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Université Paris Cité

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Bioconvergence pour la Santé
Domaine de Recherche et d'Innovation Majeur

Région îledeFrance

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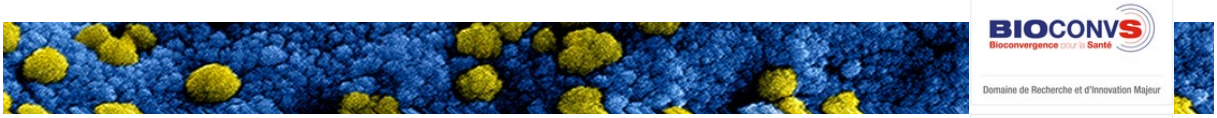
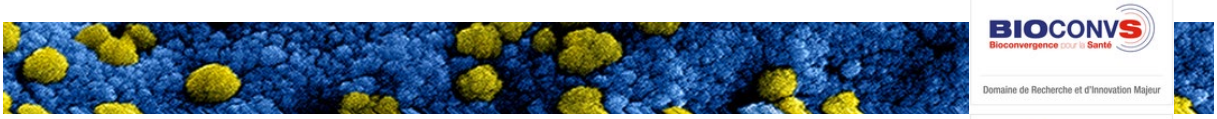
Poster session





A – Empowering Scientific Collaborations with the Consortium's Community Platform Projects

Iryna Nikolayeva (1), Eric Cherel (1)

1 - Learning Planet Institute (8bis rue Charles V 75004 Paris France)

In an era of rapidly advancing scientific endeavors, effective collaboration lies at the heart of breakthrough discoveries and innovation. This poster presents a transformative community platform designed for members of our consortium, offering a dynamic suite of tools to enhance connectivity and knowledge exchange.

The Consortium Community Platform facilitates seamless interaction within our consortium, empowering researchers to effortlessly discover and connect with fellow colleagues and labs, projects and infrastructure. With a user-friendly interface, members can search for specific expertise and research interests, gaining access to comprehensive profiles and contact information.

B – Lubritect - Bringing science to the bedroom

Louis Elverston (1), Laure Mourgue D'Algue (1)

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Sexually transmitted infections (STIs) are a serious public health issue worldwide with an alarming incidence (1M new infections/day), prevalence (80% of sexually active individuals acquire human HPV by 45) and disease burden (82,000 deaths/year from hepatitis B). Our iGEM team aimed at solutions by understanding the needs and constraints for a sustainable solution from all stakeholders (public health, NGOs, patients). Lubritect leverages the power of naturally occurring lubricant, mucin, and the generative power of AI, to inform a product that is safe, effective and easy to handle. We combine a mucin-based hydrogel, shown to reduce transmission rates of HIV and HSV, with AI-generated protein structures designed through RFdiffusion, to bind to surface proteins and catch target pathogens. This approach potentially circumvents the evolution of pathogenic escape mechanisms by using protein structures not found in nature, ultimately generating a personal lubricant product which can entrap pathogens, significantly reducing their transmissibility.

C – Clean Heat: the solution combining heating and water depollution

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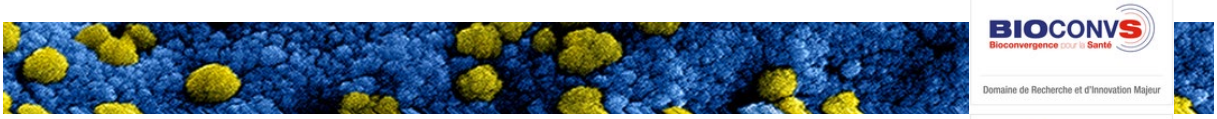

Heating is not only becoming increasingly expensive but also the main source of CO2 emissions in buildings. Clean Heat, created by the iGEM Ionis-Paris team, offers a system that recovers wastewater from buildings as a culture medium, using synthetic biology. Heat is generated through the genetic modification of the microalgae Chlamydomonas reinhardtii with the sraox gene. The latter is responsible for the thermogenic properties of Symplocarpus foetidus, which can produce a temperature difference of 35 °C.

