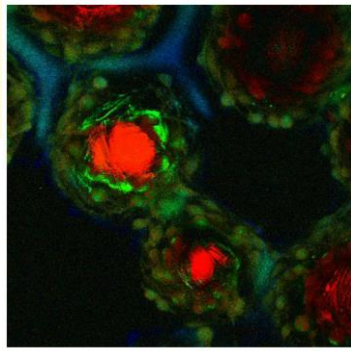
KAMUSAL ARAŞTIRMA/ENDÜSTRİ İŞBİRLİĞİ VE START-UP'LAR: DAHA DOĞAL VE SİNERJİK BİR ORTAKLIK MÜMKÜN MÜ?

Nihal Engin Vrana
SPARTHA Medical, CEO
University of Strasbourg
INSERM UMR 1121
USIMP May 2021



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 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)

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)

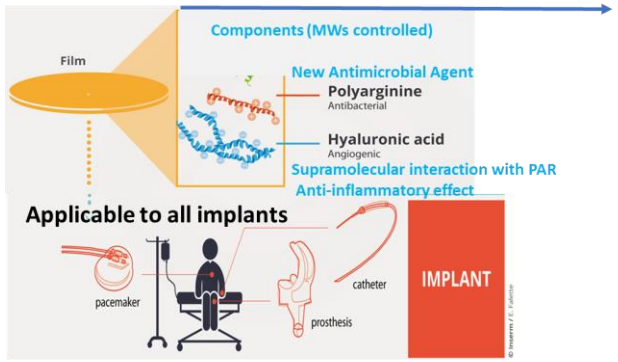
Personalisation of Implantable Device Host Interfaces (Immunoprofiling and Coatings)

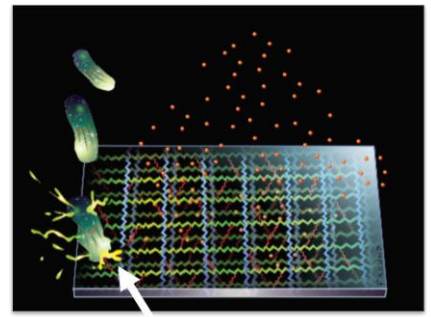
Real-time monitoring of Implanted structures

Future Aim:

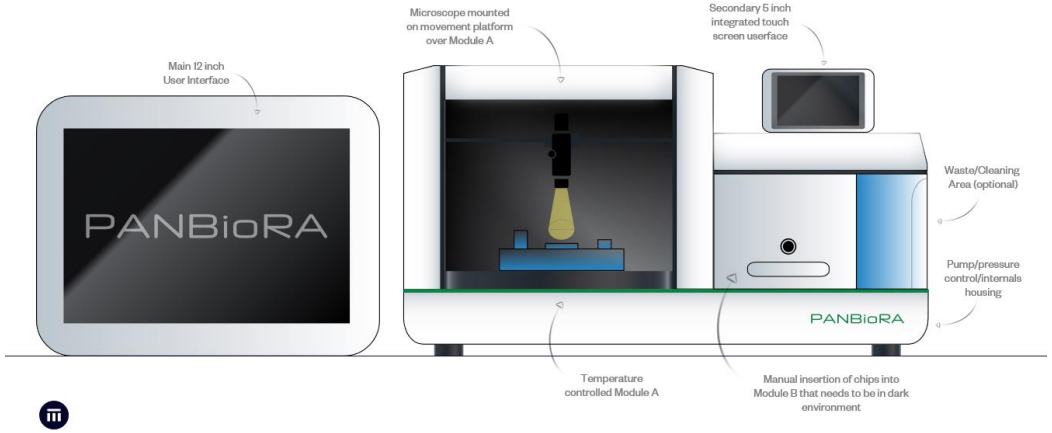
Developing new organs, Use of Tissue Engineering for Biotic Games

SOLUTION : Multifunctional SPARTHA Coating

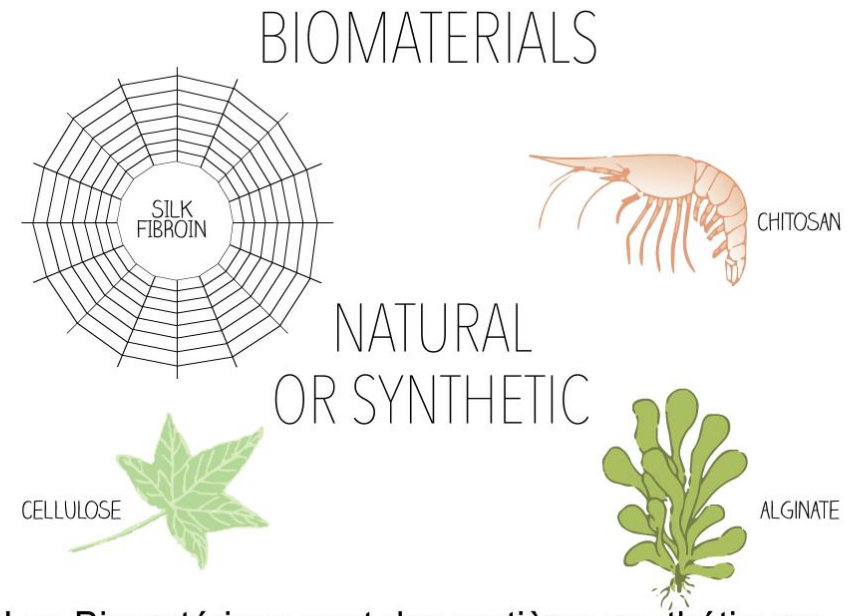




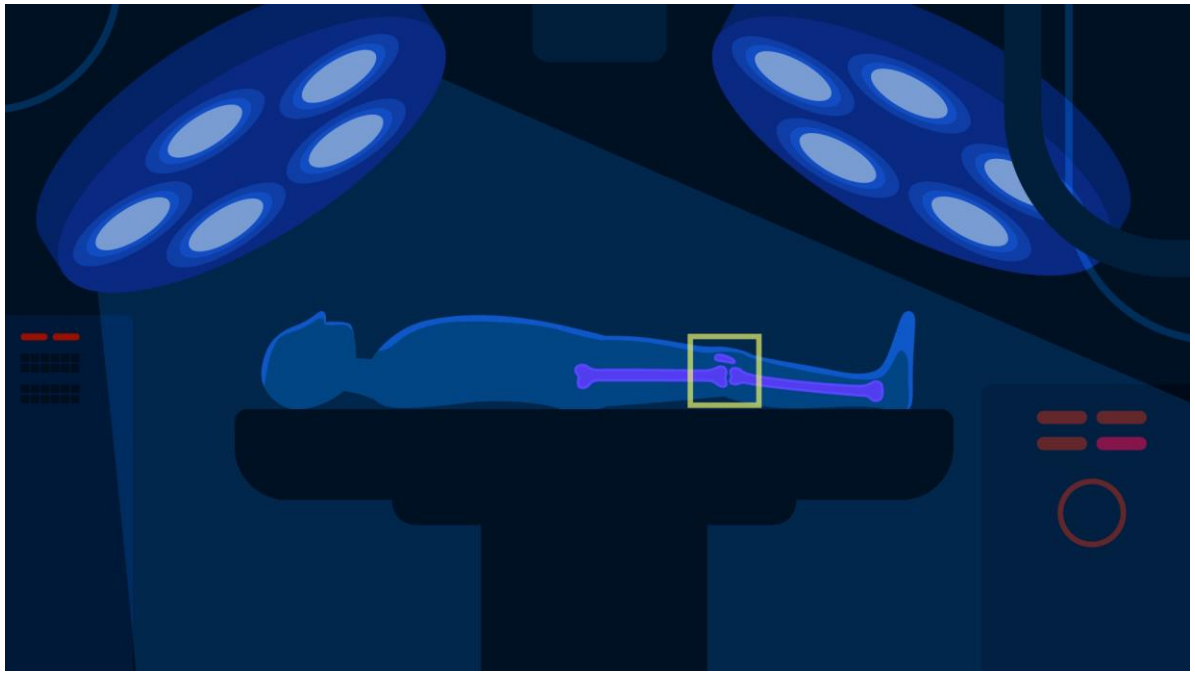
Contact Killing Technology
The bacteria cannot develop resistance



Biomaterial Related Risks- Infections around Implants



Les Biomatériaux sont des matières synthétiques ou naturelles qui sont utilisées dans les implants.

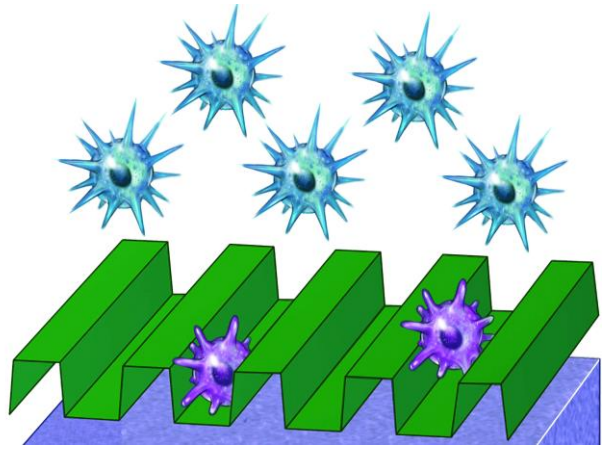


Cells on a Leash: Physical Constraints as a Method to Control Cell Behavior

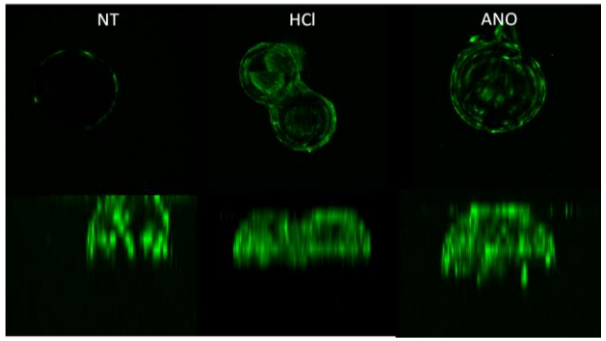
1) Outcome of an implantation or a tissue engineered product is directly related to the level of control on cell behaviour

2) Inability to control cell proliferation, differentiation and metabolism can have disastrous effects, from immature tissues to tumorogenesis.

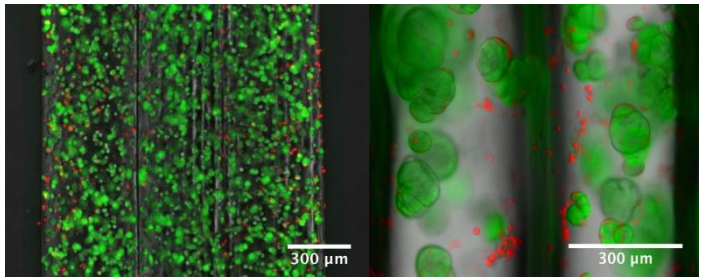
3)The easiest parameter to control in a TE setting is the physical properties of the biomaterial. As these modifications are semi-permanent and can be achieved from nano to macroscale.



1) Immunomodulation with Micropatterns

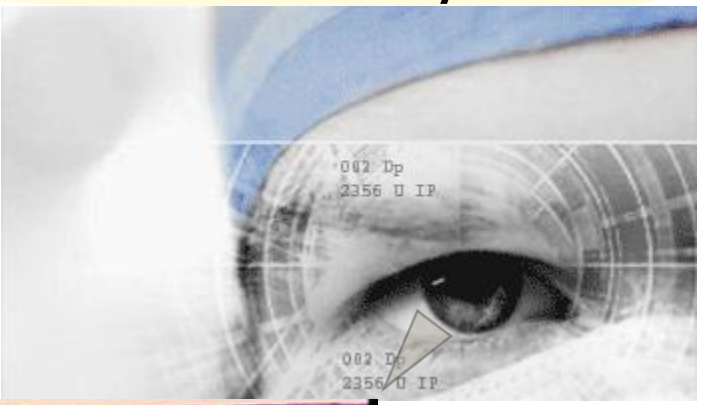


3) Effect of nanostructuration of Ti on cell attachment



2) Mouse Embryonic Stem Cells in Degradable vs. Nondegradable hyrogels

Cornea Tissue Engineering
Middle East Technical University, Ankara, Turkey



Cornea is the outermost, transparent layer of the eye.

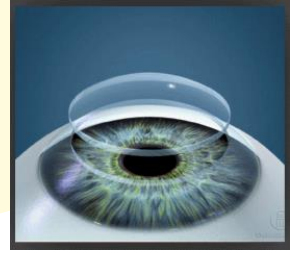
It is responsible for:

1) Physical Protection of the eye
2) Focusing of the incoming light

-Injuries or diseases may render cornea opaque, thus causing blindness

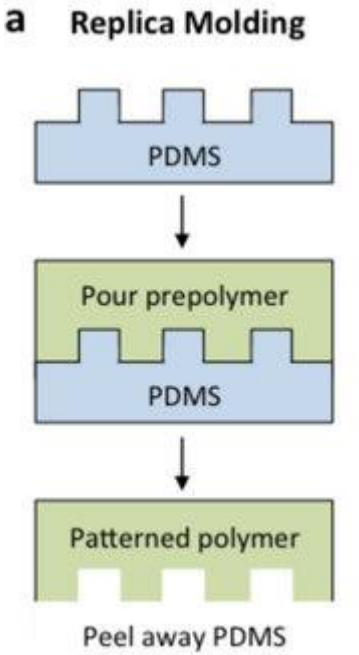
Remedy: Transplantation

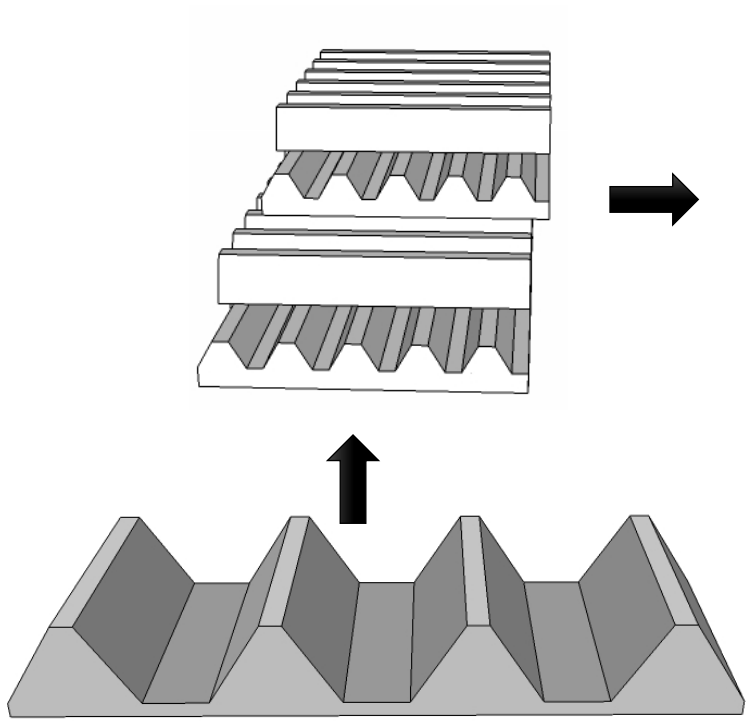
Shortcoming: Donor Shortage



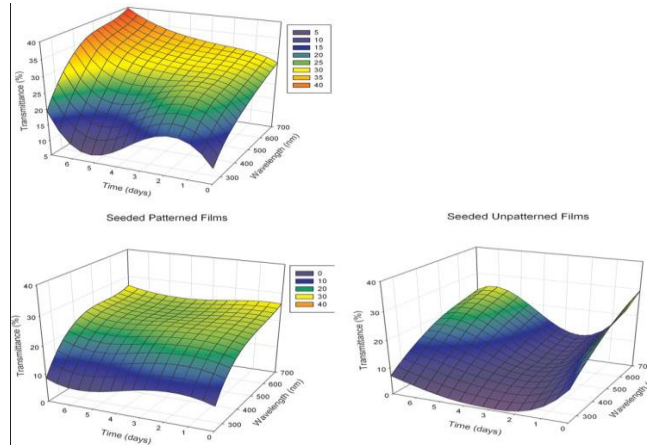
Solution I: Multilayered Micropatterned Structures

