International workshop on Biomaterial Innovations

Toward Repair of the Human Body #2

3-4 November 2022

Technical Program

Book of Abstracts

List of Participants

Toward Repair of the Human Body #2

Reparative, reconstructive and regenerative medicine, but also comfort therapy, wellness... have exploded as major scientific endeavors during the last decades. To face the challenges of medicine and biomedical healthcare, the scientific and technical propose innovative systems, that includes various and complementary characteristics and mechanisms from biological, chemical, mechanical, biotherapeutic, electronic, nanotechnologic, cognitive science...
The aim of this international, multicultural and multidisciplinary symposium is:
-to give “at a glance” a survey of the diversity of the pioneering, modern biomaterials and implantable medical devices
-to foster collaborative efforts among biologists, biochemists, chemists, physicists, clinicians and electronicians from France, Europe (especially EUTOPIA), but also all over the world
-to favor interdisciplinary collaborations, avoid gaps and gain the confidence of researchers from different scientific backgroundS to participate within biomaterial research in an interdisciplinary environment.

One mantra: **"Innovation, translation, transdisciplinary, pedagogy & popularization"** during two days with key actors of the interplay of mechanics, electronics, chemistry, biology and disruptive technologies of materials for regenerative medicine

The organizing committee

Adeline Gand (ERRMECe), Associate Professor in Biochemistry and Biomaterial Science

Cédric Plesse (LPPI), Associate Professor in Physicochemistry of Polymers

Emmanuel Pauthe (ERRMECe), Professor in Biochemistry and Biomaterial Science

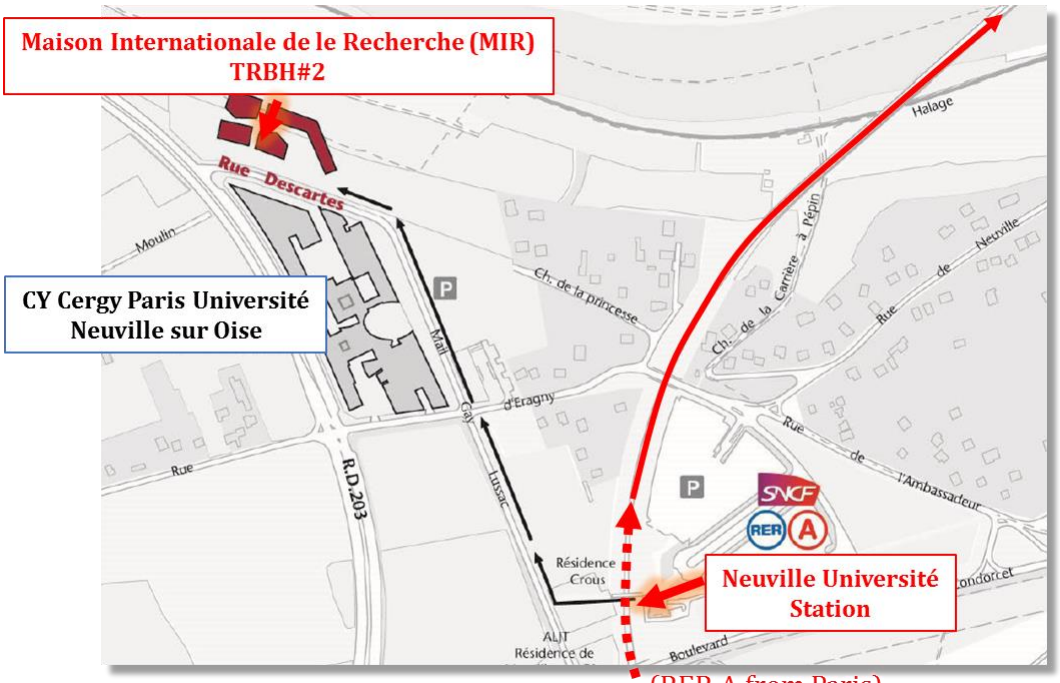
Fréderic Vidal (LPPI), Professor in Physicochemistry of Polymers

Information

- **VENUE**

CY Cergy-Paris University (35 min from Paris)
1 Rue Descartes (5 min walk from RER A station Neuville-Université)
95031 Neuville-sur-Oise (France)

(RER A Toward Cergy)



(RER A from Paris)

- **WIFI Connection**

Network : **u-cergy-wifi-invites**
Login : **mirucp**
Password : **mirwifi2016**

International workshop on
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Technical Program overview

Thursday, November 3

9h30-10h00: Registration
10h00-10h10: Introduction

10h10-12h25 : Session 1

Plenary/Keynote

John Madden, University of British Columbia, Canada - ***10h10-10h55***
Smart materials for health: towards wearable and implantable devices

Ali Maziz, LAAS-CNRS, France - ***10h55-11h25***
Implantable organic electrodes: new technologies for interfacing with the brain

Oral

Clara Brémond, ETIS Laboratory UMR 8051, France - ***11h25-11h45***
Psychovisual Evaluation Vs Metric Evaluation for Brain Culture Synthetic Image Validations Generated by Various GAN Optimizations

Franziska Hahn, LPPI/ERRMECe, Cergy-Paris University, France - ***11h45-12h05***
4D electroactive and microporous polyHIPE-PEDOT scaffolds as a dynamic in vitro cell

Chau Le Bao, LVTS (Inserm U1148), Université Paris Cité, Université Sorbonne Paris Nord, France - ***12h05-12h25***
Spatial-controlled coating of pro-angiogenic proteins on 3D porous hydrogels guides endothelial cell behaviors

12h30-13H30: Lunch

13h30-15h30 : Session 2

Keynote

Elżbieta Pamula, AGH University of Science and Technology, Poland - ***13h30-14h00***
Inhalable microcarriers as drug delivery systems to the lungs in a dry powder formulation

Pilar Rivera Gil, Pompeu Fabra University, Spain - ***14h00-14h30***
NanoTarg, a technological platform for cancer management

Oral

Carole Arnold, IS2M CNRS UMR7361, Mulhouse, France - ***14h30-14h50***
Development of a Virus-Like Particle platform for the control of cell movement

Henry Chijcheapaza-Flores, INSERM U1008 (ADDS), Université Lille, France - ***14h50-15h10***
Chitosan-based hydrogel for drug delivery and viscosupplementation treatment of temporomandibular joint disorders

Pierre Marquaille, C3M/ERRMECe, France - ***15h10-15h30***
The role of macromolecular parameters on the morphology of thermosensitive chitosan hydrogels

15h30-15H50 : Coffee Break

15h50-17h20 : Session 3

Keynote

Ahmed Eissa, University of Warwick and University of Wolverhampton, United Kingdom - ***15h50-16h20***

