



La ricerca transdisciplinare come modello di integrazione tra Ingegneria e Medicina

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Direttore del centro di ricerca BELONG – Università degli Studi di Genova

Direttore del Laboratorio di Biologia Vascolare Clinica e Sperimentale – Università degli Studi di Genova e
Ospedale Policlinico San Martino



OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria



**UNIVERSITÀ DEGLI STUDI
DI GENOVA**

DISC



DICCA



UNIVERSITÀ DEGLI STUDI
DI GENOVA



1512 > 2012

cinquecento anni di insegnamento medico a Genova

1669 Istituzione del primo insegnamento di Anatomia Umana su cadavere tenuto da un medico retribuito

1847 Primo intervento chirurgico in anestesia eterea, eseguito da Bartolomeo Gherardi

1912 Il Senatore Edoardo Maragliano dispone la costruzione del nuovo centro ospedaliero e universitario sulle alture di San Martino d'Albaro

1938 Fondazione dell'Ospedale Pediatrico "Istituto G. Gaslini"

1978 Fondazione dell'Istituto Nazionale per la Ricerca sul Cancro

2000 Centre of Excellence for Biomedical Research

2001 Nanoworld Institute

2011 Nuovo Centro di Simulazione Avanzato

2011 Fusione Ist – San Martino



1870 ➤ 2020

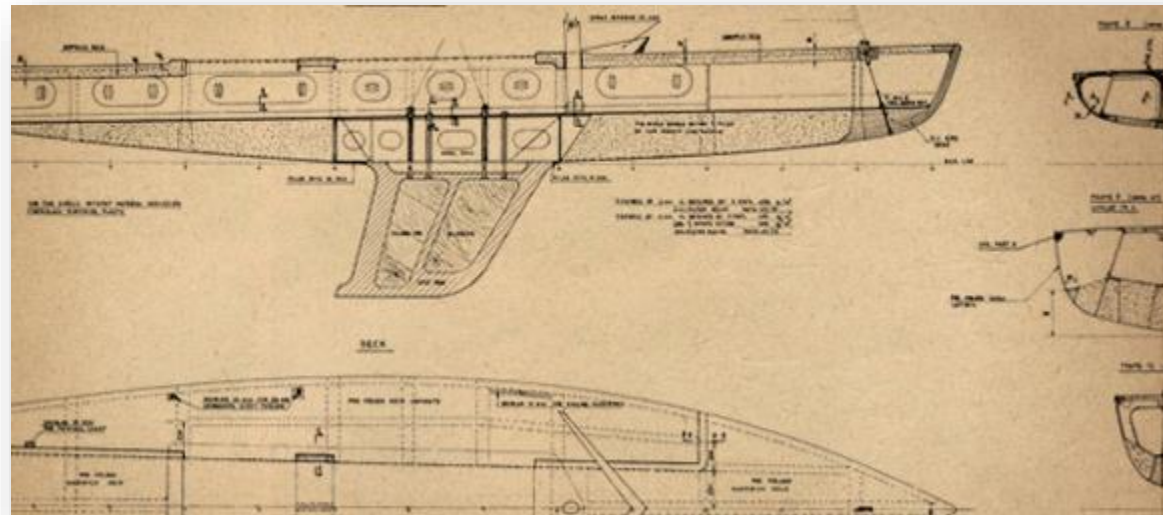
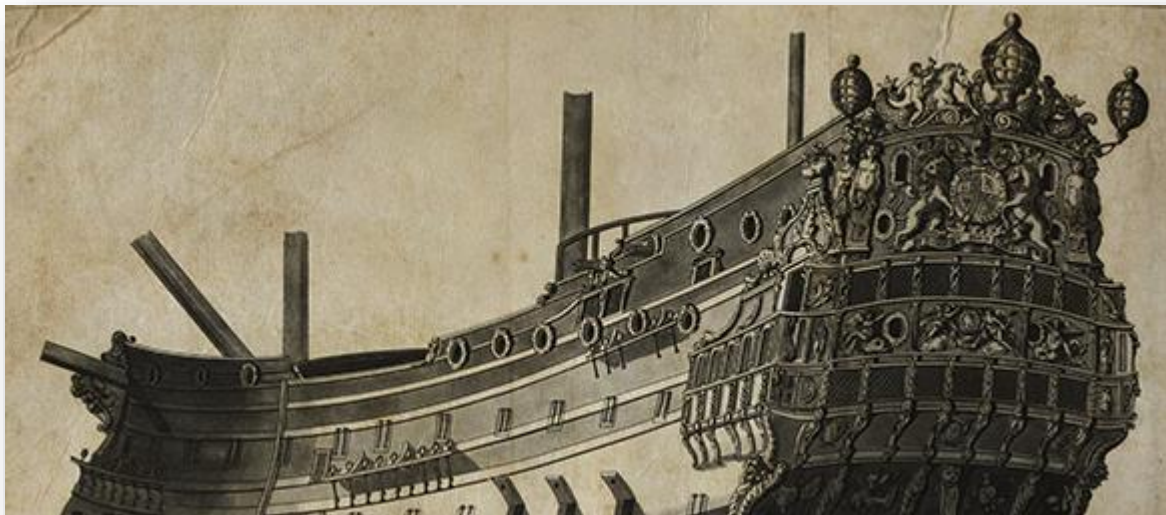
Centocinquanta anni Regia Scuola Superiore Navale a Genova

1870 Nascita della Regia Scuola Superiore Navale a Genova

1909 Inclusione nell'elenco degli istituti superiori

1921 Ottenimento della prestigiosa sede di Villa Cambiaso

1923 con la Riforma Gentile, Regia Scuola di Ingegneria Navale



HISTORICAL MILESTONES

MEDICINE AND ENGINEERING

First anatomic studies



XV century
Leonardo da Vinci

Blood fluidodynamic studies



1838
Jean Léonard Marie Poiseuille

First electrocardiograph machine



1903
Willem Einthoven

Artificial pacemaker invented



1930s
Albert S. Hyman

First kidney dialysis machine



1945
Willem J. Kolff

Artificial heart valve developed



1951
Charles Hufnagel,

First laser surgery on a human cornea



1987
Steven Troke

1st EVAR

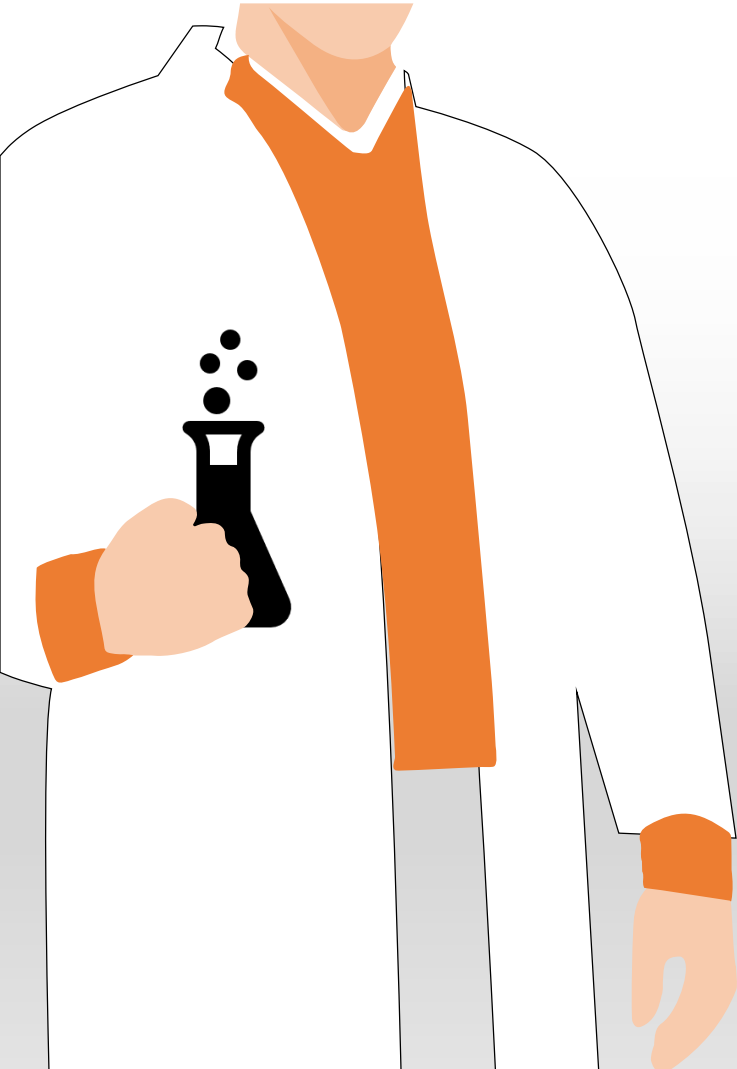


1990
Juan Carlos Parodi



HISTORICAL MILESTONES

ENGINEERING AND MEDICINE



XV century
Leonardo da Vinci



First flying machines

1930s
Edward Merrill



Studies on the viscosity of human blood

1960
Wilson Greatbatch



First totally internal pacemaker

1980s
Robert Langer



Controlled drug delivery technology developed

1943
Tofy Mussivand



First cardiac pump

1967
Godfrey Hounsfield



First TAC equipment

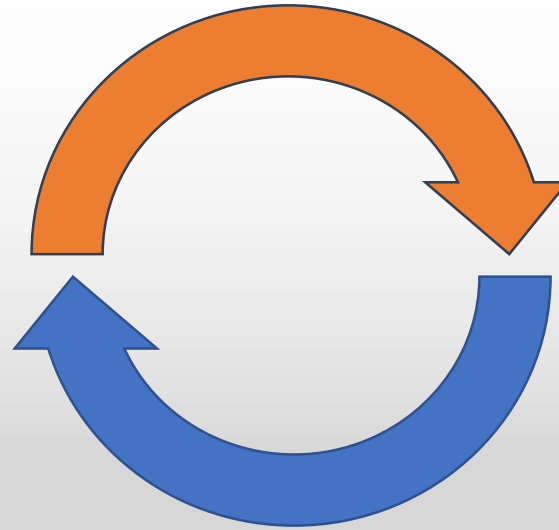
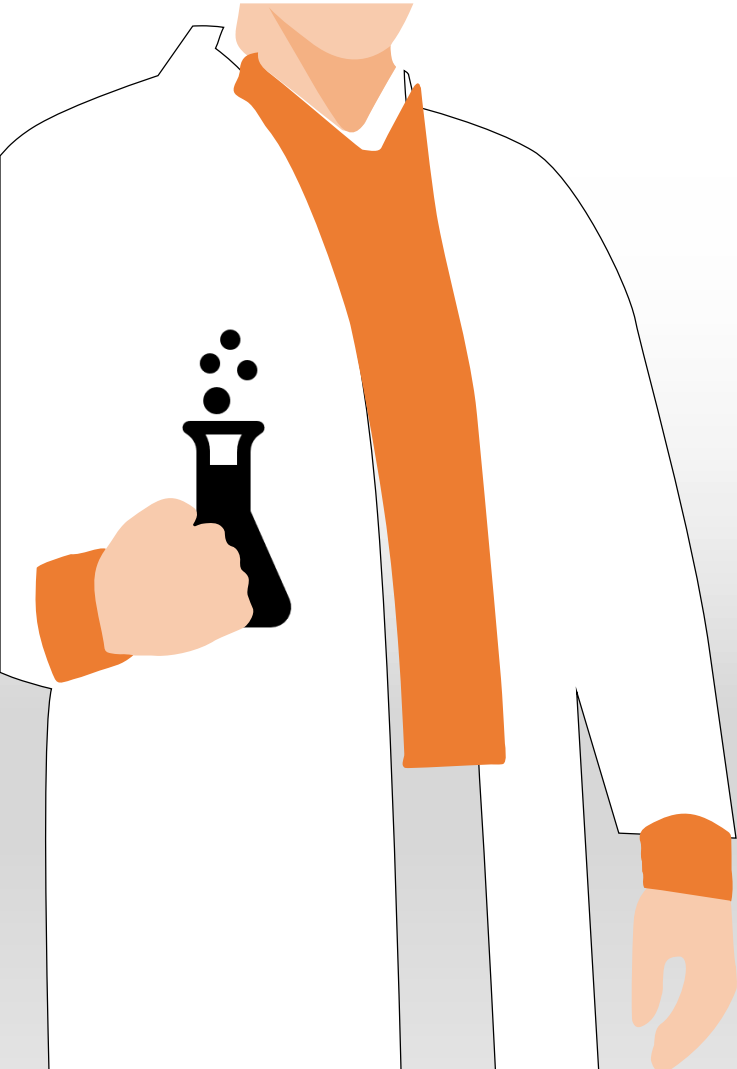
2014
Chuck Hull



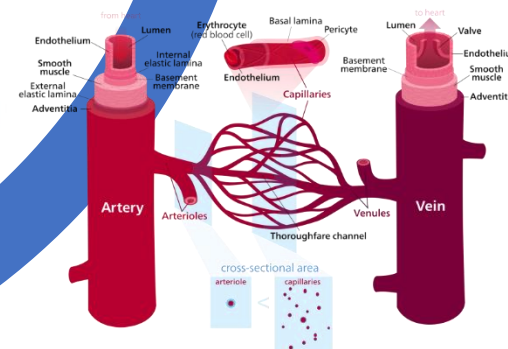
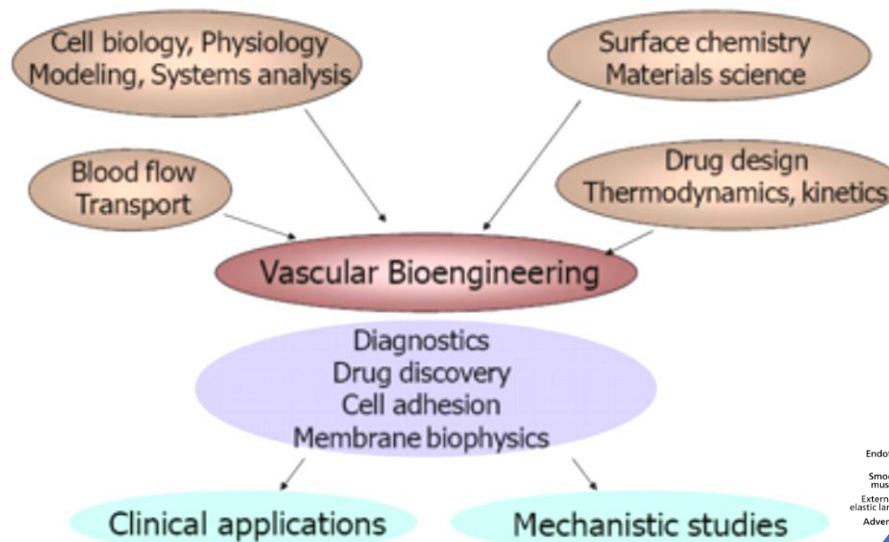
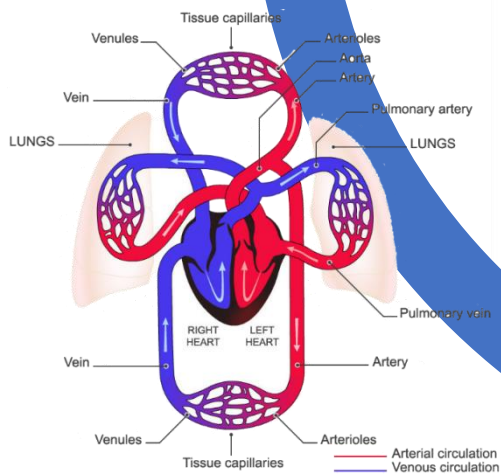
3D printing

“Coming together is a beginning, staying together is progress,
and working together is success”

Henry Ford



ANALOGY BETWEEN CHEMICAL ENGINEERING AND MEDICINE






“Teamwork is the secret that
makes common people achieve
uncommon results”

Ifeanyi Enoch Onuoha





What makes a team a good-team?

Transdisciplinary approach



Two or more professions, technologies, or departments,
working together towards a common goal

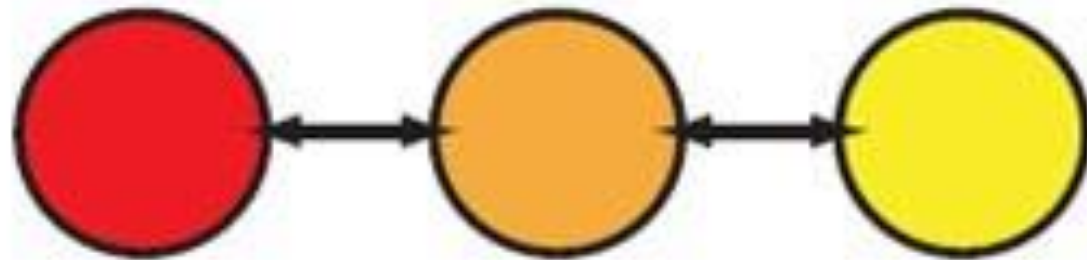
Transdisciplinary



Interdisciplinary



Multidisciplinary

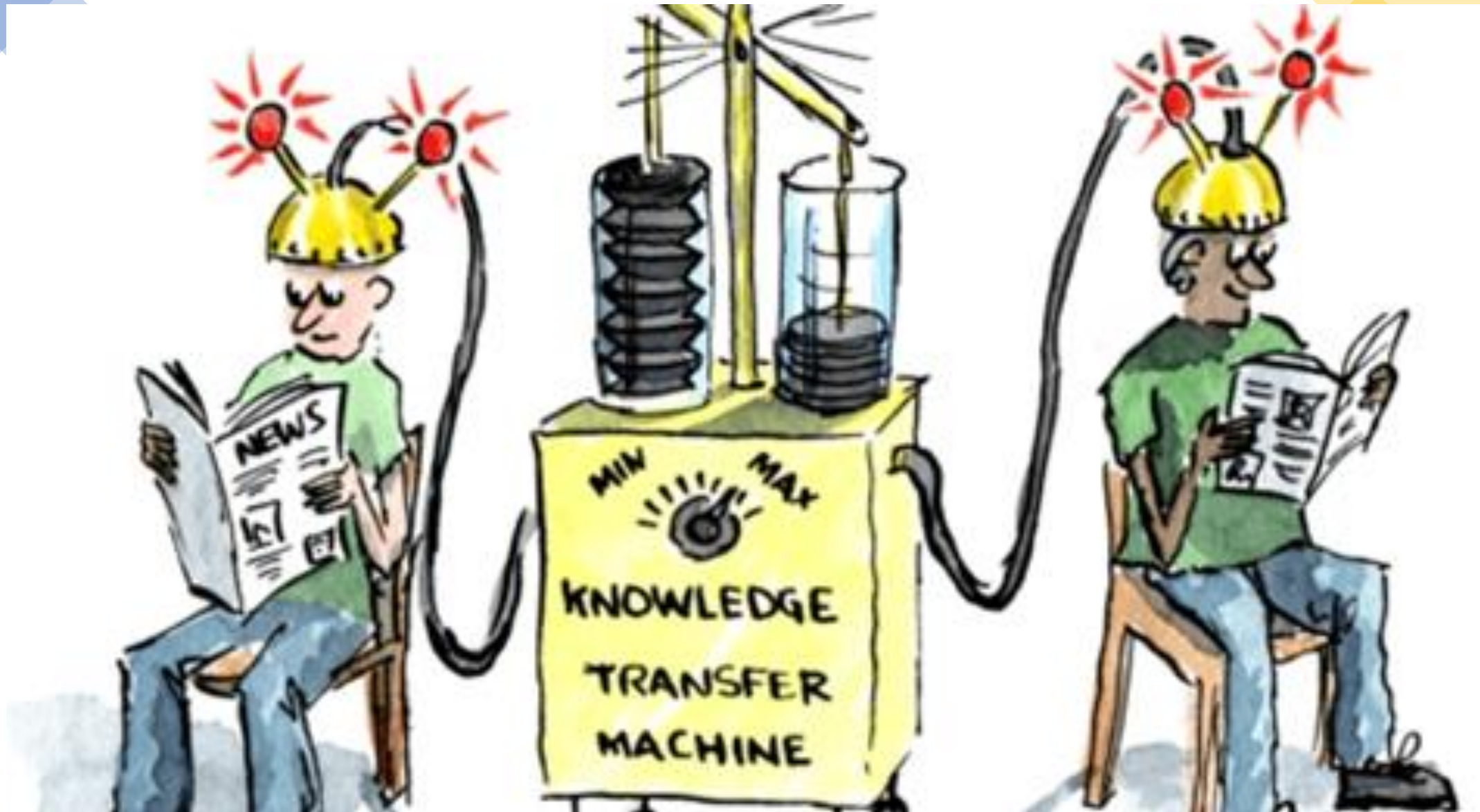


Disciplinary





TRANSDISCIPLINARITY

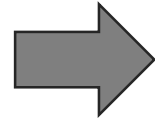


Cardiac and vascular research necessitate solutions from different backgrounds because singular disciplines are incapable of providing **a definitive solution for clinical problems**

