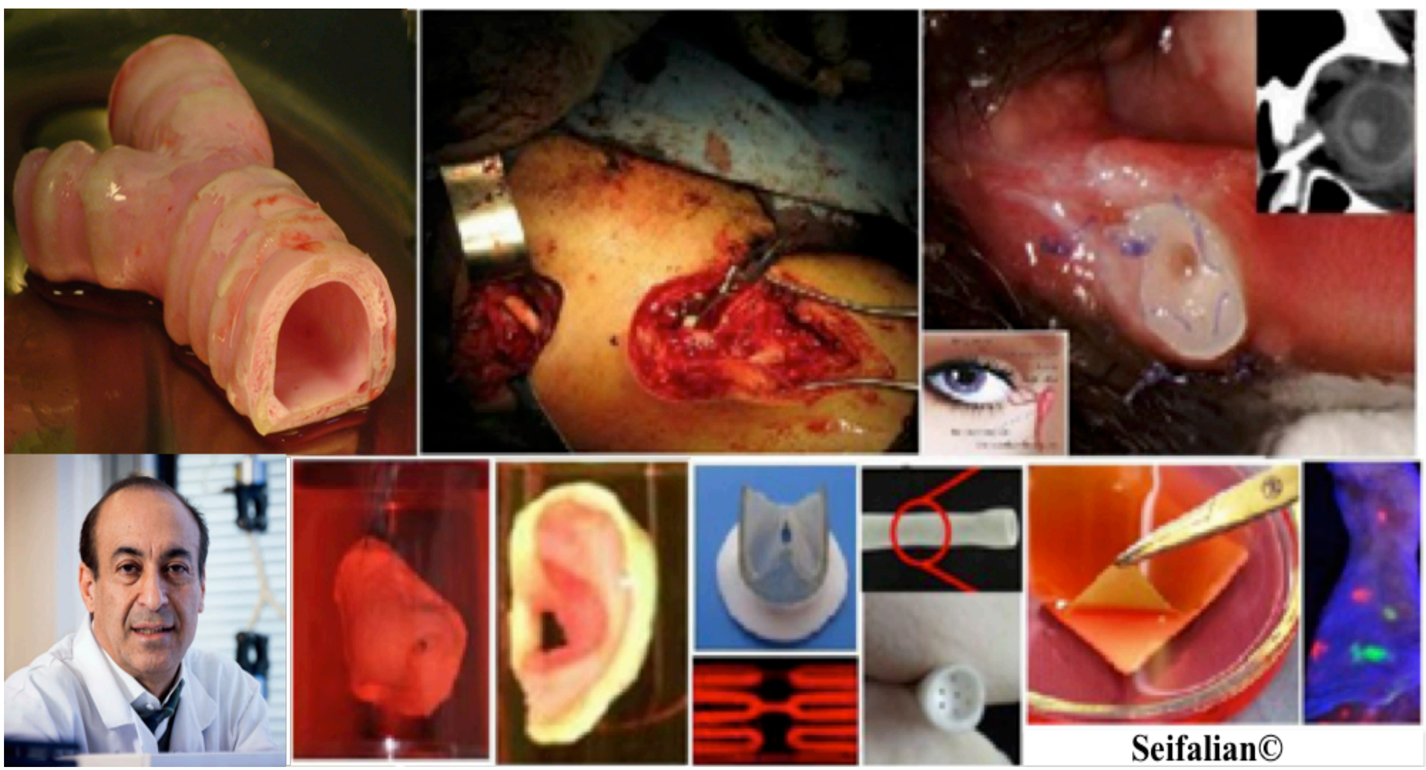
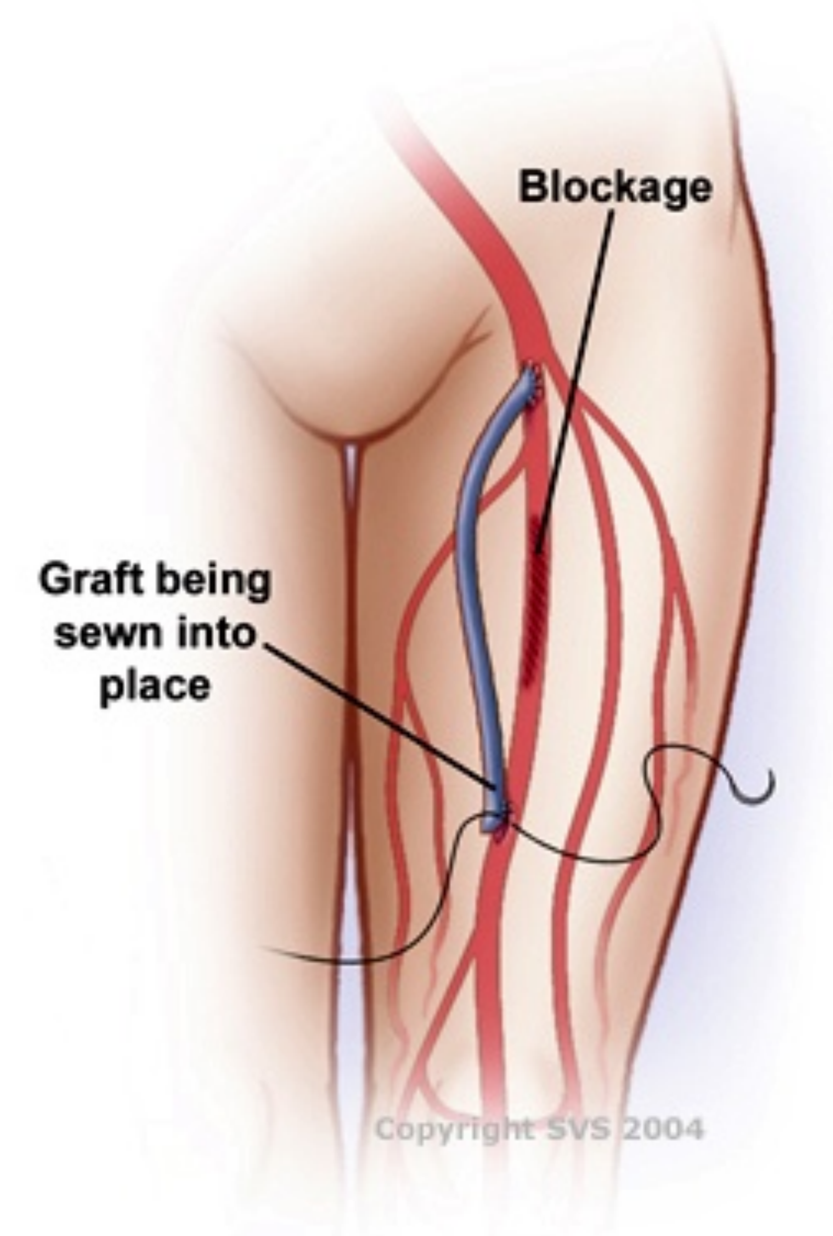
Development of human organs with nanocomposite materials, bioactive molecules and stem cells technology

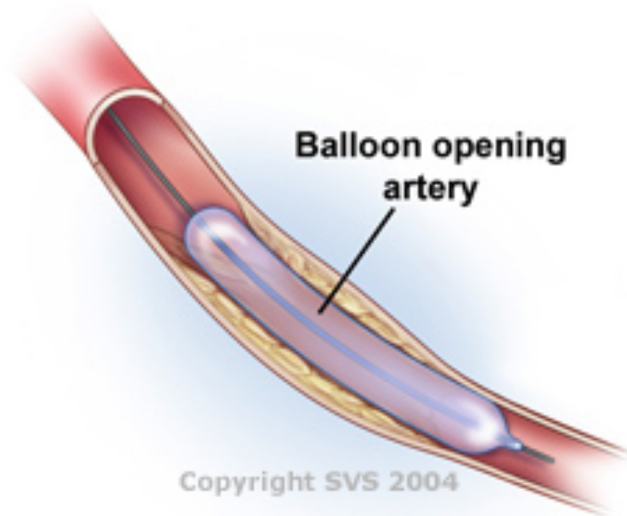
Professor Alexander M. Seifalian

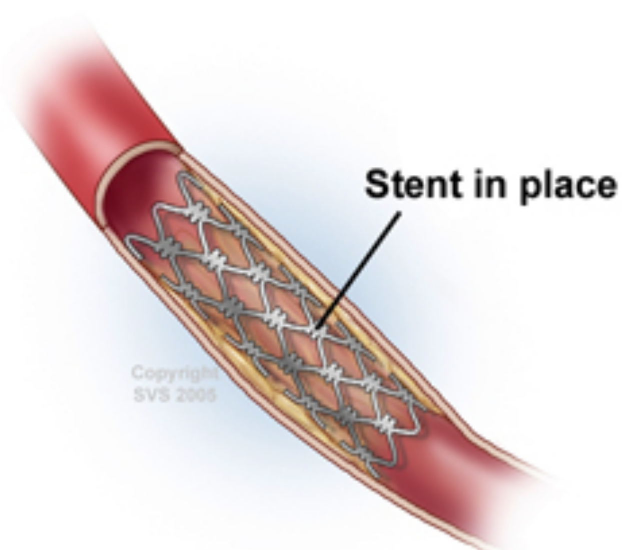
NanoRegMed Ltd

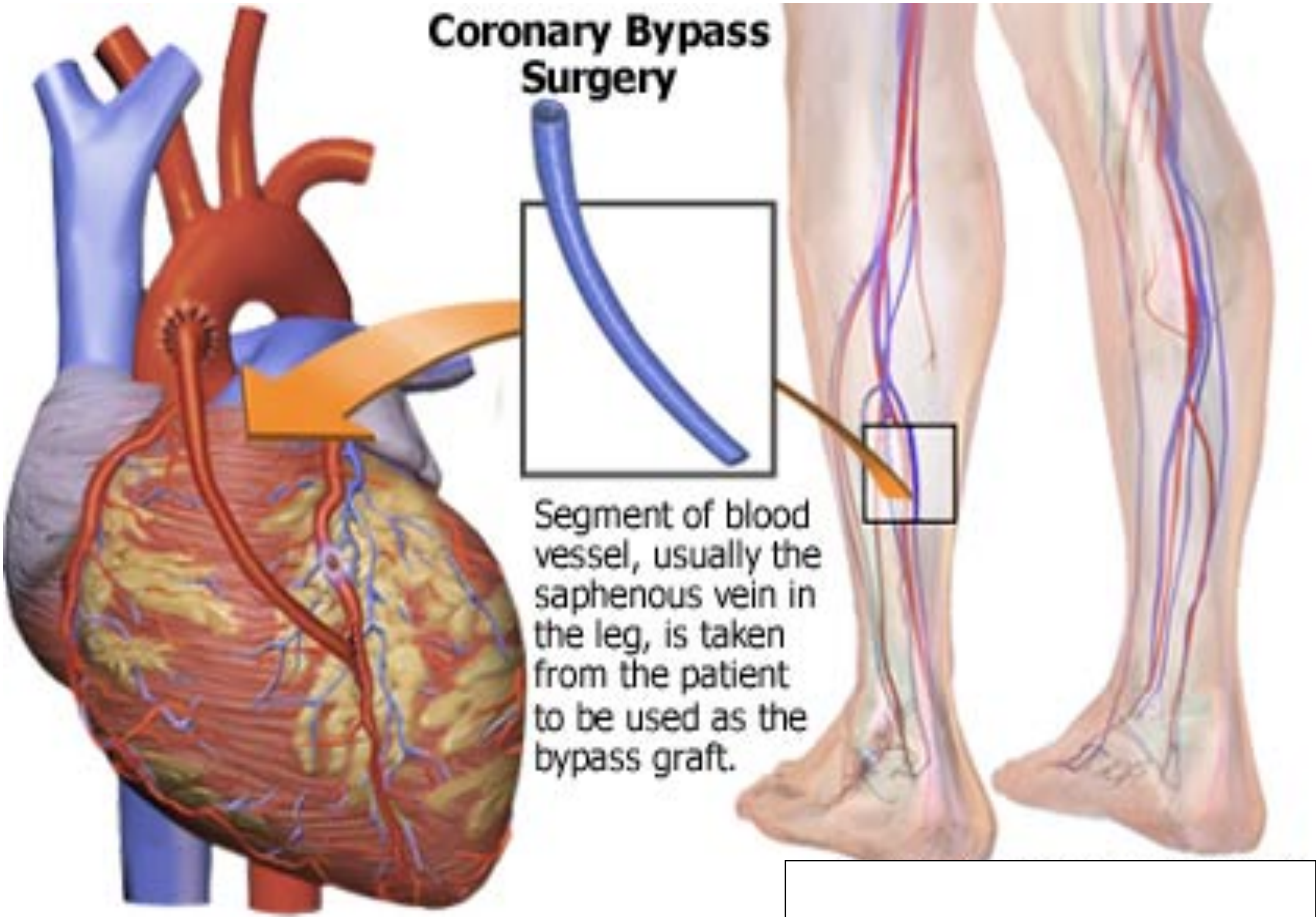
The London BioScience Innovation Centre, London, UK




Blockage
Graft being sewn into place
Copyright SVS 2004


Balloon opening artery
Copyright SVS 2004


Stent in place


Coronary Bypass Surgery
Segment of blood vessel, usually the saphenous vein in the leg, is taken from the patient to be used as the bypass graft.

Market Potential for Medical Devices

Application	Estimated Potential Market Size	Unmet Need
CABG	$15 billion 100-800 thousand pat	Thrombosis, fibrinogen build up, vein graft weakness
Renal graft	$10 billion	Thrombosis and infection
Urinary Catheter	$10 billion	Infection, irritation,
Cardiac Valves	$12 billion 82 thousand/year in US	Thrombosis, Durability, rejection
Stent	$14 billion+	Thrombosis, rejection, fibrinogen build up

Background (Cardiovascular Bypass graft)

- **5-30% of patients do not have suitable vein**
- **Grafts made from PTFE or Dacron have primary patency rates of 20-30% for vascular bypass at 4-5 yrs[1,2]**

1. Seifalian AM, et al. Artif Organs 2002; 26: 307-20.
2. Kannan RY, et al. J Biomed Mater Res B Appl Biomater. 2005;74:570-81.

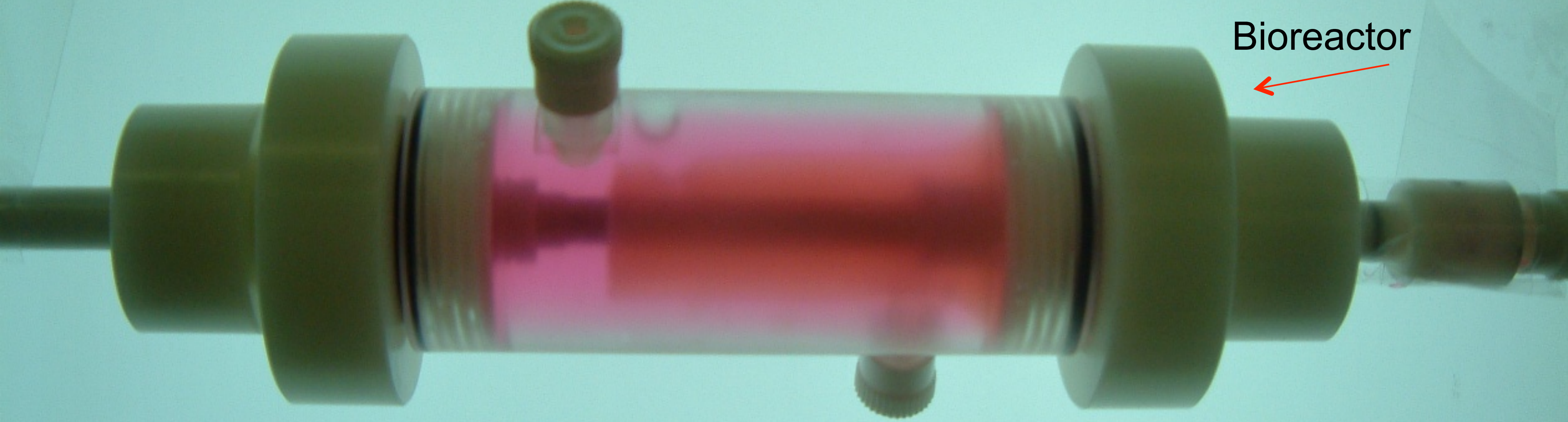
Cause of graft failure

1. **Compliance mismatch[1,2]**

2. **Thrombogenicity of the material[3-5]**

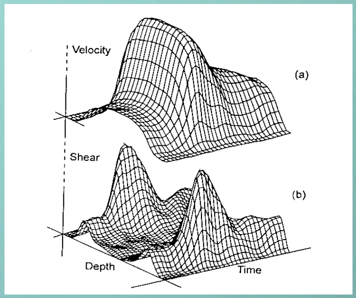
[1]Abbott et al. J Vasc Surg 1987; 5: 376-82.
[2]Sarkar S, et al. Eur J Vasc Endovasc Surg. 2006;31:627-36.
[3]Sarkar S, et al. J Biomed Mater Res. 2007;82:100-8.
[4]de Mel A, Biomacromolecules 2008;9:2969-79.
[5]de Mel A, et al. Expert Rev Cardiovasc Ther. 2008;6:1259-77.

Development of tissue engineering bypass graft
“Living graft”



Matrix mixture added:
Rat tail type I collagen+
Porcine aortic SMC
Incubated and fed
>>> rapid radial contraction +

Precondition, typically
venous flow shear stress 7 days
arterial flow shear stress 14 days

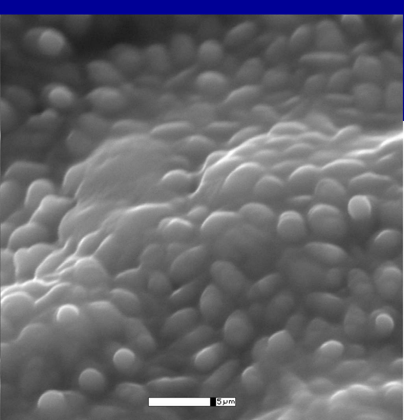


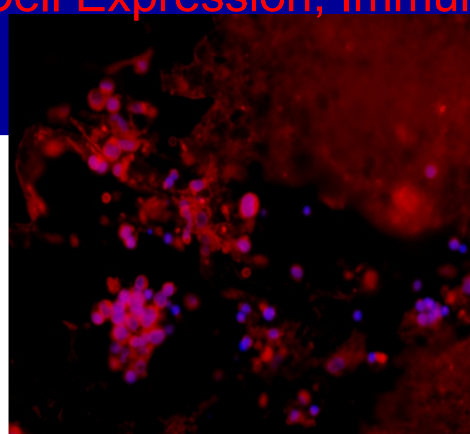
Cheng KS, et al. Cardiovasc Res. 2002;54:528-38
Baguneid M, et al.J Vasc Surg. 2001;33:812-20.
Giudiceandrea A, et al, Eur J Vasc Endovasc Surg. 1998;15:147-54

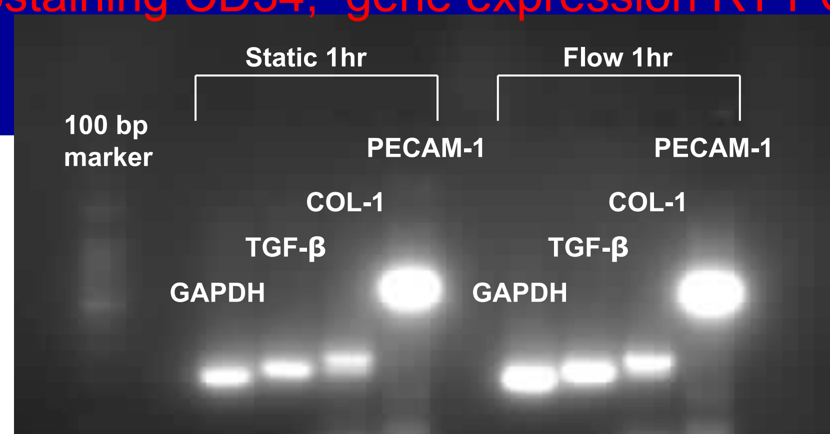
Krijgsman B, et al. Tissue Eng. 2002;8:673-80
Tiwari A, Circ Res. 2003;93:1

EC graft + in vivo test

SEM EC Cell Expression, Immunostaining CD34, gene expression RT PCR

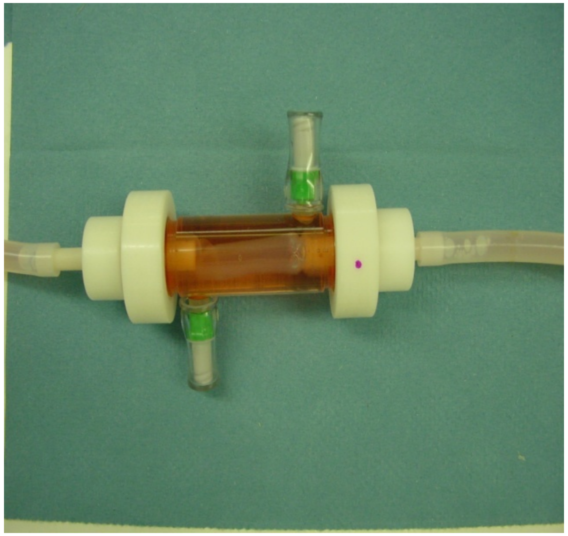






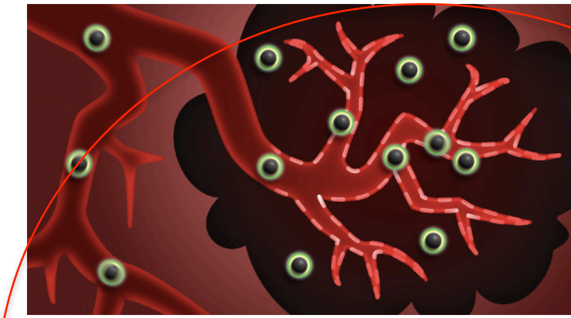
Tissue Engineering with Human Cells age > 55

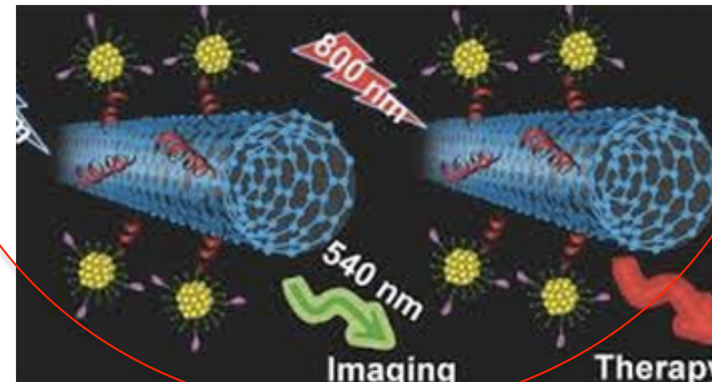
- Low burst pressure (80 mm Hg)
- Elderly cells very difficult to harvest & culture from vein or fat