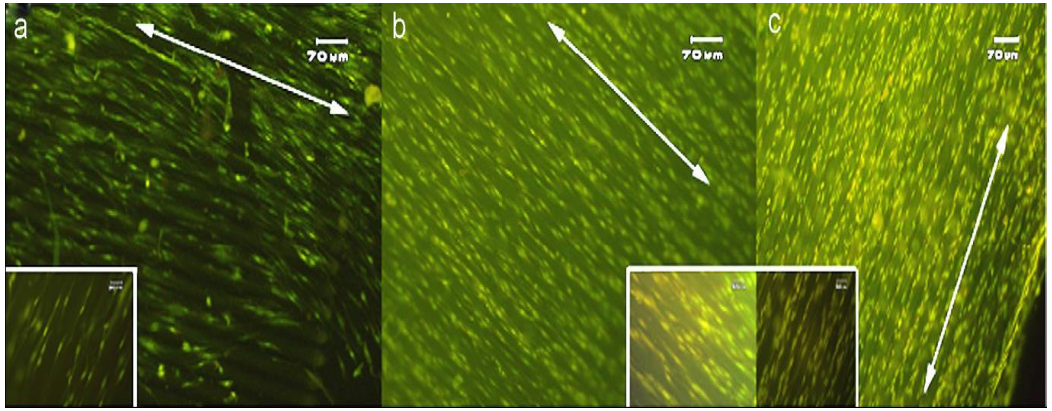
Patterned collagen film multilayers that can imitate the native corneal stroma structure





Transparency



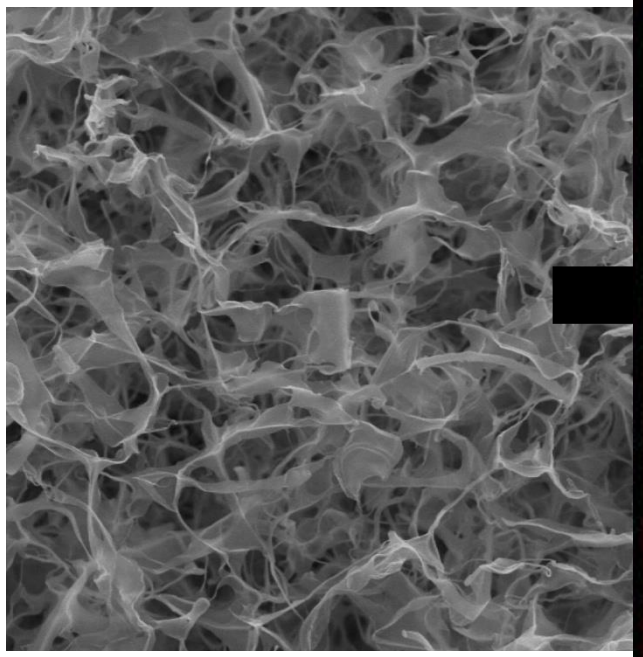


Vrana et al Biomaterials, JBMRA, Patent 12/531,91

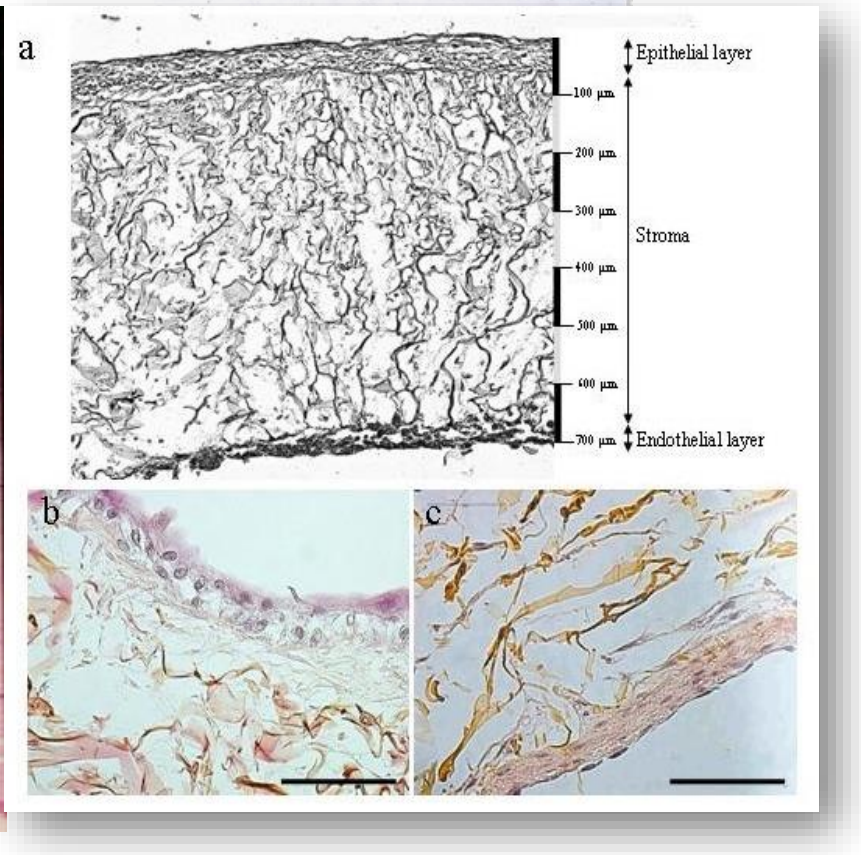
Keratocyte Behaviour on Micropatterns

Solution II: Collagen foams with a thickness close to the native cornea and can inhabit all 3 cell types

- Seeding of collagen foams with corneal keratocytes, epithelial cells and endothelial cells sequentially



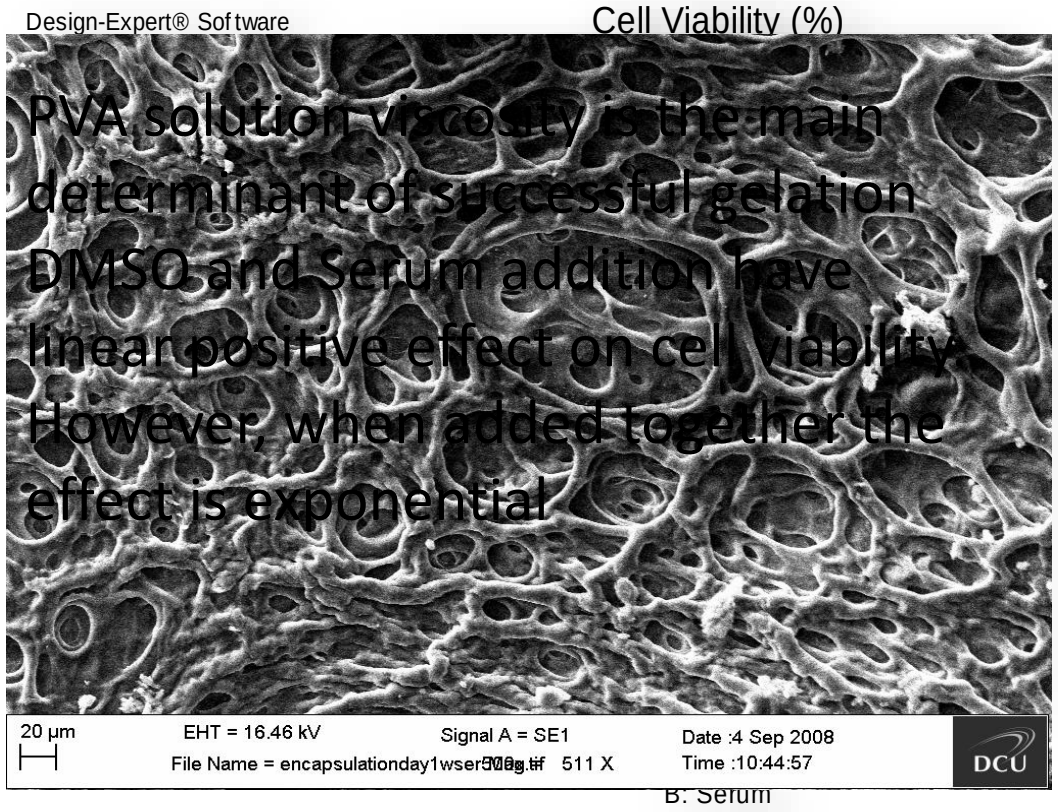
Collagen foam



Well define 3 layered Corneal structure

Vrana et al JBSPE 2017, IOVS 2018

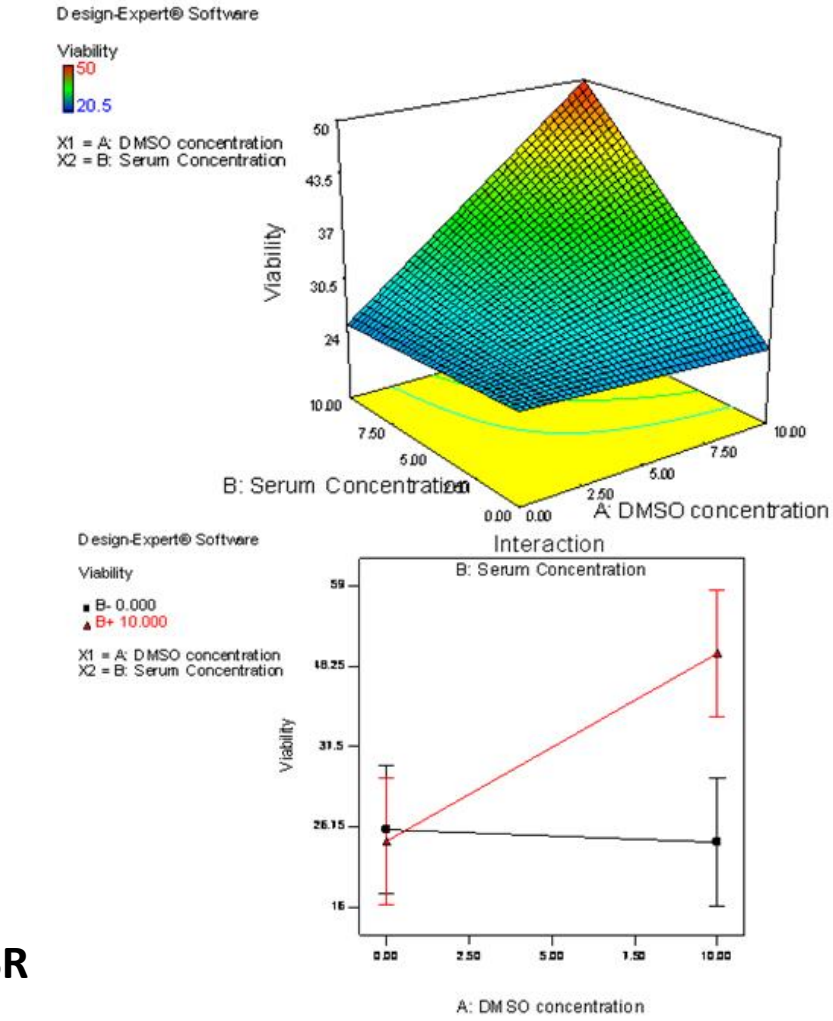
Utilisation of PVA Cryogelation for one-step Cryostorage and Cell Encapsulation System for Vascular Tissue Engineering



PVA solution viscosity is the main determinant of successful gelation

DMSO and Serum addition have linear positive effect on cell viability

However, when added together the effect is exponential

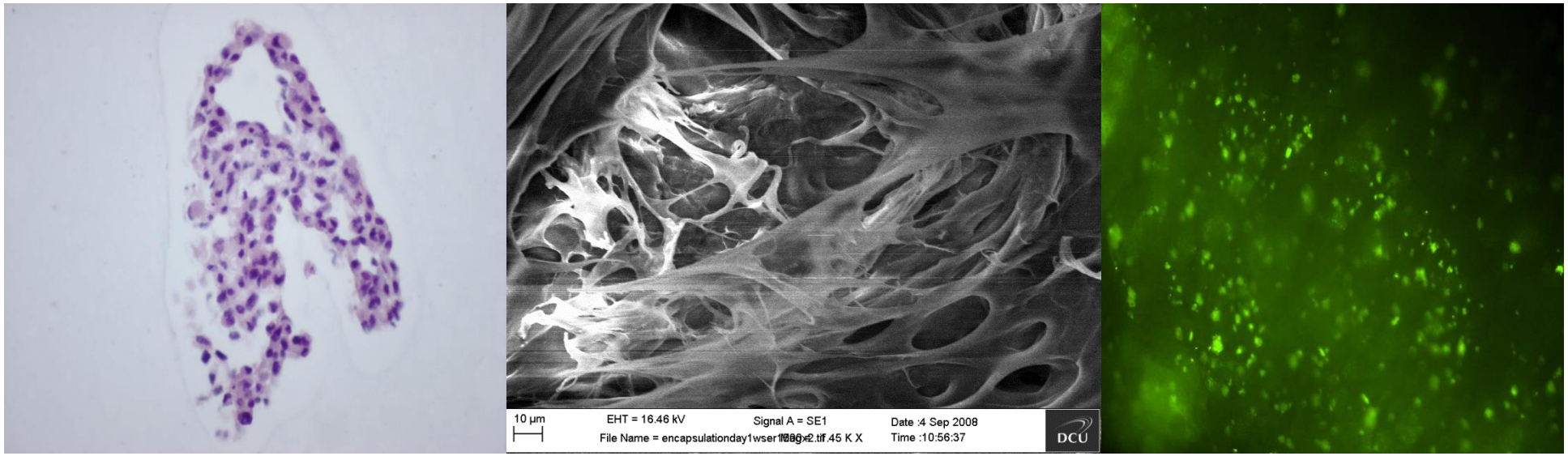


Within the framework of FP6 Marie Curie NOVELSCAFF Project: Marie Curie ESR

Vrana et al. Macromolecular Symposia 2007, JBMRB 2008, JTERM 2009

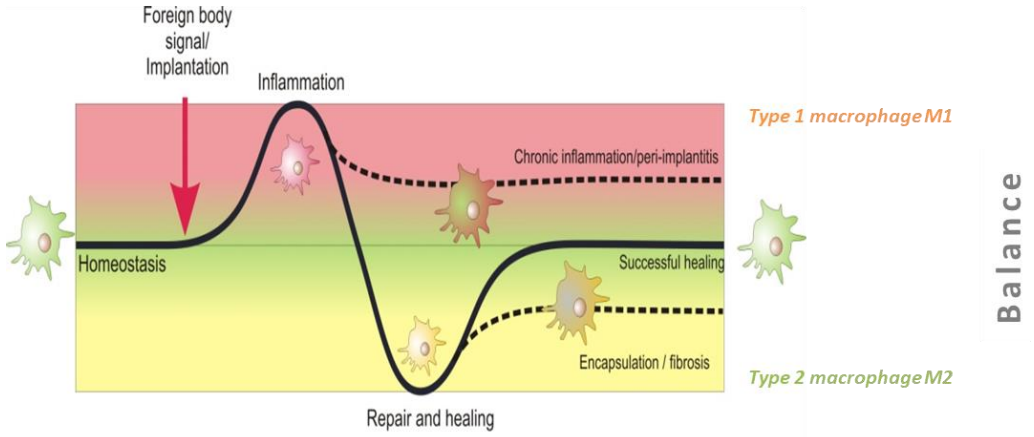
Characterisation of Cell encapsulated PVA/Gelatin Cryogels

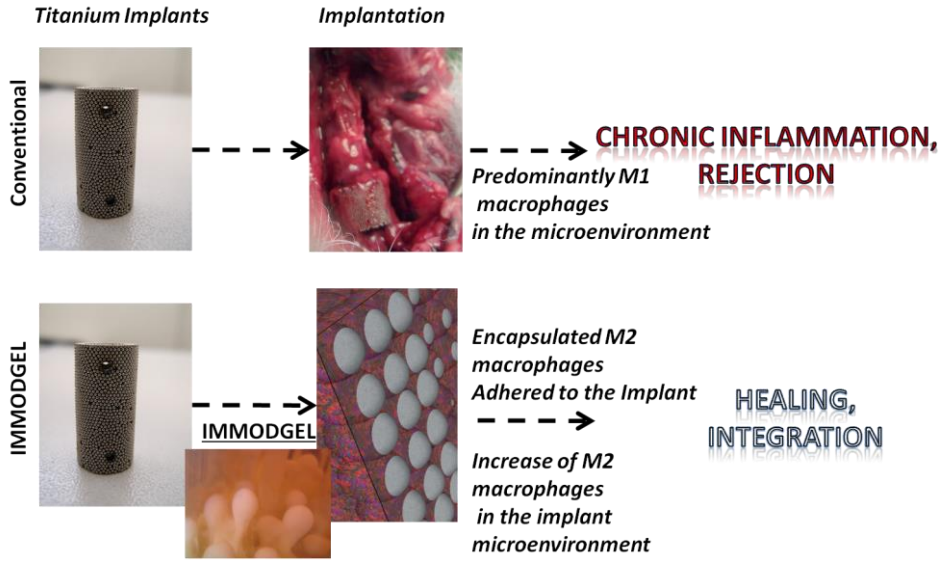
- Cells proliferate within the hydrogels up to 14 days
- Hydrogels with encapsulated cells had higher UTS and were stiffer.
- Cell initially cluster in big pores, but then were able to migrate
- Tests with cyclic strain caused an increase in proliferation