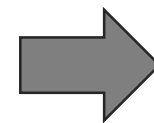
Cardiovascular research is inherently transdisciplinary



DISCIPLINARY



INTERDISCIPLINARY



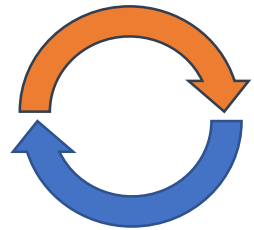
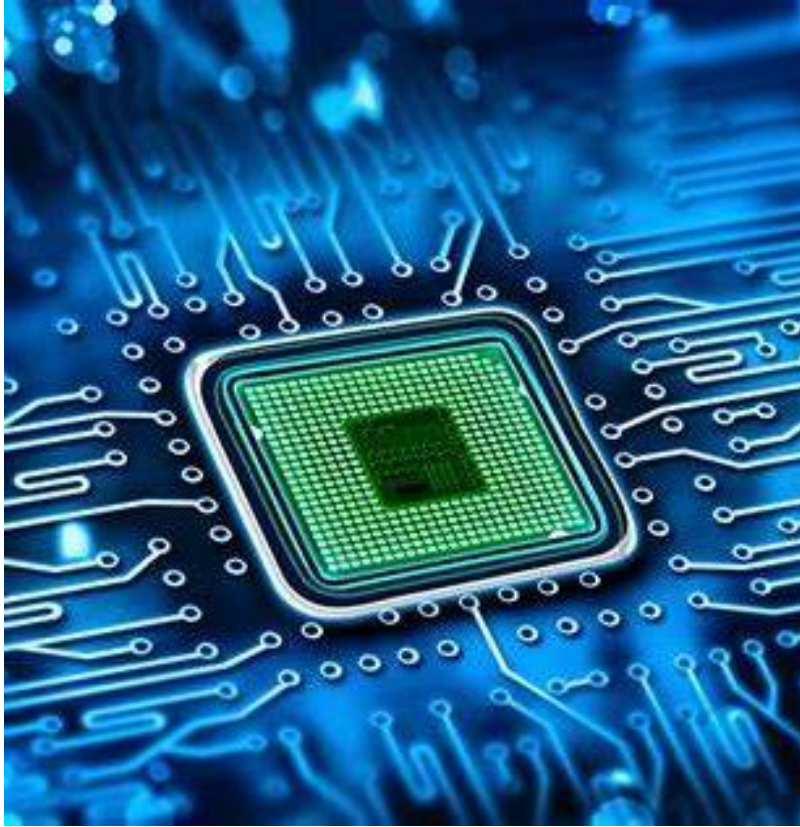
TRANSDISCIPLINARY



Transdisciplinarity: an established idea

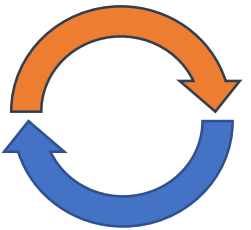
ENGINEERING AND MEDICINE WORLDWIDE





Engineer with vascular pathology competence

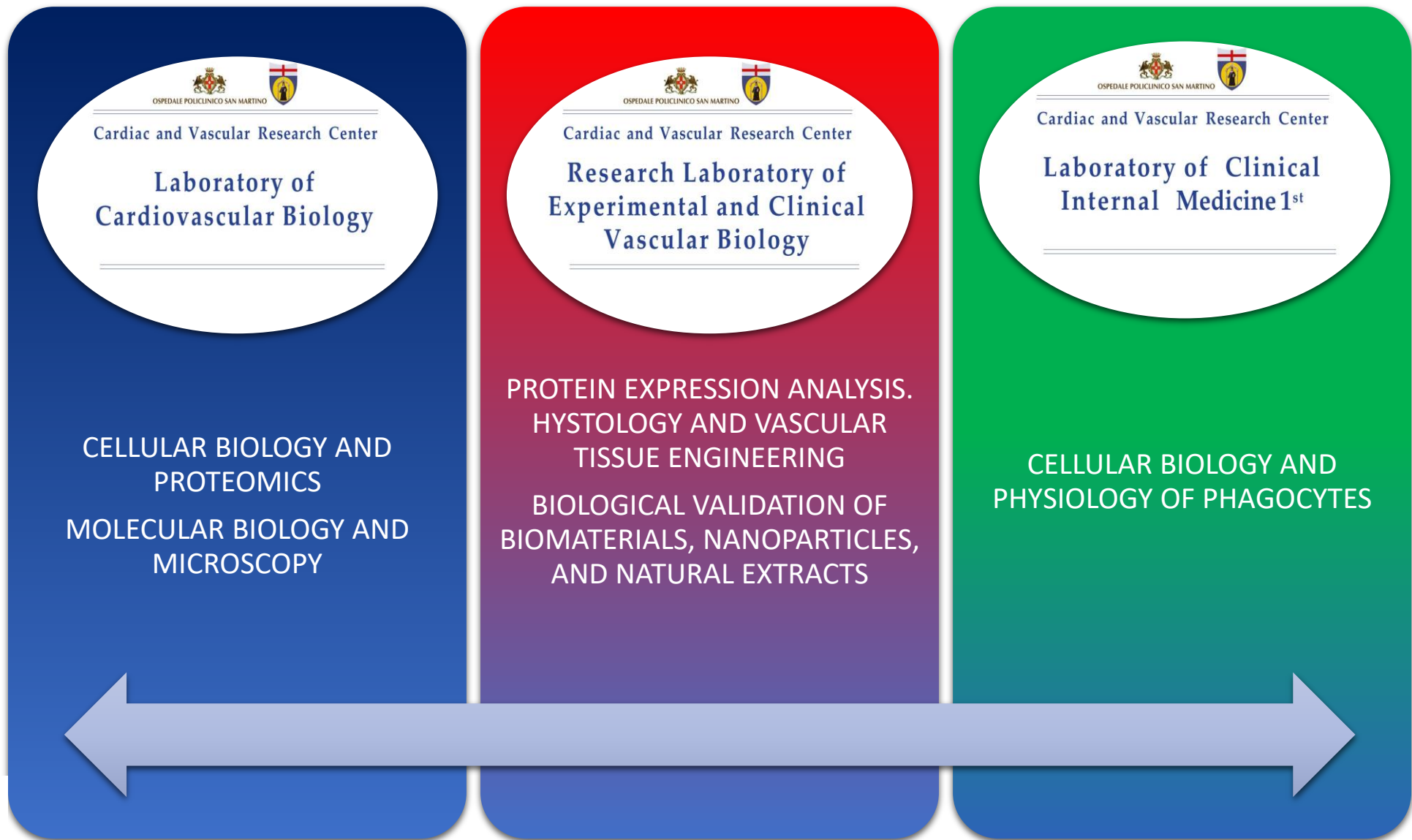
Vascular specialist with engineering competence



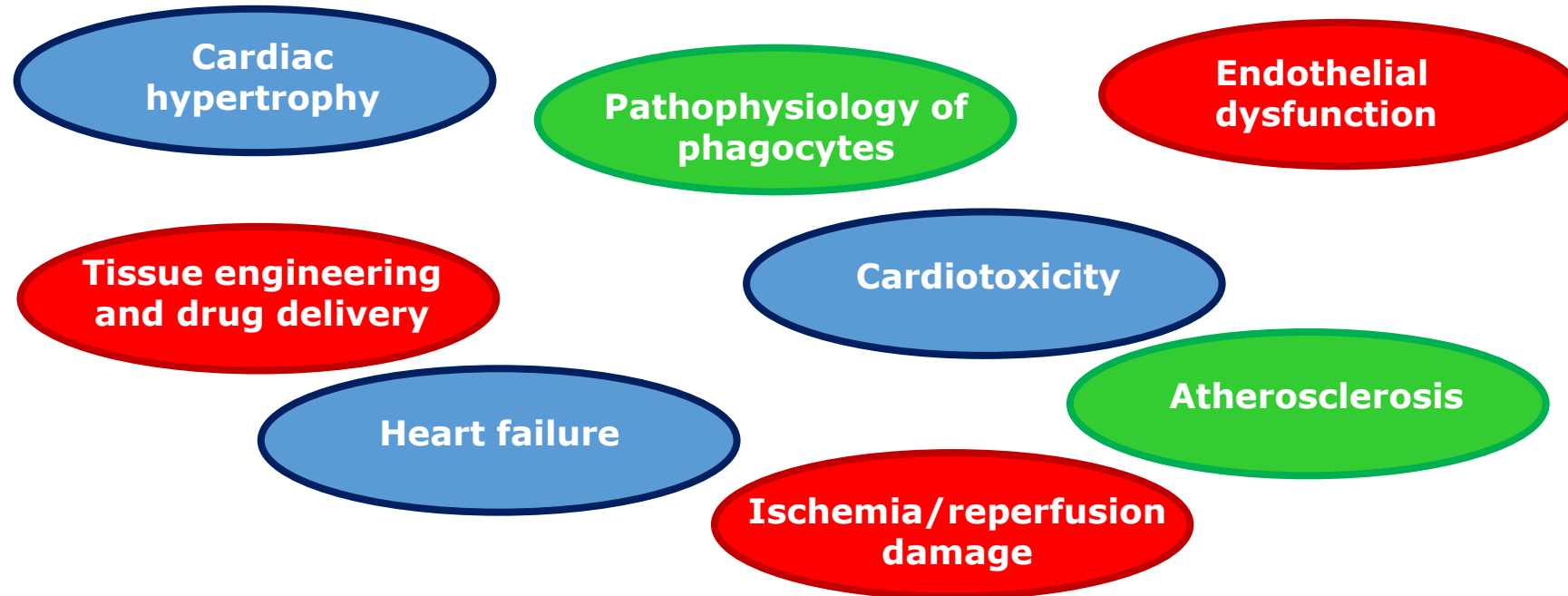





Cardiac and Vascular Research Center

INTRODUCTION – Cardiac and vascular research center

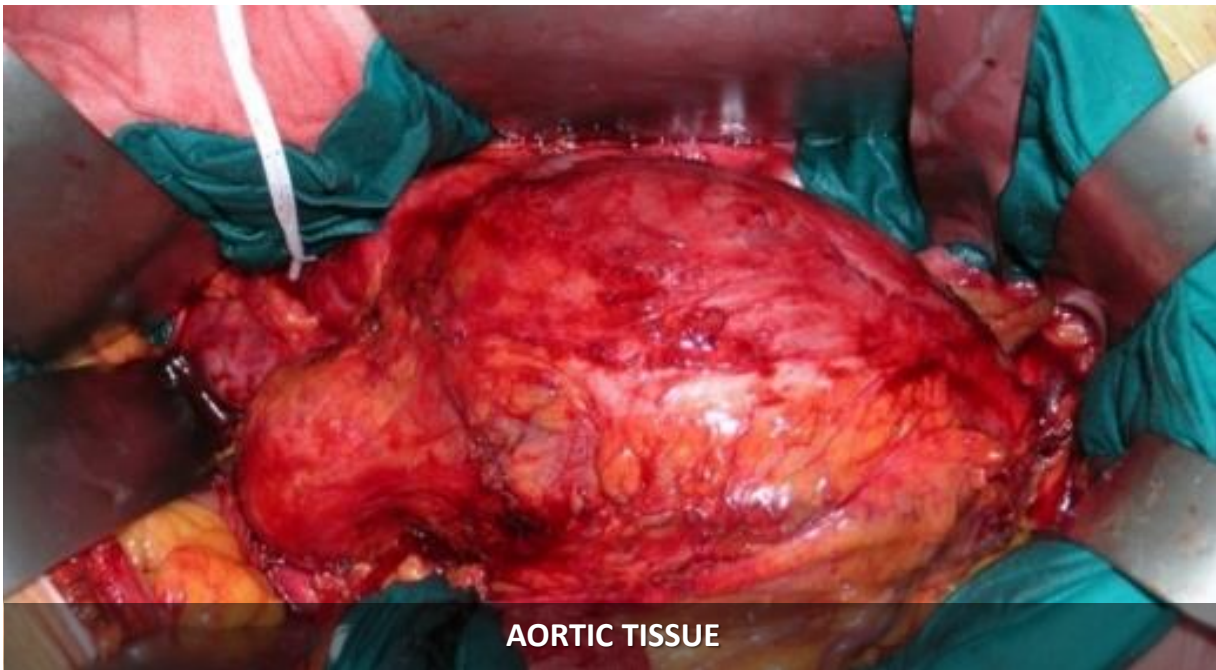


Cardiac and Vascular Research Center: research areas



-  **Research Laboratory of Experimental and Clinical Vascular Biology**
-  **Laboratory of Cardiovascular Biology**
-  **Laboratory of Clinical Internal Medicine 1**





AORTIC TISSUE



CAROTID PLAQUE



SAMPLE PREPARATION

DICCA

- Extraction of high-added value compounds with non-conventional techniques
- Micro- and nanoencapsulation of bioactive compounds
- Fabrication and characterization of polymeric biomaterials
- Mathematical modeling of biological phenomena
- Safety engineering





**Nanotechnology
and Tissue
Engineering
applied to
Vascular Medicine**



**Pathology
Microbiology
Vascular surgery
Cardiac surgery**

**Environmental safety
Material engineering
Fluid and biofluid
mechanics
Food engineering**

From VASCULAR surgery to CHEMICAL engineering

VASCULAR BIOLOGY
AND MEDICINE



CHEMICAL
ENGINEERING



RESEARCH CENTER
OF BIOLOGICALLY
INSPIRED ENGINEERING IN
VASCULAR MEDICINE AND
LONGEVITY

A MODEL OF
TRANSDISCIPLINARITY

INTRODUCTION – Our research centers



U.O. Chirurgia Vascolare ed Endovascolare



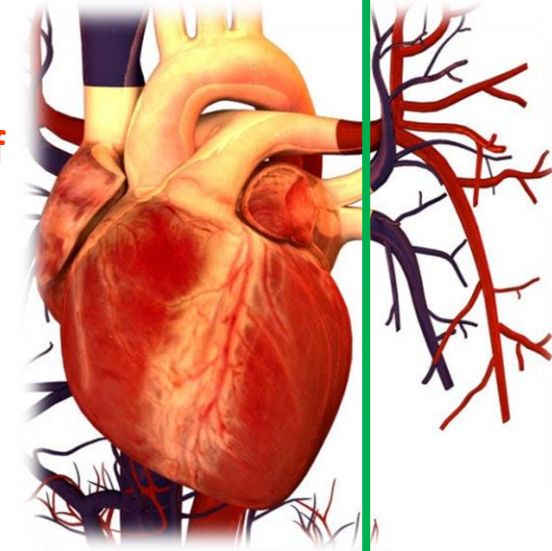
Cardiac and Vascular Research Center



BELONG

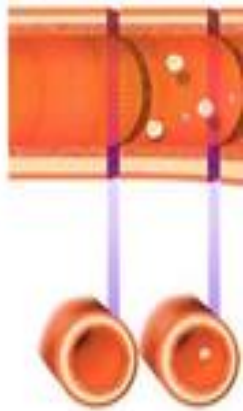
INTRODUCTION – Research topics

- **VASCULAR BIOLOGY: polyphenols and inflammation;**
- **VASCULAR DRUG DELIVERY: nanoparticles as an innovative drug delivery system for atherosclerosis;**
- **VASCULAR TISSUE ENGINEERING: biological validation of small-diameter biodegradable vascular prosthesis;**
- **BIOREACTORS AND FLUIDODYNAMICS STUDIES: mechanobiology of bioprostheses;**
- **VASCULAR REMODELING AFTER ENDOVASCULAR TREATMENT: quantitative analysis of medical images.**
- **SAFETY ENGINEERING**



