BIOREGATE

EUROPEAN REGENERATIVE MEDICINE FORUM

8 & 9 SEPTEMBER 2016

Nantes, France

ATLANPOLE biotherapies
Thinking up tomorrow's medicine

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EDITO

Organ transplantation is currently the most efficient way to restore body homeostasis upon major organ failure or degenerescence. However, transplant shortage and side effects of immune-suppression are critical bottlenecks of transplantation. Regenerative medicine technologies offer complementary strategies to help restore physiological function in patients.

Regenerative medicine strategies include the established fields of biomaterials and medical devices, as well as the emerging field of tissue engineering with cellular and gene therapies. These contribute to the "replace, repair, regenerate, and reprogram" motto of 4R medicine, a major focus of research and innovation in the western France region.

The Bioregate Network was created thanks to the Pays de la Loire region support. Bioregate groups more than 300 people involved in regenerative medicine in the Nantes, Angers and Le Mans areas. Bioregate brings together all regional scientific institutions working in the field: University of Nantes, University of Angers, University of Le Mans, INSERM, CNRS, IFREMER, INRA, the University hospitals, ONIRIS. These academia institutions and SMEs are members of the biocluster Atlanpole Biotherapies. Through this conjoined effort, Bioregate aims to boost research, training and innovation in the field of regenerative medicine.

Recent advances in regenerative medicine clinical translation have brought great results and promises. At the end of 2015, 20 products were approved and the future seems full of hope for patients, as more than 631 products were under clinical assessment. Among the challenges in the field, the technology transfer from academic labs to industrial partners is key. The emergence of clusters, such as the Bioregate Network is a tool to reinforce the links between these stakeholders. The Loire Valley innovation ecosystem has already proven its efficacy in terms of clinical translational and tech transfer with many start up creations. More than 20 clinical trials were finished or are on-going in the specific field of regenerative medicine. The Loire Valley is among the top ranked regions in France for 4R medicine technologies.

According to our philosophy, we are delighted to organize the first edition of the Bioregate Forum to bring together the expertise from academia and industry. We are honored to have many prestigious speakers this year. This conference aims to focus on R&D from biotech companies and projects from academia which have passed the proof of concept phase. The program was built with this mindset with sessions dedicated to stem cells (Session I and Session IV) and complementary sessions highlighting progress in bone therapy (Session II) and immune therapies (Session III), all fields of excellence in the Pays de la Loire region. We were also pleased to present select short talks that broaden the spectra of our meeting.

Finally, we want to hold round tables on key interest topics for the regenerative medicine players where discussion of regulations, ethics and business models can occur.

We hope that this meeting at the interface of academia and industry fulfills your expectations and that you will enjoy your time in Nantes.

Pierre Weiss and Laurent David.

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PROGRAM

BIOREGATE FORUM

8 & 9 SEPTEMBER 2016
Nantes, France

DAY 1 - 8 SEPTEMBER 2016

8 - 8:45 am	**Registration & Welcome coffee**
8:45 - 9:15 am	**Welcome speech by Organizers & Officials** *Organizers: Frédéric Benhamou (University of Nantes), Pierre Weiss (Bioregate), Jean-François Balducchi (Atlanpole Biotherapies) Officials: Stéphanie Houël (Pays de la Loire Region) and Nantes Metropole*
9:15 - 12:10	**SESSION 1**
	Cell therapy: Embryonic and adult stem cells *Chairmen: Dr Tuan N'guyen, ITUN & Pr Jean-Sébastien Hulot, ICAN*
9:15 - 10 am	**Development of a cardiac patch composed of Human embryonic stem cell-derived cardiac progenitors for severe ischemic heart failure treatment** *Pr Philippe Menasché, Georges Pompidou European Hospital, Paris*
10 - 10:30 am	**The Cardiopoiesis Platform and its application to heart failure: C-Cure Development from bench to clinic** *Dr Aymeric Seron, Program Director, CELYAD*
10:30 - 11 am	Coffee break
11 - 11:30 am	**Mesenchymal stem cells-based therapies in osteoarticular diseases** *Pr Christian Jorgensen, CHRU Montpellier*
11:30 - 12:10 am	**Short presentations** - The evolution of the regulatory and scientific context concerning the genetic stability of cell therapy products. *Dr Vasileios. Georgakakos, Clean Cells* - Advancing Cartilage Regeneration with the use of Magnetic Stem Cell Confinement within Scaffolds. *Dr Aurore Van de Walle, University Paris Diderot* - VITRICELL: new efficient method for cryopreserving cells by vitrification. *Dr Delphine Connan, University of Liege* - MIAMI neuronal committed cells combined with nano and active microcarriers. *Dr Emilie André, University of Angers*
12:10 - 1:30 pm	Lunch break in Exhibition & Poster hall

1:30 - 3:40 pm	**SESSION 2**
	Cell therapy for bone and joint repair *Chairmen: Pr Pierre WEISS, LIOAD & Pr Christian Jorgensen, CHRU Montpellier*
1:30 - 2 pm	**Irradiated bone repair with cells and materials** *Pr Florent Espitalier, CHU Nantes*
2 - 2:30 pm	**Osteogenic Superiority of Bone Marrow derived-Osteoblastic Cells (ALLOB®) over Bone Marrow derived-Mesenchymal Stromal Cells (BM-MSC)** *Dr Enrico Bastianelli, CEO - Bone Therapeutics*
2:30 - 3 pm	**Scaffold-free three-dimensional graft from autologous adipose-derived stem cells for bone defect reconstruction** Dr Denis Dufrane, co-founder & CSO – Novadip
3 - 3:40 pm	**Short presentations** - Multiporous calcium phosphates as key part of hybrid systems for therapeutic innovation in bone surgery. *Dr Thomas Miramond, Biomatlante* - Growth factor-delivery from porous scaffolds prepared by green CO2 foaming. *Dr L. Diaz-Gomez, University of Santiago de Compostela* - The sheep: a relevant animal model for nucleus pulposus regenerative medicine. *Dr Boris Halgand, University of Nantes* - Allogeneic neonatal MSC for limiting osteoarthritis progression after orthopaedic surgery. *Dr Stephane Maddens, Vetbiobank*
3:40 - 4:10 pm	Coffee break
4:10 - 5:50 pm	**SESSION 3**
	Cell immunotherapy *Chairmen: Dr Nathalie Labarrière, University of Nantes & Pr Brigitte Dreno, Nantes Hospital*
4:10 - 4:40 pm	**IGO project: Adoptive cell therapy for melanoma** *Dr Nathalie Labarrière, University of Nantes*
4:40 - 5:10 pm	**Accelerating clinical development of ATMPs** *Dr Dominic Bowers, Catapult, UK*
5:10 - 5:50 pm	**Short presentations** - Injectable biogel for local T cell delivery: a new approach for immunotherapy, *Pr Sophie Lerouge, CHUM research center of Montréal* - Injectable hydrogel for cell therapeutic treatment improves colonic radiation-induced damage. *Dr Noëlle Mathieu, IRSN* - Senescence alters IDO-dependent MSC functions. *Dr Séverine Loisel, EFS & Rennes Hospital* - Extra cellular matrix micro-environment control is a key issue to regenerative medicine and RGTA based matrix therapy a solution, *Denis Barritault, OTR3*
5:50 - 7:30 pm	Poster session & Cocktail
7:45 - 10:30 pm	**GALA DINNER**

PROGRAM

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DAY 2 - 9 SEPTEMBER 2016

9 - 11:50	SESSION 4
	Stem cells for drug discovery and regenerative medicine *Chairmen: Dr Nathalie Gaborit & Dr Anne Camus, University of Nantes*
9 - 9:30 am	**Heart disease modeling with hiPSC** *Pr Jean-Sébastien Hulot – ICAN, Paris*
9:30 - 10:00 am	**Human iPSC-derived cells in disease modeling and phenotypic screening: Using Induced, Innate and Engineered Models** *Dr Sabine Lange – Cellular Dynamics International*
10:00 - 10:20 am	**Short presentations** - GMP-compliant human platelet lysate, in liquid form or as hydrogel, for optimized expansion of cell therapy products. *Dr Bruno Delorme, Macopharma* - Benefit of HEMOXCell®, a natural oxygen carrier, in cell culture and cellularization of bone substitutes by Mesenchymal Stem Cells. *Dr Franck Zal, Hemarina*
10:20 - 10:50 am	Coffee break
10:50 - 11:20 am	**Neural cells produced from ESC for Parkinson therapy** *Dr Mark Tomishima – Memorial Sloan Kettering, New York*
11:20 - 11:50 am	**Short presentations** - Production of clinical grade temporary epidermal substitute obtained from hESC derived keratinocytes for the treatment of sickle cell leg ulcers: a challenge for regenerative medicine. *Dr. Christine Baldeschi, ISTEM, Evry* - Human tissues engineered from mesenchymal cells: tools for angiomodulation assays. *Dr Julie Fradette, University of Laval, Quebec* - MuStem cell transplantation in GRMD dogs accelerates skeletal muscle regeneration. *Dr Laëtitia Guevel, University of Nantes*
12:10 - 1:30 pm	Lunch break in Exhibition & Poster hall

1:30 - 5:00	SESSION 5
	Roundtables: Regulation and Business Models *Chairmen: Dr Alain Vertes, NxR Biotechnologies & Dr Emmanuelle Rial-Sebbag, University of Toulouse*
1:30 - 2 pm	**S-Curves and Technology Adoption Momentum in Regenerative Medicine -** *Dr Alain Vertes, NxR Biotechnologies*
2 - 3 pm	**Roundtable 1 - Business models** *Pascale Berthet, Cellular Dynamics International* *Dr Pierre-Noël Lirsac, CELLforCURE* *Alain Maiore, Shikubeisho Partners* *Dr Alain Vertes, NxR Biotechnologies*
3 - 3:30 pm	Coffee break
3:30 - 4 pm	**The Mosaic of Stem cells: how to regulate?** *Dr Nicolas Ferry, Cell Therapy Department, Hôpital Saint-Louis*
4 - 5 pm	**Roundtable 2 - Regulations** *Dr Nicolas Ferry, Cell Therapy Department, Hôpital Saint-Louis* *Dr Marc Meichenin, Clean Cells* *Dr Elhem Sbaa, Keyrus Biopharma* *Dr Franck Zal, Hemarina*

5 pm	Conclusion remarks and Closing ceremony

BIOREGATE
EUROPEAN REGENERATIVE MEDICINE
FORUM

ABSTRACTS

Invited speakers and selected short talks

DEVELOPMENT OF A CARDIAC PATCH COMPOSED OF HUMAN EMBRYONIC STEM CELL-DERIVED CARDIAC PROGENITORS FOR SEVERE ISCHEMIC HEART FAILURE TREATMENT.

BIOREGATE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

Philippe Menasche MD, PhD

Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Department of Cardiovascular Surgery ; Université Paris Descartes; INSERM U 970, Paris, France.

The rationale for the use of embryonic stem cells (ESC) in patients with heart failure primarily stems from the assumption that regeneration of scarred myocardium likely requires the supply of cells endowed with a true cardiomyogenic differentiation potential, regardless of whether they act by generating a new myocardial tissue by themselves or by harnessing endogenous repair pathways. This approach is made possible by the intrinsic pluripotentiality of ESC which allows to drive their fate in vitro towards a cardiac lineage and, so far, our approach has been to generate early SSEA-1-positive cardiac progenitors (rather than fully mature cardiomyocytes) with the assumption that the transplanted progenitors would use local cues to instruct them to differentiate into cardiomyocytes and vascular cells. The experimental results have so far been promising as these cells have been shown to differentiate into cardiomyocytes and to improve heart function, including in a clinically relevant scenario of allogeneic transplantation in nonhuman primates. Asides from ethical issues, the clinical translation of this ESC-based program has entailed a stepwise approach including the following steps : (1) the expansion of a clone of pluripotent hESC to generate a master cell bank under Good Manufacturing Practice conditions (GMP); (2) a growth factor-induced cardiac specification; (3) the purification of committed cells by immunomagnetic sorting to yield a SSEA-1-positive cell population strongly expressing the early cardiac transcription factor Isl-1; (4) the incorporation of these cells into a fibrin scaffold and the assessment of the functional benefits of this cell construct; (5) a safety assessment focused on the loss of teratoma-forming cells by in vitro (transcriptomics) and in vivo (cell injections in immunodeficient mice) measurements; (6) an extensive cytogenetic and viral testing; and (7) the characterization of the final cell product and its release criteria. Put together, these data have led to an approval for a first-in-man clinical trial of transplantation of these SSEA-1^{+} progenitors in patients with severely impaired cardiac function. The trial is currently under way with 5 patients who have already been operated on, of whom two have passed the 1-year follow-up time point without safety issues.

THE CARDIOPOIESIS PLATFORM AND ITS APPLICATION TO HEART FAILURE: C-CURE DEVELOPMENT FROM BENCH TO CLINIC.

BIOREGATE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

Aymeric Seron Program Director, CELYAD

Heart Failure (HF) is a condition in which the heart is unable to pump enough blood to meet the body's metabolic needs, affects 1% to 2% of the adult population in developed countries and approximately 5.7 million patients were diagnosed with HF in the United States in 2012, according to the American Heart Association.
Although existing therapies have been somewhat effective in the treatment of HF, there is still great unmet medical need.
C-Cure® is Celyad's lead product candidate in cardiovascular disease and is based on the Cardiopoiesis. C-Cure® is being developed for ischemic HF and consists of a patient's own cells harvested from bone marrow, treated with the Cardiopoietic growth factors and then re-injected into the heart. It is designed to induce heart repair without carrying the risk of rejection.
To assist in the reinjection of cardiopoietic cells by improving retention in heart tisssue and ease of use and, a new endocardial injection catheter was developed: the C-Cathez.
Further to preclinical development, positive outcomes were observed in ischemic HF patients treated with C-Cure in our Phase 2 clinical trial in Europe (completed in 2012). Patients treated with C-Cure showed a 25% relative improvement of median left ventricular ejection fraction, or LVEF, which is the percentage of blood that is pumped out of the heart at each beat, at six months versus baseline, whereas untreated patients showed a relative improvement of 0.7% versus baseline. Patients treated with C-Cure also demonstrated an improved exercise capacity as measured by the six minutes walking distance test, or six minutes WDT, which measures the distance a patient can walk in a six-minute period. The C-Cure treatment group's walking distance improved by 77 meters compared to the control group.
Based on those promising results, Celyad has conducted a phase 3 trial (CHART-1) in Europe and Israel and was first authorized in November 2012. CHART-1 is a 240 patient prospective controlled randomized double-blinded trial, including NYHA Class II, III and IV ischemic HF patients, with randomization ratio 1:1.
Across the complete trial population after 9 months patients follow up, a statistically-significant difference between treatment and control (sham procedure) was not reached. However, a positive trend was clearly identifiable.
For patients representing 60% of the overall study population and categorized by their End Diastolic Volume (EDV) at inclusion, a positive efficacy result was met on the primary endpoint with statistical significance.
Based on those positive results seen in this highly clinically relevant group of patients for whom treatment options are currently limited, targeted patient selection using disease severity markers should be considered for future cell therapy trials and for potential clinical use of the cardiopeitic therapy in heart failure.