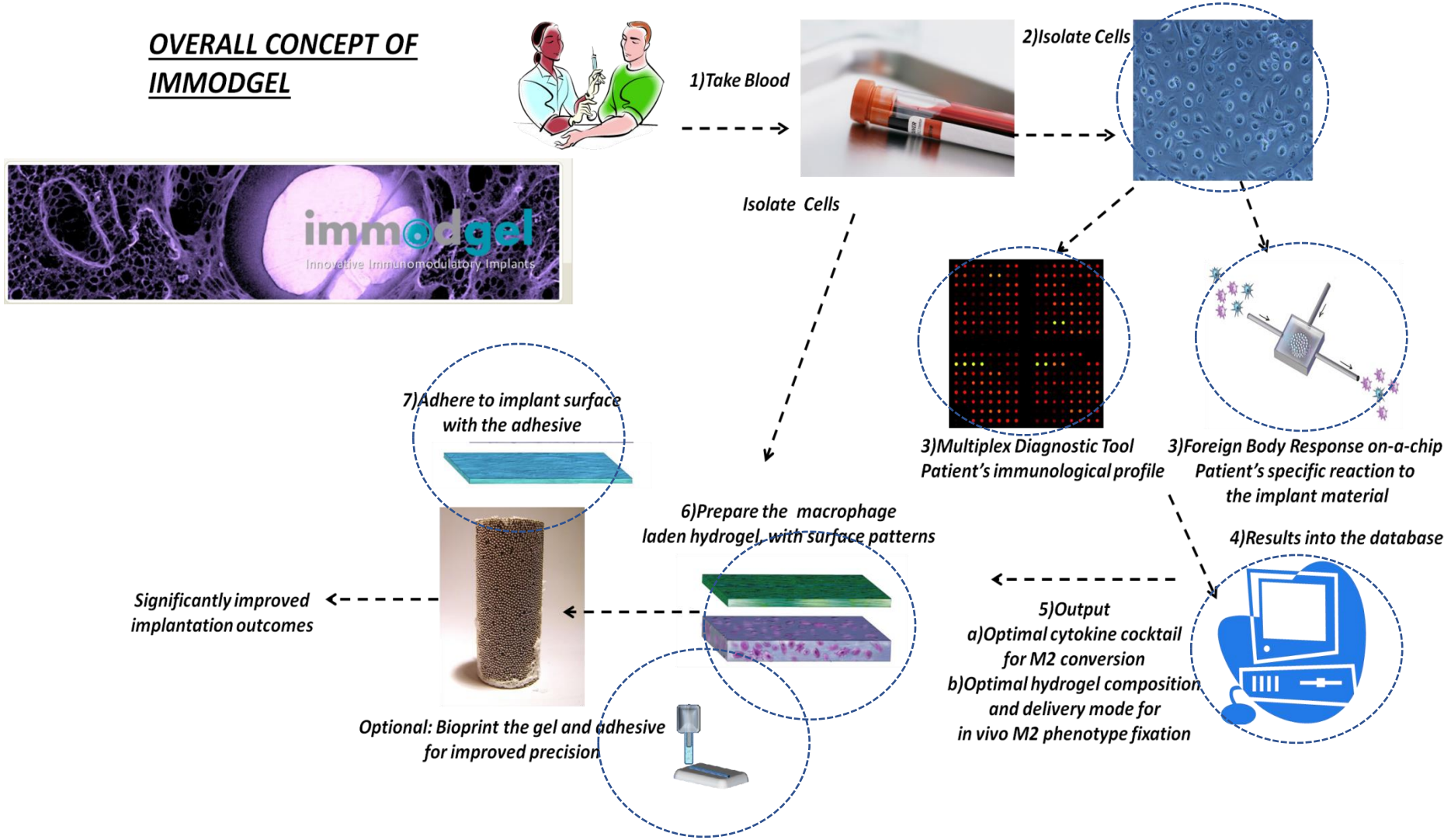
» Local immunomodulation around implants by innovative auxiliary hydrogel-based systems encapsulating autologous and phenotype controlled macrophages.

***Monocytes**: differentiation in M1 or M2 macrophages*

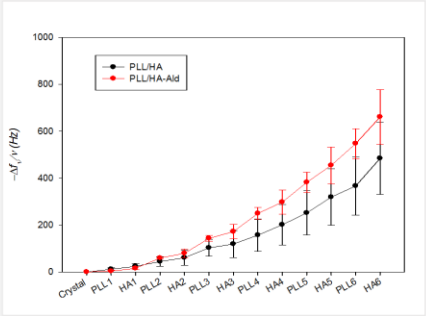




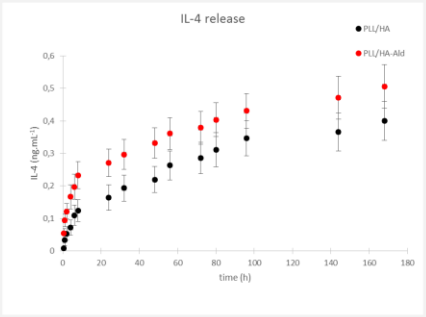
Origins: IMMODGEL



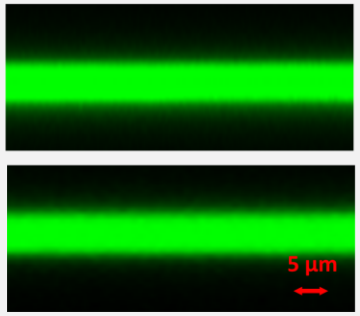
PLL/HA-Aldehyde Self-Crosslinking Coatings



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.

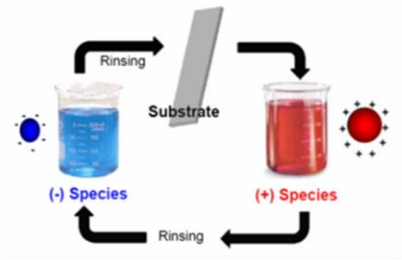


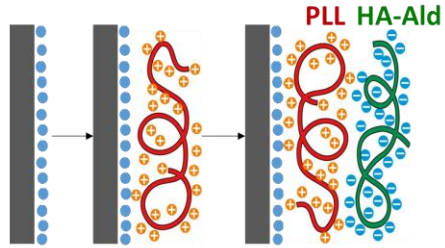
Section images, obtained by confocal laser scanning microscope, of $PLL/HA)_{24}$/PLL-FITC/HA and $(PLL/HA\text{-}Ald)_{24}$/PLL-FITC/HA-Ald multilayer films, respectively.

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

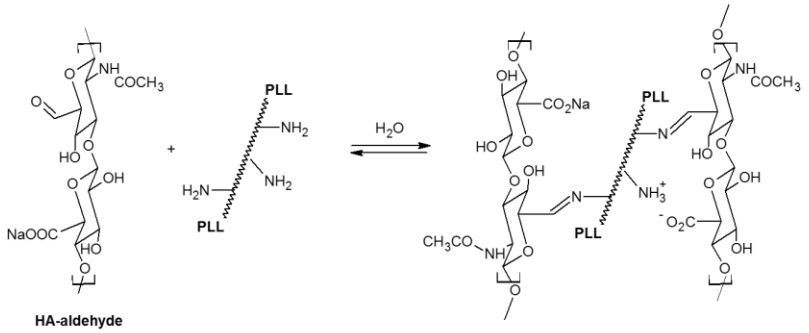
Films	Young Modulus (kPa)	±
$(PLL/HA)_{24}$	10	4
$(PLL/HA\text{-}Ald)_{24}$	142	63

Methods





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



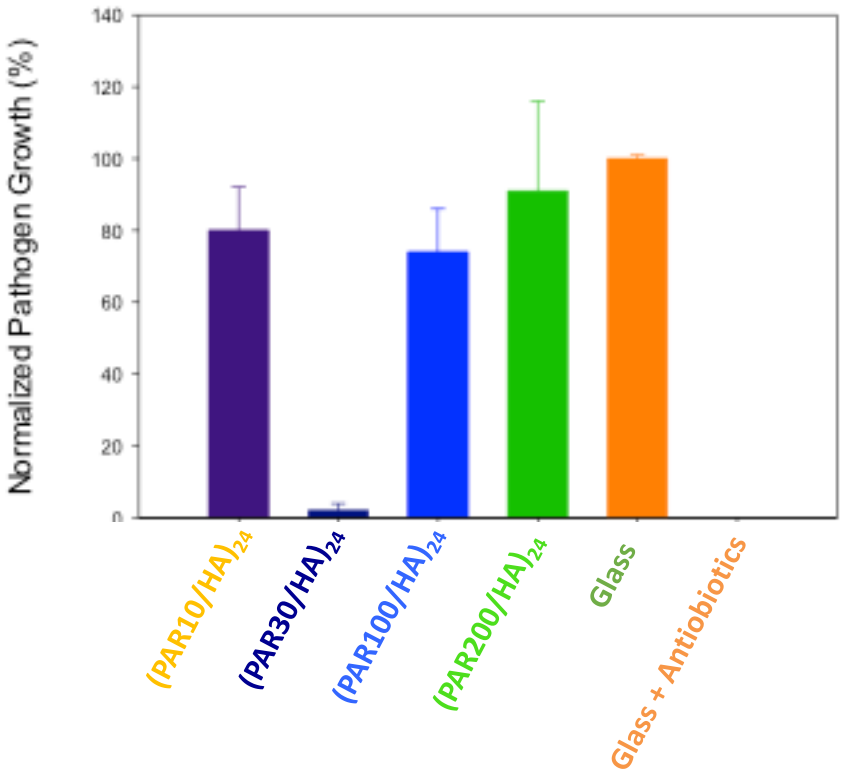
The polyelectrolyte multilayer films formed by PLL and HA-Aldehyde are crosslinked by themselves without any addition of elements or stimuli.

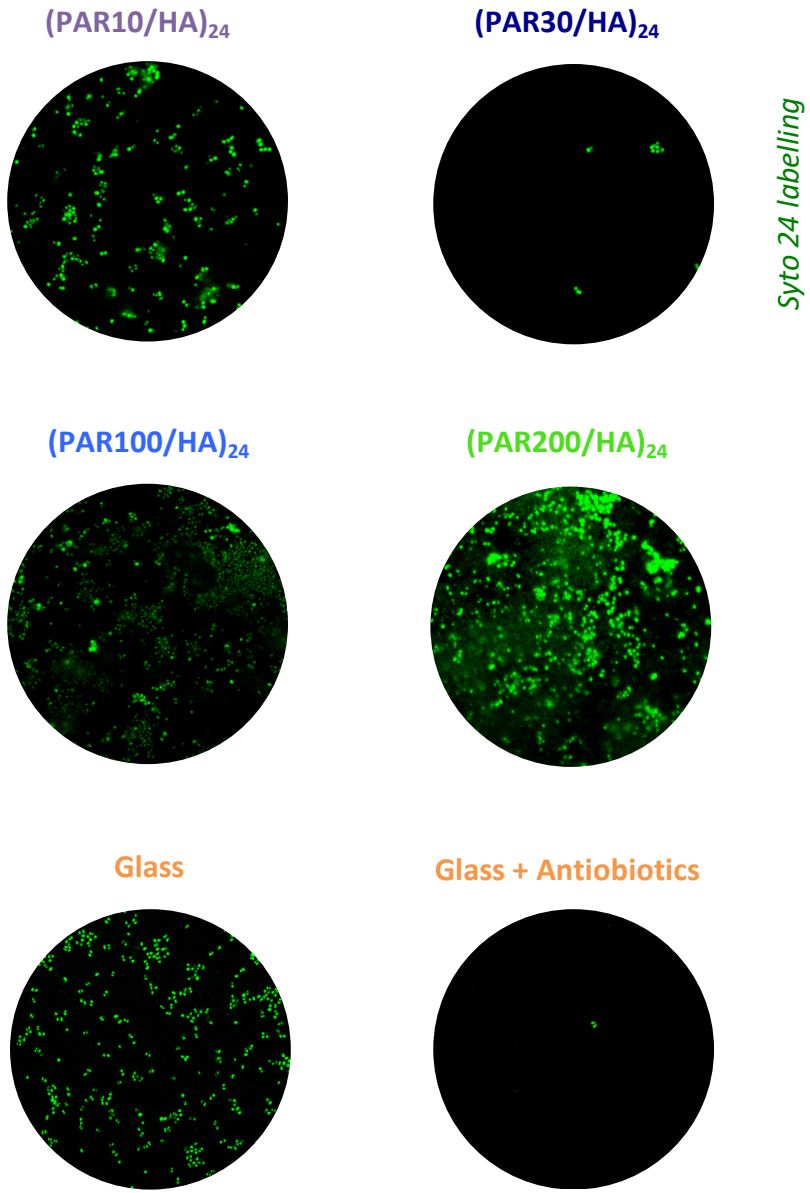
- ✓ The principle of this crosslink reaction is of hydrolytically **labile imine bond between amino groups** of PLL and **aldehydic** derivative of HA

Knopf-Marques et al. 2016, Biomacromolecules

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 !

Sector : Biotech – Medtech Activity : Multifunctional Coatings

SPARTHA MEDICAL

SPARTHA MEDICAL

Customized Coatings for Your Products

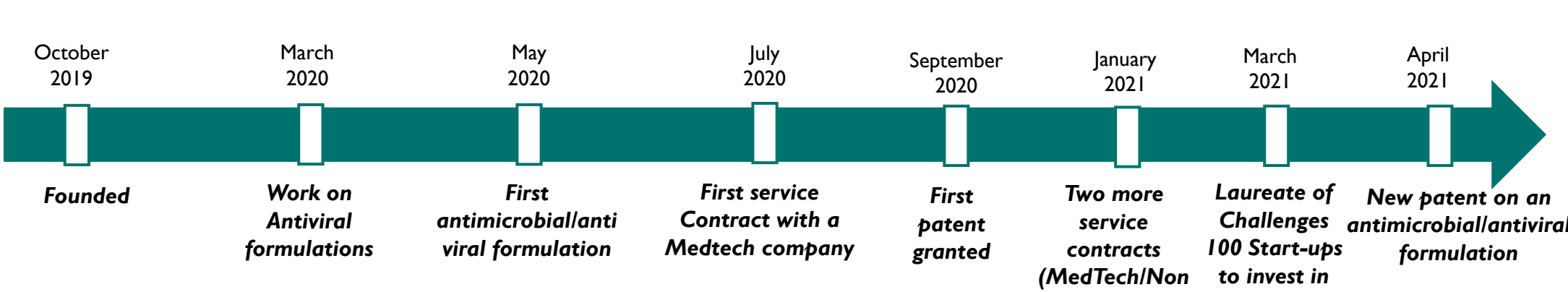
INTRODUCTION
Our Company

ABOUT US

SPARTHA MEDICAL develops nanoscale and micrometric coatings that can prevent complications and infections.
We develop antimicrobial, antiviral, anti-inflammatory formulations.
We are working to make this world healthier and to protect people from the negative impact of bacteria and viruses and help them benefit more from medical devices.

