BIOREGATE

EUROPEAN REGENERATIVE MEDICINE FORUM

21 - 23 SEPTEMBER

2022

Louvain-la-Neuve, Belgium

BIOREGATE REGENERATIVE MEDICINE CLUSTER

ATLANPOLE biotherapies Thinking up tomorrow's medicine

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UCLouvain

LIÈGE université

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EDITO

Regenerative medicine is one of the most exciting topics of modern medicine. It aims to provide solutions for patients affected by uncurable diseases and to address many unmet medical needs, mostly related to loss of function or organ failure.

This topic raises ethical issues about humans in terms of capacities and evolution. Success of this emerging field relies on an inter disciplinary and inter professional work and network. It requires experts from material sciences, robotics and complementary engineering sciences, from biologists, clinicians, bio engineers and also from human sciences. The technologies involved are cell and gene therapies, nanomedicines, biomaterials, tissue engineering, new frontiers in transplantation and immunology and more and more 3D bioprinting.

This advanced medicine is now called 4R medicine for Replace, Repair, Regenerate and Reprogram. It also involves personalised medicine tools. In all industrial countries, the market asks and waits for true and robust applicable strategies that are able to repair or even replace human organs. Big pharmas are moving to the field and numerous start-up companies are being created. New players like Fujifilm or Google invest a lot to be the future major players and influencers in regenerative medicine.

The Bioregate network was created thanks to the financial support of the Pays de la Loire region. Bioregate gathers more than 300 people involved in regenerative medicine in the Nantes, Angers and Le Mans areas. It includes universities, research hospitals, technological platforms and industries. Bioregate brings together all regional scientific institutions working in the field: Universities of Nantes, Angers and Le Mans, INSERM, CNRS, IFREMER, INRA, the Nantes and Angers university hospitals and Oniris national veterinary school. These academic institutions and SMEs are also members of the health cluster Atlanpole Biotherapies. Bioregate is also an international network with UCLouvain, ULiège, Galway university and Laval University as partners.

With the support of the regional innovation ecosystem players, Bioregate aims to boost research, training and innovation in the field of regenerative medicine with an international ambition.

The Bioregate Forum is one of the corner stones of this network and of our strategy to promote the advancement of 4R medicine. This year, Nantes Université and Atlanpole Biotherapies joined forces with UCLouvain and ULiège to set up and organise the 3rd Bioregate Forum in Belgium with a common focus: boost scientists, clinicians and industrials' discussions and partnerships. This edition aims to be international with the participation of scientists from the USA, Belgium, Switzerland, the Netherlands, the UK…

Famous scientists and industry representatives, as well as young researchers, in the fields of cell therapies, nanomedicine, 3D printing and bioprinting, smart biomaterials will present their latest advances in these hot topics. One-to-one meetings will also be organised for this edition to stimulate new collaborations and extend and deepen our Bioregate network.

It is thus my pleasure to welcome you to Louvain-la-Neuve after a 4-year break due to Covid, to share ideas, methods and most of all to strengthen and initiate new collaborations! And last but not least, I hope you will have fun!

Anne des Rieux

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ORGANIZERS

Organizing committee

Pr Anne des Rieux, UCLouvain, Louvain Drug Research Institute
Pr Christine Jérôme, University of Liège,
Director of the Center for Education and Research on Macromolecules (CERM)
Pr Pierre Weiss, Nantes Université, Regenerative Medicine and Skeleton Lab (RmeS)
Florence Hallouin, Atlanpole Biotherapies, Director
Lynda Guérineau, Atlanpole Biotherapies Cluster Networking Manager
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Olivier Roussel, Nantes Université, Bioregate, Administrative Officer

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Pr Pierre Weiss, Nantes Université, RMeS
Catherine Le Visage, Nantes Université, INSERM Manager
Pr Alain Colige, University of Liège
Dorien Van Hede, University of Liège
Pr Christiani Amorim, UCLouvain
Pr France Lambert, University of Liège
Karine Glinel, UCLouvain
Sophie Vériter, Independent Consultant
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CHU Rennes, University of Rennes I

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PROGRAM

BIOREGATE FORUM

21 - 23 SEPTEMBER 2022
Louvain-la-Neuve, Belgium

DAY 1 - Wednesday 21 SEPTEMBER 2022

7:45 - 8:30 am	**Registration & coffee**
8:30 - 9:00 am	**Welcome speech by organisers and officials**

	SESSION 1
	Cell therapy *Chairs: Sophie Vériter, Independent Consultant (Belgium) and Nicolas L'Heureux, University of Bordeaux (France)*
9:00 - 9:45 am	**Keynote:** Arnaud Scherberich, University of Basel - Basel (Switzerland)
9:45 - 10:10 am	**Keynote:** Denis Dufrane, Novadip - Mont Saint-Guibert (Belgium)
10:10 - 10:40 am	Coffee Break
10:40 - 11:05 am	**Keynote:** Stefan Braam, Ncardia - Leiden (Netherlands)
11:05 - 11:30 am	**Keynote:** Etienne Sokal, Cellaion - Mont Saint-Guibert (Belgium)
11:30 am - 12:30 pm	**Short presentations** - The teeth: an unexpected tissue type containing promising stem cells for tissue regeneration. *Annelies Bronckaers, Faculty of Medicine and Life Sciences, Biomedical Research Institute - BIOMED, UHasselt - Hasselt University (Belgium)* - Preclinical subcutaneous transplantation of a bio-pancreas optimized for O2 as an innovative therapy for type 1 diabetes. *Sawsen Bekir, Ecole Nationale Vétérinaire/Laboratoire d'Immuno-endocrinologie Cellulaire et Moléculaire - Nantes (France)* - Liver-derived signaling cells improve senescence and modulate ductular reaction in biliary cirrhosis. *Giulia Jannone, Pediatric Hepatology and Cell Therapy Unit, IREC, UCLouvain (Belgium)* - Canonical pro-inflammatory response of osteoarthritic human chondrocytes differs from that of non-osteoarthritic human chondrocytes. *Anaïs Defois, RMeS - Nantes (France)*

12:30 - 2:00 pm	**Lunch**
13:15 - 13:45 pm	**Poster Session**

	SESSION 2
	Decellularization *Chairs: Lisa White, University of Nottingham (United Kingdom) and Christiani Amorim, UCLouvain (Belgium)*
2:00 - 2:45 pm	**Keynote:** Nicolas L'Heureux, University of Bordeaux - Bordeaux (France)
2:45 - 3:05 pm	**Keynote:** Diletta Trojan, Fondazione Banca dei Tessuti di Treviso Onlus - Trevise (Italy)
3:05 - 3:30 pm	**Keynote:** Jeff Ross, MiroMatrix - St-Paul (USA)
3:30 - 4:00 pm	Coffee Break
4:00 - 4:45 pm	**Short presentations** - A naturally derived crosslinking agent for extracellular matrix hydrogel modulation. *Lisa White, Biodiscovery Institute, University of Nottingham (UK)* - Minimum concentration and time to obtain a decellularized extracellular matrix from ovarian tissue. *Cécibel L. Félix, Laboratory of Animal Reproduction, University of Brasília (Brazil)*
5:10 -6:10 pm	**B2B Session**

6:30 - 8:00 pm	**Welcome party**

DAY 2 - Thursday 22 SEPTEMBER 2022

8:00 - 8:30 am	Welcome Coffee

	SESSION 3
	3D Printing vs Bioprinting *Chairs: Karine Glinel, UCLouvain (Belgium) & Christine Jérôme, Uliège (Belgium)*
8:30 - 9:15 am	**Keynote:** Daniel J. Kelly, Trinity College Dublin - Dublin (Ireland)
9:15 - 9:40 am	**Keynote:** Gabriel Liguori, TissueLabs - Manno (Switzerland)
9:40 - 10:05 am	**Keynote:** Dr. Carlos Mota, Maastricht University - Maastricht (Netherlands)
10:05 - 10:35 am	Coffee Break
10:35 - 11:50 am	**Short presentations** - Regenerative Medicine and Skeleton, Organo-mineral 3D-Printed Scaffolds for Bone Regeneration. *Baptiste Charbonnier, Nantes Université, Oniris, CHU Nantes, INSERM (France)* - Enzymatically crosslinked hydrogel for salivary gland tissue engineering application. *Maryam Hajiabas, Laboratory of Pathophysiological and Nutritional Biochemistry, Faculty of Medicine, Université Libre de Bruxelles (Belgium)* - Towards the challenges of 3D bioprinting for salivary glands (SG) regeneration: Novel, dually crosslinked biomaterial inks for fabricating complex SG vascularized scaffolds utilizing coaxial printing approach. *Julia Simińska-Stanny, BioMatter-Biomass Transformation Lab (BTL), Université Libre de Bruxelles (Belgium)* - An original method to obtain muscle derived stem cells and their use for musculo-skeletal regeneration. *Didier Serteyn, Université de Liège/Revatis S.A. (Belgium)*
11:50 am - 12:40 pm	**Sponsor presentations:** Clean Cells ; EFS ; ThermoFischer

12:40 - 2:00 pm	**Lunch**
13:15 - 13:45 pm	**Poster Session**

	SESSION 4
	Extracellular Vesicles *Chairs: Catherine Le Visage, Nantes Université (France) FR and Alain Colige, Uliège (Belgium)*
2:00 - 2:45 pm	**Keynote:** Elena V. Batrakova, University of North Carolina - Chapel Hill (USA)
2:45 - 3:05 pm	**Keynote:** Thibaut Fourniols, Everzom - Paris (France)
3:05 - 3:30 pm	**Keynote:** Marie Morille, University of Montpellier - Montpellier (France)
3:30 - 4:00 pm	Coffee Break
4:00 - 5:00 pm	**Short presentations** - Use of intervertebral disc cells from sheep to evaluate biotherapies in vitro. *Paul Humbert, Nantes Université, RMeS (France)* - Extracellular vesicles isolated from human dental stem cells as drug delivery vehicles for neurological diseases. *Viridiane Gratpain, Advanced Drug Delivery and Biomaterials (ADDB), Louvain Drug Research Institute (LDRI), UCLouvain - Brussels (Belgium)* - Regenerative Medicine and Skeleton, Using osteocytes-derived extracellular vesicles for bone regeneration. *Floriane Kellner, Nantes Université, Oniris, CHU Nantes, INSERM (France)* - Extracellular Vesicles from Microalgae (MEVs) are effective delivery systems in human therapeutics, and in the frame of gene therapy. *Manuel Vega, AGS therapeutics (France)*
5:10 - 6:10 pm	**B2B Session and «Short pitch competition for PHd Students»**
6:10 - 7:30 pm	Free time - Hotel
7:30 - 11:00 pm	**Gala Dinner**

DAY 3 - Friday 23 SEPTEMBER 2022

8:00 - 8:30 am	Welcome Coffee
	SESSION 5
	Translational tissue repair *Chairs: Claire Vinatier, Nantes Université (France) & Pauline de Berdt, Cellaïon (Belgium)*
8:30 - 9:15 am	**Keynote:** Phillip Blondeel, Ghent University - Ghent (Belgium)
9:15 - 10:00 am	**Keynote:** Giuseppe Orlando, Wake Forest University - Winston-Salem (USA)
10:00 - 10:25 am	**Keynote:** Martin Ehrbar, University of Zurich - Zurich (Switzerland)
10:25 - 10:50 am	**Keynote:** Liesbet Geris, University of Liege (Belgium)
10:50 - 11:20 am	Coffee Break
11:20 am - 12:30 pm	**Short presentations** - Patient-derived tumor organoids as new models to investigate metabolism-based personalized medicine in advanced cancers. *Cyril Corbet, UCLouvain/IREC (Belgium)* - Formulation and characterization of hydrogel composed of LXA4 emulsion for dental pulp and periodontal regeneration. *Léna Guyon, Nantes Université, RMeS, (France)* - Encapsulation of human preantral follicles in PEGylated fibrin hydrogel with similar mechanical strength of reproductive-age ovarian tissue. *Arezoo Dadashzadeh, UCLouvain/IREC (Belgium)* - Polyphosphoesters : new opportunities as scaffolds for tissue engineering. *Raphaël Riva, University of Liege, CERM (Belgium)*
12:30 - 1:00 pm	**Closing remarks+ Prizes**
	Lunch Box

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ABSTRACTS

Invited speakers

ADIPOSE-DERIVED CELLS FOR BONE REGENERATION: BONE (PRE)FABRICATION, DEVELOPMENTAL ENGINEERING AND VASCULARIZATION STRATEGIES

Arnaud Scherberich
PhD, Adjunct Professor University of Basel - Basel (Switzerland)

This lecture will describe 18 years of research on the osteogenic potential of human adipose-derived mesenchymal stromal cells (ASC). Examples of bone formation by various human adipose derived cells-based engineered matrix/tissue, via either intramembranous or endochondral ossification processes will be presented. The lecture will also present the development of advanced therapy medicinal products (ATMP) based on an intraoperative use of the stromal vascular fraction (SVF) of human adipose, containing mesenchymal and endothelial cells, to support bone repair with tissue harvest, cell isolation, seeding onto scaffolding material and implantation within 3-4 hours. A translation of this concept into a first-in-man clinical trial (http://clinicaltrials.gov/show/NCT01532076), demonstrating safety, feasibility and providing proof-of-principle of the biological functionality (i.e., bone formation) of the implanted graft will be presented. Another clinical case, based on the use of ATMP to prefabricate a pedicled bone graft for maxilla reconstruction will be shown.

AUTOLOGOUS BONE TISSUE ENGINEERED AND ALLOGENIC BIOACTIVE MATRIX (DERIVED FROM ADIPOSE STEM CELLS) TECHNOLOGIES FOR BONE RECONSTRUCTION: PRECLINICAL EVIDENCE TO CLINICAL PROOF OF CONCEPT

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Denis Dufrane
Novadip - Mont Saint-Guibert (Belgium)

Critical size bone defect is one of the most challenging pathologies in orthopaedic surgery. Novadip developed initially an autologous bone tissue-engineered product intended to improve bone healing in severe pathophysiological conditions (a congenital pseudarthrosis of the tibia is difficult, many cases are associated with non-union leading to the amputation). The autologous bone tissue-engineered graft derived from adipose tissue cells was designed as a biologically active mineralized bridge with the objective to restore and promote the bone healing process. The autologous graft was easily handled, shaped, and implanted. A continuous remodelling (with bone formation) was found to obtain a sufficient bone fusion (allowing walk without pain) and no recurrence of the disease up to >4 yrs follow-up. Based on the understanding of the mode of action of the autologous bone tissue engineered product, an allogenic bioactive matrix was developed to elevate the standard of care for common orthopedic conditions. The in vitro & the in vivo safety/bioactivity was demonstrated in relevant preclinical models in comparison to current gold standards.