MESENCHYMAL STEM CELLS-BASED THERAPIES IN OSTEOARTICULAR DISEASES.

Pr Christian Jorgensen, Director of Institute Regenerative medicine Biotherapy, Head of Department of Immunotherapy and innovative therapies of osteo articular diseases, INSERM U1183, IRMB Hôpital Saint Eloi - 80 rue Augustin Fliche 34295 Montpellier cedex 5 France

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C Jorgensen clinical interest are in stem cell , immunology and rheumatology. He is head of the clinical unit, «Immuno-therapy Rheumatology", University Hospital "Lapeyronie" (Montpellier). He leads Institute Regenerative Medicine and Biotherapy IRMB dedicated to regenerative medicine. IRMB gathers scientist and clinicians on regenerative medicine and innovative immunotherapies. The objectives of IRMB are to increase the knowledge of stem cell biology, interactions between stem cells and immune cells, stem cell niches and homing, as well as the role of epigenetics mechanisms in chronic and age related diseases. These researches include both basic biological aspects and innovative applications of regenerative therapy.

The aim of IRMB is to facilitate the transfer of research on stem cell biology to clinical applications in coordination with clinicial specialists in chronic diseases (aging, rheumatoid arthritis, rare genetic diseases, autoinflammatory disorders, diabetes, liver disease, neurodegenerative disease, musculoskeletal disorders).

The clinical research is conducted in the clinical department for immunotherapy with 20 beds dedicated to biotherapy applied to Rheumatoid Arthritis and other autoimmune diseases. Pr Christian Jorgensen, specialist in Therapeutics and Rheumatology, is head of research INSERM unit U1183 ("Stem cells, cell plasticity, regenerative medicine & immunotherapies") and department of biotherapy. C Jorgensen is a professor in the Faculty of Medicine Montpellier-Nimes (responsible teacher of DES Rheumatology). He is also responsible for teaching the Master Pro «Evaluation & methodology of therapeutic trials. He is expert for Biologics at French National Authority or Health (HAS), where he was former member of Transparency Comity at HAS, and member of national scientific board of Inserm.

THE EVOLUTION OF THE REGULATORY AND SCIENTIFIC CONTEXT CONCERNING THE GENETIC STABILITY OF CELL THERAPY PRODUCTS.

BIOREGATE EUROPEAN REGENERATIVE MEDICINE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

Vasileios Georgakakos, PhD, Clean Cells, Boufféré, France

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During twentieth century small molecule and protein drugs proved remarkably successful in battling disease and extending lifespan. In the twenty-first century the aging population faces an increased burden of organ failure and neurogenerative disease. Despite the fact that transplantation of whole organs has become routine in modern medicine and has saved countless lives the current therapeutic strategies are limited by donor availability and immunologic barriers or are pertinent to a minor range of conditions.

Thus, innovative applications of tissue engineering and novel cell therapies derived from pluripotent and tissue-restricted stem cells represent major frontiers for the future as cell therapy products. The majority of these cells obtained from various sources are typically negligible in quantity hence, it becomes a necessity to promote the long-term culture of these cells. However, the long-term expansion can provide additional stress to the stem cells which contributes to the genetic instability of the cells.

This short talk will provide a concise review on the evolution of the regulatory context and the available tools to evaluate the genetic stability of stem cell-based based therapy products with particular focus on classical (karyotype analysis) and molecular cytogenetics (including FISH).

ADVANCING CARTILAGE REGENERATION WITH THE USE OF MAGNETIC STEM CELL CONFINEMENT WITHIN SCAFFOLDS.

BIOREGATE EUROPEAN REGENERATIVE MEDICINE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

Aurore Van de Walle[1], Vicard Du[1], Waïss Faissal[1], Alain Richert[1], Florence Gazeau[1], Catherine Le Visage[2], Claire Wilhelm[1], Nathalie Luciani[1]

(1) Laboratoire Matière et Systèmes Complexes (MSC), UMR 7057 CNRS and University Paris Diderot, Paris, France

(2) National Institute of Health and Medical Research, INSERM U791, Nantes, France

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Repair of the cartilaginous layer of the condyle in case of disease or trauma remains a significant clinical challenge. An approach recently explored to engineer autologous cartilage replacements is the differentiation of stem cells into chondrocytes. As cell-cell contact is known to initiate chondrogenic differentiation, our lab has developed a new approach to condense cells based on magnetic labeling and seeding. Human mesenchymal stem cells were first labeled magnetically using iron oxide (maghemite) nanoparticles and seeded within porous polysaccharide scaffolds via magnetic condensation. The seeded scaffolds were then cultured for 21 days in a bioreactor that offers a dynamic mechanical environment as well as improved nutrient and gas diffusion. The constructs were also subjected to various levels of oxygen tension (normoxia vs. 3% hypoxia) to assess their effect on the synthesis kinetics of extracellular matrix components. Under optimal culture conditions, cartilage tissue production was highly improved, with a 50-fold increase in collagen II expression, an overexpression of aggrecan, and a very low expression of collagen I and RUNX2. Additionally, the expression of collagen X was modulated by hypoxic conditions. This unprecedented cartilage tissue production within porous polysaccharide scaffolds represents a major step forward in producing replacement tissue for cartilage defects.

VITRICELL: NEW EFFICIENT METHOD FOR CRYOPRESERVING CELLS BY VITRIFICATION.

BIOREGATE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

D. Connan[1], F.J. Ectors[2], P. Vanderzwalmen[3], N. Antoine[4], L. Grobet[1]

(1) University of Liege, Embryology Unit, FARAH & GIGA, Belgium

(2) University of Liege, Mammalian transgenic platforms, FARAH & GIGA, Belgium

(3) IVF Centers Prof. Zech, Bregenz, Austria

(4) University of Liege, Laboratory of Animal Histology, FARAH, Belgium

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Using stem and related cells for clinical purposes requires efficient and bio-safe handling. Cryopreservation is a mandatory key step of storage and transportation, during which cells undergo extreme physical and chemical conditions prone to alter their viability as well as their biological properties. Conventional slow-freezing often results in poor survival rates mainly due to excessive cell dehydration and water crystallization. We have addressed this problem by developing a new cryopreservation method based on aseptic and automatable vitrification in sealed french straws. Furthermore, only bio-safe and chemically defined cryopreservation media are used.

We have demonstrated that, despite additional constraints, our aseptic vitrification process is more efficient (recovery rates, morphology, pluripotency…) than conventional slow freezing for cryopreserving human pluripotent stem cells (hPSCs). These results have been confirmed on various sensitive stem cell-like lines and embryos from human and non-human species.

VITRICELL will soon provide researchers and clinicians with its vitrification kits, allowing to upgrade the current yields and safety after cryopreservation of their high-value cells.

MIAMI NEURONAL COMMITTED CELLS COMBINED WITH NANO AND ACTIVE MICROCARRIERS.

BIOREGATE EUROPEAN REGENERATIVE MEDICINE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

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Regenerative medicine strategies combining stem cells, nano and microcarriers is an emerging field for neurodegenerative disorders, such as Huntington's disease (HD). Preclinical studies using mesenchymal stem cells (MSCs) or neurotrophic factors, although promising, are limited principally by the poor retention, the short survival rate and differentiation of transplanted cells and the quick degradation of the proteins' supplementation into the damaged striatum. For this study, we selected a subpopulation of MSCs: Marrow-isolated adult multilineage inducible cells (MIAMI), which possess immunomodulatory properties, a high neurogeneic potential and secrete more tissue repair factors than other MSCs. In order to drive and maintain the neuronal commitment of the cells, we used a small interfering RNA against an inhibitor of neurogenic genes (REST) delivered in a controlled manner with lipid nanocapsules prior to their transplantation. Furthermore, we developed polymeric microcarriers providing a 3-dimensional biomimetic surface of laminin for the implanted cells and releasing in a prolonged manner brain-derived neurotrophic factor, a protein under-expressed in HD. These pharmacologically active microcarriers (PAMs) allow a high rate of engraftment. Promising preliminary results of this wide-ranged strategy have been observed in a new ex-vivo model of HD, further encouraging the evaluation in-vivo in genetic models of HD.

IRRADIATED BONE REPAIR WITH CELLS AND MATERIALS.

BIOREGATE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

Florent Espitalier CHU Nantes

Surgery and radiotherapy are both necessary to treat squamous cell cancer of the upper aerodigestive tract. The side effects of these treatments are important. Reconstruction of the mandible bone requires a vascularized bone autograft. Complications are observed with this technique, which cannot always be performed after radiotherapy. Bone tissue engineering gives an alternative. Previous animal studies showed that an association of a bone marrow graft with a calcium phosphate scaffold was necessary to regenerate bone in irradiated areas. More recently, an association of bone marrow cells or adipose tissue cells with calcium phosphate scaffold has been performed in irradiated areas. These cells have shown better bone repair abilities than bone marrow graft in healthy bone. Furthermore, adding a lysate of bone marrow cells intravenously was performed. Bone marrow graft showed its superiority in bone repair in irradiated areas when compared to bone marrow cells or adipose tissue cells. However, the contribution of vascular fraction of adipose tissue allowed neovascularization without bone formation. Hypotheses were in favour of the trophic role of the bone marrow, through growth factors and cytokines present in the bone marrow and secreted by the cells. The addition of a lysate of bone marrow cells intravenously allowed a better new bone formation in irradiated areas. The association of bone marrow and calcium phosphate scaffold is currently the most effective filling material for bone reconstruction in irradiated areas and can be improved by adding a lysate of bone marrow cells intravenously in a rat model.

OSTEOGENIC SUPERIORITY OF BONE MARROW DERIVED-OSTEOBLASTIC CELLS (ALLOB®) OVER BONE MARROW DERIVED-MESENCHYMAL STROMAL CELLS (BM-MSC).

BIOREGATE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

Sandra Pietri, PhD, Hélène Dubout, MSc, Sabrina Ena, PhD, Candice Hoste, PhD, and **Enrico Bastianelli*,** MD, MBA. Bone Therrapeutics, Charleroi, Belgium.

Cell-based therapy offers new hopes for the treatment of complex orthopaedic conditions. Bone Therapeutics is bringing a unique value proposition in the market by developing a range of innovative osteoblastic cell therapy products administrable via a minimally invasive technique. The implantation of biologically active differentiated cells locally into the fracture site is intended to mimic the natural process of bone formation and eventually to recreate a healthy bone environment by recruiting endothelial and osteoprogenitor cells. The company has developed a unique allogeneic osteoblastic cell product (ALLOB®) derived from adult bone marrow which is currently tested in humans in the indication of delayed-union fractures. The purpose of this study was to directly compare ALLOB® vs. non-differentiated mesenchymal stromal cells (MSCs) for their in vitro osteogenic characteristics and their in vivo osteogenic potential in order to determine which cellular type would be the most efficacious for bone fracture repair.
Methods: Healthy volunteers' bone marrow aspirates (n=6) were expanded (i) into BM-MSCs using a complete MSC culture medium or (ii) into ALLOB® cells according to its manufacturing process. Cells were characterized in vitro by morphology, phenotype, gene expression using RNAseq technology (n=4) and their differentiation potential. Additionally, their osteogenic potential was assessed in vivo in the calvaria bone formation model in nude mice.
Results: The in vitro comparison studies showed that although ALLOB® and BM-MSC shared some common general characteristics such as the 3 minimal MSC key criteria defined by Dominici in 2006, ALLOB® expressed significantly higher levels of osteoblastic genes such as BMP2 (fold change (FC)=125.8; $p<0.001$), ALPL (FC=11.4; $p<0.001$), CBFA1 (FC=2.9; $p<0.01$) and differentiated significantly earlier than BM-MSC toward the osteogenic lineage. Moreover the bone formation model in nude mice demonstrated that used at the same cellular concentration, ALLOB® was able to induce significantly more (169 % vs.107% for control animals) bone formation than BM-MSC (118% vs. 107 % for control animals) only two weeks after administration ($p<0.001$).
Conclusion: our side-by-side comparison studies demonstrated that in vitro and in vivo, ALLOB® displays superior osteogenic capacity compared to BM-MSCs, and is therefore a better candidate for the treatment of bone fractures.
Preliminary results from the ongoing Phase I/IIA delayed-union fracture trial indicate quantitative clinical and radiological improvements shortly after ALLOB® treatment. ALLOB® has therefore the potential to become a first-line and early treatment for delayed-union fractures, thanks to its minimally invasive administration which avoids the need for major surgery.

SCAFFOLD-FREE THREE-DIMENSIONAL GRAFT FROM AUTOLOGOUS ADIPOSE-DERIVED STEM CELLS FOR BONE DEFECT RECONSTRUCTION.

BIOREGATE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

Denis Dufrane MD, PhD

Novadip Biosciences, Bruxelles, Belgium

Background. Long bone non-union is one of the most challenging pathologies in orthopaedics surgery. We then assessed the feasibility and safety of human autologous scaffold-free osteogenic three-dimensional (3D)-graft (derived from adipose-derived stem cells,ASCs) to cure a bone non-union in extreme clinical and pathophysiological conditions.

Methods. Human ASCs (obtained from subcutaneous adipose tissues) were incubated in osteogenic media and supplemented with Demineralized Bone Matrix to obtain the scaffold-free 3D osteogenic structure as confirmed in vitro by histomorphometry,volumetric bone mineral density,BMP-2 quantification and surface analysis for osteogenesis and mineralization. The 3D "bone-like" structure was finally transplanted for patients with bone tumor and bone pseudarthrosis to assess the clinical feasibility,safety and efficacy. Although minor clones with structural aberrations (clonal trisomy 7 in 6%–20% of cells) were detected in the undifferentiated ASCs, the osteogenic differentiation significantly reduced these clonal anomalies. The final osteogenic product was stable, did not rupture with forceps manipulation, did not induce donor site morbidity and was easily implanted directly in the bone defect. No acute (impaired wound healing, pain, inflammatory reaction, and infection side effects) or long-term side effects (tumor development), were associated with the graft up to 4 years post-transplantation. Conclusions. We report for the first time that autologous ASC can be fully differentiated into a 3D osteogenic-like implant without any scaffold and can safely promote osteogenesis in extreme conditions of bone non-union, leading to restoration of bone anatomy and function. A prospective controlled trial is needed for clinical relevant indications to clinically assess the 3D osteogenic-like implant.

MULTIPOROUS CALCIUM PHOSPHATES AS KEY PART OF HYBRID SYSTEMS FOR THERAPEUTIC INNOVATION IN BONE SURGERY.