Our inspiration *is the 300 Spartans during the Thermopylae war which has held an army of 150.000 strong by themselves. Our thin coatings in a similar way can kill millions of bacteria and inactivate viruses*
570.000 Euros raised (Non-dilutive)/ Currently fundraising (600.000 Euros)

Chronology



SPARTHA Customized Coatings

Mission :

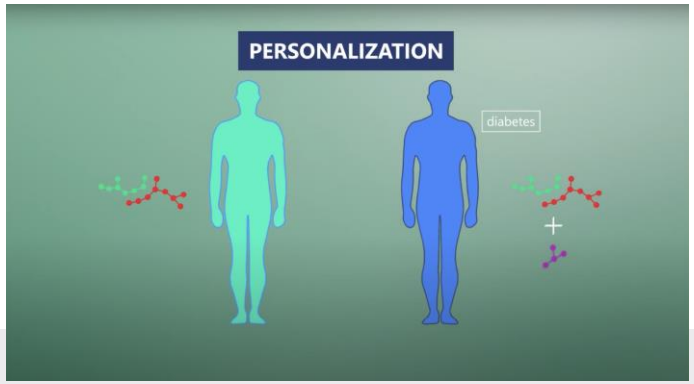
Customisation of surfaces with innovative coatings (such as implant personalisation)

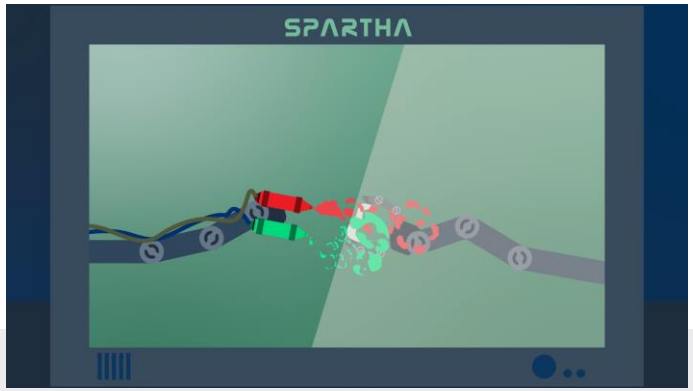
What we develop :

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





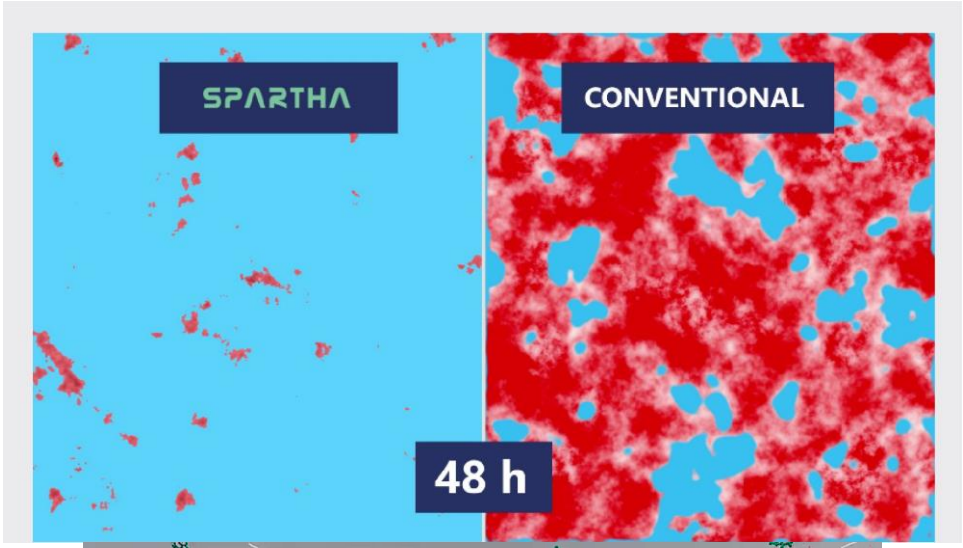
SPARTHA Multifunctional Coatings- Value Proposition

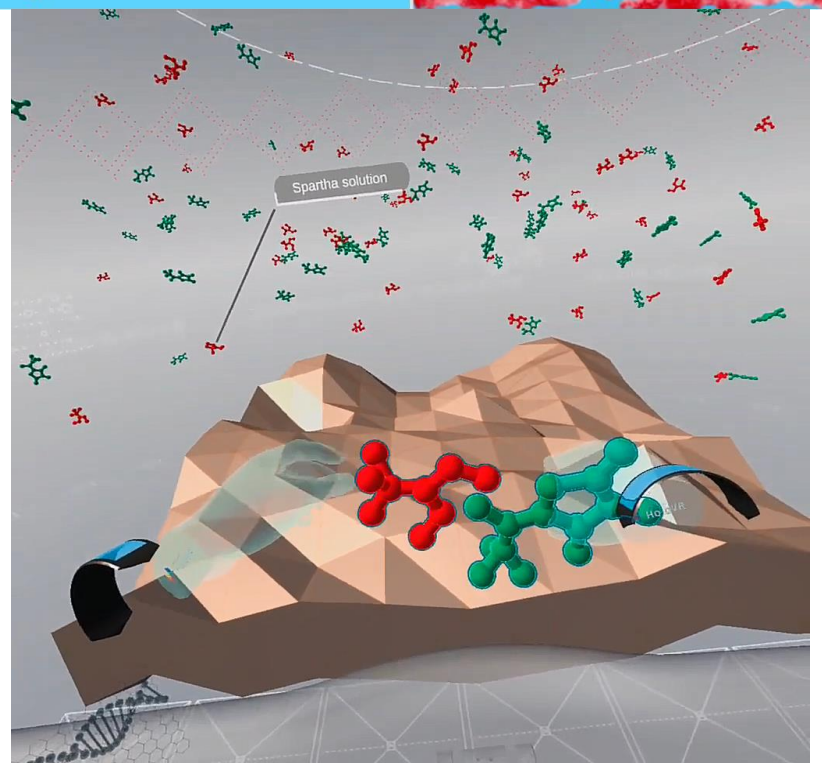
01 **Unique Selling Point 1 :**
Antimicrobial/Anti-viral combination
Which forms a coating on the surfaces

Longer activity, 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, environment friendly.
- Can be applied to living tissues

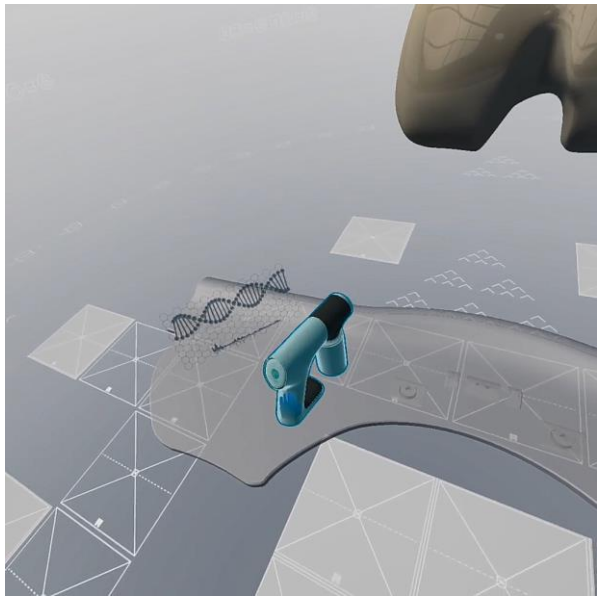




Next step: Medical Implants

Medical Coating kit- Using the established production and marketing capacity for higher added value products

Medical product: SPARTHA MultiProtectION
Product features: Antimicrobial/Anti-inflammatory coating kit with its own spray gun
Classification: Class III Medical Device
Stage of development: Pre-clinic



Application areas:
Advanced Woundcare products
Catheters
Dental Implants
Orthopaedic implants
ORL implants

Current Clients/Collaborators

A new tool for safety in the operating theatre

Antimicrobial activity against other strains

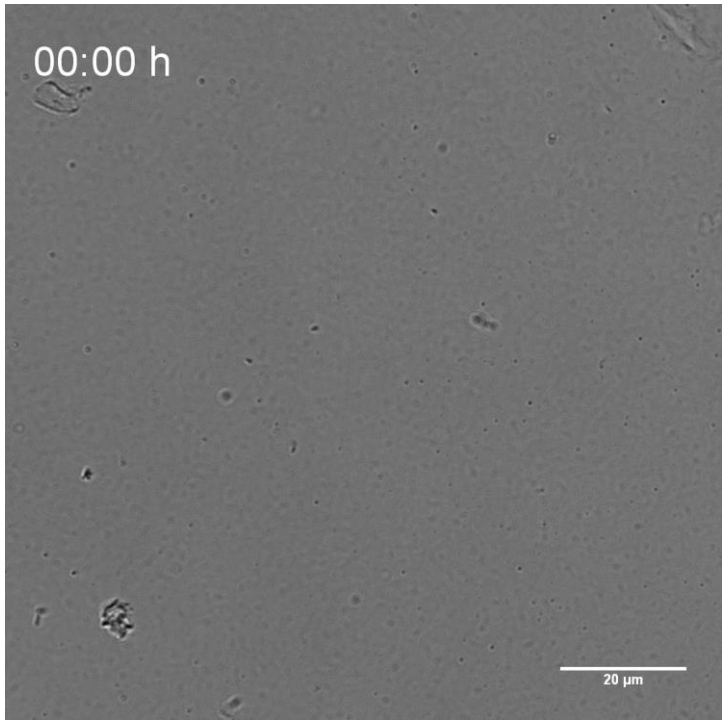
Microorganism growth in contact with (PAR30/HA)24 coating - **ISO22196 assay**

	$(PAR30/HA)_{24}$
Escherichia coli	1.22 ± 0.38
Pseudomonas aeruginosa	2.36 ± 0.92
Candida albicans	1.20 ± 0.46
Staphylococcus epidermidis	6.86 ± 0.28
Staphylococcus aureus	7.00 ± 2.55
MRSA	6.91 ± 2.67
Enterococcus faecalis	5.42 ± 2.53

Log reduction in CFU/mL (mean ± S.D.) at 24 h versus control (substrate without coating)

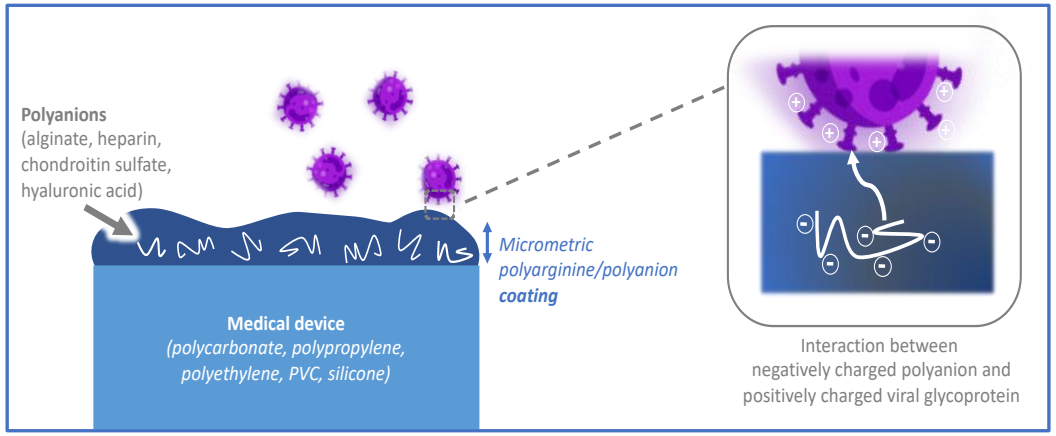
Bacteriostatic activity
(≥ 1 log reduction in CFU/mL)

Bactericidal activity
(≥ 5 log reduction in CFU/mL)

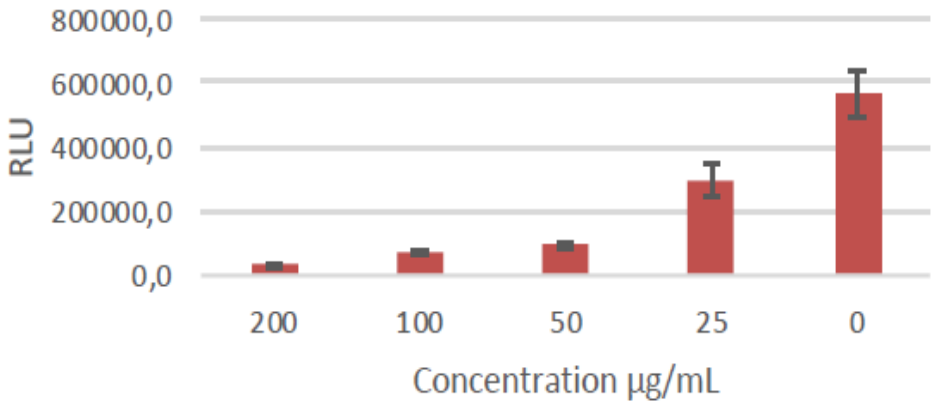


Only **(PAR30/HA)24** films shows antimicrobial properties

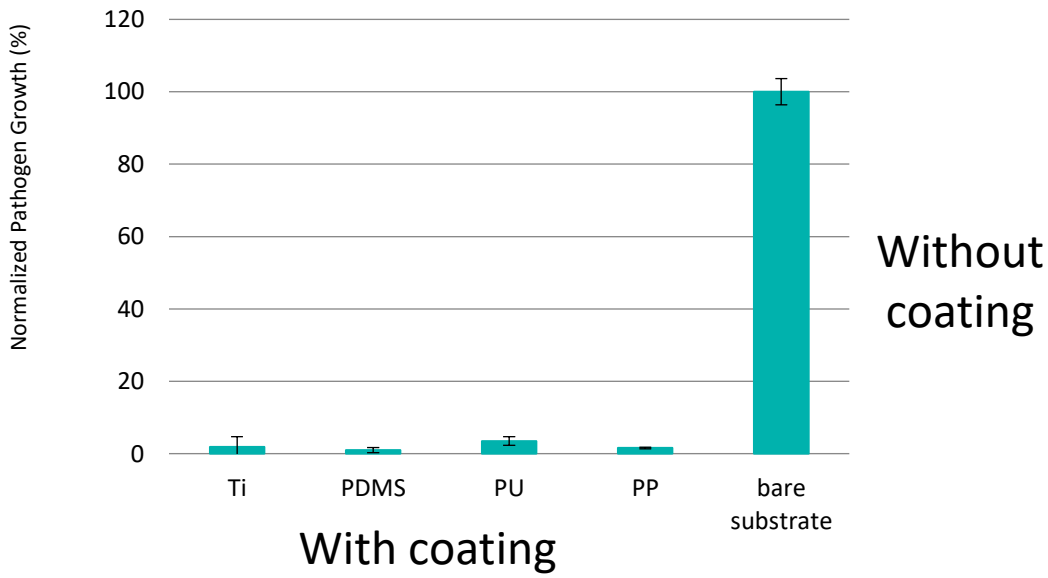
Bacteria removed systematically with SPARTHA use independent of substrate



Inactivates Viruses (Including SARS-COV-2)



It is equally effective on different surfaces



Ti : titanium
PDMS : polydimethylsiloxane
PU : polyurethane
PP : polypropylene

Coating is effective on several medical grade materials

Works against viruses also

SPARTHA MEDICAL

Technology Validation

- **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)

- **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)

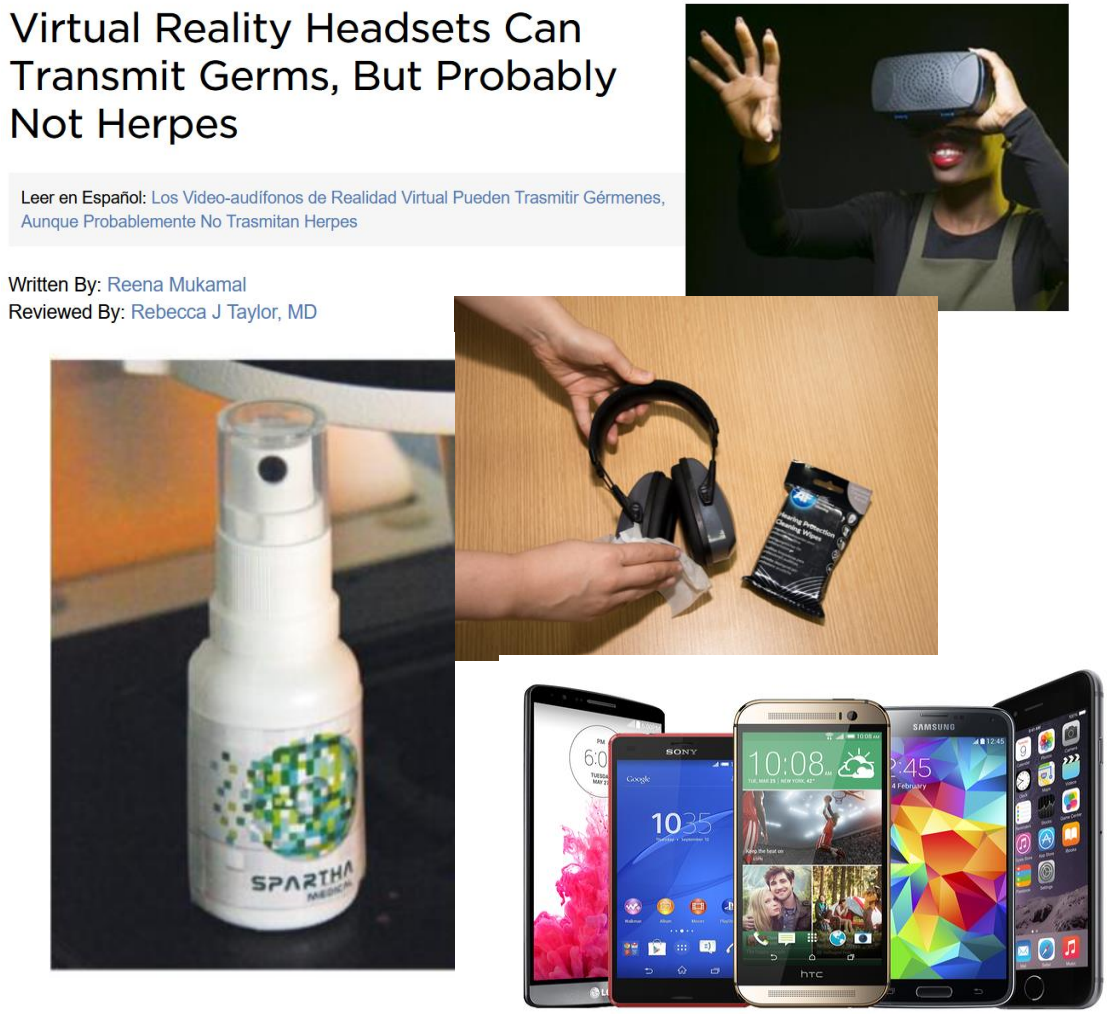
SPARTHA Activity

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:

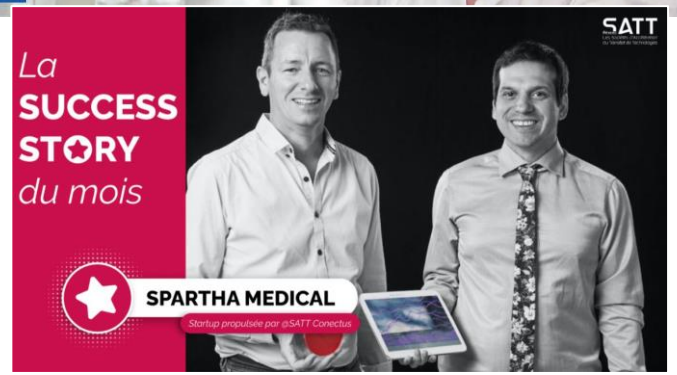
Clients- Industry (SME/Start-up):

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)

DANS LA PRESSE



Actu › Grand-Est › Actu Strasbourg › Coronavirus

Strasbourg. Jeune start-up prometteuse, Spartha Medical développe un spray anti Covid-19

Inoffensif pour le corps humain, le spray anti-Covid-19 développé par la startup Spartha Medical pourra être utilisé comme un "masque pulvérisable", sans pour autant le remplacer.

