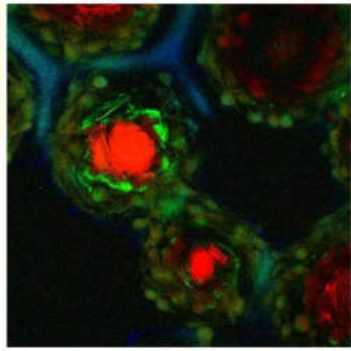
Biomaterial Risk assessment for medical devices and tissue engineering

Nihal Engin Vrana
SPARTHA Medical, CEO
University of Strasbourg
INSERM UMR 1121
SENET Webinar Series October 2020



All Opinions expressed are personal and not binding for SPARTHA Medical

Nihal Engin Vrana, Strasbourg, France

NE Vrana, CEO SPARTHA Medical
Affiliated Researcher INSERM UMR 1121
Scientific Coordinator of H2020 PANBioRA project

- >10 years experience in medical devices
- Involved in the development of 2 CE marked implants

Previous projects: IMMODGEL (FP7 Scientific Coordinator), FASSIL (FUI, Industrial partner)

Interest in 3D printing: Originally with Bioprinting, Personalised Intralaryngeal Implants (Silicone based), Surface treatments of implantable structures

Involved in the development of World's first Artificial Larynx (Published in New England Journal of Medicine)

Development of a Swallowing Robot based on personalised Laryngopharyngeal models

Background in Tissue Engineering, Hydrogels, in vitro models and Biomaterial testing

Advanced Biomaterial Based Systems-How to Incorporate the Personalisation Aspect?

Our Research

Use of Tissue Engineering Technologies in Hybrid, Mechanically Active Implant Development

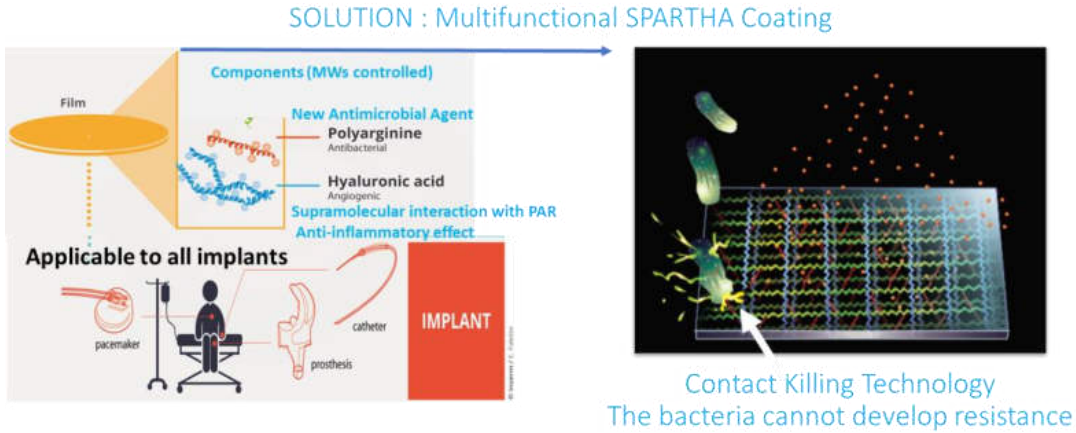
Incorporation of Immune Components in Tissue Engineering (Immune Assisted Tissue Engineering)

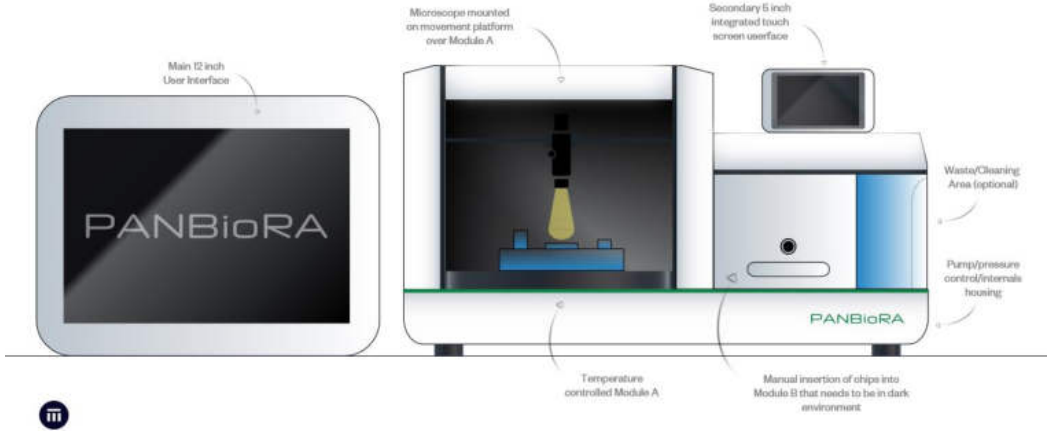
Personalisation of Implantable Device Host Interfaces (Immunoprofiling and Coatings)

Real-time monitoring of Implanted structures

Future Aim:

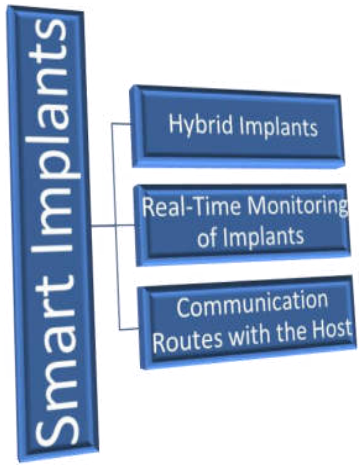
Developing new organs, Use of Tissue Engineering for Biotic Games

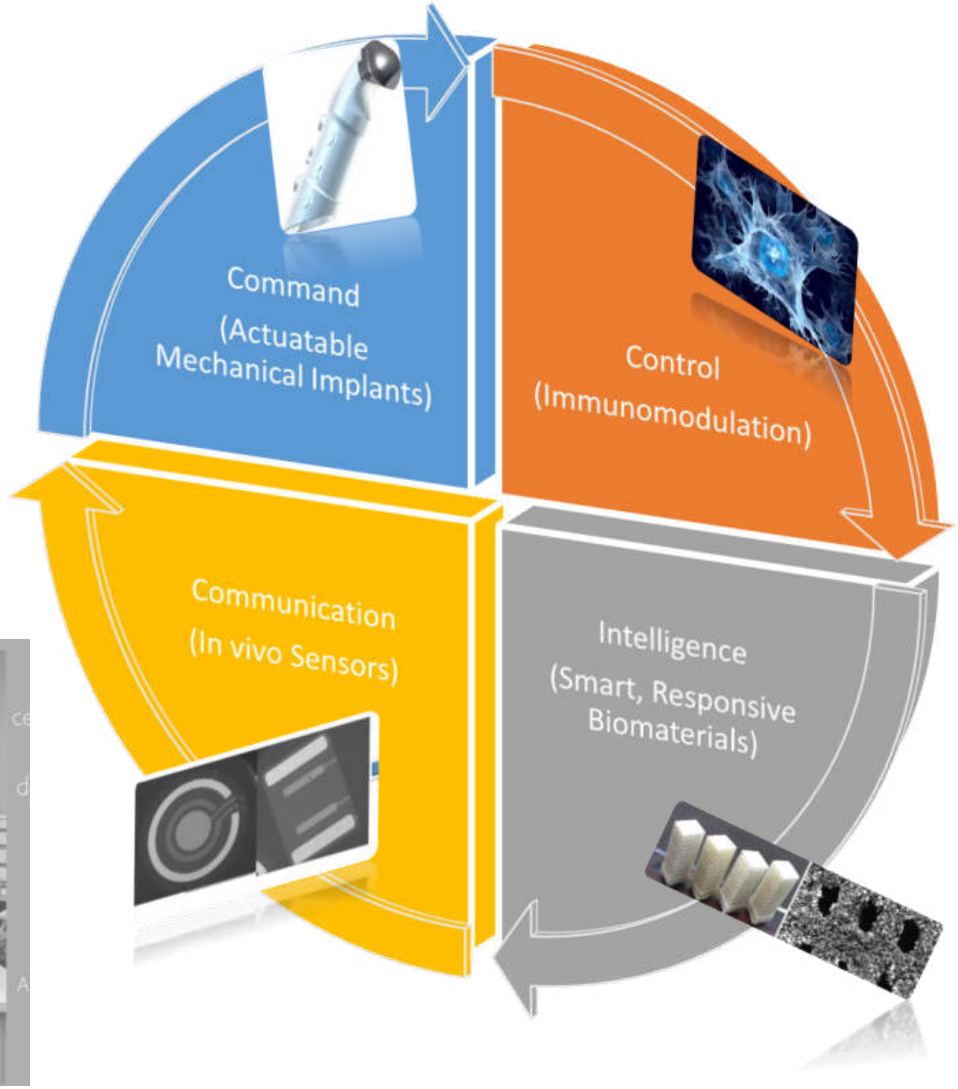




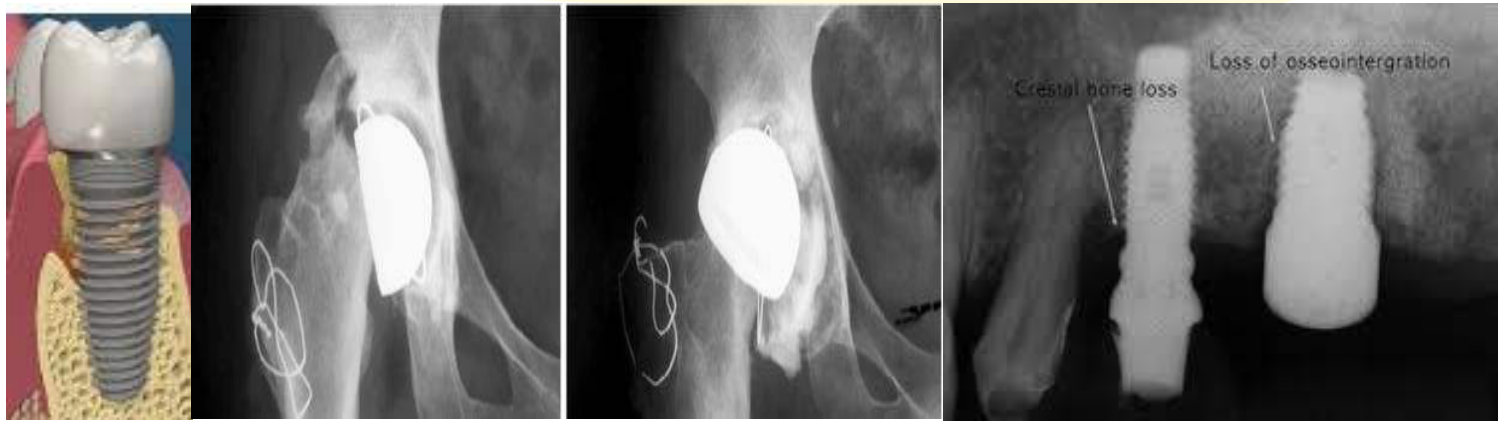
Taking Control of Biomaterial-based Systems
C3I (Command, Control, Communication, Intelligence)

- Command: The exercise of authority based upon certain knowledge to attain an objective.
- Control: The process of verifying and correcting activity such that the objective or goal of command is accomplished.
- Communication: Ability to exercise the necessary liaison to exercise effective command between tactical or strategic units to command.
- Intelligence: Includes collection as well as analysis and distribution of information.





Biomaterial Related Risks



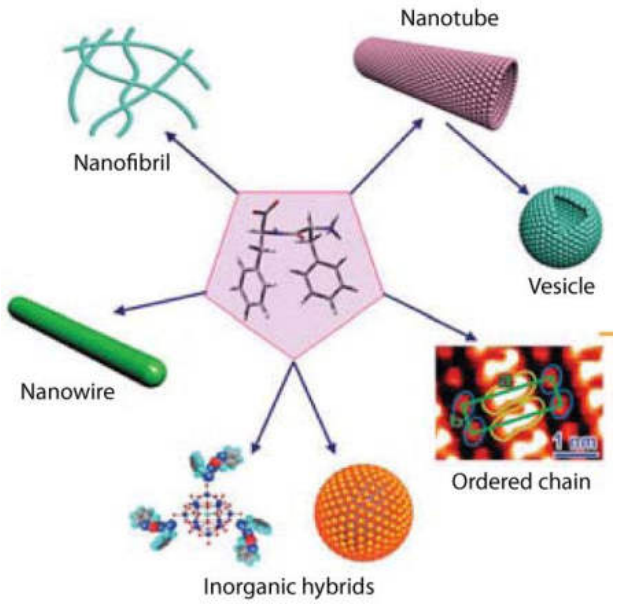
A multi-scale problem:

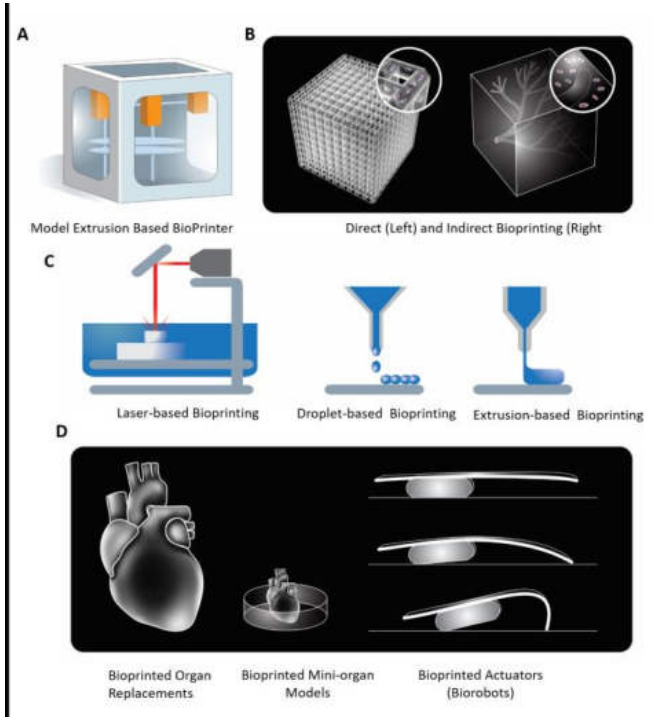
1) Complications with the existing biomaterials

- Peri-implantitis,
- Chronic Inflammation,
- Patient specific reaction to biomaterials
- Long-term effects (mechanical)

2) Potential risks with new biomaterials

- Potential epitope mimicry (immune reaction)
- Unforeseen secondary effects
- Unexpected short-term/long-term activities





A current example: Textured Breast Implants

- The textured breast implants are put into market as they were shown to decrease fibrous encapsulation (capsular contracture).
- However, now, it is shown that they are linked with anaplastic large cell lymphoma and being banned.
- We lack the tools now to detect these potential side effects

The New York Times

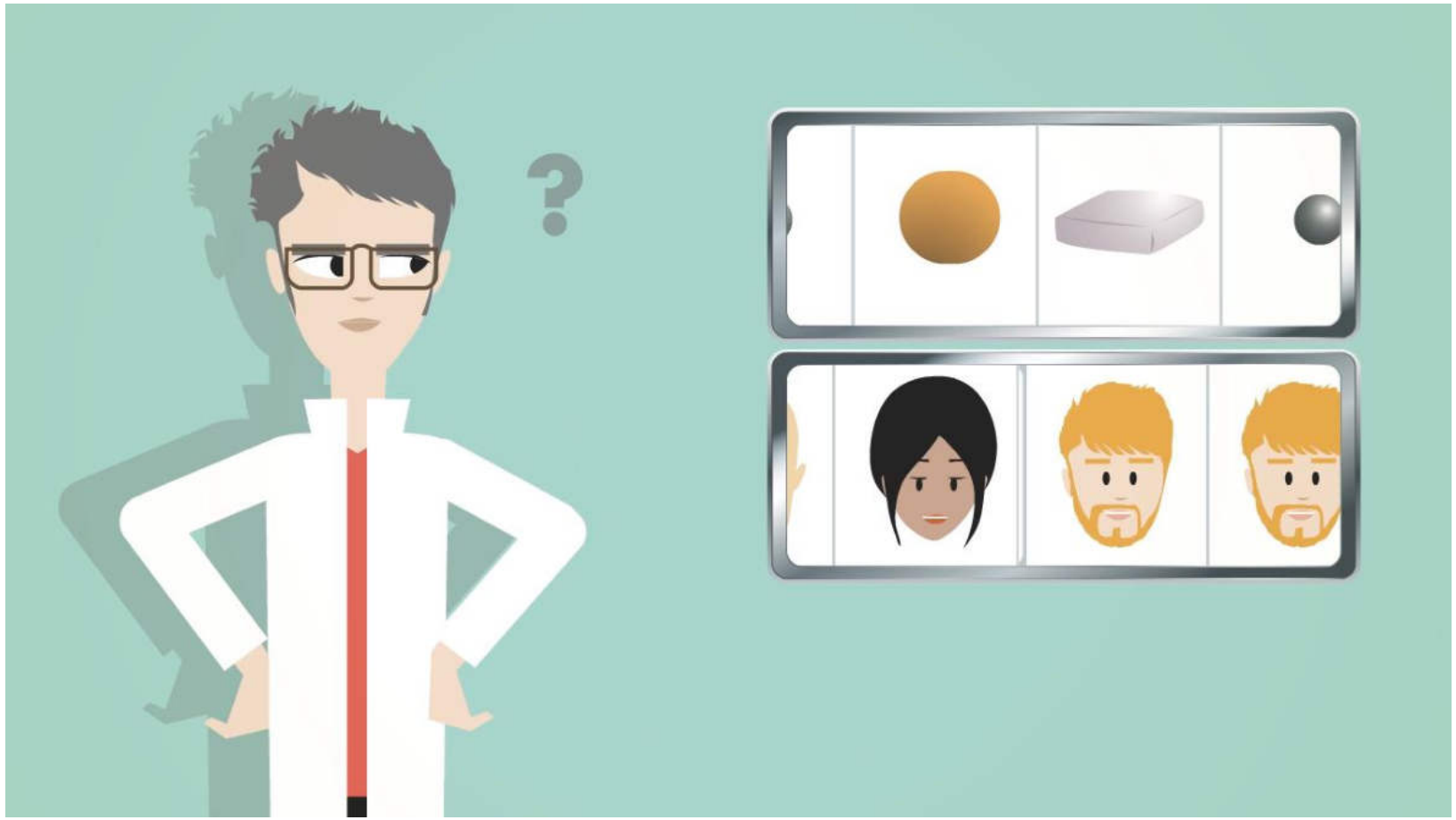
France Is First to Ban Breast Implants Linked to Rare Cancer