BIOREGATE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

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Through two successive projects Atos (ANR-06-TECS-0024) and Reborne (HEALTH - 2009- 1-4-2), a scientific and clinical research cluster helps to clarify the contours of the medical paradigm nowadays, with its constraints and prospects. By the establishment of a collaborative dynamic between academics, hospitals and industrials, several therapeutic solutions are set up to the benefits of better treatment of patients with a concern for social responsibility associated with innovation. Clinical results obtained from the implementation of joint efforts between these actors in the biomedical field involve both real performance of hybrid cellularized medical devices and controlling risks and costs inherent to the use of advanced technologies. The use of synthetic multiporous platforms with versatile properties that are biomimetic calcium phosphate (MBCP©) allows modularity of biological interactions in the context of bone tissue engineering. Through the engineering of ceramic scaffolds with relevant physicochemical properties towards bone bioactivity, the association of alloplastic grafts and living tissue derivatives, such as stem cells or concentrated bone marrow, allows to compete with the gold standard autologous bone graft without risks including morbidity associated thereof. Such are the promising results of more than 8 years of these collaborative research programs being reviewed.

GROWTH FACTOR-DELIVERY FROM POROUS SCAFFOLDS PREPARED BY GREEN CO2 FOAMING.

BIOREGATE EUROPEAN BIOMATERIALS INDUSTRY FORUM
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Compressed CO2 foaming is an attractive green approach to create advanced porous scaffolds promoting cell attachment, proliferation and colonization for tissue engineering applications. An ideal scaffold should not only mimic the morphology of extracellular matrix but also provides a suitable environment for cell recruiting and tissue in-growth guidance[1]. To achieve this, the incorporation of autologous growth factors and a biodegradation rate matching the growth rate of the tissue regeneration are highly beneficial[2, 3]. In this work, a modified compressed CO2 foaming method for the preparation of porous scaffolds containing low-inherent viscosity PLGA and autologous growth factors (PRGF) is reported for the first time. This technique overcomes the processing limitations of low-inherent viscosity polymers in a solvent-free, simple and reproducible process. The resulting scaffolds presented a highly porous structure and mechanical properties similar to human cortical bone. PRGF yield was ca. 100% and its activity was retained after processing. Scaffolds were cytocompatible and provided sustained release of PRGF over 15 days enhancing cell attachment, proliferation and migration of mesenchymal stem cells.

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THE SHEEP: A RELEVANT ANIMAL MODEL FOR NUCLEUS PULPOSUS REGENERATIVE MEDICINE.

BIOREGATE EUROPEAN REGENERATIVE MEDICINE FORUM
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Intervertebral disc (IVD) degeneration is conceptualized as the consequence of the nucleus pulposus cell inability to maintain IVD extracellular matrix homeostasis. We recently demonstrated the ability of human adipose derived-stromal cells (ASC) to give rise to nucleus pulposus cells namely the nucleopulpocytes (NPCy) and to support the neo-formation of a NP-like tissue when transplanted associated to hydrogel in nude mice subcutis. To go further, the use of a clinically relevant animal model of IVD degeneration is required. Sheep exhibit a process of IVD degeneration quite superimposable to that of human and the size of sheep IVD allows the development of surgical protocols easily transferable to the human.

Our data have first confirmed the stemness properties of sASC by demonstrating their proliferation, clonogenicity and multipotency. In the context of IVD regenerative medicine, sASC were able to give rise to nucleopulpocytes when cultured in an inductive medium. Finally, a large volume of hydrogel in sheep IVD has been successfully injected, compatible with future preclinical experiments. In this context, sheep could be considered as a preclinically relevant animal model for comparing IVD regenerative strategies. Further studies dedicated to evaluate the regeneration of NP niche through biomaterial-assisted transplantation of sASC are now under investigation.

ALLOGENEIC NEONATAL MSC FOR LIMITING OSTEOARTHRITIS PROGRESSION AFTER ORTHOPAEDIC SURGERY.

BIOREGATE EUROPEAN REGENERATIVE MEDICINE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

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Introduction: Osteoarthrosis continues to evolve after patient knee surgery despite joint stability restoration and NSAID. We hypothesized that Mesenchymal Stromal Cells (MSC), as a disease-modifying-osteoarthritis therapy could change this fate. As a model for patients, this study evaluates the safety and effects of neonatal MSC, in the post-op management of dogs operated for cranial cruciate ligament rupture (CCLR).

Material & methods: 20 owner's dogs suffering from CCLR were included in a prospective, controlled, double-blinded field trial. Animals were randomized in 2 groups: «MSC group" (intra-articular MSCs after surgery, then dietary supplement for 1 month) VS «control group" (intra-articular MSCs vehicle after surgery, then NSAIDs for 1 month). Postoperative (1, 3, 6 months) evaluations consisted in a clinical score, radiographic osteoarthritis assessment, and an objective gait analysis (GaitRite®) by a single blinded evaluator. Pre- and postoperative evaluations were compared between each groups.

Results: 16 dogs completed the trial. Favourable outcomes were reported in both groups, with no significant difference for clinical score, radiographic and gait evaluations at each follow up visit. No local or systemic adverse event was reported after MSCs injection.

Conclusion: Intra-articular injection of neonatal MSC is a valuable therapeutic approach for pain and lameness management following orthopaedic surgery.

IGO PROJECT: ADOPTIVE CELL THERAPY FOR MELANOMA

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We developed a clinical-grade production process of T lymphocytes specific for melanoma antigens, usable for adoptive cell transfer in melanoma patients. These specific T cells are produced from HLA-A2 patient's PBMC by a peptide stimulation step, followed by a sorting/amplification step. Sorted T lymphocytes are polyclonal, fully specific of targeted antigens and reactive against melanoma cells.

An extensive analysis of these specific T cells showed that a fraction of these T lymphocytes constitutively expressed the PD-1 molecule that could potentially compromise their in vivo functions, while another fraction remained unable to express this molecule. This result prompted us to characterize the mechanisms leading to PD-1 expression on melanoma specific T lymphocytes, and to define culture conditions for amplifying optimized specific T cells.

We isolated Melan-A and MELOE-1 specific T cell clones stably expressing different levels of PD-1 at rest. We showed that PD-1^{neg} T cell clones remained unable to express this molecule, even after activation. The regulation of PD-1 expression occurs at the transcriptional level, with major differences in the methylation pattern of the PD-1 promoter. From a functional point of view, activation of PD-1^{pos} T cell clones was strongly inhibited in response to PD-L1 expressing melanoma cells, whereas no inhibition was detected for PD-1^{neg} T cell clones. More surprisingly, we observed that PD-1^{neg} T cell clones were altogether of lower avidity than PD-1^{pos} ones. These results suggest that in physiological conditions, high affinity specific T cell clones negative for PD-1 expression are not or rarely present in peripheral blood, as they are probably eliminated by negative selection, due to a too high reactivity. Thus, the selection of PD-1^{neg} T cell clones would not be a good option for adoptive cell transfer, while blocking PD-1 signalization during the selection procedure of melanoma specific T cells could lead to the amplification of high avidity effector T cells.

We thus modified the production procedure of specific T cells, adding a PD-1 blocking antibody during each step. We showed that the absolute number of antigen specific T cells increased upon addition of this Ab during the peptide stimulation step, and that the recovered specific T cell repertoire was biased towards a higher avidity T cell repertoire. Therefore, we reckon that the use of anti-PD-1 blocking Ab during the production process of melanoma specific T cells will ensure recovery of high affinity polyclonal T cells potentially more efficient for melanoma immunotherapy.

ACCELERATING CLINICAL DEVELOPMENT OF ATMPS

Dr Dominic Bowers Catapult, UK

An overview of the pathway for ATMP's from the pre-clinical stage through clinical development into commercialisation. A review of achievements within the field to date and a discussion of barriers to streamlined and effective clinical development pathways. An examination of strategies to overcome key development barriers to ensure progress can be made to expedite safe translation towards commercialisation.

INJECTABLE BIOGEL FOR LOCAL T CELL DELIVERY: A NEW APPROACH FOR IMMUNOTHERAPY.

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8 & 9 SEPTEMBER 2016
Nantes, France

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Adoptive T cell therapy (ACT) is a very promising form of cancer immunotherapy, but it is limited by the large numbers of T lymphocytes (TL) that must be expanded before intravenous systemic delivery due to their loss to non-cancerous sites of inflammation. We here propose a new approach consisting of encapsulating TL in an injectable scaffold to increase their concentration and retention close to the tumor. To that purpose, chitosan-based thermosensitive hydrogels (CTGels) were developed by mixing CH acidic solution (Mw 250kDa, DDA 94%) with a combination of phosphate buffer (PB) and sodium hydrogen carbonate (SHC) as gelling agents. CTgels present rapid gelation at 37°C, high mechanical strength (Secant Young modulus > 100 kPa), macroporosity and excellent cytocompatibility due to low salt concentration and the absence of chemical crosslinker. One formulation clearly outperforms the others by providing an environment suitable for the encapsulation of viable CD8+ TL, supporting their proliferation in 3D colonies and their gradual release. Encapsulated TL expressed cytotoxic markers, released IFN- and induced annexin V expression when co-cultured with specific melanoma cells. Finally, the biogel was injected subcutaneously in mice and it degradation and cell survival was evaluated over 4 weeks. Use alone or as adjunct system with intravenous delivery, it might improve ACT outcomes and increase the number of patients who can benefit from it, whilst minimizing side effects.

INJECTABLE HYDROGEL FOR CELL THERAPEUTIC TREATMENT IMPROVES COLONIC RADIATION-INDUCED DAMAGE.

BIOREGATE EUROPEAN REGENERATIVE MEDICINE FORUM
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Nantes, France

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Radiation therapy is crucial in the therapeutic arsenal to cure cancers; however, non-neoplastic tissues around an abdomino-pelvic tumor can be damaged by ionizing radiation, leading some specialists to define these specific gastrointestinal complications as "pelvic radiation disease". This is particularly important as the number of patients suffering from this disease is increasing with increased life expectancy of patients treated for cancer.

Mesenchymal Stromal Cells (MSCs) represent a promising strategy to reduce intestinal lesions. Indeed, we previously demonstrated in rat, mini-pig then patients over-irradiated during radiotherapy for prostate cancer, that intravenous injections of MSCs reduces severe colorectal lesions. However, this effect seems temporary and repeated injections have been recommended. The beneficial effects of MSCs have been related to their capacity to engraft, survive and secrete bioactive factors in the host tissue. In this study, we propose to use a colonoscope to deliver MSCs embedded in a biocompatible hydrogel (Si-HPMC) directly into the colon. We demonstrated in vivo using a rat model of radiation-induced severe colonic damage that MSC+Si-HPMC improve epithelial structure and colon hyperpermeability. These results could open up new perspectives in regenerative medicine in particular with the co-administration of MSC and ex-vivo expended "mini-gut".

SENESCENCE ALTERS IDO-DEPENDENT MSC FUNCTIONS.

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Owing to their immunosuppressive and anti-inflammatory properties, mesenchymal stromal cells (MSCs) obtained from bone marrow (BM-MSCs) or adipose tissue (ASCs) are considered a very promising tool for cell therapy. However, important issues should be considered to ensure the reproducible production of efficient and safe clinical-grade MSCs. In particular, expansion rate was recently proposed as one of the parameters that could influence MSC functionality. In agreement, we previously demonstrated that cultured MSCs enter replicative senescence independently of the rare occurrence of genomic alterations. In this study we directly address the consequences of replicative senescence on BM-MSC and ASC immunomodulatory properties. We demonstrate that clinical-grade senescent MSCs inhibit less efficiently T-cell, unlike NK-cell, proliferation than their non-senescent counterpart, in association with a decreased indoleamine-2,3 dioxygenase (IDO) activity in response to inflammatory stimuli. In particular, whereas IDO expression is transcriptionally induced at a similar level in senescent and non-senescent MSCs, IDO protein is specifically degraded by the proteasome in senescent ASCs and BM-MSCs. These data encourage the use of appropriate quality controls before translating clinical-grade MSCs in the clinic.

EXTRA CELLULAR MATRIX MICRO-ENVIRONMENT CONTROL IS A KEY ISSUE TO REGENERATIVE MEDICINE AND RGTA BASED MATRIX THERAPY A SOLUTION.

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Extra Cellular Matrix (ECM) microenvironment regulates locally our continuous ability to replace dead cells by new cells. This central law of all living is known as tissue homeostasis. Heparan sulfates (HS) are key elements of the ECM scaffold that store, protect and position the various Cell Communication Peptides (CCP) in the cellular microenvironment. HS play a pivotal role in the regulation of the bioavailability of CCP, cell proliferation, migration and differentiation required for tissue regeneration. Tissue injury will lead to destruction of cells and surrounding ECM. CCP released by inflammatory and circulating cells can then promote tissue repair, but with a loss of tissue quality, leaving scars or fibrosis. We have engineered biodegradable nano-polysaccharide mimicking HS, named RGTA for ReGeneraTing Agent. Introduced at the site of injury, RGTA will bind to the matrix proteins of the damaged ECM, and to the CCP produced by healthy neighboring cells, thereby restoring the ECM microenvironment and conditions for tissue homeostasis. This matrix therapy approach has considerably improved the quality of healing in various animal models with reduction or absence of fibrosis resulting in a real regeneration process. The RGTA technology has been validated in clinics and over hundred thousand of patients treated both for corneal and skin ulcers with no adverse effect. Adapted RGTA are in development for more tissue injuries extending RGTA as a new therapeutic class in the field of regenerative medicine exploiting our natural potential without need for exogenous cells. RGTA can combine with cell therapy by constructing a niche to favor homing. The future of regenerative medicine lays in a proper adjustment of the microenvironment to optimize cell colonization, expansion, replacement and recovery of their functions.

HEART DISEASE MODELING WITH HUMAN IPS CELLS

Pr Jean-Sebastien Hulot, MD PhD

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In this talk, Pr Hulot will present his work related to the modeling of monogenic cardiac disorders with hiPSC. In particular, he will show how the cardiomyocytes defferentiated from hiPSC recapitulate individual susceptibility to cardiotoxic.

In the second part of his talk, he will present some of his new projects aiming to use genome-editing techniques to target missense mutations causing genetic cardiomyopathies. Through this project, he will give an insight into CRISPR use to correct inherited cardiac disorders.

HUMAN IPSC-DERIVED CELLS IN DISEASE MODELING AND PHENOTYPIC SCREENING: USING INDUCED, INNATE AND ENGINEERED MODELS.