Spartha Medical est une startup strasbourgeoise créée en octobre 2019 qui développe un spray antiviral et antimicrobien. (©Spartha Medical)

CONFIDENTIEL

Spartha: des revêtements customisés pour vos produits

Par Challenges.fr le 25.03.2021 à 09h00
Lecture 2 min.

Spartha Medical a développé des revêtements multi-fonctionnels dont la particularité est de prévenir les infections et de diminuer l'inflammation sans affecter les fonctions des dispositifs médicaux. Cette start-up fait partie de la sélection "100 start-up où investir en 2021" de Challenges.

bpifrance i-Lab ANR

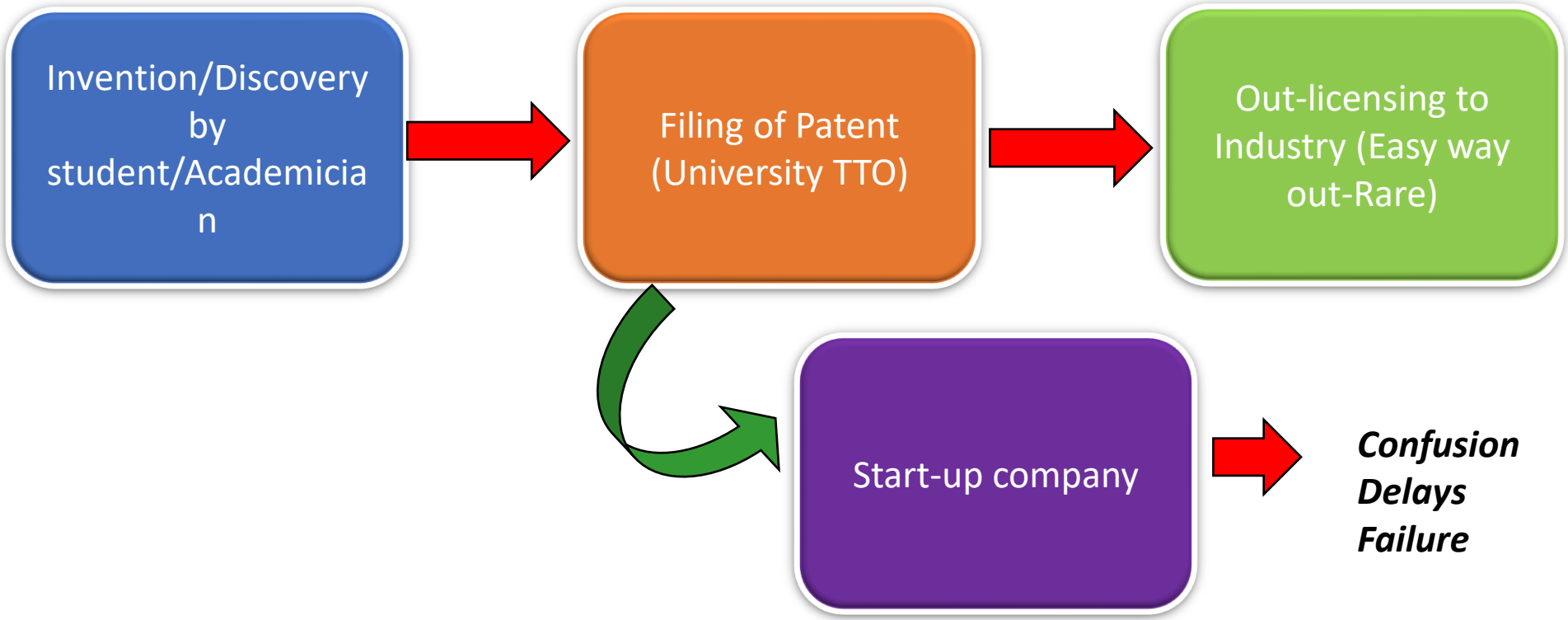
SEMIA CONECTUS OFFICIAL INNOVATION PROVIDER PANBIORA European Commission Horizon 2020 European Union funding for Research & Innovation Grand Est ALSACE CHAMPAGNE-ARDENNE LORRAINE Strasbourg.eu eurometropole INSTITUT CARNOT MICA

Rencontres Economiques 2021

https://vimeo.com/541986700

Rencontres Economiques - 03 - Unistra - Spartha Medical

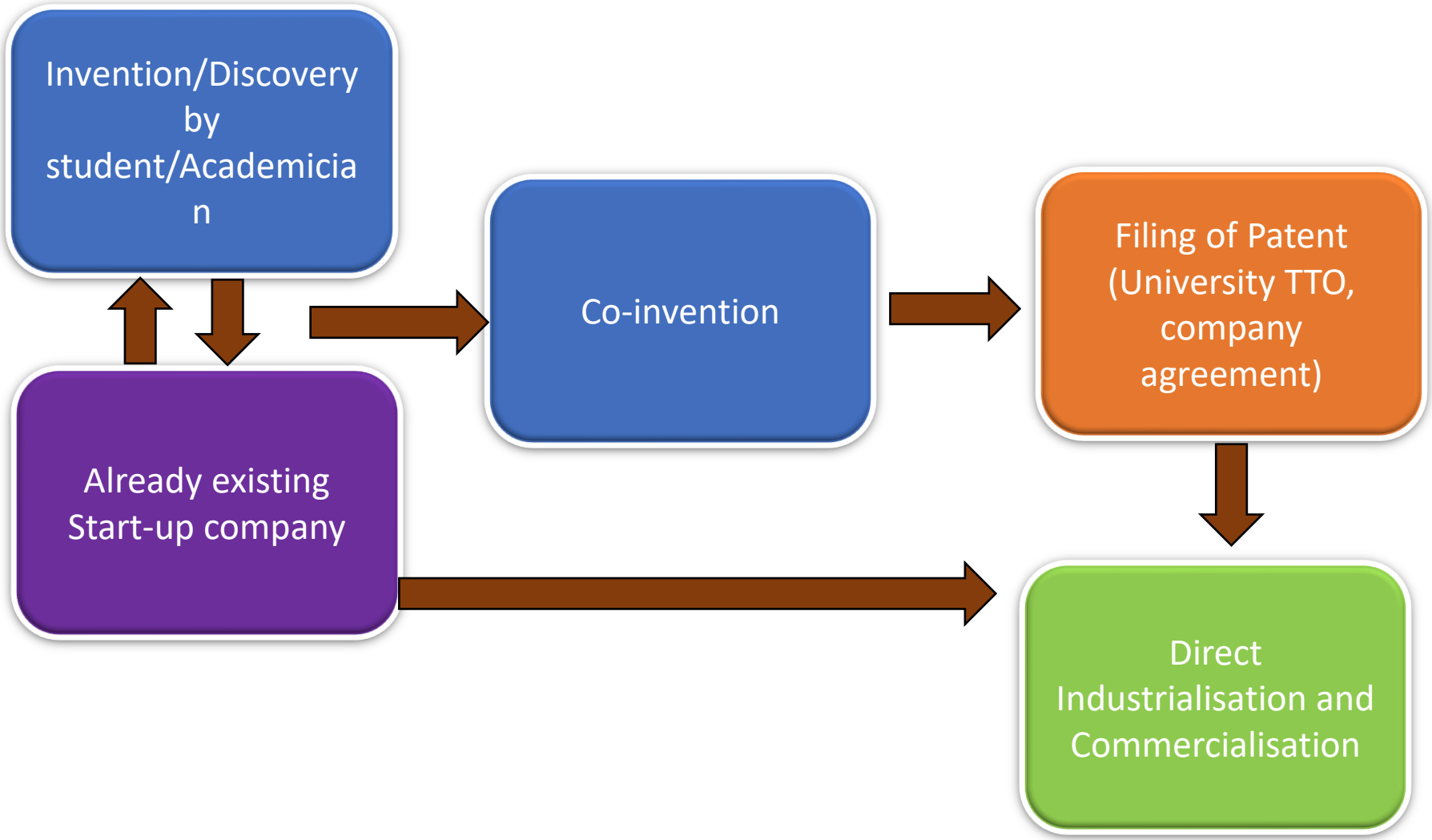
The Standard Route of Technology Transfer



Reasons for confusion and failure

- Re-inventing the wheel fo reach start-up
- The discovery/invention does not fit well with Industrial needs, academicians cannot know this
- The discovery/invention is not upscalable, hard due to regulatory or logistics aspects- not the job of academician
- The advance is not worth the expenses of industrialisation and commercialisation- Not all interesting scientific solutions are worth pursuing.
- Targeted market, market analysis or business plan are not right- Lack of knowledge and experience
- Fish out of water effect: You expect somebody with scientific background and credentials to suddenly a businessman-not a good formula.

Our way of Technology Transfer



Pre-requisites

- Previous product experience
- Core capacities in place- conception, production, regulatory affairs, scientific affairs, marketing and distribution
- Well-defined, unique competencies/technologies
- Alignment of capacities and competencies with that of the collaborating academic institutes

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]

To cite: Wang C, Luan J, Panayi AC, *et al*. Complications in breast augmentation with textured versus smooth breast implants: a systematic review protocol. *BMJ Open* 2018;**8**:e020671. doi:10.1136/bmjopen-2017-020671

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-020671).

ABSTRACT

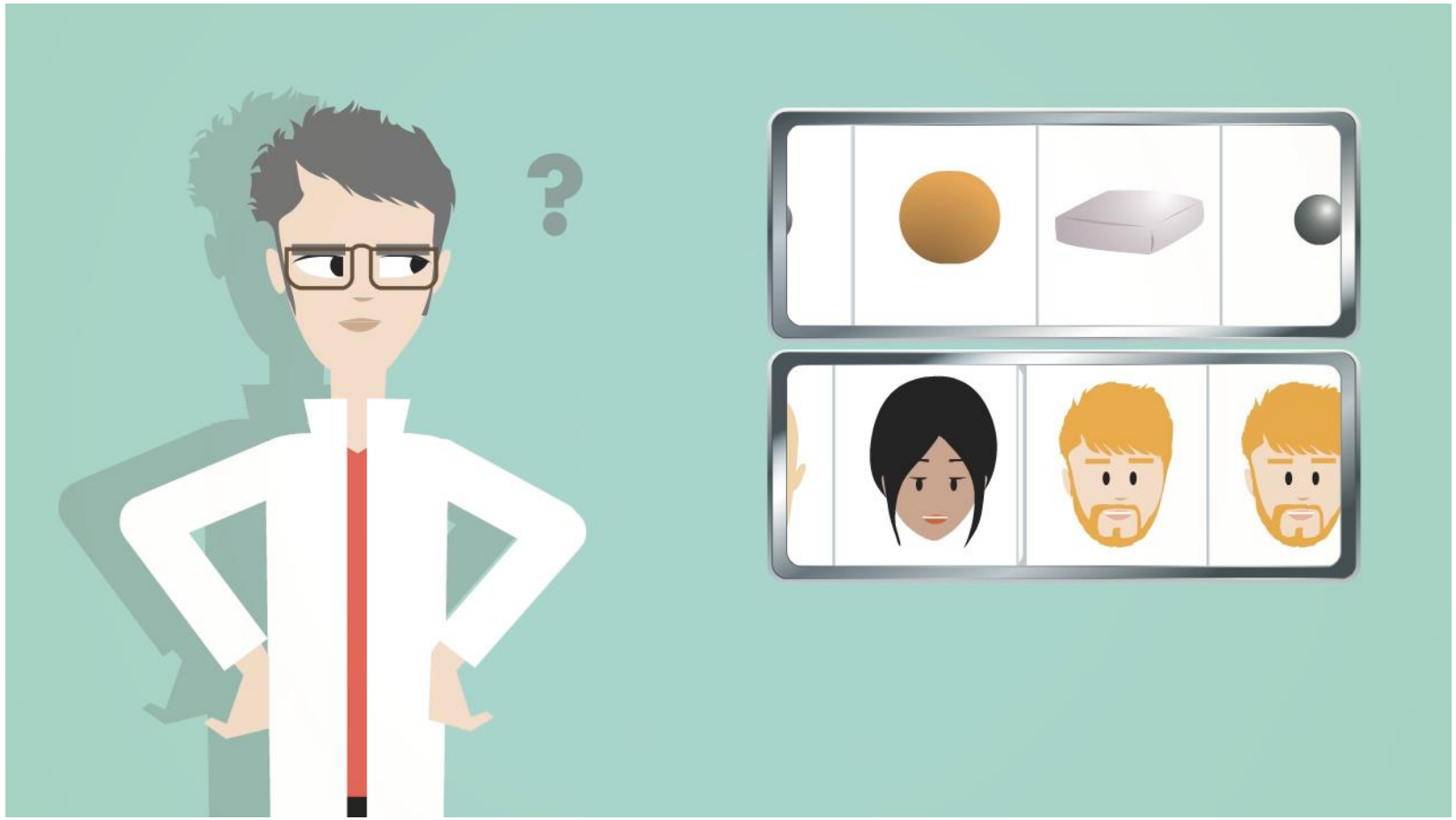
Introduction Breast augmentation is one of the most popular aesthetic plastic surgeries worldwide. There are various types of breast implants, and these can be categorised into different broad groups based on their content, shape or surface, to name a few. When looking at the surface of the shell, they can be categorised into two main kinds: textured and smooth implants. To our knowledge, a literature review and meta-analysis of the complications of these two types of implants when used for aesthetic breast augmentation has yet to be written.

Methods and analysis The PubMed, EMBASE and Cochrane electronic databases will be searched from their inception to 1 October 2017. Only cohort studies,

Strengths and limitations of this study

- The study findings will provide evidence for plastic surgeons to understand the different complications of textured and smooth breast implants.
- The review includes as many complications of breast implants as possible.
- The review will not include unpublished studies or those published in a language other than English. The quality of the primary studies to be included in this review may be a limiting factor due to the different study design.