Open Access Protocol

BMJ Open **Complications in breast augmentation with textured versus smooth breast implants: a systematic review protocol**

Chenglong Wang,[1] Jie Luan,[1] Adriana C Panayi,[2] Dennis P Orgill,[3] Minqiang Xin[1]

PANBioRA



PANBioRA

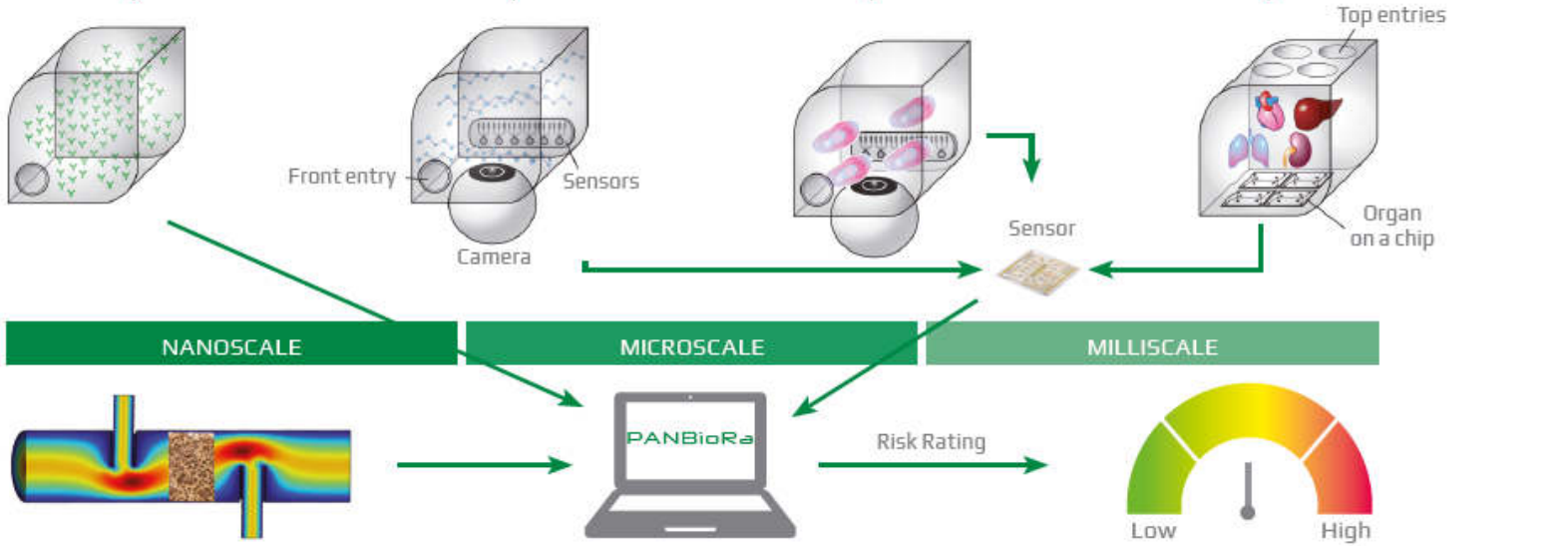
Components of the PANBioRA Biomaterial Risk Assessment System

ANTIBODY TESTING
Patient-specific interactions between biomaterials and the immune system will be assessed using the ground-breaking Mimotope Variation Analysis technology.

BIOMATERIAL TESTING
Biochemical responses of cells to the presence of biomaterials will be monitored in real time and by integrated biosensors. In addition, PANBioRA includes cytotoxicity and genotoxicity tests with microscopic real-time monitoring capacities

CELL TESTING
Real-time electrochemical sensing will be used to determine the cellular response to a given biomaterial. A set of cytokines released to the extracellular environment will be used as biomarkers to assess the cell response to different biomaterials.

ORGAN ON A CHIP
Respiratory epithelium, gut and liver tissues will be miniaturized into organoids on chip to allow the determination of possible systemic and target organ-specific effects in both healthy and disease conditions.



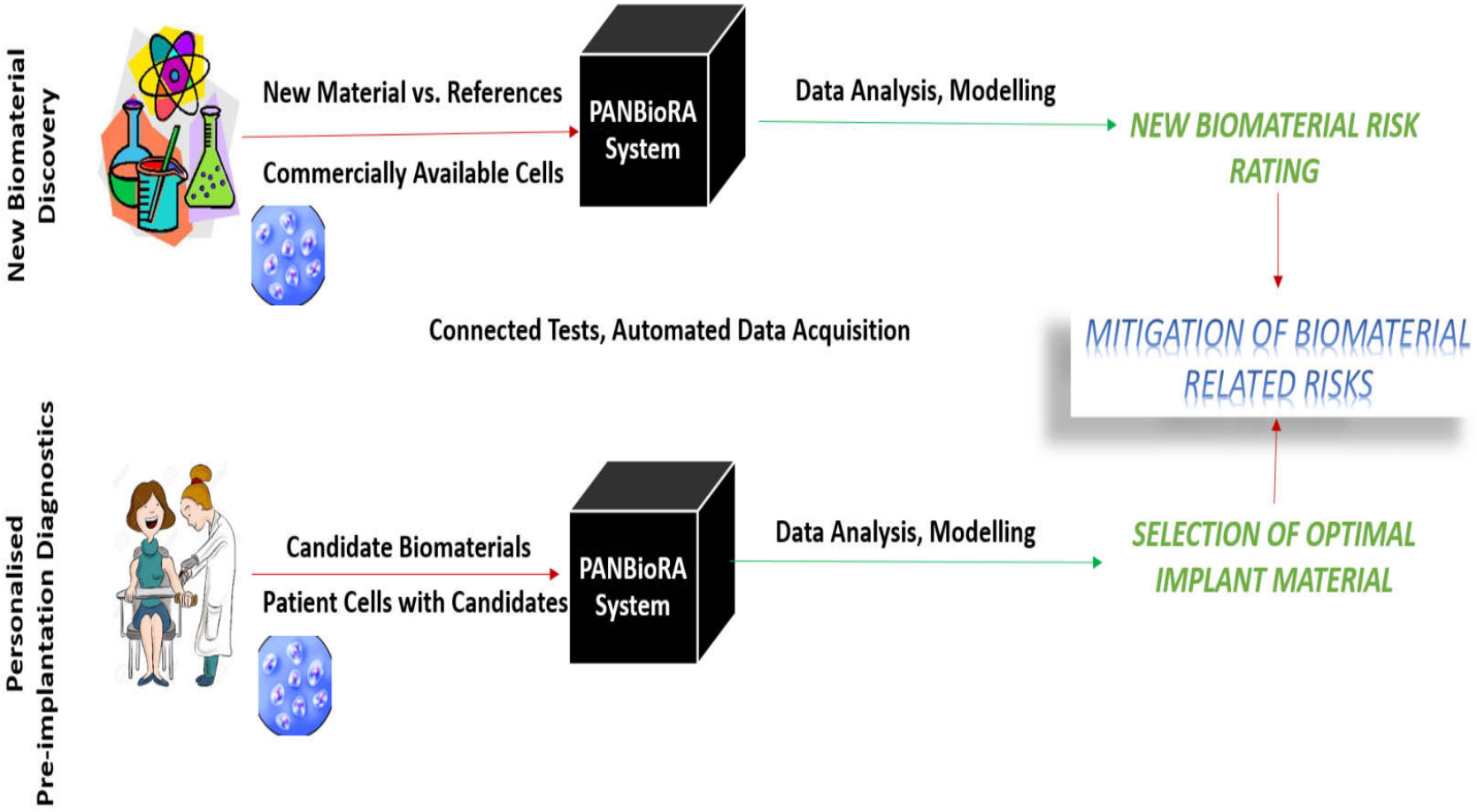
SIMULATIONS
Potential risks that are difficult to assess experimentally – such as explosion hazards or full-scale biomaterial/microbiota interactions – will be covered by simulations developed within the project.

DATA ANALYSIS
The readouts of the modules will be fed into a model developed within PANBioRA using known biocompatible and hazardous materials to provide a quantitative risk assessment.

RISK RATING
PANBioRA will develop a risk rating system that will display the suitability of the tested biomaterial.

Objectives

PROPOSED USE OF PANBioRA System



PANBioRA

SPARTHA MEDICAL

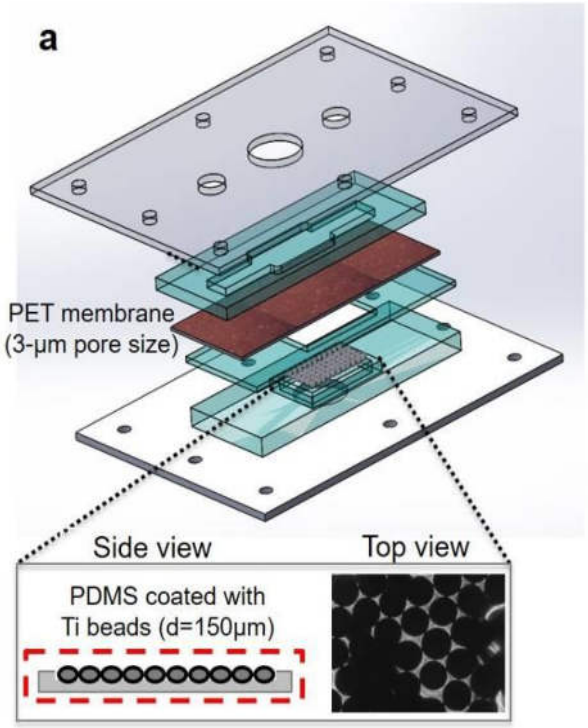
Panbiora	Elvesys microfluidic Innovation center SAS
Pro-Active	Consejo Superior de Investigaciones Cientificas
Dolmen Design And Innovation	Steinbeis Advanced Risk Technologies Institute doo Kragujevac
Aalto University Foundation	Dublin City University
Biodevice systems s.r.o	Steinbeis Advanced Risk Technologies GmbH
Turgut Ozal Education SHA – Epoka University	Inserm UMR-S 1121, Biomaterials and Bioengineering
Protobios LLC	Commissariat à l'énergie atomique et aux énergies alternatives
The University of Nottingham	Centre Hospitalier Universitaire de Liège

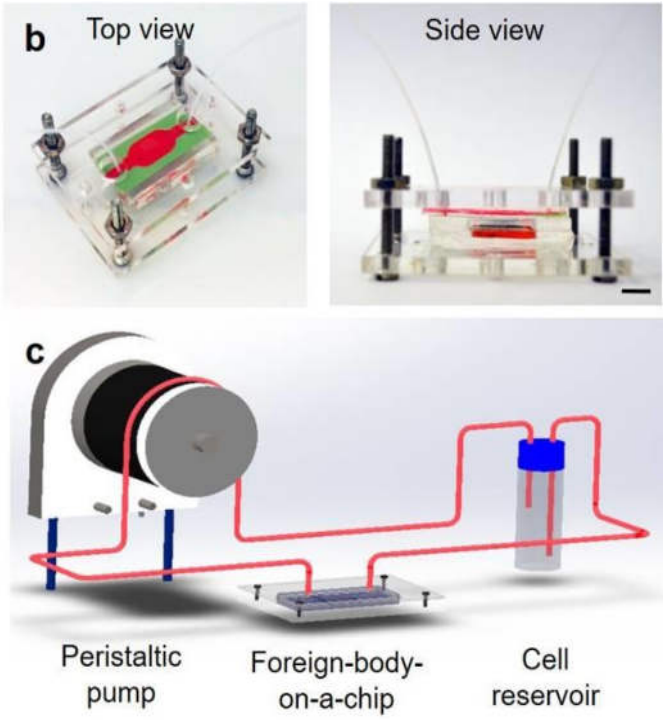
17 partners, 8 M€ total Budget
SPARTHA Accesion Oct 2019

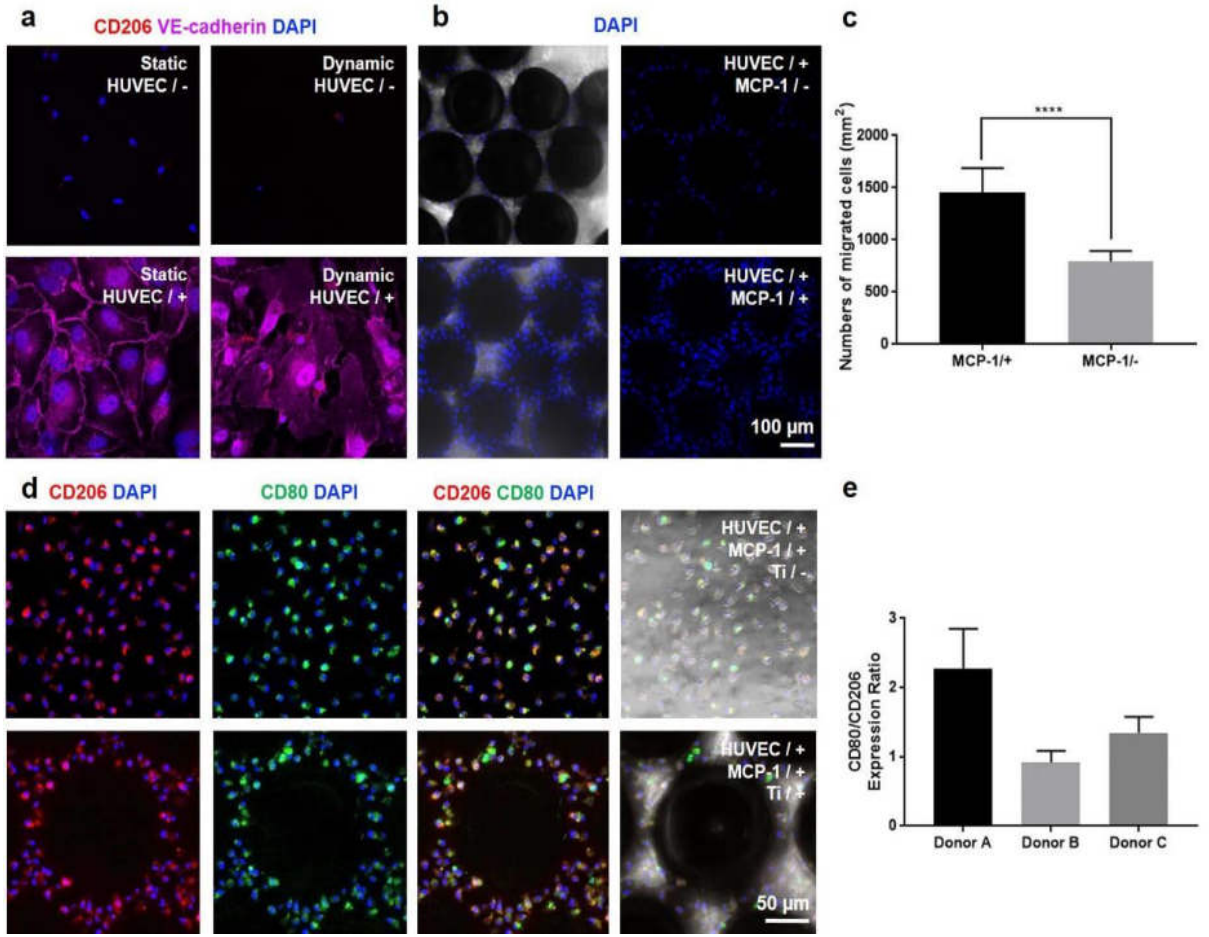
EU Horizon 2020 project :

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 760921

Foreign Body Response on a Chip



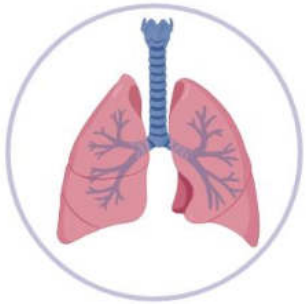


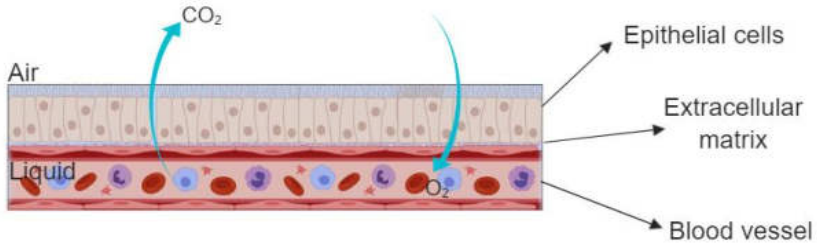


Sharifi et al. Advanced Healthcare Materials, in press 2019

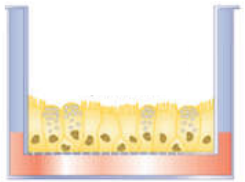
Task 2.1 Fabrication and characterization of biomimetic *in vitro* tissue models for epithelial barriers and liver tissue models