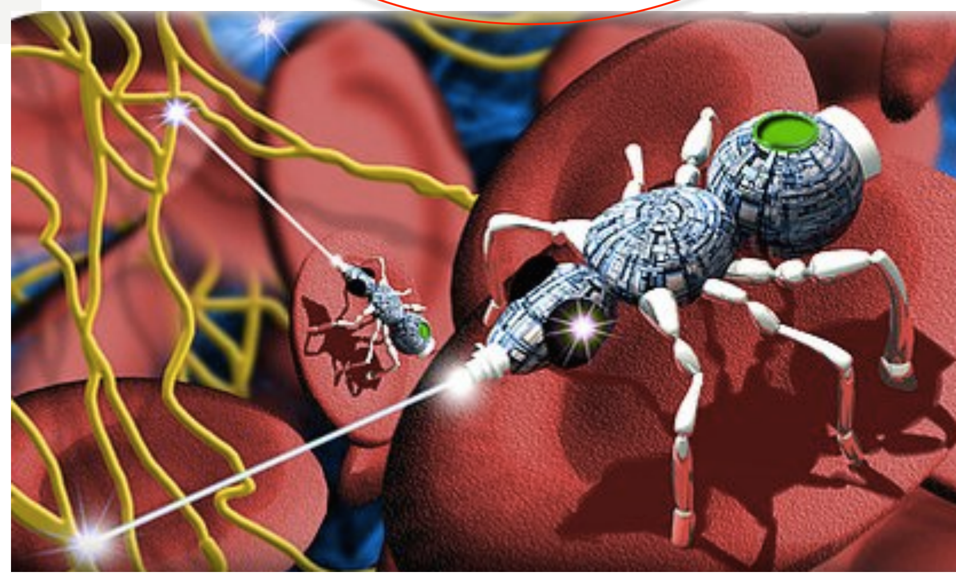


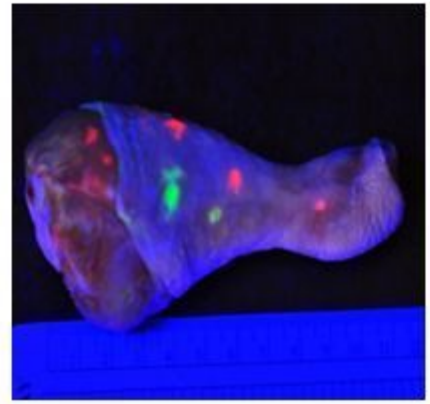
- These and logistical problems make introduction of totally autologous TEVG in the foreseeable future for adult unlikely

Nanomedicine









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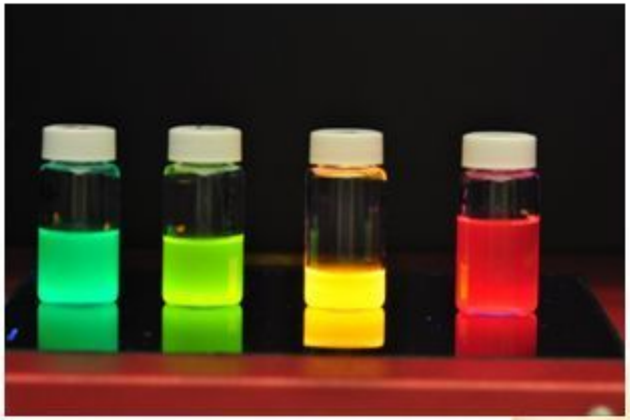
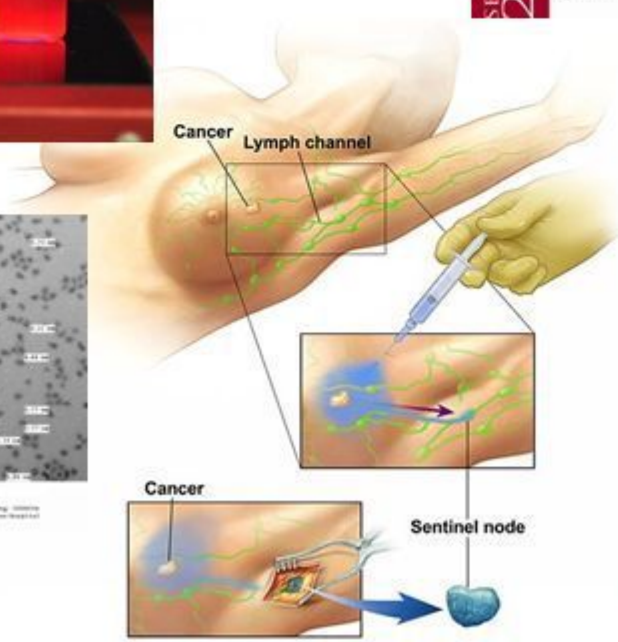
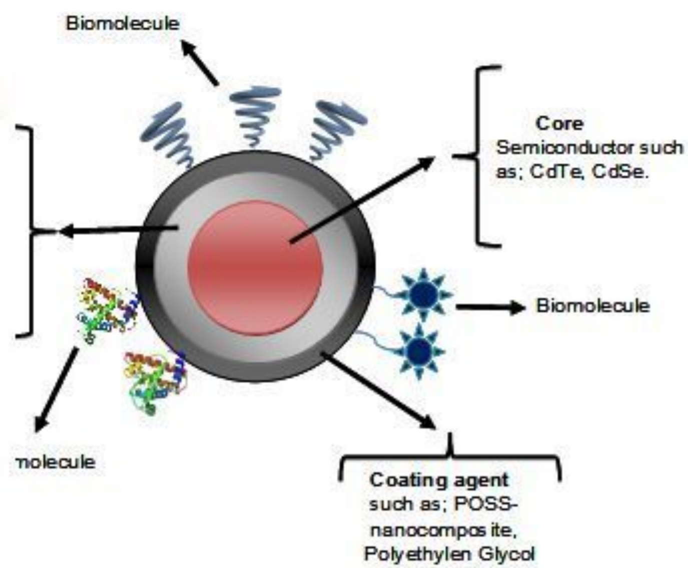
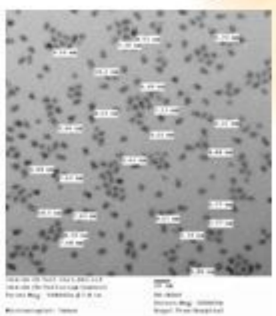


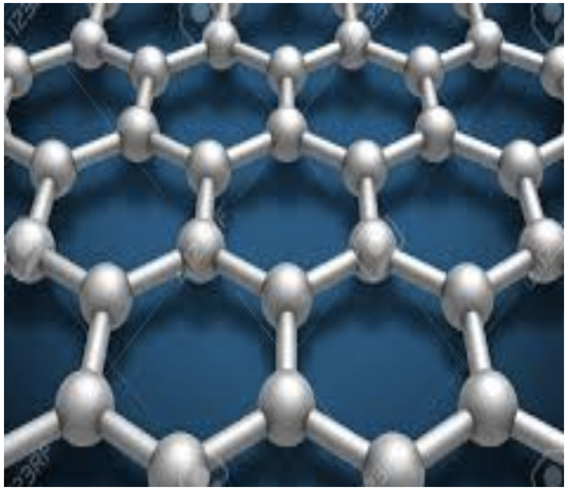


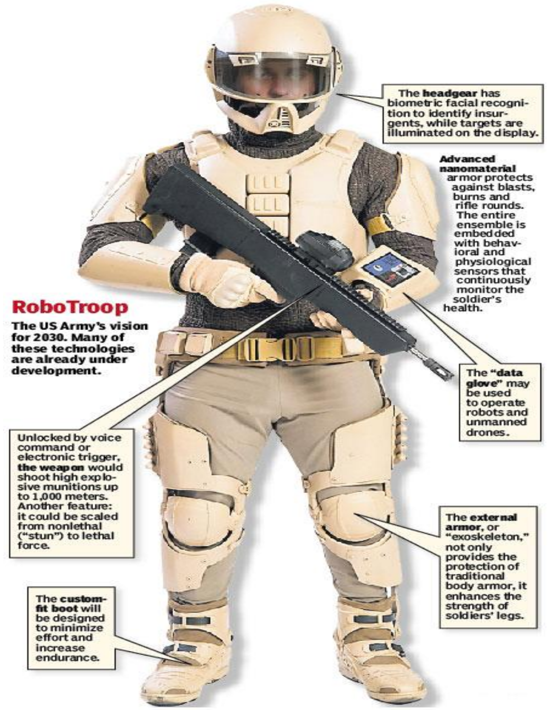


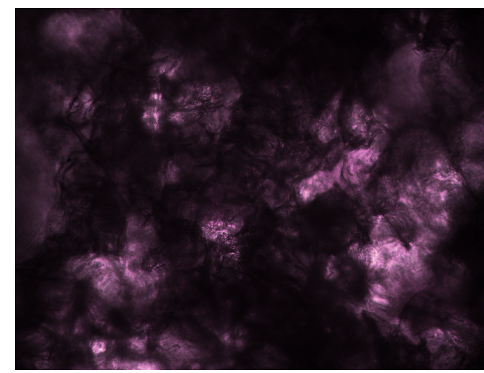


Dr Bala Ramesh, Senior Research Fellow
Miss Shirin Ghadiri, PhD student

CNT & Graphene





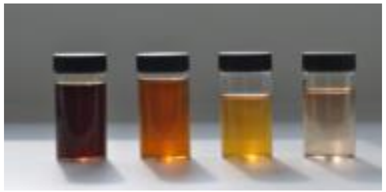


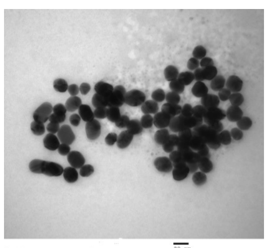
Cardiac Patch

Bulletproof Suit

R&D Nanoparticles

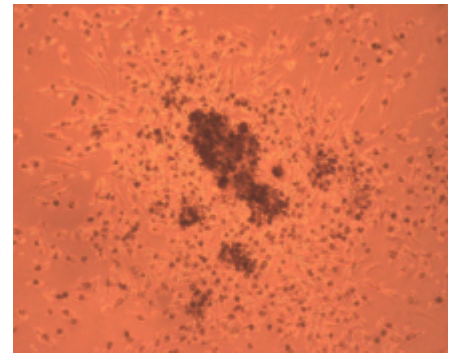
Silver & Gold

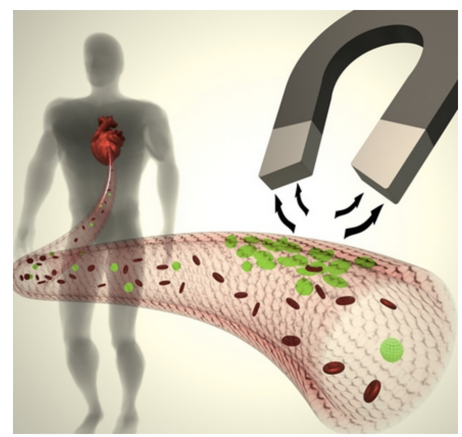




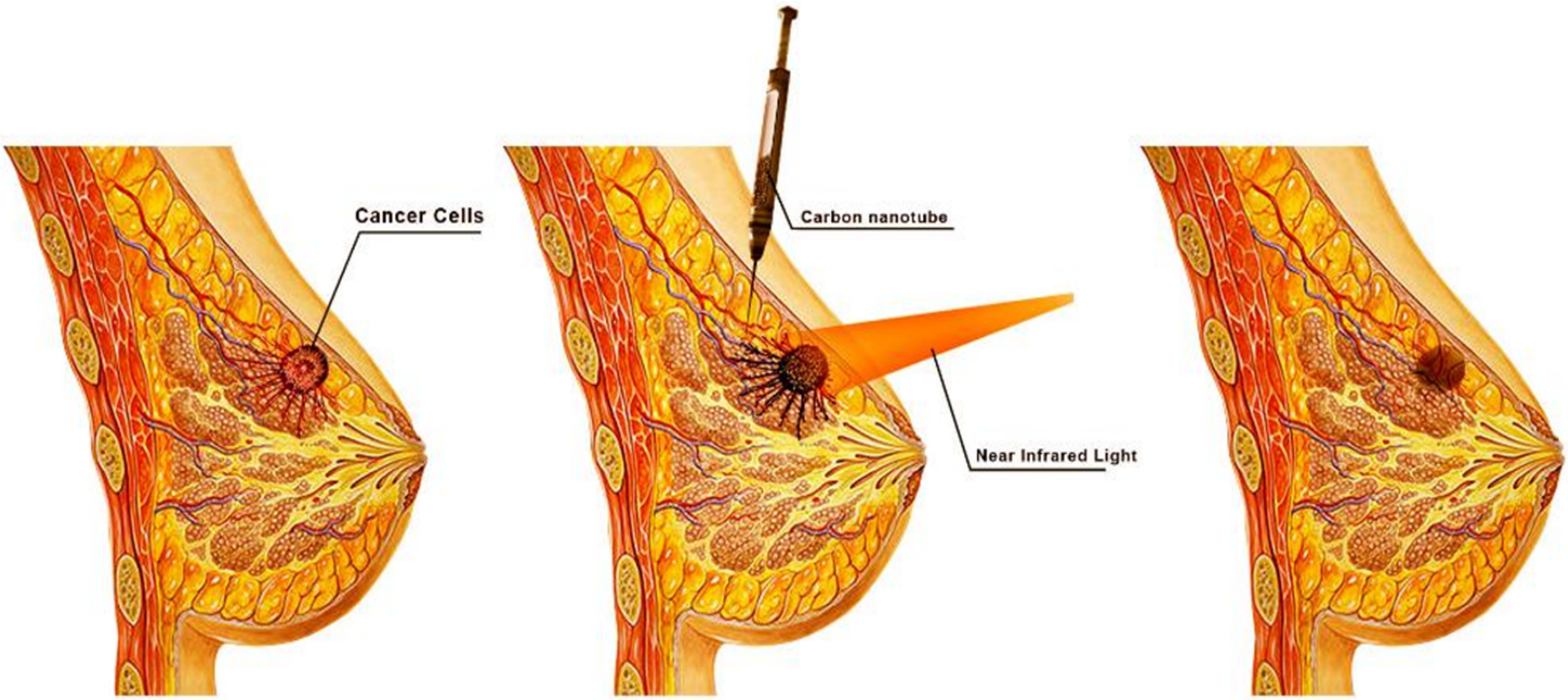
inhibit microbial growth

Superparamagnetic





Thermal treatment of cancer

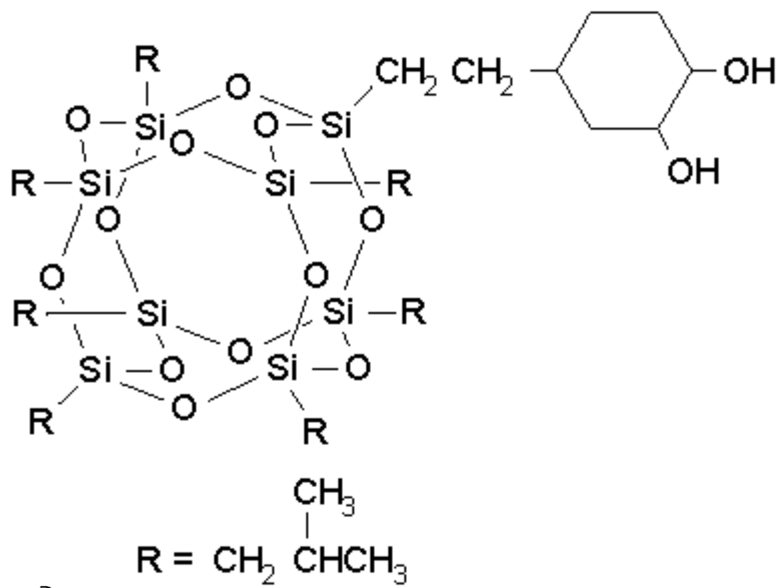


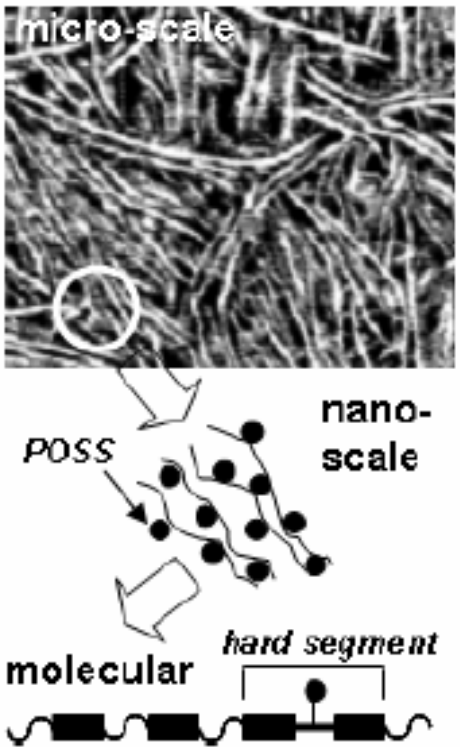
Pre-treatment During treatment Post-treatment

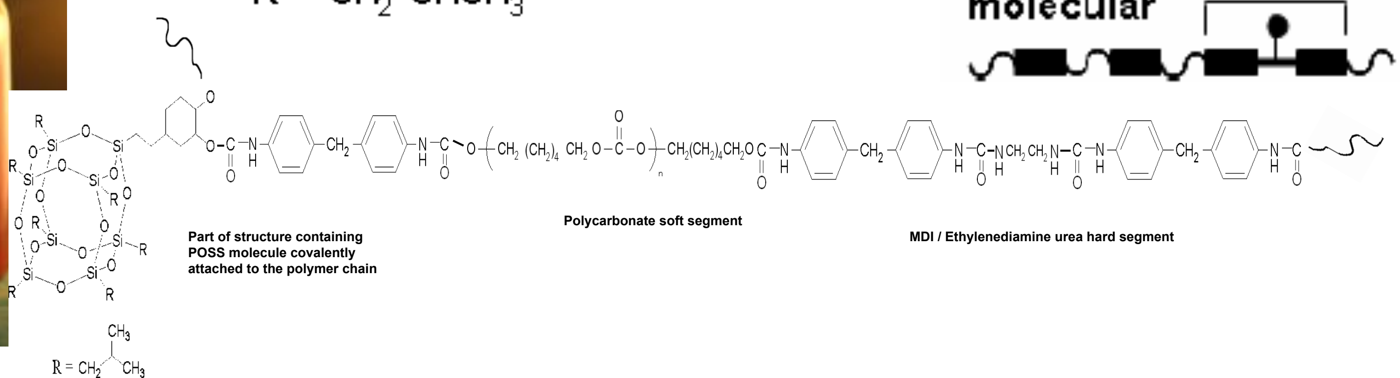
Developed a family of bioactive nanocomposite materials, example:

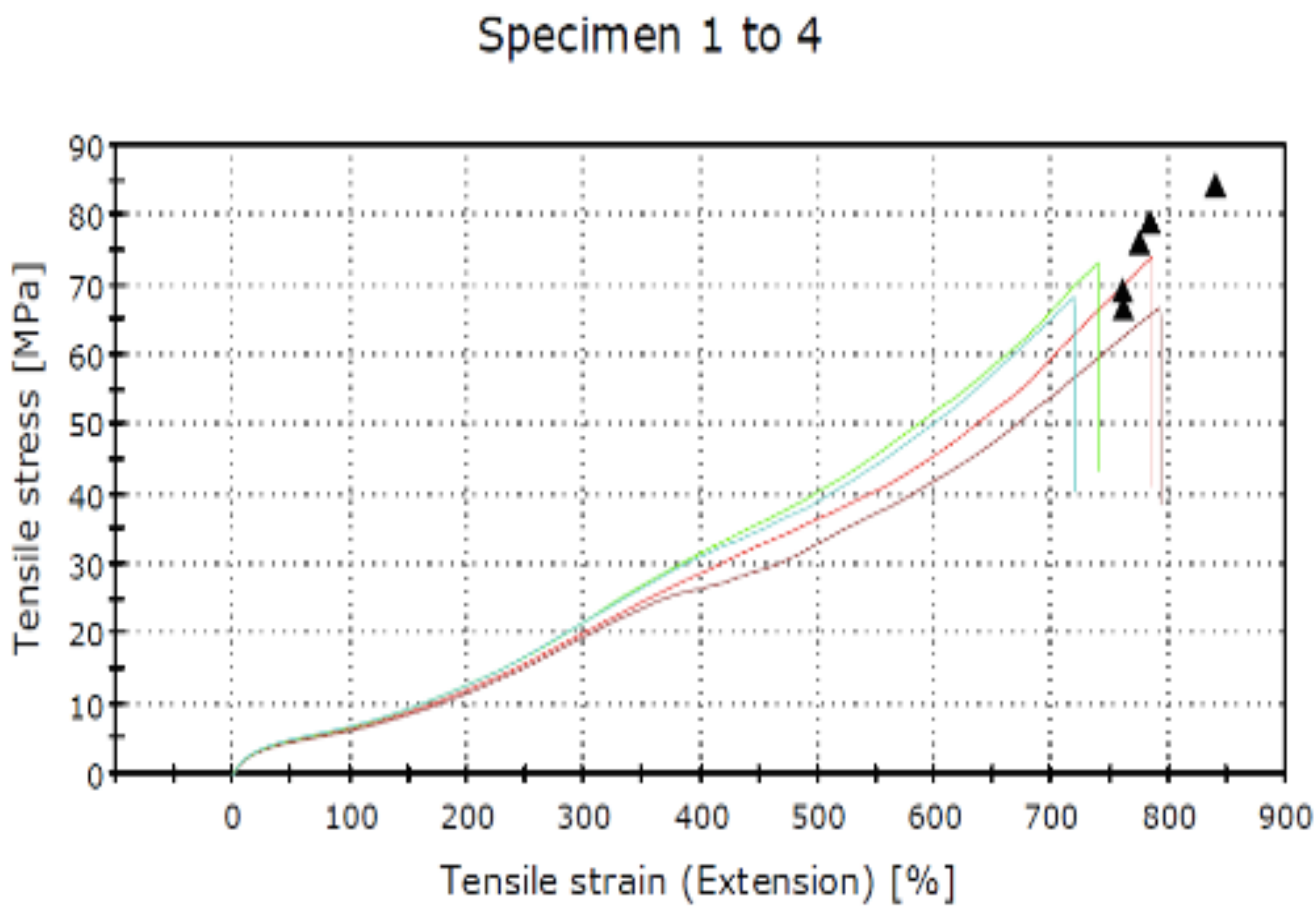
Based on POSS+poly(carbonate-urea)urethane (PCU)

trans-Cyclohexane Diol Isobutyl-Polyhedral Oligomeric Silsesquioxane (POSS)