Furthermore, alpha-ethinylestradiol (EE2) is an omnipresent endocrine disruptor in water resources that threatens human health and biodiversity. In the Clean Heat system, the bacterium Sinorhizobium meliloti is genetically modified using the amoA and hao genes to enable the bioremediation of EE2 molecules. Due to its ability to produce vitamin B12, this strain is known to increase the heat resistance of C. reinhardtii. Through this co-culture, Clean Heat aims to develop a more sustainable and affordable solution, hosted in a photobioreactor, to generate heat while purifying water.

D – OptoGenEYEsis, an iGEM Evry-Paris-Saclay project to restore vision

Sainte-Rose Georges (1) (2)

1 - iGEM team Paris Saclay, 2 - SynBioDrop

The retina, a specialized tissue at the back of the eye, houses photoreceptor cells, each containing opsins molecules that respond to light, a crucial element in vision. The loss of these cells leads to the depletion of opsins, resulting in blindness. Our mission is to find a solution to this challenge. We, the iGEM Evry Paris Saclay team, are excited to introduce OptoGenEYEsis, a groundbreaking tool designed to address this issue. OptoGenEYEsis sets itself apart by focusing on the development of light-sensitive microbial opsins for genetic therapy. Our ultimate goal is to restore the retina's capacity to detect and respond to light, thereby restoring vision. This approach contrasts with existing microbial opsin-based therapies, which suffer from narrow absorption spectra, suboptimal sensitivity, and limited efficiency in converting light into nervous electrical signals.Our solution harnesses the power of enhanced microbial opsins through synthetic biology and microfluidics-based directed evolution. This innovative approach promises superior absorption, heightened sensitivity, and efficient conversion of light into electricity during visual processing. It's not just a potential solution; it's a game-changer in the battle against blindness. We are also developing an AI driven digital microfluidic lab automation apparatus, to serve our en goal in fast variants screening.

01 – Critical contribution of mitochondria in the development of cardiomyopathy linked to desmin mutation

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Beyond the observed alterations in cellular structure and mitochondria, the cellular mechanisms linking genetic mutations to the development of heart failure in patients affected by desmin defects remain unclear due, in part, to the lack of relevant human cardiomyocyte models. We investigated the role of mitochondria using cardiomyocytes derived from human induced pluripotent stem cells carrying the heterozygous DESE439K desmin mutation, that were either isolated from a patient or generated by gene editing. To increase physiological relevance, cells were either cultured on an anisotropic surface to obtain elongated and aligned cardiomyocytes, or as spheroids to create a microtissue. When applicable, results were confirmed with heart biopsies from the family harboring DESE439K mutation. We show that mutant cardiomyocytes reproduce critical defects in mitochondrial architecture, respiratory capacity and metabolic activity as observed in patient's heart tissue. To challenge the pathological mechanism, normal mitochondria were transferred inside the mutant cardiomyocytes. This treatment restored mitochondrial and contractile functions. This work demonstrates the crucial role of mitochondrial abnormalities in the pathophysiology of desmin-related cardiomyopathy, and opens-up new potential therapeutic perspectives.