Lung model

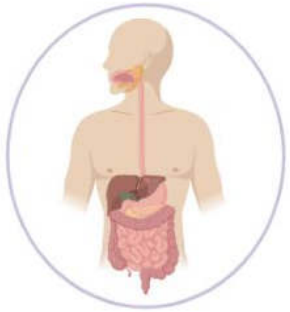


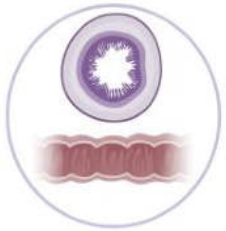


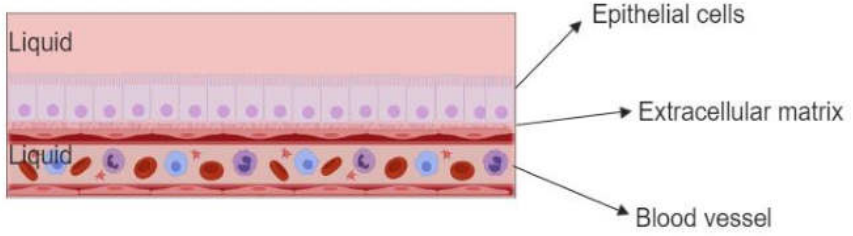
Calu-3



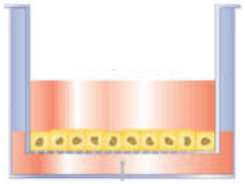
GI model



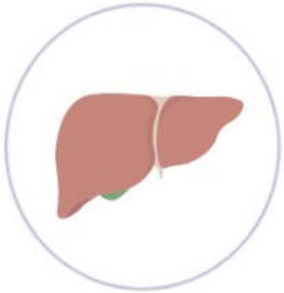


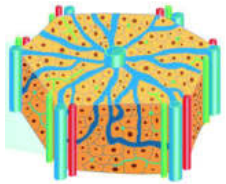


Caco2

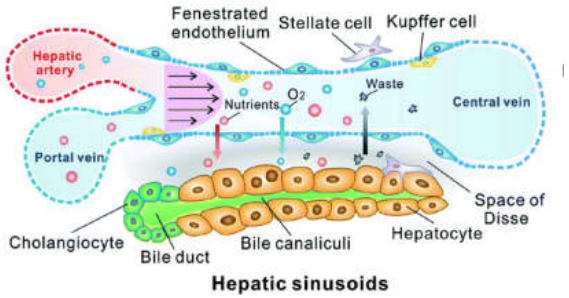


Liver model



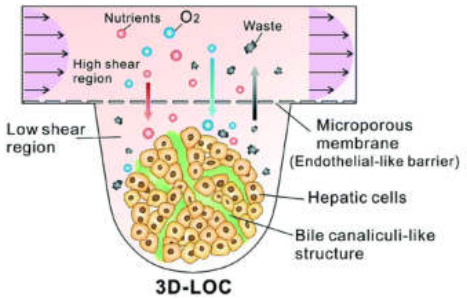


Hepatic lobule



Hepatic sinusoids

HepaRG

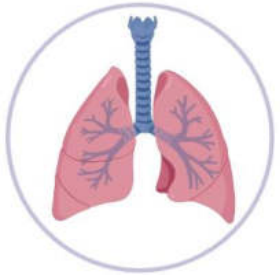


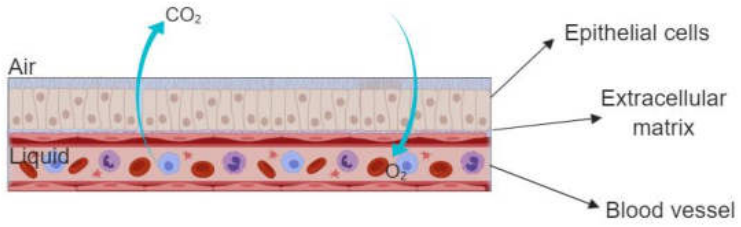
3D-LOC

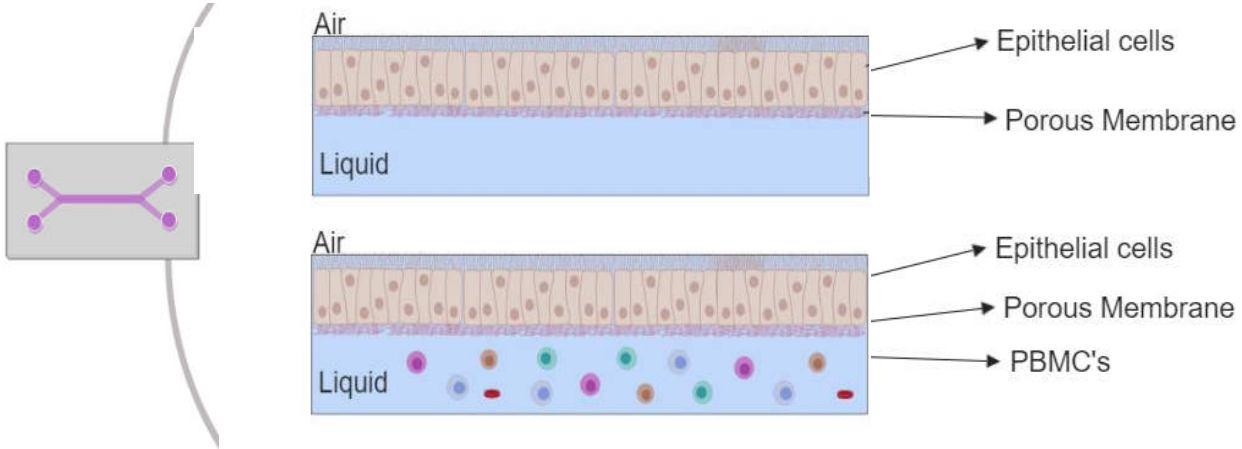
Developing immune component tissue models and optimised material delivery methods under flow and static conditions

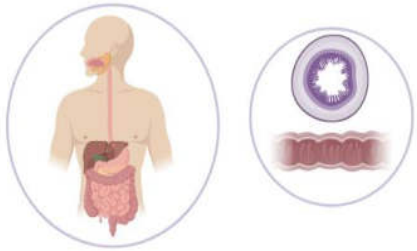
PANBioRA

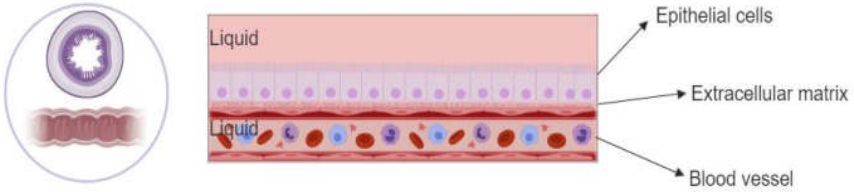
Epithelial systems

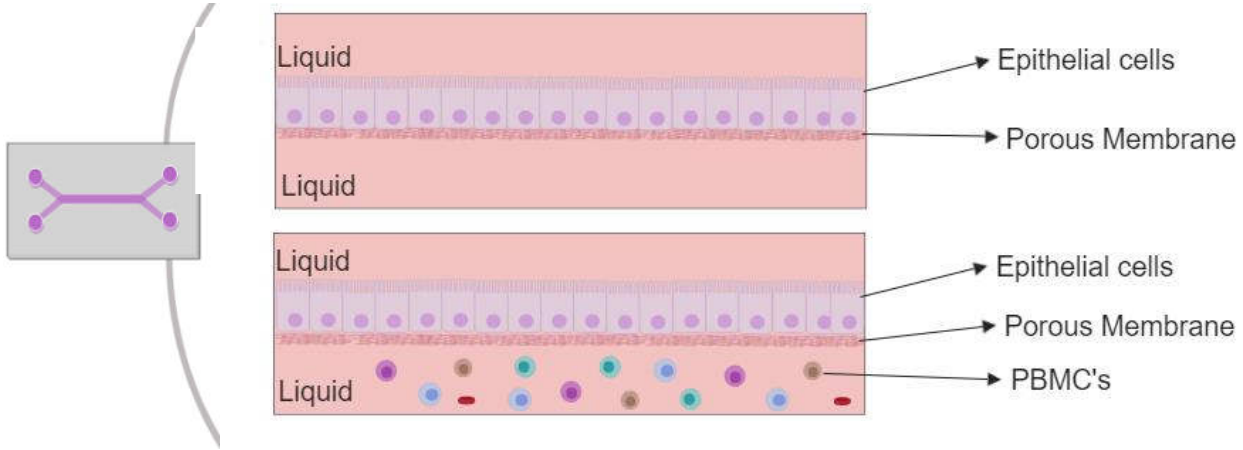










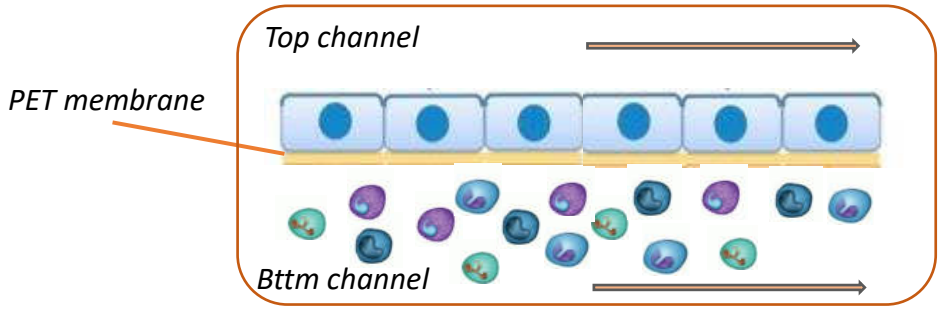


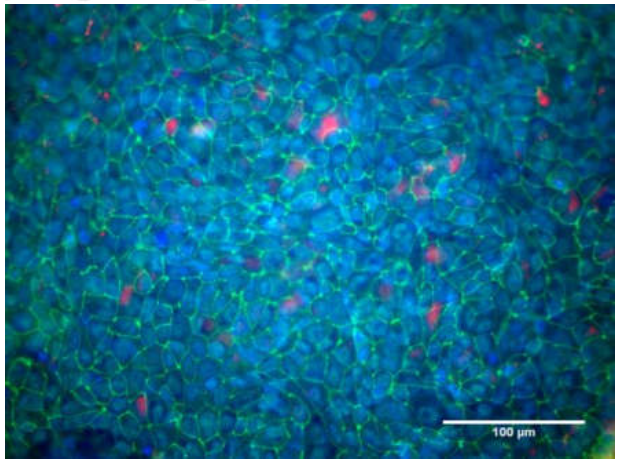
Developing immune component tissue models and optimised material delivery methods under flow and static conditions

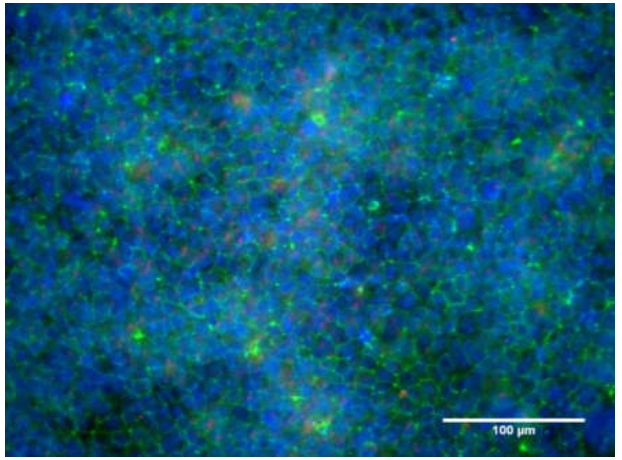
PANBioRA

Immune component Respiratory and GI epithelial systems (lung and gut):