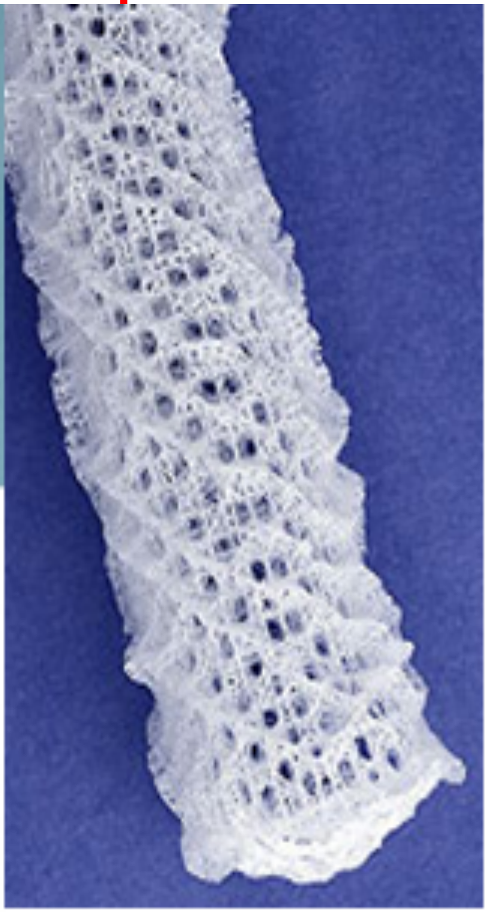


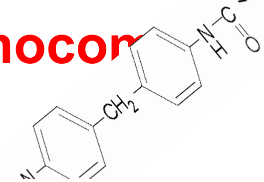


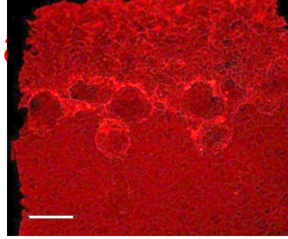


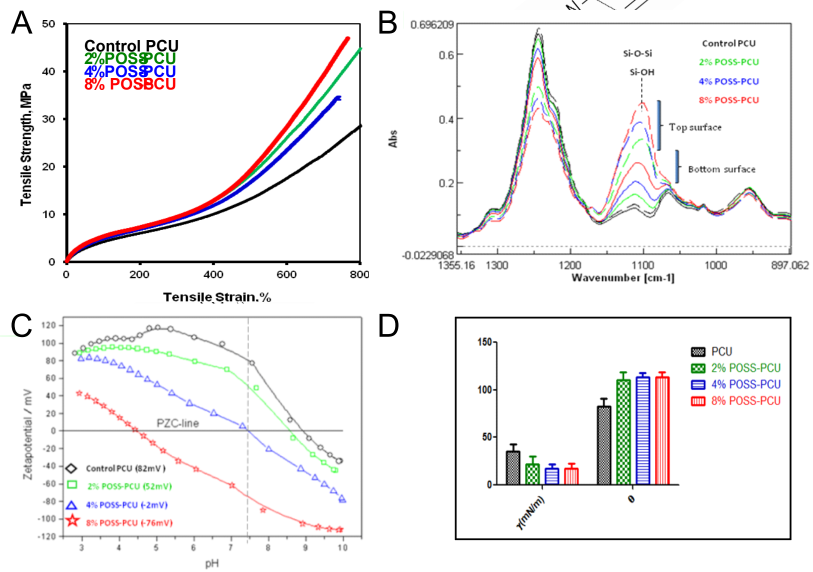

Specimen 1 to 4
Tensile stress [MPa]
Tensile strain (Extension) [%]
0
10
20
30
40
50
60
70
80
90
100
200
300
400
500
600
700
800
900

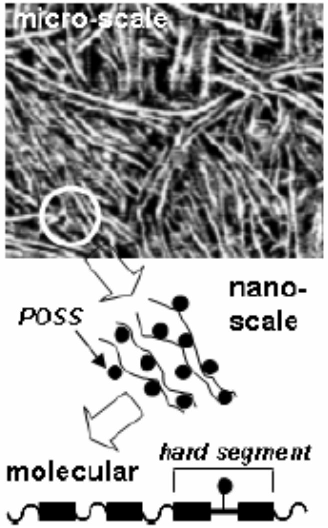
Development of two families of bioactive nanocom[...]e materi[...]

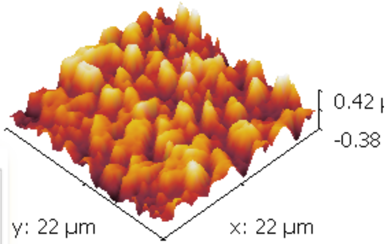


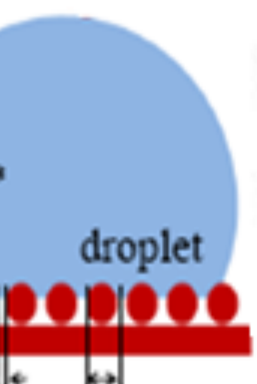


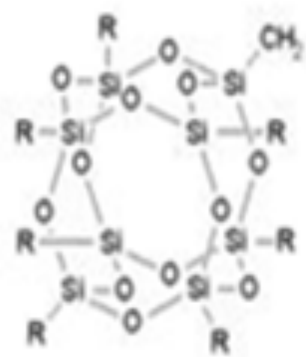


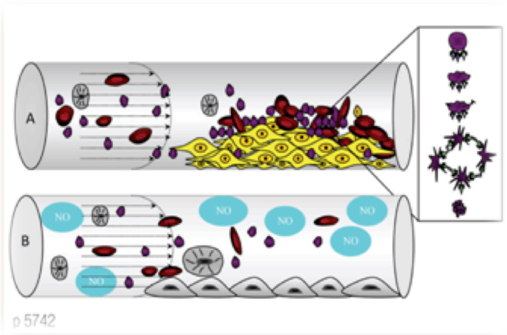


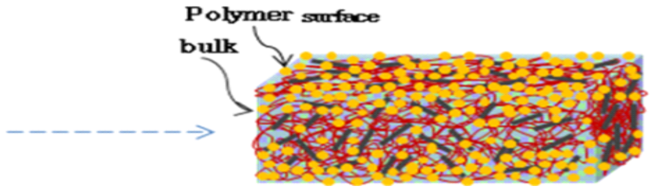


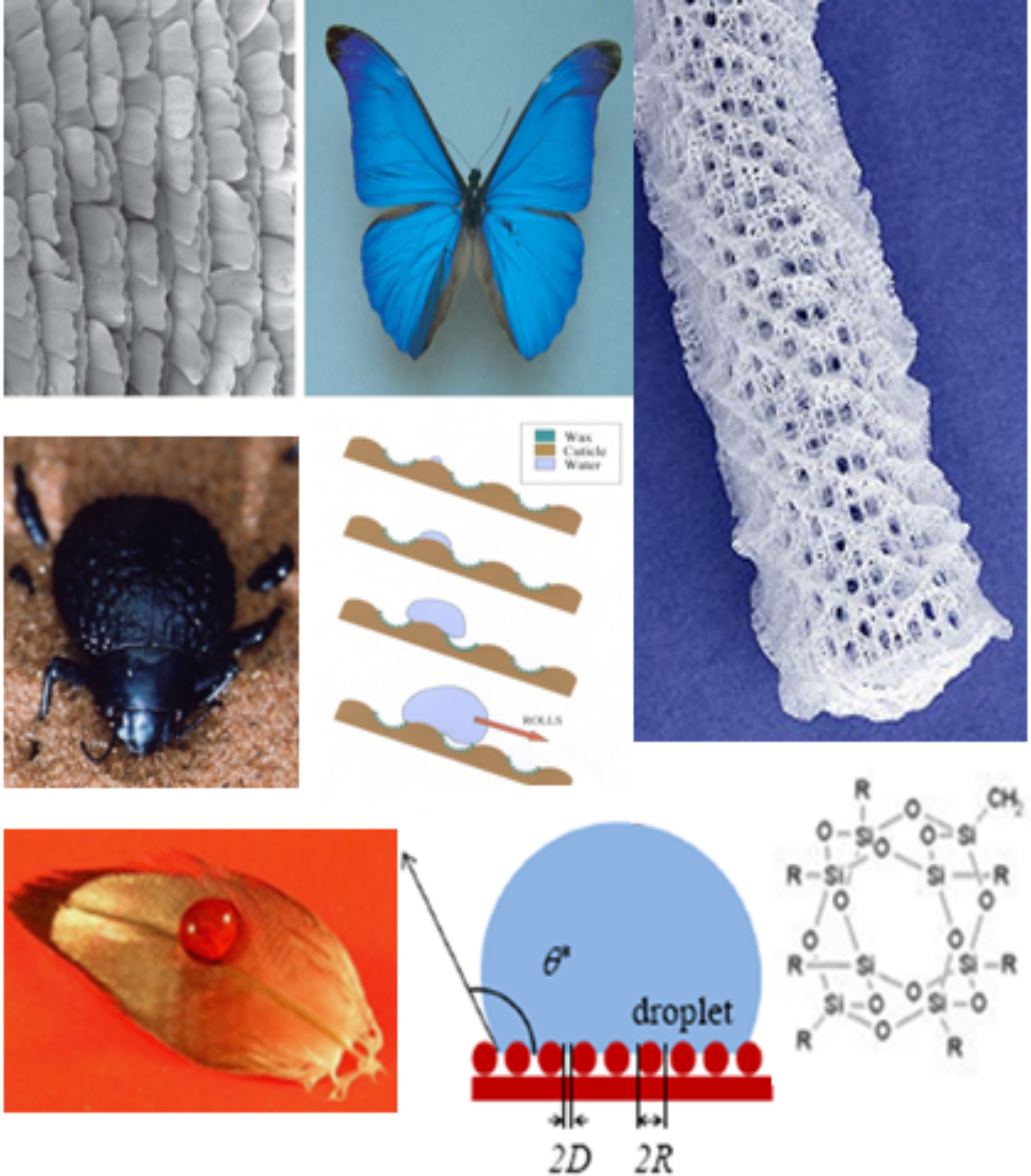




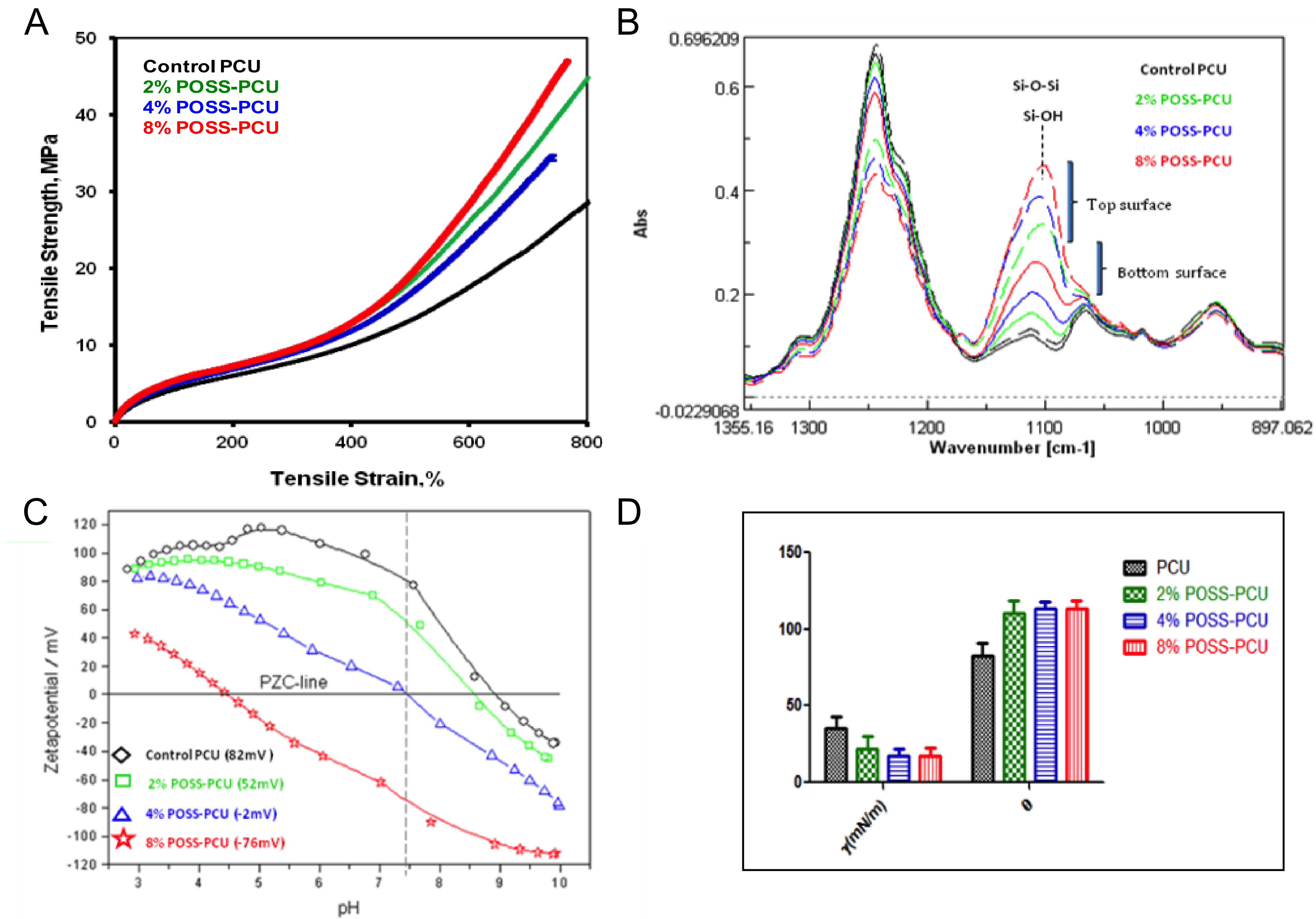




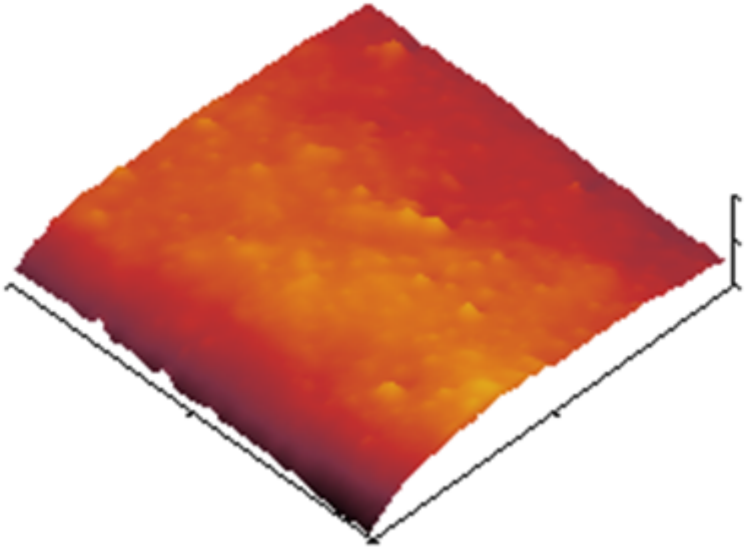


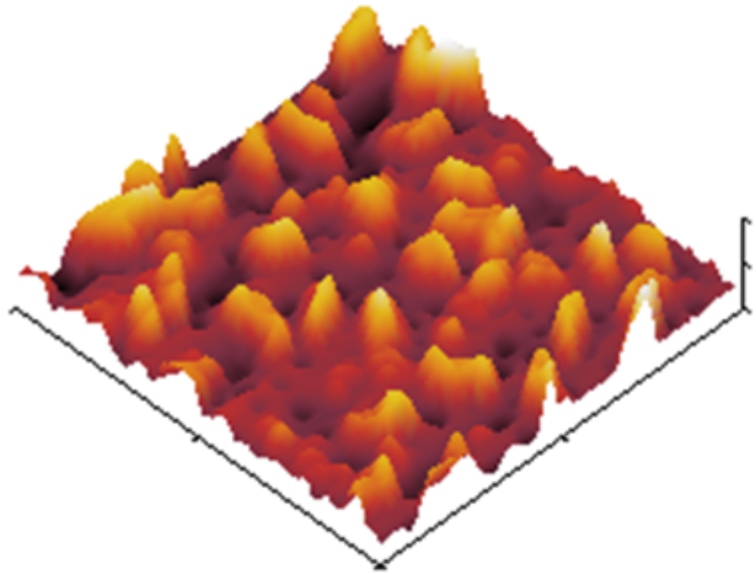


Wax
Cuticle
Water
ROLLS
θ*
droplet
2D
2R

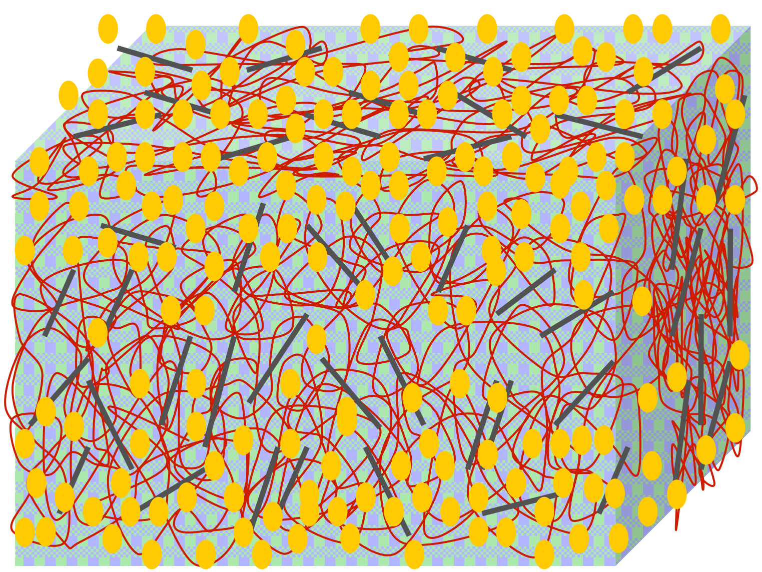

A
Control PCU
2% POSS-PCU
4% POSS-PCU
8% POSS-PCU
Tensile Strength, MPa
Tensile Strain,%
B
Control PCU
2% POSS-PCU
4% POSS-PCU
8% POSS-PCU
Si-O-Si
Si-OH
Top surface
Bottom surface
Abs
Wavenumber [cm-1]
C
PZC-line
Control PCU (82mV)
2% POSS-PCU (52mV)
4% POSS-PCU (-2mV)
8% POSS-PCU (-76mV)
Zetapotential / mV
pH
D
PCU
2% POSS-PCU
4% POSS-PCU
8% POSS-PCU
γ(mN/m)
θ