BIOREGATE FORUM
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Sabine Lange

Human iPSC-derived cells in disease modeling and phenotypic screening: Using Induced, Innate and Engineered Models

A major hurdle in developing relevant disease models for drug discovery is access to the healthy and diseased tissue of interest. A solution to this limitation is presented in the form of induced pluripotent stem cell (iPSC) technology affording access to biologically relevant human tissues in essentially unlimited supply. Here we describe examples of iPSC-derived disease models which yield screenable phenotypes owing to their genetic backgrounds from either innate (donor specific) or engineered disease relevant variants and/or the application of pathway inducing culture conditions to elicit a specific phenotype. Examples are shown in three different iPSC-derived cell types: cardiomyocytes, neurons and hepatocytes. Engineered iPSC-derived neuronal models are presented with data from genetic variants e.g. in the amyloid precursor protein (APP) yielding a model suite for Alzheimer's Disease as well as an epilepsy model resulting from a specific KCNT1 point mutation. Specific induced disease models highlighted include the application of iPSC-derived hepatocytes in hepatitis virus infectivity as well as an endothelin-1 induced cardiac hypertrophy model using iPSC-derived cardiomyocytes with a workflow suitable for high throughput screening. A variant of the induced cardiac hypertrophy model was also adapted to closely mimic the innate phenotype of iPSC-derived cardiomyocytes from diabetic patients. This model was used in a phenotypic screen to identify compounds that rescue from the pathological phenotype and hits identified that could potentiate hypertrophy in the diabetic donor iPSC-derived cardiomyocytes. These data show how iPSC technology offers reliable and predictive model systems not previously attainable, thus creating new tools and opportunities for drug discovery. Our current efforts are aimed at generating large iPSC clone banks from disease backgrounds that will serve to expand access to cell models for phenotypic drug discovery.

GMP-COMPLIANT HUMAN PLATELET LYSATE, IN LIQUID FORM OR AS HYDROGEL, FOR OPTIMIZED EXPANSION OF CELL THERAPY PRODUCTS.

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We describe the development, the production and the characterization of a GMP-compliant human Platelet Lysate (hPL) as a xeno-free and powerful substitute for foetal bovine serum (FBS) for expansion of cellular therapy products. We showed a robust standardization between batches in terms of osmolality, pH, GF contents (EGF, VEGF, bFGF, TGF-beta1, PDGF-AB, IGF-1), and biochemical analyses (total proteins, albumin, fibrinogen, glucose, ions). We compared expansion and functional characteristics of human mesenchymal stem cells (MSC) grown in GMP-compliant hPL versus MSC-screened FBS+bFGF. We showed a powerful and reproducible increase in cell growth kinetics using hPL and a maintenance of MSC morphology, membrane marker expression, clonogenic and differentiation potential, and immunosuppressive properties of MSC (on conA-activated T cells and MLR tests). Similar experiments were performed on MSC grown on a clinical grade jellified hPL (hPLGel), as a 3D nutritive matrix for MSC. MSC were migrating inside the hydrogel and proliferating in multi-layers, progressively degrading the hydrogel and releasing the GF entrapped in the gel with specific kinetic profiles. Blocking antibody experiments identified PDGF as a key mitogen for MSC growth on hPLGel. We demonstrated the feasibility to use a standardized, efficient and GMP-compliant hPL or hPLGel for research and cell therapy applications.

BENEFIT OF HEMOXCELL®, A NATURAL OXYGEN CARRIER, IN CELL CULTURE AND CELLULARIZATION OF BONE SUBSTITUTES BY MESENCHYMAL STEM CELLS.

BIOREGATE EUROPEAN REGENERATIVE MEDICINE FORUM
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HEMOXCell® is a natural oxygen carrier extracted from the marine worm Nereis virens and developed by HEMARINA SA. This extracellular haemoglobin, which can carry 50 times more oxygen molecules than the human haemoglobin and presents a SOD-like activity, enables oxygen release in a simple oxygen gradient according to cellular needs and presents most properties of an efficient oxygen additive during cell culture manufacturing.

HEMOXCell® used to supply oxygen in a bubbling-free batch culture system using CHO-S cell line, the most-used expression system for large-scale production of recombinant proteins, showed both an increase of growth rate and cellular bioproduction.

The benefit of the addition of HEMOXCell® in the culture of mesenchymal stem cells in bi- and three-dimensional scaffolds has also been evaluated. It has been shown that HEMOXCell® induced a 25%-increase of bone marrow Mesenchymal Stem Cells (MSCs) growth rate associated with the maintenance of cell characteristics. In addition, it seems to promote multilayer structure formation of MSC-seeded bone substitutes under perfusion culture associated with an up-regulation of collagen-I expression levels.

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MANUFACTURING MSK-DA01: A HUMAN EMBRYONIC STEM CELL-BASED THERAPY FOR PARKINSON'S DISEASE.

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Parkinson's disease (PD) is the second most common neurodegenerative disease affecting around 5 million people worldwide. Many of the most debilitating symptoms occur due to the progressive and irreversible loss of midbrain dopamine neurons. Here, we outline our progress on manufacturing a human embryonic stem cell-derived cell product (MSK-DA01) to replace lost midbrain dopamine neurons in patients. A research-grade protocol was adapted to clinically compatible raw materials and methods were derived to cryopreserve neurons. We have now manufactured billions of cells in a GMP facility that were cryopreserved in hundreds of vials per run, with four lots at scale manufactured. One product lot will be used for definitive preclinical studies and for patients if safety and efficacy are established and the FDA allows us to progress to the clinic. Our timeline to finish the preclinical studies and approach the FDA is the end of 2017. This work is funded by NYSTEM (C028503), New York State's publicly funded program to advance stem cell biology.

PRODUCTION OF CLINICAL GRADE TEMPORARY EPIDERMAL SUBSTITUTE OBTAINED FROM HESC DERIVED KERATINOCYTES FOR THE TREATMENT OF SICKLE CELL LEG ULCERS: A CHALLENGE FOR REGENERATIVE MEDICINE.

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Skin is the largest organ of the body involved in self-protection against external damages. Epidermis, the upper layer of the skin is mainly composed of keratinocytes organized to form a physical barrier at the interface of the environment. Some of diseases associated to genetic mutations or not could weaken this protection and lead to the disruption of skin integrity. Cell therapy approaches using adult keratinocytes are currently envisaged however these cells present limited proliferative capacities and variability in genetic background. Access to an unlimited source of embryonic pluripotent stem cells (hESC) will aim at overcoming these limitations since these cells are available in unlimited quantities thanks to their unlimited proliferation capacity and their pluripotency.

In this context, a protocol allowing the generation of keratinocytes from hESC able to perform functional pluristratified epidermis was developed. In the perspective of a human clinical application, the entire protocol have been optimized and adapted following good manufacturing practice (GMP) conditions from a clinical grade hES cell line (RC9) obtained at the Biotech Company Roslin Cells. A quality control of the keratinocytes was established. These controls include the checking for contaminations, karyology, and viability. Specific controls such as the analyses of the expression of keratinocytes markers and the absence of pluripotency markers were performed to verify the quality of the keratinocytes cells bank. In addition, a clinical grade support was selected for this capacity to allow the formation of a pluristratified epidermis in vivo.

HUMAN TISSUES ENGINEERED FROM MESENCHYMAL CELLS: TOOLS FOR ANGIOMODULATION ASSAYS.

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Beyond their use for regenerative medicine, human 3D engineered tissues are powerful 3D models to study key biological processes such as inflammation and angiogenesis. Our core technology is based on the self-assembly approach of tissue engineering. The latter exploits the capacity of adult mesenchymal/stem cells to secrete and assemble extracellular matrix elements upon ascorbic acid supplementation in vitro, leading to three-dimensional constructs devoid of exogenous or synthetic biomaterials. Highly natural connective, adipose tissues and skin substitutes featuring in vitro capillary-like networks formed by microvascular endothelial cells (hMVECs) were therefore produced. In particular, the use of human reconstructed adipose tissues featuring a preformed capillary network revealed the impact of a prolonged inflammatory microenvironment (TNF/IL-1ß), resulting in a less extended and less ramified CD31+ network with apoptotic hMVECs in the remaining capillary structures. In addition, the tissue's secretory profile was altered after cytokine exposure, with increased secretion of monocyte chemoattractant protein-1, interleukin-6, MMP-2 and -9 along with a significant reduction in adiponectin secretion. Various studies using our human skin models also established these engineered tissues as useful in vitro tools to assess the angiomodulation properties of selected molecules, highlighting how tissue engineering can contribute to the field of pharmaceutical testing.

MUSTEM CELL TRANSPLANTATION IN GRMD DOGS ACCELERATES SKELETAL MUSCLE REGENERATION.

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Duchenne Muscular Dystrophy (DMD) results from mutations in the dystrophin gene leading to the protein lack. Membrane disorganization and alterations in signaling pathways play crucial roles in the muscle fibre necrosis. Systemic delivery of allogeneic MuStem cells generates a clinical benefit concomitantly to a profound muscle remodeling in Golden Retriever Muscular Dystrophy (GRMD) dog. To assess more specifically the impact of the MuStem cell delivery on the skeletal muscle, we combined a transcriptomic study with a quantitative proteomic analysis and an exploration of miRNAs expression levels on muscles 6 months post-transplantation. This multi-omics approach exhibits major effect of the MuStem cell administration. We identified the enhancement of the muscle fibre regeneration in parallel to a global remodeling of fibre type composition and an effect on the connection between the muscle fibre and the extracellular matrix. Also, we demonstrated an effect on the miR-133, miR-222, miR-206 expression in the biceps femoris and diaphragm muscles. Overall, omics data allow to pave the way to the understanding of the consequences of the MuStem cell administration on muscle fibres. This strategy contributes to the identification of therapeutic tissue markers and represents an interesting tool to monitor the therapeutic effects during DMD-dedicated preclinical studies.

S-CURVES AND TECHNOLOGY ADOPTION MOMENTUM IN REGENERATIVE MEDICINE

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Cell-based therapies define a novel and fast emerging pharmaceutical product class. The precursors of these novel treatments include both the practice of bone marrow transplantation, which was initiated about 50 years ago to treat to this date more than one million patients, and the first tissue engineering products Apligraf and Dermagraft-TC that were approved by the FDA as early as 1998 and 1997, respectively. After more than 25 years of fundamental research, the concepts of therapeutic stem cells and engineered cells of human origin are finally reaching clinical trial signals that promote the view that safe and efficacious minimally manipulated and even engineered cell-based therapy products are now within the reach of commercialization. A clear-cut expression of this tendency is the new pharmaceutical franchises that have emerged in the past 4 years (e.g., TemCell HS Inj. and the autologous myoblast culture kit HeartSheet in Japan, or Holoclar and Glybera in Europe). Despite these remarkable advances, the adoption in clinical practice of the novel treatments is still slow albeit these revolutionary treatments have the potential to treat diseases that have remained intractable using conventional therapies. As a result, the commercial value of the product class of cell-based and gene-based therapies still remains to be fully leveraged. With already a solid adoption momentum at most big pharmaceutical firms and many midsize pharmaceutical companies, the technology of CAR-T cells is not only changing the paradigm in certain liquid cancer treatments, but also has imposed the perception that cell therapeutics are not passing fads and that they will change medicine in that the new technology is a solution of continuity in the product space of pharmaceuticals, from symptomatic, to disease-modifying, and to curative treatments. However, formidable challenges still remain and numerous advances must still be achieved. It is possible to take a glimpse of the future by exploiting the concept of the technology S-curve. The history of the enterprise of therapeutic mAbs, and the first steps in the full development of the technology of CAR-T cells can be put to use to anticipate on the “chunks of innovation” and technical voyage that still lie ahead. One can anticipate how these could serve as impulse-engines for the global adoption of the technology of live therapeutic cells, from the 1st generation and beyond.

THE MOSAIC OF STEM CELLS: HOW TO REGULATE?

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In the past years Stem Cells have been used increasingly in Life Sciences and for medical purposes. Recent discoveries are bringing results close to the market for the benefit of patients but are still posing huge difficulties in terms of regulations and ethical issues. In this presentation, we will analyse the status of the different types of Stem cells (Embryonic, adults, IPs) with regards to their legal regime. We will, then, highlight the specific ethical challenges they are raising depending on the sources of the cells and of their uses (medical treatment, research). We will show how Ethics and Law can speed up or slow down the access of new products or processes to the market and we will propose some recommendations to face these challenges, in particular in an international context.

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POSTER ABSTRACTS

POSTER 1

VITAMIN E-TPGS STABILIZED LAPATINIB NANOCRYSTALS: IN VIVO PHARMACOKINETIC AND PHARMACODYNAMIC EVALUATION.

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Aim: Development of Vitamin E-TPGS stabilized Lapatinib Nanocrystals (LPT-NCs) to improve its anticancer activity.

Methods: Nanocrystals were prepared through High pressure homogenization and the optimized formulation was further characterized on the basis of in-vitro and in-vivo evaluations.

Results: Optimized formulation had 282.2 ±9.48 nm average particle size, 0.288 ±0.006 PDI and +33.63 ±3.59 mv zeta potential values. Microscopic examination displayed formation of rod shaped nano-sized crystals. DSC thermogram showed that crystallinity of Lapatinib was retained in formulation. Formulation significantly enhanced saturation solubility of LPT in water. LPT-NCs were found to be stable during 4 months study period when stored at 4 0C. In-vivo pharmacokinetics study comprising of crude Lapatinib suspension and LPT-NCs by oral route performed in healthy adult female Sprauge-Dawley rats demonstrated significant enhancement in AUC, Cmax and reduction in clearance of LPT in LPT-NCs treated group. Tumor regression study performed in 4T1 cells induced syngenic breast cancer female BALB/c mice revealed significant reduction in tumor burden and overall improvement in survival in LPT-NCs treated group compared to crude Lapatinib suspension.

Conclusion: LPT-NCs significantly enhanced anticancer activity of LPT by improving its oral bioavailability possibly due to solubility enhancement and P-gp inhibition.

Keywords: Lapatinib, Nanocrystals, TPGS, breast cancer.

POSTER 2

OPTIMIZATION OF SILANIZED HYDROXYLPROPYL METHYL CELLULOSE (SI-HPMC) HYDROGEL FOR GUIDED PERIODONTAL TISSUE REGENERATION.

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Periodontitis, a recognized disease worldwide, is a serious gum infection that damages soft tissue and results in loss of tooth-supporting alveolar bone. The POsTURE project aims to develop innovative periodontal procedures to obtain complete tissue reconstruction, by using a bone substitute and a dental membrane, both devices being based on a self-setting injectable hydrogel.

In this study, we focused on the bone material and synthesized calcium phosphate (CaP) needle-like nanomaterials through wet chemical precipitation. To enhance bioactivity and osteoconductivity, Sr, Mg or Si substituted CaP were obtained (diameter, length, HA:beta TCP ratio).

Incorporation of CaP into Si-HPMC viscous solution was then successfully performed and we observed an homogeneous dispersion of the nanoneedles in the resulting hydrogel. Rheological and mechanical properties of hydrogels were assessed, as a function of the polymer concentration. Ongoing characterization include ion release in conditions mimicking biological environment, i.e., culture medium and TRIS-HCl, in order to assess the stability of the substituted CaP nanomaterials. In a future work, we will investigate Si-HPMC as a dental membrane that could be applied on the bone substitute to prevent excessive proliferation of gingival tissue and enhance bone regeneration.