02 – Functional understanding of the role played by mucus-associated microbiota in health and disease

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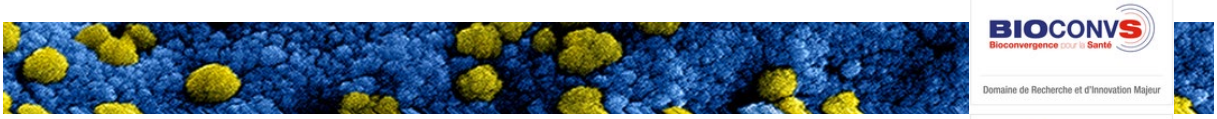
The gastrointestinal tract is normally protected from its microbiota via various adaptive and innate immune mechanisms, including a multilayered mucus structure that covers its surface and keeps the vast majority of intestinal bacteria at a safe distance from the intestinal epithelium. We and others have previously reported that dietary emulsifiers €“ detergent-like molecules highly used by the food industry €“ can disrupt mucus-microbiota interaction and promote mucus invasion and encroachment by select microbiota members, suspected to play a central role in the downstream intestinal inflammation and metabolic dysregulations observed in mice consuming dietary emulsifiers. In this study, we hypothesize that mucosal bacteria that invade the normally sterile mucus layer have the potential to directly drive chronic intestinal inflammation and downstream metabolic dysfunction. We observe that mucosal microbiota transplanted from mice consuming dietary emulsifiers into germfree mice is sufficient to induce chronic low-grade intestinal inflammation and severe metabolic dysregulations when fed a high fat diet regimen.



Altogether, these data suggest that mucosal microbiota plays a central role in regulating host metabolism. These findings also suggest that innovative strategies aiming to modulate the mucosal microbiota could be therapeutic approaches to treat and/or prevent various chronic inflammatory diseases.

03 – Gene Therapy for Heart Failure with Type 3A Phosphodiesterase

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The production of cyclic adenosine monophosphate (cAMP) following stimulation of beta-adrenergic receptors (beta-AR) by catecholamines allows for an adaptive increase in cardiac function during stress or physical exertion. Essential to this regulatory mechanism are phosphodiesterases (PDEs), pivotal enzymes responsible not only for cAMP degradation but also for confining this second messenger within specific subcellular compartments. Among these enzymes, the PDE3A isoform is classically considered the primary cardiac PDE in large mammals and humans, responsible for degrading cAMP. In heart failure (HF), characterized by inadequate pump function, chronic elevation of catecholamines, and decreased expression of PDE3A contribute to disease progression. Our research, utilizing cutting-edge approaches such as AAV-9-mediated gene therapy encoding for PDE3A in rat models of HF, focuses on testing whether increased or restored cardiac PDE3A activity can mitigate maladaptive hypertrophy and associated arrhythmias accompanying HF. Furthermore, we will explore the translational potential by assessing PDE3A overexpression in cardiomyocytes isolated from non-failing and failing patients or derived from human induced-pluripotent stem cells. This project aims to define the precise role of specific PDE3A in controlling signaling pathways, shedding light on these enzymes as potential therapeutic targets for treating HF.

04 – Immortalized cell line for megakaryocytes and platelets production

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Blood products from donors are used to treat a variety of diseases and conditions that cause cytopenia. However, the blood transfusion system needs to be strengthened because

the number of blood donors is decreasing. Platelets play a key role not only in hemostasis and thrombosis, but also in tissue regeneration after injury and in the pathophysiology of inflammation.

We propose CD34-derived cell lines that have been genetically modified to retain the proliferative capacity associated with their progenitor-like state. We developed a protocol to generate megakaryocytes in vitro, they have a large polyploid nucleus with cytoplasmic protrusions indicative of proplatelet activit and they carry glycophorin membrane markers CD41a, CD42a, CD42b (ie antigens classically found on the surface of megakaryocytes). Upon shear stress, we obtained mature platelets and the ability to be activated by induction of thrombin. For further functional evaluation, the cells were injected into sublethally irradiated NSG mice and the presence of human platelets in the circulation was demonstrated by cytometry. In addition to a new cell therapies oriented approach, we provide a model of robust megakaryotic differentiation to deepen our understanding of this complex process. Through further gene editing, we will be able to mimic platelet-associated malignancies.