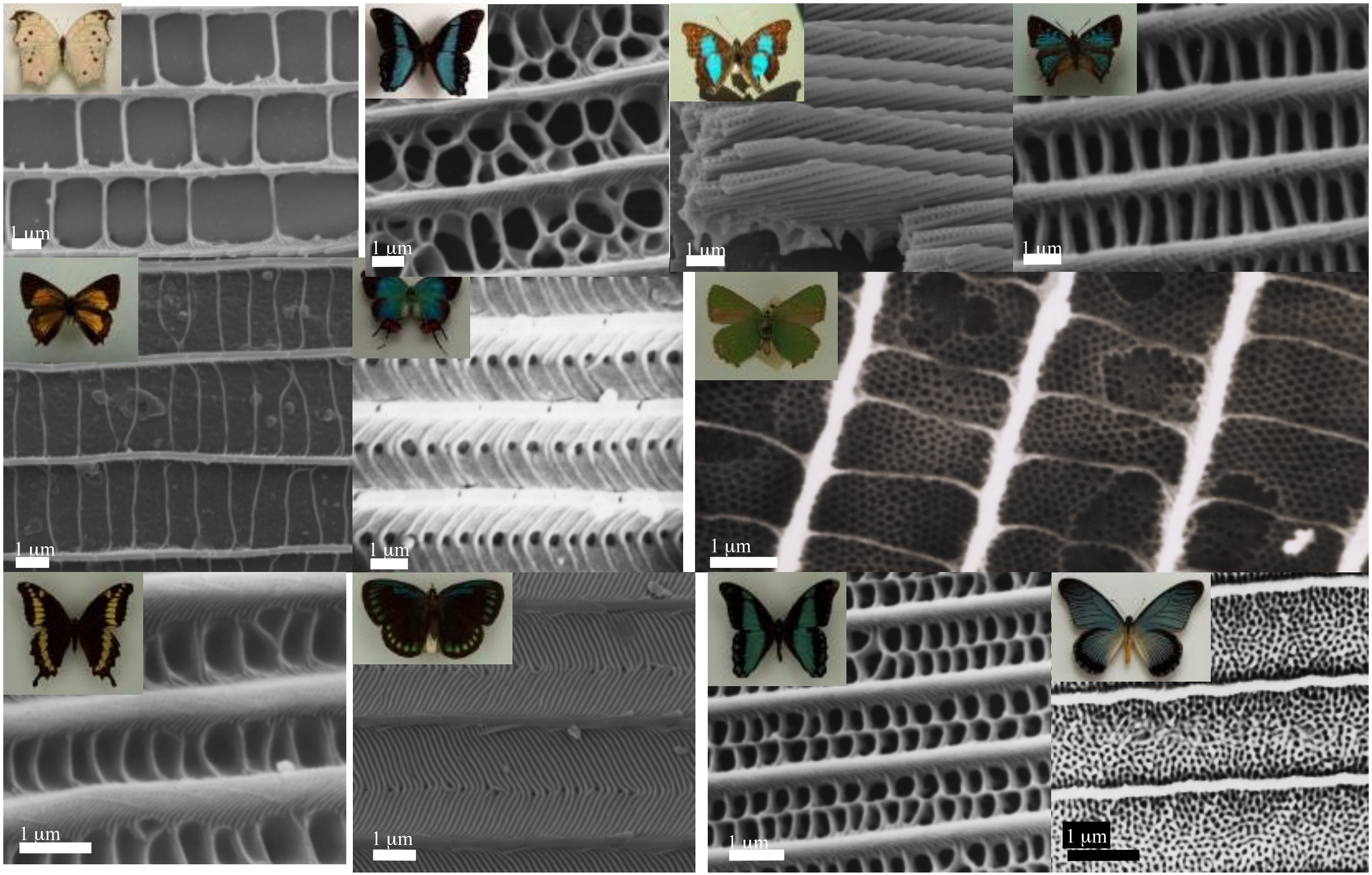
AFM





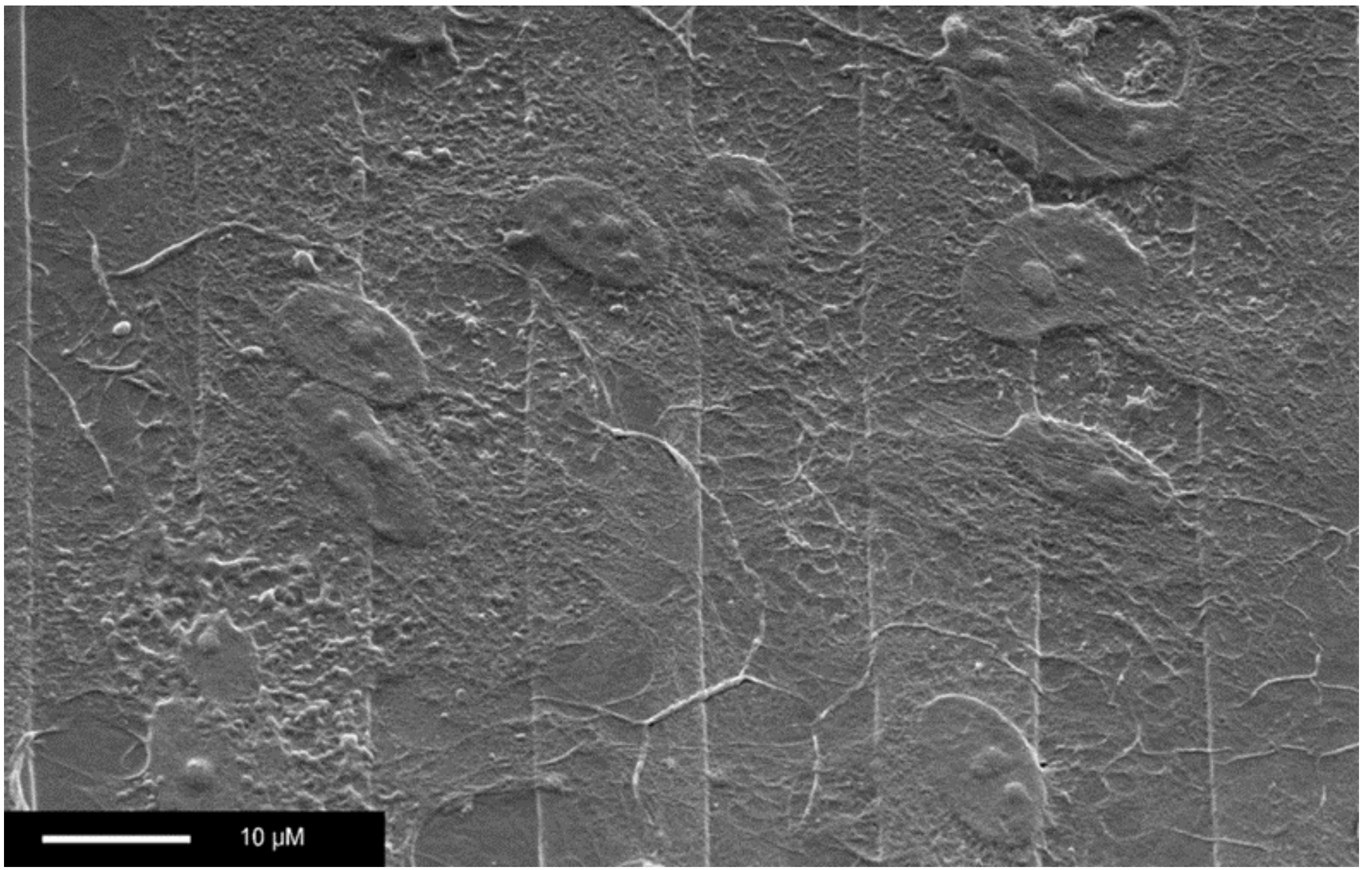
Superhydrophobic nanomaterial coating for clothes could reduce scalding injuries

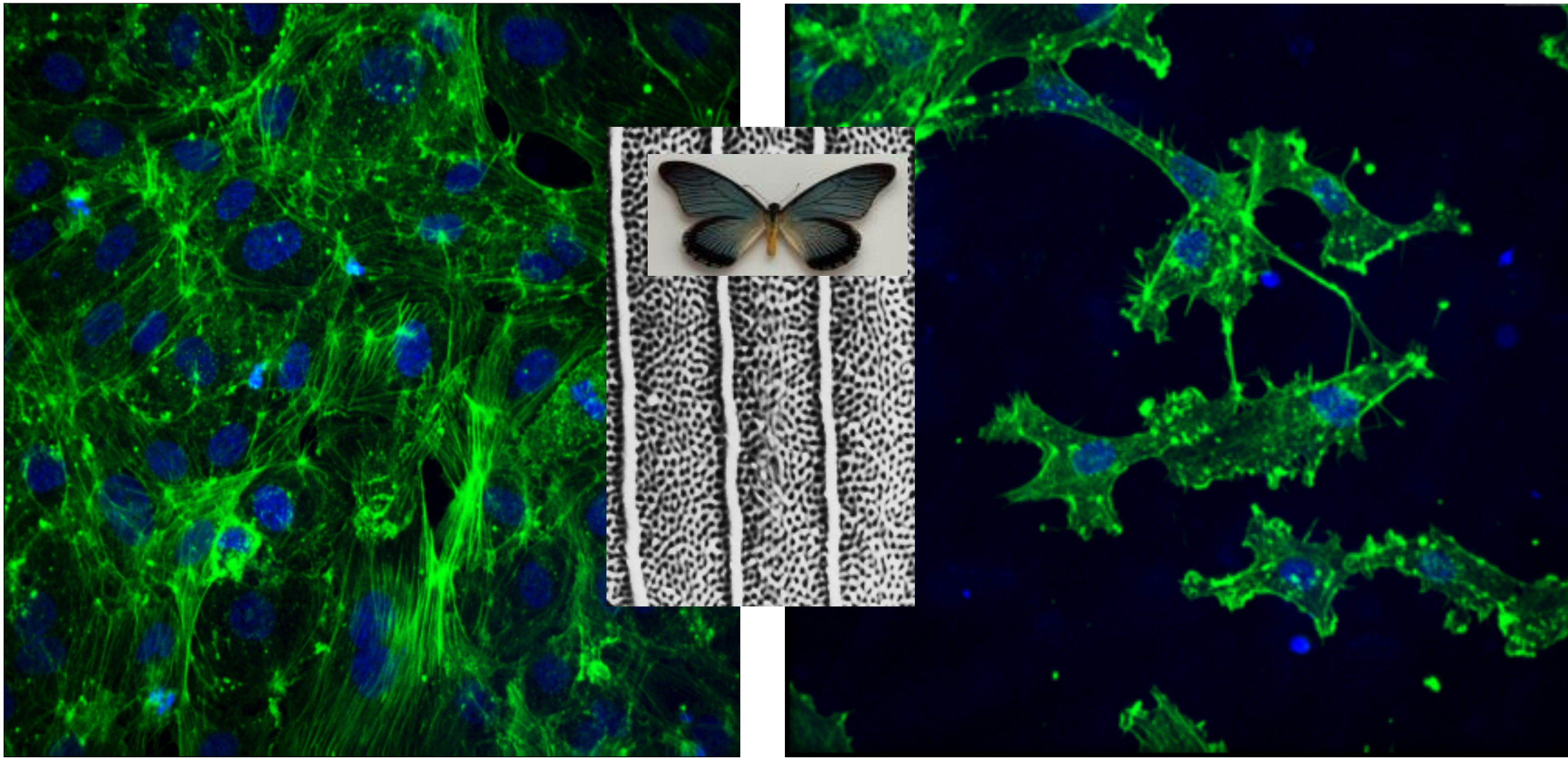




Prof. Parker
Natural History Museum

SEM further shows HUVECs adhering to the grooved surface





GROOVE FLAT

Miss Debra Chong , PhD UCL
Prof Dalby, University of Glasgow

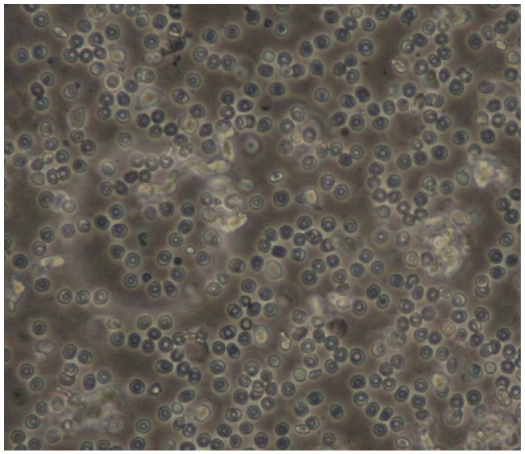
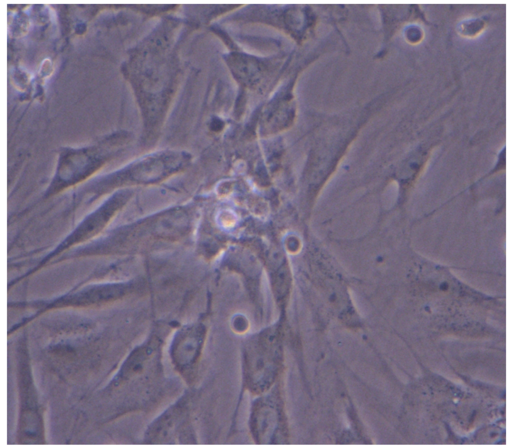
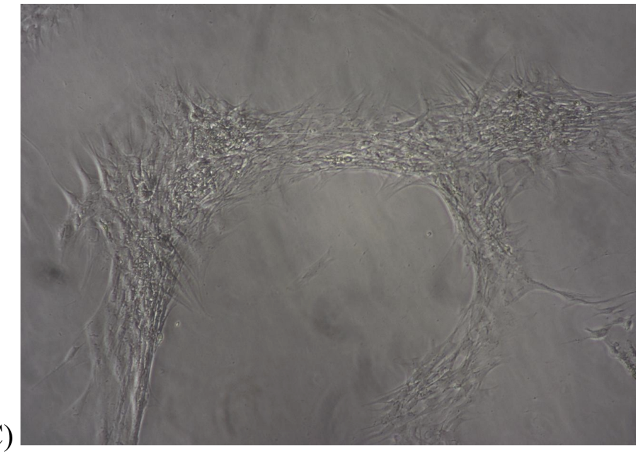
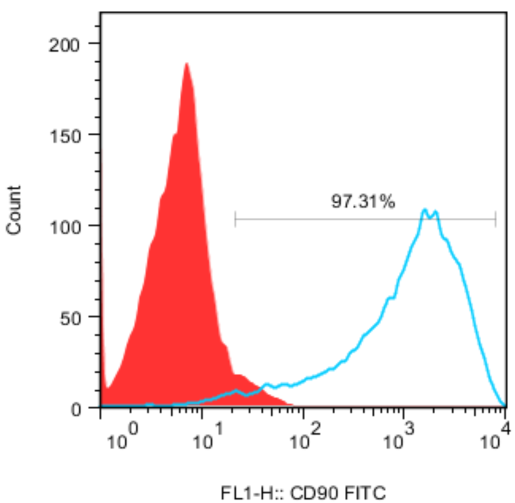
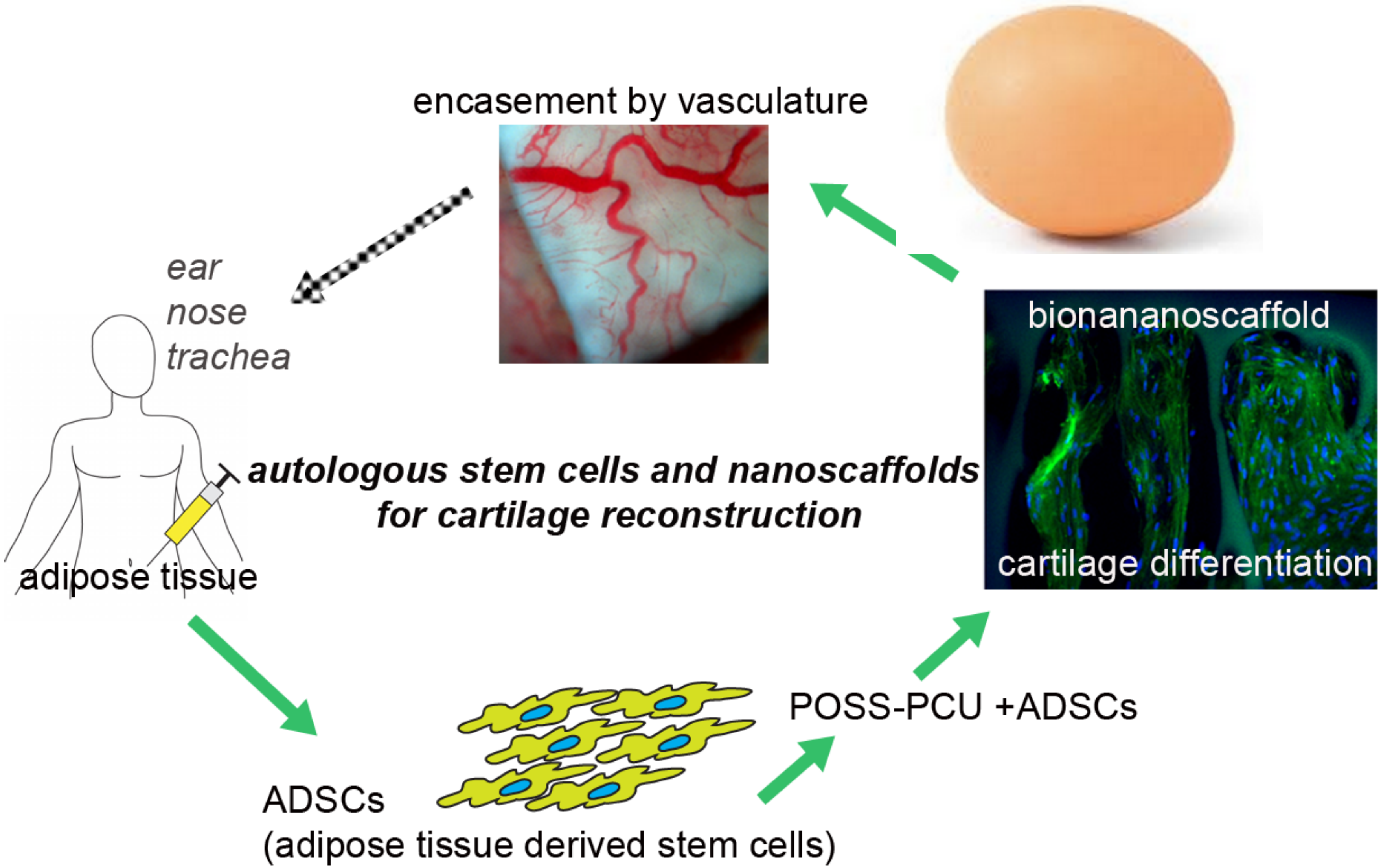
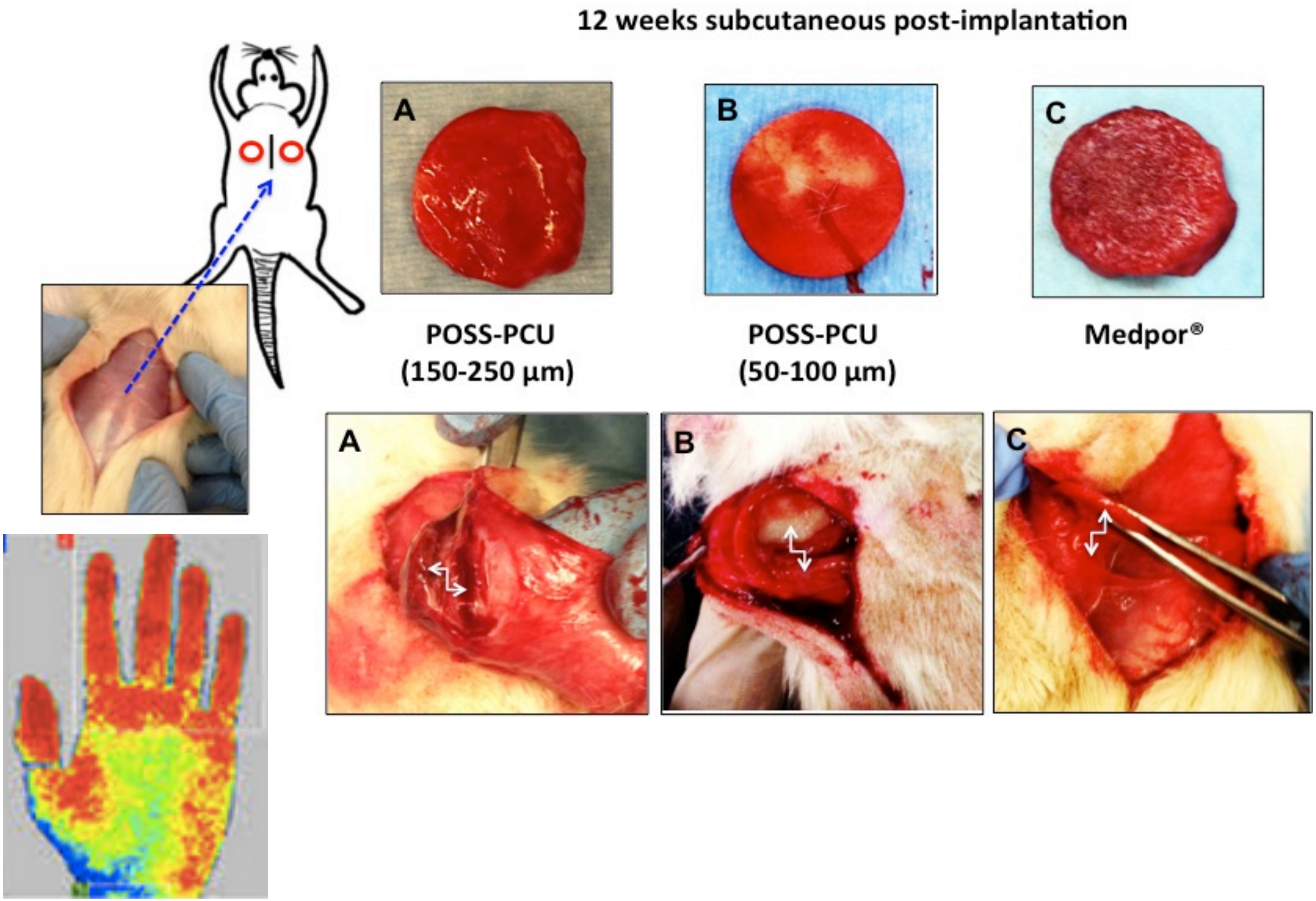
A)  B)  C) 

Figure 4. A. Freshly isolated adipose-derived stem cells**; B.** ASCs cultured in media for 7 days**; C.** ASCs after 7 days of culture, appearing to begin neovessel formation.