Tissue Engineering Polymer Scaffolds

Oral

Ana Ferrandez Montero, Institute of Ceramic and Glass (ICV-CSIC), Spain - ***16h20-16h40***

New ion delivery 3D printed scaffolds based on hybrid biocomposites

Chloé Dujardin, LVTS (Inserm U1148) - Université Paris Cité, France - ***16h40-17h00***

Development of a 3D polysaccharide porous membrane for the modelling of the outer blood-retina barrier

Marie-Stella M'Bengue, INSERM U1008 (ADDS), Université Lille, France - ***17h00-17h20***

Ageing study and in vitro biological evaluation of 3D-printed vascular endograft for the treatment of complex aortic aneurysms

17h30-22h00 : Poster session - Networking and cocktail

17h30-18h15: Flash poster presentations from selected abstract (3min/poster)

18h15: Poster session and networking

Friday, November 4

8h30-9H30 : Meet the professors for breakfast (Young scientists)

9h30-11h05 : Session 4

Plenary/Keynote

Engin Vrana, Spartha Medical, France - ***9h30-10h15***
Personalised Cell/Material Interfaces in Biomedical applications

Sylvain Catros, Inserm U1026Biotis, Université de Bordeaux / Service de Chirurgie Orale, CHU de Bordeaux, France - ***10h15-10h45***
Development of a 3D in vitro model to mimic the osseo- and soft tissue-integration process of dental implants

Oral

Varvara Gribova, Inserm UMR 1121, Biomaterials and Bioengineering, France - ***10h45-11h05***
Prediction of Medical Device Coating Properties via Machine Learning

11h05-11H30: Coffee Break

11h30-12h40 : Session 5

Keynote

Herbert Shea, EPFL, Switzerland - ***11h30-12h00***
Soft electrostatic actuators for wearable robotics

Oral

Alvo Aablo, IMS Lab, Institute of Technology, Nooruse 1, Estonia - ***12h00-12h20***
Biofriendly ionic electroactive polymers for multifunctional devices

Hyacinthe Randriamahazaka, ITODYS, CNRS, Université Paris Cité, France - ***12h20-12h40***
Bio-inspired ion-assisted piezoelectric energy harverster

12h40-13H40: Lunch/Poster session

13h40-15h10 : Session 6

Keynote

Laeticia Petit, Tampere University, Finland - ***13h40-14h10***
Fabrication of (bio)photonic glass-based materials

Oral

Adel Francis, CY Cergy Paris University and CMRDI, Egypt - ***14h10-14h30***
Exploring the potential of preceramic organosilicon polymers for biomedical engineering applications

Oscar Gallardo, Robeaute/IEMN/UPHF, Paris, France - ***14h30-14h50***
Characterization of force, displacement and temperature in air and water of a nitinol wire for a medical device application

Loïc Scomazzon, BIOS EA-4691, Reims University, France - ***14h50-15h10***
Characterization of genipin crosslinked Wharton's jelly membranes for bone regenerative medicine application

15h10: Closing ceremony

Detailed Program and Abstracts

Thursday, November 3

9h30-10h00: Registration

10h00-10h10: Introduction

Plenary lecture

Smart materials for health: towards wearable and implantable devices

John D.W. Madden

University of British Columbia, Canada

Keynote Lecture

Implantable organic electrodes: new technologies for interfacing with the brain

Ali Maziz

LAAS-CNRS, France

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Psychovisual Evaluation Vs Metric Evaluation for Brain Culture Synthetic Image Validations Generated by Various GAN Optimizations

Clara Brémond Martin, Camille Simon Chane, Cédric Clouchoux, Aymeric Histace

ETIS Laboratory UMR 8051, CY Cergy Paris Université, ENSEA, CNRS, 6 Avenue du Ponceau, 95000 Cergy, France

Witsee project from the Neoxia Compagny, 33 Av. des Champs-Élysées, 75008 Paris, France

The generation of synthetic images with Generative Adversarial Network is widespread in the biomedical field for deep learning requirements. However, the validation of synthetic images with metrics is still controversial.

Here we propose to validate synthetic images of Brain organoid bright field images generated by various GAN optimizations, only previously validated by metrics, with psychovisual evaluation. Eight biological experts class these images as synthetic or natural with our in-house software. For each GAN optimization we count the number of answers, the error rate and hesitation time compared to the original dataset. Then we compare psychovisual answers with metrics and elligiate the best metric combination which could replace the Human psychovisual evaluation.

A group of synthetic images are mostly selected by all the experts as natural as the original datasets with no increase of decision time. This optimization is also highlighted by metrics. Comparing psychovisual assertions and calculated similitude and quality metrics, we find a particular combination of metrics could replace the psychovisual evaluation.

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4D electroactive and microporous polyHIPE-PEDOT scaffolds as a dynamic in vitro cell culture platform

Franziska Hahn[1,2], Ana Ferrández Montero[1,2], Mélodie Culot[2], Cédric Vancaeyzeele[1], Rémy Agniel[2], Cédric Plesse[1], Johanne Leroy-Dudal[2]

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(2) Equipe de Recherche sur les Relations Matrice Extracellulaire-Cellule (ERRMECe) - CY Cergy Paris Université - 1 rue Descartes, 95000 Neuville sur Oise, France

In vivo, cells are surrounded by an extracellular matrix (ECM). Signals from the ECM such as biochemical or biophysical cues regulate cell behavior in physio-pathological processes. Therefore, mimicking this cell microenvironment is one of the most important challenges in the fields of physio-pathological research, tissue engineering or drug screening. Although 3D cell cultures offer biologically superior structures, there is still a lack in the transmission of dynamic mechanical signals that exist in the microenvironment of cells *in vivo*.

The aim of this work is to develop a 3D microporous and electroactive scaffold as an innovative cell culture platform that enables the *in situ* electromechanical stimulation of cells and the real-time monitoring of the cell behavior. For this purpose, a 3D microporous scaffold is polymerized from a high internal phase emulsion template. This, so called polyHIPE, is characterized by a high interconnectivity and a suitable porosity for a rapid cell colonization. In a further step the polyHIPE-scaffold was homogenously functionalized with a conducting polymer, the poly(3,4-ethylenedioxthiophene) (PEDOT), via vapor phase swelling and an oxidative polymerization process with iron(III) chloride. The functionalization leads to a 4D electroactive polyHIPE-PEDOT scaffold with stimuli-responsive properties such as changes in shape, morphology, pore size or stiffness under time-dependent external stimulation. These properties are kept after sterilization via autoclavation, in cell culture medium and also in the presence of human dermal fibroblast. The polyHIPE-PEDOT scaffolds support cell adhesion, spreading, migration, cell viability, and ECM secretion. Furthermore, it was possible to achieve 10% volume variations on the polyHIPE-PEDOT scaffolds during stimulation. The electromechanical stimulation was reversible and had no cytotoxic effect on the cells.