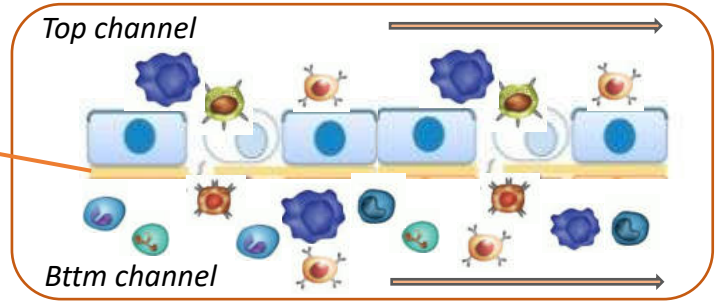
Normal flow conditions



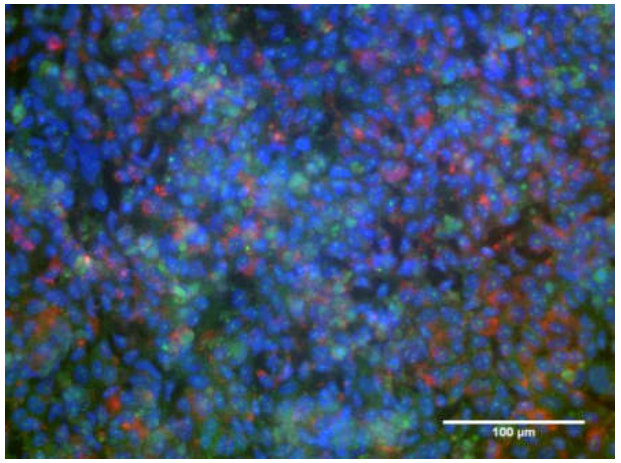




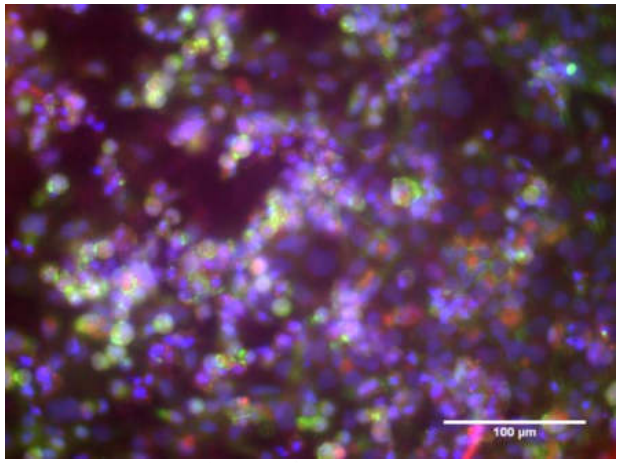
Stimulated flow conditions



Calu-3

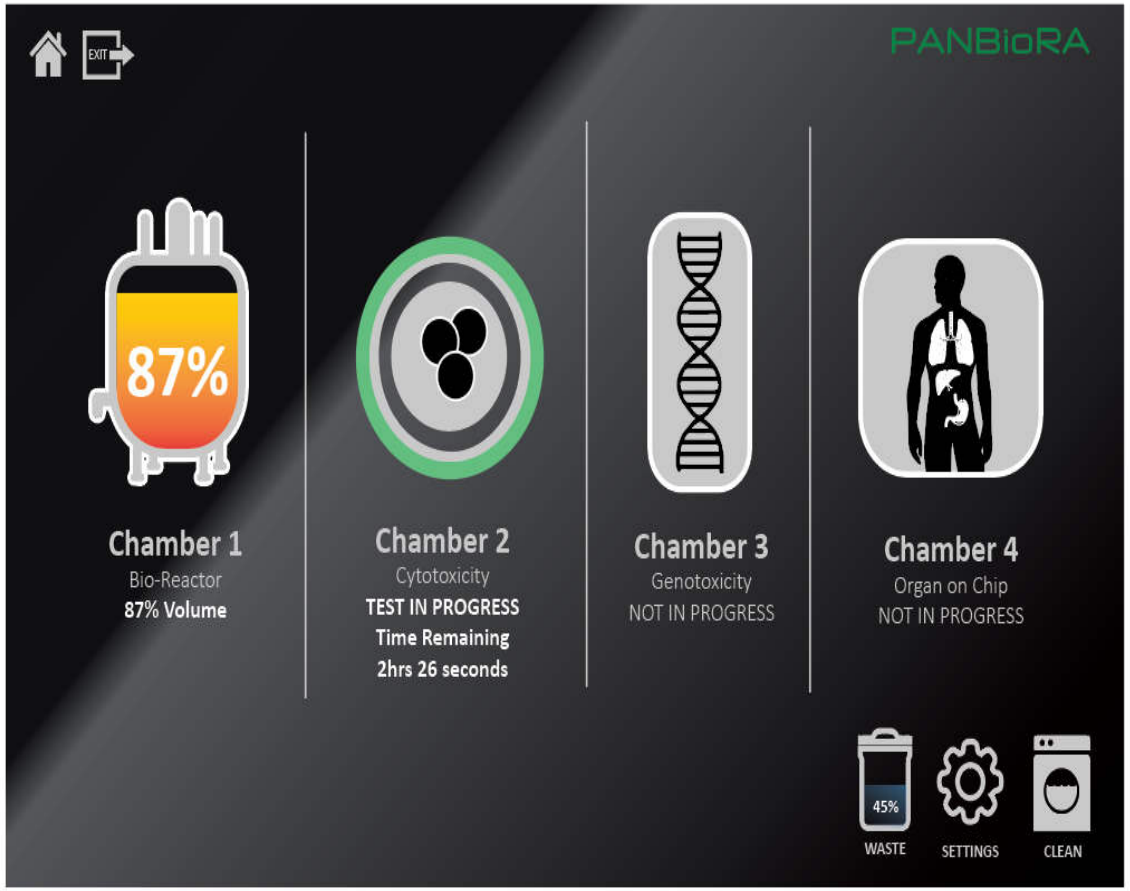


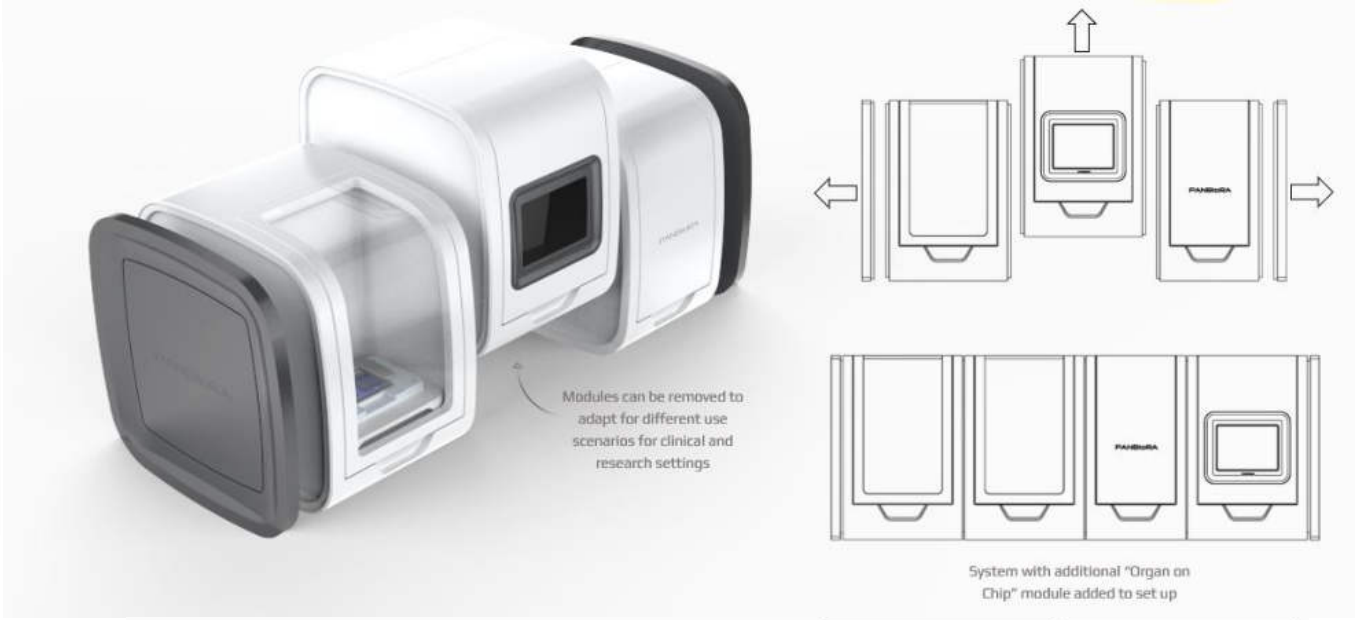
Caco2

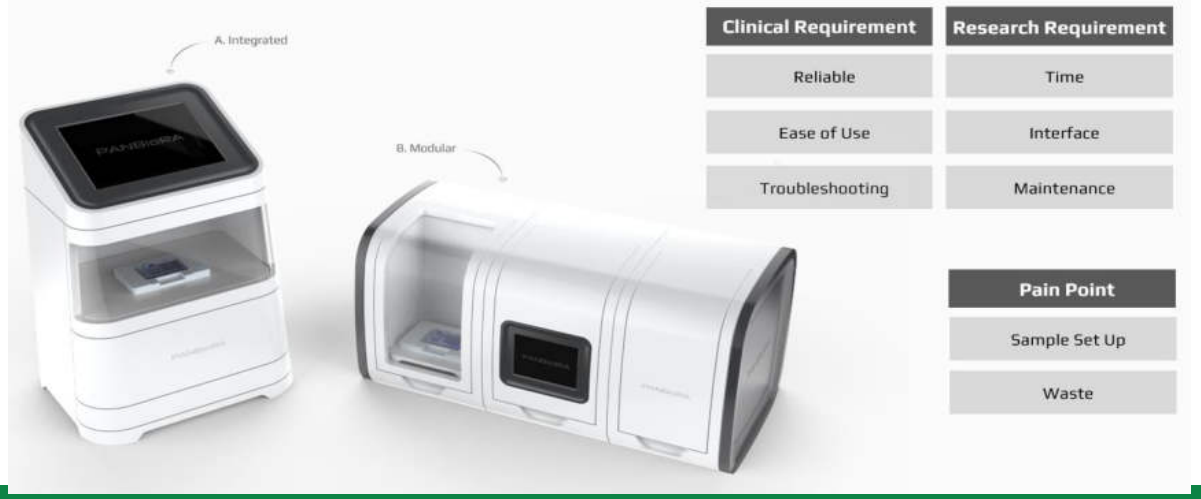


Blue- nuclei; Green-tight junctions; Red-PBMC's

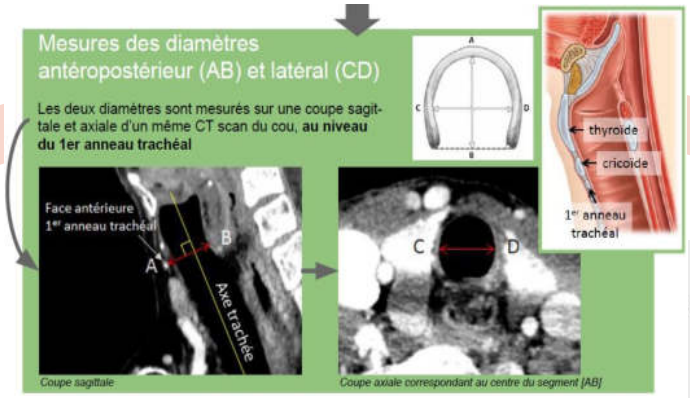
PANBioRA Modular Biomaterial Testing Instrument





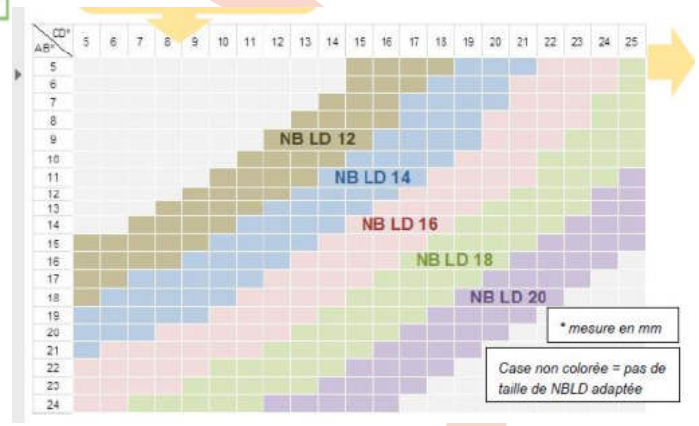


3D-Printed Intralayrngeal Implant Production



1. CT scan

2. Initial sizing



3. Designs based on extracted info from CT scan converted to STL

4. G-Code generation and 3D printing

5. Post-treatments

Surface treatments to decrease surface roughness (for less inflammation

6. Packaging and Sterilisation

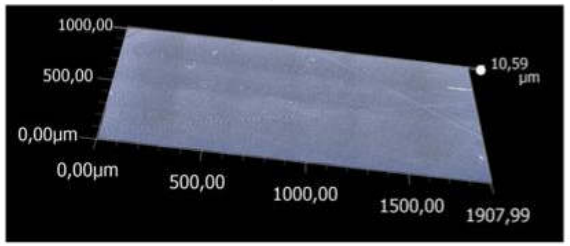
PRODUCTION

Effect of 3D Printing of Implants on Surface and Biomechanical Properties

SilM

2D pictures

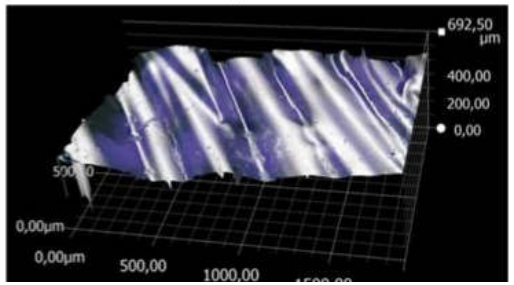
3D pictures

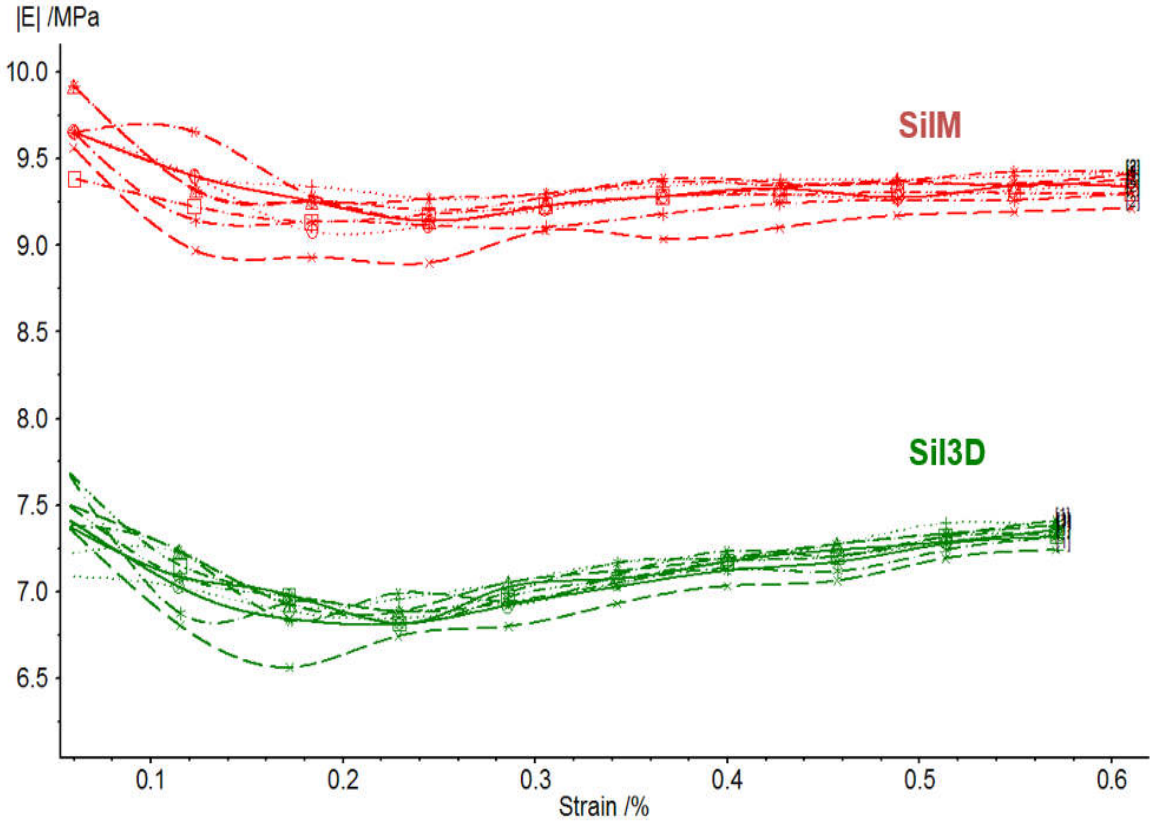


Sil3D

3D pictures

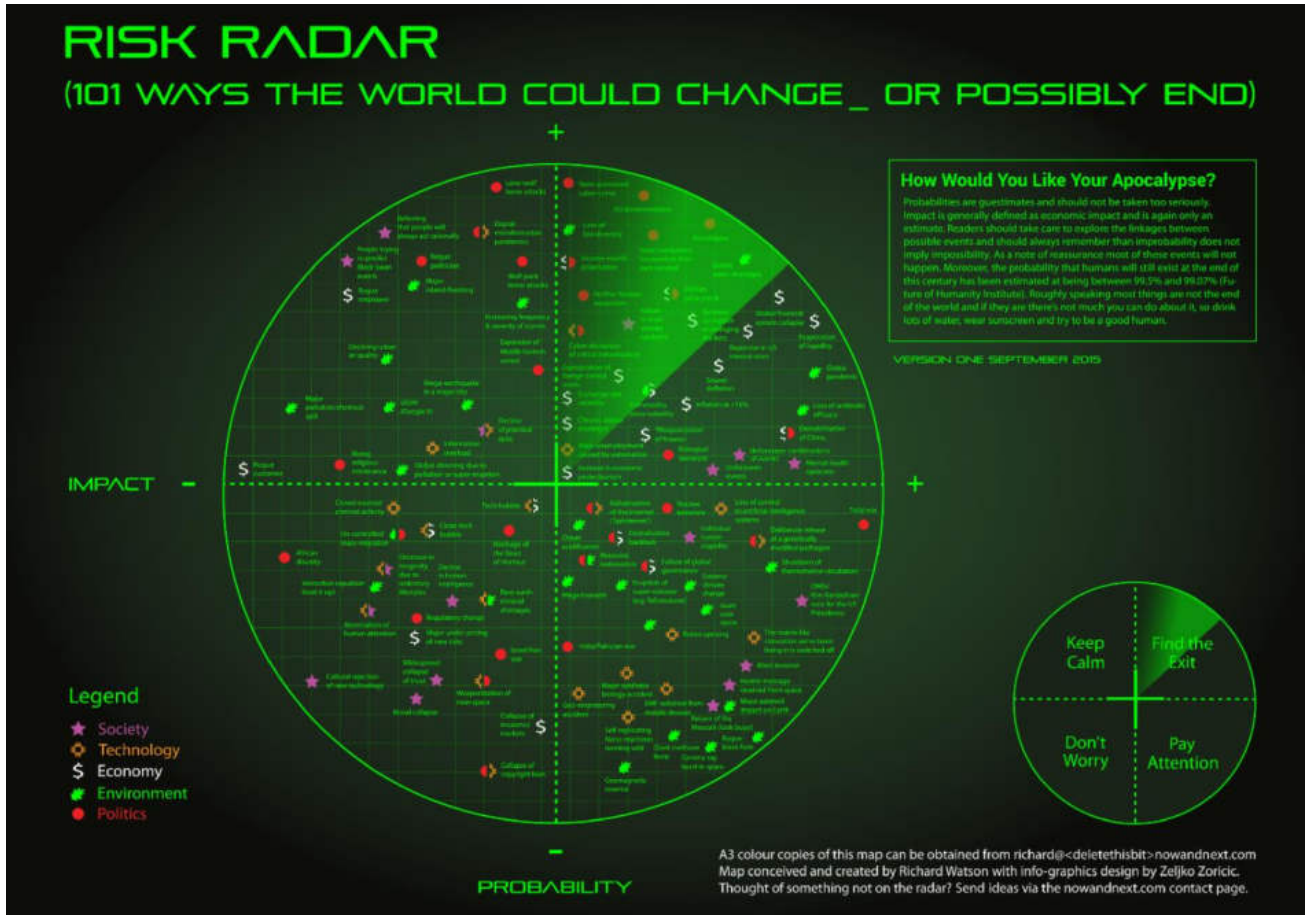
3D pictures





Collaboration with Aalto University (H2020, PANBioRA project)

PANBioRA-Risk-Radar



News: Google News, BBC

Regulatory bodies: ECHA, EPA..

Blogs: Wordpress.

Research database: Sciencedirect, Nature..

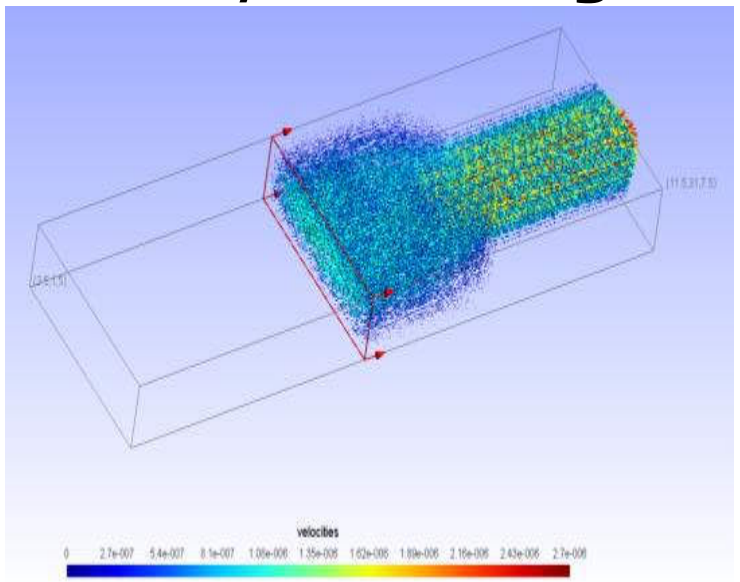
Review and Analysis

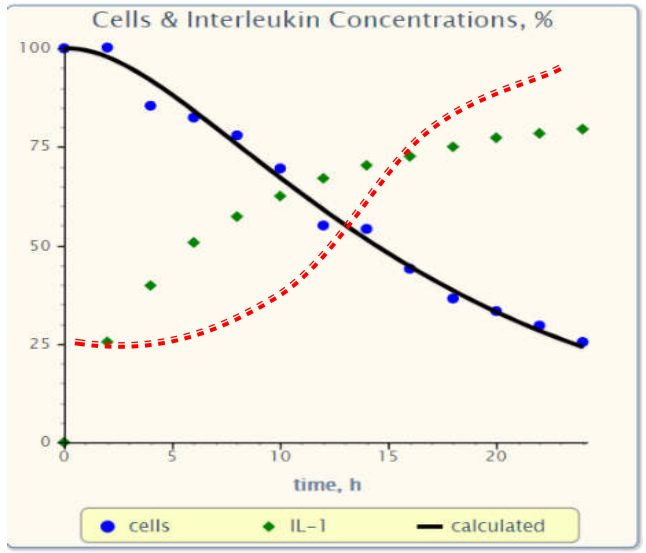
R&D info service: Cordis..