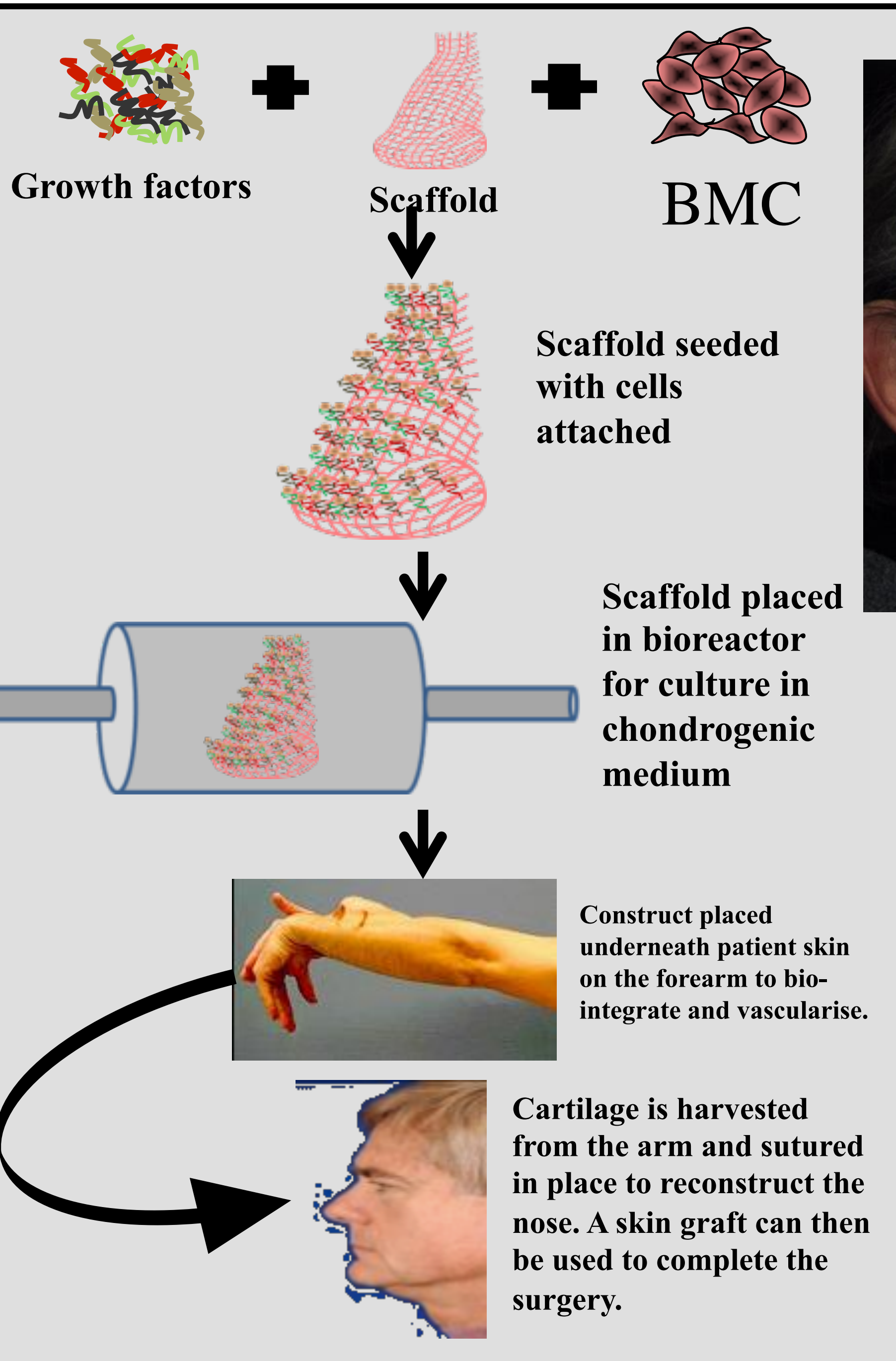


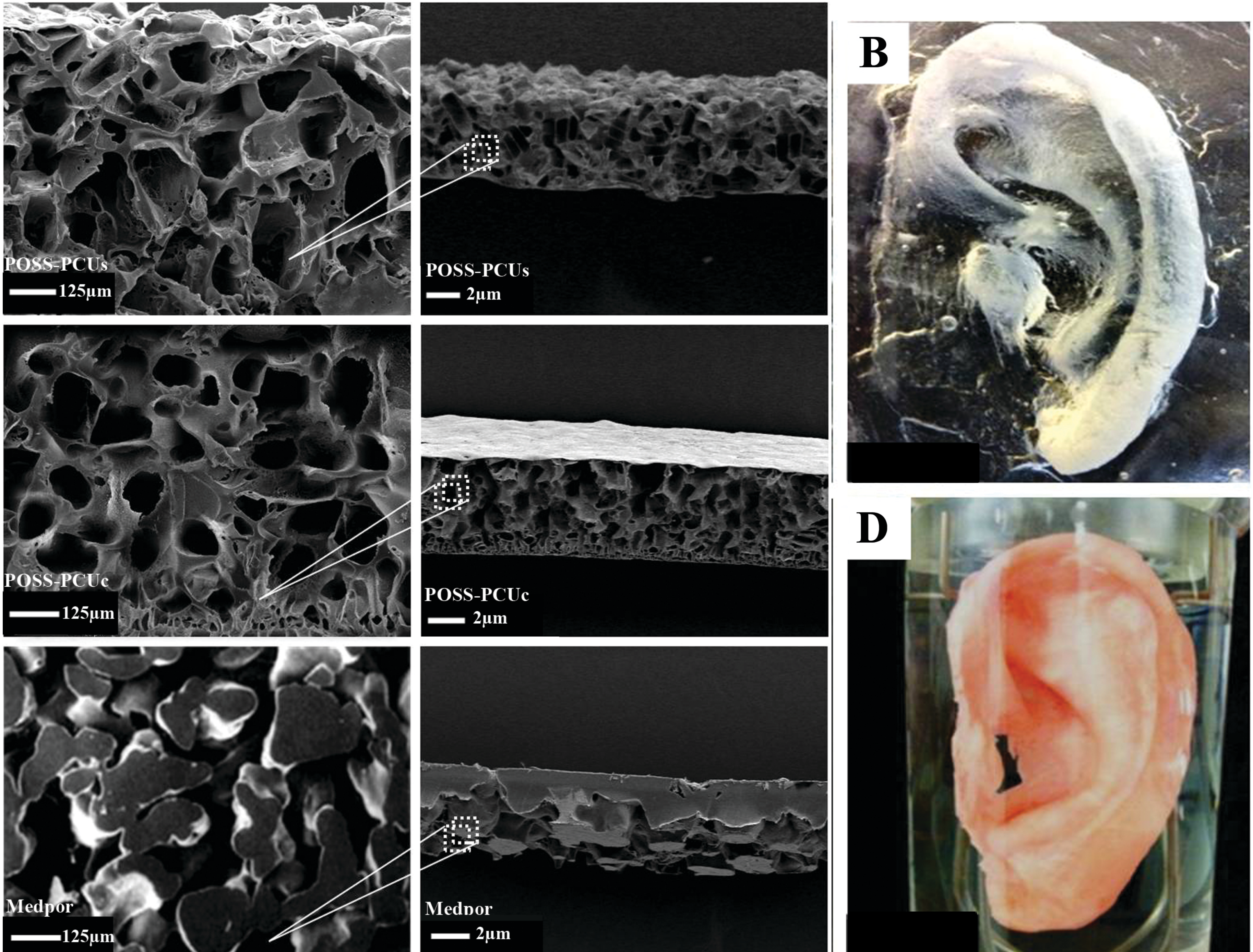


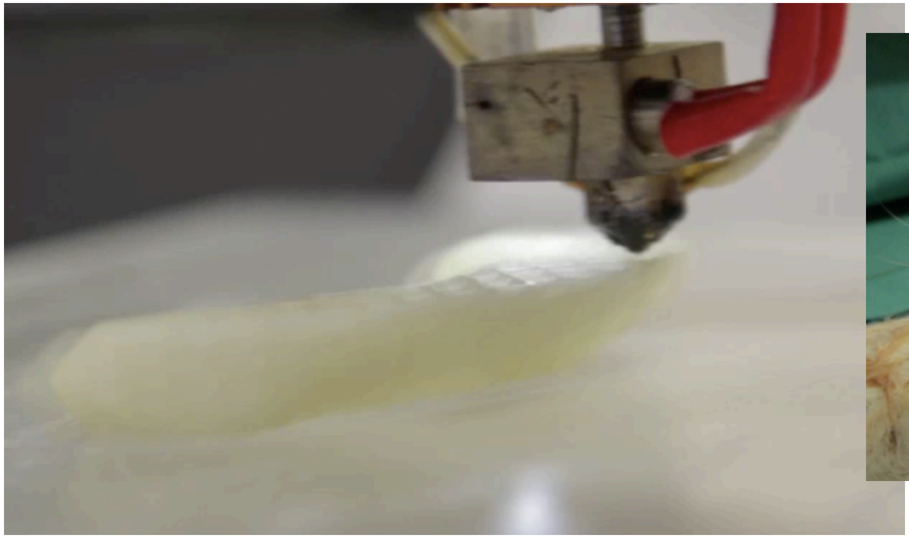
In collaboration with Professor Ferretti, UCL


12 weeks subcutaneous post-implantation
A
B
C
POSS-PCU
(150-250 µm)
POSS-PCU
(50-100 µm)
Medpor®
A
B
C

Tissue Engineering

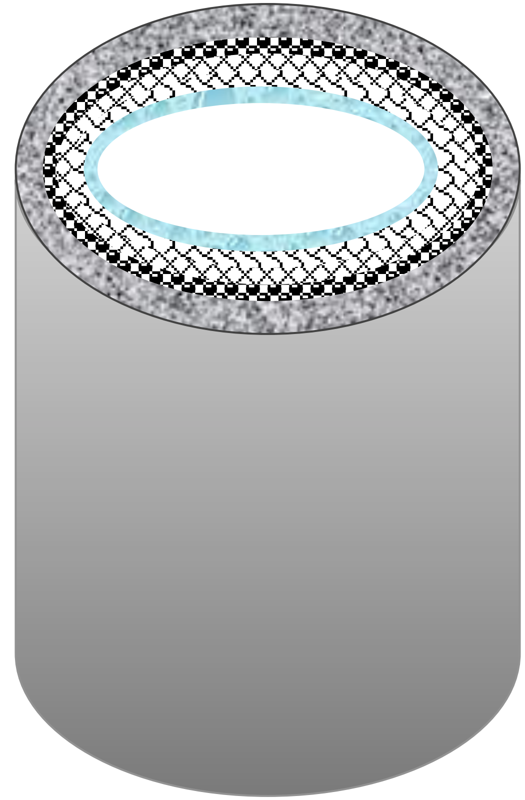



POSS-PCUs
125μm
POSS-PCUs
2μm
B
POSS-PCUc
125μm
POSS-PCUc
2μm
D
Medpor
125μm
Medpor
2μm

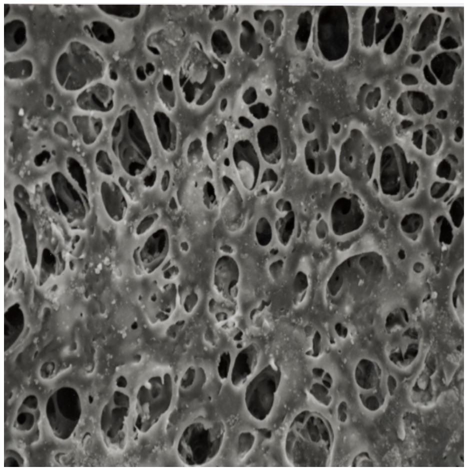


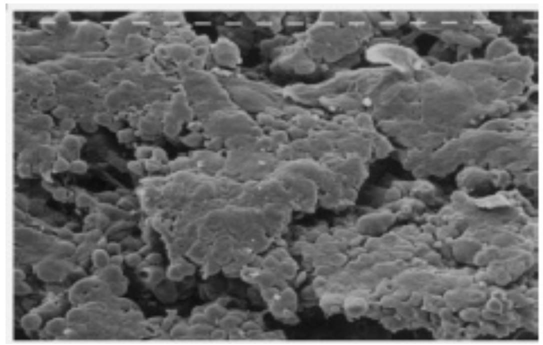

08:13

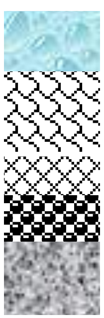
We developed a bypass graft with based on **Poly(carbonate-urea)urethane** Bonded with bimolecules



SEM: Honeycomb Structure







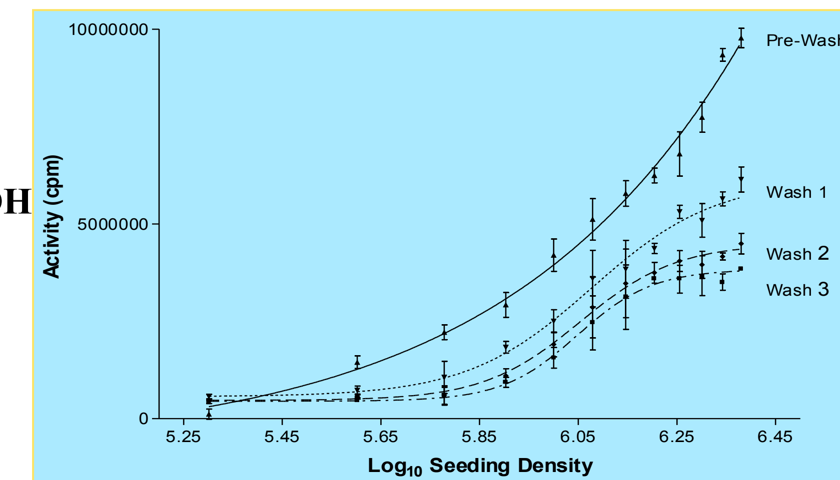
Cells (SMC, EC)

Moieties (E.g. - RGD, Heparin)

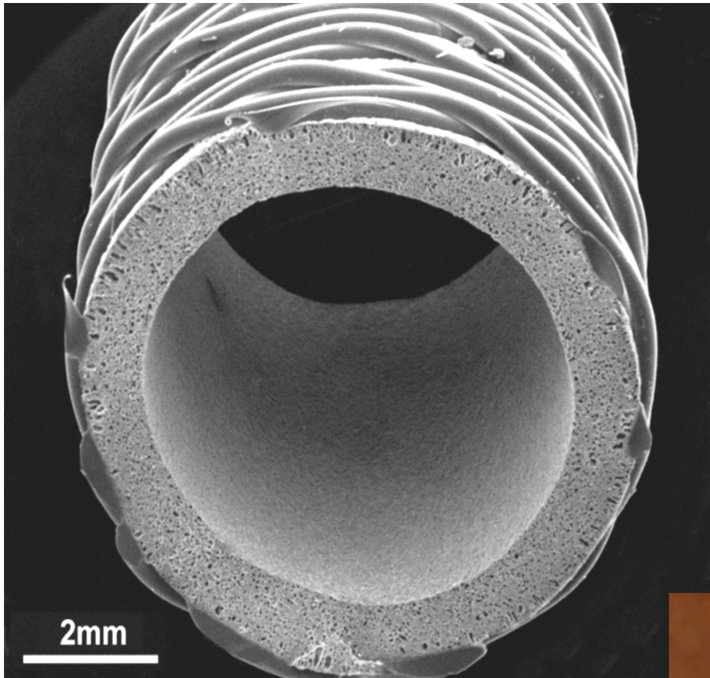
Acrylamide attached to activated surface

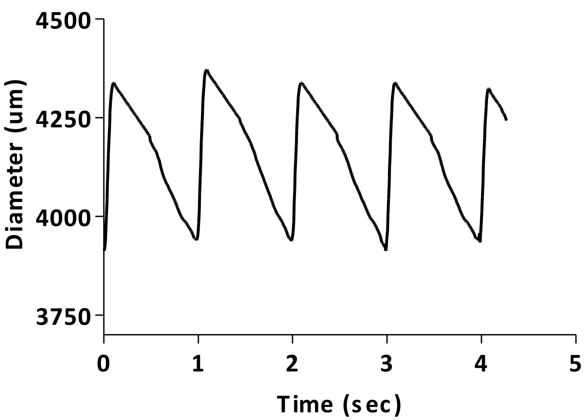
from which was abstracted hydrogen leaving OH

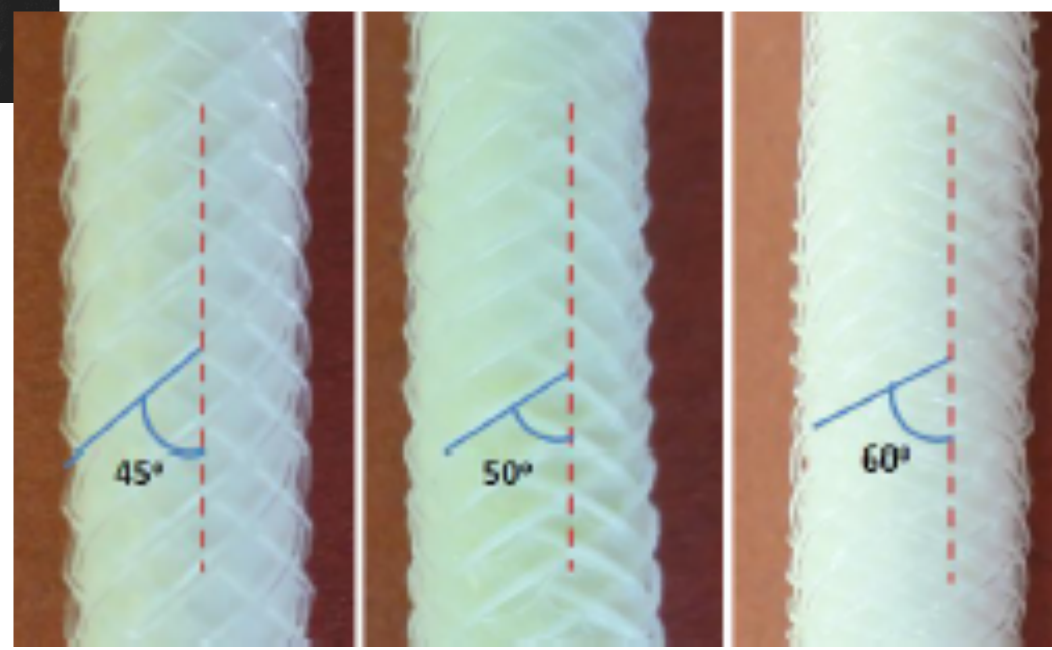
Elastic basement layer (polymer)



Tiwari, et al. FASEB J. 2002;16:791-6.
Tiwari,et al. Cardiovasc Surg. 2002;10:191-7.
Seifalian, et al. Biomaterials. 2003;24:2549-57.
Baguneid, et al. Br J Surg. 2006;93:282-90.
Vara, et al.Biomaterials. 2005;26:3987-93.


2mm


4500
4250
4000
3750
Diameter (um)
0
1
2
3
4
5
Time (sec)

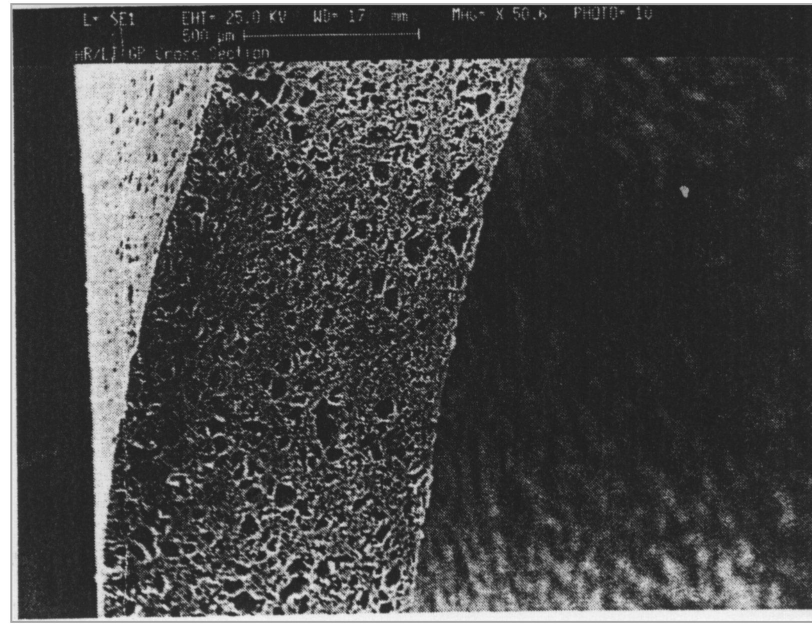

45°
50°
60°

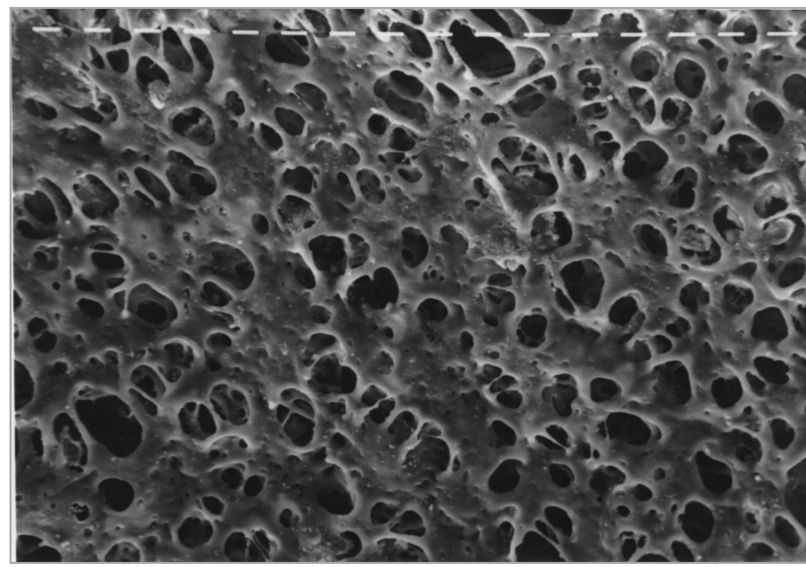
Compliant arterial prosthesis design

Obtaining long-term compliance is difficult as to date PU based grafts have relied on overall external dilation which is negated by perivascular in-growth.

The design approach used here has been to develop a prosthesis that maintains compliance and pulsatile flow *in vivo* by enabling the transmission of energy and a better quality of flow.

This is achieved via the honeycomb structure which accommodates increases in volume without the need for external dilation-a mechanism of wall compression.



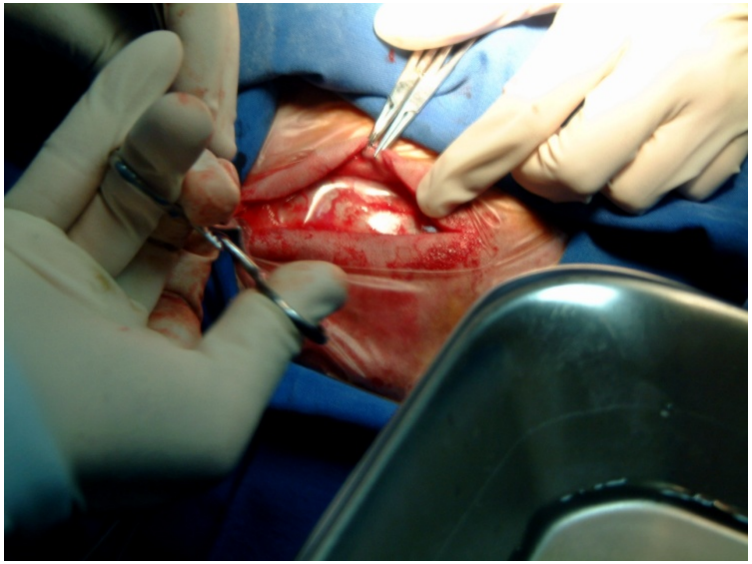


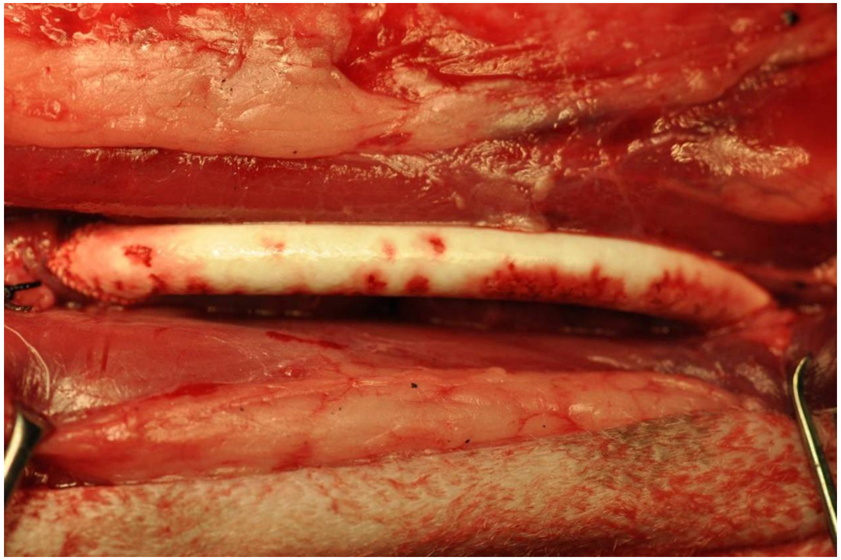
ESEM cross-section (×50) and surface (×250) micrographs

Biocompatibility Studies

In Vivo Studies:

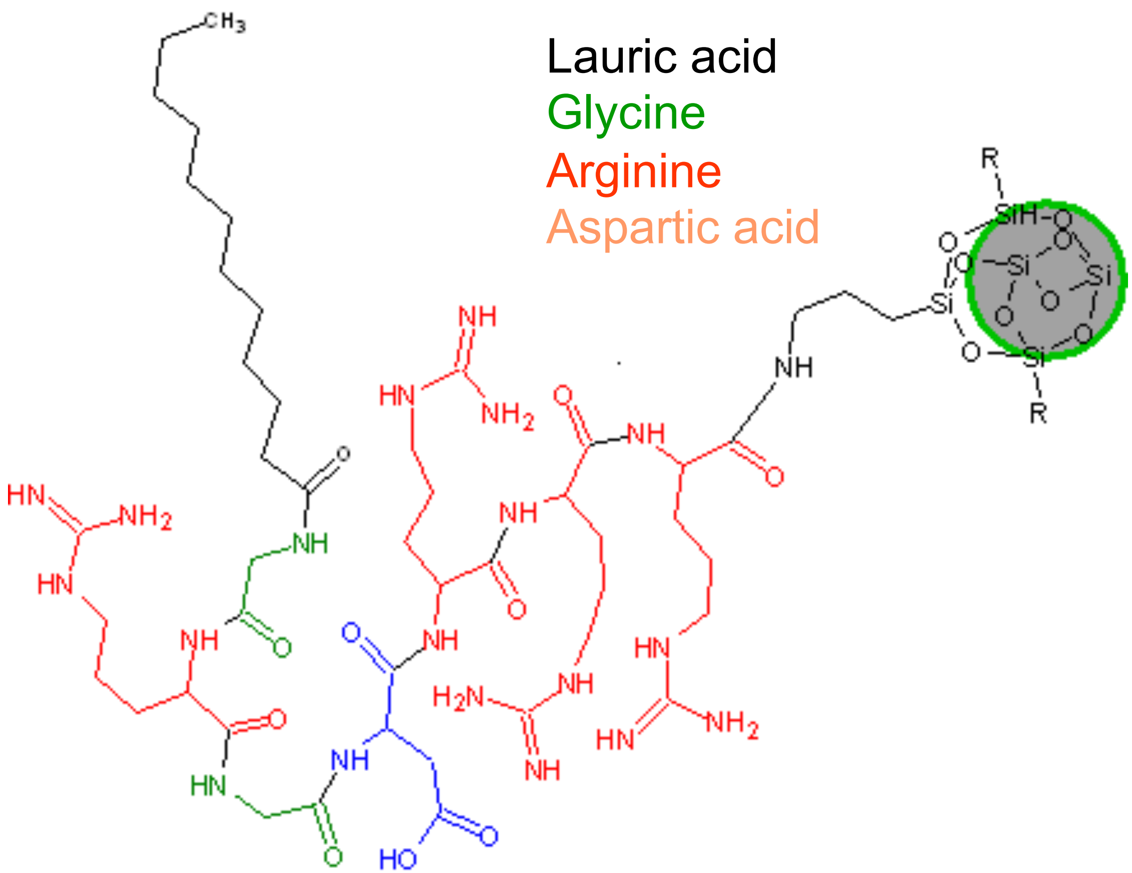
- 36 months in a sheep model for biocompatibility studies
- 9 months in a sheep model as a bypass graft
- Undergone all biocompatibility tests to the international standard ISO10993.