Conclusion: Based on a deep understanding of the biological component and activity, a new arsenal of autologous and allogenic products was designed in respect of the bone pathophysiologic conditions.

IPSC TECHNOLOGY FOR DRUG DISCOVERY AND CELL THERAPY

Stefan Braam
CEO, Ncardia - Leiden (Netherlands)

How the iPSC field has matured the past 10 years from drug discovery applications to cell therapy? Where current patient and donor derived cell therapies have fell short and how iPSC technology can overcome these obstacles? What are the challenges and opportunities with respect to better cell therapy product development and manufacturing technology?

CLINICAL DEVELOPMENT OF MEDICINAL SIGNALING CELLS (HEPASTEM™) FOR LIVER REGENERATIVE THERAPY

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Prof Etienne M Sokal, MD, PhD (1) (2)
Cliniques Universitaires St Luc, UClouvain (Belgium)
Founder & CEO of Cellaïon
(1) Cellaïon, rue Granbonpré 11, 1435 Mont-Saint-Guibert, Belgium
(2) UCLouvain, Institute of Experimental & Clinical Research, Laboratory of Pediatric Hepatology & Cell therapy, Belgium

Human Allogeneic Liver-derived Progenitor Cells (HALPC; HepaStem™) are an advanced therapy medicinal product composed of medicinal signaling cells derived and expanded from healthy human liver. Their mesenchymal and hepatocytic features make them promising cell therapy candidates for the treatment of life-threatening fibro-inflammatory liver diseases.

Safety, tolerability, and preliminary efficacy of HALPC infusion have been shown in a phase I and II prospective, open label, multi-center, randomized clinical trial in paediatric patients suffering from metabolic disorders, such as urea cycle disorders or Crigler-Najjar syndrome (HEP001 – NCT01765283; Smets et al., 2019), and in adults with Non Alcoholic Steato Hepatitis (NASH) and Acute on chronic Liver Failure (ACLF). HALPC act as a cargo inducing a hit-and-run decreasing of systemic and local inflammation and deactivation of stellate cells through paracrine activity. In vitro studies have shown a significant secretion of anti-inflammatory and anti-fibrotic cytokines including prostaglandin E2 (PGE2), indoleamine 2,3- dioxygenase (IDO), and hepatocyte growth factor (HGF), upon incubation of HALPC with an inflammatory cocktail.

The first clinical study led to European clinical authorization for further investigation via a phase II study in a patient with acute decompensation (AD) (phase IIa) or ACLF (phase IIa and IIb). ACLF is a life-threatening complication of cirrhosis, associated with deterioration of liver function followed by multiple organ failures. ACLF is linked to multiple cell type dysfunction, immunological imbalance and increased local and systemic inflammation. It is expected that HALPC exert immunomodulatory effects by interacting with immune cells of the patient and by paracrine effects through the various factors they secrete.

The phase IIa clinical trial (HEP101 – NCT02946554) assessed the safety of repeated infusions and intermediate doses in cirrhotic patients with ACLF or AD. The results of this study support the subsequent proof-of-concept study in a larger cohort of patients to further confirm the efficacy of HALPC therapy (Nevens et al., 2018). An ongoing phase IIb is currently recruiting patients across multiple centers in Europe (HEP102 – NCT04229901). This is an interventional, double blind, randomized, and placebo-controlled study of 1 dose regimen of HALPC intravenously infused in patients newly diagnosed with ACLF grade 1 or 2 on top of Standard of Care (SoC).

Pre-clinical data coupled with clinical data support a continued investigation in the context of a clinical development platform program, targeting ACLF, NASH, Acute Alcoholic Hepatitis, Acute decompensation of cirrhosis and other fibro inflammatory liver diseases.

CELL-ASSEMBLED EXTRACELLULAR MATRIX (CAM) FOR THE PRODUCTION OF HUMAN TEXTILES

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Nicolas L'Heureux
University of Bordeaux - Bordeaux (France)

Tissue engineering was, and still is, often simplified to the basic recipe: scaffold + cells = replacement tissue. In this equation, the scaffold is so often a synthetic polymer that the two concepts have become synonyms in the minds of many. Unfortunately, even the most inert synthetic polymers are recognized by the innate immune system as a foreign body to be destroyed. In many applications, this foreign body reaction will cause complications like obstructive fibrosis and thrombosis as a result of the chronic inflammation it generates. In addition, synthetic materials are prone to infection and have non-physiological high stiffness. An alternative approach is to use biological materials to provide a scaffold that the body can recognize and work with. However, this means that the body's adaptive and innate immune system will also recognize and destroy, respectively, xenogeneic proteins and extracellular matrix (ECM) proteins that have been denatured (i.e., damaged). This is why animal-derived implants are treated with powerful crosslinking agents, making them unrecognizable to the cells but transforming them in a sort of foreign material). This also explains why extracellular matrix proteins that have been chemically solubilized and re-assembled are rapidly degraded after implantation. Another alternative is to have human cells assemble an ECM in vitro that can be used as a strong, unprocessed, completely biological, human scaffold for tissue engineering and/or surgical repair. This talk will present how Cell-Assembled extracellular Matrix (CAM) can be produced as a sheet, as a thread, and as particles to provide a new toolbox to address various regenerative medicine challenges. Past, present, and future applications will be discussed with a special emphasis on the development of human textiles.

DECELLULARIZATION OF HUMAN TISSUES FOR TRANSPLANTATION

Diletta Trojan
Fondazione Banca dei Tessuti di Treviso Onlus - Trevise (Italy)

Fondazione Banca dei Tessuti di Treviso (FBTV) is a non-profit healthcare organisation tasked with procurement, processing, preserving, validating and distributing human tissue for clinical use.

Set up by the Veneto Regional Authorities and National Authorities, FBTV is specialized in the procurement, processing, storage and distribution of cardiovascular tissue, musculoskeletal tissue, adipose tissue and amniotic membrane. It distributes these homologous tissues throughout Italy and beyond.

In the last years, the decellularization process became very important in the use of human tissues.

FBTV has validated several protocols to decellularize different tissues such as heart valves, dermis and pericardium. The challenge for the tissue bankers and researchers is to keep the same propertiers of the native tissues and at the same time demonstrate the absence of vital cells.

Each tissue should have a different type of protocol and the goal is to have a quick but effective procedure to perform in clean rooms. There are several storage options: room temperature and freeze dried, deep frozen or cryopreserved according to the validation performed in the tissue bank.

BIOENGINEERING TRANSPLANTABLE LIVERS WITH PERFUSION DECELLULARIZATION

Jeff Ross
MiroMatrix - St-Paul (USA)

Organ failure remains a significant clinical problem, and the only curative solution in many cases is organ transplant. However, there is a chronic shortage of donor organs available to patients on the organ waiting list. The development of perfusion decellularization and recellularization technology as a means to bioengineer whole organs provided a pathway to expanding the total number of available organs. Progress down the pathway has been hindered by challenges with reestablishing the vasculature of the decellularized organ to allow for long-term patency of clinical scale engineered organs. Our recent work demonstrates that we can reestablishing the vasculature in a revascularized liver with long-term patency in clinically relevant sized organs. These studies were followed by the implantation of recellularized whole livers into an acute liver failure model demonstrating patency and key liver function, providing a critical step in the effort to bioengineered organs that can address the chronic need for transplantable organs.

BIOFABRICATION AND 3D BIOPRINTING STRATEGIES FOR TISSUE REGENERATION

Daniel J. Kelly
Trinity Centre for Biomedical Engineering, School of Engineering, Trinity College Dublin (Ireland)

Our musculoskeletal system has a limited capacity for repair. This has led to increased interest in the development of tissue engineering and biofabrication strategies for the regeneration of musculoskeletal tissues such as bone, ligament, tendon, meniscus and articular cartilage. This talk will demonstrate how different musculoskeletal tissues, specifically cartilage, bone and osteochondral defects, can be repaired using emerging biofabrication and 3D bioprinting strategies. This will include examples from our lab where cells and/or growth factors are bioprinted into constructs that can be implanted directly into the body, to approaches where biomimetic tissues are first engineered in vitro before in vivo implantation. The efficacy of these different biofabrication strategies in different preclinical studies will be reviewed, and lessons from the relative successes and failures of these approaches to tissue regeneration will be discussed.

3D BIOPRINTING TO FABRICATE ORGANS AND TISSUES IN THE LAB

Gabriel Liguori
TissueLabs - Manno (Switzerland)

Tissue and organ engineering has evolved for decades but still faces significant limitations towards becoming a reality in clinical practice. Some issues imposing such limitations relate to the conventional methods' low throughput, scalability, and automation potential. In addition, such techniques cannot recreate the complex, vascularized tissues and organs' spatial structure. To address these limitations, 3D bioprinting has emerged as a technique capable of combining cells, biomaterials, and enhancing factors to recreate the native architecture of tissues and organs. The technique leverages additive manufacturing technologies and opens extensive possibilities in tissue engineering and regenerative medicine. Dr. Gabriel Liguori will bring an overview of the sector and explore the opportunities brought by the most recent advances in 3D bioprinting.

BIOFABRICATION APPROACHES FOR TISSUE ENGINEERED CONSTRUCTS AND IN VITRO MODELS

Dr. Carlos Mota
Maastricht University - Maastricht (Netherlands)

Biofabrication is a relatively new field that aims make use of plethora of techniques to create three-dimensional (3D) scaffolds, tissue constructs and organs. With the advent of computer controlled additive manufacturing (AM) techniques applied to medicine, gradually researchers have adopted and transform these techniques to manufactured functional temporary 3D scaffolds for tissue regeneration. Examples of the use of AM techniques such as fused deposition modelling (FDM), to create scaffolds for critical size defects will be demonstrated. A novel FDM AM technique capable of producing continuous bulk and surface gradients has been recently developed to manufacture scaffolds for long bone regeneration. Scaffolds with osteoinductive and osteoconductive continuous gradient properties have been manufactured, characterized and pre-clinically investigated demonstrating the potential of continuous gradient scaffolds for the regeneration of bone defects. Other examples that will be showcased are AM techniques modified to allow the inclusion of cells in the process, termed bioprinting, which have been largely used to manufacture in vitro models for tissue and organ-like constructs. Bioprinting techniques allow to manufacture more biologically relevant models and ultimately implants. The currently applications of bioprinting investigated will be covered. Finally the ultimate ambition of using these techniques to build tissues and organs for patients will be covered highlighting the challenges and the future roadmap.

BIO-INSPIRED DRUG DELIVERY SYSTEMS FOR TREATMENT OF NEURODEGENERATIVE DISORDERS

Elena V. Batrakova
PhD, University of North Carolina - Chapel Hill (USA)

Increasing evidence suggests that extracellular vesicles (EVs) are promising natural nanocarriers that can be used for delivery of various types of therapeutics. We reported earlier engineered EV-based formulations for treatment of neurodegenerative diseases and cancer. Herein, we investigated the use of EVs for brain delivery of different therapeutic proteins, including a soluble lysosomal enzyme tripeptidyl peptidase-1, TPP1; a potent antioxidant, catalase, and glial cell-derived neurotrophic factor, GDNF. The therapeutic proteins were loaded into EVs using two methods: (i) transfection of EV-producing cells, macrophages, with drug-encoding plasmid DNA, or (ii) incorporation of the therapeutic protein into naive empty EVs. The second approach utilized sonication, or extrusion, or freeze-thaw cycles, or permeabilization of EVs membranes with saponin to achieve high loading efficiency. The utilized methods provided effective incorporation of functional therapeutic proteins into EVs. Notably, along with the enzyme, EVs released by pre-transfected macrophages contained drug-encoding pDNA. EVs significantly increased stability of the proteins against protease degradation and provided extraordinary drug delivery to target cells in in vitro and in vivo models of neurodegeneration. A robust accumulation of EVs carriers was detected in the inflamed brain. Finally, systemic administration of drug loaded EVs significantly increased neuronal survival and decreased neuroinflammation. We hypothesized that EV-based formulations have a potential to be a versatile strategy to treat different neurodegenerative disorders.

EXTRACELLULAR VESICLE PRODUCTION FOR REGENERATIVE MEDICINE: A CRO PERSPECTIVE ON CURRENT CHALLENGES AND PROPOSED SOLUTIONS MANUFACTURING PLATFORM OF EXTRACELLULAR VESICLES

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Thibaut Fourniols
Everzom - Paris (France)

EVerZom is a spin-off from the University of Paris/CNRS established in 2019 and working as a contract research and development organization with expertise in the field of extracellular vesicles (EVs). Mesenchymal stem cell (MSC)-derived EVs represent a promising alternative for cell therapy in regenerative medicine since EVs have the same properties as their parent cells. However, the clinical translation of EVs faces several bottlenecks, which hinder the diffusion of this innovation. This presentation will address some of the main challenges, with the dual vision of research and industrialization. First, the possibility of having an EV biomanufacturing process that would be both scalable and reproducible. To tackle this challenge, EVerZom has invented and developed a patented technology to produce EVs by turbulence triggering massive EV release : 10 times more EVs in 1/10th of the time for MSCs. Regarding the downstream process, there is still a debate in EV scientific community on what is the active substance in the secretome, either EVs or the whole secretome with soluble factors. This is why we have developed a scalable downstream process based on different techniques such as TFF and chromatography to provide a flexible level of purity. Finally, there is the challenge of qualification, to find the right parameters to ensure the quality, safety and efficacy of EV products. Some of the results from the translation from vitro to vivo, and from potency testing to biomolecular content of EVs, pave the way for better understanding and thus qualification for clinical translation.

PHARMACEUTICAL DEVELOPMENT TO ENHANCE SMALL EXTRACELLULAR VESICLES (SEV) THERAPEUTIC POTENTIAL

BIOREGATE EUROPEAN BIOMATERIALS INDUSTRY FORUM
21 - 23 SEPTEMBER 2022
Louvain-la-Neuve, Belgium

Marie Morille

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Despite the proof of concept of their efficiency as drug delivery systems (DDS) compared to synthetic nanoparticles, the rationale of using extracellular vesicles (EVs) in therapy for their intrinsic properties or as DDS still requires improvements due to technical limitations (handling, drug loading reproducibility and rates, blood instability of allogenic EVs). Working in a chemistry institute and coming from the field of drug delivery vector, we decided to use the tool we use with synthetic vectors to manipulate mMSC EV and try to find solution to alleviate these limitations. One of our research lines focuses on transient functionalization of EVs surface to increase their plasma stability while maintaining their cell internalization capacity. Our strategy relies on the post insertion of fine tuned bio-inspired polymers: the poly(2-oxazoline)s (POx). Known for their excellent biocompatible properties, POx also constituted an excellent alternative to poly (ethylene glycol) (PEG) as clinical awareness has risen around its overuse (e.g. anti-PEG Abs). We will present here a quick overview of what we have been doing with EV field in term of pharmaceutical development, especially on the evaluation of surface modification to develop allogenic EV that can be more rational as therapeutics.