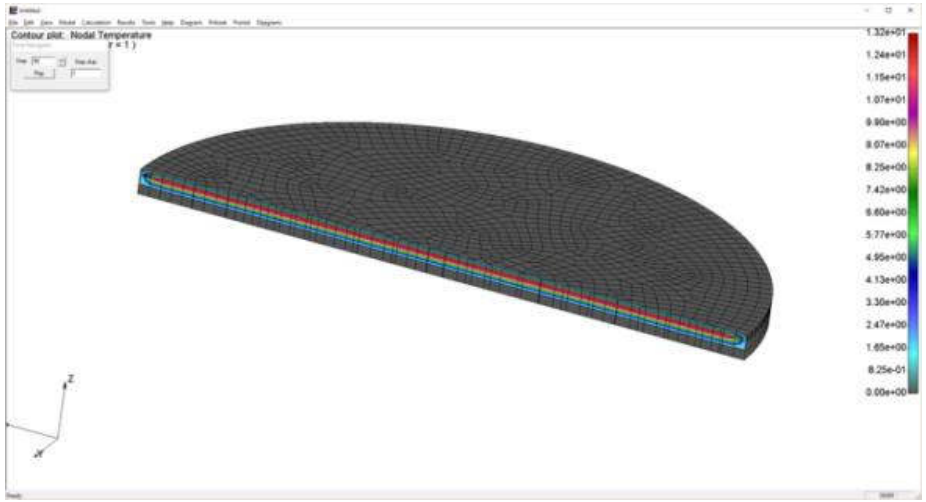
PANBioRA-Risk-Radar

Complementary Modelling

- Modelling of macrophage behaviour under flow and their attachment on surface
- Modelling of macrophage attachment for on-chip systems
- Model of macrophage aggregation and also the effect of the interleukin-1 secretion on the macrophages spheroids
- Cell/microbiota interactions using Lotka-Volterra models







Sector : Biotech – Medtech Activity : Multifunctional Coatings

SPARTHA MEDICAL

SPARTHA MEDICAL

Customized Coatings for Your Products

SPARTHA Customized Coatings

Mission :

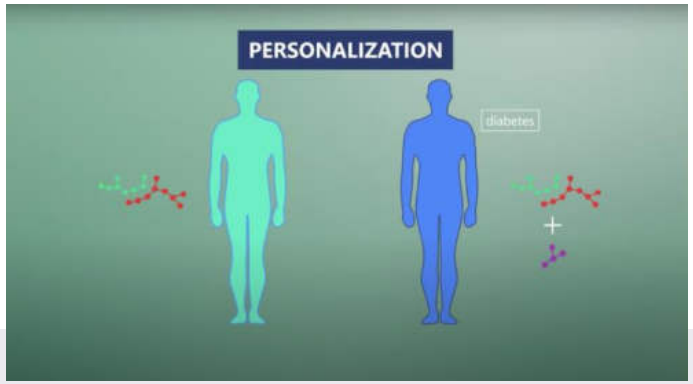
Customisation of surfaces with innovative coatings (such as implant personalisation)

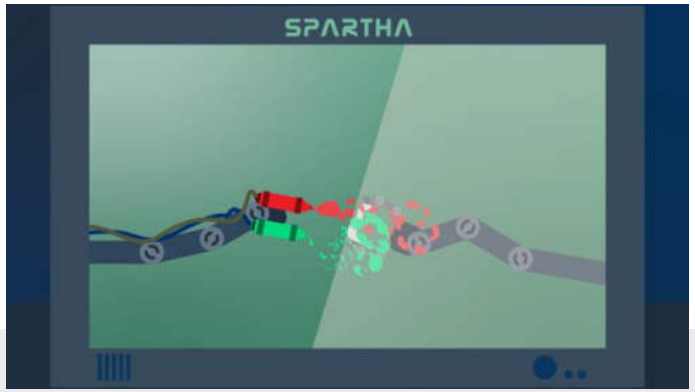
What we develop :

SPARTHA MEDICAL develops nano-, microscale coatings which can prevent complications (Antimicrobial, antiviral, anti-inflammatory)

Vision :

Decreasing complications ((infection, inflammation) / providing biocompatible preventive measures by multifunctional coatings





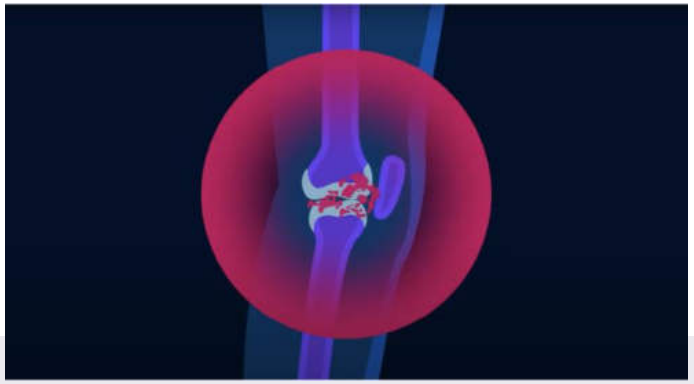
Problem : Hospital Acquired Infections

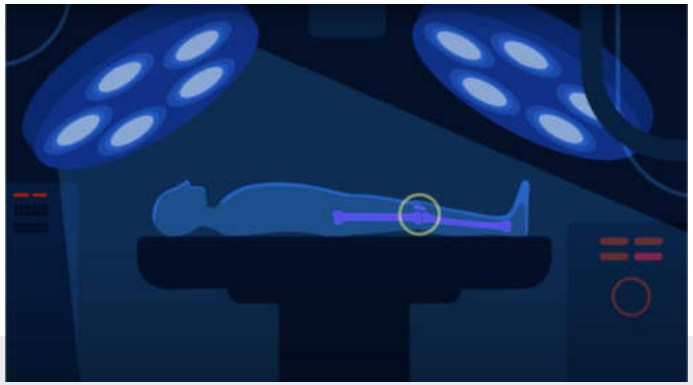
5% of all hospitalised patients has a case of nosocomial infection

50 to 70 % of the cases are related with medical devices

-An additional cost of 10.000 Euros / patient per infected implant

- Infection rate doubles in revision surgeries





Our solution :

Supramolecular coatings that can be applied to any kind of implant

SPARTHA Personalised Multifunctional Medical Device Coatings

SPARTHA
MEDICAL

SPARTHA Multifunctional Coatings- Value Proposition

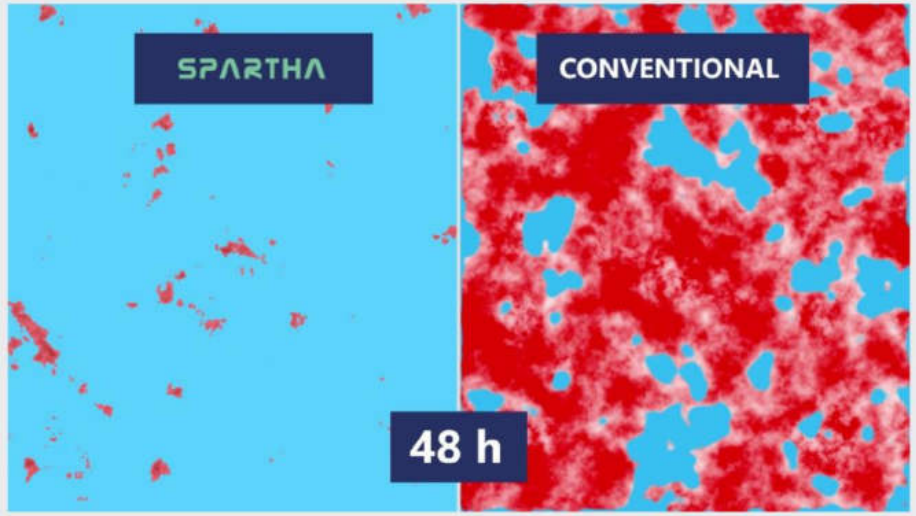
01 **Unique Selling Point 1 :**
New antimicrobial agent
(Large spectrum, Gram + / Gram-)

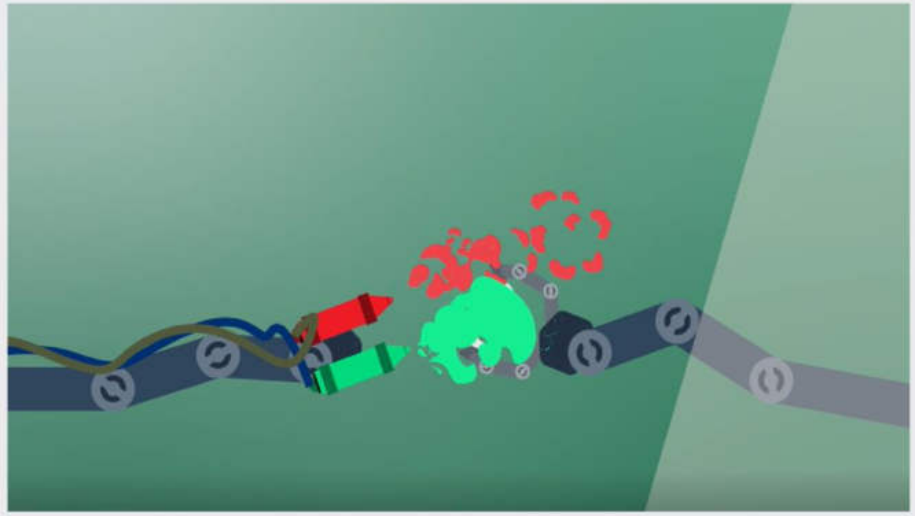
The bacteria cannot develop resistance against the coating

02 **Unique Selling Point 2 :**
Simultaneous Antimicrobial, Antiviral and Anti-inflammatory activity

Can be applied to any type of surface (Material and geometry)

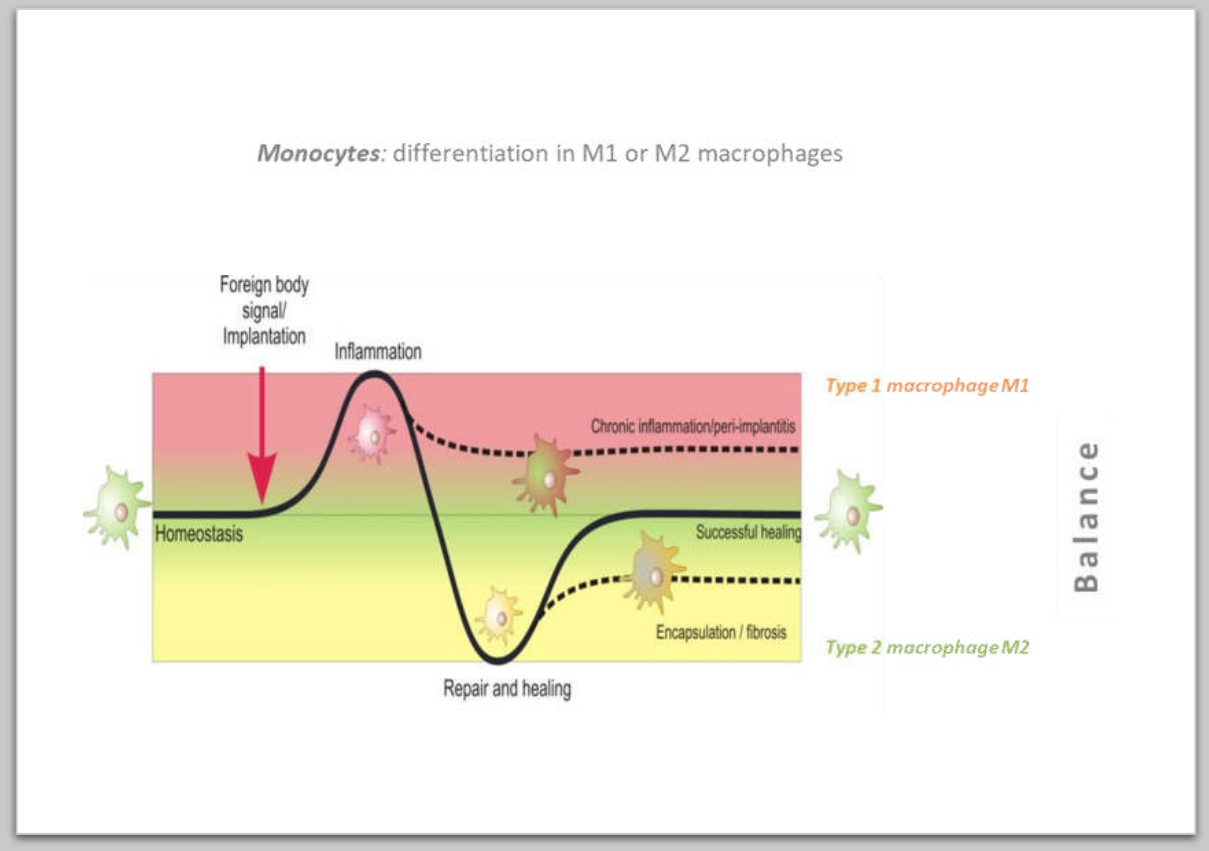
Easy to industrialise (spraying/dipping robots), no chemical treatments.

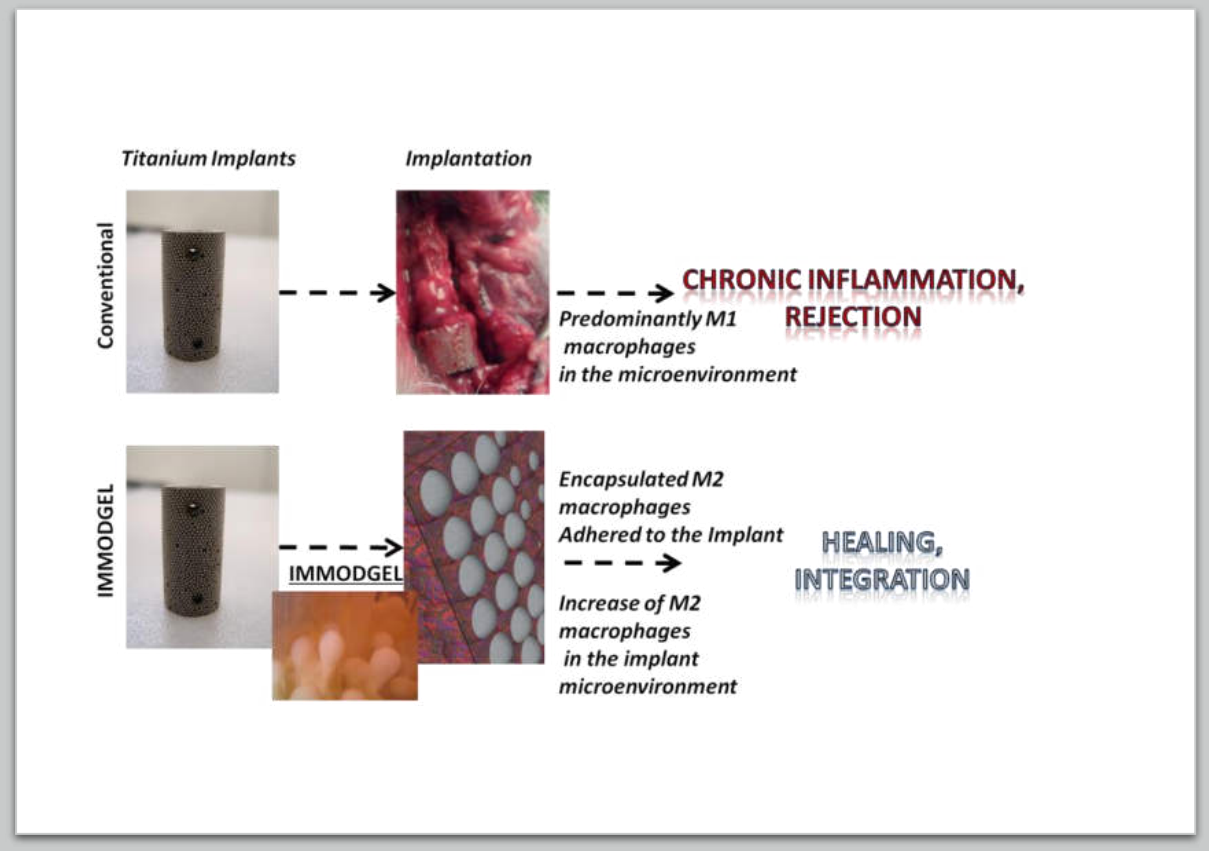




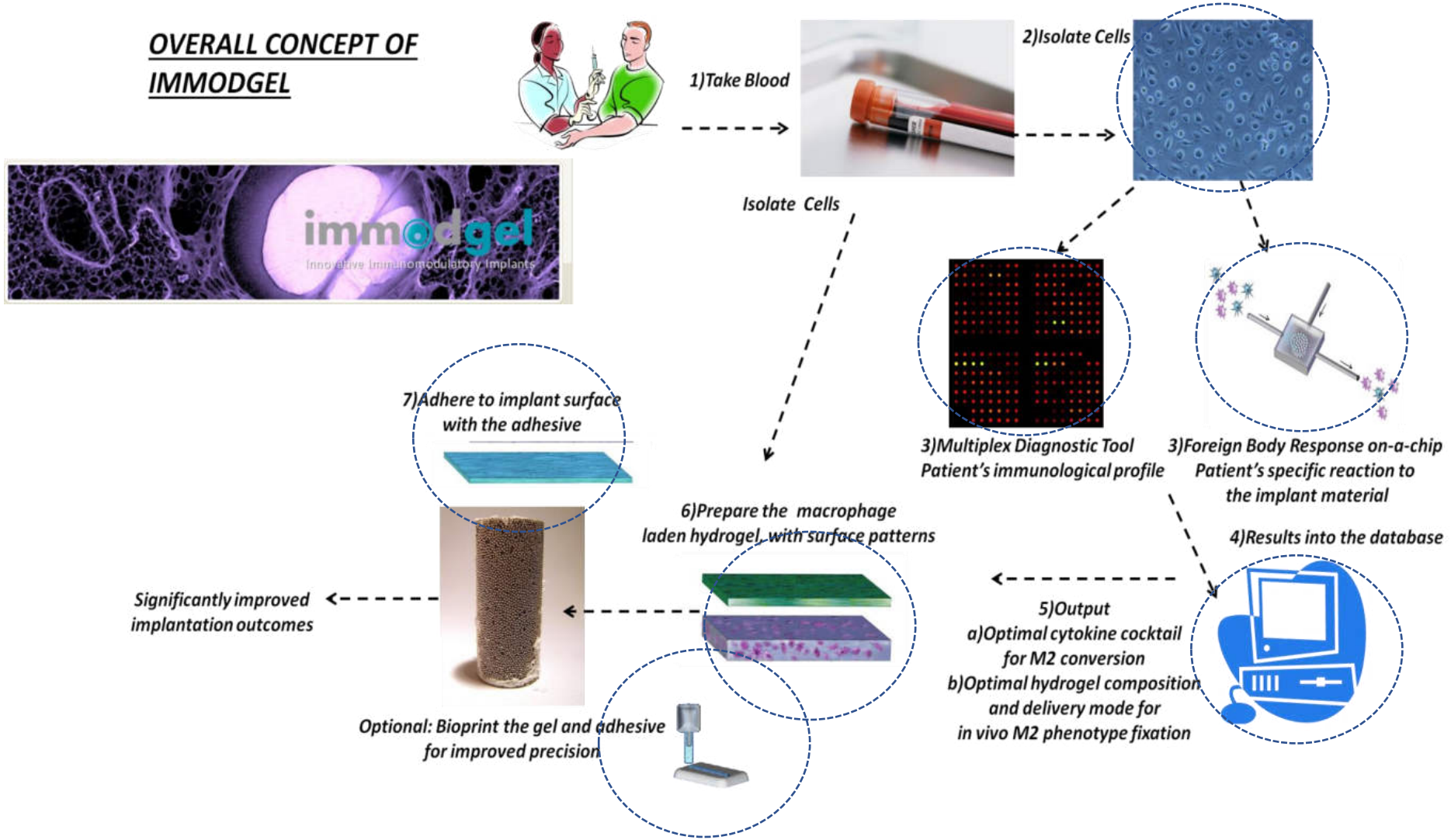

SPARTHA

- Local immunomodulation around implants by innovative auxiliary hydrogel-based systems encapsulating autologous and phenotype controlled macrophages.