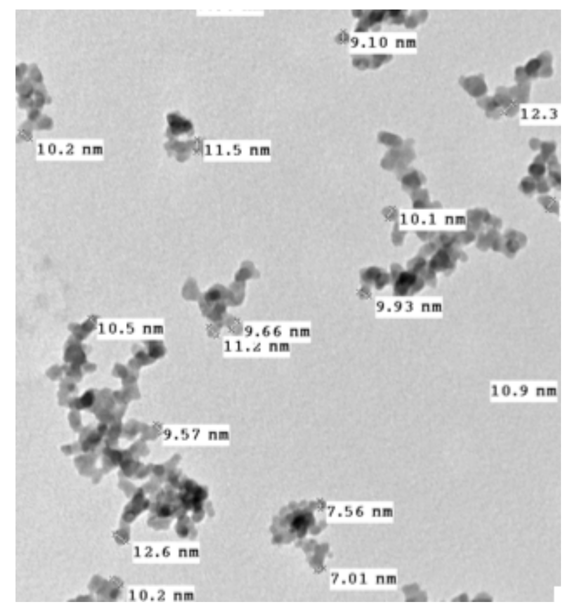


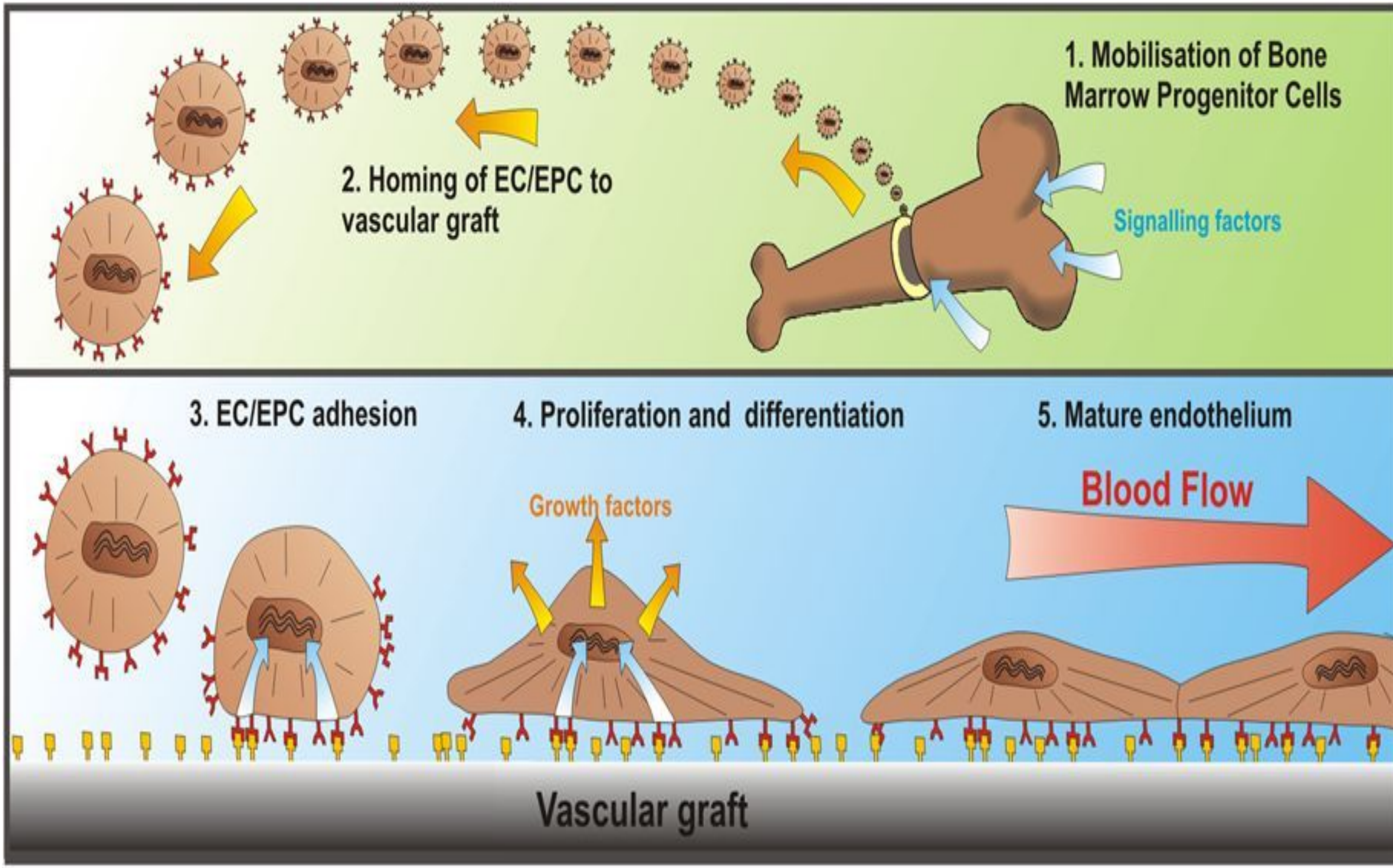
We have used silica nanoparticles to “couple” RGD into polymer

Aerosil 504 is fumed silica reacted with Hexamethyldisilazane and Aminosilane to form a hydrophobic fumed silica with functional surface amine groups.



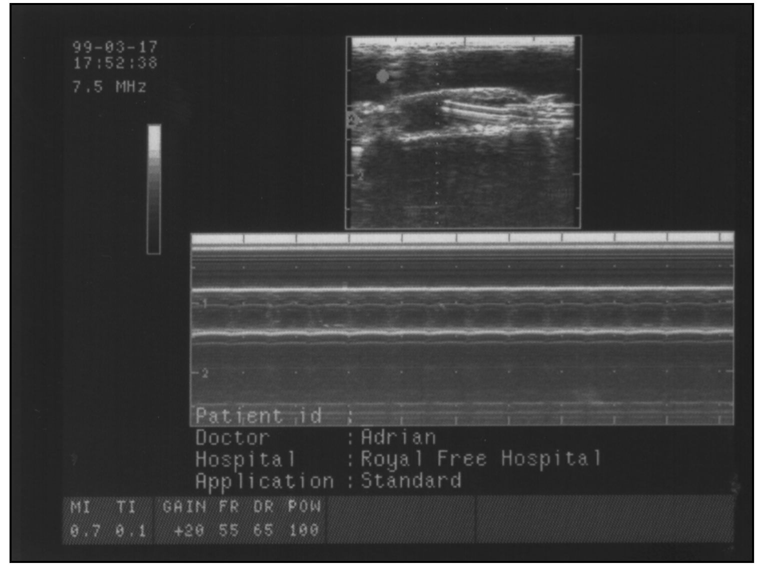
RGD is reacted via the amine group and covalently attached to the surface of the silica.



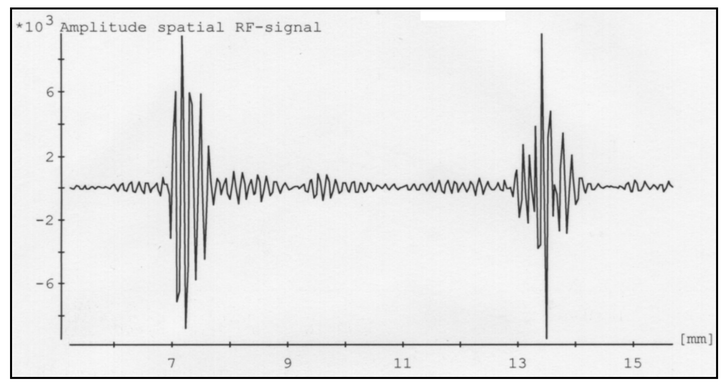


1. Mobilisation of Bone Marrow Progenitor Cells
2. Homing of EC/EPC to vascular graft
Signalling factors
3. EC/EPC adhesion
4. Proliferation and differentiation
5. Mature endothelium
Growth factors
Blood Flow
Vascular graft

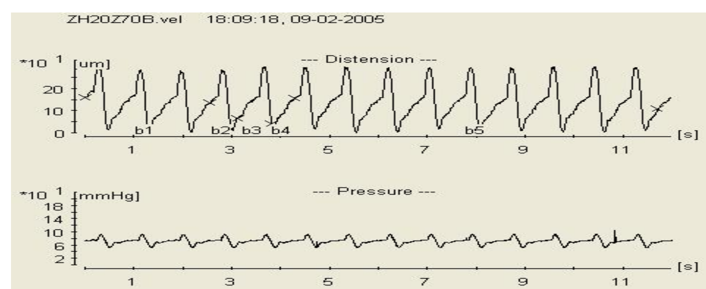
B and M Mode imaging of longitudinal vessel segment

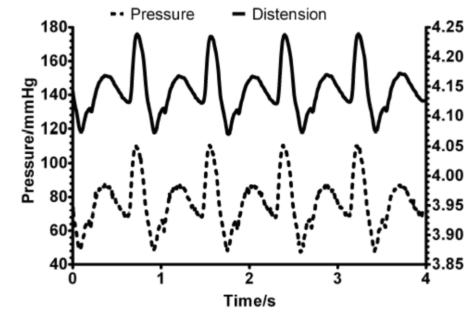


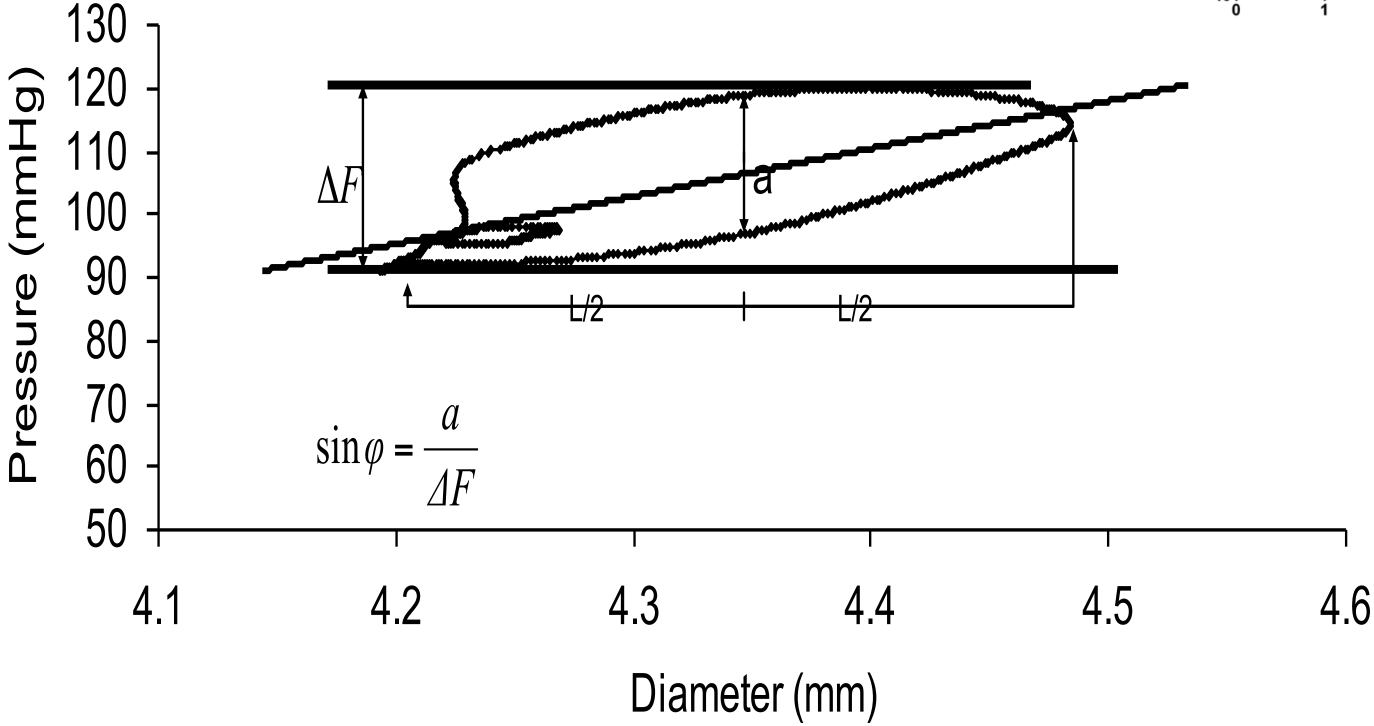
Acquisition of induced radiofrequency signal received from anterior and posterior walls



Tracking of signal over time to generate distension curves

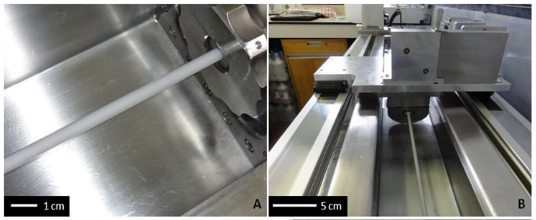


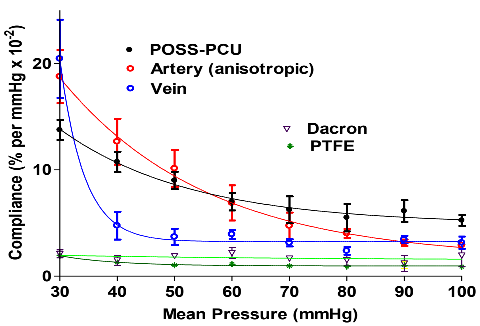




Elasticity/compliance C=(Ds-Dd)/(Dd(Ps-Pd))
Viscous component sin (angle)