05 – Role of Dact3 in the intestinal homeostasis: Elucidating the mechanisms of Action of the anti-inflammatory Commensal bacterium Faecalibacterium duncaniae A2-165

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The commensal bacterial strain Faecalibacterium duncaniae A2-165 (former species Faecalibacterium prausnitzii) plays a key role in the pathogenesis of inflammatory bowel disease (IBD) and represents a biomarker of general health. However, the host molecular mechanisms responsible for these anti-inflammatory effects remain poorly studied. In order to determine the impact of F. duncaniae on intestinal epithelial cells (IECs) such as HT-29 (tumoral cells), we performed a transcriptomic approach on these cells, stimulated with TNF-alpha and exposed to F. duncaniae culture supernatant (SN). Our results showed that this SN up-regulates the expression of Dact3, a gene linked to the Wnt/JNK pathway, which is part of the inflammatory process. The up-regulation of Dact3 was also validated in normal human IECs such as HIEC-6 cell line. Interestingly, the knockout of Dact3 gene by CRISPR-Cas9 results in a significant loss of the anti-inflammatory effect of F. duncaniae SN. In addition, we were able to determine that butyrate, one of the major metabolites produced by F. duncaniae, is the effector for Dact3 modulation. Finally, we demonstrated that gut microbiota directly influences Dact3 expression. These exciting results provide new clues about the host molecular mechanisms involved in the anti-inflammatory effects of F. duncaniae.

06 – Specific DMPK-promoter targeting by CRISPRi reverses myotonic dystrophy type 1-associated defects in patient muscle cells

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Introduction: Myotonic dystrophy type 1 (DM1) originates from an amplification of CTG microsatellites in the DMPK gene. The pathology is primarily explained by a toxic gain of function where the expanded-CUG DMPK transcripts induce the loss of function of the MBNL proteins, triggering a wide spliceopathy. Several therapies have been tested to neutralize the toxic DMPK transcripts or their consequences. Here, we investigated a new therapeutic strategy consisting of the silencing of the DMPK promoter by a CRISPRi system in patient-derived myotubes. Results: The efficacy and specificity of our therapeutic strategy were then assessed in differentiated myotubes. Our DMPK promoter inhibition strategy is highly efficient to reduce toxic DMPK transcript quantities up to 80%. This level of inhibition leads to correct the DM1 hallmark defects by reducing the presence of foci, improving the spliceopathy and normalizing an electrophysiological parameter in DM1 myotubes. Furthermore, this approach displays unprecedented high specificity as evidenced by a complete lack of off-target effects on the transcriptome from unaffected myotubes. Conclusions: We conclude that DMPK promoter inhibition is a promising strategy to be developed for DM1 treatment.

07 – The therapeutic potential of targeting immune checkpoints in IPF

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Idiopathic pulmonary fibrosis (IPF) is a lethal interstitial lung disease with a high mortality rate. The mechanisms behind the pathophysiology of IPF development remain poorly understood. However, recent developments in fundamental and translational studies demonstrate that immune cells play a significant regulatory role in IPF. Immune players generate multiple growth factors and mediators that greatly affect the initiation and progression of IPF. Immune checkpoints are known for their capacity to regulate the

intensity of immune responses. Our project aims to study the implications of these receptors in IPF. Based on a transcriptomic approach, we did identify the most relevant receptors in lung immune cells from IPF patients. Flow cytometry analyses are used to compare the expression of the identified receptors between IPF patients and healthy donors in a stratification approach. Ex-vivo experiments are also implemented to understand how the inhibition or overexpression of these receptors can impact the profibrotic activity of immune cells. In parallel, several models of transgenic mice are currently generated to investigate the implication of the identified receptors in the development of pulmonary fibrosis. Overall, this project might have the potential to uncover novel immune mechanisms leading to new diagnostic and therapeutic tools against a fatal disease.

