular small intestinal submucosal matrix(SIS) ; complete resorption (Badylak, 1989)
- Fibrin gell; from patient's own blood (Ye, 2000)
- Moulding technique (Jockenhoevel, 2001)
- Collagen scaffold ; (Rothenburger, 2001)
- Construction of tissue using "natural" materials by producing completely human autogeneic tissue without the use of a supporting scaffold;



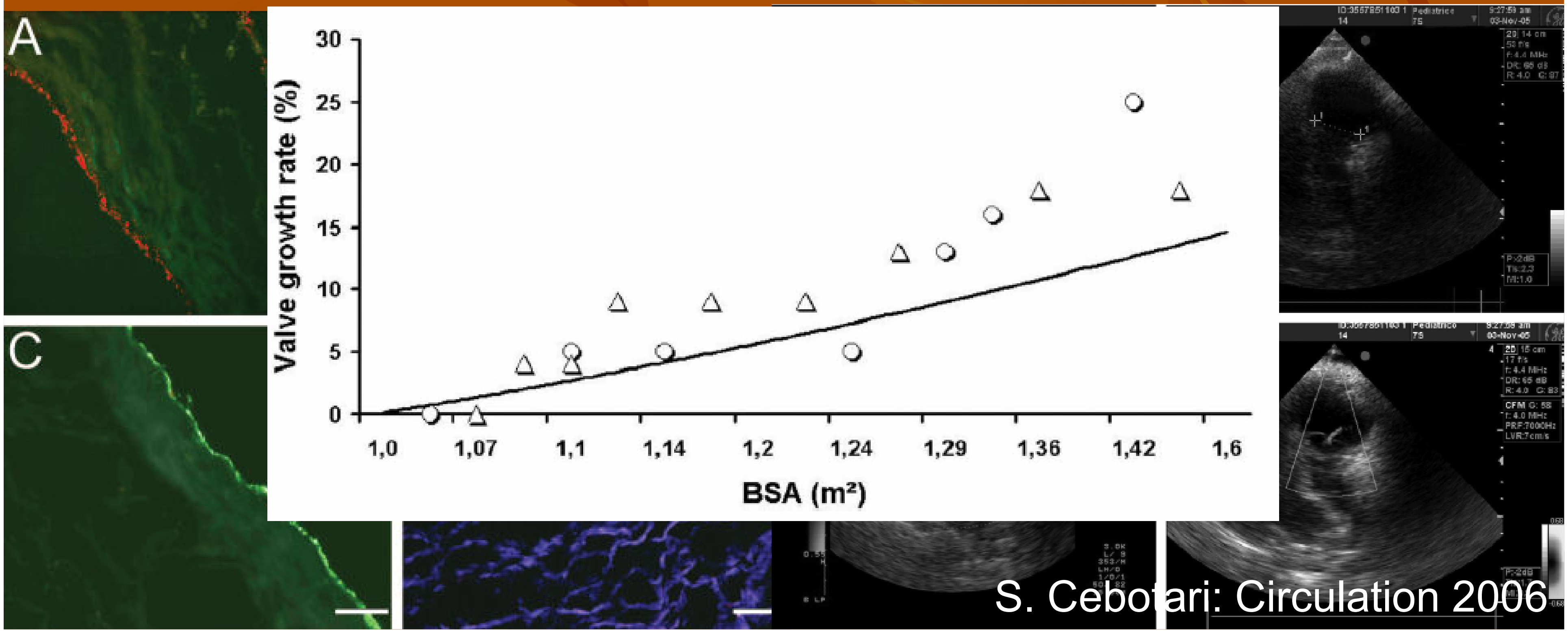
A. Ramamurthi. Biomaterials 2005

# Signalling Factors

- Mechanical stimulation or physical signalling; (Hoerstrup, 1999)
- Pulsatile flow condition; (Niklason, 1999); much higher deposition of ECM, improved tissue organisation, better mechanical properties –lack the mechanical strength required for functional performance in the anatomical position
- More efficient biomimetic protocols
- Gene therapy; promote the expression of suitable mitogenic, angiogenic or neurogenic factors (Yla-Herttuala, 2000)