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Spatial-controlled coating of pro-angiogenic proteins on 3D porous hydrogels guides endothelial cell behaviors

Chau Le Bao, Helen Waller, Daniel Peters, Jeremy Lakey , Didier Letourneur, Frédéric Chaubet, and Teresa Si-mon-Yarza

. Université Paris Cité, Université Sorbonne Paris Nord, INSERM U1148-LVTS, Paris, France

Introduction

Vascularization of 3D hydrogels (HGs) remains a major challenge in tissue engineering and a key prerequisite for in vitro angiogenesis. Porous HGs are ideal candidates for vascularization strategies as they facilitate nutrient and oxygen diffusion, thus enabling cell migration[1]. Moreover, the addition of channels inside a porous scaffold can facilitate cell growth and rapid vascularization, resulting in enhanced tissue formation[1]. The presence of proangiogenic molecules on hydrogels have also been shown to promote cell adhesion, proliferation, sprout formation, and lumen formation[2]. In this work, porous HGs with preformed microchannels were developed and functionalized with a novel bioengineered protein polymer, capsular antigen fraction 1 (Caf1), which was inserted with cell-adhesive motifs[3]. Spatial-controlled coating of hydrogels was achieved through a combination of freeze-drying and physical absorption with Caf1-YIGSR and Caf1-VEGF.

Experimental methods

HG synthesis: Pullulan-dextran HGs (named PUDNA) were synthesized using a patented method4 based on the addition of porogens and a freeze-drying step. Microchannels within HGs were formed by mechanical removal of suture filaments. The HGs underwent a double freeze-drying process: the first one to tune the porosity, the second one after incubation in the Caf1 solution (1 mg/mL) to create a thin physical coating of only the channel, or both the channel and the pores.

HG functionalization: Briefly, a small amount of DEAE-Dextran (D), (20 wt%; ζ = +29.5 mV) was added to the standard gel formula. HGs were incubated in the Caf1 solution (pI = 4.56; ζ = -23.5 mV) at RT for 2h before or after FD.

Hydrogel characterization: Porosity, swelling ratios, and water content were evaluated as per standard protocols[4]. Young Modulus were evaluated both in bulk and through a nanoindentation mapping.

Hydrogel cellularization: Human umbilical vein endothelial cells (HUVECs) were cultured in EGM-2. Cell morphology and distribution were observed using confocal microscopy and cellular metabolic activity was evaluated up to 7 days.

Statistical analysis: All experiments were carried out at least in triplicates. Statistical analysis was performed using ANOVA One-way test. Statistical significance was indicated as * $p < 0.05$.

Results and discussion

Consistent with previous work, our porous 3D hydrogels presented porosity of ~30%, a swelling ratio of 11, and a final water content of 92%. Bulk rheology evaluation resulted in a shear storage modulus of 1.4 - 1.6 kPa and surface rheology Young's modulus of 12 kPa. Cells in functionalized scaffolds adhered and proliferated over 7 days. Adhered cells with elongated morphology were observed only in the coated channel together with an increase in cell metabolic activity compared to those seeded on non-coated scaffolds. Caf1-YIGSR induced cell adhesion and proliferation. Caf1-VEGF did not promote cell adhesion, but contributed to cell migration and sprouting. However, directed cell migration driven by Caf1-VEGF only occurred in the presence of Caf1-YIGSR. Together, Caf1-YIGSR and Caf1-VEGF synergistically guided ECs towards angiogenic sprouting.

Conclusion

By spatial control the distribution of pro-angiogenic cues on the HGs we could modulate cells behaviors, guiding them towards angiogenic sprouting within in the 3D scaffolds. Our results strongly suggest that these hydrogels can be used as proangiogenic biomaterials for tissue engineering.

References

1. Kang Y. et al. Regen. Med., 705–715, 2018.
2. Dellaquila et al. Adv. Sci., 2021.
3. Roque A. et al. Adv. Mater., 2014.
4. Labour MN. et al. Int. J. Mol. Sci., 2020.

Acknowledments

The authors would like to thank the “Recherche Hospitalo-universitaire” Innovations for Liver Tissue Engineering (RHU iLite), grant no. ANR-16-RHUS-0005) and DILI-on-chip, grant no. ANR-21-CE19-0025 for providing financial support to this project.

Keynote lecture

Inhalable microcarriers as drug delivery systems to the lungs in a dry powder formulation

Elżbieta Pamula

AGH University of Science and Technology, Poland

Keynote lecture

NanoTarg, a technological platform for cancer management

Pilar Rivera Gil

Pompeu Fabra University, Spain

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Development of a Virus-Like Particle platform for the control of cell movement

Carole Arnold, Hasna Maayouf, Thomas Dos-Santos, Isabelle Brigaud, Tatiana Petithory, Karine Anselme, Laurent Pieuchot

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Introduction

Protein self-assemblies derived from nature are attracting growing interest in medicine and nanotechnology fields[1]. Organized from repeated association of monomers, they are able to spontaneously form well-defined and repetitive molecular architectures. Some self-assembled structures have the advantage of being very stable. This is the case of virus-like particles (VLPs)[2]. These particles lacking genetic material can be produced and genetically modified on their coding sequence, giving them great adaptability for applications in vaccinology and immunology[3,4]. However, the field of biomaterials still makes little use of these tools, which are promising for many applications, particularly those related to cell fate control.

Experimental methods

Production of VLPs. The RNA bacteriophage AP205 VLPs we worked with, are formed from 180 copies of a coat protein. By molecular cloning, we added to particles surface different bioactive peptides to the N- and C-termini level. The resulting constructs were produced in bacterial systems and purified by affinity and size exclusion chromatography. The purity of the productions was analyzed by SDS-PAGE and the production yield by protein assay.

Cell adhesion test. The adhesion of C2C12 mouse cells in response to "adhesion" particles adsorbed on PDMS was analyzed by confocal microscopy. Cell spreading was analyzed via the fiji plugin (imageJ). Statistical analyses were performed using t-test and ANOVA.