08 – Towards the structural characterization of MAM (Microbial Anti-inflammatory Molecule) from Faecalibacterium

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The genus Faecalibacterium, a predominant constituent of the intestinal microbiota, playing a crucial role in gut health and protection. Its anti-inflammatory attributes come from various factors, including metabolite production and active peptides within the unique protein, MAM (Microbial Anti-inflammatory Molecule). While the anti-inflammatory properties of MAM have been established through in vivo and in vitro studies, its precise function within Faecalibacterium remains unknown. This study seeks to elucidate MAM's role by characterizing this protein across different Faecalibacterium species. Employing AlphaFold, we predicted MAM's structure, revealing flexible regions denoted by disorder regions. Furthermore, molecular docking experiments indicated a strong interaction between MAM's N-terminus and the peptidase domain of the ABC transporter, suggesting that MAM can be cleaved and exported through this transporter. Subcellular localization studies using LC/MSMS proteomic analysis unveiled MAM's abundance, predominantly within the membrane. Our findings highlight MAM's prevalence in the Faecalibacterium genus, indicating a possible role in the membrane, and bringing new findings about this unique protein with huge biotechnological potential.

09 – Neuropathological features of Gaucher disease in Microglia-containing Cerebral organoids.

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Gaucher disease is a sphingolipidosis resulting from mutations in the GBA1 gene. It leads to a defect in the beta-glucocerebrosidase enzyme, which is involved in the lipid catabolism. Macrophages are mainly affected but a proportion of patients also develop progressive encephalopathy (nGD) associated with neuronal damage or death. Unfortunately, we do not know enough about the mechanisms involved, and enzyme replacement therapy has not been able to prevent nGD. Our objective is to develop an in vitro model of nGD and to study the neuronal, astrocytic and microglial components. In order to understand the physiological aspects in humans, we used iPSCs from healthy and nGD individuals to produce and characterised microglia-containing cerebral organoids. The cellular and structural development of the organoids was not affected in nGD organoids but we observed clear cytological abnormalities. Some cells showed fibrillar/tubular structures that resemble lipids aggregates. Defects in organelle integrity point to a defective autophagy. We also observed the presence of reactive astrocytes. The question now is how these identified mechanisms are involved in neuronal lesions and are only consequences of GBA1 mutations. We are now pursuing our study by establishing isogenic controls and comparing our results with transcriptomic and quantitative molecular biology studies.

10 – Quantifying emergence of gene expression and metabolic landscapes in microbial colonies and tumors using microfluidics and spatial transcriptomics

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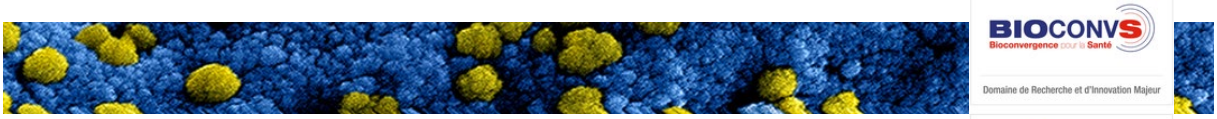
As technology advances, there is an increased need for precise quantification of genetic and metabolic processes that govern complex self-organized environments like microbial colonies, microbiomes, and the tumor microenvironment. Microbial colonies are fascinating structures in which growth and internal organization reflect complex morphogenetic processes, while the tumor microenvironment is even more complex as many types of cells, including microbes, interact to result in many different phenotypes that can have serious effect on anti-cancer therapy. We generated a microfluidics device with arrays of long monolayer yeast colonies to further global understanding of how intercellular metabolic interactions affect the internal structure of colonies within defined boundary



conditions. We also fabricated and used the metabolic microenvironment chamber (MEMIC) €“ a 3D-printed ex vivo model of intratumoral heterogeneity. The MEMIC simulates differential access to nutrients, allows co-culturing any number of cell types, and it is optimized for live imaging and other microscopy-based analyses. Finally, we are developing a method which couples microfluidics with spatial transcriptomics with the goal of understanding and predicting regulatory networks that govern microbial colonies and the tumor microenvironment. These approaches will be used both in the context of the native tumor microbiome as well as bacteria engineered to kill cancer.