POSTER 3

THE PEPTIDE NFL-TBS.40-63 TARGETS AND AFFECTS NEURAL STEM CELLS.

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The recruitment of neural stem cells (NSCs) occurs in several brain disorders. NSCs can proliferate, self-renew and differentiate into neurons, astrocytes and oligodendrocytes. Thus, manipulating these cells represents a promising approach to develop new regenerative strategies.

We showed previously that the NFL-TBS.40-63 peptide, a neurofilament derived-peptide, targets glioblastoma cells in vitro where it disrupts microtubules and inhibits proliferation. In vivo, it decreases the tumor size by 70% when injected in rat brain tumor (Bergès et al., 2012).

Here, we show that this peptide also targets neural stem cells when isolated in vitro from the subventricular zone, and when injected in vivo in the lateral ventricle of adult rats. Although neurosphere formation was not altered, the self-renewal capacity and proliferation of NSCs were reduced while their adhesion and differentiation were increased. Thus, the peptide represents a promising tool to target NSCs and to develop new strategies for regenerative medicine.

Supported by AFM (Association Française contre les Myopathies), ARC (Association de Recherche contre le Cancer), CIMATH (Ciblage Moléculaire et Thérapeutique), MATWIN (Maturation & Accelerating Translation With Industry), and UNAM (Université Nantes, Angers, Le Mans).

POSTER 4

PHOTO-CROSSLINKABLE INTERPENETRATED POLYMER NETWORKS FOR BIOMEDICAL APPLICATIONS.

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Injectable natural hydrophilic polymers forming networks in situ offer many advantages in drug delivery and tissue engineering. Indeed, they allow delivery of cells and bioactive molecules and might serve as scaffold for tissue defects repair in a minimally invasive manner. Therefore, it reduces the need for surgical incisions.

In our study, we developed an injectable photo-crosslinkable chitosan, i.e. Methacrylated Carboxymethyl Chitosan (CMCS-MA) that can be applied as a viscous solution and cured in situ by a visible light lamp using a photoinitiator system of Riboflavin and triethanolamine. In order to improve the mechanical properties of this chitosan network, we formulated an Interpenetrating Polymer Network (IPN) by pH induced crosslinking of Silated Hydroxypropylmethyl Cellulose (HPMC-Si). By this process, each polymer is able to form an independent network.

The gel point of the solution was determined by rheology and remained below 1 minute. The rheological tests also confirm the formation of the second network of Cellulose derivative leading to an increase of the measured moduli. IR studies evidence the homogeneity of the IPN. These preliminary results are quite promising for the development of novel IPN systems for biomedical uses.

POSTER 5

STUDY OF THE INTERACTION OF MARINE POLYSACCHARIDES OF BIOLOGICAL INTEREST WITH SCANDIUM THERANOSTIC TRACERS.

BIOREGATE FORUM

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The anti-metastatic properties of an exopolysaccharide (EPS) derivative, produced by a deep-sea hydrothermal bacterium, were beneficially evaluated from mouse osteosarcoma. This EPS called GY785 EPS has a high-molecular weight and is slightly sulfated. So the GY785 EPS was chemically modified (depolymerization and oversulfation) to isolate heparin-like derivatives; they have anticoagulant properties and target cancer metastasis. Heparin is currently used in therapy; and EPS derivatives would mimic and replace it. The coupling of EPS with scandium, a promising theranostic agent, could pave the way to new therapeutic uses.

Here, we aim to scrutinize the feasibility of such coupling. Among the available theranostic tracers, Sc is of interest. 44Sc for diagnostic / 47Sc for therapy are an alternative to 68Ga or 64Cu for PET-imaging of cancer prior to 177Lu / 90Y-based radionuclide therapy. 44Sc has an isomeric state 44mSc, co-produced with 44Sc that can be used as an in vivo 44mSc/44Sc generator. The complexation between these EPS with Sc was studied: from a molecular point of view (TRLIFS using Eu as probe) using osidic references, EPS and heparin systems, to the stability constants determination (ESI-MS). Size and size distribution of EPS, coupled or not to Sc, were characterized by A4F-MALS.

POSTER 6

TOWARD A CLINICAL USE OF SYNTHETIC HEPATOCYTES FOR TREATING CRIGLER-NAJJAR.

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Cell therapy represents an exiting clinical alternative to liver transplantation. Human induced pluripotent stem cells (hiPSCs) have been investigated as a renewable source of transplantable hepatocytes-like cells (HLC). However, the demonstration that HLC produced according to a cGMP protocol could treat an inherited liver disease is still waiting. Here, we report the production of hepatic progenitors from hiPSCs (pStemHep) using xeno-free, feeder-free and chemically defined culture media and recombinant laminin as an extracellular matrix. pStemHep were transplanted intrasplenically in the Gunn rat, modeling Crigler-Najjar, which is characterized by high levels of unconjugated bilirubin due to absence of UGT1A1 activity. Following transplantation of freshly-prepared or frozen pStemHep, we show significant correction of hyperbilirubinemia for at least 5 months without adverse events. Most of pStemHep were found in the spleen and expressed UGT1A1 (immunochemistry and activity). These results demonstrate that pStemHep underwent maturation in vivo to gain UGT1A1 expression. In conclusion, we establish for the first time the efficacy hiPSC-derived liver cells using a cGMP cell production protocol for treating an inherited liver disease. Importantly, these results were obtained in absence of any selective growth advantage of transplanted cells over resident hepatocytes thereby mimicking the pathophysiological situation encountered in human.

POSTER 7

IPSC CORE FACILITY OF NANTES

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In this poster we present an overview of the iPSC core facility of Nantes. In particular, we discuss our reprogramming methods en our R&D projects.

One of the challenges of iPSC core facility is the diversity of cells we are asked to reprogram. This could be at the cell type level, with samples commonly originating from skin biopsies, blood samples or urine samples. Additionally, some of our partners are interested in other species, such as rodents or domestic species. We present the summary of the reprogrammations we have performed with the sendaï virus across species and cell types.

Additionally, the CRISPR/CAS9 system has allowed tremendous progress in genome edition of pluripotent stem cell. We will discuss one of the projects we have developed in our core facility using this approach.

POSTER 8

CATWALK: A PROMISING METHOD FOR THE STUDY OF ANALGESIC BIOMATERIALS.

BIOREGATE EUROPEAN REGENERATIVE MEDICINE FORUM

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Postoperative pain following bone reconstruction is regarded as one of the major undesira-ble complications. This pain, which can become chronic, significantly disrupts patient recovery. However, the administration of local anesthetics has proven to be an effective analgesic technique for the treatment of postoperative pain with a significantly reduced drug use (e.g. morphine). In this way, we would like to develop new injectable combined Calcium Phosphate Cements (CPCs) that deliver “in situ” active drug such as local anesthetics.

Different formulations are prepared from a commercial CPC loaded with anesthetics. After their physicochemical characterizations, cements were implanted. Eighteen Wister female rats were operated with 0% (unloaded cement), 8% of bupivacaine and 8% ropivacaine, in critical cylin-drical defect in distal femur. The implantation impact on functional recovery and locomotion of the animals was studied using a “Catwalk” gait analysis system.

The use of this method seems to be an important tool for the discrimination of different implanted cements. Indeed, several gait parameters were determined and highlighted the reduction of pain as soon as 24 hours post-operatively (HPO) for loaded cement. Some relevant parameters can discriminate also cement loaded with bupivacaine (more efficient) and cement loaded with ropivacaine.

POSTER 9

SILANIZED HYALURONIC ACID HYDROGELS FOR TISSUE ENGINEERING APPLICATIONS.

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8 & 9 SEPTEMBER 2016
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In recent years, injectable hydrogels have shown great promise owing to their biocompatibility and ease of use for practitioners. However, they face the limitations of slow degradation and lack of mechanical integrity, making them non-optimal for bone and cartilage repair. Here, we report the development of an injectable hyaluronic acid formed through a self-hardening process occurring without additives at physiological pH. This process was previously established for the silanization of HPMC. This crosslinked scaffold can be tuned to control its degradability and swelling behavior using the properties of hyaluronic acid in a network state. Rheological studies showed a gel point around 20 minutes at 23°C and a stiffness over 1 kPa. Both physical and chemical interactions form a very elastic, but covalent, hydrogel where 37.5 mg of this polymer absorbs 12 g of water. A 1% grafting percentage was found by ICP-AES. Ongoing mechanical studies will be pursued to thoroughly characterize this product and soon, biological experiments will be conducted to study cytocompatibility, cell proliferation and differentiation and growth factors release within the hydrogel. Then addition of calcium phosphates and other silanized polymers will be performed to obtain versatile synthetic matrices relevant for bone and cartilage tissue engineering.

POSTER 10

ESTABLISHMENT OF A NOVEL TISSUE ENGINEERED PRODUCT CONSISTING OF RPE DERIVED FROM HUMAN EMBRYONIC STEM CELLS CULTURED ON HUMAN AMNIOTIC MEMBRANE FOR CLINICAL APPLICATIONS.

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Retinitis pigmentosa (RP) and age-related macular degeneration (AMD) are the main causes of blindness in the developed world. Stem cell-based therapy represents an alternative approach in the treatment of retinal diseases. The Retinal Pigment Epithelium (RPE) is a continuous monolayer of cuboidal epithelial cells, localized between the photoreceptors and fenestrated choroid capillaries. The RPE interacts with the photoreceptors for the maintenance of visual function. RP and AMD could be caused by degeneration or malfunction of the RPE cell layer. Maintaining the epithelial morphology of RPE cells is a crucial parameter to consider in order to restore some visual function by cell therapy. To achieve this goal, we have developed a tissue engineered product (TEP) that consists of RPE derived from human embryonic stem cells (hESC) cultured on denuded human amniotic membrane (hAM). Indeed spontaneous RPE differentiation of hESC was achieved after depletion of FGF2 in a clinically compatible medium. In parallel, we have established high quality standard to definite their characteristics and impurities. This cells could be banked and maintain their phenotype when cultured on hAM. Finally, our TEP will be used for phase I/II clinical trials.

POSTER 11

MESOPOROUS SILICA NANOFIBERS: NEW DRUG-DELIVERY SYSTEM FOR IVD REGENERATIVE MEDICINE.

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Intervertebral disc degeneration is a leading cause of low back pain and intradiscal delivery of therapeutic factors able to promote regenerative processes is considered with interest. We thus aim at using mesoporous silica nanofibers (MSNFs) as a bioactive carrier for nucleopulpogenic growth factors such as TGF-ß1. The loading/release capability of MSNFs, and the protein-silica interactions were explored using lysozyme.

Lysozyme was successfully adsorbed onto MSNFs and the highest amount of adsorbed lysozyme was obtained at pH 10, concentration of 200 mg/mL and 48h of incubation.

The ATR/FTIR study comparing amides, Si-O-Si, Si-OH and water bands between lysozyme, MSNFs and MSNFs/lysozyme combined with ZP results, suggest that protein-silica interactions should be mostly driven by hydrogen bound involving the amide II of the protein.

Release experiments showed a burst within the 1st hour followed by a slower release, leading to a sustained release for up to 20 days while maintaining the biological activity.

Finally, we demonstrated TGF- 1 adsorption and release from MSNFs while conserving its bioactivity.

MSNFs are promising nano-carriers for therapeutic factors delivery and further experiments will focus on the association of TGF-ß-loaded MSNFs with human adipose stromal cells with an adapted scaffold for in vivo proof of concept.

POSTER 12

3D SCAFFOLDS GUIDE MSCS NEURONAL DIFFERENTIATION AND ENHANCE THERAPEUTIC SECRETOME.

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Mesenchymal stem cells (MSCs) combined with biodegradable injectable scaffolds releasing growth factors hold great promises in the treatment of several neurological disorders. We here integrated human marrow isolated adult multilineage-inducible (MIAMI) stem cells with pharmacologically active microcarriers (PAMs) and injectable non-toxic Silanized-hydroxypropyl methylcellulose (Si-HPMC) hydrogel. The goal is to obtain an injectable non-toxic cell and growth factor delivery 3D device that stimulates the survival and/or neuronal differentiation of the grafted cells and enhance their tissue repair properties. A model protein was used to optimize the nano-precipitation conditions of brain-derived neurotrophic factor (BDNF). BDNF nano-precipitate was encapsulated in fibronectin-coated (FN) PAMs and the in vitro release profile evaluated. It showed a prolonged and complete release (96.3±0.5%) of bioactive BDNF. We demonstrated that PAMs and the Si-HPMC hydrogel increased the expression of neural/neuronal differentiation markers of MIAMI cells after 1 week. Moreover, the 3D environment provided by the PAMs alone or with the hydrogel increased MIAMI cell secretion of growth factors and chemokines. These results show that FN-PAMs combined with Si-HPMC hydrogel could be a useful tool to deliver BDNF and stem cells, guide their neuronal differentiation and improve the protective/reparative properties of the delivered cells in the context of neurological disorders.

POSTER 13

COMPARATIVE OSTEOGENICITY OF HUMAN ADIPOSE TISSUE AND BONE MARROW DERIVED STEM CELLS.

BIOREGATE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

Brennan MA, Renaud A, Amiaud J, Guilloton F, Deschaseaux F, Sensebé L, **Layrolle P**

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Adipose tissue derived stromal cells (ASCs) may be an alternative to those derived from bone marrow (BMSCs) for bone repair. The objective of this study was to compare the osteogenecity and angiogenesis of human ASC and BMSC. Human MSCs from 3 bone marrow donors and 4 adipose tissue donors were either cultured in vitro for osteogenic differentiation assays or mixed with biphasic calcium phosphate granules for 1 hour prior to subcutaneous implantation in nude mice for 8 weeks. Undifferentiated MSCs were implanted alone or as mixtures of BMSC and ASC in ratios of 1:1, 9:1 and 1:9. Additional groups of MSCs were pre-differentiation towards the osteogenic lineage were also implanted. Results reveal that ASCs are superior to BMSC in terms of in vitro osteogenic differentiation; however histomorphometry of Masson trichrome stained paraffin-embedded sections revealed significantly less bone formation in ASCs compared to BMSCs groups. Immunohistochemistry using CD146 revealed more angiogenesis within constructs in the ASCs groups. These findings show the significantly inferior bone formation capacity of ASCs compared to BMSCs and have major implications for the use of ASC in bone repair.

POSTER 14

ENHANCING RADIODENSITY OF INJECTABLE CALCIUM PHOSPHATE WHILE MAINTAINING 100% RESORBABILITY AND BIOCOMPATIBILITY.