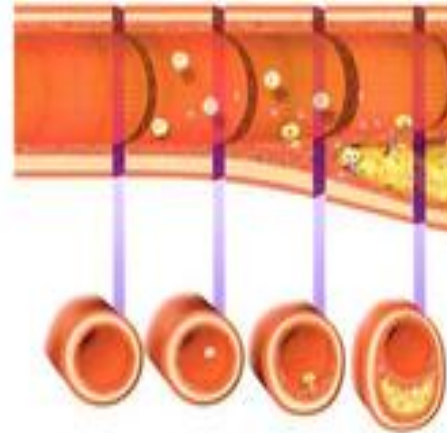
MODULATING INFLAMMATORY PROCESS

PREVENTION



Normal artery Endothelial activation

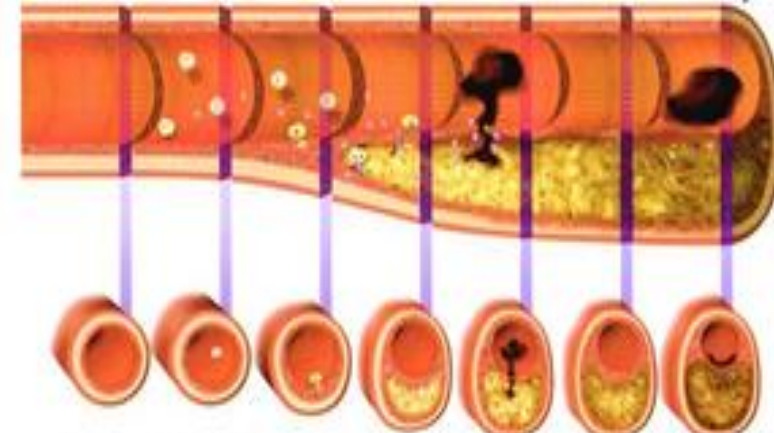
THERAPY



Normal artery Endothelial activation

REMODELLING

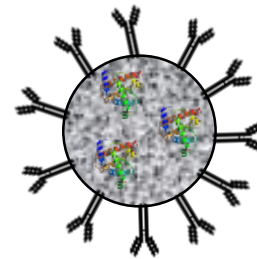
SUBSTITUTION



Normal artery Endothelial activation



BIOACTIVE COMPOUNDS



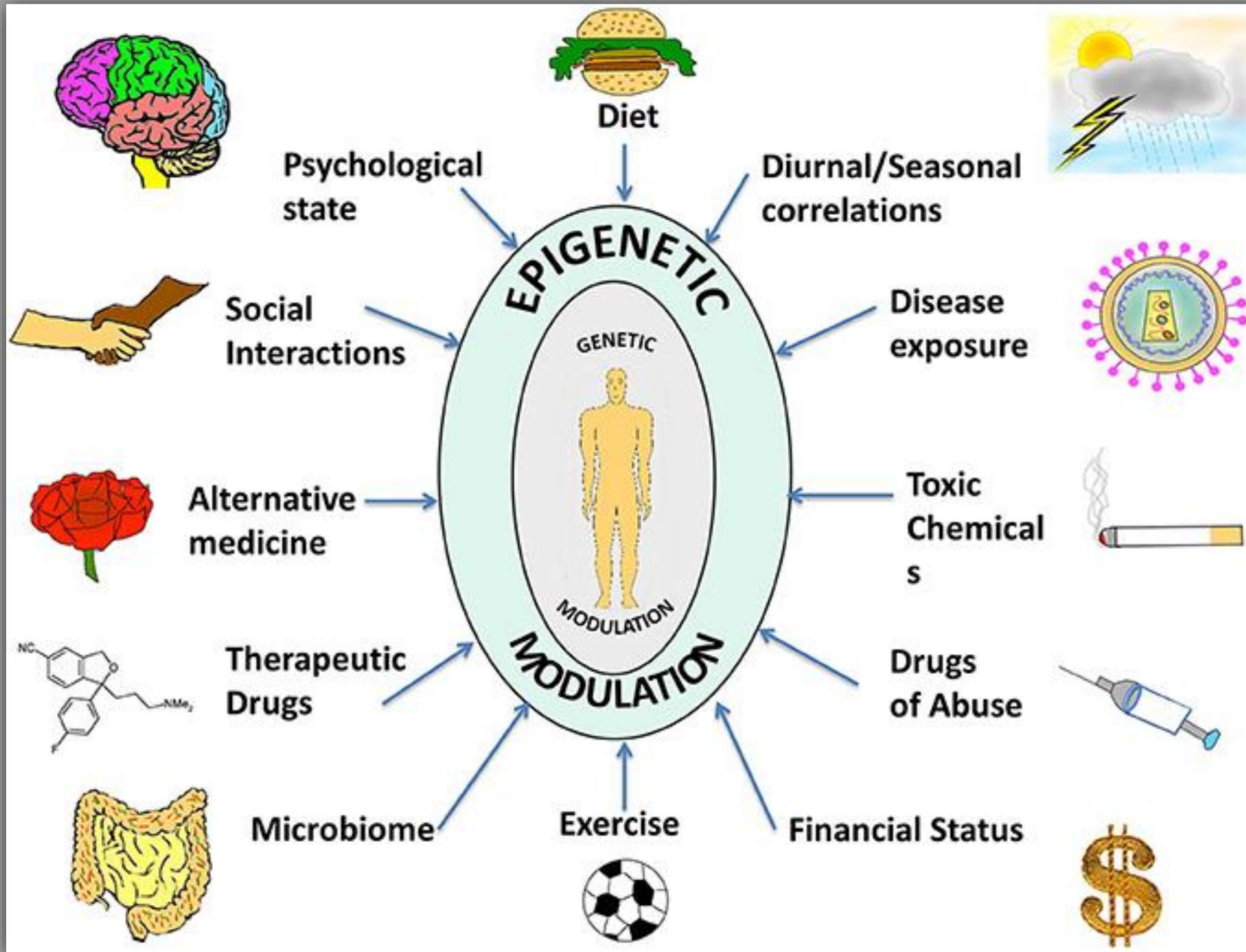
NANOSYSTEMS FOR DRUG DELIVERY



VASCULAR TISSUE ENGINEERING

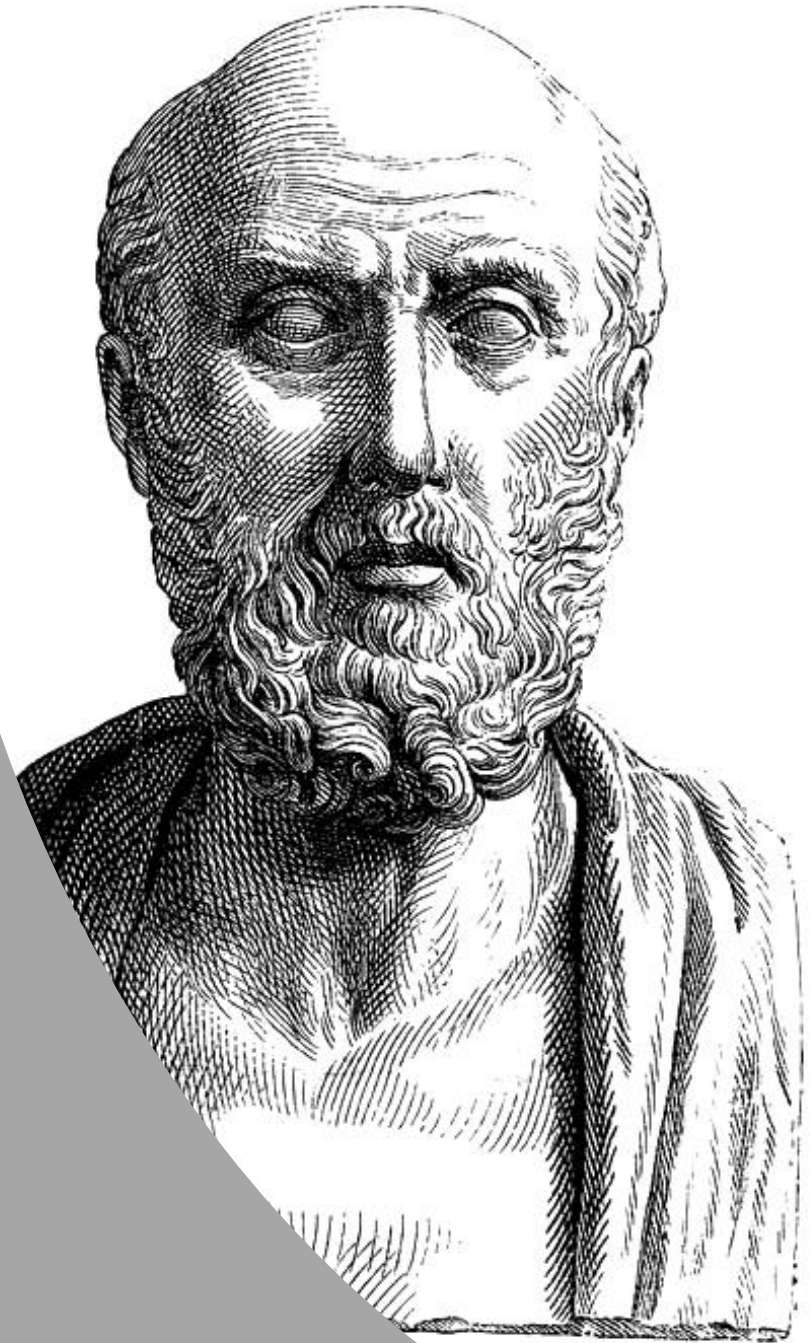


Food engineering in vascular diseases



« Let food be thy medicine,
And let medicine be thy
food »

Hippocrates of Kos





«An apple a day keeps the doctor away, as long as you aim well! »

W. Churchill

Lifestyle

Polyphenols

Prevention

Anti-inflammatory activity

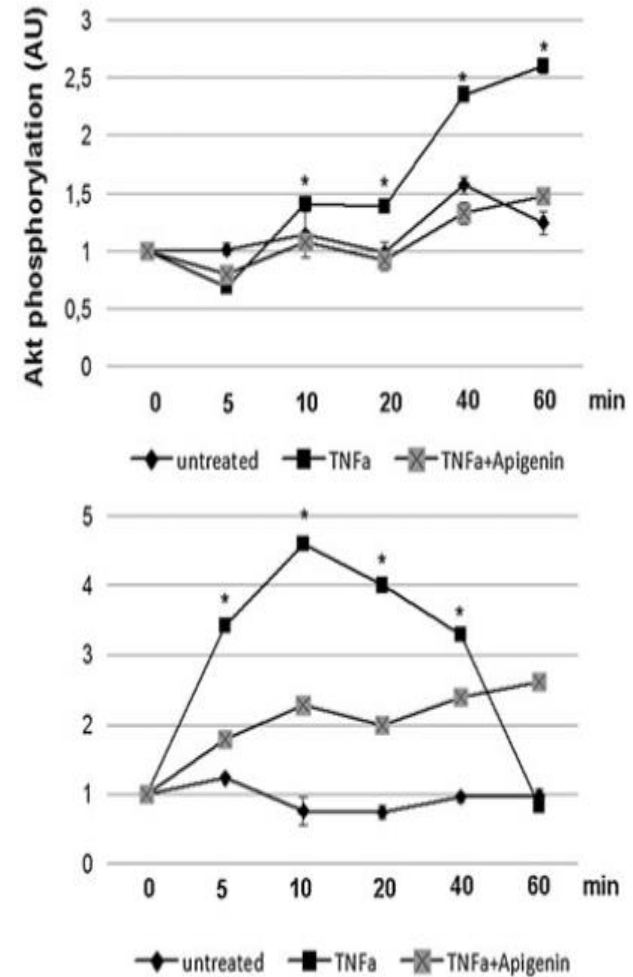
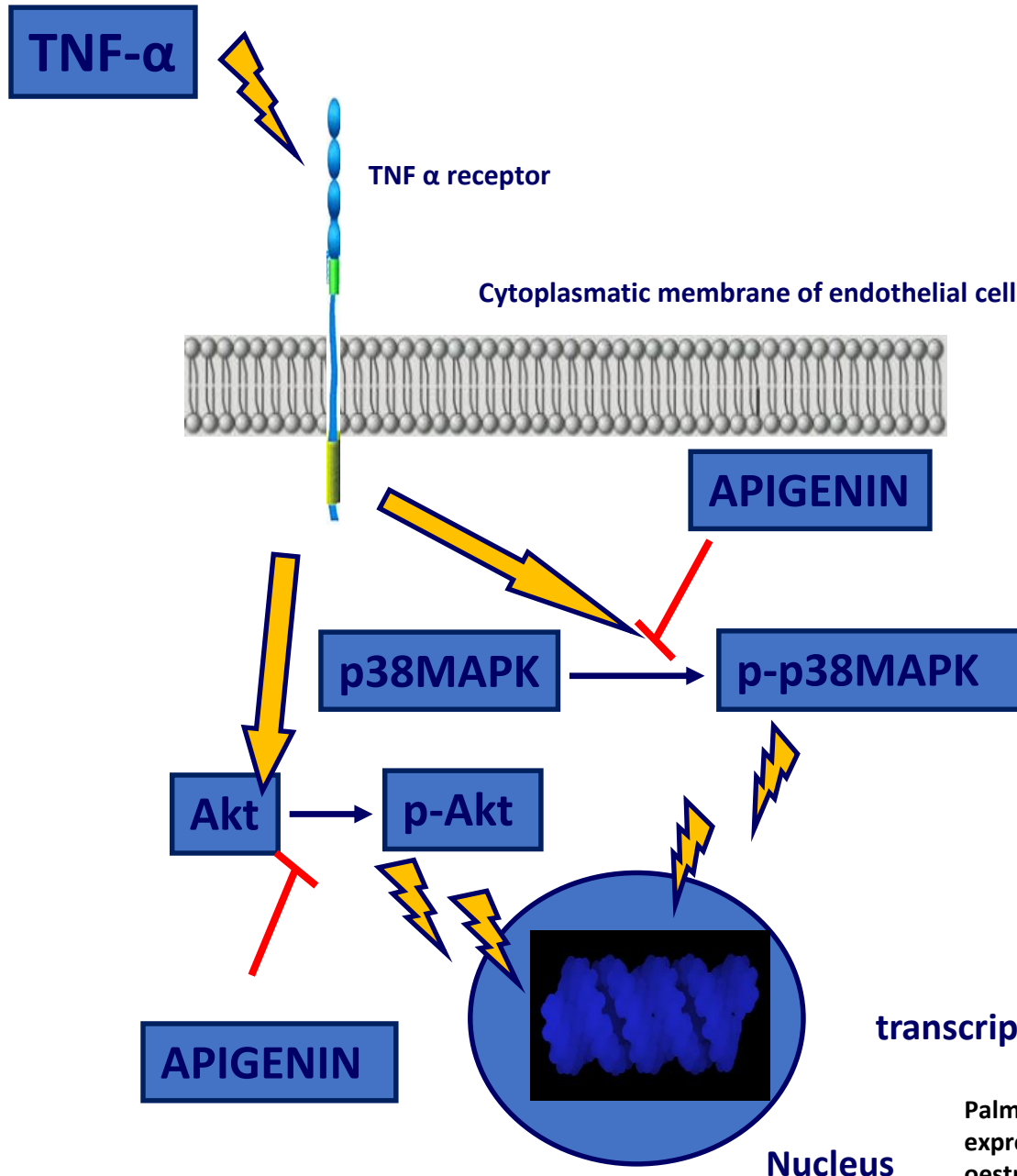
Mura M. et al. «Simultaneous ultrasound-assisted water extraction and β -cyclodextrin encapsulation of polyphenols from *Mangifera indica* stem bark in counteracting TNF α -induced endothelial dysfunction». *Nat Prod Res.* 2015; 29(17): 1657-63. doi: 10.1080/14786419.2014.996753.

Palmieri D. et al. «Effects of polyphenol extract from olive pomace on anoxia-induced endothelial dysfunction». *Microvasc Res.* 2012; 83(3): 281-9. doi: 10.1016/j.mvr.2012.02.010.

Aliakbarian B. et al. «Antioxidant activity and biological evaluation of olive pomace extract». *Nat Prod Res.* 2012;26(24): 2280-90. doi: 10.1080/14786419.2012.660692.

Palmieri D. et al. «Apigenin inhibits the TNF α -induced expression of eNOS and MMP-9 via modulating Akt signalling through oestrogen receptor engagement». *Mol Cell Biochem* 2012 ; 371(1-2): 129-36. doi: 10.1007/s11010-012-1429-1.

Polyphenols and *in vitro* inflammation



Palmieri D, Perego P, Palombo D. Apigenin inhibits the TNF α -induced expression of eNOS and MMP-9 via modulating Akt signalling through oestrogen receptor engagement. *Mol Cell Biochem* (2012) 371:129–136

Polyphenols and *in vivo* inflammation

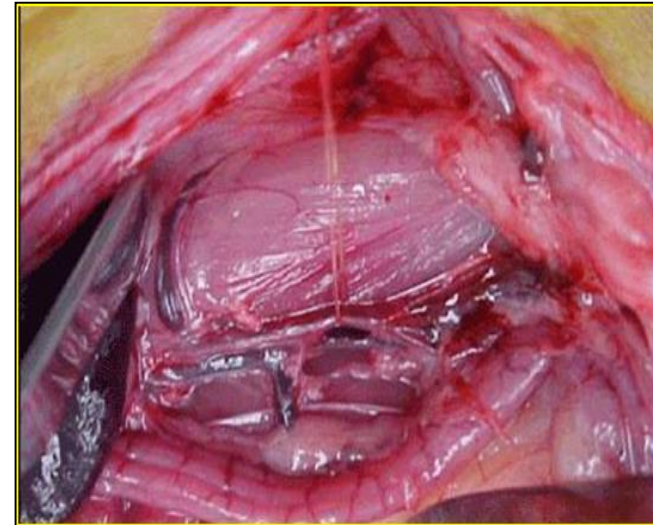
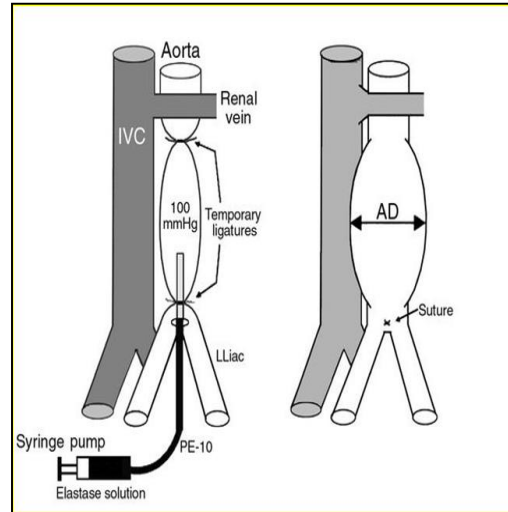
30 male rats Sprague Dawley



15 rats treated with RESVERATROL (10 mg kg/die in etanolo)
15 rats treted with placebo (just ethanol)



Infusion of pancreatic elastase





Engineered nanosystems for vascular drug delivery

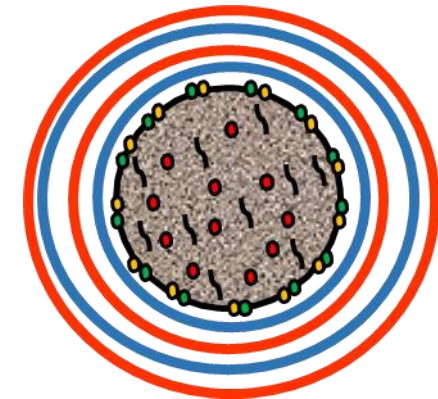
VASCULAR DRUG DELIVERY - Micro- and nanoencapsulation techniques