11 – Bone marrow niche on chip to study vascular aberration upon leukemia

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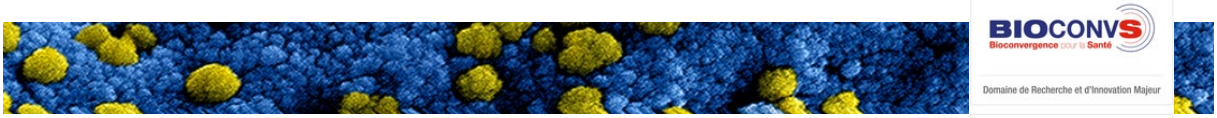
The bone marrow (BM) is vital for adult hematopoiesis and is implicated in blood cancer development. However, the complex nature of the local environment, comprising both hard (bone) and soft (marrow) matrixes, poses challenges in bioengineering effective humanized experimental models. We have developed a novel vascularized BM-on-chip (vBM-on-chip) that recapitulates the native vascular architecture within a BM-like matrix. This platform allows to investigate the remodeling of the BM niche in the context of leukemia. Our vBM-on-chip contains two matrices with varying stiffness and a perfusable reproducible capillary-sized vascular system. This unique setup enables us to examine BM vascular aberrations in acute myeloid leukemia (AML). We first validated the model's support for human healthy hematopoiesis, establishing its suitability. We are currently in the process of assessing vascular parameters like flow, permeability, junctions, and architecture in healthy and AML conditions. We plan to further analyse with spatial OMICs endothelial transcriptomic profiles and their association with vascular changes, identifying potential therapeutic targets. Promising candidates will undergo pre-clinical validation using primary AML patient samples in combination with standard chemotherapy in our vBM-on-chip. These findings will pave the way for translational applications in the development of potential treatments.

12 – Characterizing the epigenetic response to AAV9-SMN1 gene therapy for SMA.

Arnould Alice (1), Grandi Fiorella (1), Smeriglio Piera (1)



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Gene therapies based on adeno-associated virus (AAV) hold great promise for treating rare diseases, including Spinal Muscular Atrophy (SMA), a severe neuromuscular disorder. A recent breakthrough involved AAV9-mediated gene therapy, which gained approval for SMA treatment by introducing a healthy SMN1 gene copy, mutated in SMA patients. However, significant challenges persist. Effective therapy with AAV9-SMN1 needs mimicking the native SMN1 gene regulation, which is lost in SMA and requires long-term, physiologically reliable SMN1 expression. Gene expression, influenced by epigenetic changes like DNA methylation and chromatin regulation, plays a crucial role in achieving this goal. The proposed research aims to understand the epigenetic response to systemic SMN1 therapy, providing insights for enhancing other gene therapies. During my PhD project, I will: i) profile the epigenetic changes in a mouse model of SMA pre- and post- gene therapy, ii) evaluate the epigenetic regulation of AAV9 after injection and overtime, iii) test if the newly identified regulatory regions can achieve a more physiological gene expression level after gene therapy. By comprehensively examining the epigenetic dynamics associated with SMA and gene therapy, this work aims to contribute to the development of more effective and long-lasting treatments for SMA and other rare diseases.

