BIODEVICE SYSTEMS

PANBioRA

Mathematical platform for screening evaluation of biomaterials

The problem

In the development, production and post-marketing survey of medical devices, medicinal products and combinations, existing procedures are often insufficient for the prediction of adverse immunological, toxicological and inflammatory effects in the host.

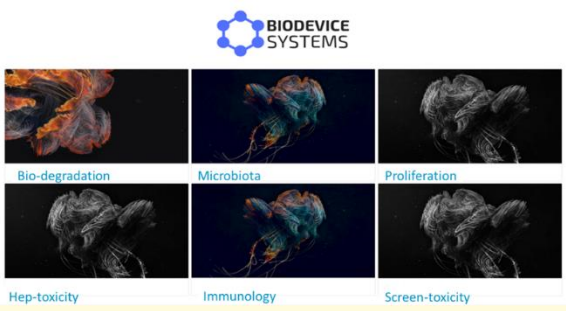
Hence more effective approaches are required and the here applied special *in silico* approach is offered allowing better ranking and comparison of the sample, aiding critical knowledge to in vitro / in vivo data and clinical translation, compatible with the modern regulations (2017/745, 2017/746, 2021/2282, 1394/2007, 2010/63/EC).

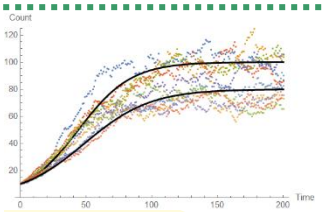
"Selecting solution with maximal safety and efficacy"

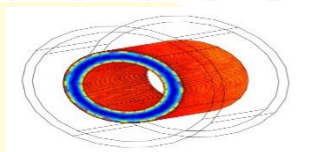
The solution

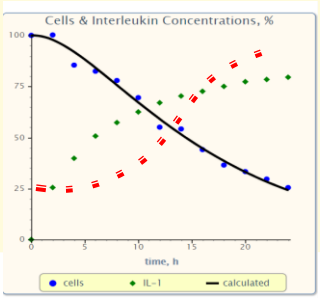
The *in silico* platform for initial safety and efficacy prediction based on *in vitro* tests of a material has been elaborated during PANBIORA project. This platform can be applied as risk assessment tool for further lead development and optimization of the solution. In particular the parameters obtained as a result of simulation can be used for the "Risk Radar" or "PANBIORA prototype system" for the decision aiding of a biomaterial or medical device evaluation.

The service is designed for the identification of the most perspective biomaterial from a group of similar compounds with the minimum number of steps and the least manipulation for further experimental investigations or risk assessment using sophisticated techniques. The set of bio-kinetic (in vitro) models serve as a tool, which is developed to facilitate follow-up steps for in vitro-in vivo extrapolation and prediction of biomaterial risk for the human organism. The platform can be accessed here: https://www.biodevicesystems.com/panbiora









Name	Expression	Value	Description
Rg	1e-6 [1/s]	(1e-6)[1/s]	Maximal cell proliferation rate
Mp	80 [g/mol]	0.08[kg/mol]	Molar mass of monomer
tau	24*365.25 [h]	3.15576e7[s]	Reference time of polymer biodegradation
Hcell	100 [um]	(1e-4)[m]	Cell layer thickness (recalc when geometric model change!)
Kg	50 [nmol/ml]	0.05[mol/m^3]	Cell saturation rate of half saturation
Rm	25e-8 [nmol/(s*mol)]	(2.5e-16)[1/s]	Maximum rate of oxygen consumption
Km	5 [nmol/ml]	0.005[mol/m^3]	Oxygen half saturation constant
Dtox	5e-9 [m^2/s]	(5e-9)[m^2/s]	Toxin diffusivity
Hplate	0.5 [mm]	(5e-4)[m]	Thick of polymer plate
Doxy	2e-9 [m^2/s]	(2e-9)[m^2/s]	Oxygen diffusivity
Dcell	1e-13 [m^2/s]	(1e-13)[m^2/s]	Cell diffusivity
Dens	1000 [kg/m^3]	1000[kg/m^3]	Density of polymer
Vwc	0.461 [ml]	(4.61e-7)[m^3]	Fluid folume into work cell (outer cell layer) (recalc when g...
Vf	10*Vwc	(4.61e-6)[m^3]	Total fluid volume
A	1.844114e-4 [m^2]	(1.844114e-4)[m^2]	Area of cell layer (recalc when geometric model change!)
Vp0	A*Hplate	(9.22057e-8)[m^3]	Initial volume of polymer plate
Tmax	Vp0*Dens/(Vf*Mp)	250.015456[mol/m^3]	Maximal toxin concentration (at total plate degradation)
N0	100 [nmol/ml]	0.1[mol/m^3]	Initial oxygen concentration
delta	0 [m^3/(s*mol)]	0[m^3/(s·mol)]	Chacter rate of toxicological damage of goal cells
U0	1 [mm/s]	0.001[m/s]	Fluid velocity at enter
d_ts	1/3600	2.777778e-4	Time-scalling coefficient
Cmax	10e6 [mol/ml]	10e12[mol/m^3]	Maximal cell dendity (billion cells per ml)
c0	0.90*Cmax	9e12[mol/m^3]	Initial cell density