BIOREGATE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

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The use of potentially hazardous materials in the long term, such as heavy metals, to improve medical diagnoses thanks to 2D radiography and 3D X-ray tomography is a powerful way from a technical viewpoint. Calcium phosphate, and especially apatites acting as ion exchangers through multiple mechanisms of possible solid solutions in their crystallographic mesh. However such an approach is risky from the difficulty of controlling ions release, their biological effects over time and the transition to the industrial realities facing increasingly drastic regulatory constraints. This is why simple and cost-effective solutions by modulating the proportions, sizes and types of biomimetic mineral filler in a synthetic polymer matrix is suggested through a study based on the fundamental principles of electromagnetic physics. The design of injectable and safe medical devices leads to a range of fully biocompatible and resorbable pastes able to enhance bone remodelling without harm effects. A combination of in vitro assays on such biomaterials with animal and human ex vivo testing has been set up so as to compare different formulations, taking into account the most commonly used parameters by surgeons in order to stay closer to clinical realities.

POSTER 15

ROP MODEL IN TRANSLATIONAL RESEARCH.

BIOREGATE FORUM

8 & 9 SEPTEMBER 2016
Nantes, France

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Introduction

ROP is an intelligence tool in research, based on an exhaustive numerical analysis strategy. For a given factor, it identifies clusters for which a contrary effect is noticed. We show the interest of this model to identify the involvement of immunological factors in the clinic.

Material and methods

For 44 patients, 15 immunological data were performed using IHC. The ROP model was used to identify sources of variability in the effect of capsular breaking on relapse.

Results

ROP identified 17 patients for whom the reduction in risk of relapse at 6 months was paradoxically related to capsular breaking and 4 patients for whom there was no correlation between the decrease of the risk of relapse in cases of capsular breaking. Logistic regression performed on the remaining 36 observations, showed that reducing the risk of recurrence was positively correlated with the expression of Melan-A ($p = 0.021$) and negatively with the expression of PD-L1 ($p = 0.021$).

Conclusion

The ROP model was used to identify specific subgroups to effect described but not shown and identified the immunological factors involved in reducing the risk of recurrence of melanoma stage IIIB, in case of capsular breaking.

POSTER 16

UNDERSTANDING TISSUE ENGINEERING SCAFFOLDING OXYGENATION USING IN-VITRO HYDROGEL MODELS.

BIOREGATE FORUM

8 & 9 SEPTEMBER 2016
Nantes, France

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Cellular viability of hydrogels loaded with mesenchymal stem cells showed that oxygen was a limiting factor in cell viability

The oxygenation properties of the modified hydroxypropylmethylcellulose (si-HPMC) were studied to understand its oxygen diffusion relationship.

The unique methods and mathematics used to measure the oxygen diffusion are presented here. In brief, the core oxygen partial pressures were followed by Stern-Volmer fluorescent oxygen sensors at 5mm depth of a 10mm thick hydrogel which the oxygen pressure upon the hydrogel was changed. Afterwards, the hydrogels ability to diffuse oxygen was calculated from the experimental data using mathematical analysis.

This procedure is not limited to si-HPMC and is valid for any hydrogel system. Work has already begun on comparing the oxygen permeability of gelatin, agar, alginate to si-HPMC. This oxygen diffusion information allows for calculations which can more accurately suggest a maximum implantation size before anoxina within an implanted material.

POSTER 17

EVALUATION OF BONE RECONSTRUCTION WITH BIOMATERIALS IMPLANTED INTO RAT CRITICAL-SIZE CRANIAL BONE DEFECT.

BIOREGATE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

Collaboration between TBF-Lab and Atlantic Bone Screen
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The osteoconductive and flexibility properties of demineralized bone blocks make them very useful, more particularly in the treatment of bone defects in the dental, maxillofacial, spine, orthopedic and neurosurgery.
TBF developed virally inactivated, cleaned, freeze-dried and sterile demineralized cortico-cancellous bone blocks.
The aim of the present study is to evaluate the osteogenesis properties of blocks of Demineralized Bone Materials(DBM Blocks) in comparison with mineralized bone powder and Collagen/HAP (HydroxyAPatite) particles implanted) into a cranial bone defect generated on 2 months-rats which will be covered by chorioamniotic membrane during 12 weeks.
Inflammatory process was induced after drill-hole surgery in all groups implanted with materials and membrane. This inflammation remains present 8 weeks after surgery and decreases subsequently to reach low intensity.
Whatever the groups and the delay after surgery, the process of bone healing is at late stage at the edges of bone defect with lamellar mature bone and at early stage deeper into the defect with large fibrosis with vessels.
However, some isolated nodules of mature bone are seen in samples belonging to Group 2 (mineralized bone powder) and the extent of defect filling with mature bone is more prominent in Group 3 (DBM blocks) suggesting a bone healing process more efficient in these groups.
Interestingly, residual bone powder is noticed whereas there is no evidence of DBM blocks into bone defect suggesting that DBM blocks is already resorbed or integrated to new mature bone, helpful by the stabilization of block compared to the powder groups.

POSTER 18

EVALUATION OF CHORIOAMNIOTIC MEMBRANE ON EXPERIMENTAL CRANIAL BONE DEFECT ON RAT.

BIOREGATE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

Collaboration between TBF-Lab and Atlantic Bone Screen
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Chorioamniotic membranes are sampled from placental tissues and are composed of both membranes named amnion and chorion closely linked to each other's. They are used for guided tissue regeneration in the dental surgery field, because of their barrier function and their content of growth factors.
TBF developed a virally inactivated, cleaned, freeze-dried and sterile chorioamniotic membrane.
The aim of the present study is to evaluate the apposition and integration of this chorioamniotic membrane put onto a cranial bone defect generated on 2 months-rats during 12 weeks.
Inflammatory process was induced after drill-hole surgery in all groups implanted with membrane with / or without bone material. This inflammation slightly remains into the defect, 8 weeks and 12 weeks after surgery. It slightly increases at the parietal bone level where sutures were achieved but is not deleterious. Indeed, it can be considered as background changes, or associated with basal tissue reconstruction at the defect level and/or following surgery.
Residual membrane fragments can be observed in a minority of rats, as a very dense and acellular collagen membrane whereas the porous part of the membrane cannot be discriminated from the endogenous connective tissue developed in the defect (fibroplasia) and the pre-existing connective tissue.
All the parameters indicate that the membrane is very well tolerated by the animal and largely integrated into the animal tissues at this stage following implantation above the defect. No significant adverse tissue changes are observed.
Whatever the groups and the delay after surgery, the process of bone healing is at late stage at the edges of bone defect with lamellar mature bone and at early stage deeper into the defect with large fibrosis with vessels.
However, some additional isolated nodules of mature bone are seen distant from the edges of the defect in 2 samples belonging to Group 3 (bone powder + chorioamniotic membrane), whereas bone proliferation remains limited to the margins in animals of Group 2 (empty defect + chorioamniotic membrane), suggesting a bone healing process more efficient in the Group 3.
The fraction of mature bone surface and the process of bone formation is not increased in Group 2 (empty defect + chorioamniotic membrane) when compared to Group 1 (empty defect) suggesting that the chorioamniotic membrane alone without bone material does not help the bone healing process.

POSTER 19

MSCS ENCAPSULATION IN CYTOPROTECTIVE HYDROGEL: NEW PROSPECT IN OSTEOARTHRITIS TREATEMENT?

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Osteoarthritis is a degenerative joint disease in which cartilage degeneration goes along with synovium inflammation. Mesenchymal Stromal Cells (MSCs) ability to secrete anti-inflammatory and immuno-modulatory factors represents an attractive tool in the treatment of diseases with inflammatory components. In this context, MSCs could offer a great support to manage inflammation. Considering the risk of cell leak and the massive cell death upon intra-articular injection, cell encapsulation therefore could (i) allow limitation of cell death upon injection, (ii) avoid cell effusion outside the articular space, and (iii) supply a suitable micro-environment supporting the biological activity of MSC. Here we have selected biocompatible biomaterials (alginate and silanized hydroxypropylmethylcellulose (Si- HPMC)) and encapsulated human MSCs into these hydrogel-based particles. We have compared several methods (dripping, emulsification, soft lithography) to prepare particles with a controlled size, ranging from 80 microns to more than 1.5 mm. and demonstrated cell viability after encapsulation. Future works will focus on the bioactivity of the encapsulated MSCs, i.e their capacity to modulate the immune response through the secretion of factors that have immune-modulatory, pro-angiogenic, anti-apoptotic, anti-fibrotic, and anti-inflammatory effects.

POSTER 20

NEW INSIGHTS ON GLYCIDYL ALKOXYSILANES REACTIVITIES FOR INJECTABLE HYDROGELS SYNTHESIS.

BIOREGATE FORUM
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Nantes, France

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Hydrogels made from biocompatible biopolymers are widely used in biomaterials for tissue engineering. Among them, injectable hydrogels are of particular interest for application in micro-invasive surgery. Those hydrogels are obtained from functionalized macromolecules (e.g. polysaccharides, polymers) bearing pH sensitive functions in order to trigger the gelation at appropriate pH change. In this strategy, functional alkoxysilanes Y (CH2)n Si(OR)3 where Y represents a functional group (e.g. glycidyl, amine, isocyanate, etc.) are very useful. Indeed, the alkoxysilane functions are hydrolyzed in silanol groups (-Si(OH)3) at physiological pH, which can crosslink by condensation through siloxane bonds (Si O Si) resulting in the formation of the gel. In this context, (3 glycidyloxypropyl)trialkoxysilanes are widely employed due to their reactive epoxy function.

We recently published the first comprehensive study of their reactivity in organic media towards common nucleophiles representing the functions found in natural polymers. Thorough investigations of the reactions allowed us to draw clear conclusions about the reactivities of both epoxide and alkoxysilane functions. Furthermore, the nucleophile properties and the method of activations have a great influence on the reaction outcomes, and unexpected results were found in some cases. We also demonstrated the importance of the nature of the alkoxy residues to achieve chemoselective reactions on glycidyl silane derivatives.

POSTER 21

IN SITU PRODUCTION OF A VASCULARIZED BONE GRAFT USING A 3D PRINTED CHAMBER IN RABBITS.

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The reconstruction of large bone defects resulting from severe trauma or resection of tumors remains a challenge for orthopedic and plastic surgeons. Today, a free muscle flap with fibula bone and its vascularized bed is often used but this transplantation technique is very harmful for patients. We propose to produce a vascularized bone graft in situ by using an anatomic chamber made by 3D printing from image scans. The chamber was loaded with calcium phosphate granules and the stromal vascular fraction from autologous adipose tissue and then implanted under the skin of rabbits with a vascular pedicle going through for its pre-vascularization before transplantation. After 8 weeks, this vascularized bone graft was transplanted into a large ulna defect for its regeneration. Micro computed tomography and histology of the contents of the implanted chambers revealed abundant vascularization and fibrosis between the calcium phosphate granules. After 8 weeks, the vascularized bone grafts regenerated the ulna defect while no bone was found in the left empty critical size defect. This study demonstrated the feasibility and efficacy of a pre-vascularized bone transplant for large defect reconstruction in a pre-clinical model.

POSTER 22

PUTTING THE HLA PARADIGM TO THE TEST IN NON-HUMAN PRIMATES.

BIOREGATE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

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Human pluripotent stem cell (hPSC)-based therapy is a promising option for the treatment of neurodegenerative disorders caused by loss of specific cell populations. Clinical trials using foetal cell therapy in Parkinson's and Huntington's diseases have highlighted the risk of rejection of the allogenic grafts showing frequent alloimmunisation to fetal donor antigens resulting, although not systematically, in neuroinflammation and immune rejection. Despite the associated risk, chronic immunosuppression is used to protect allogenic grafts from rejection. Availability of induced PSCs derived from the patient himself or from selected donors harboring some degree of HLA matching open up opportunities to secure scalable sources of cell therapy product with enhanced or full immunological compatibility. We performed a comparative assessment of the immunogenicity of autologous, MHC haplotype-matched and two-haplotypes mismatched neuronal grafts in the excitotoxically-lesioned striatum of non-human primates (NHP). First, blood cells from NHPs, homozygous for MHC Class I & II, were reprogrammed into iPSCs. Next, striatal cell populations were generated tested in QA lesioned nude rats. Finally, we assessed their potential immunogenicity at 3-6 months after intra-striatal grafting in mis-matched, matched and autologous NHP recipients. Preliminaries results indicate that unlike autologous neuronal grafts, allogenic grafts elicit a local infiltration of CD8+ T cells.

POSTER 23

ASSEMBLY OF A MARINE EXOPOLYSACCHARIDE INTO MICROGELS FOR PROTEIN DELIVERY APPLICATIONS.

BIOREGATE FORUM
8 & 9 SEPTEMBER 2016
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Assembly of biopolymers into microgels is an elegant strategy for bioencapsulation with various potential biomedical applications. Such biocompatible and biodegradable microassemblies are developed not only to protect the encapsulated molecule but also to ensure its sustained local delivery. In the present study, an unusual polysaccharide from marine origin, namely HE800 EPS was structured for the first time using microfluidics in functional microcarriers that can be used as protein delivery systems[1, 2]. The significant advantage of the present delivery system is based on peculiar polysaccharide glycosaminoglycan (GAG)-like structure and its biological properties, which can both be explored to create an innovative biomaterial for tissue engineering applications. This high-added value polysaccharide was shown to be able to form microparticles and microfibers, through physical cross-linking with copper ions, using microfluidics[3]. It was shown that the microparticle morphology could be modulated by the polysaccharide concentration and its chain length, and that either homogeneous or heterogeneous structures could be obtained. A model protein, namely Bovine Serum Albumin (BSA) was subsequently encapsulated within HE800 microparticles in one-step process using microfluidics. The protein release was tuned by the microparticle morphology with a lower protein amount released from the most homogeneous structures. Our findings demonstrate the high potential of HE800 EPS based microassemblies as innovative protein microcarriers for further biomedical applications.

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(2) Zykwinska et al., (2016). Assembly of HE800 exopolysaccharide produced by a deep-sea hydrothermal bacterium into microgels for protein delivery applications. Carbohydrate Polymers, 142, 213-221.

(3) Marquis et al. (2015). Microfluidics assisted generation of innovative polysaccharide hydrogel microparticles. Carbohydrate Polymers, 116, 189-199.

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BIOSKETCHES
of the invited speakers

Mr. Bastianelli has several years of experience in working within the pharmaceutical industry in fields as broad as R&D, licensing, corporate development and strategy and sales & marketing.

His career started in the Pathology Department of the Erasme University Hospital in Belgium. He then joined Procter & Gamble Pharmaceuticals in 1996, where he was involved in the marketing of drugs in the field of bone diseases. In 1999, he became a consultant for McKinsey & Co, where he was involved in strategic and organizational missions for major pharmaceutical as well as biotechnology companies all over Europe.

From its creation in 2002 until mid-2006, Mr. Bastianelli worked as VP Corporate Development for ProSkelia, spin-out of Aventis focused on bone diseases and hormone disorders (which then became ProStrakan, after the merger with Strakan, a Scottish pharmaceutical company). As a member of the executive committee, he was responsible for the management of the R&D portfolio, resources allocation and planning, alliances, collaborations and downstream integration. He was one of the main contributors to the merger with Strakan.