SPRAY DRYING



SONICATION



LAYER-BY-LAYER

Step 1: coacervation

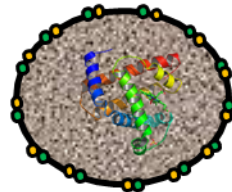


Nanoaggregate



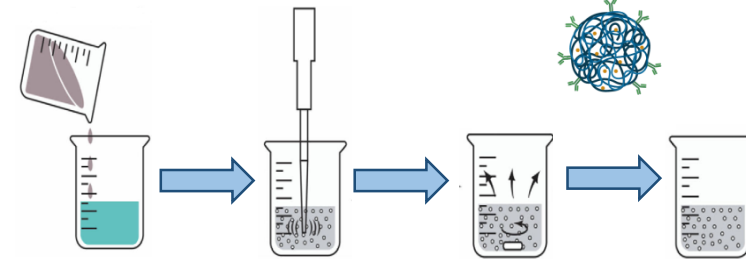
Carbonate addition

Step 2: mineralization



CaCO₃ nanoparticle

COMPLEX COACERVATION



EMULSION SOLVENT EVAPORATION

In collaboration with:

ENGINEERED CaCO₃ NANOPARTICLES WITH TARGETING ACTIVITY: A SIMPLE APPROACH FOR A VASCULAR INTENDED DRUG DELIVERY SYSTEM

Pier Francesco Ferrari,^{1*} Bahar Aliakbarian,^{1,2} Elena Zattera,³ Laura Pastorino,³ Domenico Palombo^{2,4} and Patrizia Perego^{1,2}



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The Italian Association of Chemical Engineering
Online at www.aidic.it/cet

Microencapsulation of phenolic compounds from olive pomace using spray drying: A study of operative parameters

Marco Paini^{a,b,*}, Bahar Aliakbarian^{a,b}, Alessandro A. Casazza^{a,b}, Alberto Lagazzo^a, Rodolfo Botter^a, Patrizia Perego^{a,b}

^a Department of Civil, Chemical and Environmental Engineering, University of Genoa, via Opera Pia 15, I-16132 Genoa, Italy
^b Research Center for Biologically Inspired Engineering in Vascular Medicine and Longevity (BELOG), Via Montallegro 1, I-16145 Genoa, Italy

Effect of encapsulating agent on physical-chemical characteristics of olive pomace polyphenols-rich extracts

Bahar Aliakbarian^{a,b*}, Marco Paini^{a,b}, Alessandro Alberto Casazza^{a,b}, and Patrizia Perego^{a,b}

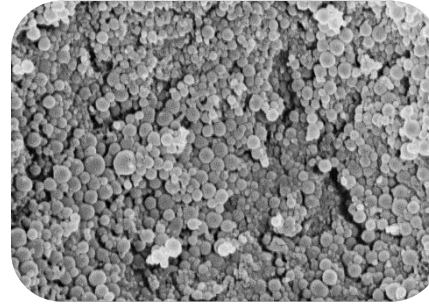
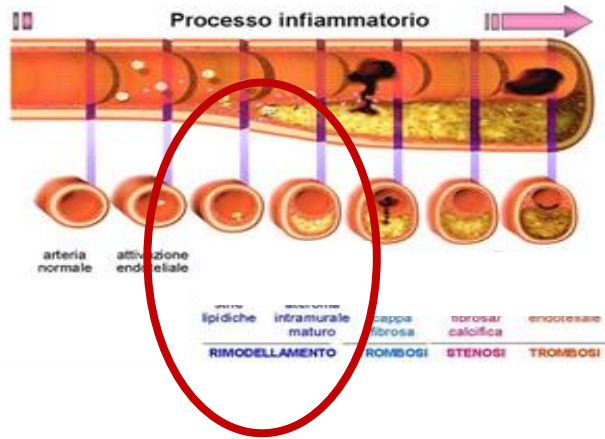


Civil, Chemical and Environmental Engineering Department

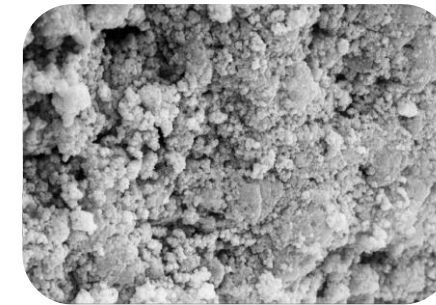
Polytechnic School



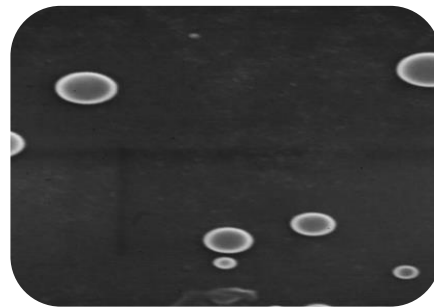
VASCULAR DRUG DELIVERY - Micro- and nanoparticles



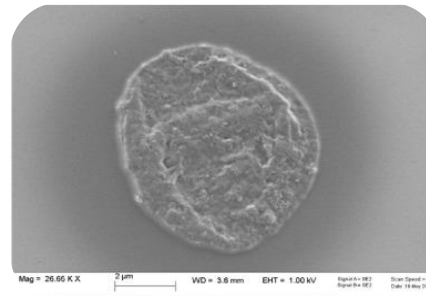
POLYMERIC NANOPARTICLES



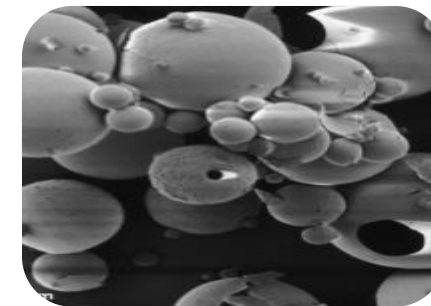
NANOLIPOSOMES



CaCO₃ NANOPARTICLES



LAYER-BY-LAYER-BASED PARTICLES



SPRAY DRYER-BASED PARTICLES

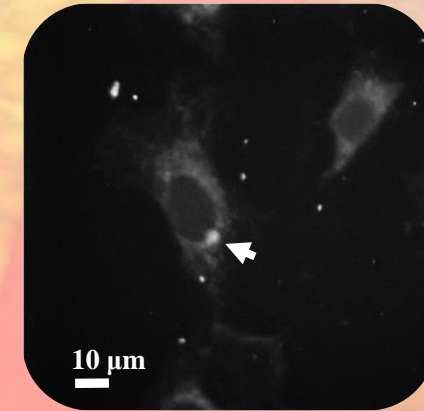
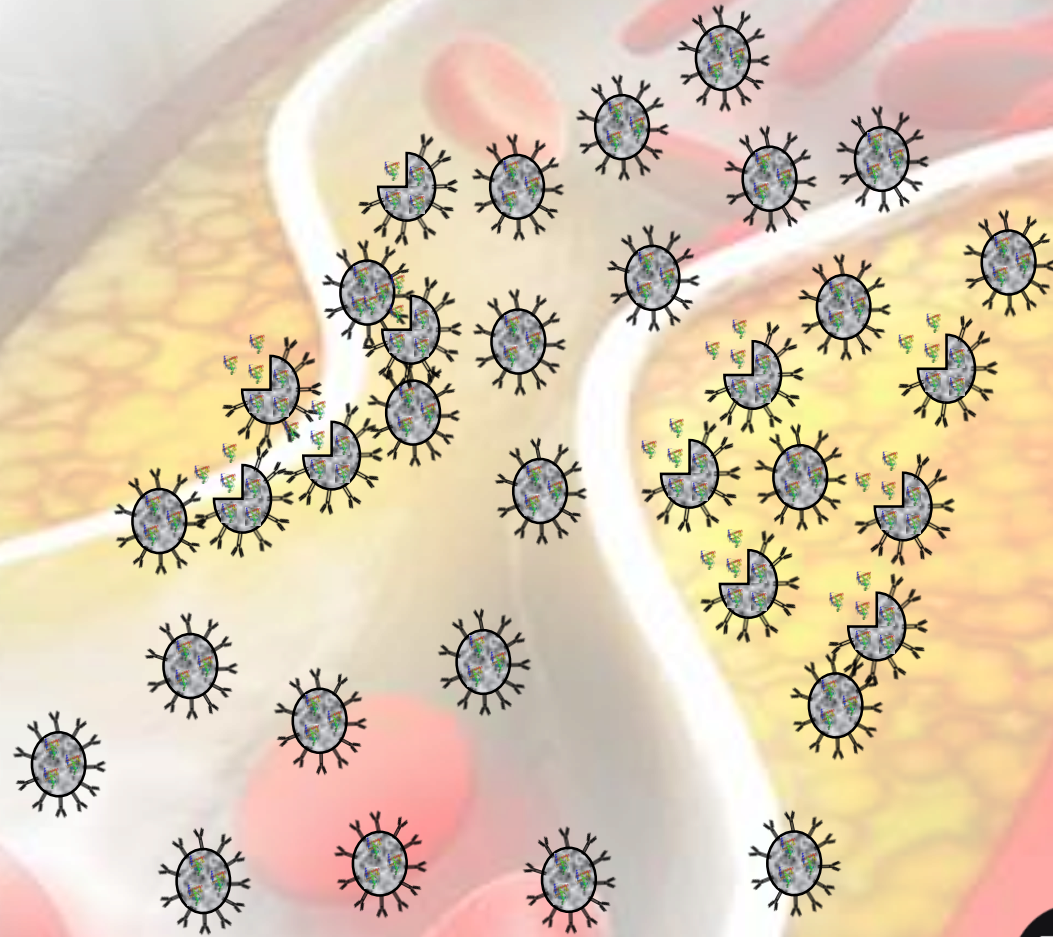
In collaboration with:



Ferrari PF, Aliakbarian B, Zattera E, Pastorino L, Palombo D, Perego P, 2017. Engineered CaCO₃ nanoparticles with targeting activity: a simple approach for a vascular intended drug delivery system. *The Canadian Journal of Chemical Engineering* 95: 1683-1689.

Ferrari PF, Aliakbarian B, Bagnato P, Palombo D, Perego P, 2017. An innovative drug delivery system for atherosclerosis. **ESCVS 2017 YOUNG VASCULAR AWARD**

Drug delivery system for atherosclerosis



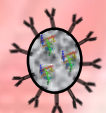
In collaboration with:



University of Lorraine
(Nancy, France)

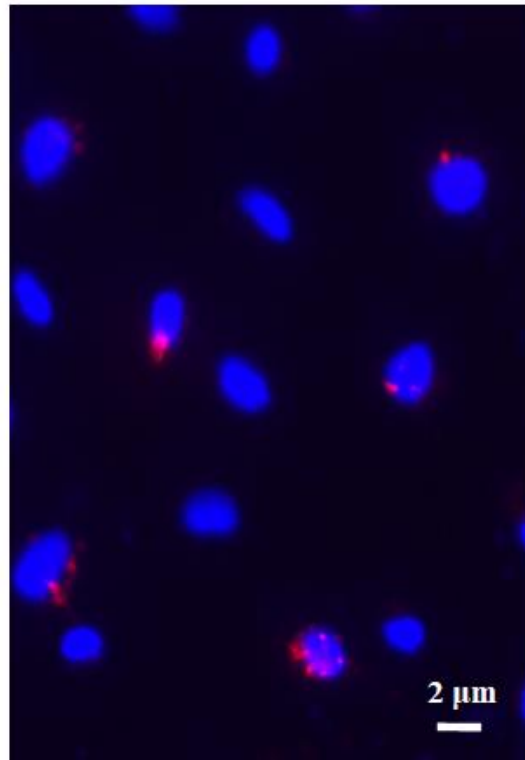
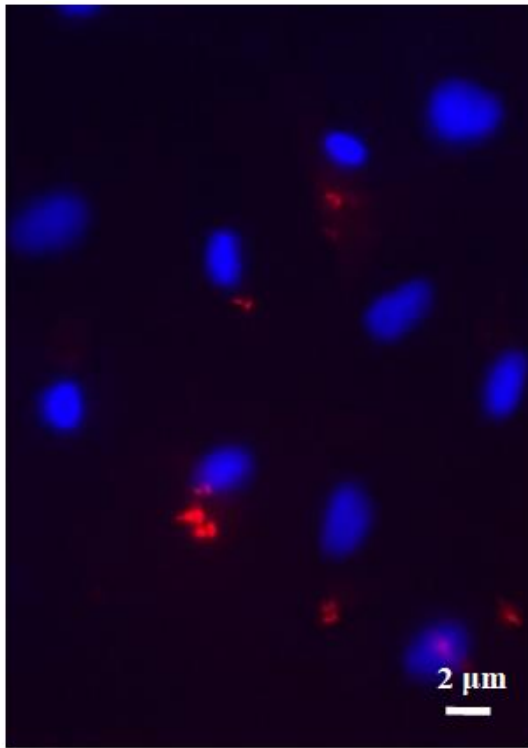


University of Porto
(Porto, Portugal)

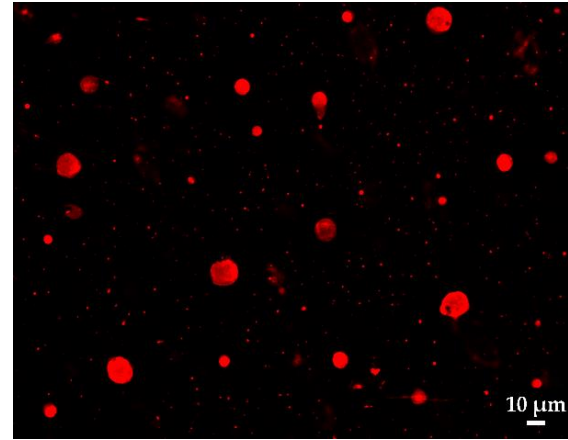


Schematic representation of nanoparticles encapsulating
therapeutic proteins

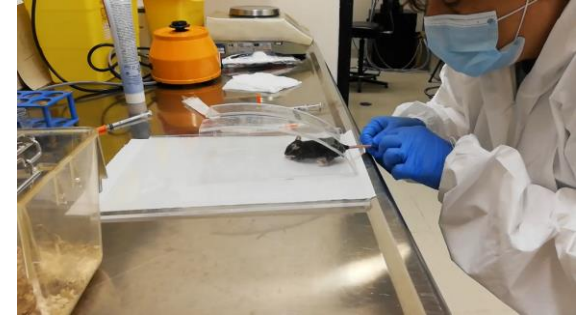
In vitro



In vivo



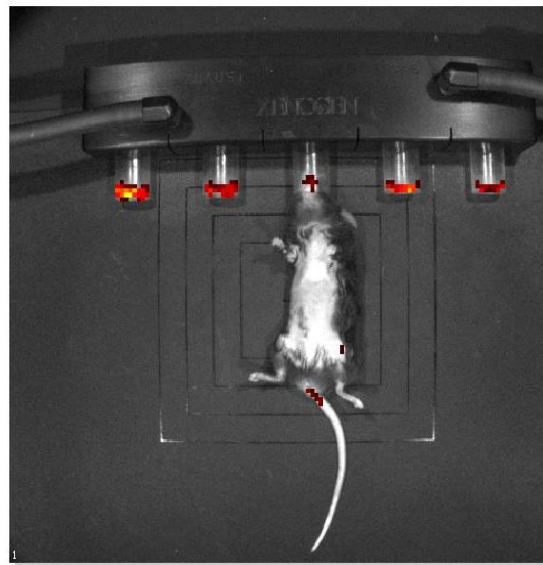
**Functionalized
polymeric nanoparticles
marked with rhodamine**



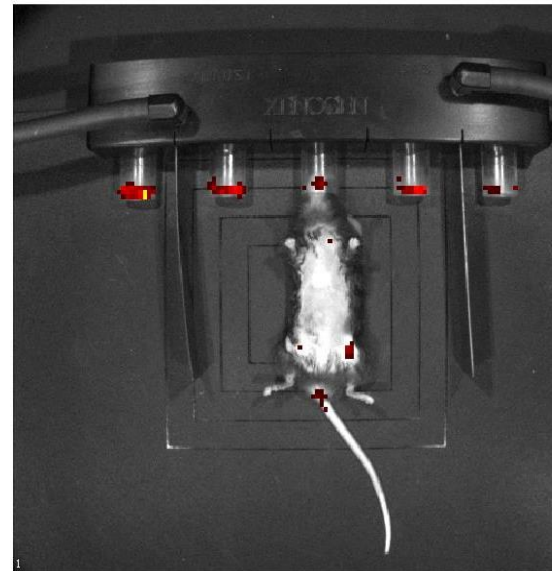
VASCULAR DRUG DELIVERY - *In vitro* cellular uptake & *in vivo* test

VASCULAR DRUG DELIVERY - *In vivo* test

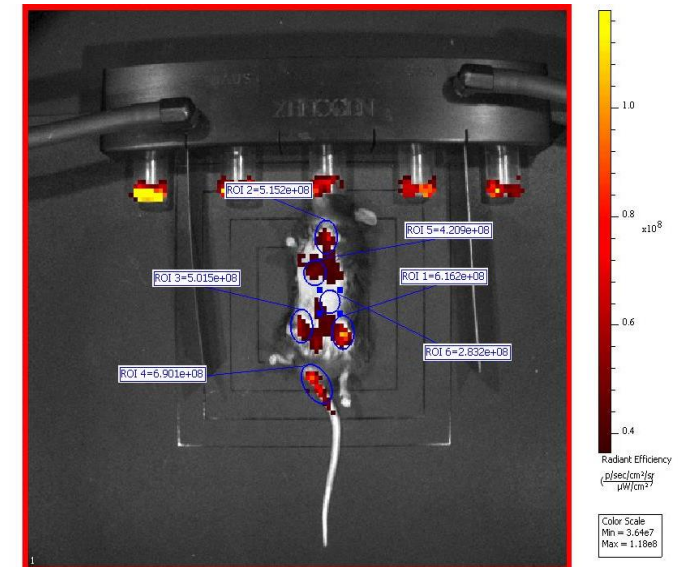
DISTRIBUTION OF NANOPARTICLES MARKED WITH RHODAMINE