Biodevice Systems focus on novel approaches exploring the toxicodynamic response of cells to a tested biomaterial.

The *in silico* approach is very efficient for the evaluation of parameters defined and elaborated in PANBIORA *in vitro* systems that closely mimic the in vivo environment, especially with respect to metabolism, cytotoxicity and bioactivation, with secretion of bioactive agents (markers, cytokines, chemokines, growth factors etc.) which can be monitored during a long-term period.

The WEB-tool opens a possibility to forecast the feasibility of the biomaterial and its interaction with the cells. Kinetic experimental data of cytotoxic tests, immune reactivity, cells development and proliferation rates under probable toxic inhibition, are used for the selection of the most suitable solution from the tested alternatives.

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

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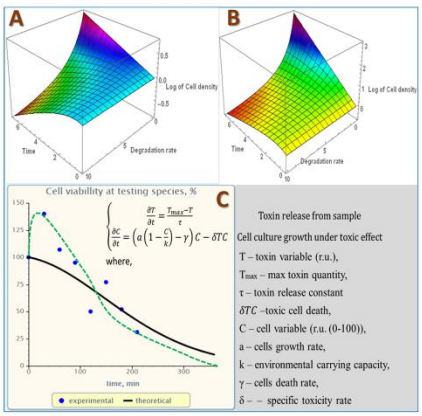
The advantages

- A method that can be crucial to choose feasible components for biomaterials on early stages of manufacturing.
- Adaptable for different flow/components configurations of experimental tool.
- Simplified but validated approach with evaluation of integral parameters characterizing the cell system.
- The availability of a web-tool helps to accelerate the progress in new biomaterials R&D, manufacturing, QMS and RAQA.
- Decrease of error margin (uncertainty quantification) in cells dynamics.
- Forensic application for PMS decisions and CAPA to improve the product quality.
- Faster and cheaper simulation to better predict potential risks and effects to meet regulatory needs.

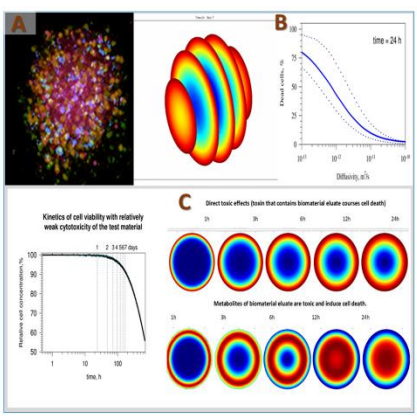
Critical risks for implementation

Description of risk	***Proposed risk-mitigation measures***
High fluctuation of outcomes, read-outs and endpoints	Increasing cohort size and/or narrow the testing parameters to physiologically relevant ranges
Methodology challenges with cell-culture protocols (often 1-3 limited read-outs only for the most of conventional experiments)	Adapting of experimental protocols with specialized tools for supporting of long-term cell cultures and sensors for evaluation of parameters in dynamic (The "PANBIORA system for biomaterial evaluation")
Difficulties in personalized evaluation of biomaterial or a device (individual features of patient, comorbidities, high-risk patients etc.)	Accumulation of data using specialized database with adapting of simulation modules for defined pathology