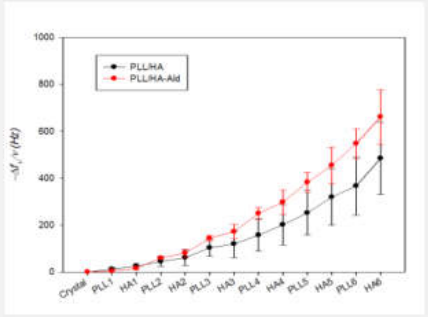




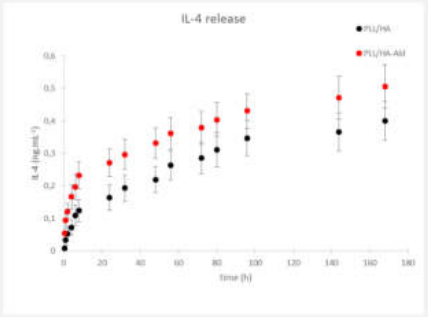
Origins: IMMODGEL



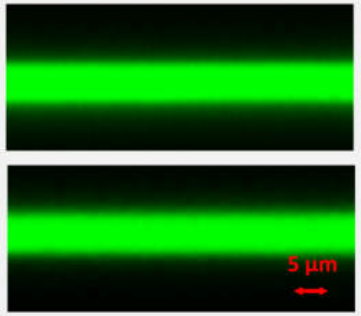
PLL/HA-Aldehyde Self-Crosslinking Coatings



Buildup at pH 7.4 /150 mM NaCl of $(PLL/HA)_6$ and $(PLL/HA\text{-}Ald)_{24}$ multilayer films on a SiO_2-coated crystal followed by QCM-D, evolution of normalized frequency - $\Delta f/v$.



Kinetic of interleukin 4 (IL-4) release from PLL/HA and PLL/HA-Aldehyde.

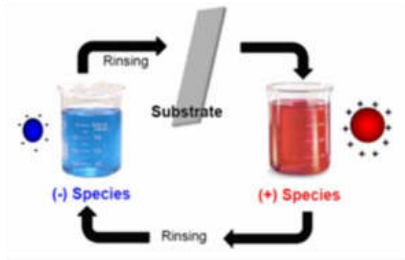


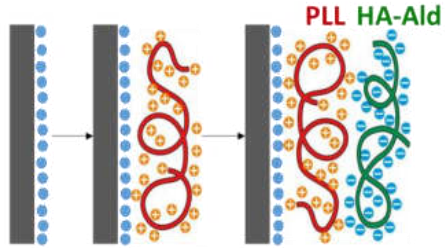
Section images, obtained by confocal laser scanning microscope, of $PLL/HA)_{24}$/PLL-FITC/HA and $(PLL/HA\text{-}Ald)_{24}$/PLL-FITC/HA-Ald multilayer films, respectively.

Young Modulus of $(PLL/HA)_{24}$ and $(PLL/HA\text{-}Ald)_{24}$ films measured by AFM nanoindentation.

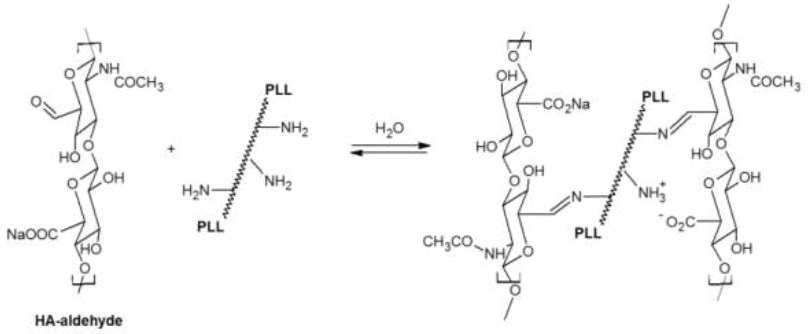
Films	Young Modulus (kPa)	±
$(PLL/HA)_{24}$	10	4
$(PLL/HA\text{-}Ald)_{24}$	142	63

Methods





Production of PLL/HA-Aldehyde multilayers by Layer-by-Layer method.

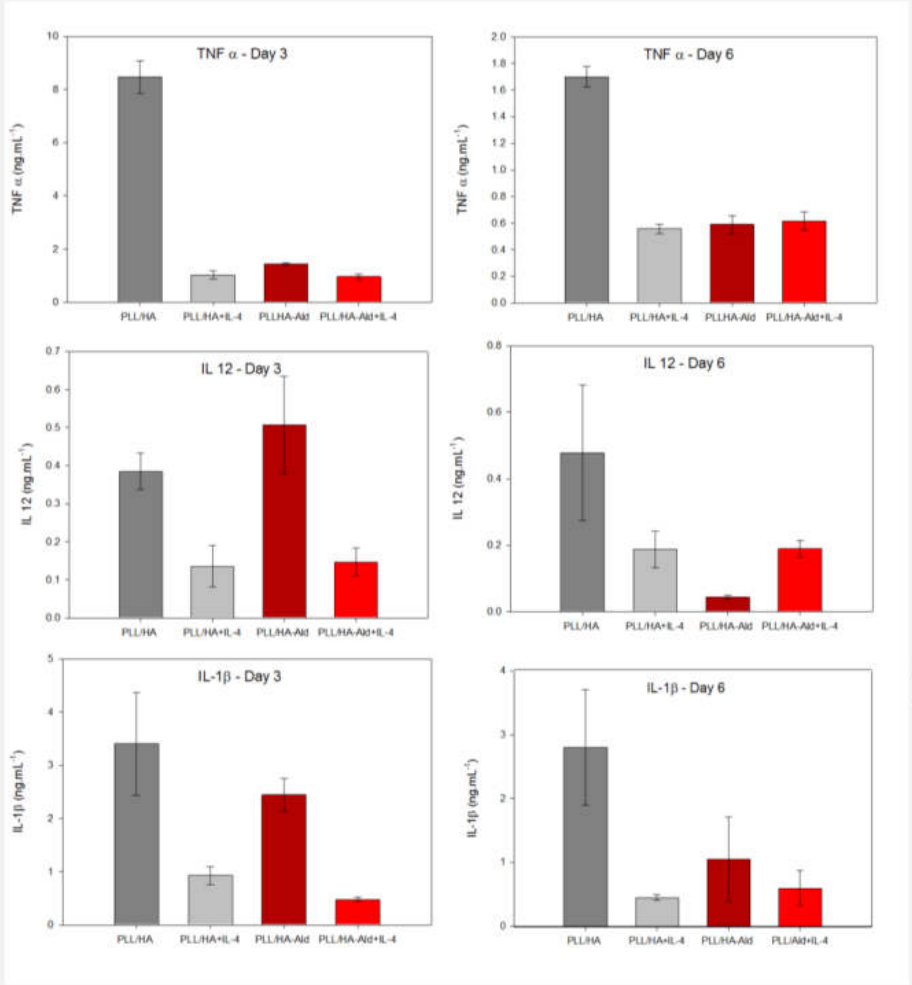


The polyelectrolyte multilayer films formed by PLL and HA-Aldehyde are crosslinked by themselves without any addition of elements or stimuli.

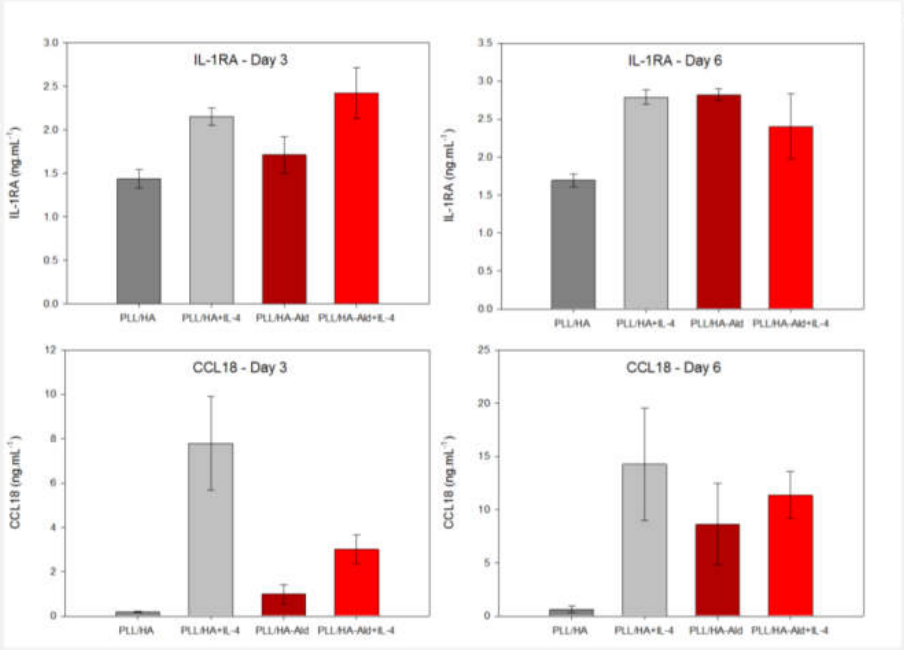
✓ The principle of this crosslink reaction is of hydrolytically **labile imine bond between amino groups** of PLL and **aldehydic** derivative of HA

Knopf-Marques et al. 2016, Biomacromolecules

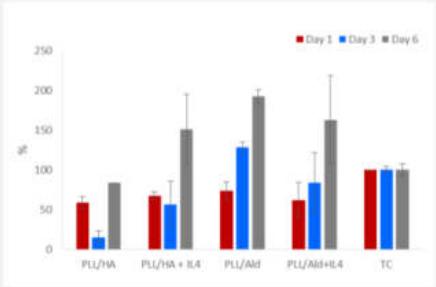
Anti-inflammatory activity



Pro-inflammatory cytokines produced from monocytes seeded on PLL/HA, PLL/HA-Ald with or without IL-4



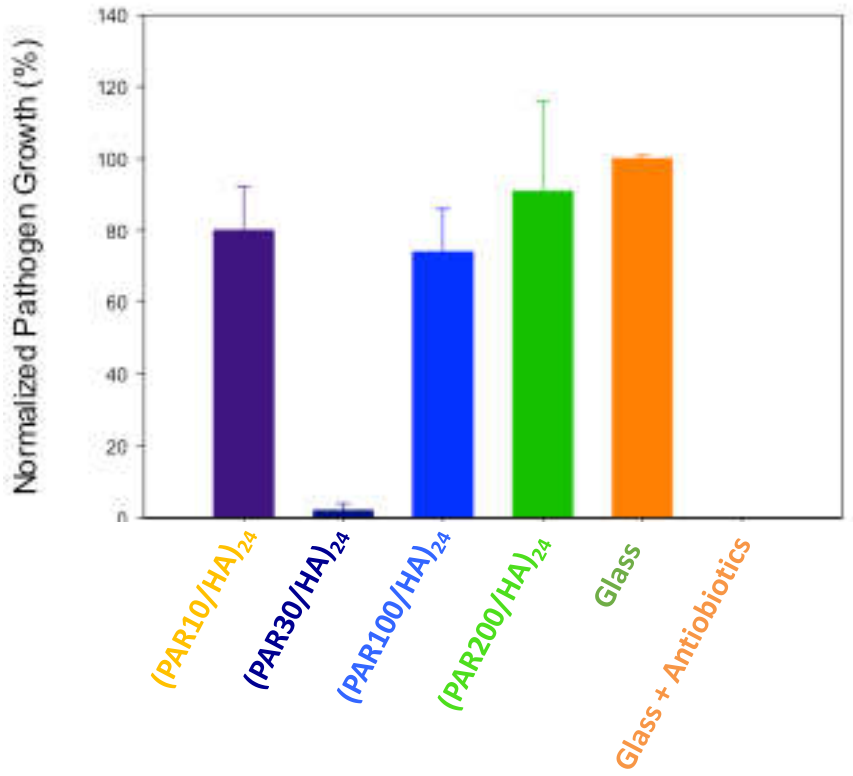
Anti-inflammatory cytokines produced from monocytes seeded on PLL/HA, PLL/HA-Ald with or without IL-4

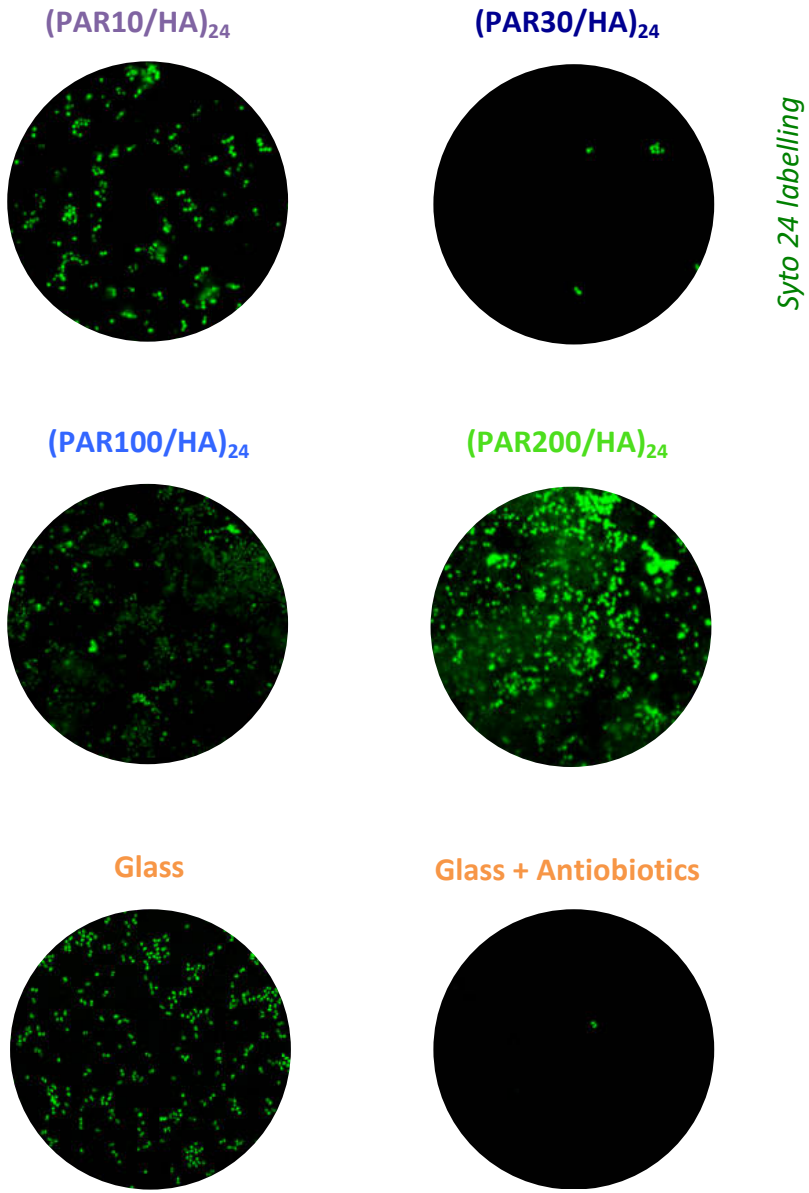


Cell viability: metabolic activity of monocytes seeded on PLL/HA and PLL/HA-Ald with or without IL-4.

Antimicrobial activity of PAR/HA films with various numbers of Arginine residues

S. aureus growth in supernatant with PAR / HA films

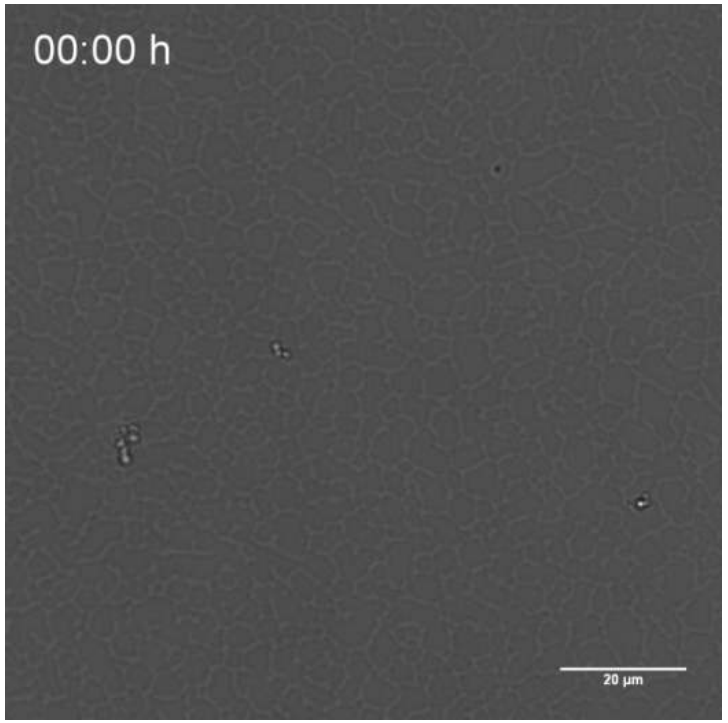




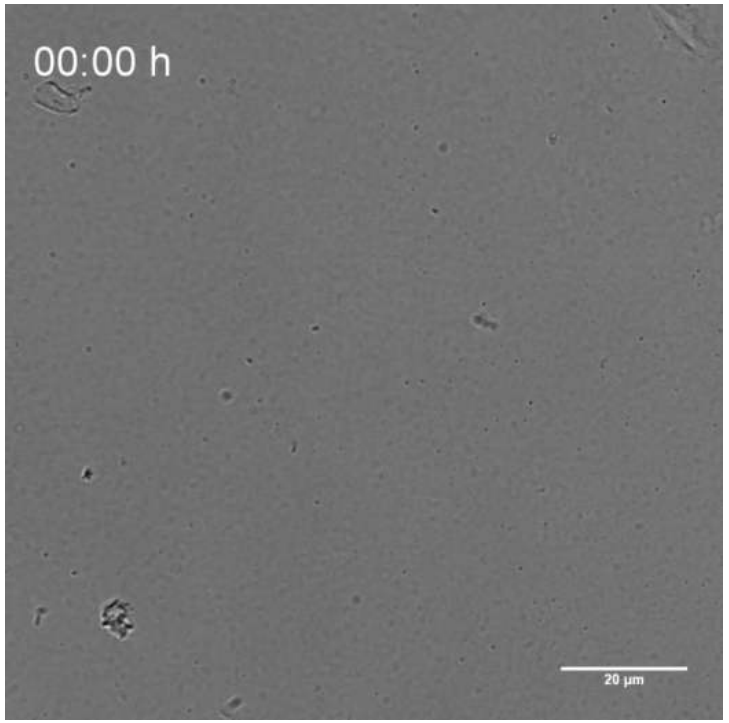
➔ Only PAR30/HA films show antimicrobial properties !