10 minutes



30 minutes

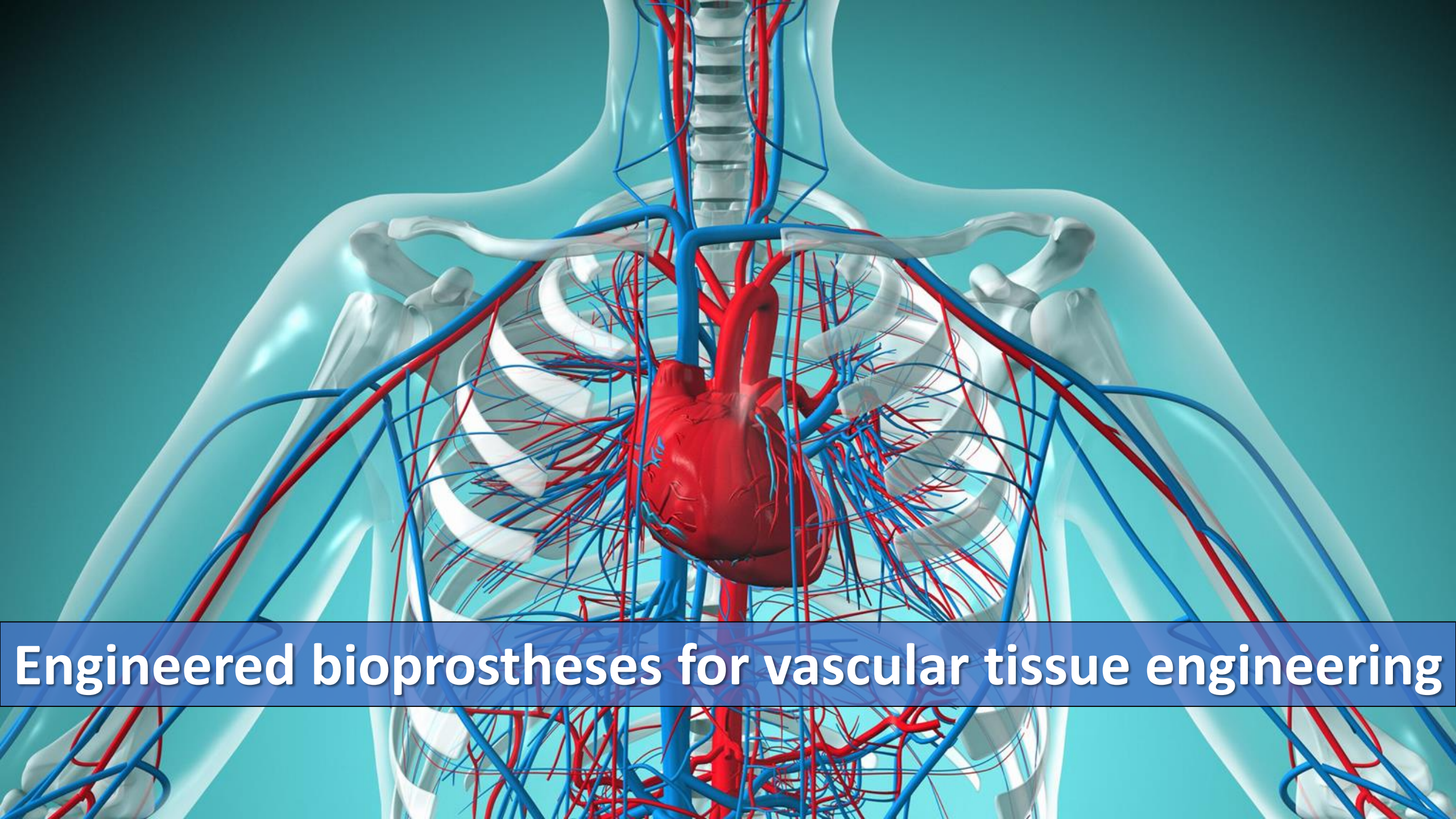


60 minutes

TIME

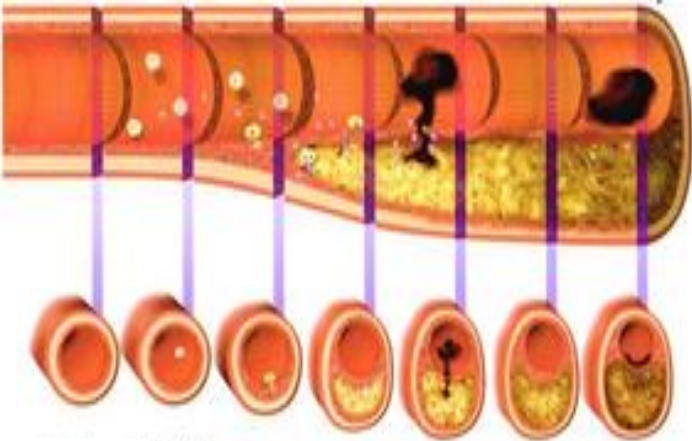
PATENT:

Perego P, Palombo D, Ferrari PF, Campardelli R, Pratesi G, 2019. Engineered nanoliposomes for a targeted therapy of atherosclerosis and their preparation procedures. Application number: 102019000008745, registered on 12th June 2019.



Engineered bioprostheses for vascular tissue engineering

VASCULAR TISSUE ENGINEERING



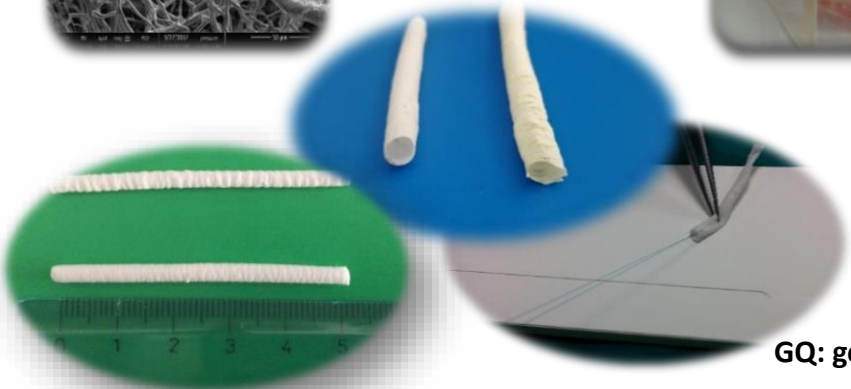
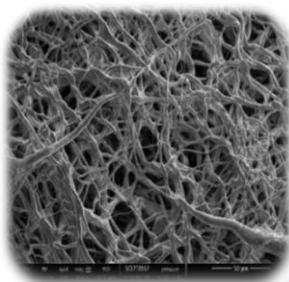
Normal Endothelial
artery activation



OCCLUSION



**Small diameter
vascular prostheses
(2 and 5 mm in diameter)**



Q: quercetin
GQ: gelatin and quercetin

In collaboration with

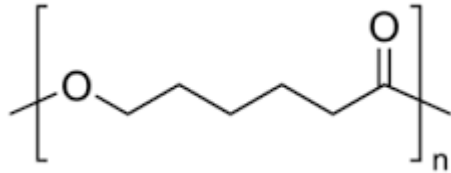


Ferrari PF, Aliakbarian B, Lagazzo A, Tamayol A, Palombo D, Perego P, 2017. Tailored electrospun small-diameter graft for vascular prosthesis, *International Journal of Polymeric Materials and Polymeric Biomaterials* 66, 635-643.
 Ferrari PF, Aliakbarian B, Palombo D, Perego P, 2017. Small diameter vascular grafts coated with gelatin. *Chemical Engineering Transactions* 57.
 Aliakbarian B, Ferrari PF, Bagnato P, Palombo D, Perego P. Engineered small diameter vascular grafts with anti-inflammatory properties. *The Journal of Cardiovascular Surgery*, abstract book, Vol. 58 – Suppl. 2 to n° 3, 14.

Biodegradable and biocompatible polymers for vascular bioprostheses

Poly (ϵ -caprolactone) (PCL)

- Biodegradable polyester
- FDA approved
- Suitable for electrospinning
- Good mechanical properties
- Hydrophobic properties

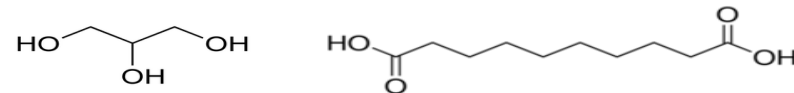


PCL



Poly (glycerol sebacate) (PGS)

- Synthetic elastomer
- Biodegradable
- Biocompatible
- Hydrophilic properties



glycerol

+

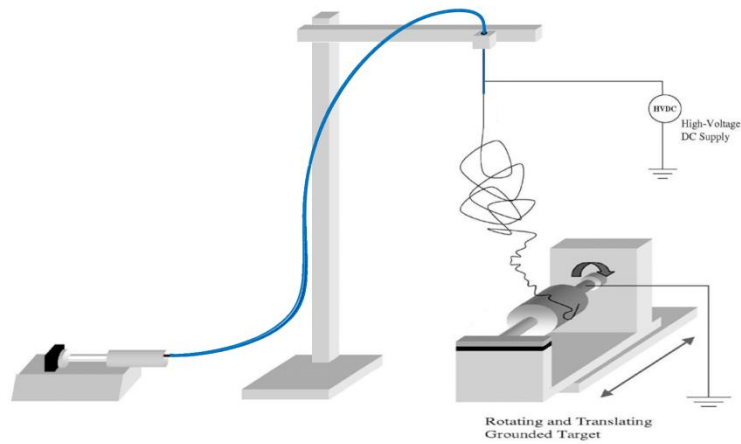
sebacic acid

PGS



PCL:PGS (1:1, v/v)

Materials and methods – Electrospinning



Small-diameter electrospun vascular scaffolds:

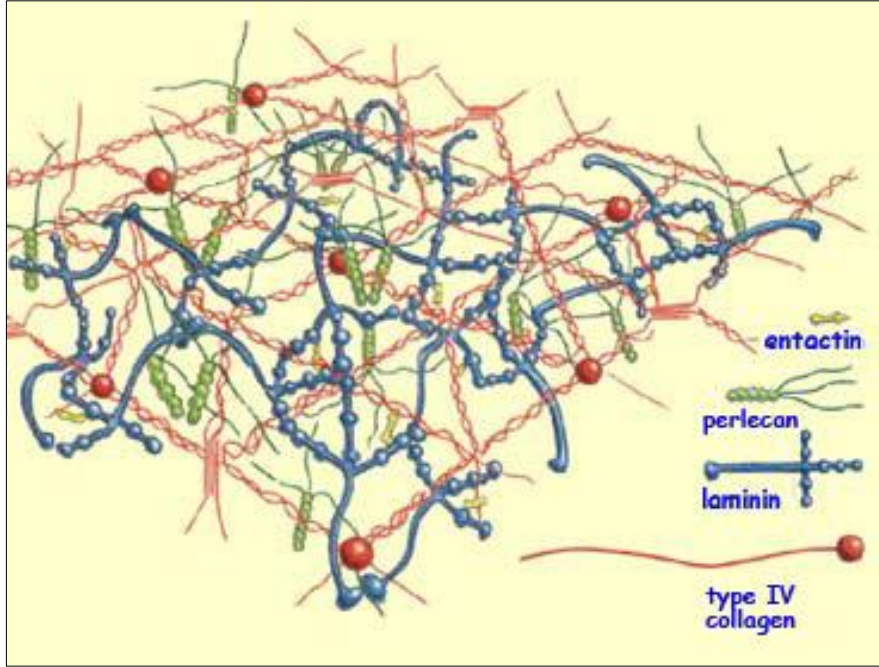


2 mm in diameter

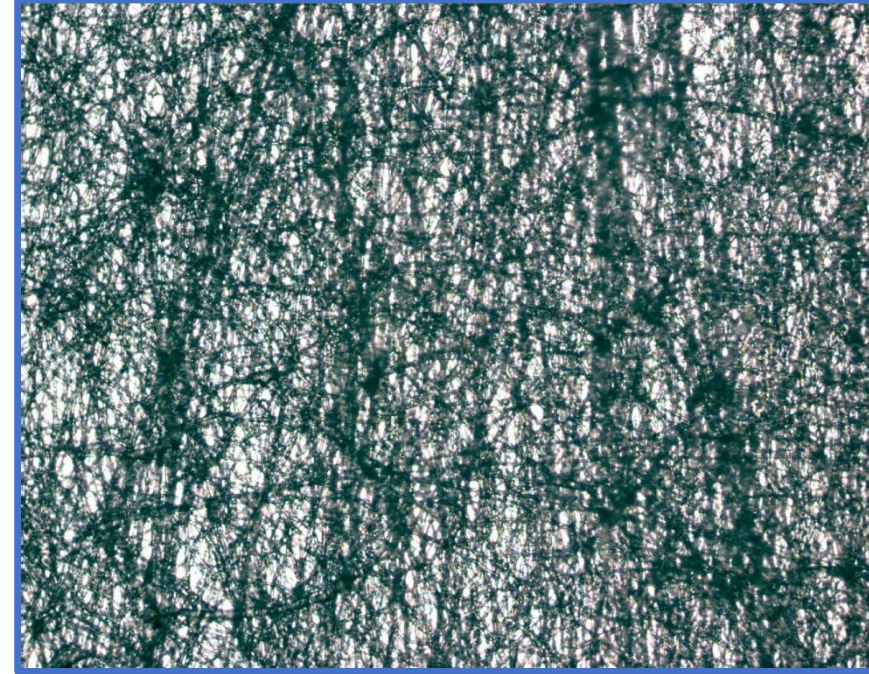


5 mm in diameter

Why electrospinning?



Extracellular matrix



Electrospun scaffold fibers

Electrospinning is a fiber-forming technique to fabricate nanofibers from different natural or synthetic polymers
These fibers mimic the complex 3D architecture of extracellular matrix

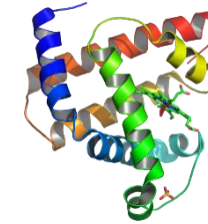
Scaffold functionalization



To modulate post-surgery inflammation



To induce re-endothelialization



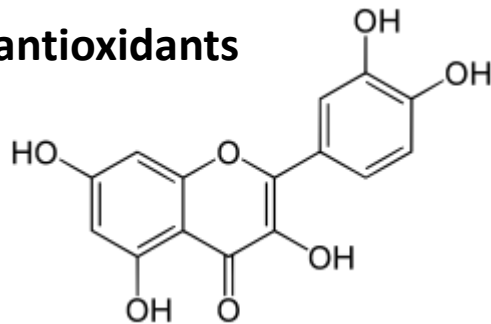
proteins

Green sustainable extraction techniques

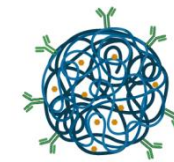
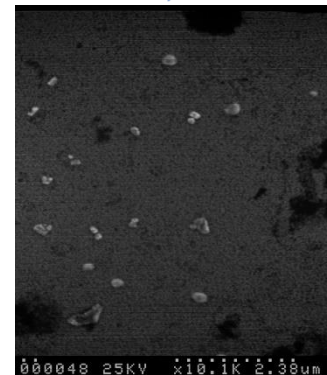
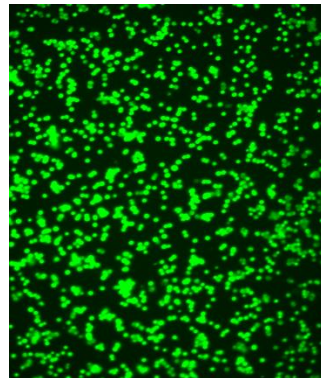
SCAFFOLD FUNCTIONALIZATION

nanoencapsulation

antioxidants



quercetin



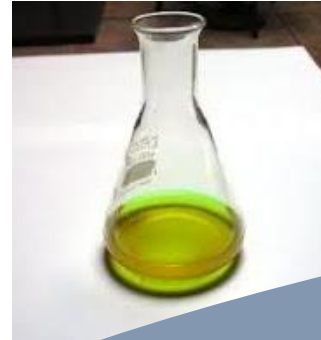
Nanoparticles

Morphological characterization of nanoparticles

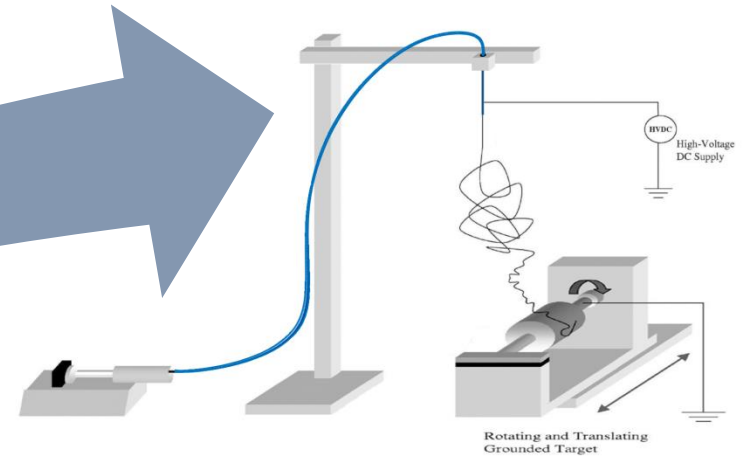
Functionalized scaffolds with antioxidants and proteins



HPTE



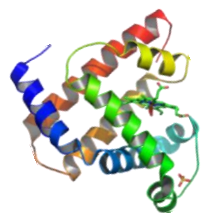
PCL:PGS solution containing **QUERCETIN**



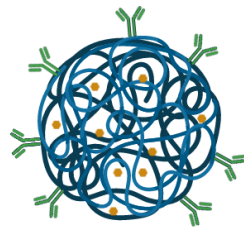
Electrospinning



Vegetables



PROTEINS



Nanoparticles encapsulating **PROTEINS**



PCL:PGS solution containing nanoparticles encapsulating **PROTEINS**

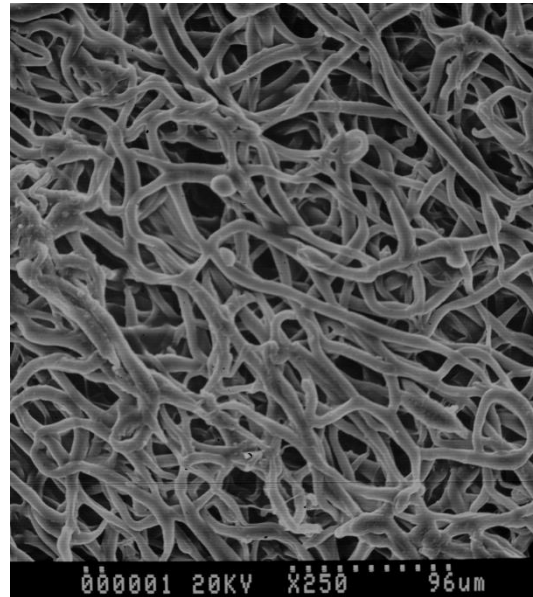
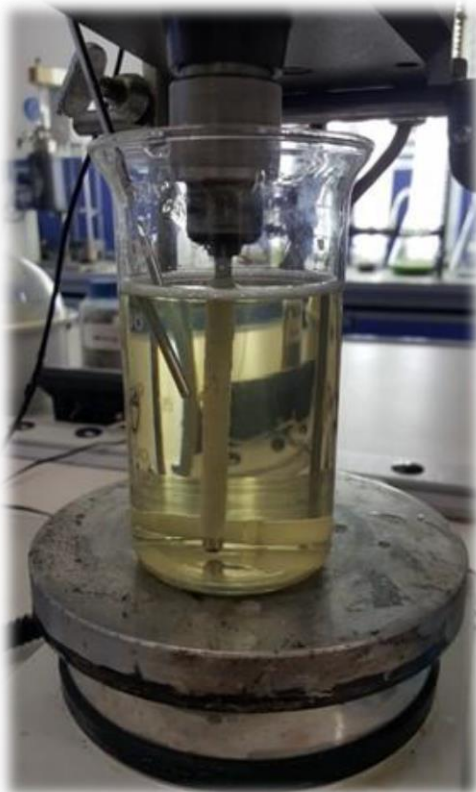
Surface coating with gelatin