Results and discussion

We were able to produce particles expressing at their surface different signaling domains known to trigger similar cell responses as their native proteins. Adsorption of “adhesion”-particles on PDMS surfaces allows mouse cells C2C12 to adhere. The control of the concentration of the fibronectin peptide RGD expressing particles (AP205-RGD) provides control of cell spreading and cell density on the culture surface. A similar effect was observed with native fibronectin at different concentrations. Cell transfection with a paxillin-mCherry fluorescent probe enabled to track in real time the dynamics of focal adhesions of cells cultured on VLPs-adsorbed PDMS. We are currently working on the grafting of our particles on glass surfaces via APTES and p-phenylene diisothiocyanate.

Conclusion

These results suggest that recombinant VLPs can be used to control cell adhesion and we expect, in a near future, to use AP205 VLPs as a general modular platform to finely control cell fate. Our future goal will be to use VLPs to create multifunctional biomimetic hydrogels with bioactive peptides at high densities and specific stoichiometries, in order to control stem cell physiology. This project will open new avenues for the development of next-generation biomaterials and biomimetic microenvironments.

References

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2. Pushko, P., Pumpens, P. and Grens, E. (2013), Intervirology, 56(3), pp. 141–165.
3. Nooraei, S. et al. (2021), Journal of Nanobiotechnology, 19(1), p. 59.
4. Brune, K.D. et al. (2016), Scientific Reports, 6(1), p. 19234.

Chitosan-based hydrogel for drug delivery and viscosupplementation treatment of temporomandibular joint disorders

Henry Chijcheapaza-Flores[1], Maria José Garcia-Fernandez[1], Romain Nicot[1], Nicolas Tabary[2], Frédéric Cazaux[2], Feng Chai[1], Nicolas Blanchemain[1], Bernard Martel[2]

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Temporomandibular joint disorders (TMJD) are myoarthropathies that can trigger chronic pain symptoms. Patients concerned by this disease reach 12 % of the population in developed countries[1]. This work aims to the development of an innovative intraarticular drug delivery system, merging the properties of a viscosupplementation hydrogel with the pharmacological activity of a nonsteroidal anti-inflammatory drug (NSAID).

In this context, a formulation containing chitosan (CHT, a cationic polymer obtained from crustacean shells) and an anionic polymer of cyclodextrin (PCD, forms "Host-Guest" complexes) was prepared in order to form a polyelectrolyte complex (PEC) hydrogel[2]. Next, naproxen (NX), a NSAID used in TMJD treatment, was added into the formulation. In order to characterize and to demonstrate the mechanical properties of the hydrogel, a rheological and a tribological study were made. Then, a cytocompatibility assessment was made on a NIH3T3 fibroblast cell line by an indirect method. Finally, the effect of drug inclusion complexes in the hydrogel on the release kinetics was studied in a physiological medium.

The role of PCD as an anionic agent to interact with CHT amino groups improved the viscoelastic properties of the hydrogels in terms of elasticity (Tan δ). Besides, the hydrogel showed a shear-thinning behavior (injectability) and self-healing (hydrogel structure recovery after high shear-strain). The tribology study confirmed the lubricant property of the hydrogel in a pin-on-disk (PTFE-PTFE) model. In addition, the hydrogel cytocompatibility was higher than 70%, which is an acceptable result according to ISO 10993-5. Furthermore, a NMR study proved the PCD:NX inclusion complex and finally, the release kinetics study demonstrated the sustained release of NX from the hydrogel.

To conclude, an innovative viscosupplementation product for TMJD treatment was developed in this work. Further studies in an in vivo model will be done in order to prove the efficacy of this new approach.

References

1. Facial Pain [Internet]. [cited 2022 July 25]. Available from: https://www.nidcr.nih.gov/research/ data-statistics/facial-pain

2. Blanchemain N, Martel B, Flores C, Cazaux F, Chai F, Tabary N, Lopez M. Method for the production of hydrogel comprising chitosan and negatively charged polyelectrolytes, and cellular, porous material resulting from said hydrogel. WO2017001808A1, 2017 [cited 2020 Nov 6]. Available from: https://patents.google.com/patent/WO2017001808A1/fr

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The role of macromolecular parameters on the morphology of thermosensitive chitosan hydrogels

Pierre Marquaille, Carla Palomino Durand, Phuong Anh Dang, Sonia Ortega, Raphaël Michel, Rachel Auzély-Velty, Emmanuel Pauthe, Laurent Corté and Sophie Norvez

Chimie Moléculaire, Macromoléculaire, Matériaux (C3M), ESPCI Paris Tech, PSL / ERRMECe, CY Cergy Paris Université

Thermosensitive hydrogels are widely studied matrices for cell encapsulation and delivery. Solutions of chitosan (CS) and phosphate salts are particularly interesting as they exhibit a thermosensitive sol/gel transition which can be achieved within minutes at 37°C. The gelation, induced by phase separation, gives rise to macroporous hydrogels. A formulation platform using mixtures of two phosphate salts, β-glycerophosphate (βGP) and ammonium hydrogen phosphate (AHP), has been recently developed, where pH, osmolarity and gelation kinetics of CS/βGP/AHP mixtures can be finely adjusted to be compatible with cell encapsulation[1]. Here we develop tools to study and quantify how the gelation kinetics and gel microstructure evolve upon variation of chitosan characteristics, e.g. molecular mass M_w, degree of deacetylation DD, or animal origin, using rheological measurements and quantitative analysis of confocal microscopy images. For that, we compare the thermosensitive hydrogels produced with seven different grades of chitosan at a fixed chitosan concentration of 0.8wt%.

Variations in DD can have an effect on the solution pH and on the gelation kinetics. We show that these effects can be suppressed by adapting the salts ratios. In particular, a pH of 7.4 and a gelation time of 2 ± 0.5 min at 37°C were maintained for DD ranging from 90 to 95%. Confocal observations of the hydrogels obtained at 37°C as shown in Figure 1A revealed that for a same animal origin (shrimp), the microstructure depends weakly on the molecular weight. Image analysis indicated that the mean pore size is almost constant over one decade in M_w. Conversely, we found that the mean pore size is greatly affected by the animal origin, whether chitosan is obtained from squid- or shrimp-extracted chitin (**Figure 1A&B**). This could be explained by different chitin polymorphs found in squid or shrimp, which affects solubility, crystallinity, pore size and porosity, as chitosan is obtained from partial deacetylation of chitin.

These results and methodology show how the proposed formulation platform can be adjusted to account for the macromolecular parameters of the chitosan and ensure essential properties such as pH and gelation kinetics. They also provide guidelines to formulate injectable and cytocompatible hydrogels which macroporosity can be varied over a wide range of macropore sizes.