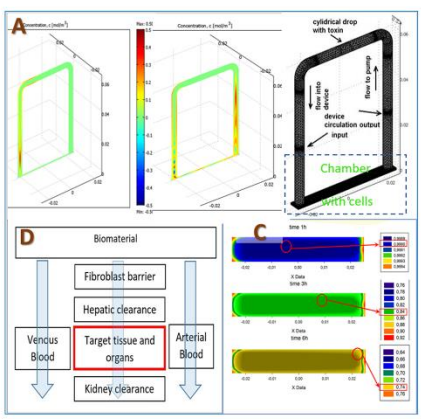
Methodology



The 3D visualization of the model of biodegradable material cytotoxicity in cell systems in vitro *(on the example of acetaminophen release).*
A – hepatocellular model.
B – epithelial cell model.
C – Evaluation of cytotoxicity profile using simplified model applied for the development of web-tool. There is an initial lag-phase that confirm predominant metabolite toxicity.



Model of spatial distribution of dead cell density inside spheroids under the influence of toxin.
A – Photo of a spheroid with cells degraded under the influence of toxin (fluorescent microscopy).
B – 3D simulation of toxin diffusion inside a spheroid.
C – Distribution of relative cell viability density upon a time depends on direct and indirect toxicity.



The model of toxin circulation in microfluidic system with cell chamber (Elvesys).
A – Toxin kinetic and distribution in system.
B – Scheme of circulation circuit.
C – Toxicodynamic of cell on the bottom of cell chamber in time.
D – The presented models define parameter set for further development of the compartmental toxicokinetic model.

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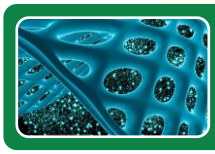
Product examples



New biomaterials

- Polymers and biopolymers
- Metals and ceramics
- Composites and hybrid materials

New medical devices

- Class IIa, Iib and III implants
- In vitro and diagnostic medical devices
- Drug-device combinations

New products for the world

➔ Antomicrobial coatings

➔ Antiviral materials

➔ Veterinary applications

Patient specific (personalised) solution

➔ Assitance in improvement and tailoring of biomaterial suitability for the person

Industry sectors

Medical device companies

- New product development and testing
- Biomaterial screening and optimisation

Policy makers

Identification and assessment of biomaterial specific trends related to safety and efficacy impacting public health

University laboratories and CROs

- Laboratory managers in universities
- Academicians in the biomaterial research fields

Regulatory authorities, NBs, expert labs and HTA actors

Recommendations for the evaluation of new compound`s biocompatibility

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Advantages to the market needs

- ✓ Low-cost testing methods
- ✓ High-throughput screening with new tool for fast and effective registration of parameters in cell culture
- ✓ Personalisation of biomaterials solutions
- ✓ Resource-saving and time efficient operation with less technical skills required for the end-user
- ✓ Elaborated platform is compatible with existing and prospective innovative technologies in the sector

Market potential

The global biomaterials market size is expected to reach USD 348.4 billion by 2027, registering a CAGR of 15.9% over the forecast period. All new biomaterials require proof that they are safe and effective before they can be approved for marketing. In the US, the process for approval follows strict guidelines and regulations. Biomaterial-based products, such as implantable pacemakers, stents, and heart valves, are classified as Class III devices, which pose the highest potential risk of illness or injury.

The simulation software developed within the PANBIORA project offers a complementary approach for understanding how biomaterial safety can be estimated on early stages of manufacturing.

Broader impact

The mathematical platform enables proper screening of biomaterial`s and device properties for selection of most suitable compounds for further testing and application. The service will provide the assessment of biomaterial biocompatibility, where the importance of the model lies in monitoring the integral cell reactions, selection of most perspective components for development of biomaterials and influence of different material properties on output variables. Furthermore, the method can facilitate and simplify certain policy (regulatory and standardization) requirements for pre- and post-market monitoring and vigilance.

Existing alternatives / Competition

In silico toxicology and computational models for the prediction of chemical toxicity which use compartmental methodology and software are elaborated for e.g., tissue engineering and regenerative medicine (ATMP) and use sophisticated multicomponent approaches that consider a lot of important factors but cannot easily be applied by a usual non-professional customer. The abundance of evaluated criteria increases an error margin and can cause misinterpretation of related parameters.

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Key partners

PANBioRA consortium partners

Biomaterial manufacturers and research labs

Early adopter university labs: use case development

Special database of WEB-tool. Data management tools and facilities: cloud tools, local server or 3rd party services

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