Coating with gelatin (process)

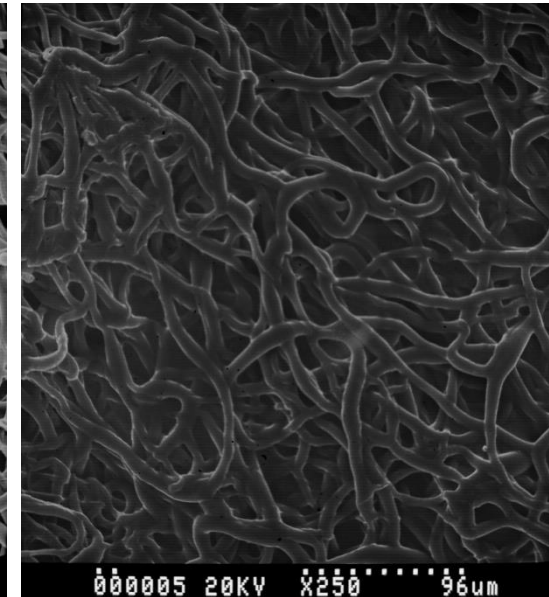
1 hour under controlled temperature (37°C) and at constant velocity of 135 rpm



Fully immersed in a gelatin solution (67 mg/mL)

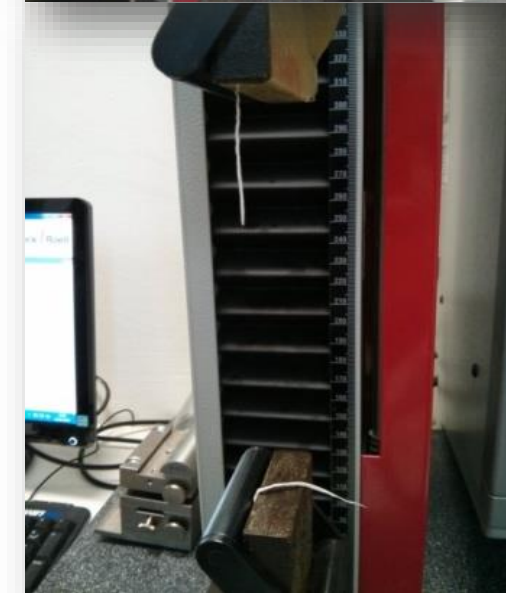
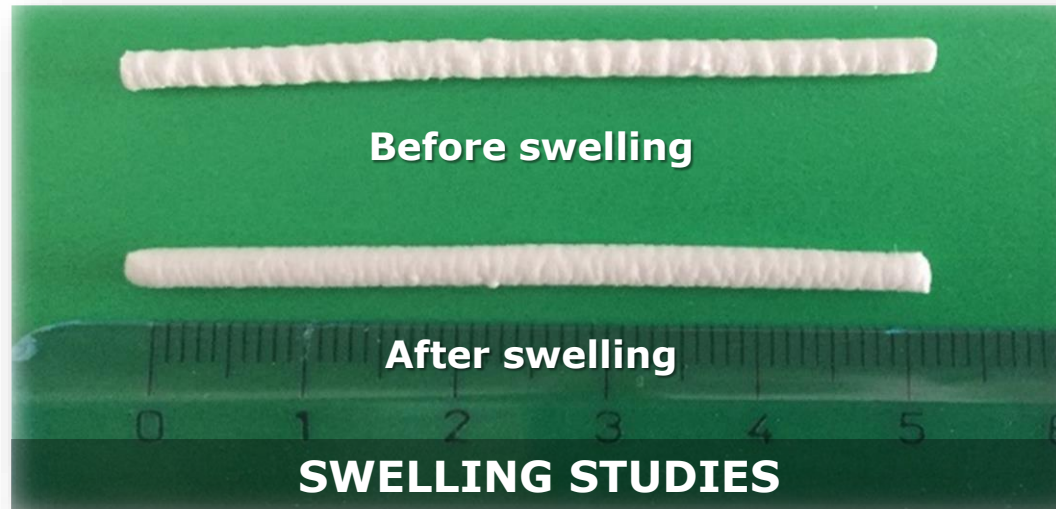


without surface coating:
highly porous



with surface coating:
poorly porous

RESULTS – Scaffolds functionalized with nanoparticles (proteins)



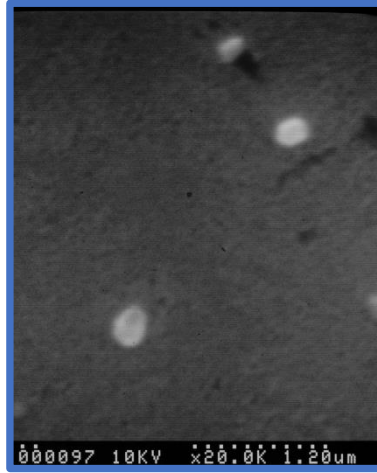
MECHANICAL CHARACTERIZATION

The background of the image is a complex, three-dimensional molecular structure rendered in shades of blue. It features a network of interconnected spheres (atoms) and lines (bonds), forming a lattice-like pattern that recedes into the distance, creating a sense of depth. The lighting is soft, highlighting the spheres and giving the structure a glowing appearance. A semi-transparent purple horizontal band is positioned across the lower half of the image, serving as a background for the text.

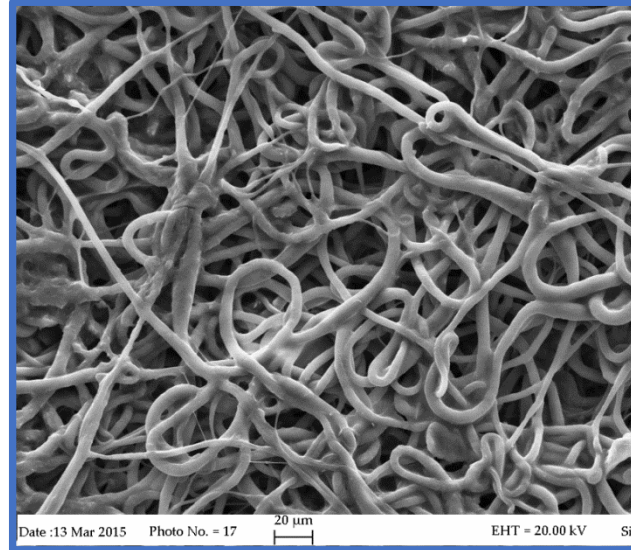
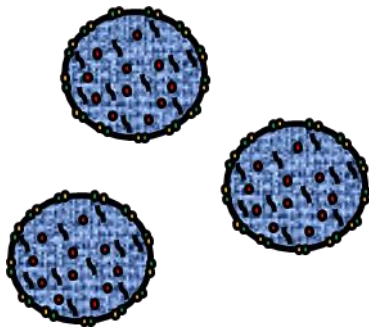
**Nanoparticles and functionalized materials as
nanoengineered tools for vascular
regenerative medicine**

RESULTS – Scaffolds functionalized with nanoparticles (proteins)

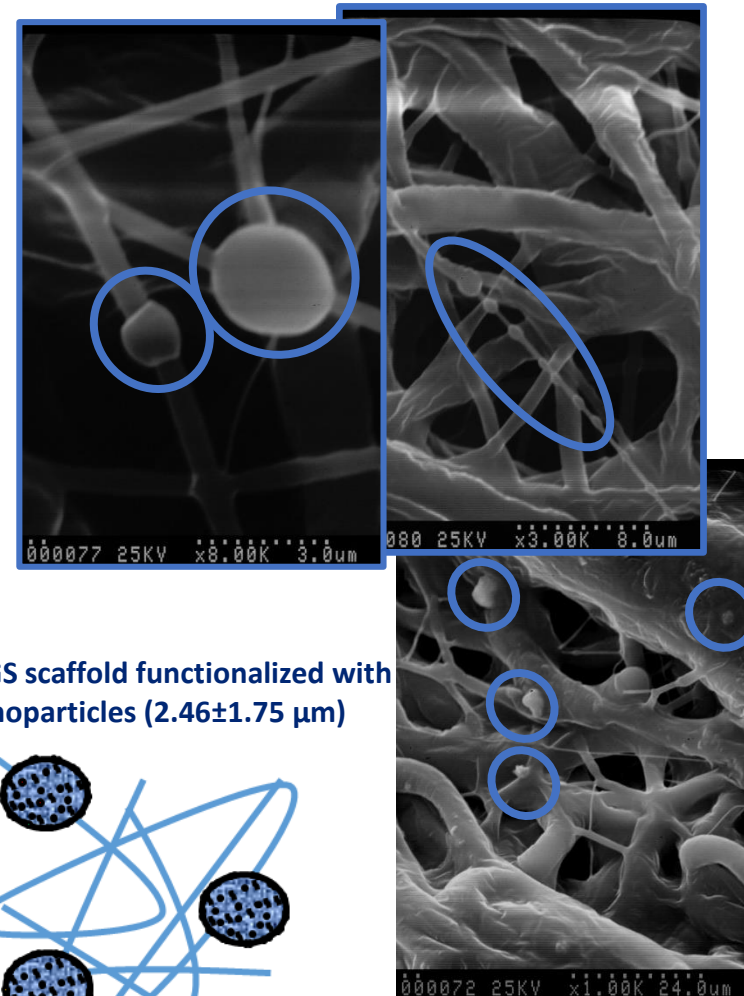
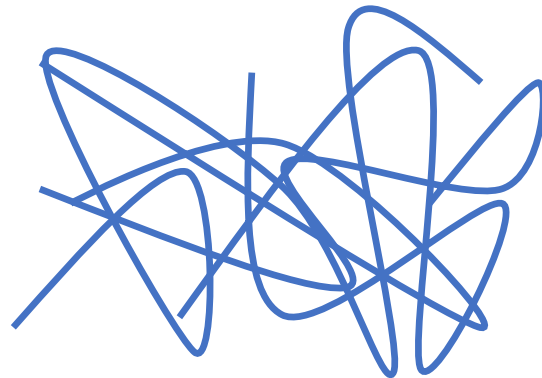
Microscopy analysis



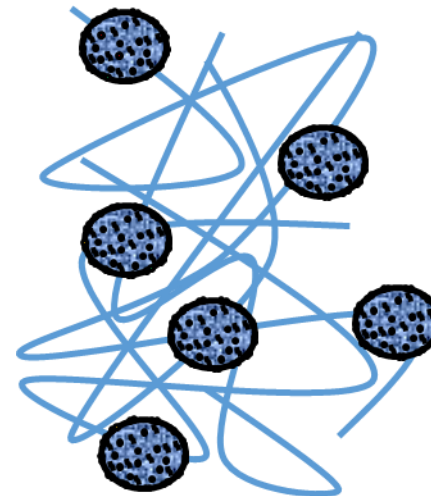
Nanoparticles (151.90 ± 31.66 nm)



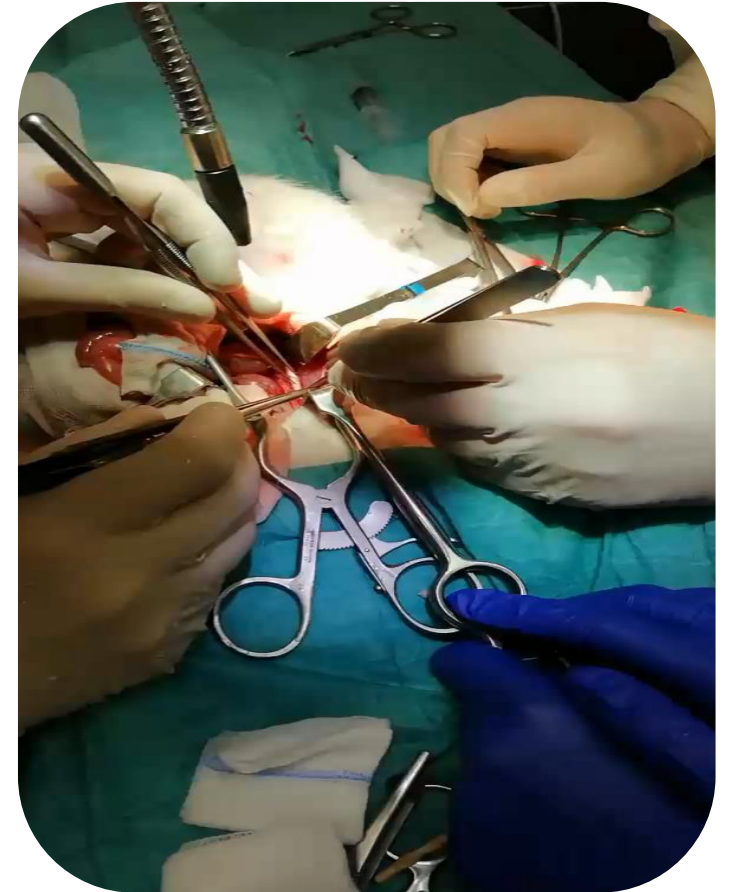
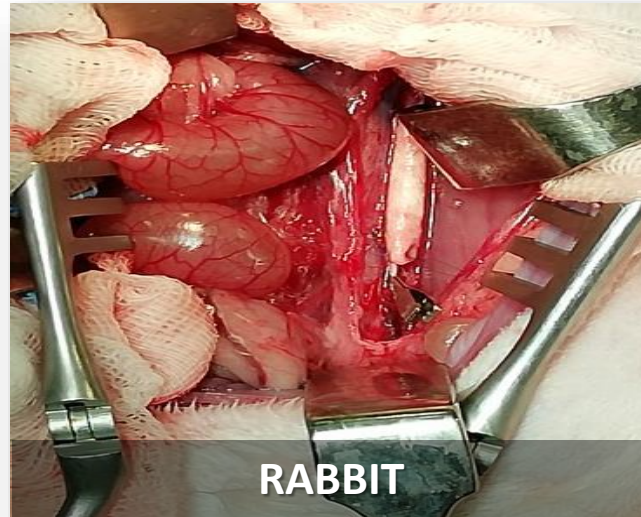
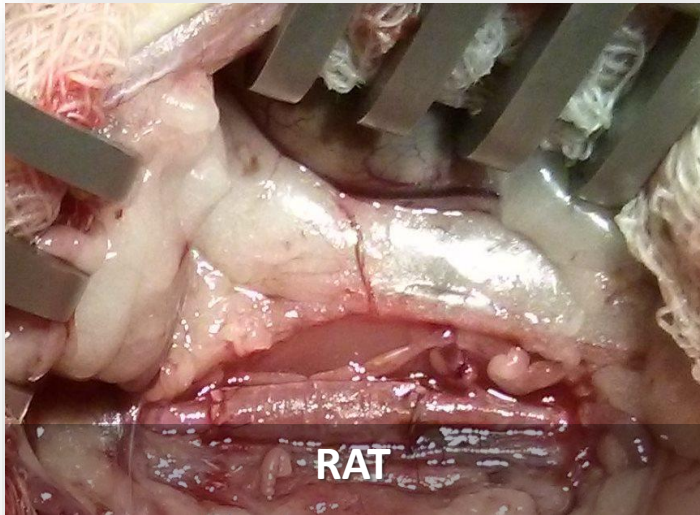
PCL:PGS scaffold (5.11 ± 1.11 μ m)



PCL:PGS scaffold functionalized with nanoparticles (2.46 ± 1.75 μ m)