(A) *(B)*

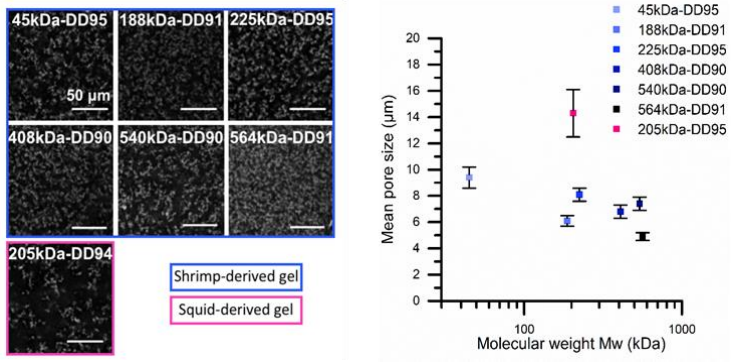

Figure 1. (A) Confocal microscopy pictures of the different hydrogels at 0.8wt% chitosan concentration (chitosan was previously marked with AlexaFluor 488). (B) Mean pore size in the different hydrogels as a function of molecular weight, obtained through to a morphological sieve algorithm. *All samples are denoted as xxkDa-DDy (molecular weight and deacetylation degree of the studied chitosans)*

(1) Dang, P. A. et al., Carbohydr. Polym. ***2022****.*

Keynote lecture

Tissue Engineering Polymer Scaffolds

Ahmed Eissa

University of Warwick and University of Wolverhampton, United Kingdom

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New ion delivery 3D printed scaffolds based on hybrid biocomposites

A. Ferrández-Montero, A. Eguiluz, P. Ortega, A.J. Sanchez-Herencia, B. Ferrari

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Among several ions playing a vital role in the mechanism of bone formation Sr^{2+}, Ca^{2+} and Mg^{2+} are especially useful for the development of new ion delivery systems for bone regenerative applications. Biodegradable polymers, including polylactic acid (PLA), are commonly used in bone tissue related clinical procedures and they can work as carrier-delivery substrate of different ions or drug to provide a constant and controlled release of bioactive factors. In this work, a new group of polymer based composites, which integrates several osteoinductive compounds as Magnesium or Hydroxyapatite particles or drugs as Strontium Ranelate (SrR) in a biodegradable polymeric matrix have been proposed.

Over recent years, AM techniques have gained a special attention in order to process complex scaffolds and patient-customized structures for biomedical application. Among AM techniques, the Fused Deposition Modelling (FDM/FFF) is one of the most simple and inexpensive techniques, which allows high printing speeds using thermoplastics as structurers. Recently, an alternative colloidal processing technique to prepare composites improving the inorganic particles dispersion in order to obtain new functional filaments or granules feedstocks for FFF manufacturing have been developed. This colloidal approach have been extended to a wide variety of biomaterials as ZrO_2, Al_2O_3, TiO_2, and Graphene and it is especially useful for the processing of polymer based composites. This new AM approach allows the successful 3D printing of a new family of hybrid composite with different loading of bioactive phases, which promotes the lixiviation of bioactive ions of interest. This polymer based ion delivery systems and their processing paves the way to generate a new family of interesting biocomposite for bone healing applications allowing the incorporation of bioactive phases, drugs and bio molecules along the process.

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Development of a 3D polysaccharide porous membrane for the modelling of the outer blood-retina barrier

Chloé Dujardin[1], Paola Aprile[1], Walter Habeler[2], Christelle Monville[2], Didier Letourneur[1], Teresa Simon-Yarza[1]

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2. INSERM U861, I-Stem, AFM, Corbeil-Essonne, France

The integrity of the retina is maintained by the outer blood-retina barrier (oBRB) composed of the monolayered retinal pigment epithelium (RPE), the acellular collagenous Bruch's membrane and the vascularized choroid. Pathologies affecting the oBRB are characterized by a communication disruption between the choroid and the RPE. There are neither effective treatments to these diseases nor human cell models recapitulating the oBRB structure and all the clinical hallmarks so far. Thus, our goal is to engineer a 3D oBRB for tissue modelling and for cellular therapy, based on a polysaccharide membrane, co-cultured with endothelial cells (ECs) and RPE cells. Here, we present the optimization of the 3D membrane, its functionalization, and its suitability for ECs culture.

The membranes were synthesized from an aqueous solution of pullulan and dextran[1,2], and were further freeze-dried (FD)[3] to create the inner porous network and mimic the oBRB structure. The porosity of the scaffold was evaluated both in its dried state using scanning electron microscopy (SEM), and in its hydrated state using confocal microscopy. To enhance cellular adhesion, collagen type I and laminin coatings were applied on the membranes. Primary human retinal microvascular endothelial cells (HRMVECs) were seeded in vitro on the membranes for up to 7 days to assess their viability, adhesion and proliferation in the membranes.

By optimizing the FD protocol, we obtained membranes with, on one side, a smooth surface intended for the RPE monolayer culture, and, on the other side, a porous surface connected to the inner porous network with elongated pores, for the formation of the vascular network. The collagen coating was observed on the surfaces of the gels and in the pores and the laminin was selectively added on the smooth side for RPE seeding. HRMVECs were seeded on the porous side of the membrane, previously placed in a Cell Crown system. The ECs were able to colonize the entire thickness of the membrane without crossing to the smooth RPE side. Moreover, they adhered to the porous surface and to the pores, proliferated forming tubular structures, and survived for at least 7 days.

In conclusion, we obtained membranes mimicking the oBRB structure, with a rough surface allowing ECs penetration in the porous network and a smooth surface to form the RPE monolayer. The seeding of RPE cells on the smooth side is on-going and we will shortly focus on the co-culture of the two cell types to fully model the oBRB.

Acknowlegments

The authors thank the AMX program of the Ecole Polytechnique for the PhD funding, the ImagoSeine core facility of the Institut Jacques Monod, member of the France BioImaging infrastructure (ANR-10-INBS-04) and GIS-IBiSA and the CRI U1149 Imaging facility.