FROM TISSUE TRANSPLANTATION TO TISSUE ENGINEERING

Phillip Blondeel
Chairman of the Department of Plastic Surgery, Chairman Burn Center, University Hospital Gent - Ghent (Belgium)

In one generation, the surgical techniques for breast reconstruction have changed dramatically. One of the last tools added to the toolbox is the technique of lipofilling. Although the clinical success of this tool was proven a few decades ago, long before the working mechanism was discovered in the laboratory, we now realize that lipofilling is actually the first step to modern regenerative medicine. It is a great tool to add volume to human tissues but it is also an enormous source of mesenchymal stem cells and precursor cells.

In this presentation an overview is given of the historical evolution of breast reconstruction, how it transitioned into combined procedures that involve conventional surgery and regenerative medicine and finally what the vision on the future for breast reconstruction is by involving tissue engineering.

ORGAN DECELLULARIZATION TO MANUFACTURE TRANSPLANTABLE ORGANS: PROMISE AND PITFALLS

Giuseppe Orlando
Wake Forest University - Winston-Salem (USA)

Transplantation, a field that has traditionally been immunology-based, in the next few decades will become a regenerative medicine (RM)-based discipline. What is driving this historical shift is the evidence that RM bears potential to meet the most urgent and still unmet needs of transplant medicine. These are the identification of a potentially inexhaustible source of organs, immunosuppression-free transplantation and "organ on demand" – whereby, a patient will receive a graft manufactured from his/her own cells as soon as the diagnosis of end stage organ failure is formulated, without any need to be registered in an organ waiting list. However, the initial enthusiasm and hype generated by the seminal experience with the artificial vessels, bladder and the cardiac organoids obtained with decellularization and cell-on-scaffold seeding technologies, has been tempered by the numerous roadblocks that have been encountered on the roadmap to the ultimate success. Alternative approaches like blastocyst complementation and 3D printing are under development, as well as strategies that aim at repairing and regenerating untransplantable organs in order to render them transplantable. This lecture will briefly illustrated all this and will emphasize the steps that leading transplant societies like the American Society of Transplant (AST) and the Tissue Engineering and Regenerative Medicine International Society (TERMIS) are undertaking to join forces and build their mutual future.

ENGINEERING TISSUE REGENERATION BY MODULAR DESIGNED SYNTHETIC HYDROGELS

Martin Ehrbar
University of Zurich - Zurich (Switzerland)

Biomaterials that support tissue regeneration by the mobilization of stem / progenitor cells and their localized differentiation would be highly desirable in multiple situations, such as for the regeneration of bone or for the closure of fetal membrane defects. Today, natural occurring biomaterials such as collagen, fibrin, or Matrigel® are still widely used. While these biomaterials have excellent biocompatibility and support cell functions, their use in engineering approaches remains difficult due to their significant batch-to-batch variability, their materials-inherent signals, and their insufficient in vivo stability. I will introduce a modular designed biomimetic poly(ethylene glycol) (PEG) hydrogel which can be tailored towards specific applications by varying its stiffness, its proteolytic stability as well as cell and growth factor binding properties. I will show how this hydrogel system can be combined with naturally occurring biomaterials to further enrich the available toolbox. I will show how this engineered hydrogel platform is used in our lab towards the regeneration of bone. Finally, I will give an outlook on how we make use of these biomaterials for the advanced characterization of engineered tissues.

USING DIGITAL TWINS TO ADVANCE THE TRANSLATION FROM BENCH TO BED SIDE IN TISSUE ENGINEERING

BIOREGATE FORUM
21 - 23 SEPTEMBER 2022
Louvain-la-Neuve, Belgium

Liesbet Geris
University of Liege (Belgium)

Digital Twin is a classical engineering concept referring to a virtual representation (in silico model) of a physical object or system across its lifecycle, from the early phases of development to manufacturing and distribution. In healthcare, the term is used more loosely to refer to a personalized in silico model. The underlying model technology ranges from purely data-driven (bioinformatics, AI) to mechanistic models, depending on the available knowledge and the question to be answered.

In this talk I will discuss a number of digital twins developed in the context of skeletal TE and demonstrate how they contribute to the clinical translation of TE products. One use case demonstrates how an in silico model of the proliferation and extracellular matrix production of cells seeded in a porous structure has helped to optimize a 3D printed calcium-phosphate-based scaffold for oral bone regeneration. After in silico design optimisation, the superiority of the design has been demonstrated in small and large animal studies performed by our clinical partners. The other use case discusses the development of an digital twin of a perfusion bioreactor allowing to quantify the microenvironment experienced by cells during their culture on 3D printed scaffolds. Inclusion of several relevant elements (including cost) provides a tool to further optimise the bioreactor regimen to reach a desired culture end point in the most efficient way.

BIOREGATE
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POSTER ABSTRACTS

POSTER 1

THE TEETH: AN UNEXPECTED TISSUE TYPE CONTAINING PROMISING STEM CELLS FOR TISSUE REGENERATION

BIOREGATE FORUM
21 - 23 SEPTEMBER 2022
Louvain-la-Neuve, Belgium

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Despite today's technological advancements and professional health care, tooth loss remains a global health problem. The tooth is a complex structure composed of the mineralized tissues, enamel and dentin enclosing a soft vascularised tissue, the dental pulp. As dental tissues and especially human enamel cannot regenerate, missing teeth need to be replaced. Current dental restoration solutions are made of synthetic materials and are prone to mechanical and biological failure. Hence, there is an urgent need to new strategies, preferentially made of human biological materials.

Several decades ago, a mesenchymal stem cell population was discovered within the pulp tissue, designated as dental pulp stem cells. These stem cells can easily differentiate into odontoblasts and our research group has revealed their strong angiogenic properties (secreting various angiogenic factors such as VEGF), making them suitable candidates for dentin regeneration.

Recently, our research groups succeeded in the generation of unique 3D-structures that could be used as a starting point for enamel regeneration, based on organoid technology. Organoids are 3D structures derived from either pluripotent stem cells or tissue biopts (containing epithelial stem cells). In addition, they are able to mimic the composition, function and histoarchitecture of an organ. To date, primarily organoids have been established from various epidermal tissues such as small intestine, liver, brain, kidney, pituitary gland and endometrium. Since organoids typically develop from the tissue's epithelial compartment, the organoid protocol was applied on dental follicle tissue as this contains epithelial stem cells (from the epithelial rests of Malassez). Pluripotency markers SOX2 and PITX2 were detected, supporting their stem cell character with self-renewal capacity. The established epithelial tooth organoids (ETO) were found expandable for more than 10 passages while robustly keeping their characteristics. Furthermore, the ETO displayed the ability to differentiate into ameloblasts, a process that was shown to be dependent on transforming growth factor-β (TGFβ) which is in concordance with its well-known physiological role of during amelogenesis. Coculture of the ETO cells with dental pulp stem cells, which mimics the mesenchyme-epithelium interaction during tooth development, further ameliorated this differentiation process. Transplantation of ETO in 3D-printed hydroxyapatite scaffolds in mice also resulted in the formation of dens extracellular matrix and calcium-phosphate accumulations, suggesting that these cells also in vivo retain their amelogenesis abilities.

In conclusion, dental tissues contain many valuable stem cells. In the dental pulp, mesenchymal stem cells reside having odontoblastic and angiogenic properties. In addition, in the dental follicle reside epithelial stem cells which under 3D organoid conditions undergo differentiation towards ameloblasts. These novel 3D structures have the possibility to pave the way for future cell-based tooth regeneration strategies but they also hold great promise as a 'tooth-in-a-dish' model to study dental disorders or the effect of pathogens or food additives on enamel formation.

POSTER 2

PRECLINICAL SUBCUTANEOUS TRANSPLANTATION OF A BIO-PANCREAS OPTIMIZED FOR O2 AS AN INNOVATIVE THERAPY FOR TYPE 1 DIABETES

BIOREGATE FORUM
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Type 1 diabetes mellitus (T1DM) is a chronic disease resulting from the auto-immune destruction of the pancreatic β cells requiring a daily palliative insulin-therapy. However, insulin replacement alone does not fully mimic the pancreas endocrine functions nor prevent long-term diabetes complications. Pancreatic islet or pancreas allotransplantation is a clinical reality for type 1 diabetes. However, this approach requires life-long immunosuppressive treatment and is limited by the shortage of available organs. The bio-artificial pancreas (BAP) encapsulating high density pig or human pancreatic islets in an alginate sheet is a promising complementary therapy, providing a better metabolic control to manage glycaemia and overcoming organ shortage. Despite key progress made so far, the main hurdle hindering the development of a clinically efficient BAP is the lack of oxygen (O2) faced by the cells during the post-transplantation two- week period needed for the BAP neovascularization.

To counteract hypoxia in the BAP, we developed an O2 supply strategy based on the combination of an oxygen generator and an O2 carrier. In this context, we aimed to design an optimal O2-regulated BAP prototype (BAP-O2) and to validate this prototype in mouse models, in terms of biocompatibility and efficacy. We optimize d the BAP for O2 supply using design of experiments. The analysis of the surface multi-responses allowed us to define an optimal BAP-O2 configuration embarking high density of islets, superior to that previously published and allowing an e xtrapolation of the device compatible in size with humans. Moreover, the optimized O2-supplied BAP maintained neonate pig islets (NPI) viable for at least 15 days, exceeding the duration of p ost-transplantation hypoxia. Our study also showed that the O2-strategy allowed improving insulino- secretion as well as NPI maturation. The manufacturing process improvement and standardization allowe d us to obtain a prototype that could be tested in mice. This prototype grafted in immune-competent mice did not show histological inflammation up to 30 days post-transplantation nor immunological rejection against the device in vivo, assessed by serum IL6, IFNγ, CCL2 and TNFα concentrations. The BAP retrieval was easy after 30 days. Concerning efficacy, our first results suggested that the BAP-O2 embedding mouse pseudo-islets could correct glycaemia in diabetic immune-deficient mice. Moreover, human c- peptide was detected in the serum of mice grafted with the BAP-O2 until at least five weeks after graft. The BAP carrying NPI will be tested in the mouse to confirm its pre clinical efficiency with alternative islets.

In conclusion, the preclinical validation of a BAP prototype with high islet density and optimized O2 supply should open the way of a complementary clinical therapy for type 1 diabetes.

Bioartificial pancreas, T1D, xenotransplantation, O2 supply, tissue engineering, cell therapy

POSTER 3

LIVER-DERIVED SIGNALING CELLS IMPROVE SENESCENCE AND MODULATE DUCTULAR REACTION IN BILIARY CIRRHOSIS

BIOREGATE FORUM
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Louvain-la-Neuve, Belgium

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Introduction: Objectives: Premature senescence has been extensively characterized in adult chronic hepatobiliary diseases and worsens liver function and fibrosis evolution, generating a need for senolytic therapies that can be translated to clinical applications. Mesenchymal stem cells (MSCs), also referred as medicinal signaling cells, repeatedly demonstrated to improve liver function and histology in chronic liver disease and even reduced cardiac and skin senescence in aging rats. However, the effect of MSCs on liver senescence has never been investigated. Our aim was to study the effect of human adult liver-derived progenitor cells (HALPC), a suspension of liver-derived signaling cells obtained from healthy adult human liver, on liver senescence in a preclinical model of juvenile biliary cirrhosis.

Methods: Bile duct ligation (BDL) was performed on 2-months old male Wistar rats and controls underwent sham procedure. Liver senescence was extensively characterized in the BDL model through senescence-associated beta-galactosidase (SA-β-gal) activity, p21 and p16 protein/gene expression, multiple immunofluorescence staining (p21, CK19, HNF4α) and gene expression of senescence-associated secretory phenotype (SASP) markers. HALPC were then transplanted through the penile vein of BDL rats 48 hours after the surgery at two doses (12.5 x 106 cells/kg versus 1.25 x 106 cells/kg, n=6 for each group) and compared to the vehicle (n=6). All animals were sacrificed 72 hours after the injection.

Results: Our results show the progressive development of senescence in BDL livers, the earliest marker of senescence being p21, already detectable 48 hours after the surgery ($p<0.05$). Senescence first developed in cholangiocytes and subsequently extended to hepatocytes in the parenchyma. Gene expression of SASP markers IL6, IL1β and TGFβ1 increased in diseased livers ($p<0.05$). The progression of senescence strongly correlated with fibrosis and ductular reaction (DR) development in our model of biliary cirrhosis ($r=0.96$ and 0.97 respectively; $p<0.0001$). HALPC injections (high and low doses) decreased senescence in BDL rats (p21 gene expression) ($p<0.05$). The high dose injection also improved biliary injury (serum γGT) and DR (Sox9 gene expression) as compared to low dose and vehicle subgroups ($p<0.05$).

Conclusions: Our data position BDL as a robust model of senescence and provide evidence that HALPC can decrease liver senescence and modulate DR in biliary cirrhosis. Those results place liver-derived signaling cells as a potential senolytic tool to develop in chronic hepatobiliary diseases in order to limit the worsening of the disease related to senescence progression.

POSTER 4

ANONICAL PRO-INFLAMMATORY RESPONSE OF OSTEOARTHRITIC HUMAN CHONDROCYTES DIFFERS FROM THAT OF NON-OSTEOARTHRITIC HUMAN CHONDROCYTES

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Louvain-la-Neuve, Belgium

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Osteoarthritis (OA) is the most prevalent inflammatory joint disease with no cure to date. Because numerous pro-inflammatory molecules are found in the synovial fluid of OA patients, the role of chronic low-grade inflammation has emerged as a key driver of the disease. To mimic the inflammatory process associated with OA, IL-1β and TNF-α, 2 major pro-inflammatory cytokines are commonly used in vitro to treat chondrocytes. Using a multi-omic approach, our work aimed to provide an in-depth analysis of osteoarthritic (OAC) and non-osteoarthritic (NC) chondrocytes' response to IL-1β and TNF-α.