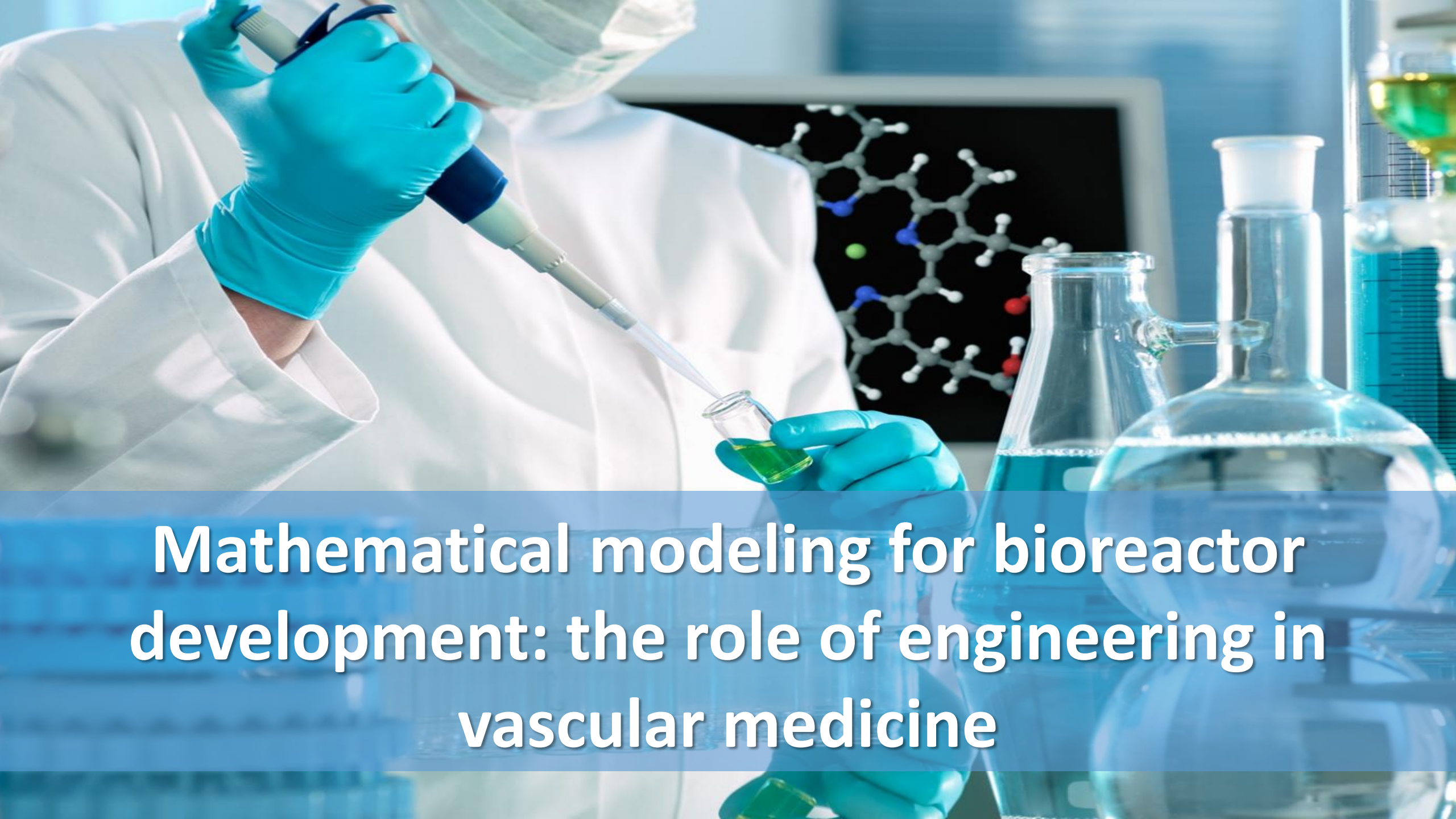


In vivo implants



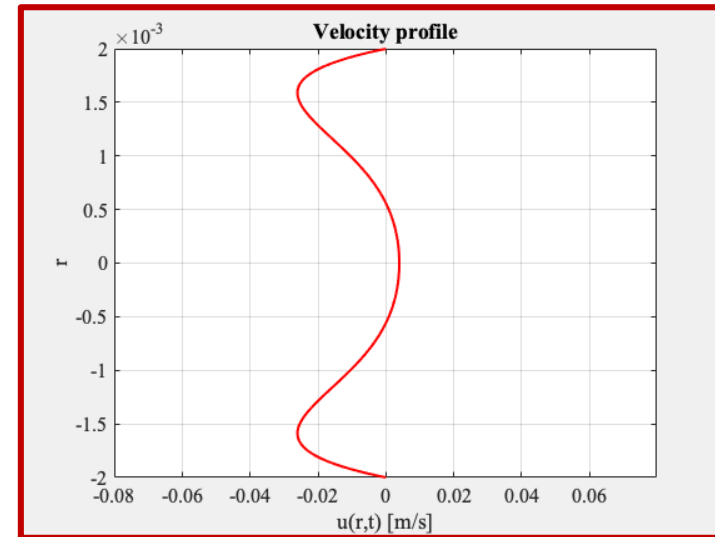
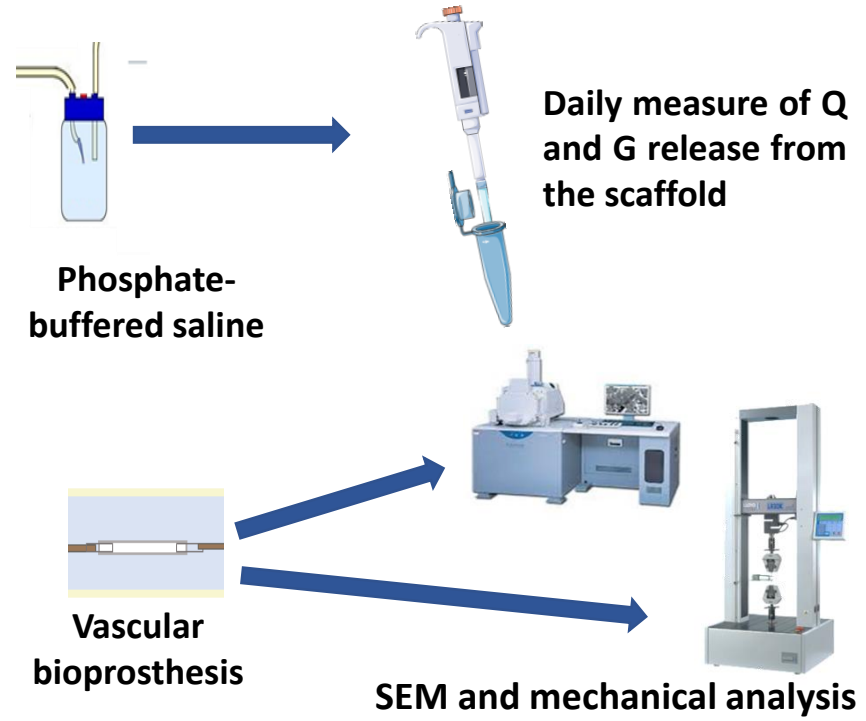
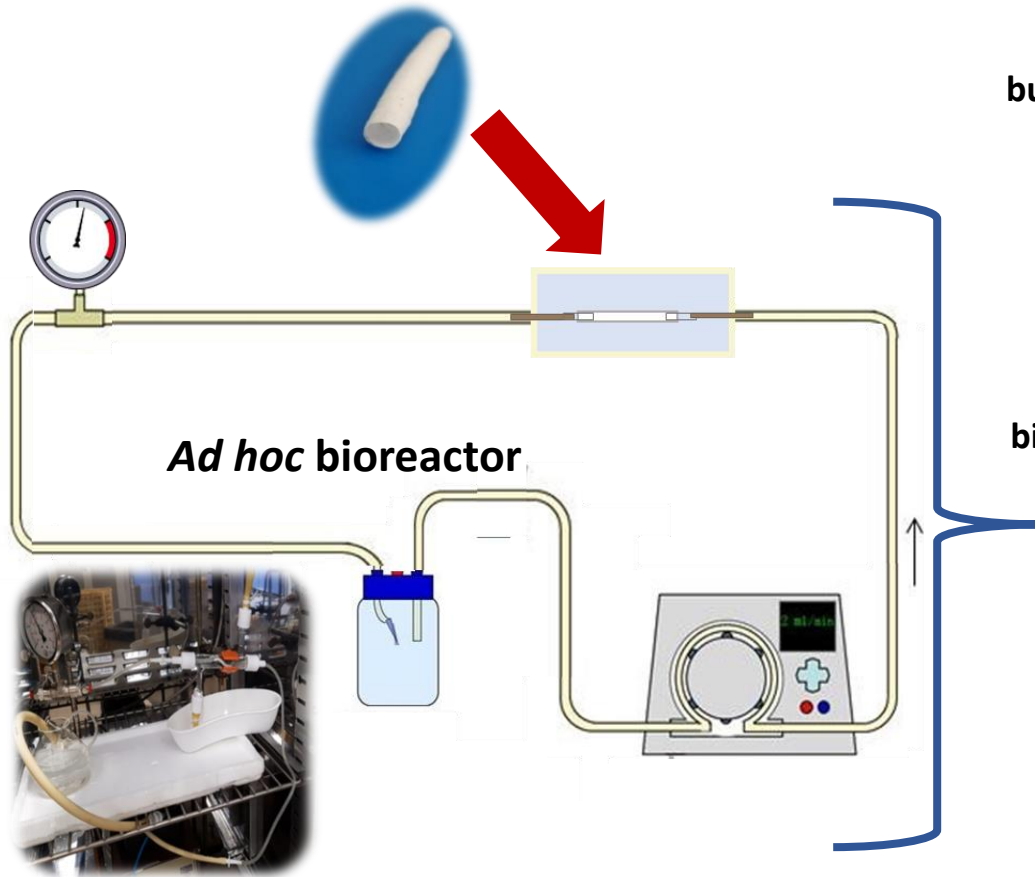
PATENT:

Perego P, Palombo D, Ferrari PF, Aliakbarian B, Pane B, Spinella GSG, 2019. Engineered biodegradable vascular bioprosthesis and their preparation procedures. Application number: 102019000014985, registered on 23rd August 2019.



Mathematical modeling for bioreactor development: the role of engineering in vascular medicine

In collaboration with:



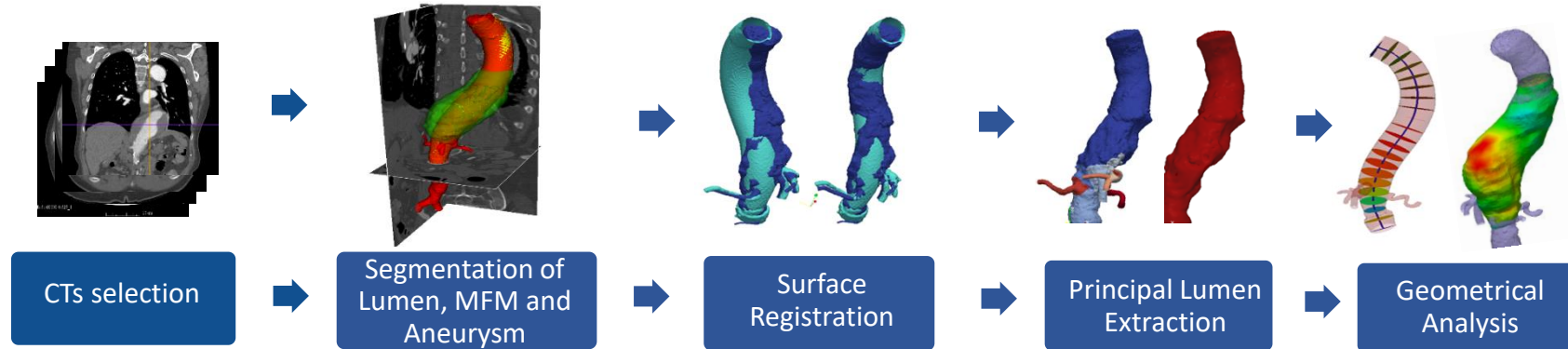
A 3D medical illustration of a blood vessel. The vessel is shown in a cross-section, revealing its internal structure. A metallic stent, composed of a series of interconnected rings, is positioned inside the vessel. The vessel is filled with numerous red blood cells, depicted as small, biconcave discs. The overall color scheme is dominated by shades of red and pink, with the stent appearing in a metallic grey. The background is dark, making the vessel and its contents stand out.

Vascular remodeling after endovascular treatment:
quantitative analysis of medical images

In collaboration with:



«Medical image analysis to measure the FU geometry changes of TAAAs treated with Cardiatis Multilayered Flow Modulator stent»



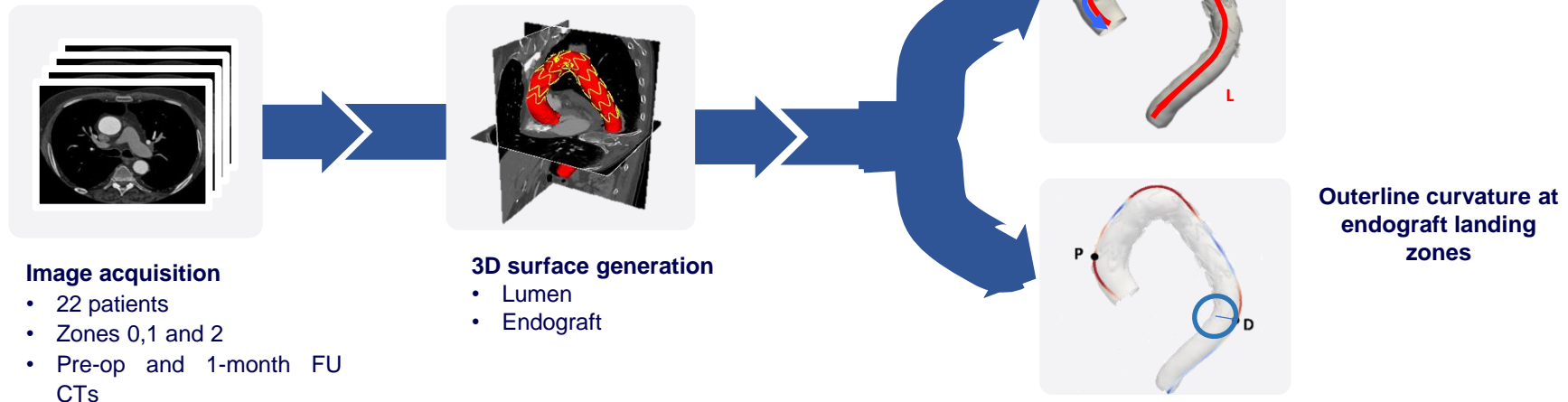
From CTs, verify, through geometrical analysis:

- **perfusion** of side branches;
- **centerline changes** induced by the Cardiatis MFM;
- presence/absence of **blood flowing in the aneurysm sac**;
- **morphological changes** of the **aneurysm sac**.

«Assessment of geometrical remodeling of the aortic arch and descending thoracic aorta after hybrid treatment»

Aim: Analyze the geometric changes of the **aortic arch** after hybrid treatment, with a particular focus on the **endograft landing zones**, attempting to enhance the understanding on the possible reasons for the development of device-related complications

Analysis Workflow: from CT scans to 3D geometric analysis

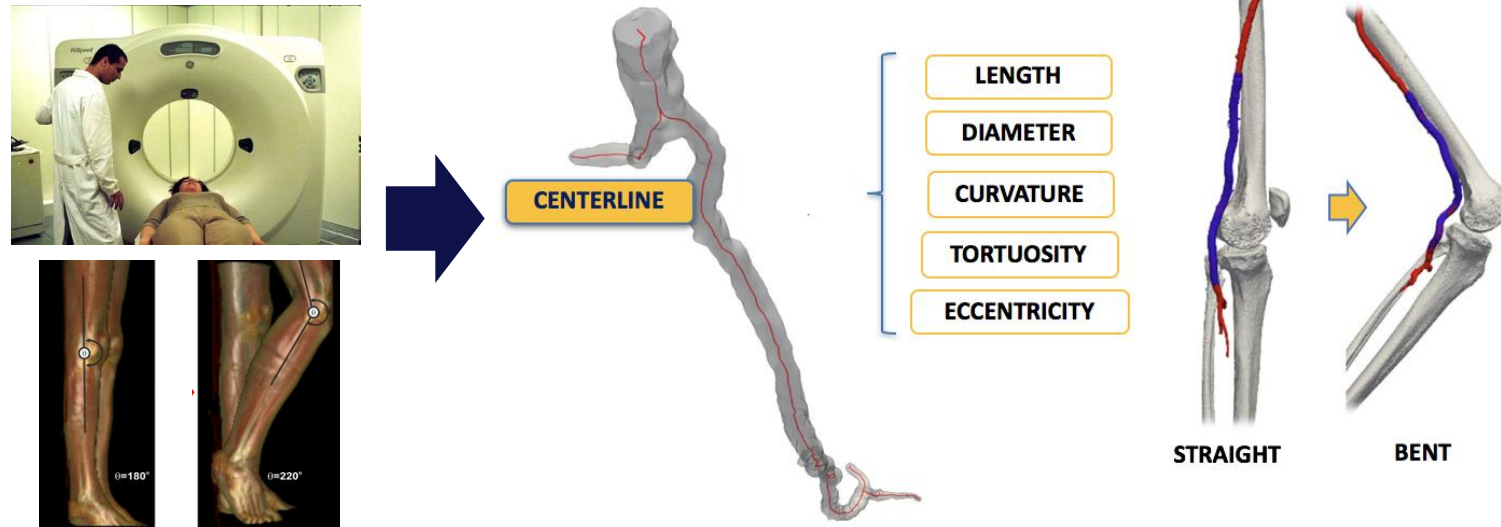


Our experience suggests that the **physiological curvature** of the aortic arch **was altered after hybrid treatment**, probably due to **spring-back force (SBF)** exerted by the stent-graft at both ends of the stent-grafts.

«Impact of peripheral endovascular repair on femoral popliteal artery kinematics: from clinical experience to in vivo biomechanical modeling»

Aim: evaluate morphological changes of stented FPA due to limb flexion

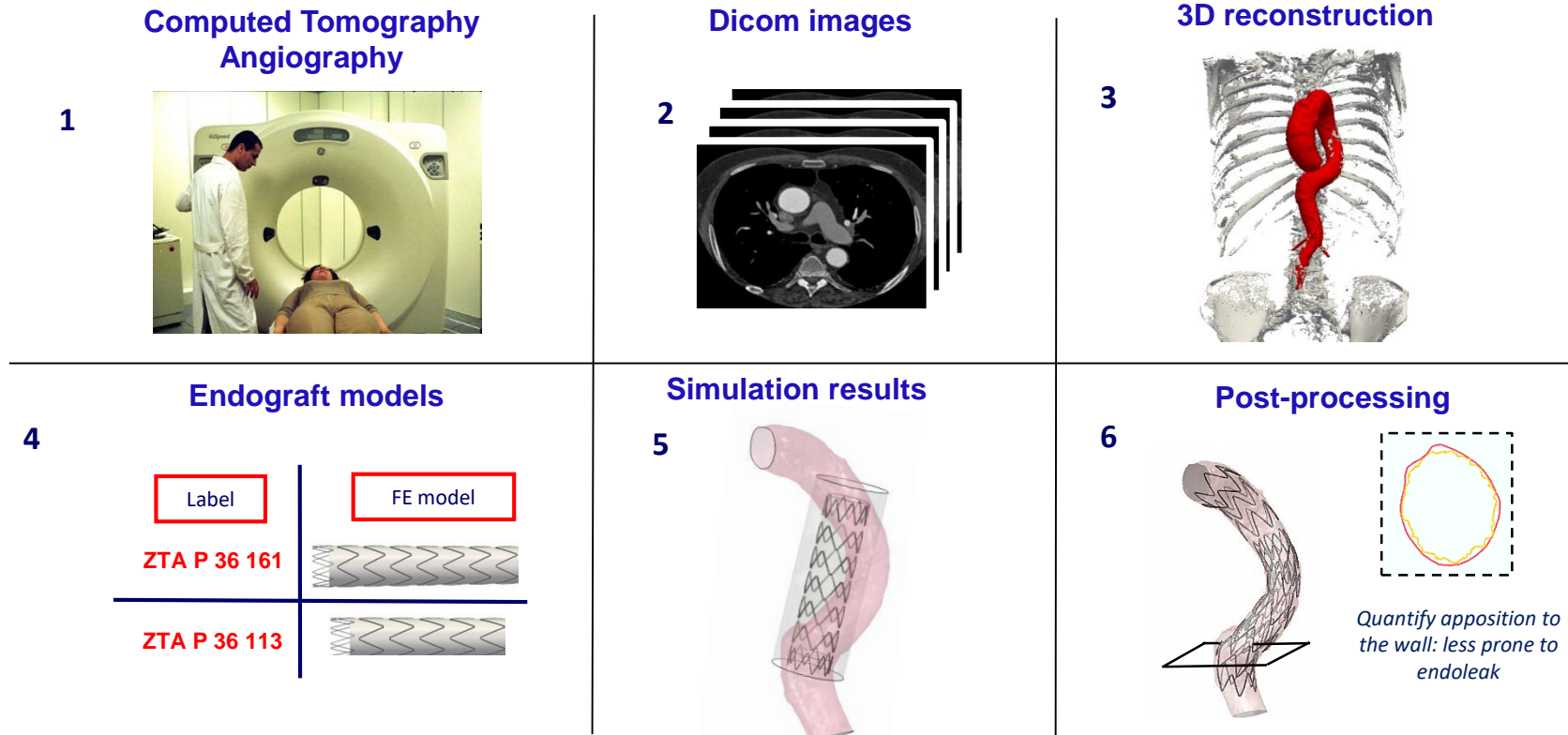
- definition of an acquisition protocol with extended and flexed knee
- vessel segmentation and geometric analysis



Credits to: Dr. Cittadini Giuseppe, Dr. Salsano Giancarlo (UO Radiology)

Spinella G, Finotello A, Pane B, Salsano G, Mambrini S, Kamenskiy A, Gazzola V, Cittadini G, Auricchio R, Palombo D, Conti M. In-vivo morphological changes of the femoro-popliteal artery due to knee flexion after endovascular treatment of popliteal aneurysm. *Journal of Endovascular therapy*. 2019