PANBioRA



PANBioRA

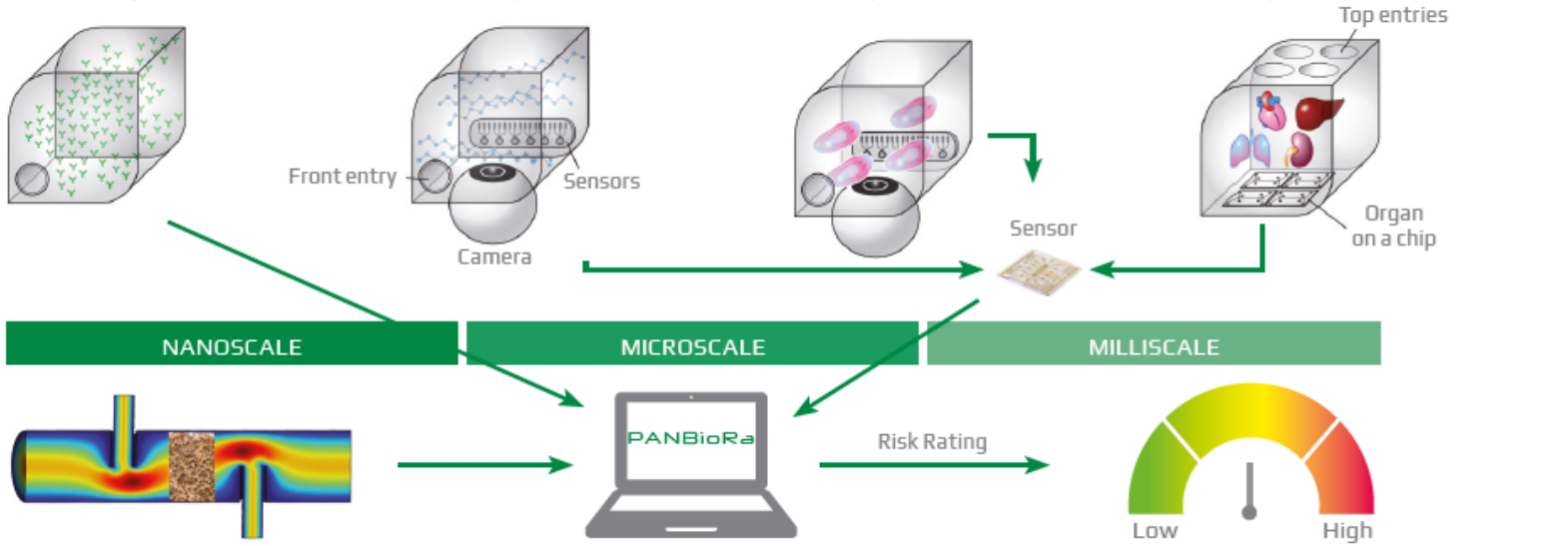
Components of the PANBioRA Biomaterial Risk Assessment System

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.

PANBioRA Consortium

PANBioRA

PANBioRA Consortium

STEINBEIS 2i

University of Nottingham
UK | CHINA | MALAYSIA

PROACTIVE

Steinbeis Advanced Risk Technologies Institute doo Kragujevac

SPARTHA MEDICAL

EPOKA UNIVERSITY

CHU de Liège

PROTOBIOS life sciences

ELVESYS Innovation Center

Inserm
La science pour la santé
From science to health

BIODEVICE SYSTEMS

FROM RESEARCH TO INDUSTRY
cea

DCU
Ollscoil Chathair Bhaile Átha Cliath
Dublin City University

dolmen
making ideas work

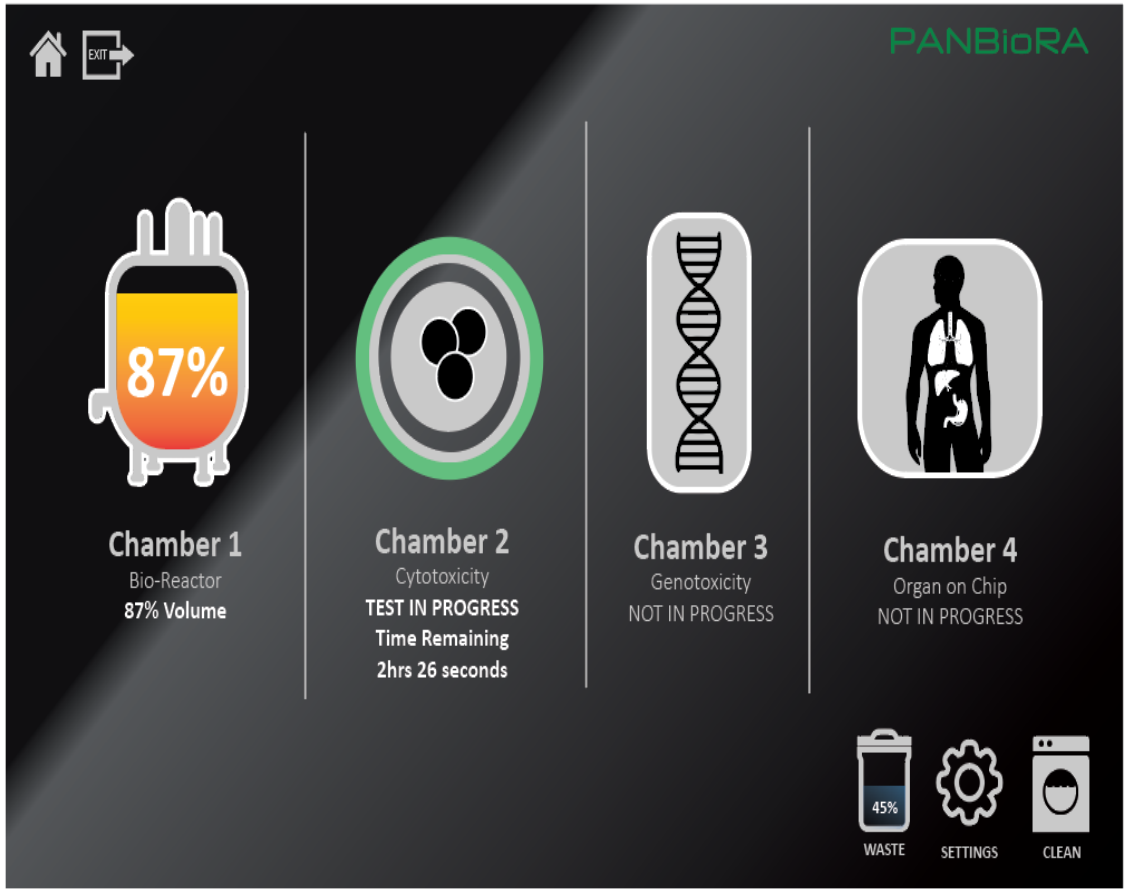
CSIC
Consejo Superior de Investigaciones Científicas

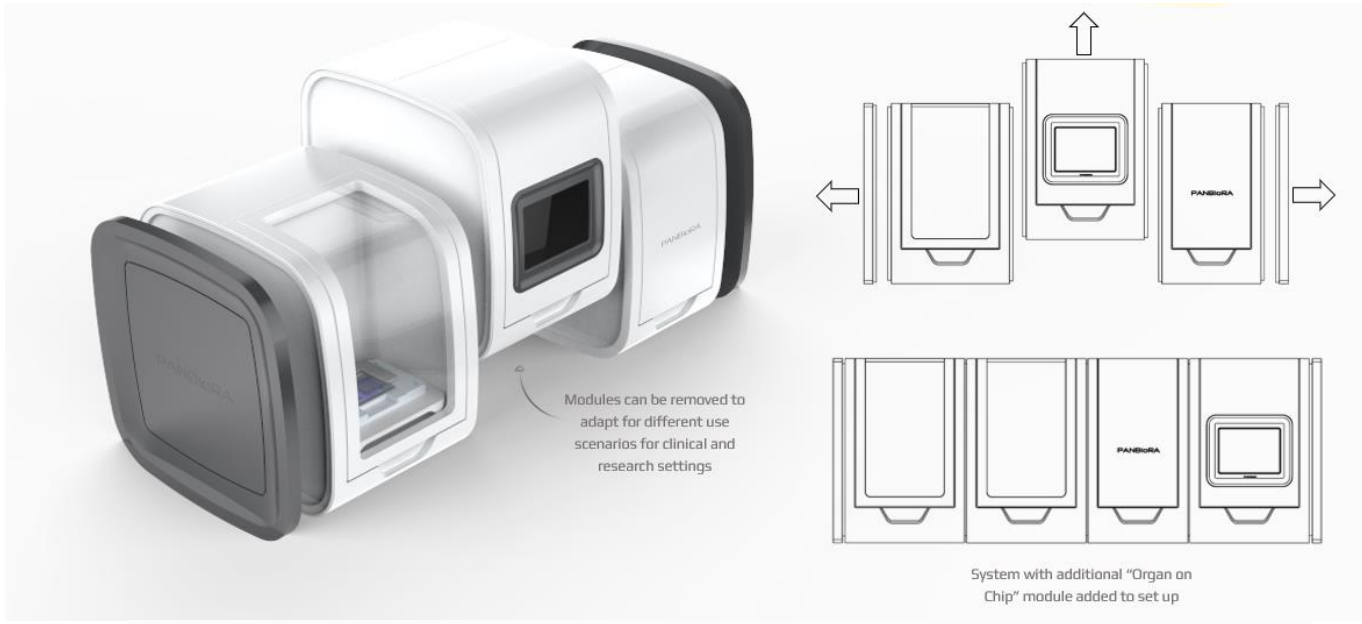
Steinbeis Advanced Risk Technologies GmbH

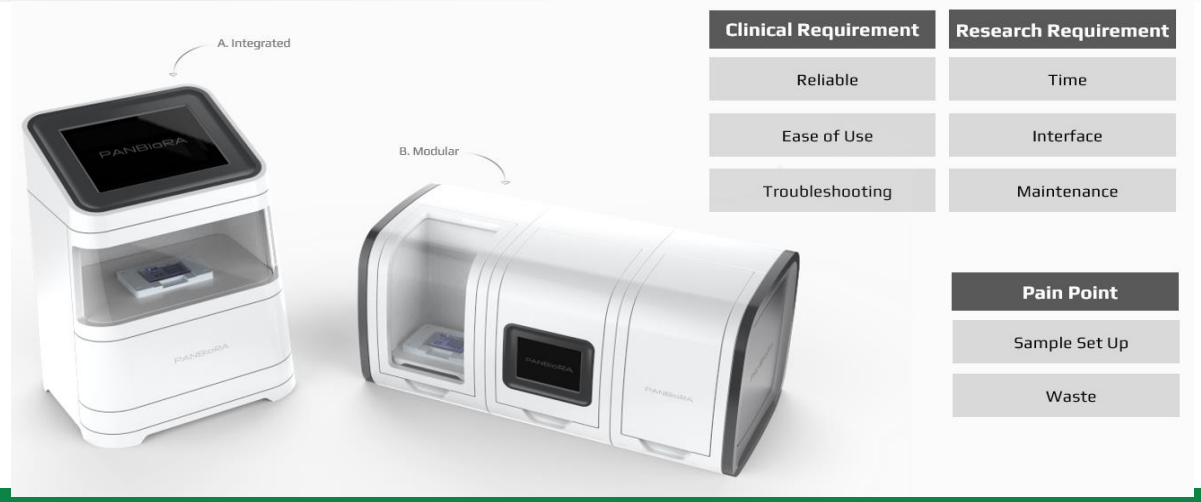
Aalto University

Visit https://showroom.panbiora.eu/

PANBioRA Modular Biomaterial Testing Instrument







Clinical Requirement	Research Requirement
Reliable	Time
Ease of Use	Interface
Troubleshooting	Maintenance

Pain Point
Sample Set Up
Waste

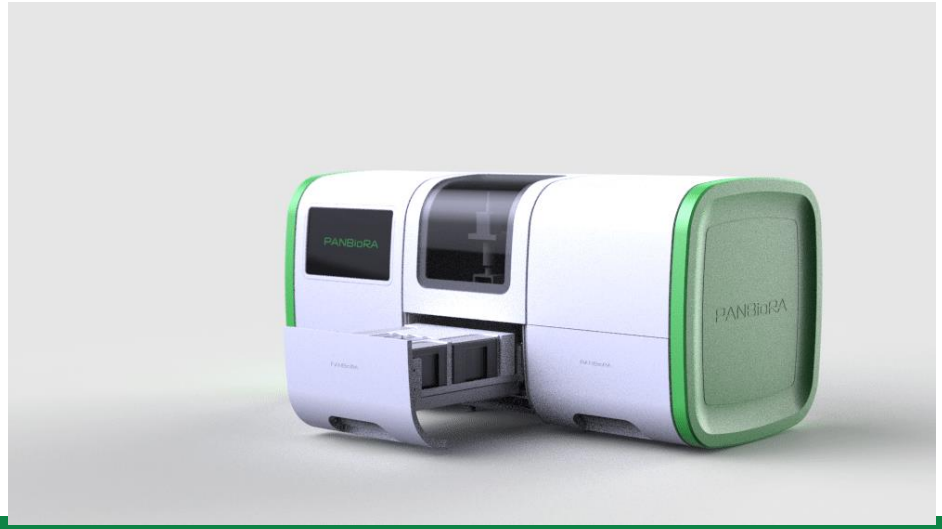
PANBioRA MILESTONES

January 2018	January 2019	May 2019	January 2020	May 2020	October 2020	December 2021	
Years of research and technical work by partners	Start of **PANBioRA** H2020 Project	MVA-based biomaterial competition assay established	Simultaneous read outs from multiple sensors	PANBioRA first prototype	Biokinetic model validation with different biomaterials	Demonstration of Risk Radar detection for a specific biomaterial	PANBioRA Final Product and spin-off	PANBioRA Market entry

PANBioRA Features

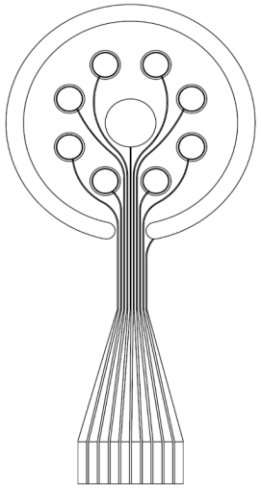
Biomaterial testing in 2D, 3D cell culture, organ-on-a-chip modes in an automated manner with integrated microscope, electrochemical sensors and cytokine sensors

New modules can be added to improve the instrument



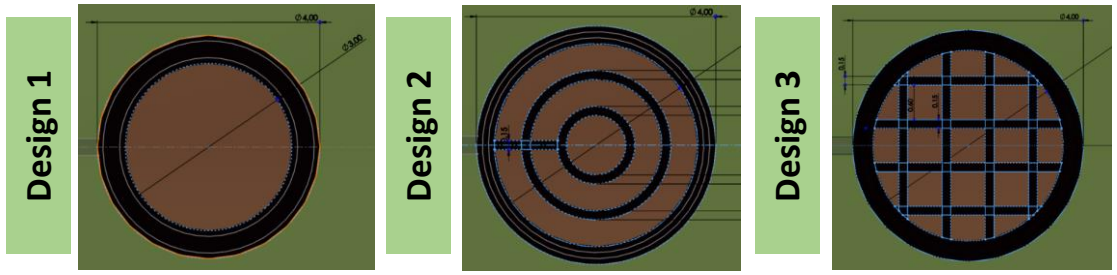
Integrated Automated Testing Modules

» Technological approaches for the aggregation of different sensors on a platform

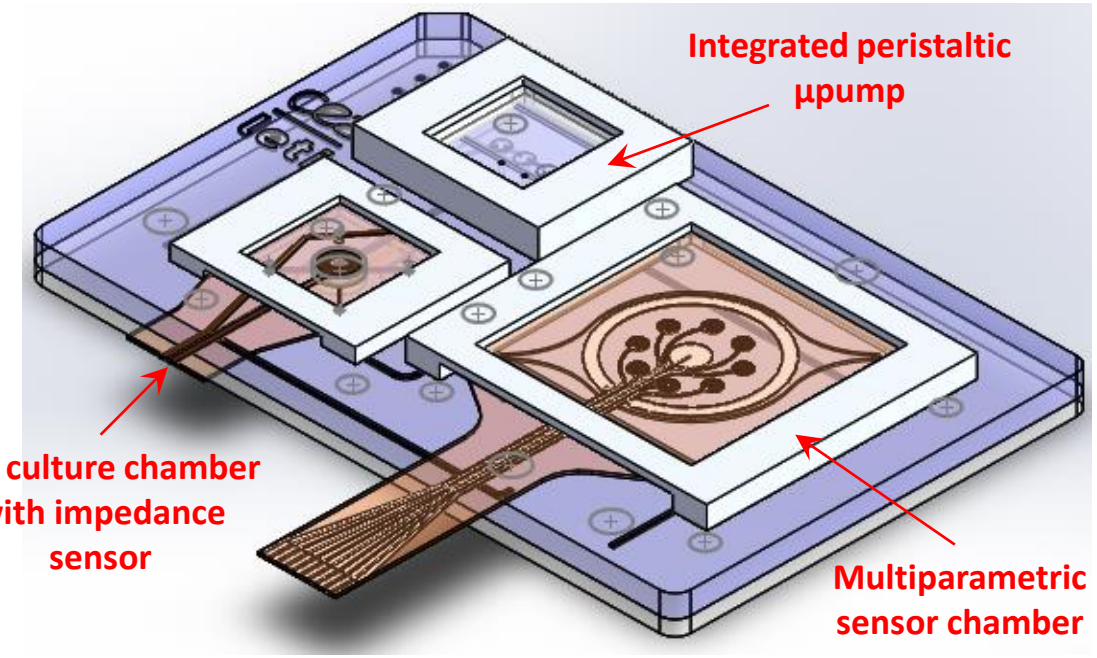


- ***Multiparametric sensor platform***
- Integration through Flex technology of all individual sensors
- Generic platform
  - 8 working electrodes
  - 1 counter electrode
  - 1 reference electrode
- Collective fabrication of 18 platforms
- Reproducibility