13 – CRISPR-based regulation circuits for host-considerate protein bioproduction

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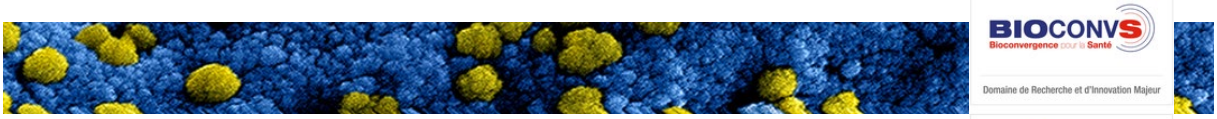
Bioproduction is a key area in the era of the fourth industrial revolution. Resources normally used by host cells for growth are diverted towards the production of desired molecules. Achieving maximal resource diversion without compromising the essential functions of the host is of critical importance but is also particularly challenging. Host-aware circuit design strategies are needed. The secretion of heterologous proteins in yeast perfectly illustrates this need. Making yeast produce and secrete heterologous proteins is generally burdensome to cells because the capacities of the secretory pathway are often exceeded. Using cybergenetics approaches, we have previously identified a sweet spot for bioproduction: the induction level should match the maximal secretion capacities of the cells, which is protein specific. Our current project aims at engineering a self-tuning regulation system that maintains cells in their sweet spots. More precisely, we are building a CRISPR-based negative feedback regulation circuit that decreases the cell responsiveness to the external demand when stress is excessive. I will present data obtained on the characterization of individual parts of the feedback regulation circuit. Using our automated bioreactor platform, we are able to generate precise data that we will combine with modeling approaches to assemble the negative feedback regulation circuit.



14 – Ex vivo biomimetic intestinal model for developmental studies

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Intestinal epithelium (IE) constitutes a single-layer epithelium that organizes into highly regular tridimensional (3D) crypt and villus structures, where cells of varied functions are found at distinct areas and undergo rapid proliferation, differentiation, coordinated cell migration, and extrusion. These spatiotemporal organization and dynamics preserve the intestinal stem cell niche and enable constant tissue replenishment. Recent research has revealed that the villus-crypt architecture and environmental factors play critical roles in IE homeostasis and mechanisms in physiological and pathological conditions. However, current planar petri-dish-based and organoid culture systems lack the control of different environmental parameters. Combining micro-engineering techniques and cell biology, we address such a disadvantage by developing hydrogel scaffolds that represent similar 3D crypt-villus architecture of intestinal epithelia. These scaffolds are further functionalized with proteins and integrated into microfluidic or Transwell set-ups for mimicking in vivo biochemical gradients. We present that primary intestinal stem cells from organoid culture can grow on our 2D and 3D scaffolds and replicate key features of the small intestine. Our novel approach to an ex vivo intestinal model can serve as a versatile platform for broad bio-mimicking applications of IE and is adaptable to model other tissues.

15 – Extracellular vesicles secreted by Plasmodium falciparum-infected erythrocytes cause significant alterations in erythroid differentiation

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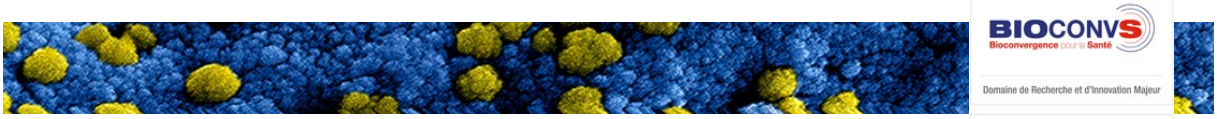
Extracellular vesicles (EVs) are small membrane-bound vesicles secreted by various cell types and play an important role in biological functions. In malaria patients, an increase in EVs correlates with the severity of the disease. Recently, our work showed that EVs secreted by P. falciparum-infected erythrocytes (iEVs) impact erythropoiesis by inducing a delay of enucleation. This delay could be associated with inefficient erythropoiesis and dyserythropoiesis reported in malaria patients, and thereby could partly contribute to anemia. Here, our aim is to characterize the impact of iEVs during erythropoiesis and to identify the molecular pathways affected in the erythroblasts. Viability, proliferation, morphology, hemoglobinization and differentiation markers were monitored, at different stages of erythropoiesis, highlighted a delay throughout differentiation and an induction of apoptosis in immature erythroblasts incubated with iEVs. Proteomic analysis of



erythroblasts in the presence or absence of iEVs revealed differences in the expression of several proteins known to play a major role in erythropoiesis, apoptosis or cell cycle, suggesting that several mechanisms are involved in this delay. These results provide insight into the molecular mechanisms of the deregulation of erythropoiesis by Plasmodium, which could partially explain malaria anemia and lead to a better long-term disease management.