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International workshop on
Biomaterial Innovations
Toward Repair of the Human Body #2
3-4 November 2022

Ageing study and *in vitro* biological evaluation of 3D-printed vascular endograft for the treatment of complex aortic aneurysms

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Aiming at the treatment of abdominal aortic aneurysms with challenging vessel morphologies, a 3D-printed prototype of aortic stentgraft (3DP-SG) was made using a medical grade biocompatible elastomer: thermoplastic polyurethane (TPU). Before *in vivo* implantation study, *in vitro* biocompatibility of 3DP-SG was evaluated according to ISO10993, i.e. cytotoxicity (extraction 24h) and cytocompatibility (direct contact 3-6 days) towards endothelial cells (HPMEC) and fibroblasts (NIH3T3), hemocompatibility with whole human blood and inflammatory response of inactivated macrophages from THP-1 human monocytes (Mϕ, M0). Moreover, the degradability of TPU was investigated by incubating 3DP-SG samples in 0,1 M NaOH and in 20% H_2O_2 + 0,1 M $CoCl_2$ to simulate respectively *in vivo* hydrolysis and oxidation occurring from 6 months up to 45 months. At predetermined time points, physicochemical properties of 3DP-SG were characterized (SEC, DSC, tensile, FTIR, hydrophilicity, SEM). Our 3DP-SG prototype was found non-cytotoxic (> 70%) towards HPMEC cells and fibroblasts, non-hemolytic (< 5%) and leads no risk of thrombotic activity. Low secretion of TNF-α and IL-6 cytokines implicates that 3DP-SG does not induce polarization of Mϕ, M0 into a pro-inflammatory Mϕ, M1 phenotype. Regarding ageing study, differences in the 3DP-SG bulk and surface properties were detected in both hydrolytic and oxidative media after simulated 6 months. Notably, it was manifested by a decrease of molecular weight and crystallinity and changes in FTIR spectra that suggest the migration at the surface of additives (1), also evidenced by SEM. Overall, the evolution of bulk and surface properties of our 3DP-SG prototype is not detrimental to its application. These promising results will help in further evaluation (*in vivo* biocompatibility) and validation of our 3DP-SG prototype performance for its introduction on the market.

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Friday, November 4

8h30-9H30 : Meet the professors for breakfast (Young scientists)

Plenary lecture

Personalised Cell/Material Interfaces in Biomedical applications

Engin Vrana

Spartha Medical, France

Keynote Lecture

Development of a 3D in vitro model to mimic the osseo- and soft tissue-integration process of dental implants

Sylvain Catros

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International workshop on
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Prediction of Medical Device Coating Properties via Machine Learning

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Introduction

Layer-by-layer (LbL) coating is a method for surface modification based on the electrostatic interactions between two polyelectrolytes[1]. LbL coatings are used for multiple biomedical applications, because natural polyelectrolytes presenting good biocompatibility can be used for LbL film build-up. It is possible to develop antibacterial surfaces, smart healing materials, and coatings for tissue engineering[2]. Moreover, LbL coatings can be used for loading drugs or other bioactive molecules, which allows their local delivery. Even though the mechanisms of LbL film development are well-established, the empirical manner of polycation and polyanion selection is an impediment on rapid new coating development, while the current health crisis has shown the importance of accelerated development of biomedical solutions such as antiviral coatings.

Experimental methods

In this work, we hypothesize that using the current state of the art data science techniques, we can determine how different parameters affect coating thickness and predict the thickness of the new coatings. To do so, we used historical and generated data for predictive model development using machine learning, an approach which uses algorithms that improve upon training on large datasets and is able to find complex patterns, make predictions and decisions.

Results and discussion

Using literature data and newly generated experimental results, we analyzed how different parameters such as polymer molecular weight, concentration, etc. affect LbL film thickness. After the determination of the most influential parameters, we used machine learning approach to verify if we can predict coating thickness from different parameters[3]. We found that construction parameters alone were insufficient to build a robust model for thickness prediction because of the overfitting. To overcome this problem, we hypothetized that generating numerical features that describe the chemical properties of polymers can improve the model performance. Thus, we analysed the relationship between 123 molecular descriptors and the coating thickness, and found that molecular features had a moderate correlation with the thickness of the coating. Finally, we combined molecular descriptors and numerical features of the polymers from the original data set to build new models, and these models had better performance for the validation set than the model constructed using the original dataset features.

Conclusion

We demonstrate, for the first time, utilization of machine learning for prediction of LbL coating properties. It can decrease the time necessary to obtain functional coatings with desired properties, as well as decrease experimental costs and enable the fast first response to crisis situations (such as pandemics) where coatings can positively contribute. Besides coating thickness, machine learning approach can be potentially used to predict functional properties of multilayer coatings, e.g. biocompatibility, antibacterial, antiviral or anti-inflammatory properties.

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Keynote Lecture

Soft electrostatic actuators for wearable robotics

Herbert Shea

EPFL, Switzerland

Biofriendly ionic electroactive polymers for multifunctional devices

Fred Elhi, Pille Rinne, Karl Karu, Tarmo Tamm, Urmas Johanson, Vladislav Ivanistsev, Alvo Aabloo, Kaija Põhako-Esko

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Electromechanically active materials change their shape under external electrical stimulation or generate electrical signal upon mechanical stimulus. These materials are in the focus of intense research as bioinspired devices need replacement for traditional actuators. The present study aims to development of biofriendly ionic electroactive polymers (IEAPs). A typical IEAP is a soft thin laminate composed of a microporous ion-permeable polymer membrane containing electrolyte (for example ionic liquid (IL)) placed between electrodes with a high specific surface area (for example conductive polymers). IEAPs can work as actuators and sensors: transducing between electric current and mechanical deformation. In addition, IEAPs can sense temperature, humidity and chemical composition of environment. Migration of ions in response to electrical stimulation enables controlled release. Combining all these functionalities leads to smart devices, which sense surroundings and react accordingly. Potential applications for IEAPs include implantable or disposable biomedical devices, smart prosthesis, soft haptic devices and wearable electronics. Mentioned applications require biocompatible materials, which has still remained challenging during decades of research in the field.

Our approach towards biofriendly of IEAPs was to use biocompatible materials for different parts of IEAPs without compromising in performance. A key component hereby was low-toxicity IL as electrolyte. For electrode material polypyrrole (PPy) was chosen due to proven biocompatibility: PPy is a suitable substrate for cell growth, implantable and can be functionalized to be biodegradable. Medically approved synthetic polymer PVdF and inherently biofriendly and biodegradable gelatin were applied and compared as membrane materials. So far mostly the conventional imidazolium based ILs had been used as electrolytes in IEAPs despite the well-known toxicological issues of these salts and a large variety of alternative ILs available. In the present study low-toxicity choline based ILs were applied instead. In the presentation preparation, characterization, and electrochemomechanical performance of the developed biocompatible IEAPs will be discussed. Significant differences in actuation were found in case of different ILs as the electrolytes although the actuators were found to be cation active and all of the ILs contained the same choline cation. Experimental results were explained using computational methods: formation of ionic clusters was studied with molecular dynamics (MD) simulations and with density functional theory (DFT) calculations.