Primary NC and OAC were isolated from young scoliotic patients undergoing arthrodesis surgery and from OA patients undergoing total knee replacement respectively. NC and OAC were treated with human recombinant IL-1β (1 ng/mL) or TNF-α (25 ng/mL) for 24h. A 3' -Seq RNA-profiling (3' SRP) was performed on both cell types and differentially expressed genes (DEGs) were extracted and compared between both cytokine treatments. A mass spectrometry experiment of OAC cell lysate was also performed and differentially expressed proteins (DEPs) were matched with DEGs. Then, String-DB was used for pathway analysis.

OAC exhibit 3061 DEGs and 154 DEPs in response to IL-1β and 1795 DEGs and 140 DEPs in response to TNF-α. 59 matched DEPs/DEGs common to IL-1β and TNF-α responses were extracted to define a pro-inflammatory signature in OAC.

When we compared the inflammatory response of OAC with that of NC, 3' SRP analysis evidenced smaller changes in the NC with only 465 and 477 DEGs in response to IL-1β and TNF-α respectively. Among the 227 common DEGs between IL-1β and TNF-α in NC, only 22 were found in the previously identified list of 59 in OAC. Interestingly, when string-DB analysis of the list of 59 was compared to this of 22, a group associated with glucose metabolism appears to be specific to OAC. In addition, all our transcriptomic data converged towards an OAC-specific overexpression of glycolysis players. This increase seems to be accompanied by a decrease in the Krebs cycle and an increase in LDHA and MCT4 which suggests a metabolic shift towards an anaerobic pathway that may lead to an over-production/ secretion of lactate. These observations establish lactate as a signaling molecule with a possible important role in OA onset.

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Chondrocytes, IL-1b, TNF-a, metabolism

POSTER 5

A NATURALLY DERIVED CROSSLINKING AGENT FOR EXTRACELLULAR MATRIX HYDROGEL MODULATION

BIOREGATE EUROPEAN BIOMATERIALS FORUM
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Louvain-la-Neuve, Belgium

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Digestion of decellularised tissues can generate extracellular matrix (ECM) based hydrogels [1]. ECM hydrogels are soft, injectable thermoresponsive materials that can direct cell function and fate in vitro and in vivo. Currently, ECM hydrogels lack the strength and durability needed for orthopaedic applications. However, it is possible to modulate hydrogel physical and mechanical characteristics by crosslinking the polymer network. Glutaraldehyde (GA) is a well-documented cross-linking agent. However, reports of cytotoxicity [2] have propelled research into alternatives, including naturally derived agents, such as genipin (GP) and others. In this study, we have assessed the efficacy of a plant derived natural cross-linking agent, referred to as 'NX' and examined the mechanical effects of crosslinking with GA, GP and NX on bone derived ECM (bECM) hydrogels.

ECM hydrogels were submerged in 10 mM or 50 mM GA or NX solutions for 2 hours. Following solution removal and washing (4 x 30 minutes PBS), frequency sweep testing was undertaken with angular frequency range of 0.01-200 rad/s, constant strain of 0.5% (Physica MCR 301 rheometer). Amplitude sweep testing used a range of 0.1-200% strain with a constant angular frequency of 1 rad/s.

Significant ($p<0.01$) 8 and 10-fold increases in complex moduli were observed from the 10 and 50 mM GA concentrations respectively when compared to the non-crosslinked control (NC). Treatment with NX exhibited a greatly increased difference in complex moduli, with concentrations of 10 mM giving a 39-fold ($p<0.0001$) increase and 50 mM causing an 85-fold increase ($p<0.0001$). Increases in storage moduli negatively affected the maximum strain tolerated by the gels.

Crosslinking with NX can greatly increase the maximum load that bECM hydrogels can endure, with the increase in strength and stiffness significantly higher than that achieved with GA or GP crosslinking. These results indicate that relatively low concentrations of NX exposure can crosslink bECM hydrogels.

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Extracellular matrix, hydrogels, cross·linking

POSTER 6

MINIMUM CONCENTRATION AND TIME TO OBTAIN A DECELLULARIZED EXTRACELLULAR MATRIX FROM OVARIAN TISSUE

BIOREGATE FORUM
21 - 23 SEPTEMBER 2022
Louvain-la-Neuve, Belgium

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Introduction: An alternative to restore fertility in women diagnosed with cancer, who would become infertile by chemotherapy and/or radiotherapy, is the development of an artificial ovary [6]. To assemble this biomimetic organ, we can use an ovarian decellularized ECM (dECM) as a 3D matrix to seed the isolated preantral follicles and ovarian cells. Currently, ovarian tissue dECM has been obtained using sodium dodecyl sulfate (SDS), usually at the concentration of 1% for 24 h. However, SDS can leave residue in the tissue, which may be toxic to the seeded cells. The objective of the present study was therefore to test different concentrations of SDS, with or without deoxyribonuclease I (Dnase), and shorter incubation times to decellularize ovarian tissue, aiming to identify the least aggressive and effective methodology.

Methodology: Bovine ovaries from a slaughterhouse were transported to the laboratory in saline solution at 37 °C. In the laboratory, the antral follicles were punctured with a needle and the capsule and the medullary region of the ovary were removed. Slices (10 mm x 5 mm x 1 mm) obtained from the cortical region of the ovary were weighed and distributed among the treatment groups. SDS stock solution was prepared with 1% SDS and 0.2M NaOH in distilled water and afterwards diluted to the desired concentrations. The SDS concentrations used were 1%, 0.5%, 0.1%, 0.05%, and 0.01%, with or without DNase I, and incubation times of 6, 12 and 24 h. Ovarian slices were individually submerged in 10 mL of each mixture, under constant stirring (100 rpm), at room temperature, and for the period defined for each treatment. They were then washed in 50 mL of distilled water for 6 h, changing the distilled water every 30 min. The tissue obtained from each treatment was analyzed by electrophoresis to assess the size of the remaining DNA fragments in the slices, DNA quantification by Qubit® 2.0 Fluorometer (Thermo Fisher Scientific), and histology.

Results and discussion: The lower concentration of SDS that showed no DNA remaining on the electrophoresis analysis was 0.1%, when incubated for 12 and 24 h, but not for 6 h. DNA quantification resulted in 7 ng DNA/mg ovarian tissue using these protocols. Furthermore, the histological analysis confirmed decellularization and Mallory's trichrome staining showed the conservation of collagen and elastin fibers in all samples after each treatment. Also, DNase I did not improve the efficiency of the decellularization protocol in any SDS concentration.

Conclusions: Our data proves the ovarian tissue can be successfully decellularized using 0.1% SDS, without DNase, for 12 h or 24 h.

POSTER 7

ORGANO-MINERAL 3D-PRINTED SCAFFOLDS FOR BONE REGENERATION

BIOREGATE FORUM
21 - 23 SEPTEMBER 2022
Louvain-la-Neuve, Belgium

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Introduction:
Developments in the field of computer-aided design and additive manufacturing have allowed significant improvements in the design and production of ephemeral scaffolds with biologically relevant features to treat bone defects. Unfortunately, the clinical and manufacturing workflow to generate personalized scaffolds is still source of inaccuracies which may lead to a poor fit between the implant and patients' bone defects. Furthermore, most scaffolds display a non-adapted mechanical behavior, an inappropriate biodegradability rate and a low potential to promote the formation of new vascularized bone tissues.
Tackling these issues, organo-mineral scaffolds with evolutive mechanical properties were 3D-printed.

Experimental methods:
Alpha tricalcium phosphate (α-TCP) and anhydrous trimagnesium phosphate (a-TMP) were used as reactive inorganic powders. They were obtained by heat treatment of apatitic TCP and hydrated TMP rods, respectively. Rods were crushed using an agate mortar and pestle and the powder sieved (20- 40 µm). As liquid phase, 6% w/v hyaluronic acid was dissolved in a 50% w/w D-glucose solution.
Cementitious pastes were prepared by mixing 60 and 50% w/w of α-TCP and a-TMP to the liquid phase, respectively. Disks were printed by robocasting using 25G cones following a rectilinear and gyroid pattern. These scaffolds were implanted in rat calvarial defects with or without total bone marrow.
Animals were euthanized after 7 weeks, and scaffold degradation and bone formation was assessed by micro-computed tomography X (µCT), scanning electron microscopy (SEM) and histology. Deep-learning routine were developed for µCT and SEM quantitative analyses. Finally, a real size 3D-printed polymeric model of a cleft lip and palate deformity was used as a proof of concept: a scaffold, 15% larger than the intended defect, was robocasted then inserted within the defect; this simulating a surgical intervention.

Results and discussion:
The simulated procedure was a success, with a deformable scaffold that could be inserted into the defect without breaking and adjusted to the edges for an optimized bone-implant contact. Bone formation in calvarial defect could be observed for both calcium and magnesium phosphates– based scaffolds up to their core; the addition of bone marrow playing a significant role. Scaffold architecture has little influence on bone formation. Significant differences in scaffold biodegradation were observed: while CaP-based scaffold largely remained, MgP-based scaffold could hardly been observed.

Conclusion:
The potential of 3D-printed organo-mineral scaffolds with evolving mechanical properties was demonstrated in this study. Biological response was driven by the inorganic phase composition. Further improvements of material formulations are currently ongoing, taking advantage of this proof of concept.

Additive Manufacturing, Bone, Hybrid cement

POSTER 8

ENZYMATICALLY CROSSLINKED HYDROGEL FOR SALIVARY GLAND TISSUE ENGINEERING APPLICATION

BIOREGATE FORUM
21 - 23 SEPTEMBER 2022
Louvain-la-Neuve, Belgium

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Salivary glands (SG) are complex secretory tissues that secret saliva, a fluid rich in proteins, ions, and water, to maintain oral health and functionality [1]. Therefore, any SG dysfunctionality influences the quality of life. Due to the lack of efficiency in traditional treatments, cell-based and cell-material-based therapies have gained extensive attention to restore SG function. Currently, particular focus has been laid on hydrogel materials to mimic physicochemical cues of SG natural tissue to obtain and evaluate the functionality of different SG compartments [2]. As mechanical properties of scaffold materials play a significant role in cell fate and branching morphogenesis, further studies to make an appropriate engineered model are still required. Accordingly, this work aims to prepare a composite Hyaluronic acid-silk fibroin (HA-SF) hydrogel scaffold for SG bioengineering application. Herein, we fabricated hydrogels with different rheological properties made of 2.5(w/v%) Tyramine conjugated-HA and SF solutions (1,2,3,4 (w/v%)) via enzymatic crosslinking to compare them with natural submandibular gland tissue and decellularized extracellular matrix (ECM). Rheological analysis revealed that blend hydrogel containing SF 4% could approximately simulate the mechanical properties of the natural SG tissue.

Furthermore, the HA-SF blend has shear thinning properties favorable for use as bioink for 3D printing applications. Live/dead cell staining and cell viability assay also showed that seeded human normal salivary gland-SV40 transformed-Squamous Cells (NS-SV-AC) with acinar phenotype on the surface of the HA-SF hydrogel with 4% SF have notable cell viability (97.14%) after seven days of culture. In summary, our data showed that HA-SF hydrogel might be a suitable candidate bioink for 3D bioprinting applications.

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Enzymatic crosslinking, Hydrogel, salivary gland, tissue engineering, Xerostomia

POSTER 9

TOWARDS THE CHALLENGES OF 3D BIOPRINTING FOR SALIVARY GLANDS (SG) REGENERATION: NOVEL, DUALLY CROSSLINKED BIOMATERIAL INKS FOR FABRICATING COMPLEX SG VASCULARIZED SCAFFOLDS UTILIZING COAXIAL PRINTING APPROACH.

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Bioinks and biomaterial inks that can be transformed into genuine 3D constructs, employing 3D printing technology signify a step towards personalized treatments and tissue engineering. Currently, many studies focused on regenerative medicine strategies also exemplify the need for vascularization within the obtained in vitro structures as it is crucial to maintain cells survival and therefore hasten the regeneration process. To date, only a handful of materials have been investigated in terms of their utilization for salivary gland (SG) tissue engineering while creating an artificial SG vasculature system still remains one of the biggest hurdles.

To confront these challenges within our work we utilize a 3D extrusion bioprinting technique to successfully obtain vascularized SG scaffolds of superior shape fidelity while preserving the inherent biocompatibility of the ink components. The entanglement of polymeric networks within our hydrogels not only endowed the material with dual-step crosslinking ability but also with high tunability of material properties. To fabricate artificial SG matrix and vessel scaffolds two shear- thinning, stackable biomaterial inks were formulated. For the SG matrix we used: methacrylated gelatin (GelMA, 4% w/v), and hyaluronic acid conjugated with tyramine (HA-Tyr, 1% w/v), while for the vessels a blend of alginate (Alg, 2% w/v) and HA-Tyr - 1% w/v. Both inks were preliminary crosslinked with horseradish peroxidase (HRP)/ H_2O_2 and enriched with methylcellulose (MC, 3% w/v), to tune their rheological profile and allow for continuous extrusion of the material. To 3D print perfusable channels mimicking blood vessels, we used a novel coaxial printing technique. In this manner simultaneous extrusion of the Alg - based ink (as the outer layer) with the crosslinking agent $CaCl_2$ (80 mM, the inner side of the nozzle) allowed the hydrogel to be cross-linked from the inside forming perfusable tube. The SG matrix was fabricated with conventional extrusion 3D printing. Following that, previously printed vessels were embedded into the SG scaffold and subjected to cell-friendly visible light photocrosslinking with a riboflavin - sodium persulfate system to generate a robust composite hydrogel. Inks' composition and polymers choice were tuned to resemble the rheological profile of vessels and SG tissue and support the viability of endothelial (90%) and SG cells (95%), respectively.

To sum up, our work may help to tackle the problem of artificial tissue vascularization and SG dysfunction from theoretical and translational standpoints. Firstly, as a model to determine SG malfunction' underpinnings, screening treatments and secondly as a method to develop vascularized tissue replacements.