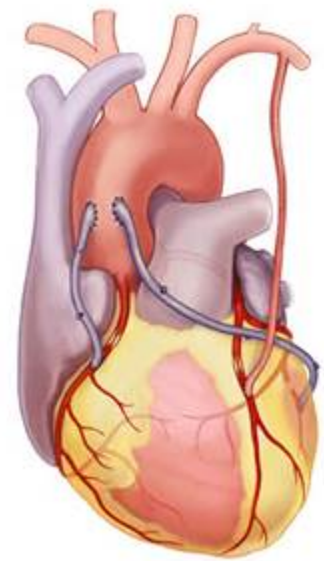
Manufacture



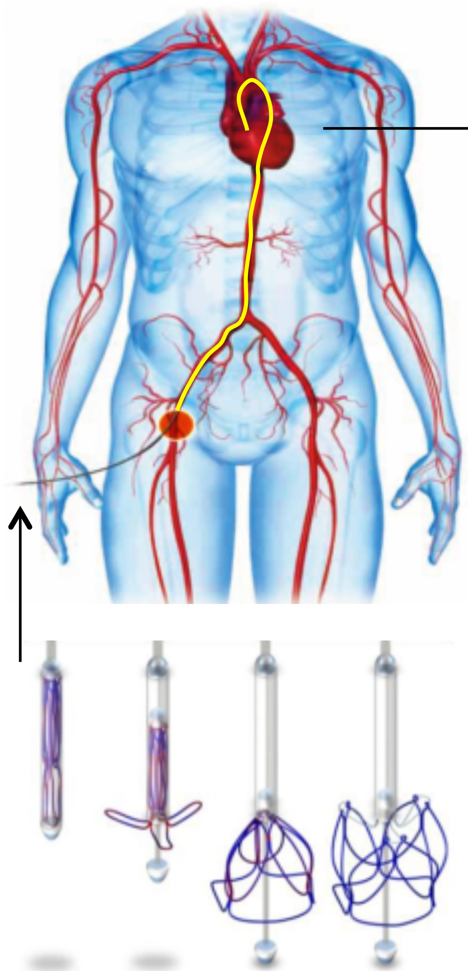


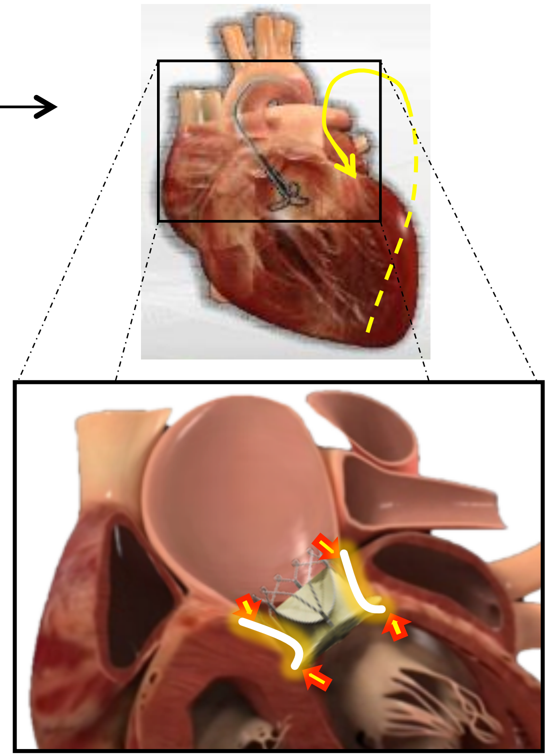
Preclinical test

Clinical trials



Heart valve through blood vessels





In collaboration with; Dr Gaetano Burriesci, UCL
Postdoc: Dr Ben Rahmani

Transcatheter Aortic Valve

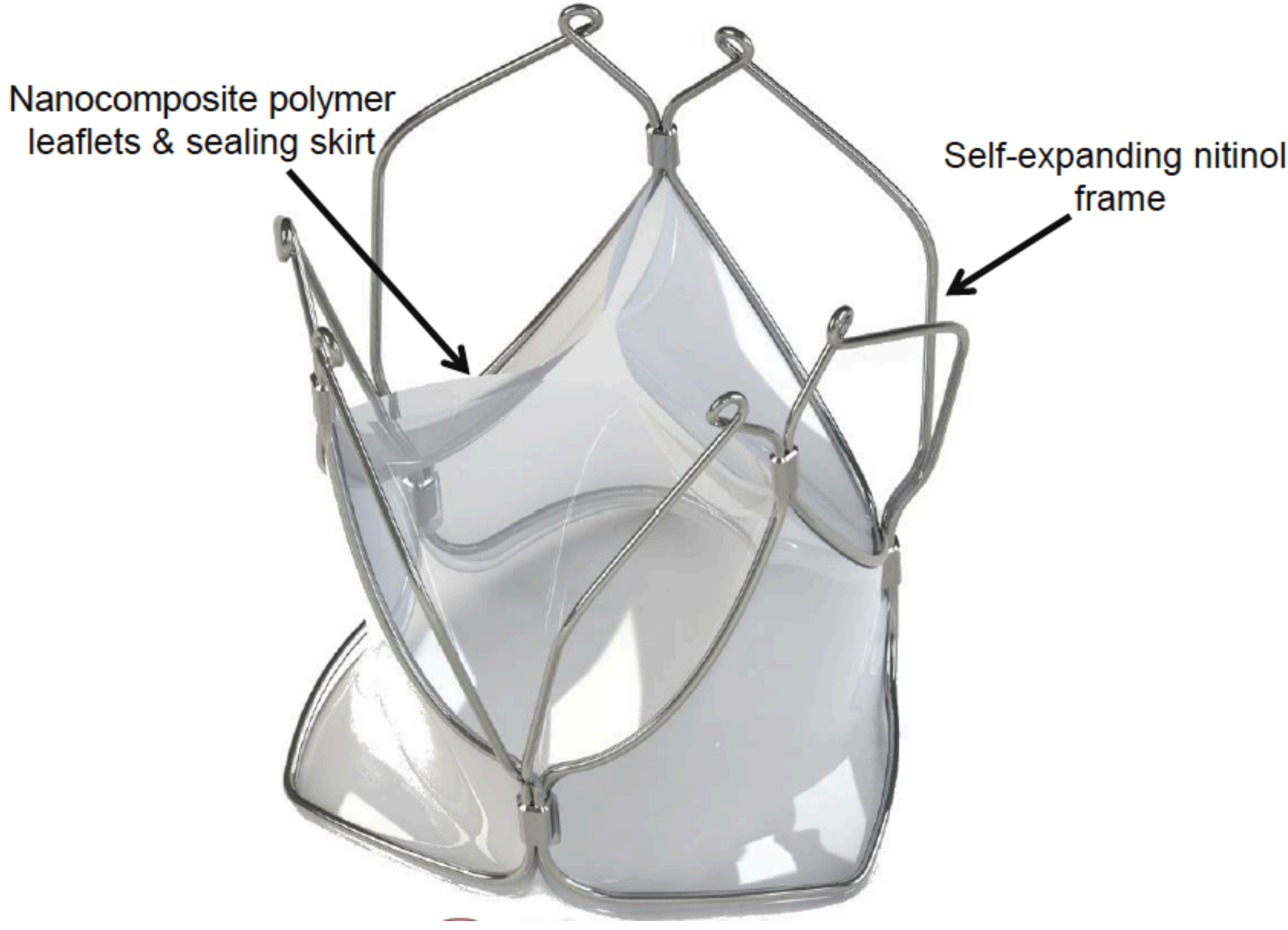
Nitinol stent

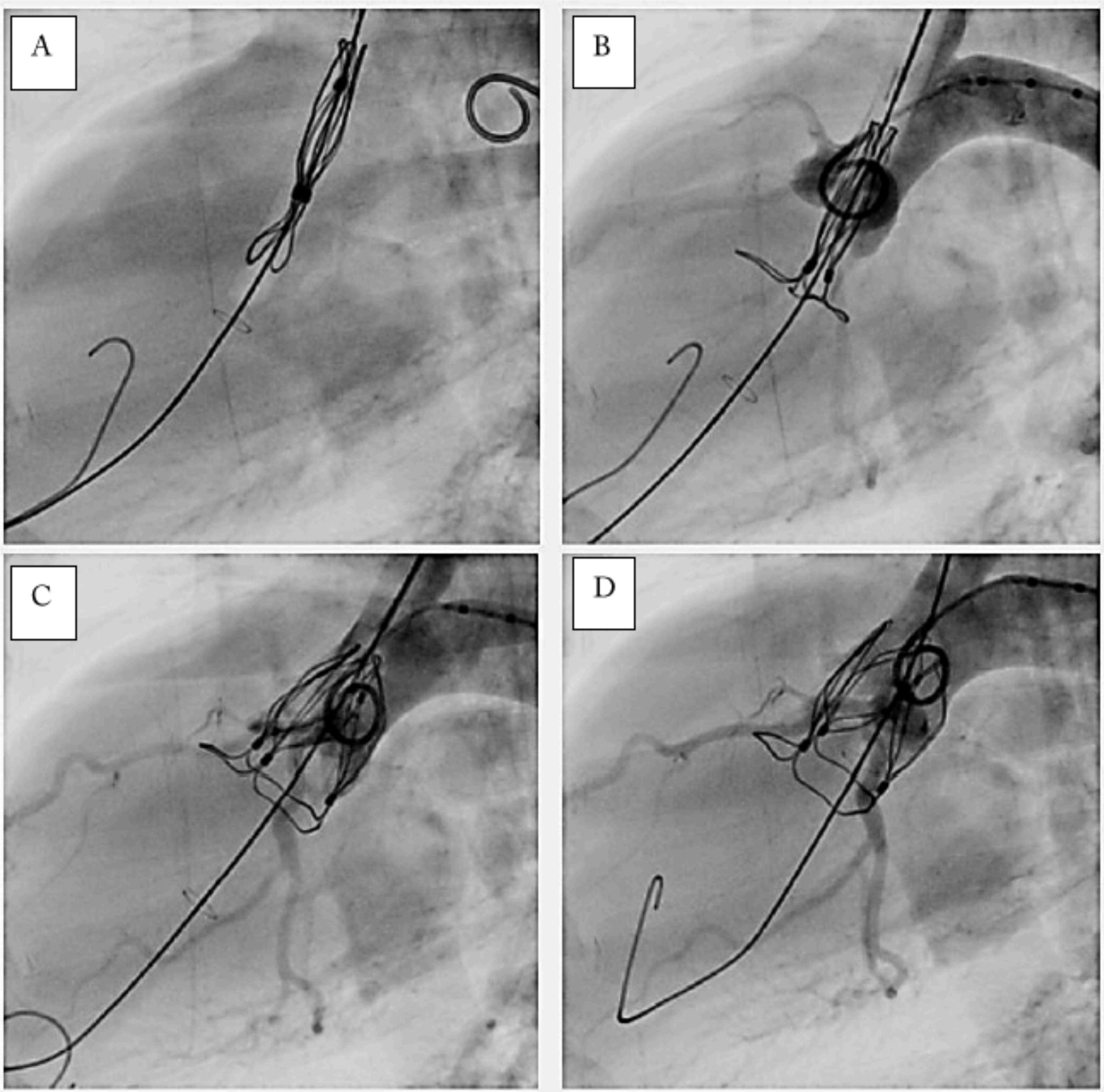
POSS-PCU leaflets

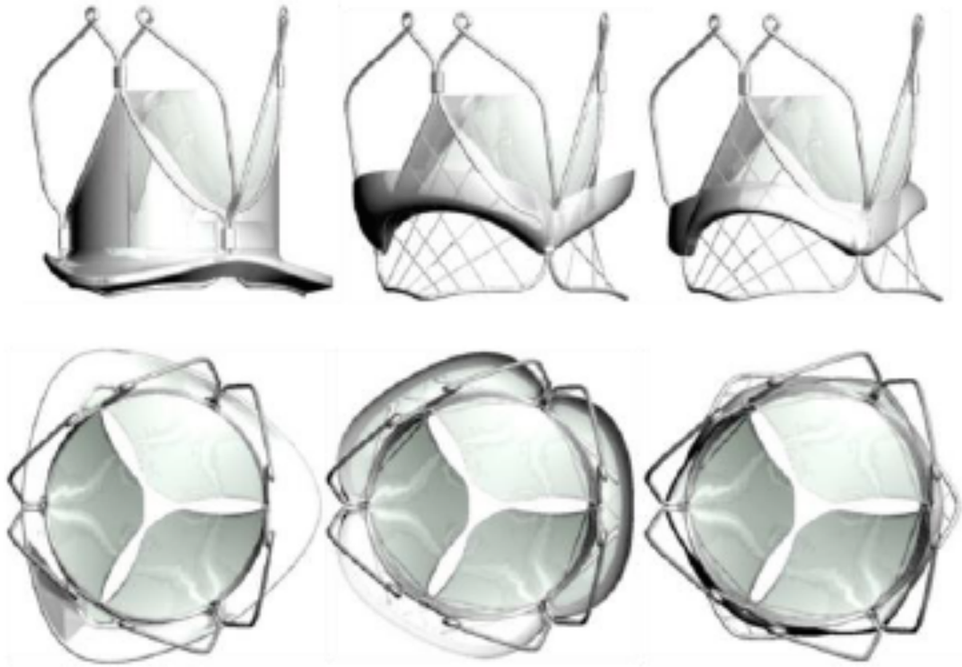
Outflow

- Self-expandable Nitinol frame
- One-piece polymeric membrane
- Fully retrievable and repositionable
- Multi-stage and controlled collapse & expansion
- Polymeric skirt to prevent paravalvular leakage
- Enhanced anchoring with no need for excessive radial force

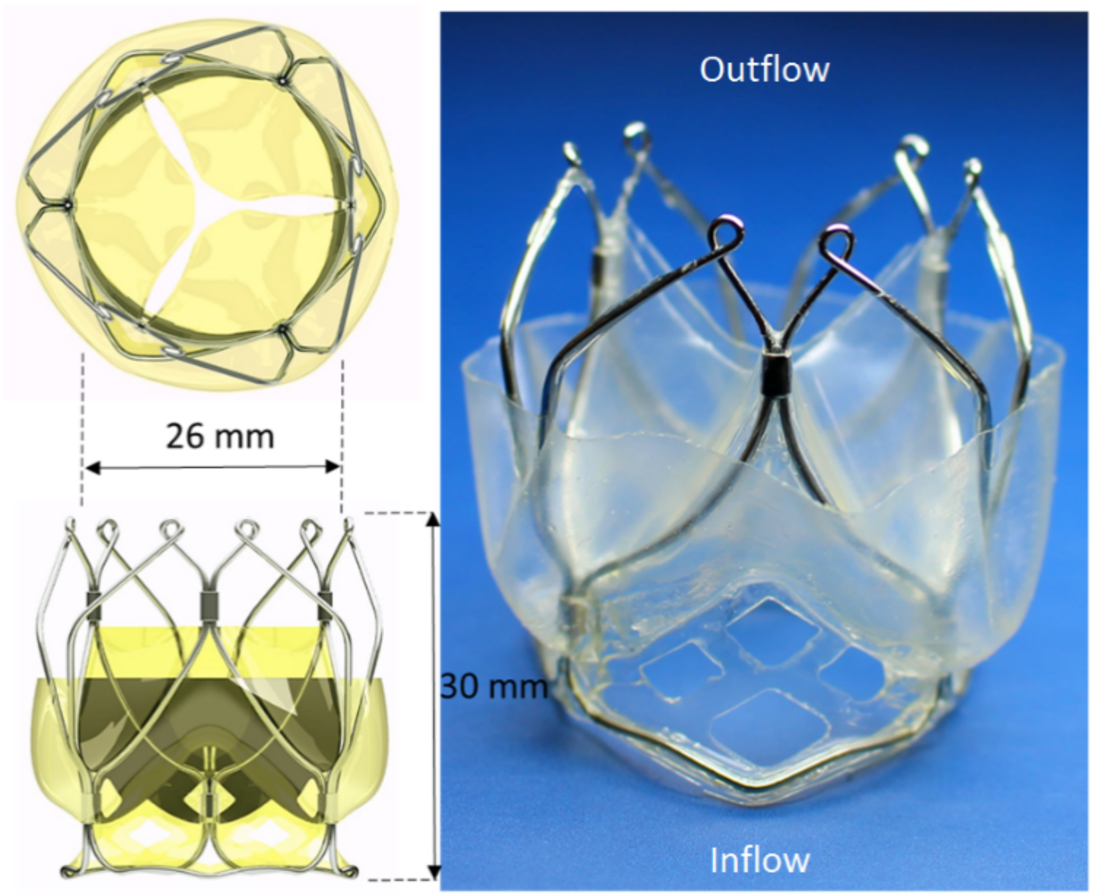
Inflow

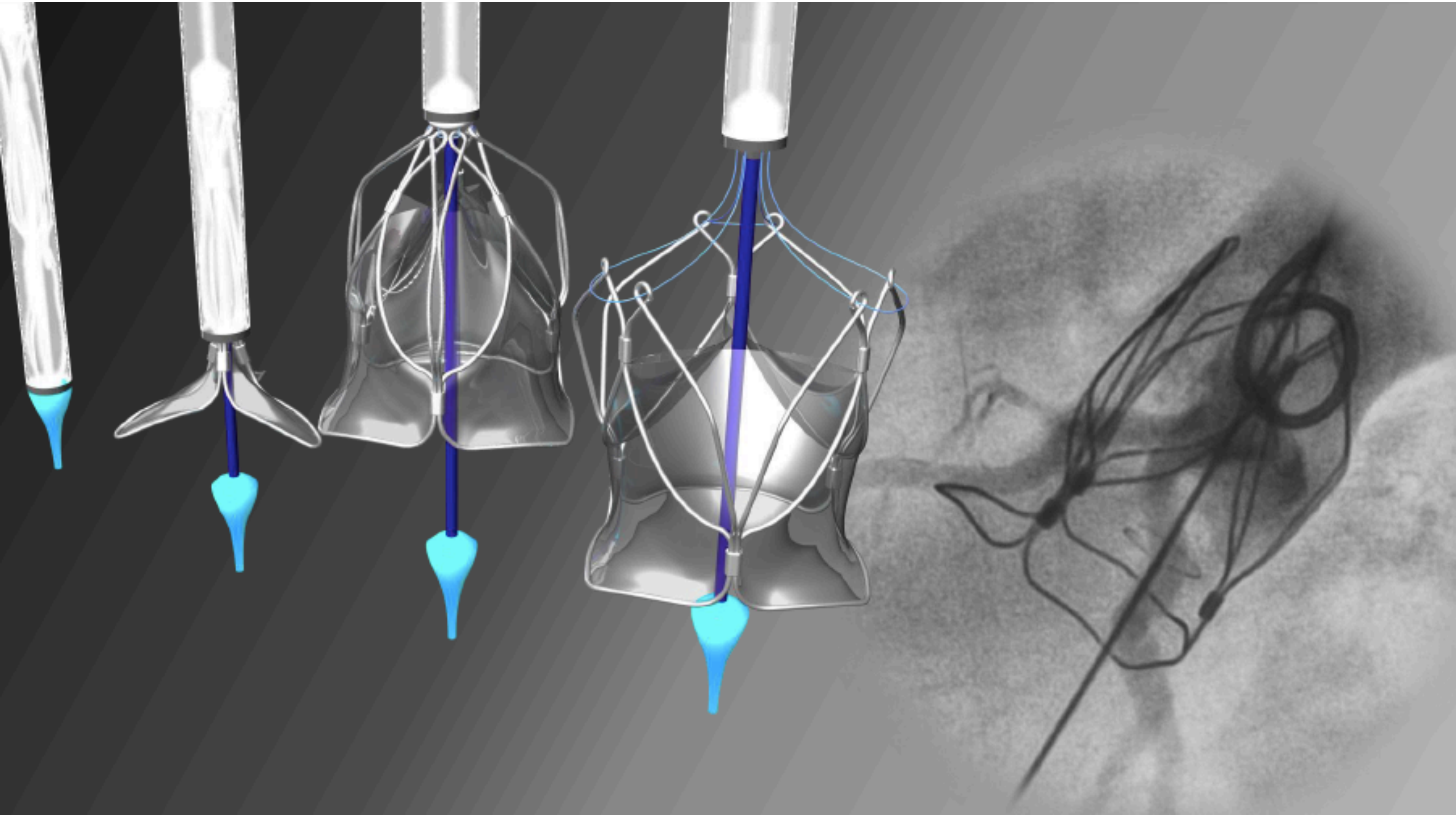

Nanocomposite polymer leaflets & sealing skirt
Self-expanding nitinol frame

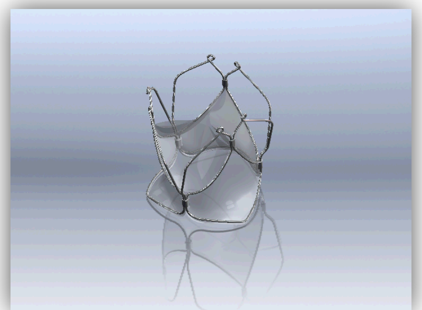

A
B
C
D

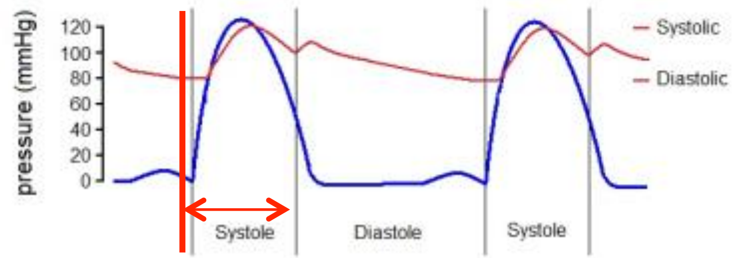


A number of sealing strategies were proposed to reduce paravalvular leakage.


26 mm
30 mm
Outflow
Inflow



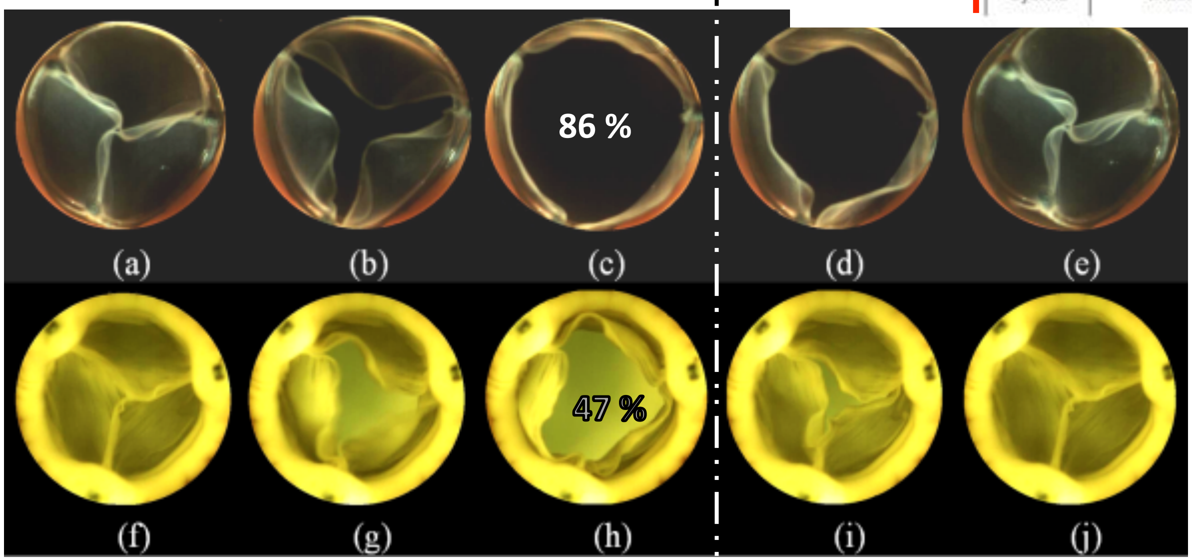


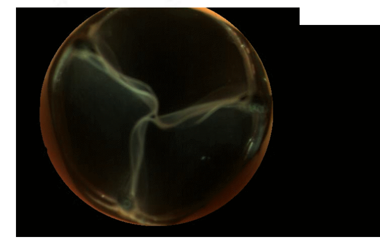


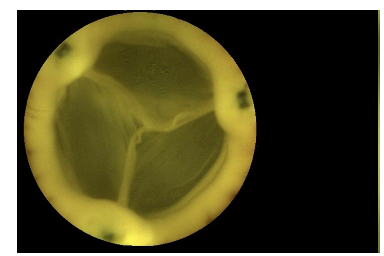
Opening phase

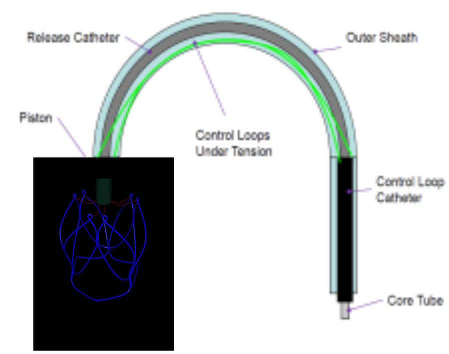
SSAV 150µm

Control (Epic™)