» Dedicated impedance sensor designs

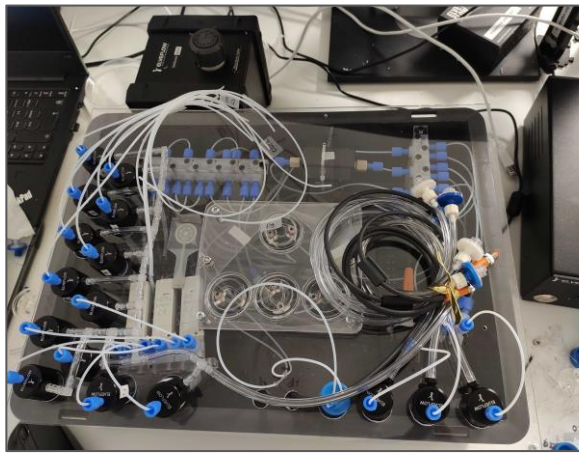


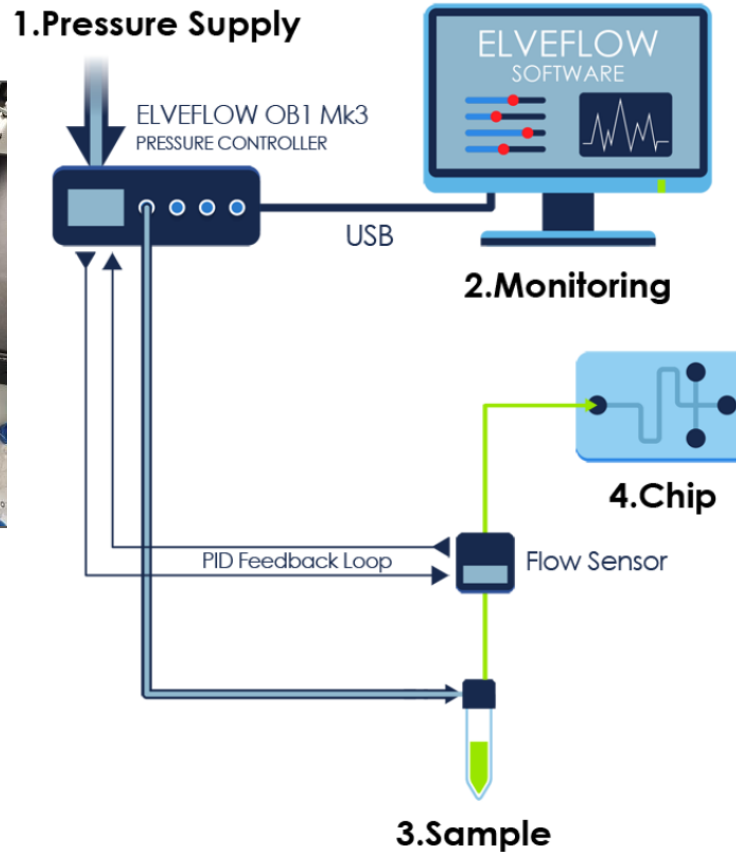
» Mechanical & electrical design of the integrated platform

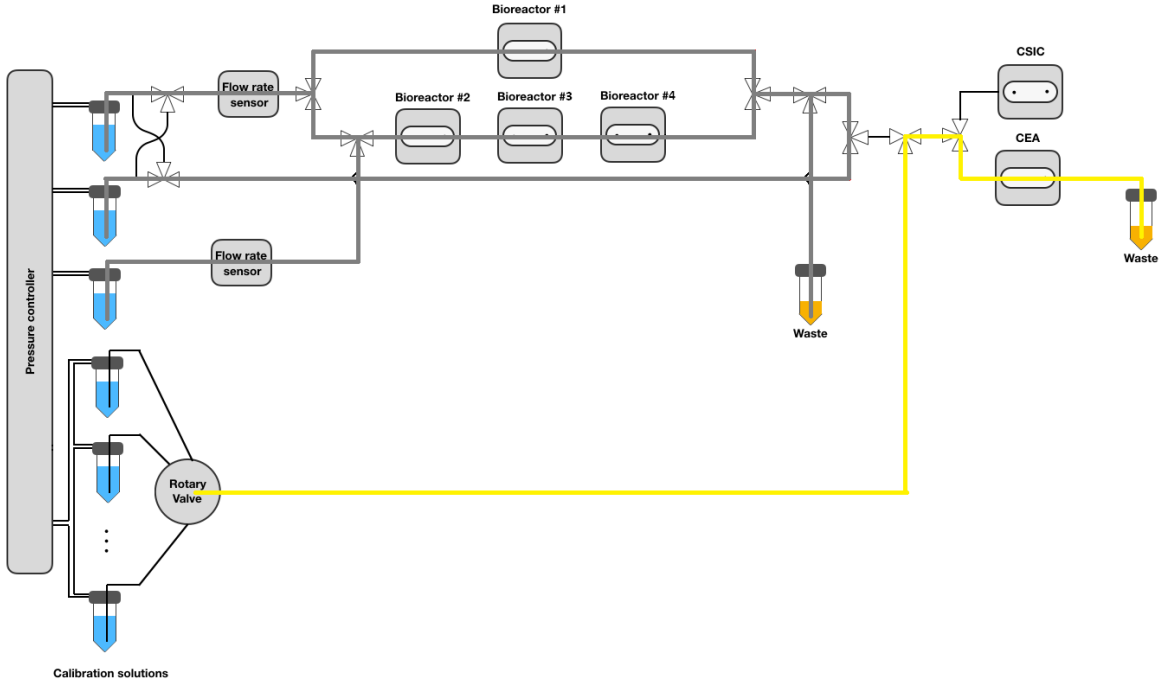


- Design of the Fluidic Circuit Board (FCB)
- Design of 3 modules
- Electrical connection via flex approach

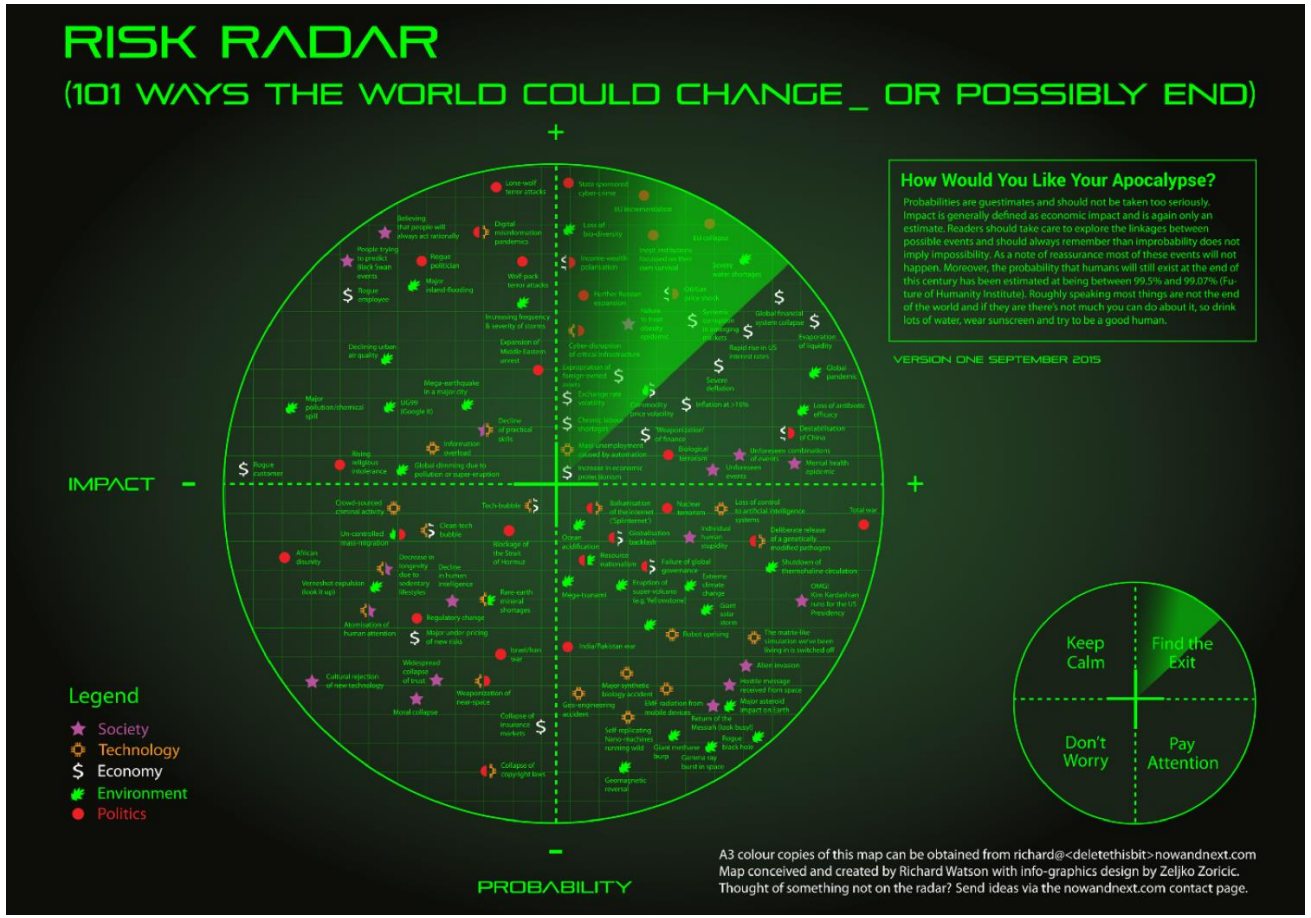
Microfluidic connections

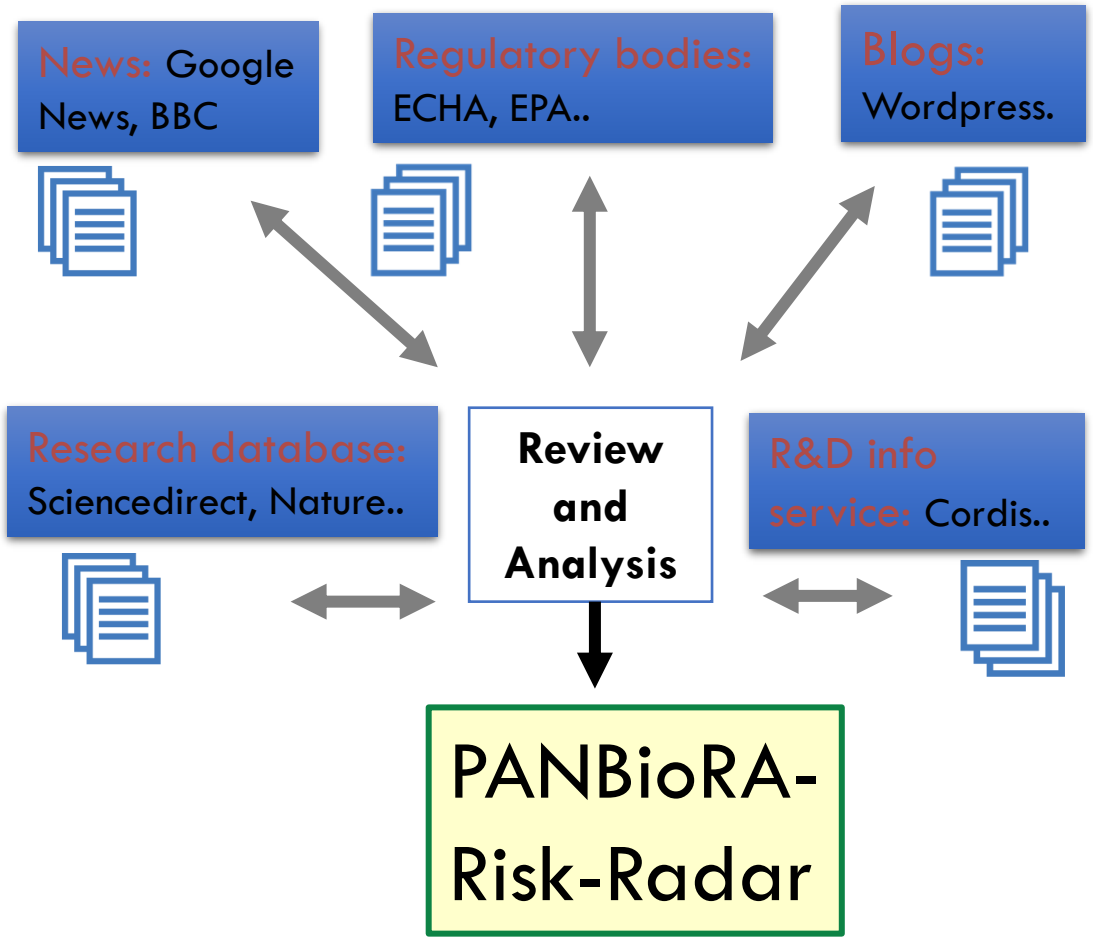






PANBioRA-Risk-Radar





Advantages of EU projects for Industry

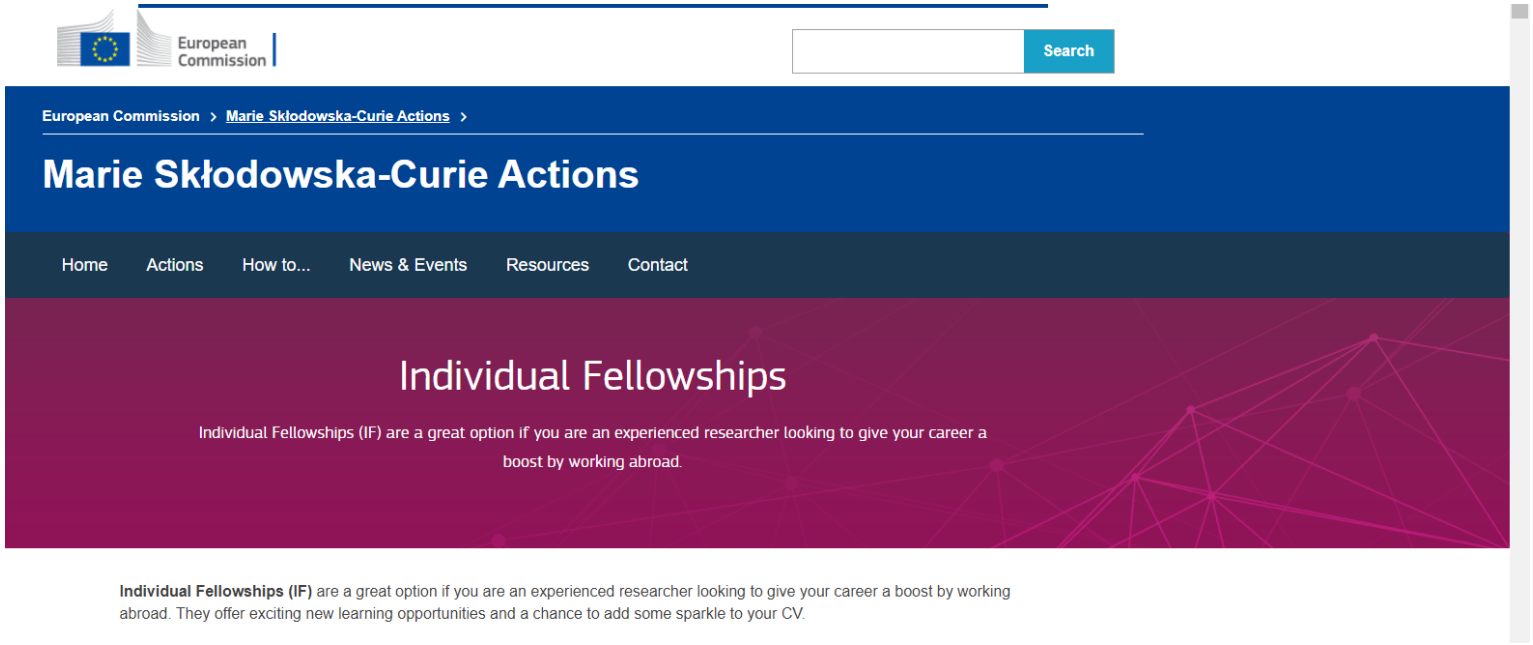
Long-term projects with significant budgets- 3, 4 years, up to 12 Million Euros
100% Grants (Cost eligibility criteria apply, but anything eligible is 100% with 25% Overhead)
All IP related issues are handled with a standardized consortium agreement, much easier to deal with collaboration than one-to-one cases.
A more natural, organic relationship with potential academic, industrial and SME partners where things get done faster for less money.
Access to support on money aspects from EU (IP, debt, commercialisation, dissemination etc.)