# Clinical Trial (I)

- 2 patients
- Decellularized human pulmonic valve
- Peripheral mononuclear cells - 42 months FU

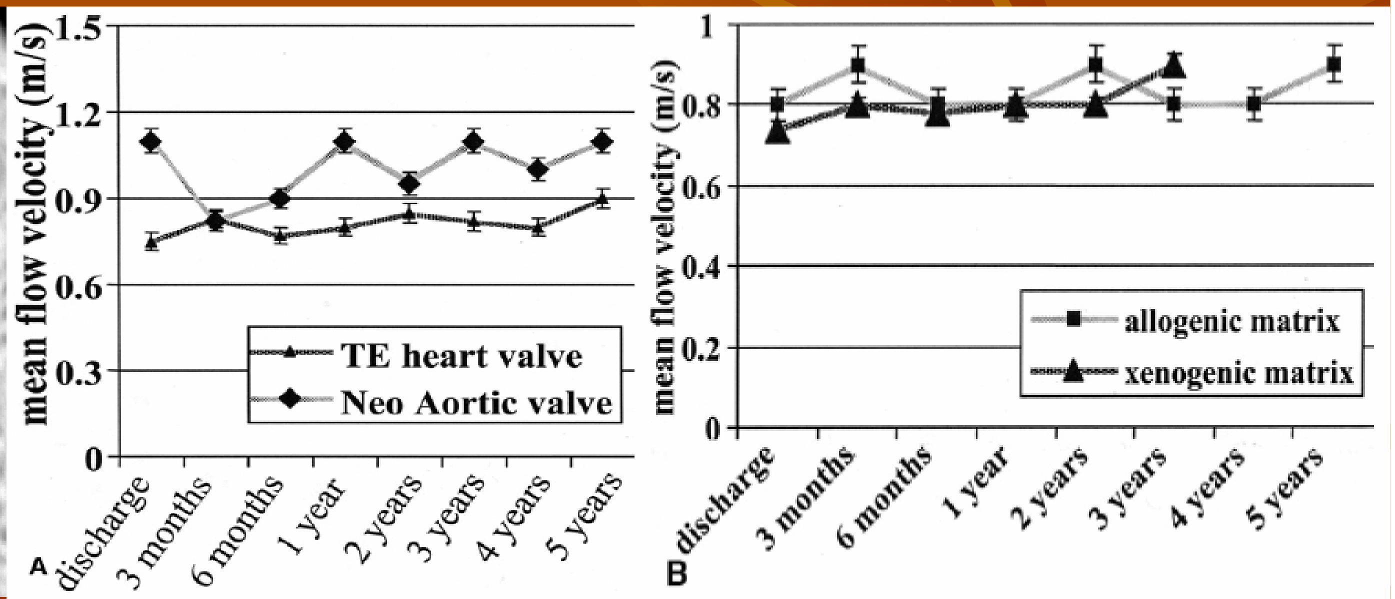



S. Cebotari: Circulation 2006

# Clinical Trial (II)

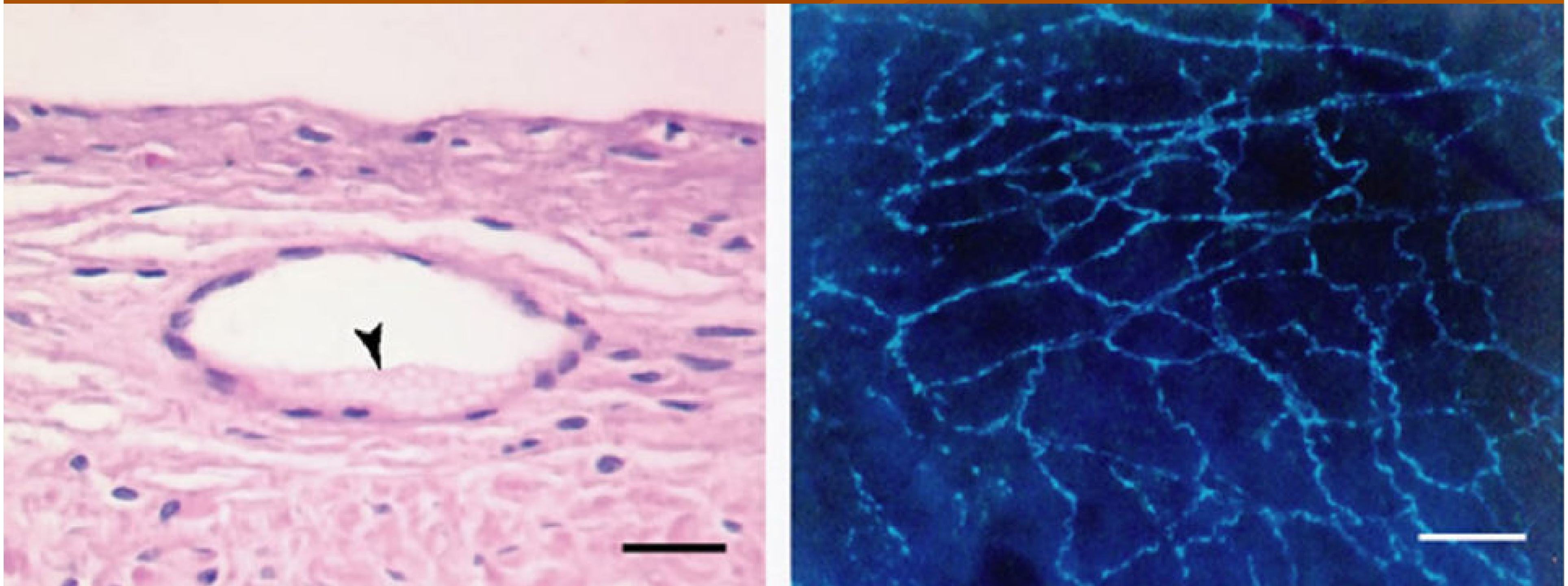
- 2000-2003; 23 명에서 Ross 수술시 PVR
- Decellularized cryopreserved homograft
- Decellularized porcine valve
- And EC seeding in the bioreactor

4 months




PM Dohmen: Ann Thorac Surg 2007

# HOWEVER



Vascular elements and neural elements have been demonstrated in the heart valve interstitial matrix

## *BIOMARKERS* for Cell and Tissue Characterization

- Tissue composition
- Cell gene expression
- Protein expression
- ECM quality
- Mechanical properties
- Residual polymer

## *ASSESSMENT* of Patient Response

- Age and underlying pathology
- Remodeling capacity
- Tissue(biopsy)
- Biomarker in blood or urine
- Anatomic imaging
- Molecular imaging

## Key *BIOLOGICAL PROCESSES* in Tissue Engineering and Regeneration

- Cell originn and fate
- Cell adhesion, migration, proliferation
- Endogenous cell recruitment
- Extracellular matrix formation remodeling
- Scaffold degradation
- Cellular viability, phenotypes and function
- Tissue adaptation and growth