Antimicrobial properties

Time Lapse sequence



Control

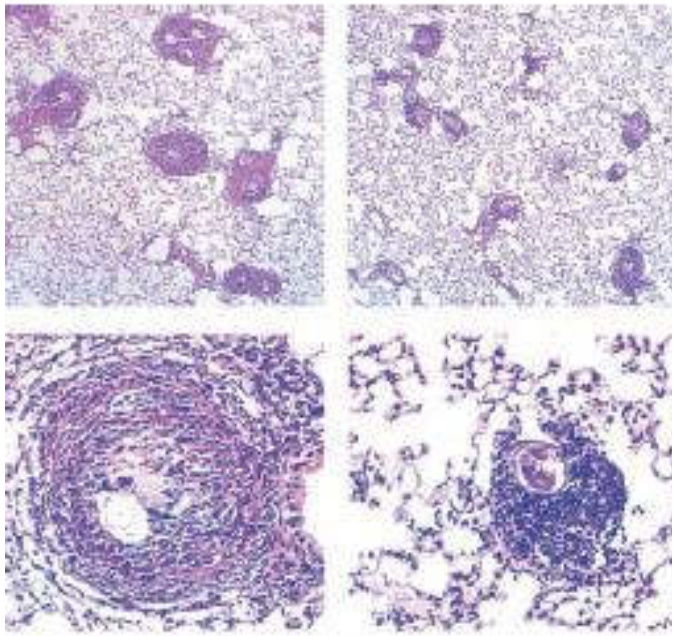


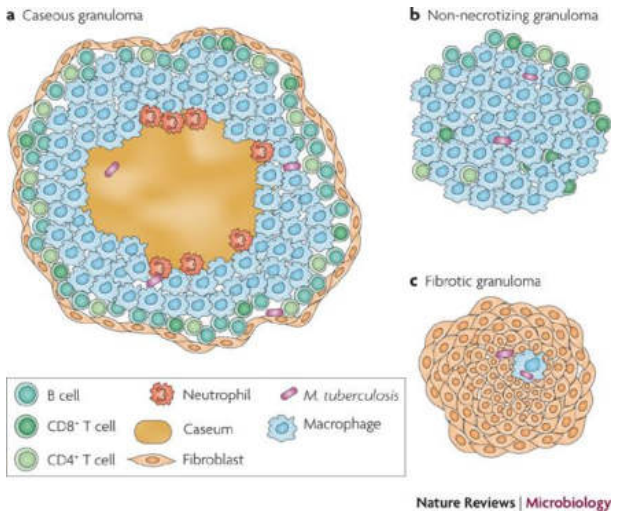
SPARTHA Multifunctional coatings

- ✓ *Staphylococcus aureus* (*S. aureus*, ATCC 25923) strain was used to assess the antibacterial properties of the samples.

What is Granuloma?

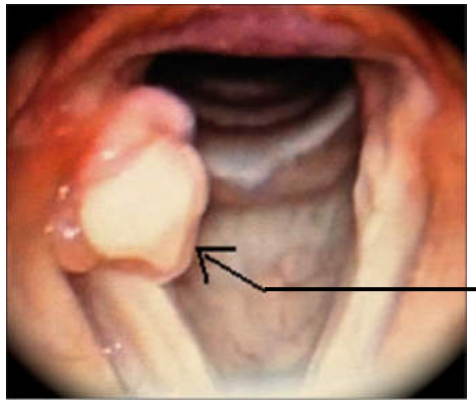
- Granuloma is due to immune cells known as macrophages. Granulomas form when the immune system attempts to wall off substances it perceives as foreign but is unable to eliminate (such as implants).
- Formation of a granuloma is a common tissue response to the presence of a variety of foreign materials including silicone and metals.
- All granulomas, regardless of cause, may contain additional cells and matrix. These include lymphocytes, neutrophils, eosinophils, multinucleated giant cells, fibroblasts and collagen (fibrosis).

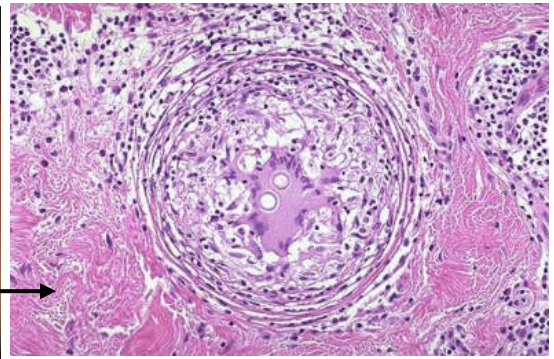




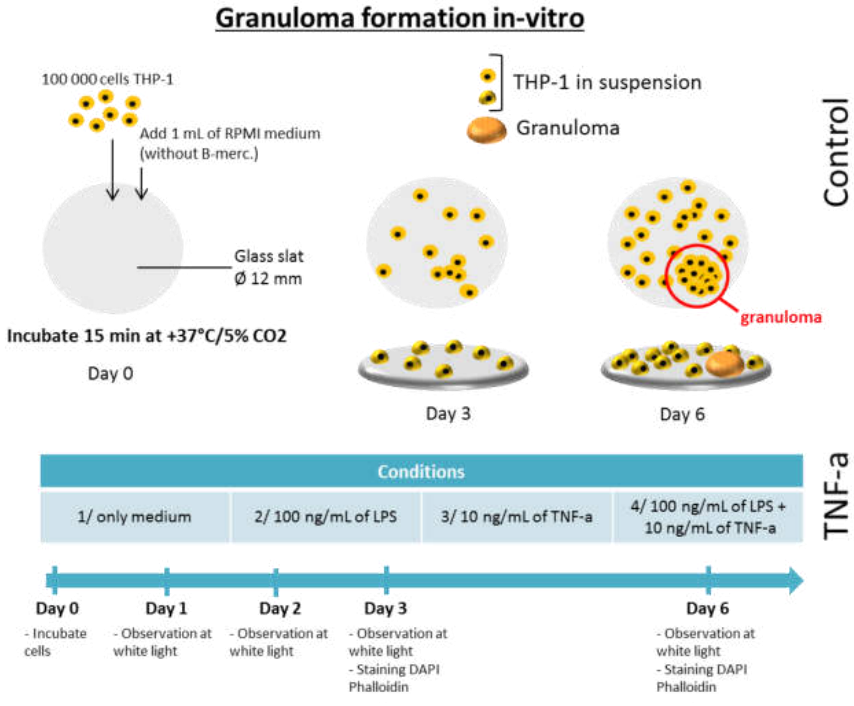
Granuloma induction by LPS and TNF-alpha

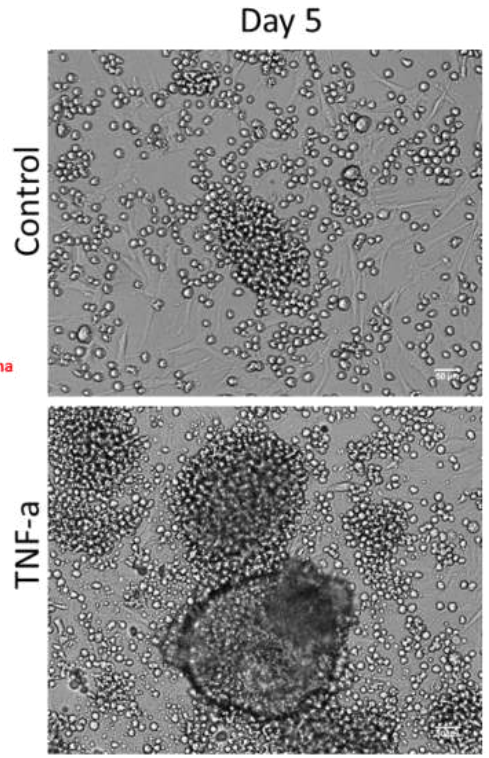
❖**Granuloma:** a mass of granulation tissue, typically produced in response to infection, inflammation, or the presence of a foreign substance. How can we mimic this in vitro?

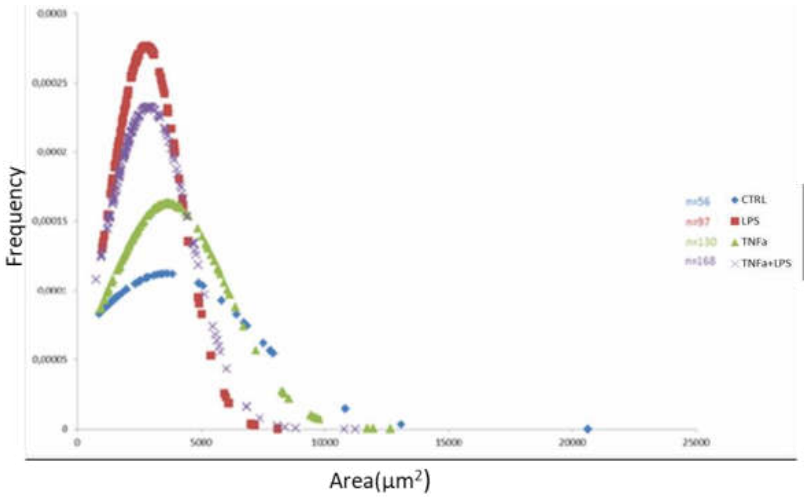


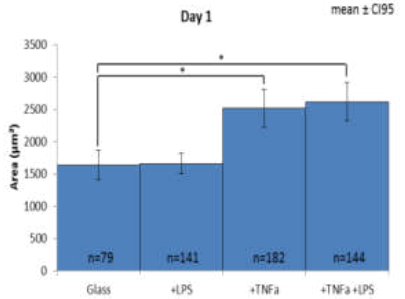


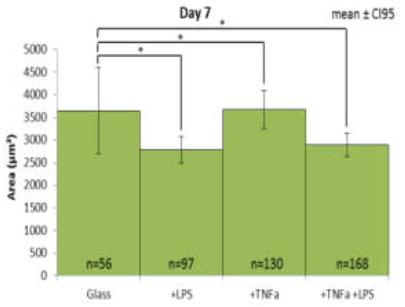
Granuloma



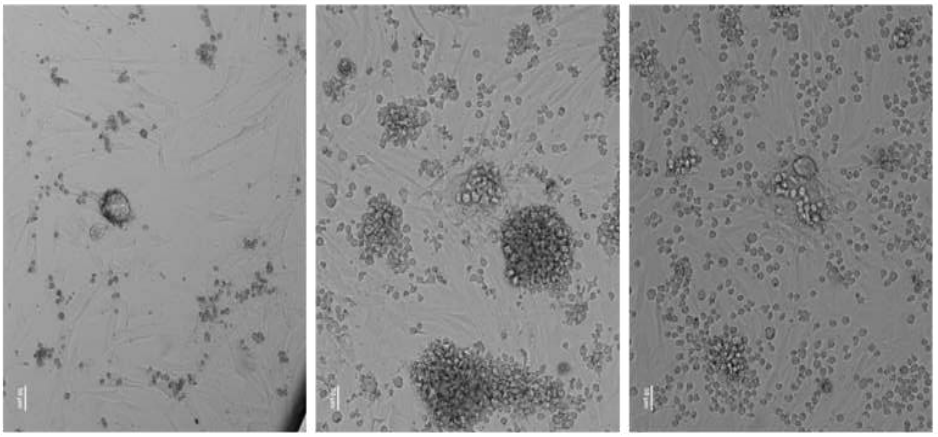


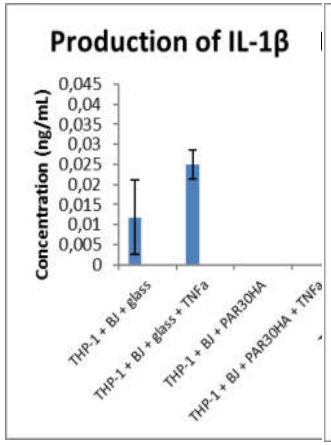


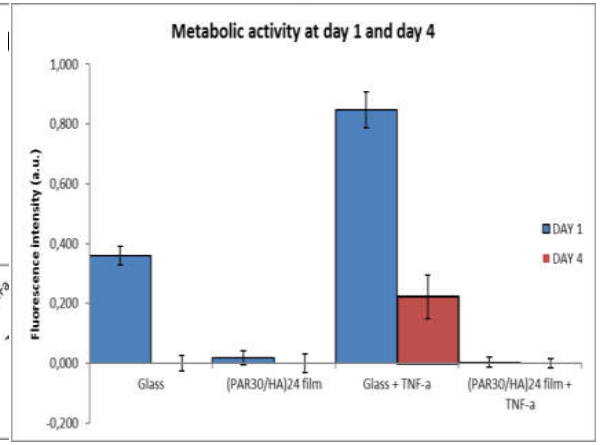




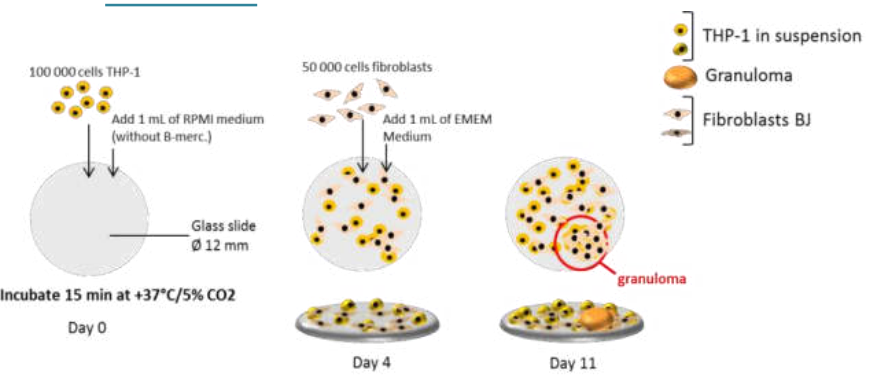
The effect of the coating on granuloma formation

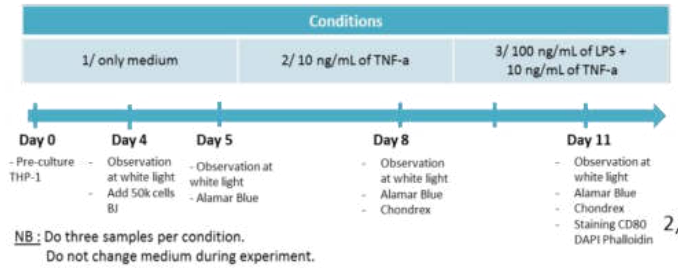




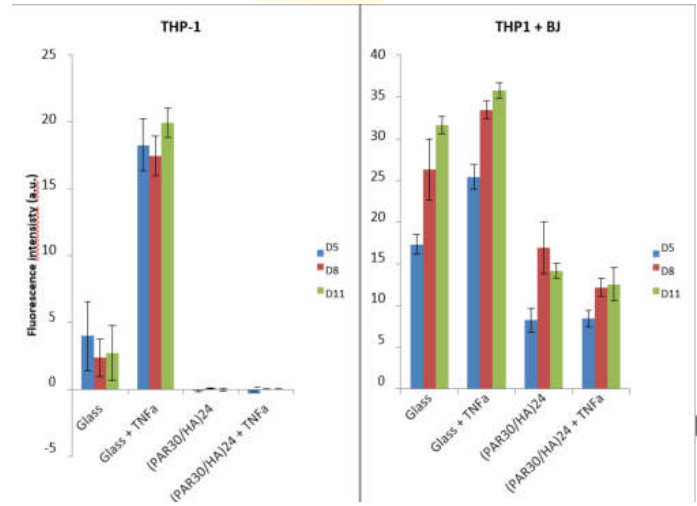


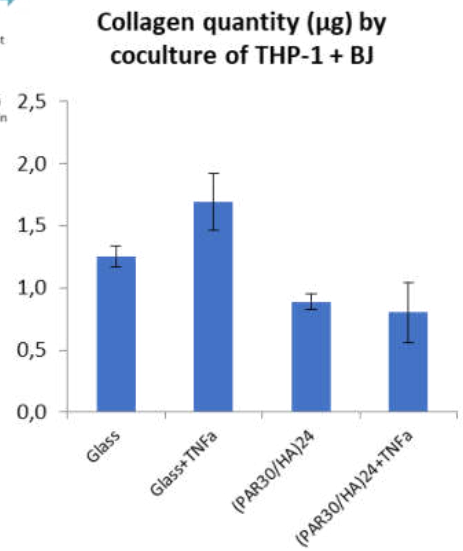
Day 5

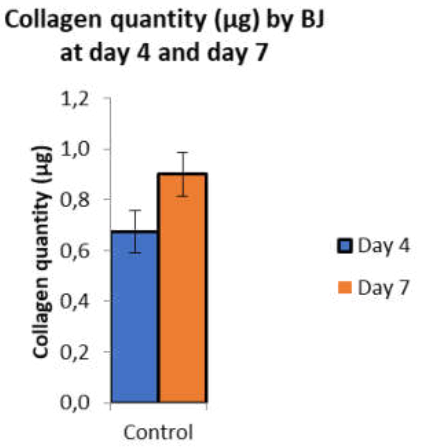




NB : Do three samples per condition.
Do not change medium during experiment.