Biomaterial ink, 3D printing, Extrusion printing, Salivary glands, Vascularization, Rheology, Photo crosslinking, Enzymatic crosslinking, Dual-stage crosslinking, GelMA, Hyaluronic acid, Shear-thinning behavior

POSTER 10

AN ORIGINAL METHOD TO OBTAIN MUSCLE DERIVED STEM CELLS AND THEIR USE FOR MUSCULO-SKELETAL REGENERATION

BIOREGATE FORUM
21 - 23 SEPTEMBER 2022
Louvain-la-Neuve, Belgium

Didier Serteyn, Hélène Graide, Julien Duysens, Justine Ceusters
University of Liège and Revatis SA

Purpose: A novel sampling method based on microbiopsy of skeletal muscle allows collecting a high number of autologous mesenchymal stem cells (WO2015091210). These types of cells have shown potential for a plethora of regenerative medicine applications. Regarding the musculoskeletal system, bone regeneration and tendon healing are the central clinical issues. Currently, 3D printing offer to create personalized synthetic matrix to improve cellular development for tissue engineering.

Objectives: To evaluate the ability of equine muscle-derived mesenchymal stem cells (mdMSC) to colonize bone and tendon 3D scaffold, and subsequently to study cell behaviour on these matrix.

Methods: Equine mdMSC have been obtained as described by Ceusters et al. (2017). Three-dimensional printing hydroxyapatite matrix seeded with mdMSC has been incubating at 37°C during 15 days in culture medium. Adherent cells have been harvested, colored with alizarin red and differentiated into adipocytes, osteocytes and chondrocytes. Tendon matrix were decellularized by freeze-thaw cycles, incubated with cells for 20 days and then observed in electronic microscopy or fixed and stained with hematoxilin-eosin and observed in optical microscopy.

Results: After 2 to 3 weeks, equine mdMSC have been able to colonize the 3D matrix, on the surface but also in depth. Furthermore, cells in contact with the matrix have lost their trilineage differentiation ability and started to spontaneously differentiate into the tissue of interest as shown by the increase in calcium deposits on the bone matrix.

Conclusion: Easily-accessible mdMSC combined with 3D matrix could have great potential in tissue engineering.

POSTER 11

USE OF INTERVERTEBRAL DISC CELLS FROM SHEEP TO EVALUATE BIOTHERAPIES IN VITRO

BIOREGATE FORUM
21 - 23 SEPTEMBER 2022
Louvain-la-Neuve, Belgium

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Intervertebral disc (IVD) degeneration is among the leading cause of low back pain. Given the lack of etiological treatments, IVD regeneration is a major public health challenge. The sheep spine exhibits biological and biomechanical similarities with the human one and is thus recognized as a relevant model for translational applications. We present here cellular models of sheep annulus fibrosus (AF) and nucleus pulposus (NP) cells to evaluate cell and extracellular vesicles (EVs) therapies for IVD regeneration.

Cells were isolated from the IVDs of five young sheep and three older ones with mild disc degeneration. The expression of the major genes involved in matrix synthesis, matrix degradation, and inflammation was compared between the animals, and between AF and NP tissues. Treatments with recombinant IL-1β (10 ng/mL) or H2O2 (500 µM) or dedifferentiation in culture (over 10 passages) were used to simulate a degenerative IVD microenvironment. The effect of EVs from human adipose-derived mesenchymal stromal cells (hASCs) on degenerative-like NP and AF cells was evaluated. In a separate experiment, hASCs cells were co-cultured with NP or AF cells, in direct or indirect (Transwell®) contact. The use of two species allowed us to analyze RNA expression from disc cells in direct co-culture with hASCs by using sheep-specific primers.

Sheep AF and NP cells exhibited differential RNA expression, notably a higher expression of COL1A1 in AF cells while NP cells favored COL2A1. Cells from older sheep also displayed those differences but with an overall lower expression of matrix proteins and higher expression of metalloproteinases (MMPs) and inflammatory cytokines (IL6, CXCL8) compared to the cells from young sheep. Prolonged culture of young cells or treatments with IL-1β or H2O2 led to a rather similar expression profile as for older cells. While EVs consistently increased basal metabolic activity of both AF and NP cells at early and late passages, they had little effect on gene expression. On the other hand, direct cocultures with human ASCs profoundly affected the transcriptional profile of disc cells. Notably, both types of cocultures led to a drastic downregulation of CXCL8 in disc cells, reduced by over 60% in indirect coculture and even undetectable in direct coculture, while we observed an upregulation of COL1A1 but also MMP1.

Surprisingly, IL6 expression by disc cells slightly increased with hASCs on Transwells but sharply decreased by over 80% when hASCs were in direct contact.

We demonstrated that healthy sheep cells expressed markers of degeneration after IL-1β and H2O2 treatment, or after numerous passages in culture. They showed biological responses to hASCs and, to a lesser extent, to hASC-derived extracellular vesicles. These results confirm the suitability of sheep disc cells to model IVD degeneration in vitro and assess biotherapies.

Intervertebral disc regeneration, sheep model, mesenchymal stromal cells

POSTER 12

EXTRACELLULAR VESICLES ISOLATED FROM HUMAN DENTAL STEM CELLS AS DRUG DELIVERY VEHICLES FOR NEUROLOGICAL DISEASES

BIOREGATE FORUM

21 - 23 SEPTEMBER 2022
Louvain-la-Neuve, Belgium

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Introduction: Most central nervous system (CNS) affections are unmet medical needs, one reason being the limited accumulation of drugs in the CNS. As drug delivery systems, extracellular vesicles (EVs) are able to cross epithelial barriers, are non-immunogenic and have an intrinsic activity. In this work, our objective was to isolate and characterize EVs from human dental mesenchymal stem cells (SCAP) to later use them as nanomedicines in the scope of multiple sclerosis.

Methods: EVs were isolated from SCAP culture medium by centrifugation, ultrafiltration and size exclusion chromatography (SEC). Impact of ultrafiltration unit cut-off (30 and 100 kDa) and SEC (Izon qEV 70 and 35 nm) on EV yield (NTA, ZetaView) and separation from proteins (DELFIA immunoassay) was evaluated.

MiRNA content (small RNAseq) and lipid composition (UPLC-MS/MS) of EVs produced by SCAP in pro-inflammatory condition (activated SCAP) vs steady-state were compared. Finally, the influence of EVs on pro-inflammatory marker gene expression of microglial cells (BV2 cells) and spinal cord slices for 8h and 24h was evaluated (RT-qPCR).

Results: Using a cut-off of 30 kDa and the qEV 35 nm SEC provided the highest number of EVs while eliminating most of the contaminating proteins. EVs were negative for calnexin and positive for CD9, CD63, CD81 and flotillin-1. 236 miRNAs, associated mainly with MAPK, neurotrophins and cancer pathways, were identified in steady-state EVs while 40 miRNAs were significantly affected in EVs produced by activated SCAP. Among the lipids detected in EVs, no significant difference were observed. In LPS-activated BV2 cells, whatever the incubation time, neither non-activated nor activated SCAP-EVs were able to significantly impact the gene expression of pro-inflammatory cytokines. Only TNFα was significantly affected by activated SCAP-EV after 24h of incubation. The same results were observed in spinal cord slices. Incorporation of bioactive drugs in SCAP-EVs is ongoing.

Summary/Conclusion: We optimized the isolation of EVs from SCAP, analyzed how their composition was influenced by the activation state of SCAP, and studied their impact on neuroinflammation. The limited effect observed could be explained by the low amount of contaminant proteins or the difficulty to compare results between different studies. The encapsulation of bioactive molecules for CNS delivery is ongoing.

Stem cell from apical papilla, neuroinflammation, miRNA, lipidomics

POSTER 13

USING OSTEOCYTES-DERIVED EXTRACELLULAR VESICLES FOR BONE REGENERATION

BIOREGATE EUROPEAN BIOMATERIALS INDUSTRY FORUM
21 - 23 SEPTEMBER 2022
Louvain-la-Neuve, Belgium

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Osteocytes play a significant role in bone homeostasis and the maintenance of bone integrity.

Age-related bone loss results from a reduction in bone formation and leads to an alteration of the osteocyte network. As a result, the aging bone deteriorates in composition, structure and function. This decreases the ability of bone for self-repair and predisposes to osteoporosis and fractures. Our objective is to mimic the major processes of physiological bone repair that are driven by osteocytes and to set the ground for the design of a novel osteoanabolic and regenerative bone approach using osteocyte extracellular vesicles (EVs) or their relevant associated cargos. EVs are composed of small (<150 nm) and large vesicles (<1 µm) that carry signature cargos from their cell of origin including proteins and RNAs.

In this study, we are interested in the potential anabolic properties of osteocytes-derived EVs. We hypothesize that EVs controls osteoblast phenotype and activity and that dysfunctions in this EVs network could occurs with aging, leading to alteration of bone quality and to bone loss.

EVs were isolated from young (8-week-old) and aged (1-year-old) mice compact bones, using differential centrifugation coupled with sucrose cushion. Functional characterization showed that EVs were able to be uptaken by stromal cell lines. We also analyzed in vitro the ability of the EVs to modulate cell differentiation overtime looking at alkaline phosphatase (ALP) activity of pre-osteoblastic cell lines.

Two populations of EVs were obtained from compact bone of young and old mice (large EVs mean diameter 316±14 nm and 330±37 nm for young and old respectively, and small EVs 142±8 nm and 162±8 nm). An average concentration around 1,2.10^9±0,5.10^9 particles/hindlimb was measured in young animals and 5,1.10^8±0,6.10^8 for the old one's indicating that old bone produce half as much EVs as the young one's. We also present evidence that addition of the same 3 doses of large EVs from young and old bones (x1 = 14.10^6/well, x10, x50) to cell culture medium of pre-osteoblastic cell lines, increases ALP activity at the highest dose. But very interestingly, we observed that the increase in ALP activity obtained with large EVs derived from old mice is half as great as with EVs derived from the youngest bone. For small EVs, no significant effect on ALP activity was observed either for young and old bone derived EVs.

In conclusion, we described for the first time that aging seems to affect EVs production in compact bone. Our results further suggest that only large EVs seems to be affected by aging. Finally, our data indicated that the old bones-derived large EVs exhibited reduced ability to increase osteoblastic activity in cell culture experiments. Altogether, these results suggest that large EVs could be involved in the bone loss aging phenotype through a reduced stimulation of osteoblast activity.

Extracellular vesicles, bone regeneration, aging

POSTER 14

EXTRACELLULAR VESICLES FROM MICROALGAE (MEVS) ARE EFFECTIVE DELIVERY SYSTEMS IN HUMAN THERAPEUTICS, AND IN THE FRAME OF GENE THERAPY

BIOREGATE FORUM

21 - 23 SEPTEMBER 2022
Louvain-la-Neuve, Belgium

Manuel Vega
AGS THERAPEUTICS

EVs in general have naturally evolved to orchestrate communication between cells via exchange of biologically active molecules. They function as intercellular and cross-kingdom communication tools that can transfer and deliver biological cargo of various nature to recipient cells. EVs, specially from mammalian origin, are being developed as delivery systems in the frame of human therapeutics and vaccines.

Microalgae, in general, bear in their genome the machineries required for EV production-secretion. They are thus an ideal biological system to source Microalgae Extracellular Vesicles (MEVs) that can be directly used to protect, transport and deliver a broad spectrum of innovative therapeutic molecules into disease target cells and it can be cultured at large industrial scale at low cost. MEVs are non-viral and natural (cell-derived, no synthetic components), easy to produce and to purify in large quantities.

Chlorella vulgaris (Chlorella) is a non-toxic, non-immunogenic unicellular haploid microalgae, that has been consumed worldwide as a food supplement for decades. Chlorella MEVs efficacious to carry different types of genetic material (mRNA, siRNA, cDNA) to human cells as well as to load a variety of molecules (proteins, peptides).

Chlorella MEVs bear a significant natural tropism for key organs relevant to human diseases with various ways of administration (including intranasal, respiratory, and intravenous), thus opening the way to address a large diversity of medical conditions by way of innovative therapeutics and vaccines. On top of the above, Chlorella MEVs are edible; they easily get through the digestive tract barrier and are internalized by the intestine when administered orally.

Microalgae extracellular vesicles, Gene therapy, Drug Delivery System

POSTER 15

PATIENT-DERIVED TUMOR ORGANOIDS AS NEW MODELS TO INVESTIGATE METABOLISM-BASED PERSONALIZED MEDICINE IN ADVANCED CANCERS

BIOREGATE FORUM
21 - 23 SEPTEMBER 2022
Louvain-la-Neuve, Belgium

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Despite the implementation of personalized medicine in the clinical management of patients with metastatic colorectal cancers (mCRC) (with BRAF/RAS genetic testing, evaluation of mismatch repair (MMR) and microsatellite instability (MSI) status), overall prognosis is still very poor, due to frequent tumor relapses. Indeed, the clinical efficacy of anti-EGFR targeted therapies (e.g. cetuximab) and immune checkpoint inhibitors (pembrolizumab, nivolumab, ipilimumab), that can be applied for KRAS/NRAS/BRAF wild-type and MSI-high/MMR-deficient (MSI-H/dMMR) mCRC respectively, is strongly limited by the development of acquired drug resistance after an initial tumor response or by the lack of effectiveness at the outset. Moreover, no validated treatment options exist for the patients who progress after these therapies (unmet medical need). Besides genotype-mediated resistance mechanisms, tumor microenvironment (TME) conditions are increasingly recognized to generate intratumoral phenotypic heterogeneity that may select for pre-resistant cell populations and actively contribute to therapeutic failures. Altogether these observations led us to integrate the concept of tumor metabolic niches (i.e. the influence of the tumor microenvironment (TME) on tumor metabolic preferences) to identify metabolic liabilities in therapy-refractory mCRC. By using patient-derived tumor organoids as relevant preclinical 3D models of mCRC, in combination with genomic, transcriptomic and metabolomics analyses, we determine how and to what extent TME-mediated metabolic preferences are associated with distinct responses to anti-EGFR targeted therapies in mCRC. More precisely, we examine (1) which metabolic pathways are common to cetuximab-resistant mCRC, (2) how TME peculiarities shape mCRC cell metabolic phenotypes prone to support anti-EGFR targeted therapy resistance and (3) evaluate whether metabolism-targeting treatments impact on anticancer immune response in mCRC. These experiments have enabled us to reveal in detail the metabolic preferences of CRC cells resistant to anti-EGFR therapy and to define new therapeutic strategies prone to overcome and/or prevent this resistance. Finally, this research program is at the center of a broader initiative that aims to develop a living biobank of tumor organoids at UCLouvain that may benefit for academic and industrial collaborations in (immuno)oncology and precision medicine fields.