## Patient *OUTCOMES*

- Success
- Failure

Correlate

Predict

## Research Goals

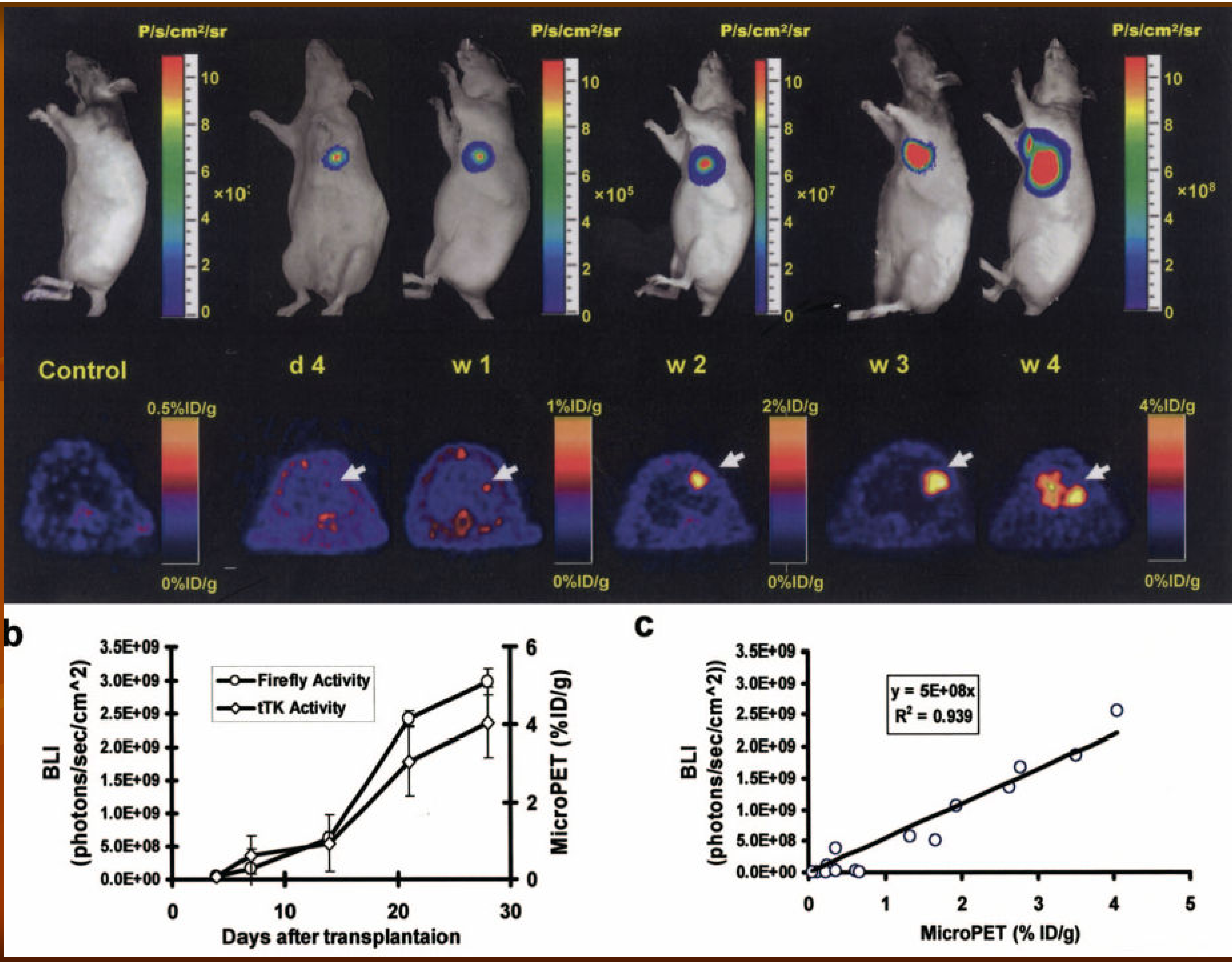
- Understand mechanisms
- Develop biomarkers
- Develop assays/ tools
- Define surrogate endpoints

**Translation**

## Clinical Goals

- Manufacture/deliver product
- Characterize tissue for use
- Predict outcome early
- Accommodate patient to p heterogenity

Paradigm for Translating Research in Heart Valve Tissue Engineering from the Lab to the Clinic



P/s/cm²/sr
×10⁵
×10⁷
×10⁸
Control
d 4
w 1
w 2
w 3
w 4
0.5%ID/g
1%ID/g
2%ID/g
4%ID/g
0%ID/g
b
BLI (photons/sec/cm^2)
MicroPET (%ID/g)
Firefly Activity
tTK Activity
Days after transplantaion
c
y = 5E+08x
R² = 0.939
BLI (photons/sec/cm^2))
MicroPET (% ID/g)