“Endovascular implants: from medical images to patient specific structural simulations”



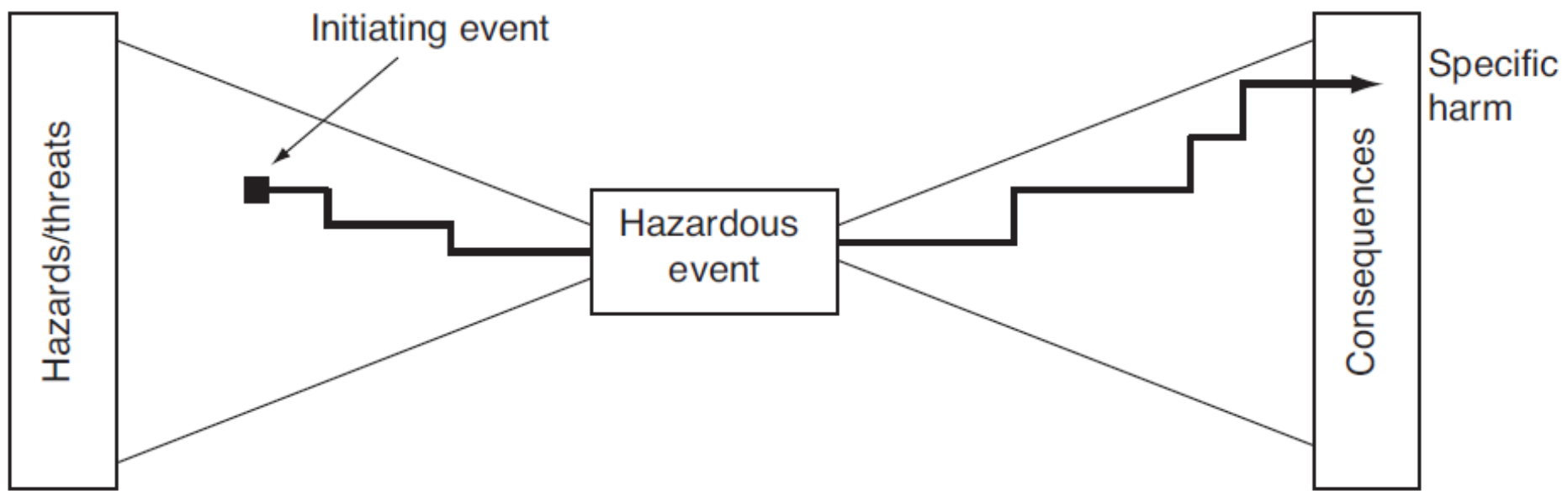
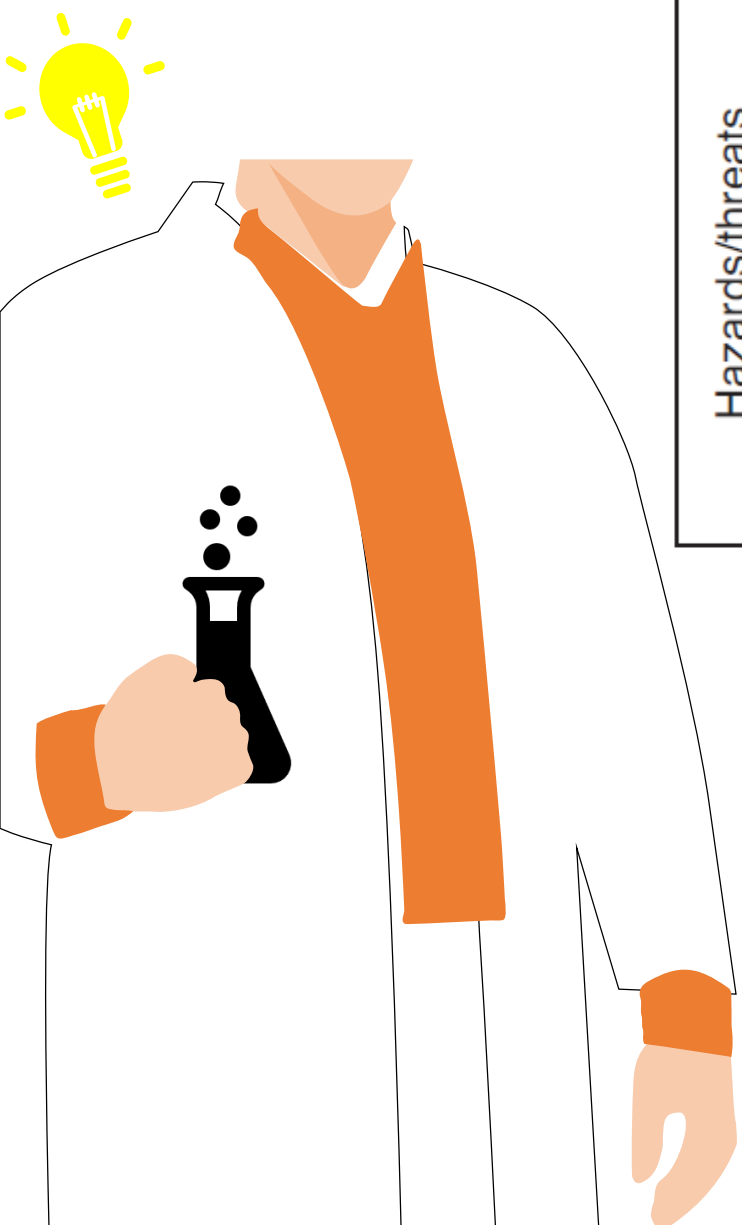
ESCVA 2018 YOUNG SURGEON AWARD 1st PLACE

A. Finotello, G. Spinella, M. Conti, B. Pane, F. Auricchio, and D. Palombo. *Toward the use of patient-specific structural simulations of endovascular repair in the clinical practice.*



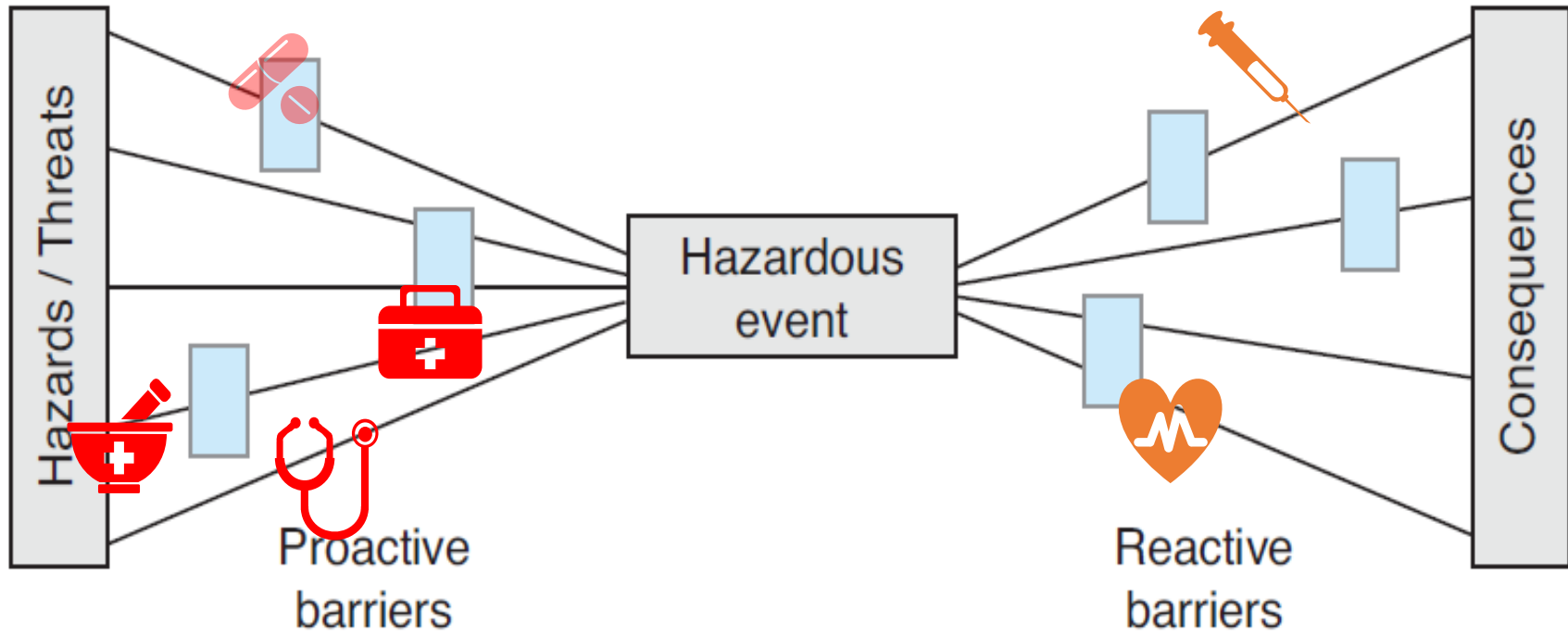


Bow-tie approach:
from process safety engineering to
medical fields



In collaboration with:





In collaboration with:

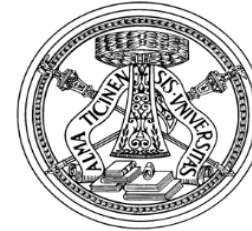
DICCA

Collaboration with Engineering Schools

Department of Civil, Chemical and Environmental Engineering, University of Genoa, Italy;



Department of Civil Engineering and Architecture, University of Pavia, Italy;



Department of Informatics, Bioengineering, Robotics and System Engineering, University of Genoa;



Department of Industrial Engineering, University of Salerno, Italy;

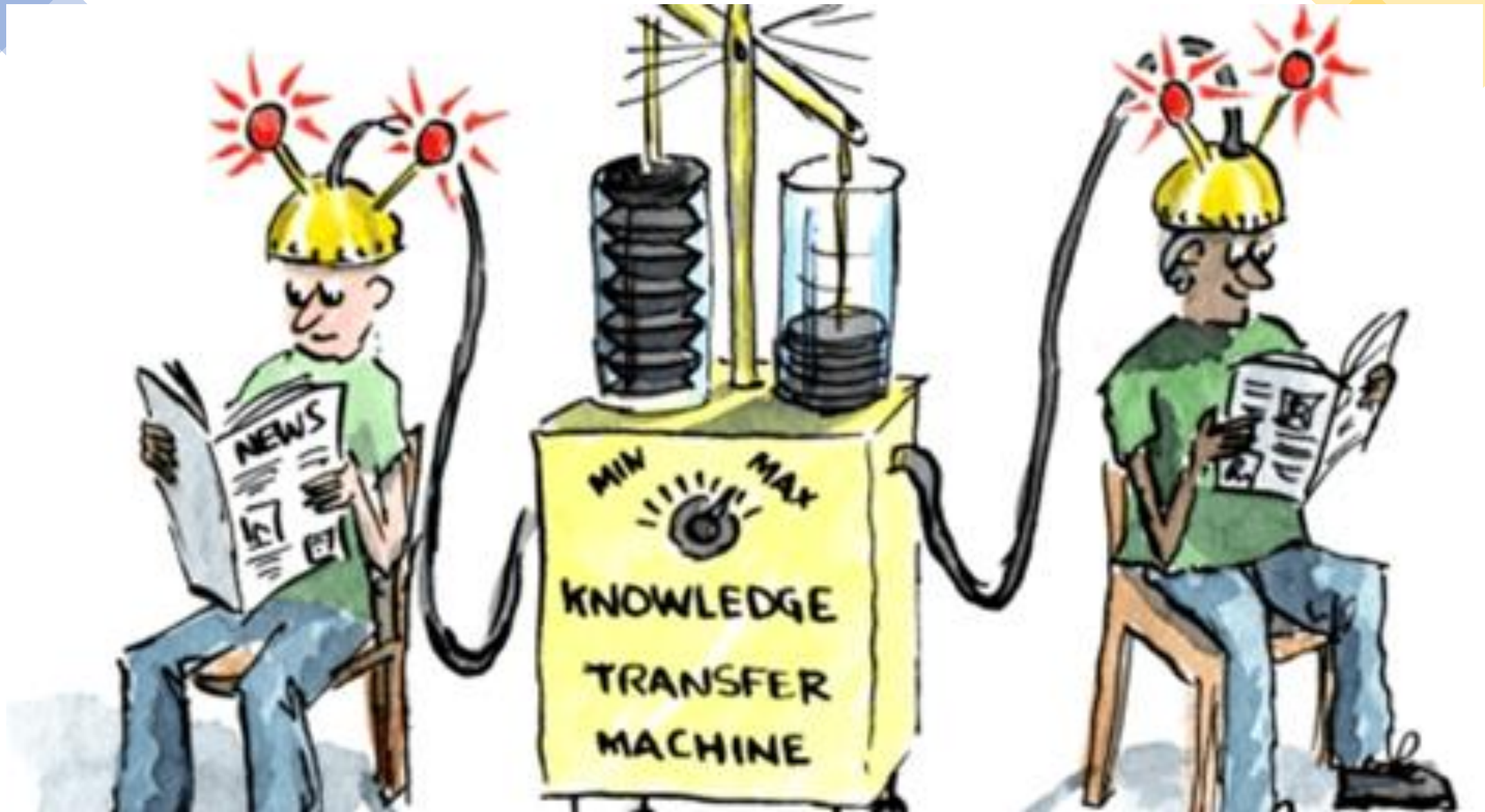


Department of Materials Science and Physical Metallurgy, Polytechnic University of Bucharest ,
Romania;

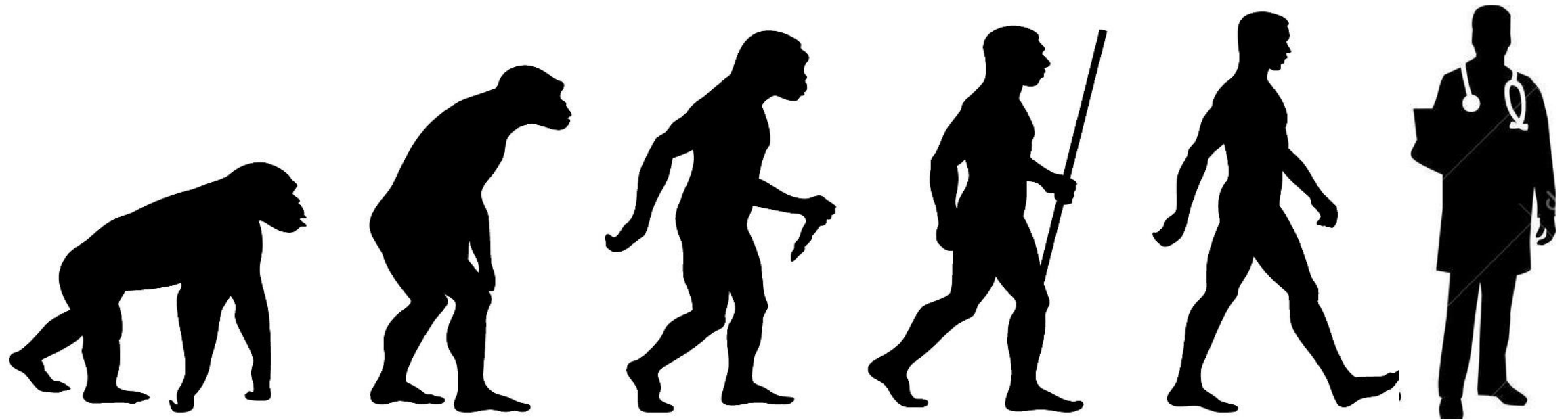


Massachusetts Institute of Technology, Boston, United States of America

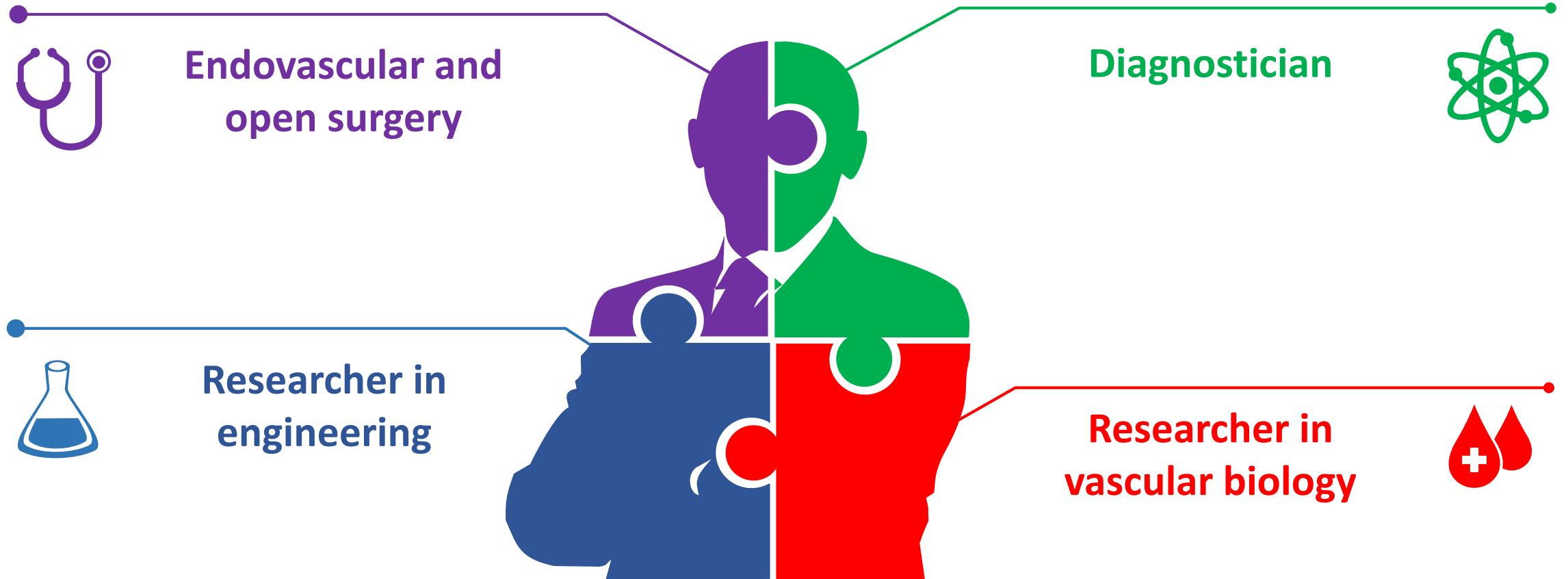




No longer just a surgeon or an engineer...



...but a «TRANSDISCIPLINAR SPECIALIST»



TEAMWORK...



...TURNS A PROBLEM INTO A SOLUTION



Together it's easier!



**Polytechnic School
(architecture and engineering)**



**San Martino Polyclinic Hospital
Pharmaceutical and Medical School**



«Surgengineering»



Thank you