Disadvantages of EU projects for Industry

Time-consuming
The book-keeping, accounting is slightly different than standard national practices, learning curve
You need to fit into the priorities of EU- Risk of digression (but also new opportunities on the other side!)
Reporting is infrequent (every 18 months in general)- but heavy.
If the innovation involves too many groups, IP part can get complicated.

Marie Curie Individual Fellowships

- Individual fellowship for 2 years for a Post-doc
- Quiet lucrative so brings in the best talent (but highly competitive)
- There is a dedicated Society& Enterprise panel and SME/start-up applications are well-regarded.
- You will have a high-quality, highly-motivated researcher for free for 2 years on a project of your choice
- Simple application 10 pages



Overall Options for Valorisation of the Output

- Out-licensing after the patents are obtained.
- Contacting Research Instrument developer companies to see if there is any co-development interest.
- Individual companies/institutes pursue their own part seperately or by small groups.
- One of the consortium companies takes over the exploitation
- Start a spin-off company.

The advantages of a spin-off

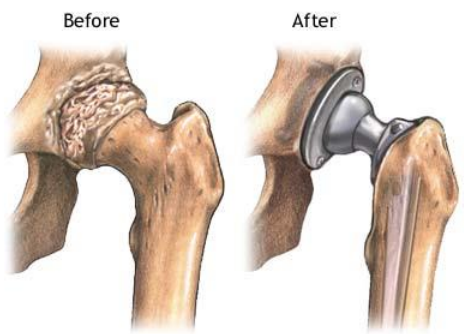
- Harnessing the identity created of the project,
- Keeping the collaboration channels open
- All partners can get in as stockholders (as organisations and individuals) regardless of their presence in the patents.
- Access to all new company, public research translation starter aids; it will give a technology a strong chance to grow.
- A potential out-licensing milieu for our future research in this area.

Bio-TUNE

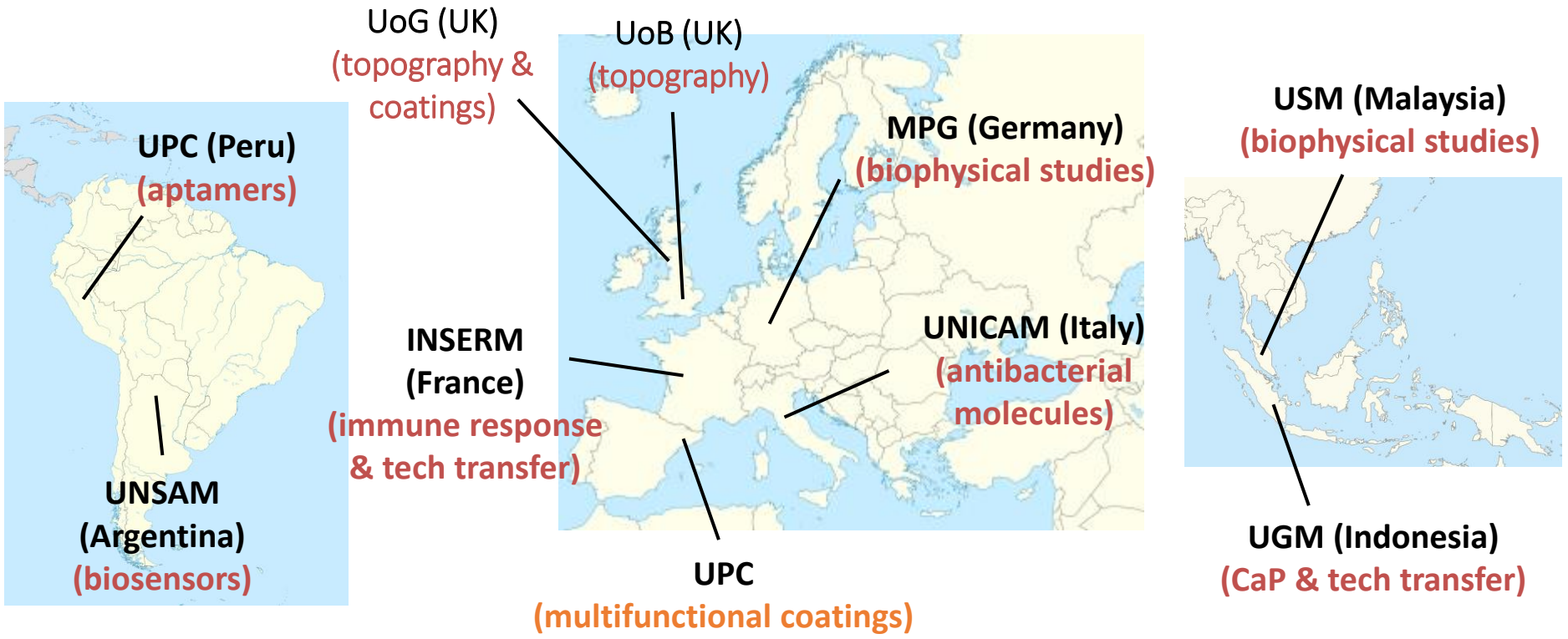
H2020-MSCA-RISE-2019

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**



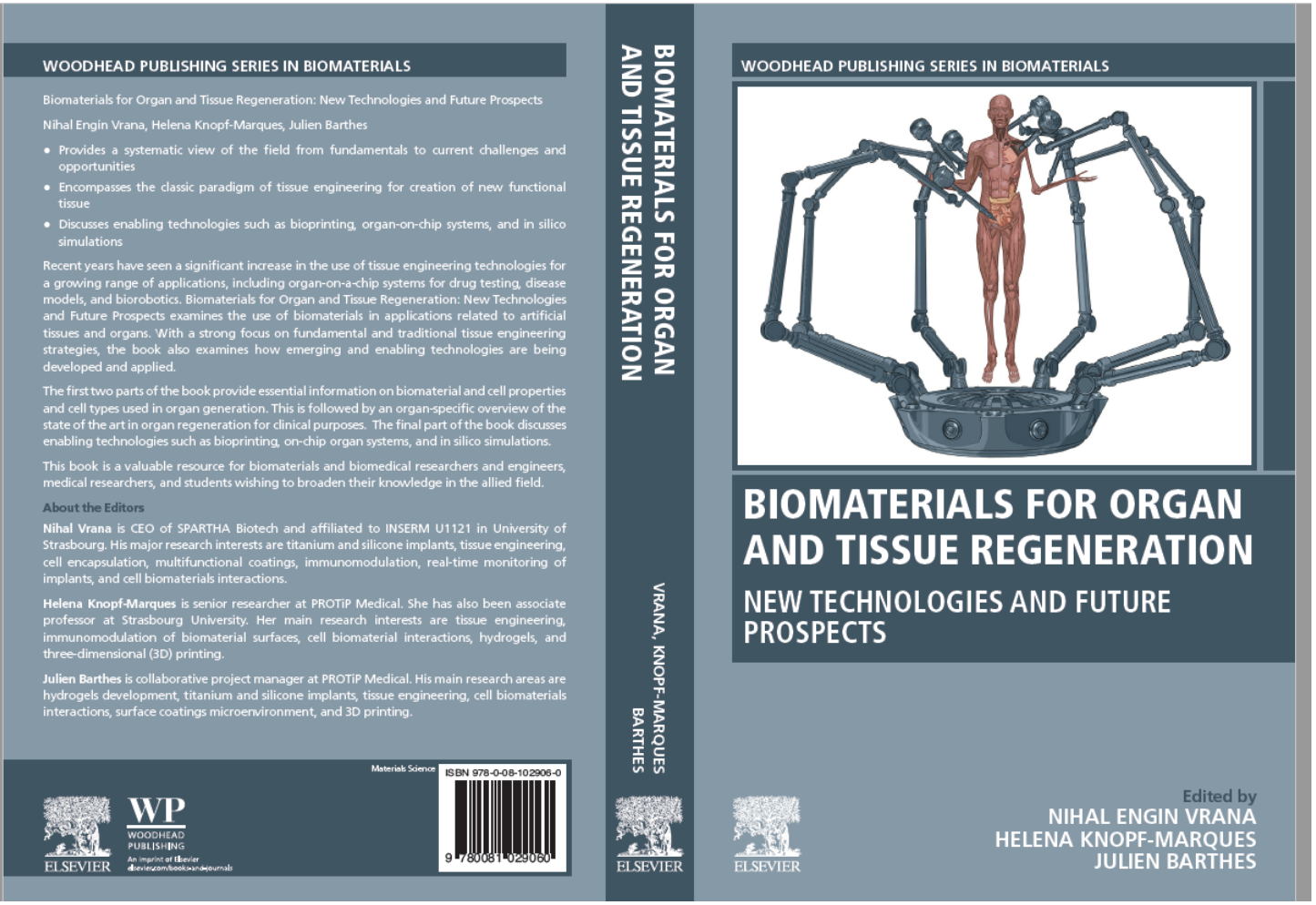
Bio-TUNE



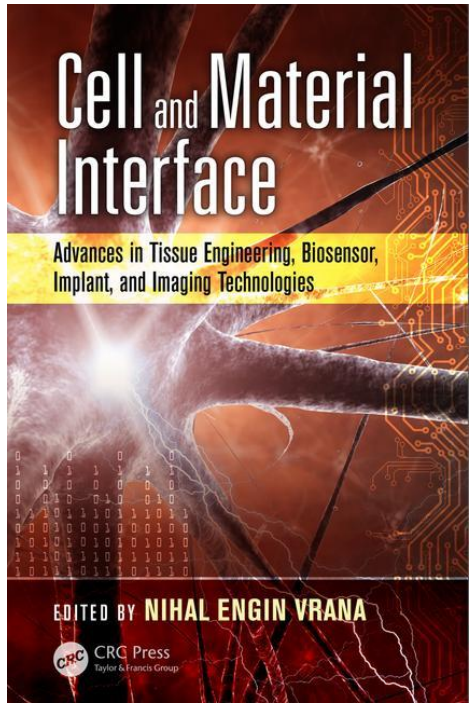
More info: https://biotune.upc.edu/en @bio_tune

Contact: Noelia.Aparicio@upc.edu

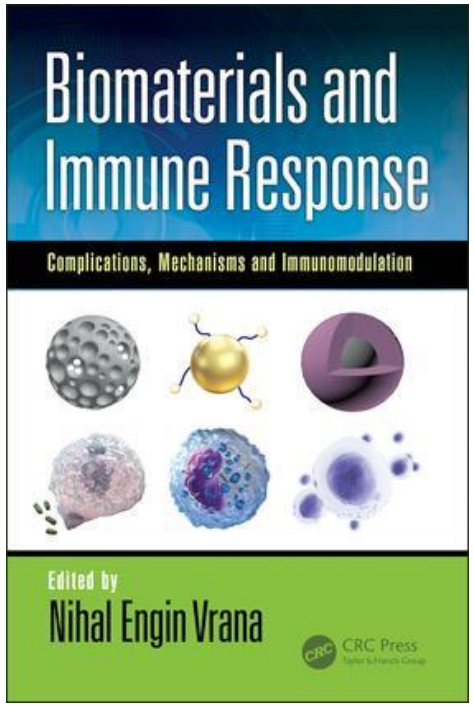
Books on the subject



Elsevier, 2020

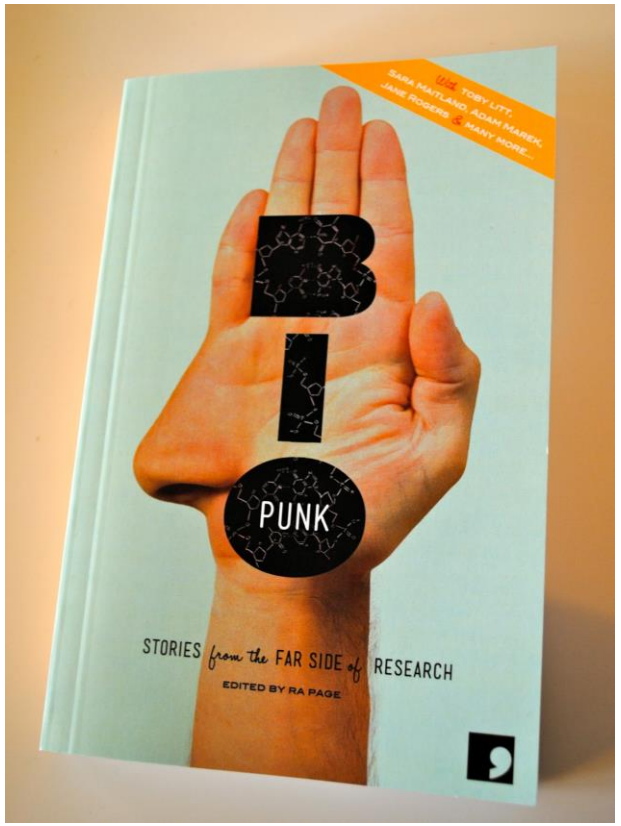


Cell and Material Interface
Nov 2015

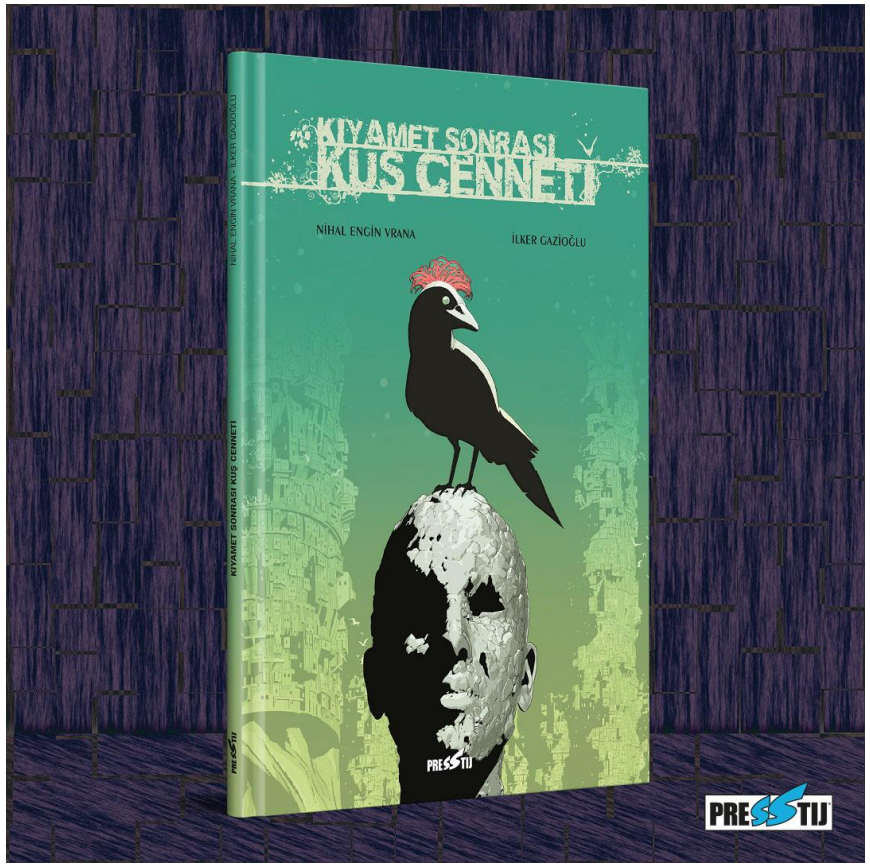


Biomaterials and Immune Response
Jul 2018

Science Fiction Books



2013
Comma Press (İngiltere)
Editor: Ra Page



2021
Presstij Yayinevi (Türkiye)
Çizer: İlker Gazioğlu

Conclusions

- Develop sought after specific capacities, technical know-how and expertise
- Develop a network of collaborators (mostly friends turn to collaborators) with different competencies, to stay ahead of the state of the art
- Work locally, think globally. Seek out international projects

Conclusions II

- Doğru Teknoloji- İnandığınız, iyi bildiğiniz, geliştirebileceğiniz teknoloji
- Doğru zaman- Hem kişisel, hem teknolojik olgunluk açısından
- Doğru ortam –Kurumsal ve kişisel destek ortamı
- Doğru takım- Amaç ve önceliklerin çakışması

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.

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INSERM UMR 1121

PANBioRA

Thanks for the inspiration
Making Science Fiction Reality