Bio-inspired ion-assisted piezoelectric energy harverster

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In this works, piezocomposite energy harvester that integrates mechanical energy harvesting and energy storage is designed, assembled, and analysed. The self-charging supercapacitor and the self-charging battery which use the mechanical piezoelectric field to drive the ions transport provide new approach for energy harvesters by combining power generation and storage. These properties are of interest for developing flexible self-powered devices such as sensors, and electronic skin technology.

From materials design point of view, the energy conversion device realized by the bionic microstructure inside the material is of interest particularly in the field of flexible wearable energy harvesters. Inspired by the rapid transportation of inorganic salts by conduits in tree trunks, we built bionic ion channels in the traditional polyvinylidene fluoride (PVDF) piezoelectric film, filling ionic liquid into the piezoelectric film to form a quasi-solid piezoelectric electrolyte layer. Ions as stable charge carriers ware used in the electromechanical conversion process. We introduce ions into the piezo-layer to solve the problem of charge carrier shortage in the piezoelectric layer. Furthermore, one has an improvement of ion mobility which is an important part of improving the output of piezoelectric composite devices. This mode of introducing carriers into the piezo-layer to improve the performance of the piezoelectric generator could provide a promising strategy for piezoelectric materials to collect and store low-frequency human mechanical energy.

Herein, the energy storage ability of the device by means of flux analysis approach. This approach allows us not only to take into account the dissipation processes occurring the charging and discharging energy. Then, the efficiency of the device is determined. Furthermore, we introduce new metrics, the electrochemical elastance, which can be used for comparing and optimizing the material's design.

Keynote Lecture

Fabrication of (bio)photonic glass-based materials

Laeticia Petit

Tampere University, Finland

International workshop on
Biomaterial Innovations
Toward Repair of the Human Body #2
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Exploring the potential of preceramic organosilicon polymers for biomedical engineering applications

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Interest in developing a variety of corrosion resistant coatings for medical implants from polymeric precursors has been underway for recent years. This is motivated primarily by: (i) a pressing need to develop materials that are stable in oxidative or chemically aggressive environments, (ii) a desire for biodegradable/secure implants with appropriate mechanical properties similar to human bone, and (iii) an interest in developing bioactive ceramic/polymer composite coatings with tailored (bio) functional and mechanical properties. In light of concerns pertaining to the use of permanent metallic implants (e.g., stainless steel, titanium alloys, Co–Cr alloys) and the vulnerability of magnesium to corrosion under physiological conditions, the deposition of protective biodegradable coatings is the subject of growing interest for enhancing the corrosion resistance of Mg, and consequently keeping its mechanical integrity intact during the completion of the bone healing process.

Research and development activities on composites of bioactive glass (BG) and polymeric materials have been underway aiming at developing systems that combine the bioactive character of BGs and the favorable mechanical properties of the polymers. Among several polymeric materials, preceramic organosilicon materials or polymer-derived ceramics (PDCs) combining the properties of a polymer and an inorganic ceramic phase are of great interest to scientists working in biomedical sciences. Given the growing interest on Mg-based degradable metallic biomaterials and intense effort to improve their corrosion properties for various clinical applications, the aim of the work at CY Cergy Paris University is to integrate the surface of biodegradable Mg as a part of the corrosion resistant coating firstly via metal-biopolymer complexation reaction process and secondly by dip coating of polysiloxane (polysilazane)/ bioactive filler composite, and later by spin coating.

Polysiloxane and polysilazane exhibit excellent abrasion and corrosion resistance, good chemical resistance, and are considered good candidates for various applications, including protective coatings. The interest in polysiloxane has been attributed to its very strong bonding between silicon and oxygen as well as its thermal and oxidative stability. The absence of PDCs bioactivity` can be resolved by the incorporation of a bioactive inorganic phase by blending to generate a composite material. The coating process, based on simple mixing /dip coating /annealing at lower temperature, yielded densely packed and dispersed plate-like polysiloxane/bioactive composite layer with some precipitation of irregular shape bioactive particles (EDX), but still there are some cracks in the coating (FESEM micrographs). These cracks are attributed to the release of water and organic fragments which results in a considerable shrinkage accompanied by the formation of pores or cracks. Although the expectations are exciting and encouraging, the use of preceramic organosilicon polymers as a novel platform for biomedical implants is still in infancy. FTIR was used as an indispensable tool for detecting the presence of cured composites on the Mg substrates. The resulting composite coatings have been characterized by field emission scanning electron microscope (FESEM), EDX spectroscopy, infrared spectroscopy (FTIR), X-ray photoelectron spectroscopy (XPS), and electrochemical impedance spectroscopy. A more detailed investigation regarding the in vitro corrosion behavior, physico-chemical properties and cell culture response of polymer-derived composite coatings is the focus of an on-going work.

This presentation will comprehensively introduce current scientific literature as well as future perspectives in the field of polymer-derived ceramic-matrix filler composites as potential candidates for biomedical applications. In the end, this work in the development of polymer-derived functional ceramic composites paves the way for future work aiming to probe and engineer new products that can successfully apply in a diverse range of engineering and biomedical domains in the hope of meeting the dream and the demands of every human being. Further research is required, however, to assess and regulate the functionality of these composite products with the potential for enhanced or novel application opportunities.

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Characterization of force, displacement and temperature in air and water of a nitinol wire for a medical device application

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In this work is presented a preliminary study of a micro-system that will compose the navigation system of neurosurgery medical device developed by Robeaute. This microsystem is based on an active actuator of Nitinol which is a bio-compatible and non-ferromagnetic nickel-titanium shape memory alloy (SMA). It is increasingly used in the medical world in applications such as endoscopy [1], for stents [2] and orthodontic applications [3] using the super-elastic effect. In addition, its shape memory effect can be used in other applications as reported in [4] for active catheters.

A characterization in terms of force, displacement and temperature is realized in three steps. The first one is to validate the structure in the air as a proof of concept. Then it is going to be immersed in a liquid, representing the blood in the human body. Finally, in a deformable matter/gel featuring the brain (not included in the scope of this work but consider to be done in the future). The proposed system is composed of a spring that is attached to one platform at each ending. One nitinol wire of Ø50 µm that makes a boucle, entering from the base platform and returning at the top platform. The stiffness of the spring has been designed in such a way that it must, on one hand apply the appropriate pre-stresses in the wire, and on the other hand allow the wire to contract when activated. Two digital microscopes were used to measure the displacement, a force sensor for the generated force and a thermocouple of Ø25µm for the temperature of the wire. A range in current from 0 to 85 mA (max current according to the supplier) was applied to characterize the nitinol behavior. When the signal is applied, the nitinol wire starts to heat. Internally it is produced a crystallographic change phase at atomic scale, and a mechanical force and displacement at the macro scale. This is the reason why it is important to characterize these three parameters.