Organoids, tumor metabolism, microenvironment, therapy resistance, personalized medicine

POSTER 16

FORMULATION AND CHARACTERIZATION OF HYDROGEL COMPOSED OF LXA4 EMULSION FOR DENTAL PULP AND PERIODONTAL REGENERATION

BIOREGATE FORUM
21 - 23 SEPTEMBER 2022
Louvain-la-Neuve, Belgium

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The background of this project is the resolution of inflammation in clinical situations associated with widespread conditions such as pulpitis and periodontitis. Recently, an emphasis has been placed on immune modulatory roles of lipoxins. Lipoxin A4 (LXA4) is an endogenous anti-inflammatory, pro-resolving molecules heralded that regulate functions of the innate immune system [1]. The major challenge in using lipoxins is their hydrophobicity and chemical instability. To overcome these drawbacks, our proposal aims to encapsulate lipoxin in emulsions entrapped in silanized hyaluronic acid (HA-Si) hydrogels.

Lipoxin-loaded emulsions were developed using an emulsifying machine Ultraturrax® (MPE5) or Luer-lock syringes (SE6P). These emulsions were entrapped in 51 kDa HA-Si hydrogels with various degree of silanization. The erosion and swelling profiles of hydrogels were studied in phosphate-buffered saline with or without hyaluronidases, in citrate buffer and HEPES at 37°C. In parallel, chemical stability of LXA4, emulsion stability and the cumulative release profiles of LXA4 from different gels were studied by mass spectrometry and digital microscope.

Lipoxin was successfully entrapped in two different emulsions composed of 10 µm micelles. Formulations were stables for at least 3 months with an encapsulation efficiency of around 20%. Interestingly, the erosion and swelling profiles of the obtained hydrogels were very different: a complete degradation of H-MPE5 was observed after 3 days in all medium whereas 11 days was required to degrade H-SE6P in hyaluronidases medium. The LXA4 release was faster in presence of hyaluronidases than in other medium with 60% of LXA4 release from H-MPE5 after 3 days. Chemical stability of LXA4 results revealed that 77% of LXA4 remained intact after 3 days at pH 7.4. However, a rapid degradation was observed at pH 8.5 and pH 5 showing the crucial role of LXA4 encapsulation.

Two different hydrogels containing LXA4 were formulated (H-MPE5 and H-SE6P). Hydrogel features were pH dependent and the system could be adapted function of the intended applications. This study highlights the importance of the platform used to vectorized LXA4 (emulsion properties, HA-Si hydrogels) to control the molecule release, stability and the degradation of the hydrogels in the perspectives of dental pulp or periodontal regeneration.

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Emulsions, hydrogels, lipoxin A4

POSTER 17

ENCAPSULATION OF HUMAN PREANTRAL FOLLICLES IN PEGYLATED FIBRIN HYDROGEL WITH SIMILAR MECHANICAL STRENGTH OF REPRODUCTIVE-AGE OVARIAN TISSUE

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Objectives: Ovary tissue engineering can be an approach to preserving the fertility of prepubertal girls and women who cannot benefit from the available fertility restoration strategies due to the presence of malignant cells in their cryopreserved ovarian fragments. The main challenge of preparing an engineered ovary is providing an appropriate substrate to maintain the 3D structure of follicles and allow them a radial growth. While fibrin is a potential candidate for ovarian tissue engineering, its main drawback is fast degradation, which results in implant volume loss within days and subsequently loss of physical support of follicles. To overcome this obstacle, physical or chemical modifications such as PEGylation have been developed.

Methods: PEGylation process was employed to improve fibrin stability. Moreover, a sequence of designed experiments was programmed by Response Surface Methodology to achieve a hydrogel formulation with similar mechanical properties to the reproductive-age ovarian cortex. Afterward, isolated human preantral follicles were encapsulated in the optimized formulation of PEGylated fibrin and cultured for 4 or 7 days to assess cell-cell communication and follicle growth, respectively.

Results: The biomechanically optimized PEGylated fibrin formulation was developed using mathematical modeling with specific targeting of Young's modulus of the human ovarian cortex at reproductive age (3178 ± 245 Pa). The PEGylated fibrin hydrogel containing 39.06 mg/ml of PEGylated fibrinogen and 50.36 IU/ml of thrombin with Young's modulus of 3512.31±656.97 Pa was found to be the most desirable condition (desirability of 97.5%). The viability of follicles was analyzed morphologically, which was 87% and 83% on days 1 and 7, respectively. The diameter of isolated follicles cultured in our hydrogel significantly increased from 48.5±10.8µm (day 1) to 222.5±84.5µm (day 7). The follicles' growth was confirmed by the presence of Ki67-positive granulosa cells in follicles analyzed by confocal microscopy on day 7.
Moreover, our results from cell-cell communication analysis on day 4 showed that 100% of these follicles were stained positive for connexin 43. On the other hand, 41.67% of follicles had complete transzonal projections (TZPs), while TZPs were partially and completely absent in 45.83% and 12.5% of the follicles, respectively.

Conclusion: Our findings indicate that our PEGylated fibrin can support the survival and growth of human preantral follicles by resembling the mechanical property of the natural human ovary at the reproductive-age stage.

Ovary tissue engineering, follicle, hydrogel, PEGylated fibrin, Young's modulus

POSTER 18

POLYPHOSPHOESTERS: NEW OPPORTUNITIES AS SCAFFOLDS FOR TISSUE ENGINEERING

BIOREGATE EUROPEAN BIOMATERIALS FORUM
21 - 23 SEPTEMBER 2022
Louvain-la-Neuve, Belgium

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In the recent decades, biodegradable and biocompatible polyphosphoesters (PPEs) have gained wide attention in the biomedical field as relevant substitutes for conventional aliphatic polyesters. The easy variation of the nature of the lateral pendant groups of PPEs allows the precise tuning of their hydrophilicity and reactivity. When the pendent group is a methyl, the PMEP is water soluble and is described as a promising degradable substitute for PEG in nanomedicines thanks to its efficiency in nanoparticle drug delivery systems [1]. Besides, when an unsaturated chain is used as pendent group, it can be used for further functionalization e.g. by thiol-ene addition [2] or for photocrosslinking of PPEs [3]. The present work aims at reporting on the preparation of PPE hydrogels with controlled hydrophilicity and mechanical properties [4]. Briefly, PPE copolymers are synthesized by ring-opening copolymerization of various mixtures of cyclic phosphate monomers bearing different pendent groups (i.e. methyl, butenyl and butyl). By UV curing, PPE networks are obtained exhibiting mechanical properties and water-swelling behavior controlled by the copolymer composition. The resulting hydrogels were found compatible with human skin fibroblast cells and exhibit no significant cytotoxicity so as their degradation products.

Therefore, this innovative PPEs platform opens new prospects for future applications as scaffolds for tissue engineering.

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Polymer network, degradable polymer, polyphosphoesters, scaffolds

BIOREGATE
EUROPEAN REGENERATIVE MEDICINE
FORUM

BIOSKETCHES

Invited speakers

Dr. Batrakova. The main focus of Batrakova's research is to develop a CNS delivery system for antioxidants and neuronal growth factors to attenuate neuroinflammation and produce neuroprotection in patients with neurodegenerative disorders, such as Parkinson's disease and Lysosomal Storage disorder, Batten disease. For this purpose, her group utilizes inflammatory-response cells, macrophages and monocytes that can migrate toward the inflammation site, cross the blood brain barrier, and release the preloaded drugs in the brain. Thus, living cells can act as Trojan horses, delivering potent therapeutics across the blood brain barrier. Recently, the main focus of Dr. Batrakova's group is on the development of personalized drug delivery systems by loading therapeutics into immune response cells or extracellular vesicles (EVs) released from these cells. She is a highly cited of total 10 scientists at UNC, and a Thomson Reuters agency named her top 1% Highly Cited Researcher.

Prof. Phillip Blondeel received his medical degree and underwent his specialty training at the Katholieke Universiteit Leuven Medical School, Belgium. In 1998, he obtained his PhD in Medical Sciences degree (*maxima cum laude*) at the Faculty of Medicine of the Ghent University. He is a fellow of the Collegium Chirurgicum Plasticum and a diplomate of the European Board of Plastic, Reconstructive, and Aesthetic Surgery.

Prof. Blondeel is the president of the ad-hoc steering committee and a founding member of GATE which offers a platform of collaboration between the research groups at the Ghent University with a focus on gene therapy, cell therapy and tissue engineering.

He is the current president of the European Association of Plastic Surgeons. He is the creator, co-founder and president of the Board of the "Beautiful After Breast Cancer Foundation". This public non-profit foundation aims to increase awareness and to fund research projects in the field of reconstructive breast surgery.

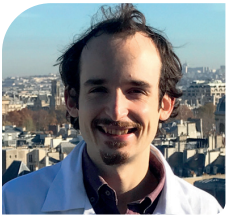
Stefan Braam is the founder and CEO of Ncardia and Cellistic. Stefan brings Ncardia/Cellistic over a decade of experience in stem cell technology, product development and general management. As co-founder and key inventor of Ncardia/Cellistic technologies he has been instrumental in the establishment and growth of the company. Earlier in his career, Stefan obtained a MSc and PhD (both *cum laude*) in stem cell biology under supervision of Prof. Dr Mummery and obtained international experience in labs in the UK and Australia. Stefan won the NGI venture challenge (2009), the Niaba biobusiness Masterclass (2010), published in multiple leading scientific journals, is an inventor on multiple patent families, secured multiple grants and technology licensing agreements and was with increasing responsibilities instrumental in Ncardia/ Cellistic pre-seed, seed, Series A and B and C financing rounds.

Denis Dufrane has a strong expertise in the field of tissue and cell banking, development of advanced cell therapies for regenerative medicine and preclinical to clinical technology transfer with the respect of cell transplantation regulations.

He completed his medical degree in 2000 and a doctorate in biomedical sciences (orientation : cell therapy) in 2006 at the University catholique de Louvain. In 2001, he started his career in the field of cell therapy (Prof. JP Squifflet, St. Luc University Hospital). After only a few years, he became the head of the Endocrine Cell Therapy Unit – St. Luc University Hospital. In 2009, he is appointed as the head at the Muskuloskeletal Tissue bank (St. Luc University Hospital) and finally in charge of the Tissue/ Cells Therapy Center (St. Luc University Hospital) in 2012. In 2014, he became a member of Belgium Superior Health Council. Denis has published more than 50 manuscripts in peer-reviewed journals, presented 40 invited lectures and has more than 120 communications with more than 3100 citations. Denis is reviewer and member of editorial boards of scientific and medical peer-reviewed journals. He also received numerous awards.

In 2013, he co-founded Novadip biosciences and joined the company as Chief Scientific Officer in 2015. Now, he is the CEO of Novadip and found Texere Biotech.

Prof. Dr. Martin Ehrbar studied Biology at the ETH of Zurich and obtained his PhD in Biomedical Engineering at the ETH of Zurich in 2004. Between 2004 and 2007, he worked as a postdoc and from 2007 as a group leader at the craniofacial surgery of the University of Zurich. He became head of research at the Department of Obstetrics at the University of Zurich in 2009. He habilitated in 2017 and in 2020 became Professor *ad personam* at the Medical Faculty of the University of Zurich, Switzerland where he leads an interdisciplinary research group. His research is dedicated to engineer healing-promoting biomaterials. He has developed a modular designed synthetic hydrogel platform that can be tailored towards specific applications by changing stiffness, degradability, cell binding and growth factor binding properties. He is using these materials to generate 3D *in vitro* models for bone, bone marrow, blood vessels, fetal membranes and ovary tissues.



Thibaut Fourniols is Doctor of Pharmacy (Université Paris Descartes (Cité), 2016) and PhD in pharmaceutical sciences (UCLouvain, 2020), former student laureate of the Inserm Liliane Bettencourt School. His research focused on therapeutic targeting in colorectal cancer and glioblastoma, using different strategies: vectorization via toxin-chemotherapy couplings, local delivery using a hydrogel, targeted therapy with the search for predictive biomarkers of response to MET inhibitors, and the development of lipid nanocapsules targeting cancer-associated fibroblasts or carrying the BET inhibitor JQ1. Since 2020, he has been working at Everzom as an R&D project manager, where he leads the extracellular vesicle projects of Everzom's various partners.

Liesbet Geris is Professor in Biomechanics and Computational Tissue Engineering at the university of Liège and KU Leuven in Belgium. Her research focusses on the multi-scale and multi-physics modeling of biological processes. Together with her team and their clinical and industrial collaborators, she uses these models to investigate the etiology of non-healing fractures, to design in silico potential cell-based treatment strategies and to optimize manufacturing processes of these tissue engineering constructs. Liesbet is scientific coordinator of the Prometheus platform for Skeletal Tissue Engineering (50+ researchers). She has edited several books on computational modeling and tissue engineering. She has received 2 prestigious ERC grants (starting in 2011 and consolidator in 2017) to finance her research and has received a number of young investigator and research awards. She is a former member and chair of the Young Academy of Belgium (Flanders) and member of the strategic alliance committee of the Tissue Engineering and Regenerative Medicine Society. She is the current executive director of the Virtual Physiological Human Institute and in that capacity she advocates the use of in silico modeling in healthcare through liaising with the clinical community, the European Commission and Parliament, regulatory agencies (EMA, FDA) and various other stakeholders. Besides her research work, she is often invited to give public lectures on the challenges of interdisciplinary in research, women in academia and digital healthcare.

Prof Daniel Kelly is an internationally recognized leader in the field of musculoskeletal tissue engineering and 3D bioprinting. Over the past 15 years, he has led a multidisciplinary laboratory based in Trinity College Dublin, developing novel biomaterial, stem cell and 3D bioprinting strategies to regenerate damaged and diseased tissues. In 2008, he was the recipient of a Science Foundation Ireland President of Ireland Young Researcher Award. In 2009, he received a Fulbright Award to take a position as a Visiting Research Scholar at the Department of Biomedical Engineering in Columbia University, New York. He is the recipient of four European Research Council awards, which have led to the development of new single stage strategies for bone and cartilage repair and pioneering innovations in 3D (bio)printing for the regeneration of musculoskeletal tissues. He has published over 200 publications in Biomaterials, Science Advances, Biofabrication, Science Translational Medicine and Advanced Materials.

Dr. Nicolas L'Heureux holds a B.Sc. in Biochemistry, a M.Sc. in Immunology and Microbiology and a Ph.D. in Molecular and Cell Biology (Laval University). He was a post-doctoral fellow of the American Heart Association at the Bioengineering Department at University of California. In 2000, he co-founded Cytograft Tissue Engineering, Inc. (San Francisco) where he held the position of Chief Scientific Office. In 2015, he returned to academia at the French National Institute of Health in the Laboratory for the Bioengineering of Tissues at the University of Bordeaux where he is currently Unit Director. At a time when synthetic scaffolds were seen as a defining part of any tissue engineered construct, he demonstrated that the cell-assembled extracellular matrix (CAM), produced by normal human cells *in vitro*, can be used to create completely biological, living, autologous and human tissues that display remarkable mechanical strength without the need for any exogenous scaffolding.