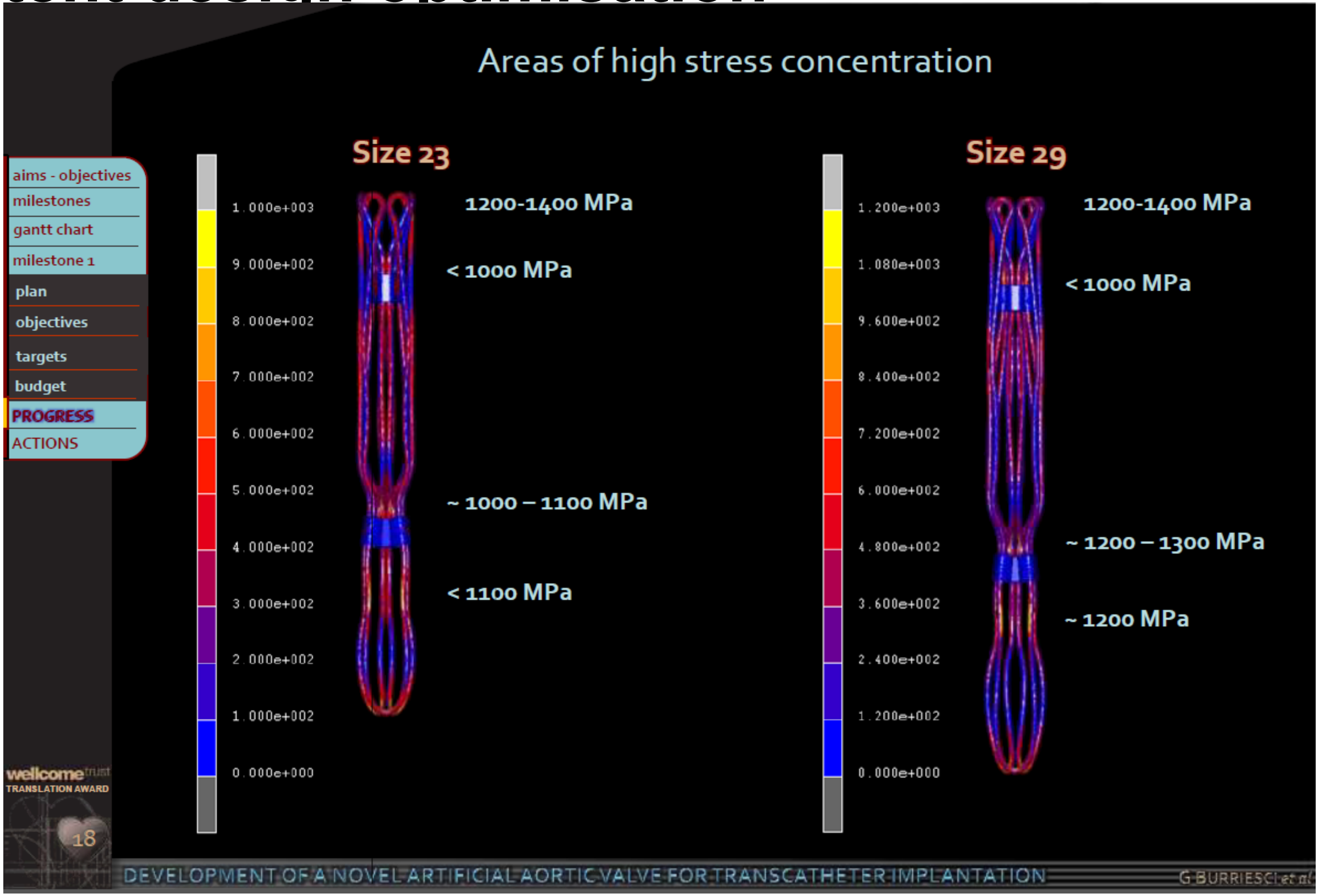






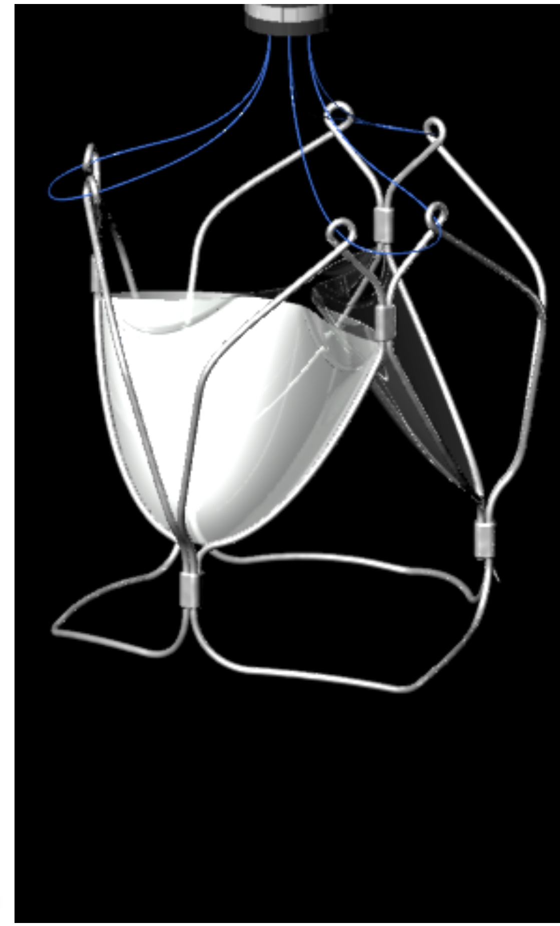


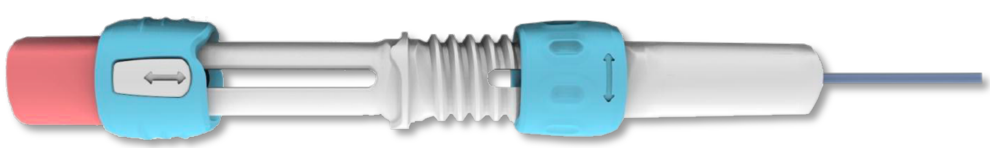
Stent design optimisation



TRISKELE Transcatheter Heart Valve

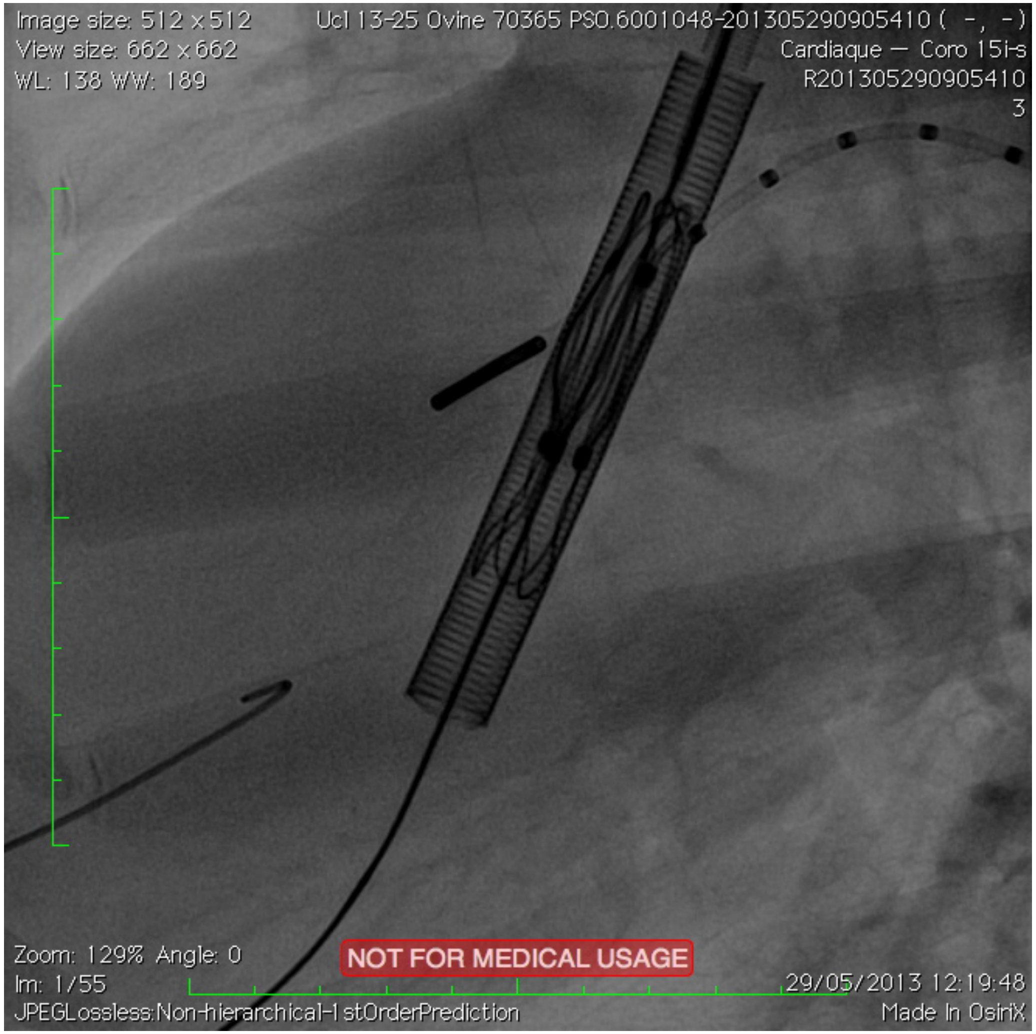
- Full repositionability and retrievability
  - 18 Fr delivery system
  - 3 stage valve expansion through three control lines
  - After full deployment catheter can be moved away and valve functionality verified.
  - If necessary, catheter can be readvanced and the valve safely recollapsed and repositioned.
  - Once the procedure is satisfactorily completed, the control lines can be released and extracted



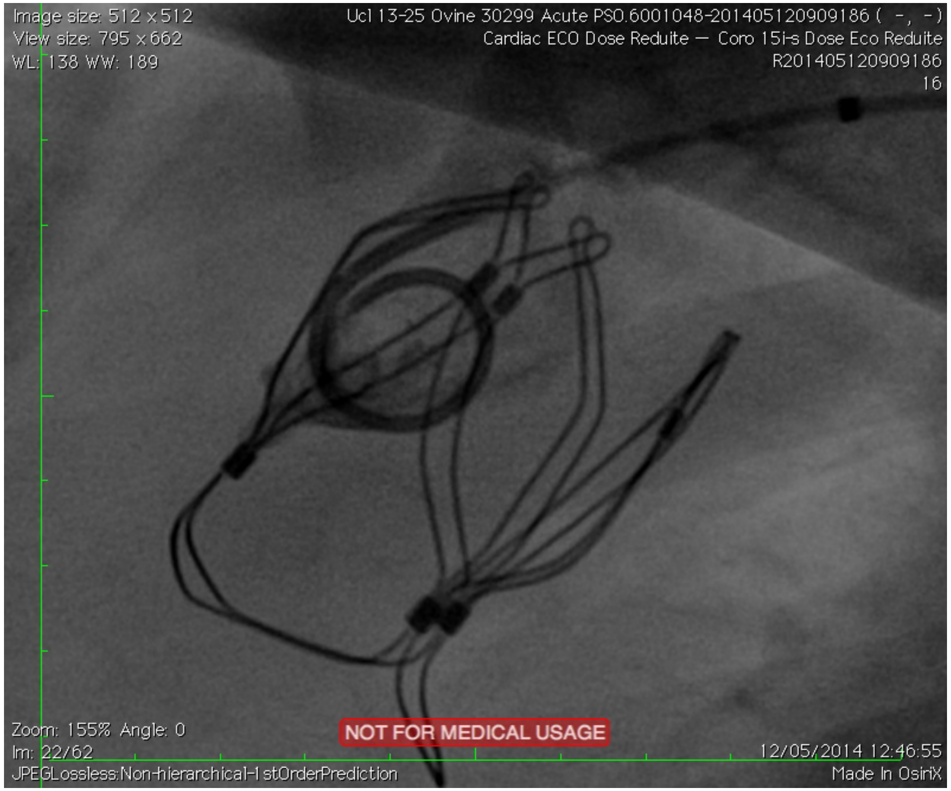


Patent Pending :1017921.6 GB – PROSTHESIS DELIVERY SYSTEM

TRISKELE Transcatheter Heart Valve



TRISKELE Transcatheter Heart Valve

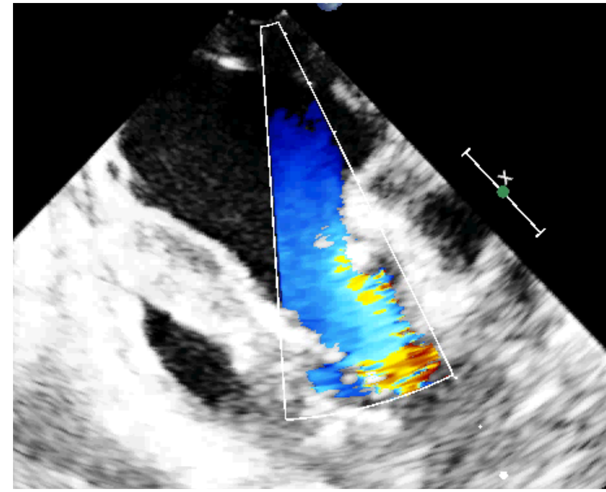


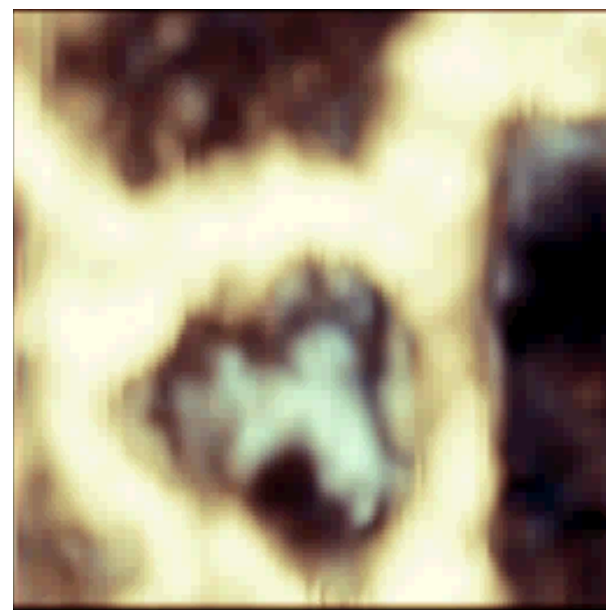
TRISKELE Transcatheter Heart Valve

First animal implant in ovine model (≈ 50 kg) in May 2013, off-pump via brachiocephalic approach in orthotopic position, using continuous ultrasonic and fluoroscopic guidance.

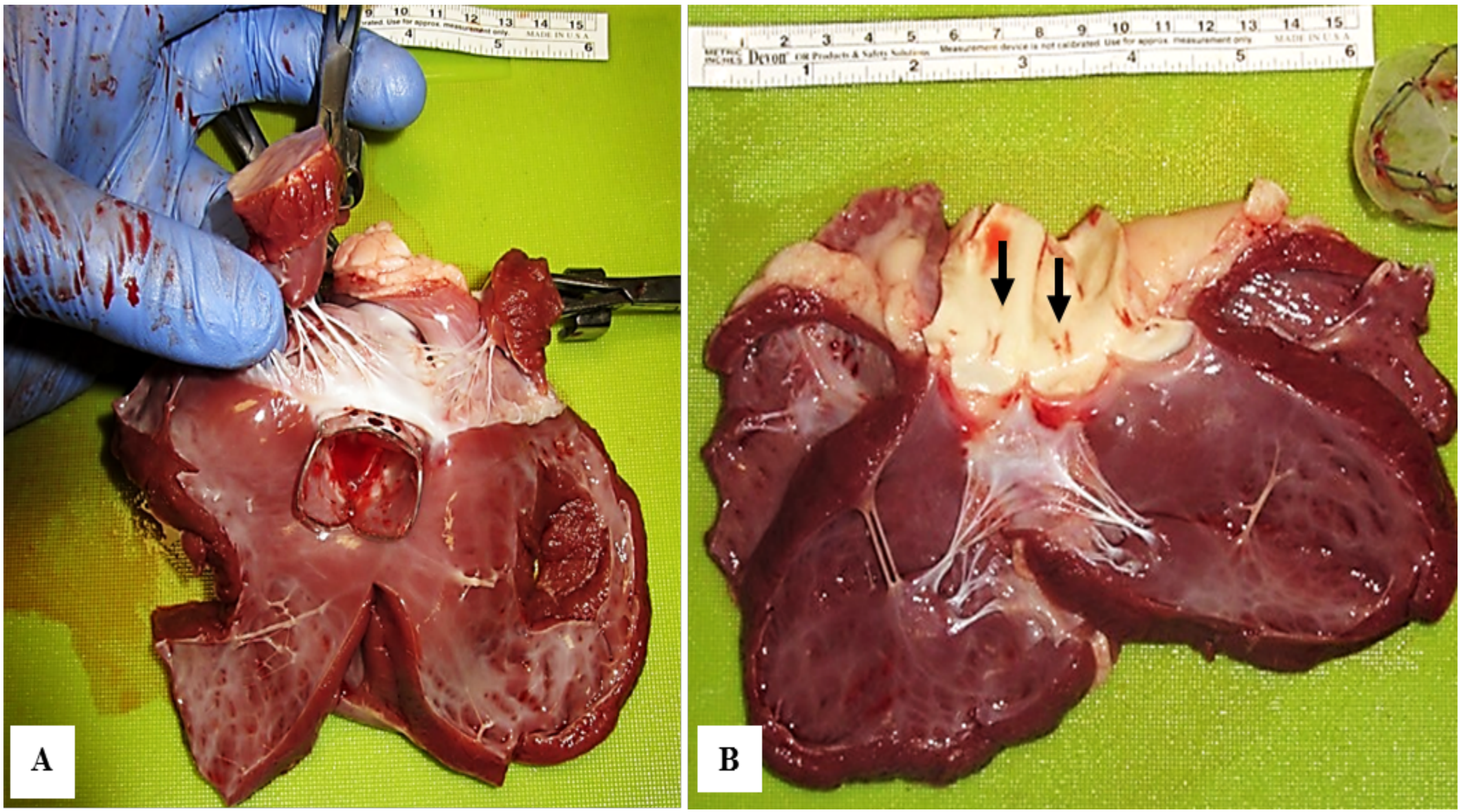
Three valves of different sizes successfully implanted and retrieved, after assessing positioning and haemodynamic performance.

No interference of coronary blood flow for two smallest sizes, and good acute valve function with no significant regurgitation.

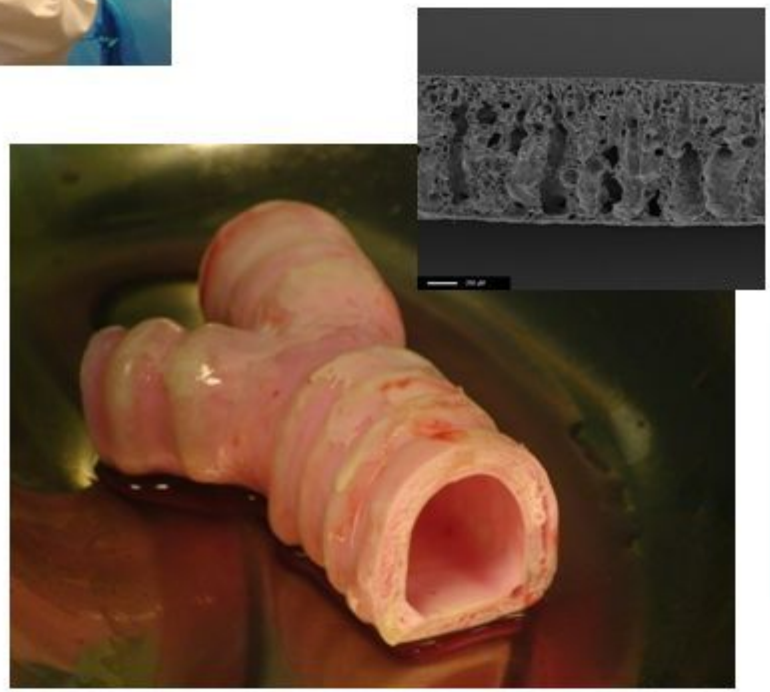




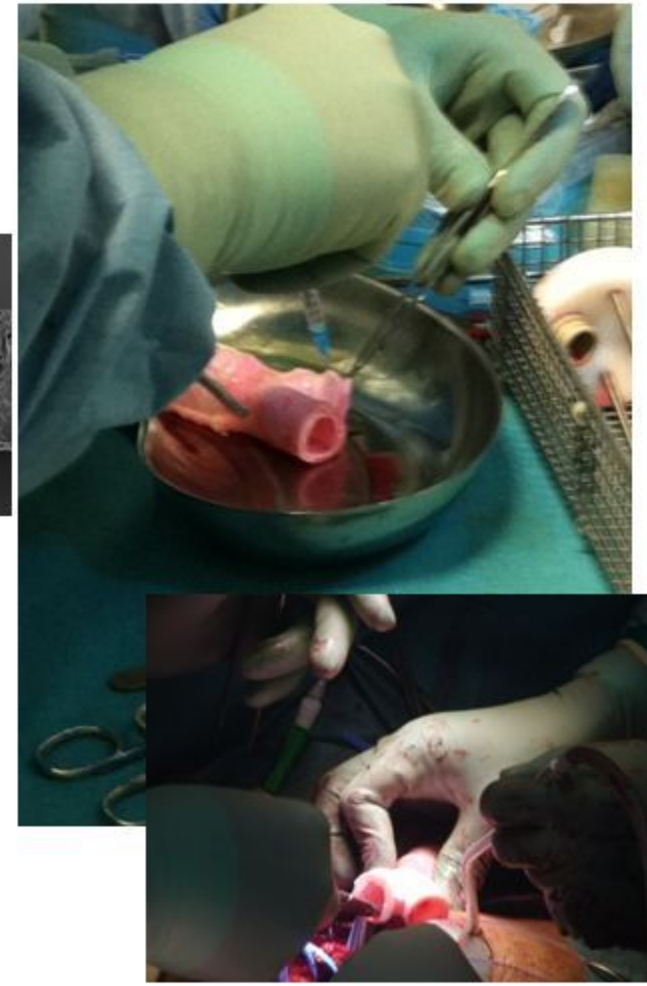
A) No interference of coronary blood flow was observed; B) the valve was self-aligned owing to its outflow protrusions which expand to assist optimal positioning



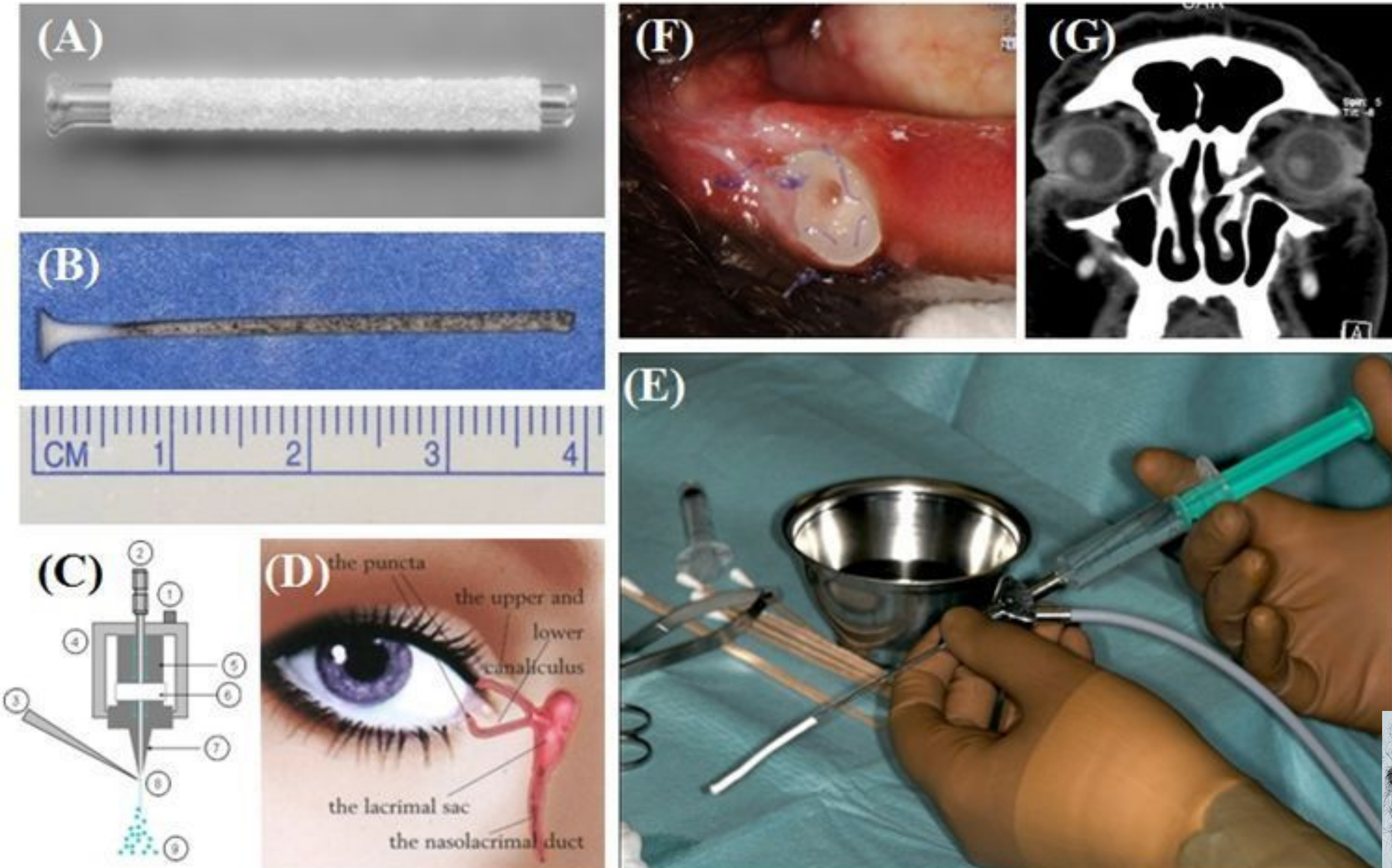
1. Patient MRI + glass moulding of exact tracheal replica

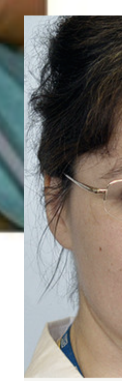


2. Synthesis of POSS-PCU based trachea / patient-own stem cells



2. Surgical implantation of tracheal construct



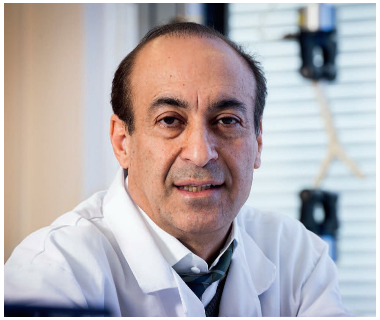


Dr Karla Chaloupka, Zurich University Hospital

Research and Development
MHRA / FDA
Funding
Industry
Commercialisation

NanoRegMed Ltd, London, UK

Co-Directors



Professor Alexander Seifalian

Mrs Hana Salussolia

Thanks, contact

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- Email: a.seifalian@gmail.com
- Tel: ++ 44 7985 380 797