Enrico Bastianelli has been the managing director of Bone Therapeutics since 2006.

Mrs Pascale Berthet works at CDI (Cellular Dynamics International a FujiFilm company) as Account Manager for South of Europe. Before moving to CDI commercial team, she worked as Business&Development Manager at several companies including Pall Life Sciences where she gained experience in cell culture technologies and bioproduction. She has a large network of contacts in the European bioproduction and the Advanced Therapies (cell & gene therapies) sectors.

Dr Dominic Bowers is the Head of Clinical Development and Operations at the Cell and Gene Therapy Catapult and is responsible for the operational delivery of clinical programmes and consultancy regarding clinical development planning.

He has nine years' experience within biopharma commercial research advisory and clinical trial delivery and also has expertise within immunotherapy, stem cells, tissue engineered products and gene modified therapies. He has previously governed global registry trials for small molecules and biologics.

Dominic is a graduate from the University of Sheffield and has practiced within the UK and Australia as an anaesthetist, critical care and pain physician.

Dr Denis Dufrane has completed his MD and PhD in cell therapy in 2000 and 2006, respectively, from the University catholique de Louvain. He developed a translational "bench to bedside" model from relevant preclinical animal models to clinical practice. He was, up to 2015, the head of the Tissue and Cell Therapy Center at the university clinical hospital Saint-Luc, Brusseles, Belgium. He is currently the chief scientific officer and the co-founder of Novadip Biosciences. Denis has published more than 48 manuscripts in peer-reviewed journals, presented 38 invited lectures and has more than 120 communications and patents with more than 1300 citations.

Florent Espitalier, MD, PhD (38 yo) is an ENT surgeon since 2008 specialized in the treatment and rehabilitation of cancer of the upper aerodigestive tract at Nantes University Hospital. He takes part in the bone tissue engineering group of the LIOAD, Centre for osteoarticular and dental tissue engineering, INSERM U791, Nantes, France. His field of research is bone regeneration in irradiated area. He has received his doctorate (phD) in 2014. He is currently Associate Professor (MCU-PH) at Nantes University Hospital.

Pr Nicolas Ferry graduated from Paris University where he received a Ph D in 1985 and a M.D. in 1990. He moved to Pasteur Institute for a post-doctoral stay in 1990 where he entered the field of gene therapy.

Nicolas served as a scientist at the french National Institute for health Science (INSERM) for more than 25 years. He focused his interest in liver research. He eventually created his own INSERM lab in Nantes in 2009 dedicated to biotherapy for acquired and inherited liver diseases. Nicolas was also involved in medical consultancy for hemochromatosis, and he contributed to clinical trials of cell based therapy for liver diseases.

Nicolas served as a gene therapy expert for the french regulatory authority from 2000 to 2010. In 2011 he joined the agency as head of the department of vaccines, blood derived products and advanced therapies. He was also appointed Committee for Advanced Therapies (CAT) of the EMA in London from 2011 to 2016.

Nicolas is now senior advisor at the cell therapy department of Saint Louis Hospital in Paris and works as a private consusltant in the field of ATMPs.

Nicolas co-authored more than 100 scientific publications.

Jean-Sebastien Hulot is Professor of Medicine, Pharmacology at Pierre et Marie Curie Paris 6 University, Paris, France. He is a medical cardiologist and received his MD degree at Paris University Hospitals and his PhD degree in clinical and experimental pharmacology at the René Descartes Paris 5 University. From 2010 to 2014, he served as an Associated Professor of Medicine, Cardiology at the Cardiovascular Research Center at Mount Sinai School of Medicine in New York, USA. He was appointed as the Director of Pharmacogenomics and Personalized Therapeutics. Since 2014, he is leading the « Biology and Pharmacology of cardiovascular remodeling » research team at INSERM/Paris6 University (http://www.ican-institute.org/team/biology-and-pharmacology-of-cardio-vascular-remodeling/). Dr. Hulot's team is investigating the potential of human induced pluripotent stem cells & genome editing in the field of cardiovascular pharmacogenomics.

Pr Christian Jorgensen has published extensively, and has a strong track record for competitive research grant from EU and ANR. He has coordinated a program of 2004-2007 FP6 integrated project Genostem : Adult mesenchymal stem cells engineering for connective tissue disorders. He is also principal investigator in the Integrated Project 6th FP-healing: Post-genomic Approaches for inflammatory rheumatic disease, Leading to the development of Improved therapy. Finally, since 2010, he coordinates the FP7 ADIPOA project, focusing on adipose-derived mesenchymal stem cells in osteoarthritis therapy.

Dr Nathalie LABARRIERE

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Nathalie Labarriere, (50), PhD and Inserm research director, is responsible for the Team 3 (Tumor immune responses and Immunotherapy) of the INSERM Cancer Research Center Nantes / Angers (France). She started to work in 1990 on tumor immunology in Nantes (France), and then switched from 1994 to 1995 to upstream biological issues dealing with transcription factors in the De Duve Institute of cellular Pathology (Brussels, Belgium). In 1995, she joined the group of F. Jotereau in Nantes and she developed research programs on translational immunology, with a strong collaboration with clinical teams, especially in the field of melanoma immunotherapy, with Pr. B. Dreno.

Since 2010, she took over the leadership of the team whose work led to several clinical trials of adoptive transfer of tumor specific T lymphocytes in melanoma patients. Nathalie Labarrière has authored 50 scientific papers and 6 patents. She is also responsible for the cytometry facility of the SFR Santé, and is involved in several councils and scientific committees in the field of immunotherapy. She was director of LabEx IGO (Immunograft-Oncology) from 2013 to 2016, and she is now deputy director of this program led now by Dr. Ignacio Anegon (Inserm UMR1064).

Dr Sabine Lange works at CDI (Cellular Dynamics International) as senior field application scientist to support CDI customers in Europe. Before moving to CDI commercial team, she worked as field application scientist at Mesoscale Discovery. Dr. Lange obtained her Ph.D. in Human Biology from the Justus-Liebig University Giessen where she gained experience in culturing and differentiation of mouse and human embryonic stem cells mainly focusing on Cardiomyogenesis and Angiogenesis.

Dr Pierre-Noël LIRSAC: Holding a PhD in biotechnologies, a former student of the top-ranked Ecole Normale Supérieure, Pierre-Noël LIRSAC assumed important responsibilities within the life sciences division of the French Atomic Energy Commission, at the French National Institute for Nuclear Sciences and Technologies, Division of and then in the 2000s, within the French Ministry of Industry in particular. These responsibilities compose a distinguished career in the field of health and biotechnologies. In 2010, he joined the LFB group, leading the company's commitment in the highly innovative field of cell and gene therapies,and llaunchingd CELLforCURE subsidiary of LFB Group dedicated to cell and gene therapies. Pierre-Noël LIRSAC has been President and CEO of CELLforCURE since March 2010.

Alain Maiore is the founder and advisor of Shikubeisho Partners, an advisory and consulting company. Formerly He was the founder and Managing Partner of KLS Partners, a life science venture fund he created in 2009, following an eight years period as head of the biotech investment team at Ventech SA. Prior to his venture investment career, Alain was a successful entrepreneur, joining Evotec AG in 1999, a Hamburg based company, as executive VP corporate and business development. He participated in floating Evotec on the Frankfurt Stock Exchange and negotiated several major strategic alliances including the merger of the business with Oxford Asymmetry. In 1996, Alain became Chief Operating Officer of Cerep SA, which he floated on the Nouveau Marché while also negotiating several strategic partnership agreements. Starting in 1991, Alain was co-founder of Gene Shears pty ltd, a gene therapy start up in Sydney, Australia, which he managed for five years. Alain has served on numerous Boards of biotech companies including as Chairman of Erytech SA (France), Blink therapeutics (UK) and Vice Chairman of Eyegate Pharmaceuticals (USA).

During his thesis on cancer biology, **Dr Marc Meichenin** used to perform some injections of cells into animals to stimulate the immune system and overcome tumor tolerance. He quickly realised, for the safety of the animals and validity of the results, the importance of the detection of the presence of adventitious agents, in particular of mycoplasma. He put all his efforts into this project, and rapidly this work became a reference for other researchers at Inserm. In 2000, he joined his partners to create Clean Cells.

"As scientific director and after more than 15 years in the field of quality control and biomanufacturing, my mission remains to ensure, day by day, that we maintain the high standard of our analyses according to regulatory requirements and state of the Art. I maintain the technical interface with our clients through advising and designing of appropriate protocols, particularly for dealing with the specificity of samples (e.g. gene and cell therapy products). For that purpose, I am involved in different groups or association (LEEM Bioproduction group, ACTIP) and discussions with EMEA and ANSM".

Dr Philippe Menasché is currently cardiac surgeon at the Hôpital Européen Georges Pompidou, Professor of Thoracic and Cardiovascular Surgery at the University of Paris Descartes, and Co-director of an INSERM (National Institute of Health and Medical Research) team devoted to cell therapy of cardiovascular diseases. The group has a long-standing interest in stem cells for the treatment of heart failure and has therefore developed small and large animal (including nonhuman primate) models of myocardial infarction and dilated cardiomyopathy. While the initial research has focused, both experimentally and clinically, on the transplantation of skeletal myoblasts, it has now moved towards the combination of cardiac progenitors derived from human embryonic stem cells (ESC) with a tissue engineering-based construct. The first-in-man implantations of this cell-loaded patch are now underway. In parallel to this phase I clinical trial, the group is increasingly looking at cell biomimetics with the objective of a streamlined clinical translation.

Dr Emmanuelle RIAL-SEBBAG: Lawyer-, Graduate in health law (Faculty Bordeaux), Ph.D in Health Law (European mention, University Paul Sabatier Toulouse). She is a permanent researcher in health law and bioethics. She is the leader of a multidisciplinary team, Health innovations 'trajectories: bioethics challenges and impact in public health, at the Inserm/Paul Sabatier University 1027 Unit in Toulouse (Epidemiology and public health analysis: risks, chronic diseases and handicaps).

She is an Associate lecturer in bio-law and bioethics at the University of Medicine in Toulouse (Purpan). She is involved in several research projects at National, European and International level, on the topics of biobanking, innovative therapies, biomedical research involving human beings and genetic testing. She is responsible for several teaching and educational sessions, especially on the ethical and legal aspects of biomedical research involving human or patients' rights regarding biobanking. She is currently developing a research on the Governance of Research in biotechnology and the role played by regulations at national and European level. She is the coordinator of the EUCelLEX project (FP7 2013-2016, Cell-based regenerative medicine new challenges for EU legislation and governance, GA 601806, https://www.eucellex.eu/). She is leading the Societal part of an "Epigenetic program" developed under the auspices of the French National agency for Research (IBISS, coord. C. Delpierre).

Dr Elhem Sbaa: I am Ph.D. in Biology from the University of Rouen (France). I have 13 years in research on stem cells and 7 years experience in regulatory affairs. I'm currently working as a regulatory affairs manager at Keyrus Biopharma, an international Contract Research Organization where I have been challenged and succeeded on setting up the department of regulatory affairs. Before, I worked for more than two years at GSKBio as a team leader Publication Manager consultant where I performed my knowledge on Health Economics. From 2008 to 2009, I was a regulatory affairs associate and medical writer at SGS Life Science. Earlier, I worked for three years at TiGenix, a biotech company. I was project manager within the R&D department where I characterized and developed the use of stem cells and differentiated cells for cell therapy, project related to cartilage and meniscus repair. Prior to TiGenix, I did my post-doc during 2 years at UCL (Université Catholique de Louvain) focusing on stem cells use for re(neo)-vascularisation.

Aymeric Seron has more than 10 years' experience in medical device for percutaneous therapy (embolization, drug eluting stent, catheters) and in Advanced Therapy Medicinal Product (ATMP).

He hold a PhD in Biomaterials Science where he developed a gelling solution composed of polymers and microparticles targeting therapeutic occlusion of arterio-venous malformation. He has been a consultant for large medical device companies where he provides technical guidance for development of embolization material.

He then changed position as project leader at AlchiMedics (French start up specialized in development of coatings for drug eluting stents).

Aymeric held R&D Manager position at Celyad (formely Cardio3 Biosciences) from 2009 and was promoted as Program Manager and Program Director respectively in 2012 and 2013.

He has overall responsibility of endocardial injection catheter (C-Cathez) and C3BS-CQR-1 (Heart Failure cell based therapy) programs.

Dr Mark Tomishima earned his Ph.D. at Princeton University in 2002. His thesis examined the directional movement of viruses through neurons, work that required extensive primary neuronal culture from animals that restricted the throughput of experimentation. At the time, pluripotent stem cells were emerging as a means to make large amounts of specialized cells in vitro, such as neurons, to model and treat disease.

Tomishima pursued stem cells to reduce this bottleneck through postdoctoral work in Lorenz Studer's group at Memorial Sloan Kettering Cancer Center. His early work in the Studer lab led to novel transgenic methods that aided transplantation and accurate gene profiling of midbrain dopamine neurons made from stem cells, a cell type important for Parkinson's disease. He was also part of an international team that used nuclear transfer to create customized stem cell lines to "cure" individual animals of a Parkinson's disease model.

For the past decade, Tomishima has run the SKI Stem Cell Research Facility that provides a number of services to the stem cell community. One recent service is cell therapy manufacturing: Dr. Tomishima is one of eight PIs in a consortium led by Dr. Studer that aims to bring a pluripotent stem cell-based therapy to Parkinson's patients. This experience has allowed follow-on funding for SKI Stem Cell Research Facility to help other groups interested in translating their research-grade protocol into a clinically compatible cell product.

Dr Alain Vertès is Managing Director at NxR Biotechnologies, a boutique consulting firm based in Basel, Switzerland, where he advises on strategy, business development, and investment.

Dr. Vertès came to this role after extensive experience in the pharmaceutical and industrial biotechnology sectors, in Europe, North America, and Asia in different functions including research, manufacturing, partnering, and sales, in pharmaceuticals (Lilly, Pfizer, Roche), petrochemicals (Mitsubishi Chemical Corporation), public research (Institut Pasteur; RITE/Kyoto), contract research (Battelle Memorial Institute, PPD) and consulting (Australian Strategic Policy Institute). Focusing on innovation commercialization, he was a key player in the evaluation, selection, deal making, implementation, and alliance management of novel products and emerging technologies. For example, he championed radical innovation for bringing to patients disease-modifying, paradigm-changing therapeutics such as siRNA and led in a scientific, strategic, and business manner Roche's global cell therapeutics strategy and implementation team from 2007-2010.

Dr. Vertès received an M.Sc. degree from the University of Illinois at Urbana-Champaign, a PhD from the University of Lille Flandres Artois, and is a Sloan Fellow from London Business School (MBA/M.Sc.).