Dr. Gabriel Liguori is the founder and CEO of TissueLabs, a 3D bioprinting startup based in Switzerland. He is a medical doctor with a PhD in Tissue Engineering. In 2018, he was elected a Forbes Under 30 and, in 2020, named by the MIT Technology Review as an MIT Innovator Under 35. He works with the goal of developing human organs and tissues in the lab for future clinical applications.

Marie Morille is Associate Professor in Montpellier University Pharmacy, Pharmaceutics development, and Biomaterials Department and Institute Charles Gerhardt of Montpellier ICGM since 2012. During her phD and post-doctoral studies, she worked on formulation of nano microcarriers (surface functionalization, nucleic acids protein loading) with a special care on coordination between carriers physico-chemical properties and impact on biological behaviour (*in vitro in vivo*). In ICGM, she focuses on the delivery of biomolecules nucleic acids, proteins for health applications (cancerology, tissue engineering) using nanocarriers lipid polymer based. In recent years, she has developed a line of research based on pharmaceutical sciences applied to extracellular vesicles EV, to increase the therapeutic potential of these promising bio nanomedicines using pharmaceutical and physico-chemical tools processes characterization, storage, surface modification, EV engineering for biomolecules loading).

Dr. Carlos Mota is an Assistant Professor in the Department of Complex Tissue Regeneration, MERLN Institute for Technology-inspired Regenerative Medicine, Maastricht University. In 2013, he was a postdoc at the department of Tissue Regeneration, University of Twente, the Netherlands where he developed, in partnership with Screvo B.V., a multiwell array platform for high content screening, targeting the effect of small molecules and biopharmaceutical in cancer therapeutics *in vitro* and *in vivo*.

Dr. Mota received his PhD in Biomaterials from the BIOS research doctorate school in Biomolecular Sciences at the University of Pisa, Italy, in March 2012. His doctoral studies were focused on the development of new approaches for the fabrication of polymeric scaffolds for Tissue Engineering applications. Furthermore, he was a researcher at the department of Neurosciences, University of Pisa, where he developed scaffolds for otology surgery applications.

Dr. Giuseppe Orlando is a kidney and pancreas transplant surgeon scientist at the Wake Forest School of Medicine, in Winston Salem, US. He hails from Rome, Italy, where he attended medical school, received training in general surgery and transplantation, and obtained a PhD in transplant sciences. During this training, he also participated in clinical fellowships in Paris (2000) and Brussels (2001-2004). 2006-2008, he was a practicing transplant surgeon at the University of L'Aquila, Italy. 2008-2011, he was the recipient of the Marie Curie International Outgoing Fellowship through the European Commission Framework Program. During this time, he specialized in regenerative medicine (RM) and transplant immunology at the Wake Forest Institute for Regenerative Medicine in Winston Salem, and the Transplant Research Immunology Group, University of Oxford, UK.

Dr. Jeff Ross brings more than 20 years of scientific, management, and regulatory experience in regenerative medicine, biologics, and medical devices. His expertise includes concept development, investor relations, preclinical trials, clinical trials, manufacturing, and product commercialization. He held technical and management positions at Guidant, Athersys, SurModics. Dr. Ross was pivotal in the development, manufacture and regulatory clearance of the innovative MIROMESH and MIRODERM product lines based on perfusion decellularization of porcine livers. He spearheaded the development, global patent strategy, and fundraising efforts for the revolutionary whole organ transplant program and its key decellularization and recellularization technologies leading to a IPO in 2021. Dr. Ross has over 30 patents and scientific publications in Nature. He holds a Master's degree in Biomedical Engineering and a Ph.D. in Molecular, Cellular and Developmental Biology (University of Minnesota). Dr. Ross serves on the Board of Directors for The Alliance of Regenerative Medicine (ARM).

Arnaud Scherberich has completed his PhD in Pharmacology in December 1999 at the University of Strasbourg (France). Since 2007, he is leading a biomedical engineering research team at the University of Basel, Switzerland. His team investigates the biology and therapeutic potential of mesenchymal stromal cells for regenerative surgery applications, in particular the generation of pre-vascularized osteogenic grafts based on adipose-derived cells. In 2019, he became Adjunct Professor in Experimental Medicine. He has published more than 85 peer-reviewed articles and has an h-index of 31. Arnaud Scherberich is an elected member of the Executive Committee and the Secretary of the Swiss Society for Biomaterials and Regenerative Medicine (SSB+RM) and he is member of the Scientific Board of 2 companies: Defymed (Strasbourg, France) and Cellec Biotek AG (Basel).

Since 2018, **Diletta Trojan** is the director of the Fondazione Banca dei Tessuti di Treviso where she previously was quality manager for 5 years. She has led various research activities and wrote publications after her specialistic University Degree in medical biology (University of Padova).

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Anne Des Rieux, is Professor at the UCLouvain (Belgium) and is part of the Advanced Drug Delivery and Biomaterials unit (Louvain Drug Research Institute).

She got her PhD in Pharmaceutical Sciences from the UCLouvain in 2006 on oral drug delivery. Then, she spent 1 year as a postdoc as a BAEF fellow at the Northwestern University in Chicago (2007) in the Shea Lab where she worked on drug delivery strategies for spinal cord repair. She became a principal investigator (FNRS Research Associate) in 2011. She then set up a research group within the Advanced Drug Delivery and Biomaterials unit focused on drug and stem cell delivery for the central nervous system repair, and more specifically for multiple sclerosis and spinal cord injury.

Pr Christine Jérôme is full Professor at the University of Liege and director of the Center for Education and Research on Macromolecules. She earned a chemical science degree from Liege University and performed postdoctoral research on the synthesis of magnetic nanoparticles at the University of Ulm under the auspice of an Alexander Von Humboldt grant. She has expertise in polymer chemistry and passion in developing biomaterials to improve health and well-being. She develops green strategies for the synthesis, functionalization and processing of polymer materials, degradable or not, to precisely tailor their properties and design supramolecular structures customised to the targeted biomedical application and needs.

Pr Pierre Weiss, PhD, DDS, received his dental doctorate in 1989. He receives his Master of Science in biomaterial (Nantes) in 1993, his PhD in Biomaterial (Nantes) in 1997. He is Professor in biomaterials of the University of Nantes in dental surgery department and hospital. He was the Head of the INSERM / Nantes University Unit 791, Centre for osteoarticular and dental tissue engineering, National institute for health and medical research (INSERM), UMRS 791LIOAD. Now he is Head of REGOS team in UMRS 1229 RMeS Unit. His scientific activities are Skeletal tissue engineering, physiochemistry in hydrophilic polymer to make hydrogels for synthetic extra cellular matrix, bone substitutes. His research interests include the chemistry and characterization of macromolecular solution and hydrogels to prepare synthetic extracellular matrices for tissue engineering of cartilage and bone. His scientific skills is on macromolecular chemistry and characterization like FTIR, Rheology, mechanical experiments and material design with nano particles blended with viscous solution before injection and cross linking into a 3 dimensional scaffold with alive cell encapsulated inside the structure. He has 2 main field of research in Biomaterials. The first is about Injectable bone substitutes like suspension of calcium phosphate ceramics or calcium phosphate cements. He also develops self-crosslinking hydrogels of polysaccharides for tissue engineering and drug delivery systems. In 2015, he began a collaboration with HTL for translation of polysaccharide silanization to hyaluronic acid. He also managed clinical research in Odontology. He is currently the scientific director of the Regenartive medicine cluster named “Bioregate” created in 2015. He has be nominated Fellow, Biomaterials Science and Engineering (FBSE) for the Worl congress of Biomaterials WBC 2020 (for WBC members who have gained a status of excellent professional standing and high achievements in the field of biomaterials science and engineering).

About 200 ISI indexed publications, more than 200 communications, 50 invited lectures, 7 patents and Hirsh index: 47, 6200 citations. Researcher ID : AAE-9260-2020

Florence Hallouin holds a PhD in the field of Biotherapies, which she obtained at the University of Nantes.

After 6 years of conducting research in the field of immuno-cancerology, she turned to the technology transfer sector, where she worked for almost 12 years on promoting the law on research and innovation among researchers. She also supported those who wished to enhance their results by creating a business.

She then worked for 6 years in the field of marine bioresources, contributing to the emergence and development of this sector within the Pays de la Loire region. This in turn led to the geographical expansion of the Pôle Mer Bretagne Atlantique competitiveness cluster to the Loire region.

Finally, since 2016, she has been managing Atlanpole Biotherapies, the health competitiveness cluster for the West of France, located in the regions of Brittany, Pays de la Loire and Centre-Val de Loire. Its main areas of excellence are immunotherapy, regenerative medicine, radiopharmaceuticals, digital for innovative therapies, nutrition and microbiota, as well as veterinary health. The network now has more than 200 members.

Jessica Walker originally studied French and Russian at the University of St Andrews, Scotland (2010-2015), before embarking on a career in European project management and policy, working for 4 years for the European Youth Information and Counselling Agency (ERYICA) in Luxembourg, as well as gaining experience in the Education Department of the Council of Europe (2015) and the Communication Division of the European Parliament (2016).

She has spent time living in the UK, France, Luxembourg, Belgium and Russia, and has worked with organisations across Europe and beyond. She has conceptualised, designed and managed a range of European projects in the youth and health sectors, organised multiple events and edited publications on a range of topics.

Since 2020, Jessica has been working as European Project Manager for Atlanpole Biotherapies, the health competitiveness cluster for the West of France, where she has successfully managed 3 European projects and organised multiple events for the members of the network.

Olivier Roussel has a Master 2 in European project management from the University of Cergy-Pontoise (France). For 10 years, he applied his skills in projects involving multiple international partners in public organisations, higher education institutions and associations.

Since 2019, he has been working at Nantes University as the manager of 4 research - training - innovation programmes, including the Bioregate programme dedicated to regenerative medicine. Each of these programmes, financed by the Pays de la Loire Regional Council and the ERDF, aims to create synergies between actors from the academic world, companies and innovation actors. Olivier Roussel also participates in the communication around these hybrid programmes, which have each been able to federate a large number of partners and initiate long-term actions.

Nicolas Rondineau : Holder of a professional baccalaureate in the accounting professions, former deputy head in charge of the billing and collection service of the Eurofins Laboratoires de Microbiologie Ouest laboratory. Now a financial and administrative assistant at the University of Nantes, he puts his skills at the service of the Bioregate.

Catherine Le Visage is a Research Director and the Deputy Director of the Regenerative Medicine and Skeleton lab in Nantes, France (www.rmes.univ-nantes.fr). She was trained as a Pharmacist, received her PhD in Paris then performed a post-doc in the Johns Hopkins University (USA). In 2007, she joined with a tenured position the French National Institute of Health and Medical Research. In 2013, she was appointed as a Research Director and joined the Regenerative Medicine and Skeleton laboratory in Nantes. In the «Skeletal Physiopathology and Joint Regenerative Medicine» team headed by Prof J. Guicheux. As a group leader, her most recent works have focused on innovative hydrogels as i) carriers of cells or bioactive molecules in the context of IVD disease and osteoarthritis and ii) tools for stem cell-based organogenesis. She is an elected member of the TERMIS-EU Council, a member of the Editorial Advisory Board of "ACS Applied Materials & Interfaces", and a reviewer for national and international funding agencies. She has coauthored 75 publications (h-index 33) and 11 patents, and has given 60 invited lectures/seminars at national and international conferences. ResearcherID: E-5460-2011

Alain Colige obtained his PhD in the Laboratory of Experimental Dermatology of the University of Liège (Belgium), in the fields of collagen and fibroblast biology. Then he completed a post-doctoral fellowship in Philadelphia (USA) focused on the identification of mutations causing bone defects, such as osteoporosis. Back in Liège, his research was more specifically dedicated to the studies of metalloproteinases involved in extracellular matrix deposition and remodeling, mainly in the fields of wound healing, tissue engineering and tumor microenvironment.

Dorian Van Hede holds a PhD in Biomedical Sciences and Pharmaceutics since 2017. Her thesis in Cancerology and Immunology focused on the role of GD T cells in the progression of HPV-related precancerous lesions. Because of her interests in medical device and biomedical engineering, she integrated the dental-Biomaterials Research Unit of the University of Liège (www.d-bru.uliege.be) as a Postdoctoral researcher in 2018. Her work focuses on the development of innovative bone substitutes for intra-oral bone regeneration applications and testing their performances in preclinical studies. She is also involved in the European Federation of Periodontology program of the University of Liège.

Christiani Amorim received her PhD in Veterinary Medicine from the Universidade Federal de Santa Maria, in Brazil, and transitioned from animal reproduction to human fertility in 2007 as a postdoctoral fellow at UCLouvain, developing alternatives to restore fertility in cancer patients. Currently, she is a professor at UCLouvain, where she also serves as head of the Research Pole in Physiopathology of Reproduction. Her group conducts research on ovarian tissue preservation, photodynamic therapy, cell differentiation, and ovarian tissue engineering. Christiani is also an honorary research associate at the Belgian National Fund for Scientific Research, Chief Scientific Officer from ProFaM (UK), Adjunct Faculty member at the Southern Illinois University (USA), and serves as president of the Low Temperature Biology Society, ESHRE's Basic Scientific Officer of the Stem Cell Special Interest Group, and associate editor for Human Reproduction Update and In vitro Models.

Pr France Lambert graduated with a DDS degree in dentistry in 2002 and also completed a post-graduate program in Periodontology at the University of Liège. In 2005, she received a 1-year scholarship to expand her education in implantology at Harvard School of Dental Medicine. Currently she is Professor and Head of the Department of Periodontology, Oral Surgery and Implant Surgery at University of Liège in Belgium and the co-director of the dental Biomaterials Research Unit (d-BRU). Her clinical activity is dedicated to periodontology and implantology. France Lambert is also the Past President of the Belgian Society of Periodontology, Delegate at the European Federation of Periodontology and the chair of the Belux ITI Section.