Technology Validation

SPARTHA MEDICAL

- **IN VIVO TESTS**
  in two infection models in rats (1) (Titanium and Silicone) and rabbits (2) (Hernia meshes)
- **PROVEN ANTIMICROBIAL EFFECT**
  against all tested Gram +/ Gram- bacteria (ISO 22196)
- **ANTI-INFLAMMATORY EFFECT**
  shown (in vivo, mice)
- **ANTIVIRAL EFFECT SHOWN IN VITRO**
- **BIOCOMPATIBLE**
  (ISO 10993-5 / ISO 10993-10 / ISO 10993-11) (in vitro/in vivo)
- **THE ABSENCE OF BACTERIAL RESISTANCE DEVELOPMENT IS PROVEN** (norme CLSI)
- **STORAGE** > 2 years in real time (@Room Temperature)
  Applied to different materials
  Stays active after industrial sterilisation (Autoclave, Gamma-, Beta rays)

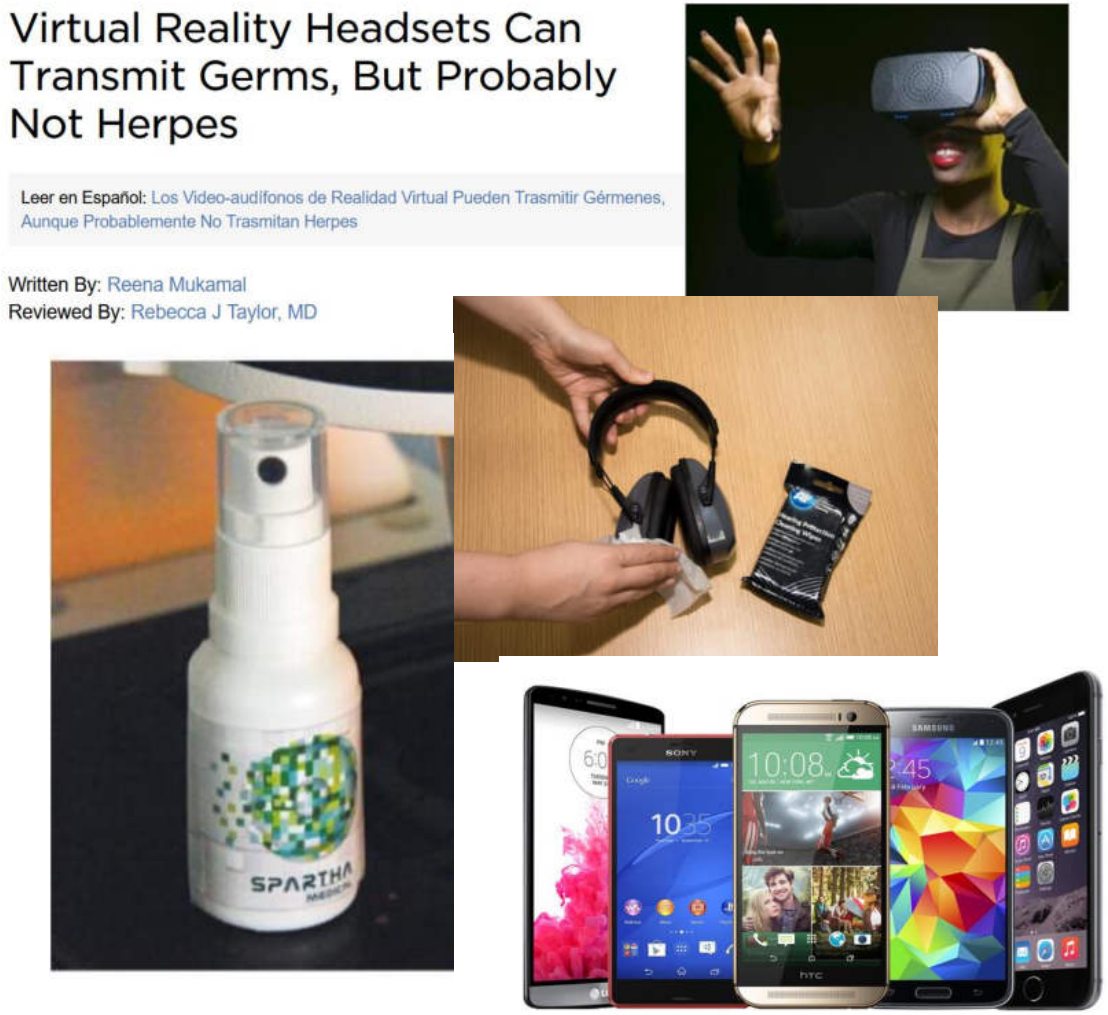
SPARTHA Activity

01 Development of Multifunctional Coatings that can be applied to any kind of surface.

02 Patented formulations for antimicrobial, anti-inflammatory and anti-viral activity: Recent reformulation which is effective against SARS-COV-2

03 Customised coating-formulation development service with respect to the customer specifications using supramolecular chemistry, secret know-how (20 years of experience) and machine learning

04 Product development: An advanced coating kit (antimicrobial/anti-inflammatory) for medical devices



SERVICE: Customised Coatings

Specifications by the client

SPARTHA Medical Lab

Feasibility Study

Literature survey, FTO, First Tests, A set of proposed coatings

First deliverable:

Go/No Go

Development phase: Customisation of the implants, physicochemical, mechanic and in vitro functional tests

Second Deliverable:

Go/No Go

Transfer phase: Optimisation of the selected coating, functional in vivo tests, technology transfer and IP resolution

Final Deliverable:

Clients- Industry (SME/Start-up):

New products with coatings, internalisation of the technology

Clients- Big Industry:

Improvement of the existing product ranges with coatings. SPARTHA Medical as a subcontractor for modification of their prodcuts (with new contracts)

Bio-TUNE

HORIZON 2020

H2020-MSCA-RISE-2019

Fine tune of cellular behavior: multifunctional materials for medical implants (Bio-TUNE)

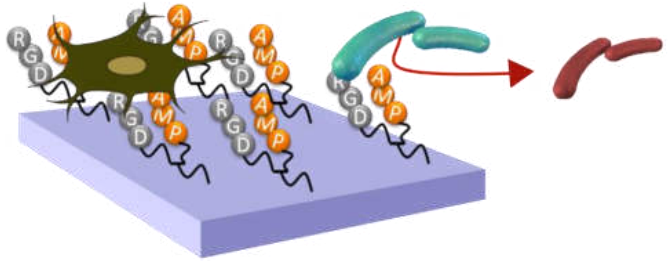
Bio-TUNE aims to develop innovative **multifunctional** materials to produce a **new generation of implants** with **cell instructive** and **antibacterial potential**

Bio-TUNE

To this end, Bio-TUNE ambitions to:

1) Study and understand the interaction of cells and bacteria
2) Develop cell instructive and antibacterial surfaces
3) Assess technology transfer to the market

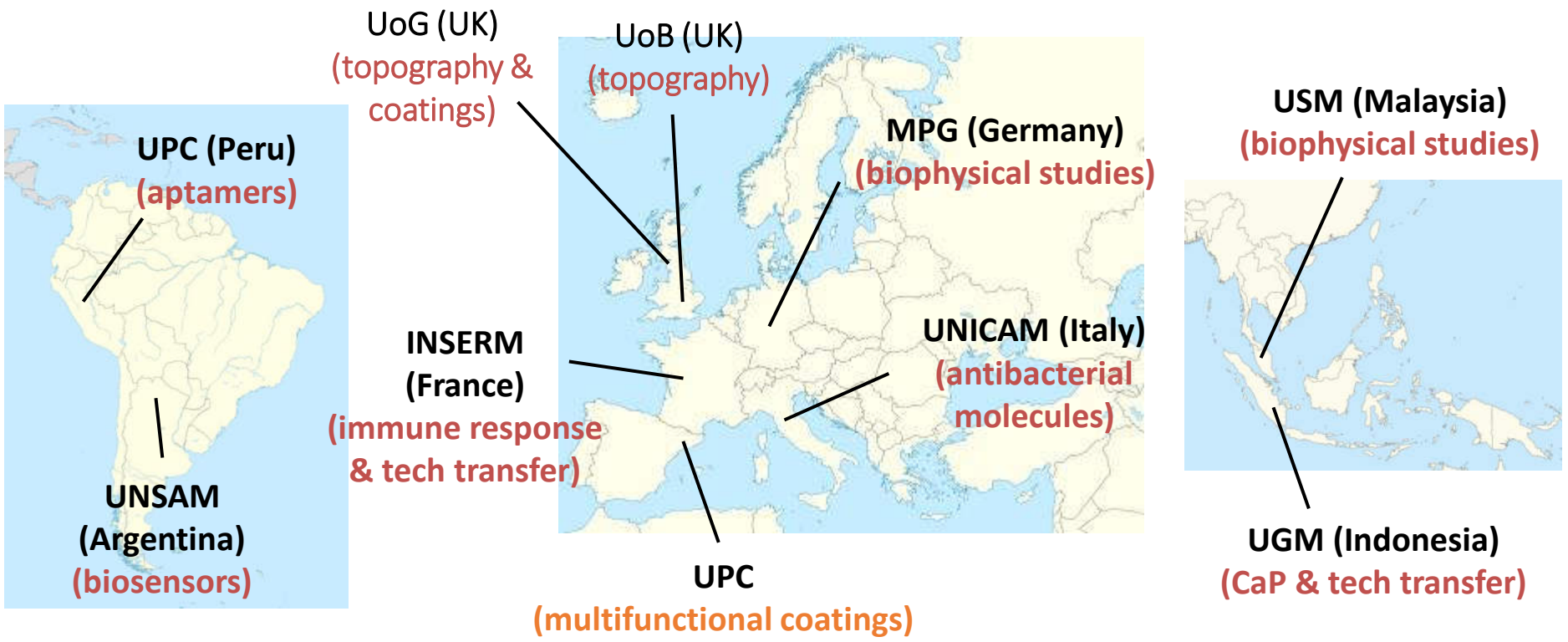
Detect



Prevent

Transfer

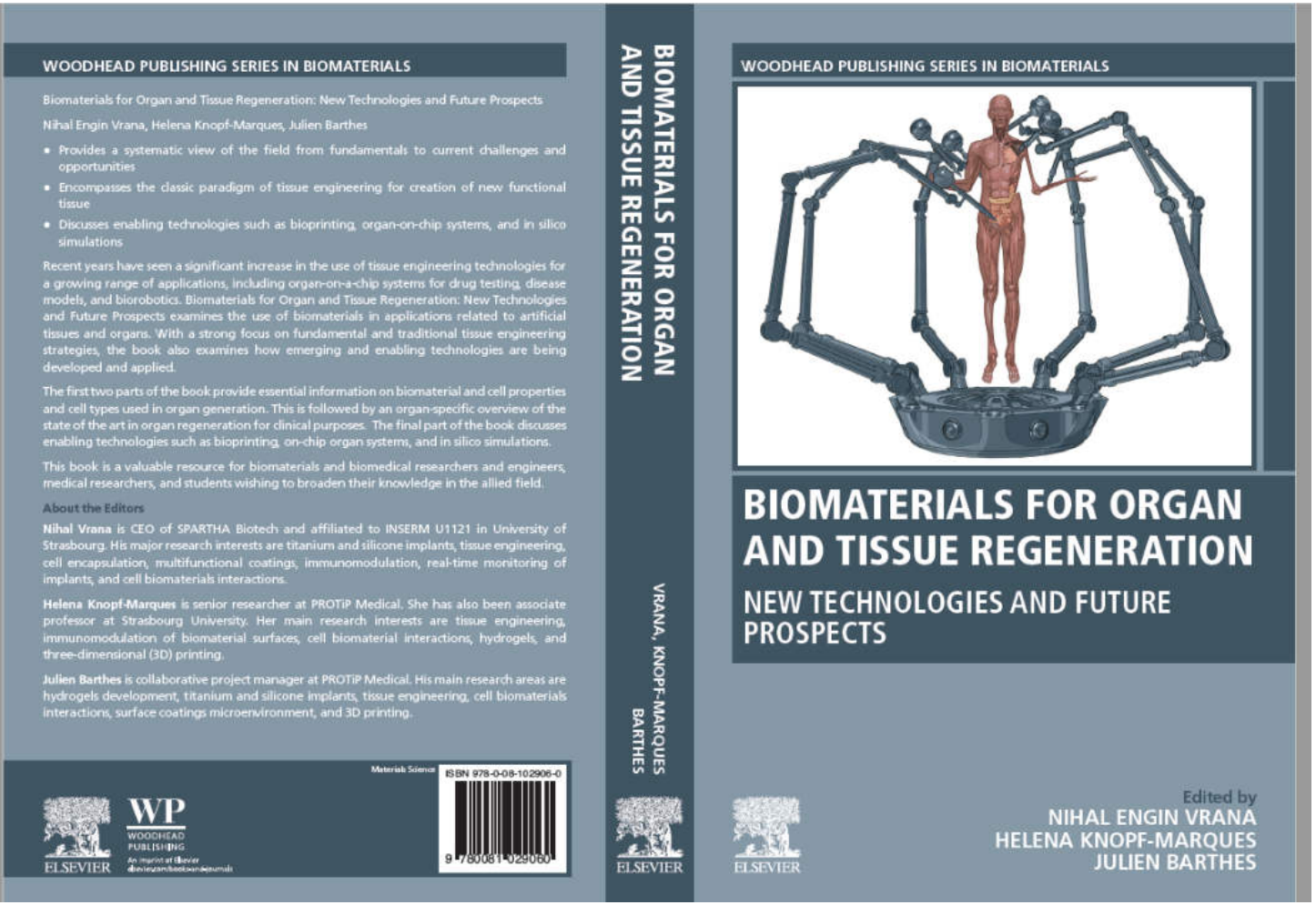
Bio-TUNE



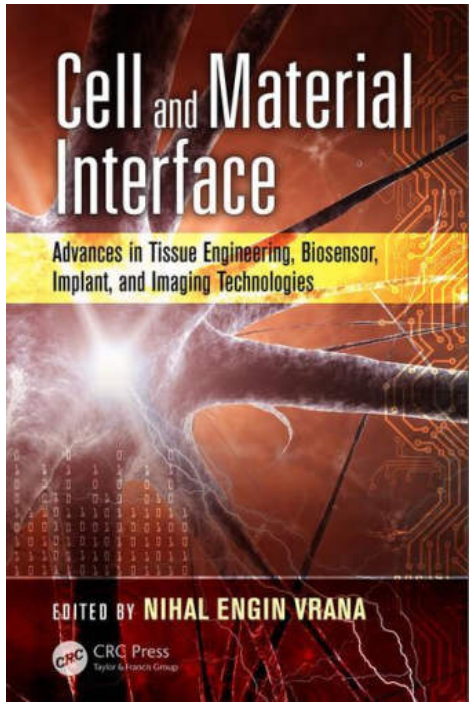
More info: https://biotune.upc.edu/en @bio_tune

Contact: Noelia.Aparicio@upc.edu

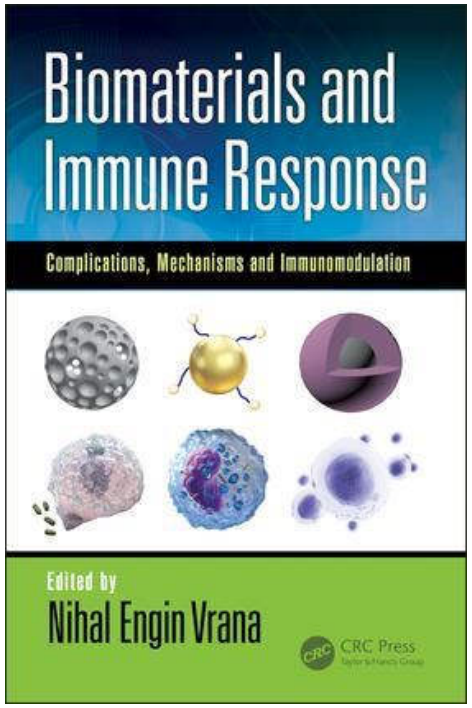
Books on the subject



Elsevier, 2020



Cell and Material Interface
Nov 2015



Biomaterials and Immune Response
Jul 2018

Conclusions

- The new generation of biomaterials require a new generation of testing methods with more focus on personalised reactions
- Personalisation of the host/biomedical device interface can significantly improve clinical outcomes
- The regulation should follow the technology not the technology the regulation. For this we need to provide the regulators the necessary tools
- The in vitro models should reach both micro and macro scale complexity of the target organs/problems to be relevant.
- Thin film based surface coatings can provide controllable interfaces for interacting with the immune cells and attenuating foreign body response
- However, such immunomodulation should not create immuneprivilaged zones and lead to infection. Thus, such coatings should have antimicrobial components.

Funding Sources

Thank you for your attention

France: BPI i-Lab, BPI BFTE, Region Grand Est (SPARTHA), ANR Terminanion
International: H2020 PANBioRA, Marie Curie Rise Bio-Tune
Disclaimer: NE Vrana is the majority shareholder of SPARTHA Medical.

Contact details
Nihal Engin Vrana
SPARTHA Medical
Strasbourg, France
+33 659081724
evrana@panbiora.eu, evrana@sparthamedical.eu
www.panbiora.eu , www.sparthamedical.eu

INSERM UMR 1121