Dr Franck Zal, co-founder of Hemarina, brings his internationally recognized scientific expertise to the field of the respiratory pigments of invertebrates. He received his Ph.D. degree with honors in oceanography in 1996 from the

University of Paris VI where his doctoral research focused on the structure-function relationships of the annelid extracellular hemoglobin. After his Ph.D. he spent three years abroad as part of his postdoc program, two years at the University

of Santa Barbara in California (UCSB), USA and one year at the University of Antwerp. For his work, he received in 2001 the bronze medal of CNRS. Dr.Franck Zal, is the author of almost 100 publications in international peer reviewed scientific

journals, the author of several patents and he presented his work in numerous international meetings.

BIOREGATE
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BIOSKETCHES
of the organizers

Olivier Boisteau. In course of his studies at the Sorbonne, Olivier integrated Inserm to carry out research as part of his thesis on an anti-colon cancer vaccine. Following this period, he returned to the team of Dr. Yannick Jacques as a Post-Doctoral scientist in a programme to develop agonists-antagonists recombinant proteins of cytokine receptors. This development is part of a European wide programme. Having a strong vision for advancement of the bio therapeutic industry, Olivier, along with Frédéric Henry and Marc Meichenin launched into a previously uncharted adventure, based on knowledge of the eradication of mycoplasma in cell culture. Consequently, the birth of Clean Cells followed on 31 July 2000. Olivier, is also a member of the board of administration of Altanpole Biotherapies, a Biotech committee of LEEM.

"As President and COO, my role is to actively encourage the development of Clean Cells by being part of the strategic decisions made in the Board of Direction, but, also by daily support of our different teams, in all the departments. Each of them are a vital part of the success of our company, and it is together we will reach our objectives."

Dr Anne Camus studied Genetics and Embryology at University Paris XI, followed by a PhD in the group of Charles Babinet, at the Pasteur Institute, Paris, France. In 1997, she performed a postdoctoral training in the group of Patrick Tam at the Children's Medical Research Institute, Sydney, Australia. In 2000, she joined Jérôme Collignon in the Jacques Monod Institute, Paris. In 2001, she was appointed as senior scientist at C.N.R.S. She has a long-standing interest in deciphering basic mechanisms that regulate cell fates during embryogenesis and in stem cells differentiation studies. She has previously worked on germ layers specification at gastrulation and nervous system formation in various animal models. In 2014, she joined the Center of osteoarticular and dental tissue engineering (INSERM UMRS 791) as the «Stem Cells and Axial Skeleton Development» Project Leader at the University of Nantes, France. Her current research focuses on human stem cells tissue engineering for intervertebral disc regenerative medicine and studying the cellular and molecular mechanisms of axial skeleton development.

Dr David received his Ph.D. from University Joseph Fourier, Grenoble, France, in 2007. During his PhD, he discovered that BMP9 and BMP10 are physiological ligands of the receptor ALK1, which stemmed an active field of research in angiogenesis, and led to new therapeutic strategies for HHT, a disease caused by mutations of ALK1.

Dr. David continued to work on TGFbeta/BMP signaling as a postdoc in Jeff Wrana lab, in Toronto, Canada. Rapidly, he started to work on somatic cell reprogramming, and became a stem cell biologist. His work led to a better understanding of the mechanisms of somatic cell reprogramming, such as the characterization of the mesenchymal-to-epithelial transition that initiates the reprogramming of fibroblasts.

In 2013, Dr. David joined the Medical School of University of Nantes as an Associate Professor. His lab is particularly interested in studying the regulation of pluripotency in human pluripotent stem cells and in human embryos. Dr David is the director of Nantes iPSC core facility, embedded in the Bioregate cluster.

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 the dental surgery department and hospital. He is currently 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. His scientific activities are Skeletal tissue engineering, physicochemistry 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 also managed clinical research in Odontology. He is currently the scientific director of the Regenerative medicine cluster named "Bioregate" created in 2015. He is also the president of the society for biohydrogels, the vice dean of the Nantes dental school and in the scientific council of Nantes University.

More than 200 ISI indexed publications, more than 200 communications, 50 invited lectures, 7 patents and Hirsh index: 37, 3500 citations. Researcher ID : P-1372-2014

BIOREGATE
EUROPEAN REGENERATIVE MEDICINE
FORUM

EXHIBITORS

CLEAN CELLS

CLEAN CELLS ACTIVITIES

Clean Cells is a CRO/CMO dedicated to biopharmaceutical products for 15 years, which offers *in vivo*, *in vitro* and custom-made tests required by international regulatory authorities to ensure the safety of biological products at every steps of their production. All of our services comply with Good Laboratories Practices and Good Manufacturing Practices (GLP and GMP).

BIOSAFETY TESTING

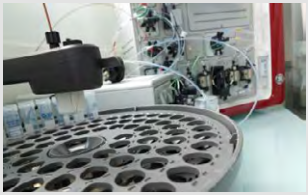
Full GMP CRO testing services with a complete range of regulatory tests in compliance with GLP and cGMP and, with more than 150 qPCR tests available. Regulatory support for EMEA, FDA, ICH and the ability to develop and validate innovative, sensitive, specific and robust tests in accordance with ICH Q2 R1

CELL & VIRUS BANKING

Full GMP manufacturing and storage of cell and virus banks with storage at different sides and with weekly monitoring and traceability of the nitrogen level and continuous temperature monitoring.

VIRAL CLEARANCE

Clean cells performs viral clearance studies required by the regulatory authorities for products in early and late phase development (Phase I/II and Phase III clinical trials): Recombinant proteins, monoclonal antibodies, vaccines and products derived from blood. The laboratories and equipment are strictly dedicated for these studies and available on a slot-booking bases. Our scientific experts solely dedicated to these studies, provide their experience and expertise in choosing the right virus model, the fractions to be collected for the tests and the interpretation of the results obtained at each step.



ASSAY DEVELOPMENT

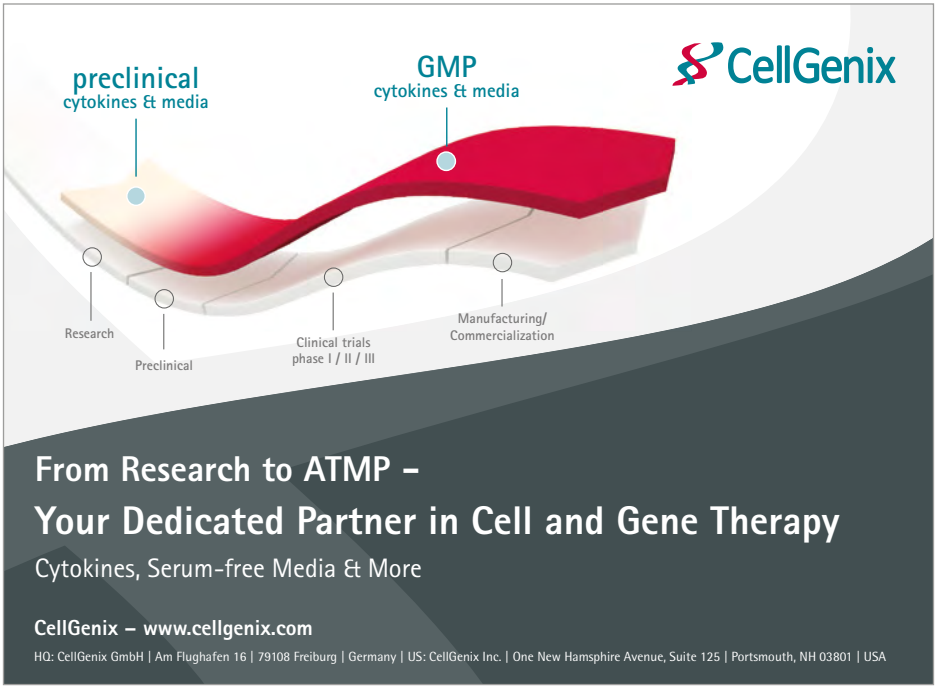
Creation and development of *in vitro* tests to measure the efficacy, safety and characterization of your biological products. These tests are particularly suitable for use in the screening of molecules and the release of clinical batches.

CLEAN CELLS
Rue Marie Curie - Parc d'Activités Vendée Sud Loire 1 - 85600 Boufféré FRANCE
Tel : +33 (0)2 51 09 27 57 - www.clean-cells.com

ASEPTIC TECHNOLOGIES

ATLANTIC BONE SCREEN

CELLGENIX



ELEMENT ORANGE

Element Orange develops, manufactures and supplies enhanced biomaterials for the medical and cosmetic industry. These powders, sponges and gels are based on biopolymers, such as gelatin and hyaluronic acid. With their proprietary technology Element Orange can influence the functionalities of these material (degradation and viscosity e.g.) and make them useful for many more and innovative applications.

Element Orange

Together we create a better future

EUROMI

LONZA

PARTNERS

BIOREGATE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

OUR PARTNERS & SUPPORTERS

OUR MEDIA PARTNER

BIOTECH.INFO 3.0

Biotechinfo 3.0 is a bi monthly digital newsletter at the convergence of technologies in the life sciences. It became a reference in France and even in Europe. Biotechinfo 3.0 tracks the evolution of a sector which value creation is based on innovations. Its objective is to provide strategic intelligence on french and international scientific innovations for professionals in education, research and industry. It is covering a broad spectrum of biotechnologies in health, medtech, cosmetic, agro-alimentary, environnement protection, green chemistry and biofuels : http://www.biotechinfo.fr

ABOUT THE ORGANIZERS

ATLANPOLE biotherapies
Thinking up tomorrow's medicine

Atlanpole Biotherapies is the Western France biocluster. It gathers more than 150 members and co-ordinates the work of laboratories, companies and platforms for a public-private complete, relevant and competitive solution, on the bio-medicine value chain from target discovery to clinical evaluation.

Within the ecosystem of the cluster, 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.

The structuring of this sector is carried out by "BIOREGATE" that brings together all of the cluster's stakeholders in this area.

www.atlanpolebiotherapies.com

BIOREGATE
REGENERATIVE MEDICINE CLUSTER
Research, Education & Innovation in PAYS de la LOIRE

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.

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 investors and its fund raising through Nantes University Foundation has just begun. For more information, please visit this webpage **www.univ-nantes.fr/fonds-medecine-regenerative.**

Contacts: Dr Réjane Bihan, Bioregate Managing Director Bioregate, **rejane.bihan@univ-nantes.fr** & Pr Pierre Weiss, Bioregate Scientific director, **pierre.weiss@univ-nantes.fr**

CLEAN CELLS is a certified Pharmaceutical Company committed to deliver high-level quality services. A GMP as well as GLP certified service provider that is specialized in cell and virus banks manufacturing (MCB, WCB, MVS, WVS), biosafety testing, potency assays, bioprocess validation and development of customized assays and Advanced Therapy Medicine Manufacturing for phase I/II. All our assays are compliant with the current international regulatory guidelines. Our expertise makes CLEAN CELLS a reliable partner to support the Biopharmaceutical Industry.

- Biosafety Testing
- Assay Development
- Advanced Medicine Therapy Manufacturing for phase I/II

http://clean-cells.com/

Hemarina SA is a privately held biotechnology company centered on the research and development of marine oxygen carriers for therapeutic and industrial applications.

Hemarina offers products that constitute a decisive technological breakthrough in regard to current or past developments of hemoglobin-based oxygen carriers (HBOCs). Hemarina's lead product, Hemarina M-101, is the only product under development that uses a natural, high-molecular-weight extracellular hemoglobin whose activity is totally independent of any cofactor. Furthermore, Hemarina M-101 functions in a wide range of temperatures (from 4°C to 37°C). Another major advantage of Hemarina M-101 is that it has no vasoconstrictor effect, which is frequently observed in first-generation HBOCs and responsible for significant side effects, particularly high blood pressure.

Hemarina positions itself as a R&D company focused on oxygen carrier molecules that have therapeutic and industrial applications. Our products have high-value market applications for which there are no true competitors — only potential partners. Therefore our business model revolves around finding win-win partnerships with life sciences or pharmaceutical companies who wish to incorporate Hemarina's technology in their medical devices or drug development process.

http://hemarina.com/

The iPSC core facility of Nantes was created in 2012. Its main activity is to generate hiPSC from patients. We routinely work with labs in Paris, Lyon, Nice, Montpellier, Spain or Germany. We have the IBiSA and Biogenouest French core facilities accreditation. The iPSC core facility of Nantes is part of the Biotherapy core facilities of Nantes, covering fundamental developments to clinical grade phase III cellular and viral batches.

UNIVERSITÉ DE NANTES

As the major pole of higher education and research in Western France, the University of Nantes is the number one multidisciplinary French university: 38 000 students in the initial part of their higher education and 8 500 in continuous higher education, 1 286 doctoral students including 246 theses defended in 2015-2016. Degrees, based upon the LMD European model (Licence, master, doctorate), are proposed in all areas of knowledge: letters, languages and communication, humanities, law and political sciences, economic and managerial sciences, sciences, health and technologies.

Research is a major growth sector for University of Nantes. As an innovative force, the University also has research agreements with industry and shares its discoveries with the society at large. This new knowledge is supported by more than 3,200 permanent and contract research staff (teachers, researchers, scientists, administrative and technical staff, PhD students) working in 76 laboratories and research structures including partnered with public organisms as CNRS, Inserm, Inra and Inria.

USEFUL INFORMATION

BIOREGATE FORUM
8 & 9 SEPTEMBER 2016
Nantes, France

MEETING VENUE

Nantes - Saint-Nazaire Chamber of Commerce - Centre des Salorges
16 quai Ernest Renaud - 44105 Nantes

HOW TO GET THERE?

Chamber of Commerce is located alongside the Loire River, approximatively 15 minutes walk from the city center. You can easily get there:

By plane: take the Shuttle Bus to Nantes City Center (Commerce) then take Tramway line 1 and stop at "Gare Maritime" station.

By train: at Nantes railway station, take the north exit and then Tramway line 1 and stop at "Gare Maritime" station.

By Tram: Line 1- "Gare Maritime" station.

By Taxi: Oh Taxi Nantes : +33 (0)2 28 00 00 82 or Allo Taxis : +33 (0)2 40 69 22 22

GALA DINNER

Have a nice networking dinner on the Nantilus boat! Facing the Nefs and the Caroussel des Mondes Marins, you will appreciate this outstanding place with its unique view on the Loire River and the city center. And maybe you will have the chance to see the Elephant of Nantes.

Location:

Parc des chantiers - Pont 3 du Nantilus
30, Quai Fernand Crouan
44200 Nantes

HOW TO GET THERE FROM THE CONFERENCE CENTER:

Agence Nantes-Saint Nazaire développement

www.salonsdunantilus.com

USEFUL PHONE NUMBERS AND ADDRESSES

Medical help/SAMU: 15

Police: 17

Fire & accident: 18

SOS - all services (recommended when calling from a mobile) 112

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BIOREGATE
EUROPEAN REGENERATIVE MEDICINE
FORUM

WELCOME BACK !

Next edition of Bioregate Forum in 2018

WWW.BIOREGATE-FORUM.COM