Pr Karine Glinel is a Senior Research Associate from Belgian FNRS. She received her PhD degree in Polymer Chemistry in 1999 from the University of Rouen (France). From 1999 to 2002, she worked as a postdoctoral researcher at UCLouvain (Belgium) and at the Max Planck Institute of Colloids and Interfaces (Potsdam, Germany). In 2002, she was awarded a full time CNRS Researcher position in Rouen (France). In 2009, she moved to UCLouvain first as FNRS MIS-ULYSSE fellow then she became permanent FNRS researcher. In 2007 and 2016, she spent one year in the Chemistry Department of the University of Cambridge (UK) and one year in the Langer Lab in MIT (USA), respectively, as visiting scholar. She is currently group leader in the Bio and Soft Matter division of the Institute of Condensed Matter and Nanosciences (UCLouvain) where she develops biofunctional surfaces and cell encapsulation approaches to control bacterial and mammalian cell processes such as proliferation, secreting activity, cell differentiation, etc.

Passionate about innovative sciences, **Sophie Veriter** received her PhD in Biomedical and Pharmaceutical Sciences from UCLouvain for her work on pancreatic islets encapsulation for the treatment of type I diabetes. She then joined the Cliniques universitaires Saint Luc to participate to the islets transplantation clinical program and to the development of a cell therapy product derived from adipose stem cells for bone reconstruction. She continued in the R&D department of Novadip Biosciences for the technology transfer of this latter product. She took part to the development of several innovative products derived from cell therapy for bone and skin reconstruction. She is currently a free-lancer in the field of biomedical sciences.

Dr Jérôme Duisit is a Plastic and Reconstructive Surgeon, with both a public (Hôpitaux Iris Sud, Brussels) and a private clinical practice, and an invited researcher at Rennes University. He owns a dental degree (Lyon University, France, 2004) and a medical degree (UCLouvain, Belgium, 2010), with a special interest in head and neck reconstruction and allotransplantation, fostered by his mentor Pr Benoît Lengelé, and trained in CMF by Pr Bob Woowdards (Manchester, UK) and Pr Bernard Devauchelle (Amiens, France). He specialized into Plastic Surgery at UCLouvain.

His PhD degree (UClouvain, 2018) was dedicated to the development of the "Vascularized Composite tissue Engineering (VCE)", as a new alternative to VCA current limitations: an immuno-suppression free transplantation provided by the regeneration of the transplants in a laboratory step, with the recipient cells. VCE first steps were successfully applied to various composite grafts, such as limbs and face subunits, for small animal as well as large porcine and cadaveric human models. This work was honored by the best TTS society young investigator scientific award (2017), the French National Academy of Surgery annual award (2017) and the Lucien Deloyers award (2017) from the Belgian Royal Academy of Medicine.

Dr Duisit is an active member of the ISVCA, the Transplantation Society (TTS) and Cell Transplant and Regenerative Medicine Society (CTRMS) and its Young Investigator Committee member. He currently serves as a Review Editor in Frontiers in Biotechnology and Bioengineering journal.

And also **Anne Des Rieux, Pr Christine Jérôme & Pr Pierre Weiss**

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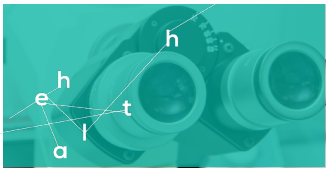

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BIOREGATE
REGENERATIVE MEDICINE CLUSTER
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Bioregate is a Western France network dedicated to the development of Regenerative Medicine technologies and skills. It gathers 3 universities, 2 university hospitals, 4 national academic research institutions, a vet school and about 50 SME partners through Atlanpole Biotherapies competitiveness pole. Bioregate cluster is piloted by Nantes University and is supported by local authorities among which the "Pays de la Loire" Region and "Nantes metropole".

Bioregate core activities:

- **Translational research:**

With competences in:

- cell and gene therapies,
- tissue engineering,
- bio and nanomaterials,
- engineering sciences.

Bioregate players have been developing products of 1st and 2nd generations in the field of repairing and regenerative medicines, mainly to treat patients with skeletal, muscle, cardio vascular, neurological, skin, metabolic or eye pathologies.

More than 20 clinical trials are ongoing thanks to intense collaborations between researchers, veterinarians, clinicians and companies and also the facilitated access to key core facilities such as those focusing on IPS cells, manufacturing of clinical grade batches, housing of small and big animals relevant for innovative therapy testing, biobanking, biotherapy clinical trials.

- **Education & training:**

- Initial training: Bioregate players are currently designing a Master and a European doctoral course specialized in regenerative medicine
- In course training: an hybrid course is being set up on a campus based and distance teaching

Bioregate is opened to provide research and clinical skills, technology platforms, education and training, innovation opportunities in a collaborative framework. Bioregate players constantly look for:

- public-public and public-private collaborations for research, R&D or education and training programs
- stable partnerships with other European clusters dedicated to regenerative medicine

Bioregate players also enjoy welcoming high level researchers or lecturers for seminars or permanent positions. Aiming at strengthening its value chain, Bioregate is also a facilitator in the establishment of new businesses in collaboration with its local partners.

Bioregate also looks for complementary fund raising through Nantes University Foundation. For more information, please visit this webpage

www.bioregate.com

Contacts:

· Olivier Roussel**, olivier.roussel@univ-nantes.fr**

· Pr Pierre Weiss, Bioregate Scientific director, **pierre.weiss@univ-nantes.fr**

Atlanpole Biotherapies is one of the 7 French bioclusters based in Western France and focused on Innovative therapies. It represents over 170 members working on personalized medicine and biotherapies:

- more than 100 companies dedicated to life sciences,

- research laboratories, hospitals and universities,

- technological platforms, engineering schools.

Within this ecosystem, restorative and regenerative medicine began by transplant technology whose growth has been marked by the development of innovative solutions, as well as alternatives to the organ shortage, and for the immunological monitoring of transplanted patients. In parallel, new therapeutic approaches have developed (biomaterials, tissue engineering, cell therapy, gene therapy) which apply to diseases of the bone and joints, dermatology, oncology, pneumology, as well as rare, neurodegenerative and cardiovascular diseases. Bioregate is the name of the local network

on regenerative medicine (located in Pays de la Loire Region, Western France). It brings together more than 3 hundred people working on Cell Therapy, Gene Therapy and Biomaterials.

Atlanpole Biotherapies is also well-known for innovative approaches such as:

- Immunotherapies specializing in Transplantation / Oncology / Inflammation and Auto-immune diseases

- Radiopharmaceuticals with the use of radioisotops for diagnostic and therapy.

- Innovative Technologies and e-Health

www.atlanpolebiotherapies.com

Nantes Université

Nantes Université is a higher education and research institution with a new University model unprecedented in France as it brings together a university, university hospital (CHU de Nantes), technology research centre (IRT Jules Verne), public scientific and technological institute (Inserm) and s higher education institutions (Centrale Nantes, École des Beaux-Arts Nantes Saint-Nazaire, École d'Architecture de Nantes).

Working together, the actors combine their expertise to develop Nantes research areas of excellence, and in particular to think and plan the Health and Industry of the future. It offers students new training opportunities, combining different approaches, different knowledge and practices.

Nantes Université is a higher education and research institution with a new University model unprecedented in France as it brings together a university, university hospital (CHU de Nantes), technology research centre (IRT Jules Verne), public scientific and technological institute (Inserm) and s higher education institutions (Centrale Nantes, École des Beaux-Arts Nantes Saint-Nazaire, École d'Architecture de Nantes).

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Nantes Université is a sustainable and committed institution and one of the driving forces behind societal development. With a global and outward-looking culture, it promotes innovativeness and openness: open science, open research, open education, open innovation.

Nantes Université has strong values that are an integral part of its identity: it is based on renewed democracy, is environmentally responsible, inclusive, invests in gender equality, guarantees academic freedom, and ensures that its students and staff have the best study, research and working conditions for their on-going professional development on all Nantes Université's campuses, in Nantes, Saint-Nazaire and La Roche-sur-Yon.

Committed at the regional, European and International level, Nantes Université works in synergy with public, private, socio-economic and cultural stakeholders. As a member of the European University for Wellbeing (EUniWell), it contributes in building a European Education Area and achieving the United Nation's Sustainable Development Goals. **www.univ-nantes.fr**

UCLouvain

The UCLouvain (UCLouvain) is the largest university in French-speaking Belgium (32 000 students). It ranks in the top 1.25% of universities worldwide. Its 14 faculties and 22 doctoral schools offer degrees and research opportunities in almost every field.

UCLouvain is headquarted in Louvain-la-Neuve, in Wallonia's most economically dynamic province. It has six additional sites in Brussels (2) and in Wallonia (4). Its 21 research institutes, 38 technology platforms, 2 university hospitals and three science parks - almost 300 companies and 66 spin-offs in activity - are a testament to its research prowess. UCLouvain commits as a whole cutting-edge research and innovation in collaboration with both the corporate world and society.

www.uclouvain.be

LIÈGE université

University of Liège is one of Belgium's leading universities, founded in 1817. ULiège welcomes 25,885 students, 23% of whom are of international origin (124 nationalities). ULiège is the public university of the Wallonia-Brussels Federation. It includes 11 Faculties representing the Humanities, Health Sciences, Sciences and Technology. With 39 bachelor's degrees and 192 master's degrees, its range of undergraduate and postgraduate courses is among the most diversified in Belgium. ULiège is located in 3 cities in Wallonia: Liège, Gembloux and Arlon. Its courses have several international quality labels (EQUIS, AACSB, EUR-ACE, EAEVE , Conférence des Grandes Ecoles). ULiège collaborates with more than 1,000 teaching and research institutions throughout the world. It boosts its research centres in fields such as biotechnologies, life and medical sciences (human and veterinary), agronomy, space and engineering sciences, environment, etc., by developing partnerships with public authorities and companies. More than 100 spin-off companies created by ULiège are in activity. ULiège is a major employer in Wallonia: more than 5,600 employees, including 635 academic staff and 2,910 people involved in teaching and research activities. Together with the University Hospital (CHU) of Liège, this represents 12,000 direct jobs spread over the provinces of Liège, Namur and Luxembourg.

www.uliege.be

CONFERENCE PLACE

Adress:
Foyer du Lac, place Raymond Lemaire 1, 1348 Ottignies-Louvain-La-Neuve

ATTENTION: Do not confuse Louvain-la-Neuve with Louvain (the French translation of the Flemish city of Leuven).

TRAVELLING TO LOUVAIN-LA-NEUVE

By air

From Brussels Airport (Zaventem), beginning at 5:30 am, you can travel by train to Louvain-la-Neuve. Seven days a week, from 9:00 am to midnight, four trains per hour depart the airport for Brussels-North station, where you have to change trains to continue to Louvain-la-Neuve.

Brussels South Charleroi Airport serves low-cost airlines. It is located 40 km from Louvain-la-Neuve. TEC buses take you from the airport to the Charleroi South station. Trains depart until 9:57 pm to Ottignies, from which a connecting train takes you to Louvain-la-Neuve-Université station in eight minutes.

By train

Louvain-la-Neuve-Université station is directly linked to the railway junction of Ottignies, on the Brussels-Namur railway line, with two trains per hour in each direction, including on weekends.

Louvain-la-Neuve is approximately 30 minutes from Brussels; change in Ottignies for the train to 'Louvain-la-Neuve-Université'. Direct trains take longer.

- If you travel from Namur or Charleroi, change in Ottignies for the train to 'Louvain-la-Neuve-Université'.
- If you travel from Luxembourg, change in Ottignies (if you take the EC 96 Iris or EC 90 Vauban train that originates in Switzerland, change in Namur for a train to Ottignies).
- If you travel from any other country, change in Brussels-Nord. Otherwise, change in Brussels-Midi, from which depart all trains to Ottignies via Brussels-Central, Brussels-Nord, Brussels-Schuman and Brussels-Luxembourg.

Schedules are available on the SNCB website.

By bus

Several TEC lines run between Louvain-la-Neuve bus station and:

- Brussels (Cbis or Conforto Bis line), departing from Roodebeek metro station and stopping at Crainhem metro station (near the UCL Brussels Woluwe campus);
- Etterbeek (C or Conforto line) via la Plaine des manoeuvres, Etterbeek train station, Delta metro station, and Wavre train station;
- Jodoigne (Rapido Bus 1) via Thorembais-Saint-Trond;
- Waterloo (Rapido Bus 3) via Braine-l'Alleud, Ohain, Lasne and Céroux;
- Nivelles train station (Rapido Bus 4) via Genappe and Beaurieux;
- Tourinnes-la-Grosse (Rapido Bus 6) via Hamme-Mille, Grez-Doiceau and Wavre (4 Sapins);
- Wavre and Ottignies (line 20);
- Dion-Valmont (line 21);
- Perwez (line 33) via Chaumont-Gistoux;
- Chastre (line 34) via Walhain, Nil, Corbais and Mont-Saint-Guibert.

Buses operate along these lines only Monday through Friday, except for lines 33 and 34 which operate on Saturday and line 20 which operates Saturday and Sunday. Schedules are available at www.infotec.be or tel. 010 23 53 53.

By car

Take the E 411 Brussels-Namur motorway to Louvain-la-Neuve (not to be confused with Louvain, the French translation of Leuven, located in Flanders): if travelling from Brussels, take exit 8a; if travelling from Namur, take exit 9. At the Nationale 4 roundabout, follow the signs to your Louvain-la-Neuve neighbourhood destination.

From UCL Brussels Woluwe

Monday through Friday, the Conforto Bis TEC bus (see above) operates 24 roundtrips per day. During the weekend, take the metro from Alma station, in the heart of the campus, toward the centre of Brussels (line 1, direction Gare de l'Ouest), to Schuman station, from which you take the train for Louvain-la-Neuve. Metro schedules are available at www.stib.be or tel. 02 515 20 00.

LOUVAIN-LA-NEUVE: THE HOST CITY

Located 30 km from Brussels, in the heart of Brabant Wallon Province, the UCL site in Louvain-la-Neuve welcomes more than 20,000 students in its 11 faculties.

The city, created in 1971 by the university, is one of Europe's youngest. Surrounded by countryside, it offers an exceptional quality of life to students, researchers, professors and residents. Museums, cinemas, theatres, concert and exhibition halls, a swimming pool and fitness centre, restaurants and cafés, commerce and green spaces all combine to form a whole that is renowned for its convivial and dynamic ambiance.

Its entirely pedestrianised centre eases access to all academic buildings and creates an environment in which students, researchers, professors and residents repeatedly cross each other's paths, weaving a unique social, cultural and economic fabric.

For more tourist information: https://en.tourisme-olln.be/

HOTELS ★★★

Martin's Louvain-La-Neuve
Ibis Styles

NOTES

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