The objective of this work is to define a correlation between the effected force and displacement at a given current while measuring the temperature in different environments. As we are working with a thermo-mechanical system, temperature is a crucial parameter to be measured and controlled. Not only because activation is dependent of temperature, but also because of the context within the human body. Finally, the performance of the nitinol wire was compared in both environments. It was concluded that due to heat dissipation, it is necessary to apply three times more current in water than in the air (considering initial water temperature at 25°C). The force of the wire is kept the same in both environments, but the time response was slower in water due to the damping effect. It should be noted that, if bubbles are formed, they can cause a local overheating around the wire and therefore, a possible breaking at this zone. Despite of the good results obtained, for future works it is considered the possibility to add an isolation layer to the system to help in the heat dissipation with the environment.

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Characterization of genipin crosslinked Wharton's jelly membranes for bone regenerative medicine application.

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Wharton's jelly (WJ), an umbilical cord component, is a recoverable surgical waste essentially made up of collagen. WJ has a privileged immunological status and bioactive properties, making it a potential alternative to xenogeneic tissue use for the tissue engineering field. Despite its intrinsic immunomodulatory and antibacterial properties, we have recently shown that membranes made from decellularized WJ (dc-WJs) were not suitable for a guided bone regenerative medicine application1,2. Their in vitro/in vivo early resorption and the poor mechanical properties were probably responsible of this drawback. This work aims at generating a functional dc-WJ for an application in guided bone regeneration using genipin, a plant-derived noncytotoxic collagen crosslinking agent.

Dc-WJs membranes were treated with 0.05, 0.1 and 0.2 mg of genipin/mg of dry tissue for 24 h. A coloration ranging from light blue to dark blue, highlighted the intra and inter molecular crosslinking reaction between genipin molecules and the free amine groups of collagen. Crosslinking degree evaluation, carried out by a ninhydrin test, revealed an increase of 32 ± 12% to 85 ± 3% of crosslinking rate following the increase in genipin concentration. SEM imaging samples showed an irregular organization of the collagen fibers for the highly crosslinked samples. Compared to uncrosslinked samples (92.1 ± 2.3%), the genipin crosslink induced a significant reduction in the total porosity (78 ± 1.6% for the most crosslinked condition). Furthermore, the crosslinked samples exhibited and low swelling rate and a hydrophobic surface versus the control. Interestingly, weakly crosslinking did not affect these properties. In vitro degradation assays revealed a strong resistance of the crosslinked samples to the collagenase action, while in the presence of a pepsin solution, the weakly crosslinked samples were degraded up to 88 ± 12%. In vitro biocompatibility tests do not show any cytotoxicity and genotoxicity release of genipin. Cells adhesion (mesenchymal stem cells, osteoblasts, and fibroblasts) was however limited in comparison with the uncrosslinked control. The subcutaneously evaluation of the concentration of 0.05mg of genipin/mg of dry tissue revealed a high inflammatory reaction after 3 weeks, leading to the formation of a thick fibrous capsule. Few calcified nodules were also observed after 8 weeks of implantation. Implanted in the rat parietal critical bone defects and microtomography analysis showed that the genipin crosslinked samples out-performed the uncrosslinked WJ in terms of de novo kinetic formation (4 fold increase at 8 weeks versus 2 weeks, p=0.01).

These results highlight the potential use of genipin crosslinked WJ as a barrier in guided bone regeneration application.

References

1. *Dubus M et al., Biomedicines 2022, 10, 227.*
2. *Dubus M et al., Frontiers in Bioengineering and Biotechnology 2022, 10.*

List of Poster Presentations

Poster ID	Title	Presenting author	Affiliation
P1	Characterization of bio-functionalized 316L stainless steel substrates and *in vitro* study of their early stage influence on osteoblasts behavior	*Mathilde HINDIE*	CY Cergy Paris Université - ERRMECe - Cergy-Pontoise, France
P2	How electroactive polymer can be used for cochlear implants micro-robotization?	*Eric CATTAN*	IEMN - Université Polytechnique Hauts-de-France - Valenciennes, France
P3	Characterization of force, displacement and temperature in air and water of a nitinol wire for a medical device application	*Sofiane GHENNA*	IEMN - Université Polytechnique Hauts-de-France - Valenciennes, France
P4	Development of a purification process for xenogeneic bone matrices using supercritical CO_2 technology	*Solène ROTA*	BIOBank - Lieusaint, France
P5	Extracellular vesicles from hUC-MSC delivered by an injectable biomaterial as a cardio-reparative therapy in a rat model of myocardial ischemia-reperfusion.	*Chloé PEZZANA*	Inserm - Paris Cardiovascular Research Center (PARCC) - Paris, France
P6	Poly-L-Lysine and Human Plasmatic Fibronectin Films as Bifunctional Coatings to Reduce Bacterial Adhesion and Enhance Tissue Integration	*Anamar MIRANDA*	CY Cergy Paris Université - ERRMECe - Cergy-Pontoise, France
P7	Highly porous hybrid scaffolds for bone tissue engineering	*Credson LANGUEH*	Université de Paris, Unité de Recherche Biomatériaux Innovants et Interfaces - Montrouge, France
P8	Cranofacial bone regeneration : an vivo non-inferiority study of two xenogenic bone matrix purification processes	*Justine PERARNAUD*	CY Cergy Paris Université - ERRMECe - Cergy-Pontoise, France
P9	Design and evaluation of a chitosan-based scaffold crosslinked with oxydized maltodextrin for the articular cartilage tissue engineering	*Salim HAMIDI*	INSERM U 1008 - Lille, France
P10	Biofunctionalization of chitosan hydrogels through covalent grafting of fibronectin	*Pierre MARQUAILLE*	ESCPI - C3M Laboratory- Paris, France/CY Cergy Paris Université, ERRMECe - Cergy-Pontoise, France
P11	Label free thrombin aptasensors with AgNPs as electrochemical probe	*Maria KANDILY*	LPPI CY Cergy Paris Université - LPPI - Cergy-Pontoise, France/ University of the Western Cape, SensorLab, Cape Town, South Africa
P12	Development of a multiscale composite platform for delivery of natural active compounds: applications of curcumin toward skin	*Rosa CALDERON-JACINTO*	CY Cergy Paris Université - ERRMECe - Cergy-Pontoise, France
P13	Development of stratified porous scaffolds based on polyesters as supports in indirect cell co-culture	*Maria HERRERO*	CY Cergy Paris Université - ERRMECe - Cergy-Pontoise, France

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