16 – Future biotherapies for tissue repair

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Cell therapy with mesenchymal stromal cells (MSC) has aroused real enthusiasm since they exert an immunomodulatory activity and promote repair of damaged tissues via various mechanisms. The most important is the release of bioactive molecules secreted in a soluble form or encapsulated within extracellular vesicles (EVs). In the Armed Biomedical Research Institute (IRBA), our team has been working for years on MSC as medicinal products and on their secreted products in tissue repair (for burn treatment) or the prevention of organ failure (in hemorrhagic shock). The Armed Forces Blood Transfusion Center (CTSA) has an Advanced Therapy Medicinal Products facility and a great expertise in the production of clinical grade MSC. The combination of these skills, leads us now to translate EVs from research to the clinic. We first worked on a culture medium additive (EV-depleted human platelet lysate) that can safely be used in a GMP process (patent EP19305142). We also optimized purification and concentration methods by tangential flow filtration. The products are evaluated with different potency assays, including the one currently used for clinical MSC batches. Finally, we are optimizing product's conservation using combinations of cryoprotectants and/or stabilizing molecules, and we work on the fill and finish process.

17 – Growth and study of tumor spheroids behavior in a biomimetic vascularized platform

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Cancer still asks for more accurate models for drug development. Monolayer cultures fail to recapitulate the complex tumor microenvironment (TME). Notably, they do not incorporate a vascular compartment, which plays a pivotal role in cancer development and drug testing. Conversely, in vivo models exhibit limited tunability and present escalating

financial and ethical implications. Therefore, three-dimensional biomimetic systems emerge as promising candidates for mimicking the pathophysiological complexity of a tumor by integrating biochemical and mechanical cues as well as enabling coculture in highly tunable matrices. Besides, it holds the possibility to add liquid microenvironments to integrate the vascular or lymphatic system. Herein, we have developed a polysaccharide-based platform, composed of two compartments: first, a microwells network of tunable architecture where we form cancer spheroids. It has been validated by testing two drugs on various cancer cell lines, giving a 2 to 10-fold increase in resistance for spheroids versus monolayers for most conditions. Then, microchannels layered by endothelial cells are matured to form tubular constructs. This vascularized gel will be combined and incubated with the spheroids network. Overall the goal is to provide an innovative co-culture platform in a biomimetic substrate in order to investigate interplays between spheroids and a vascularized TME.

18 – Iron bioengineering of extracellular vesicles

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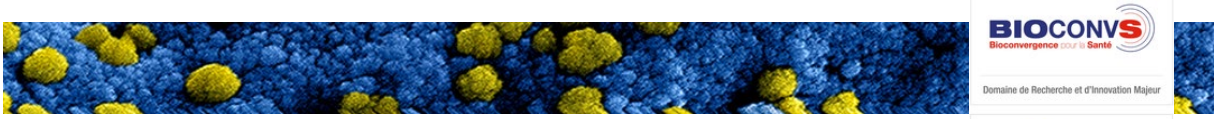
Extracellular vesicles (EVs) are cell-produced biological vectors crucial for intercellular communication and hold promises for improved drug delivery. Herein, we assess the possibility to load murine mesenchymal stem cells (mMSC) -derived EVs with iron (Fe). The goal is twofold: to explore Fe intra and extra-cellular transport, and to Fe-engineer EVs as further options for EVs-mediated iron-based therapies. EV production, induced through turbulent flow stimulation of mMSC attached to 200-µm beads, employed two loading strategies, either with iron salts or iron oxide nanoparticles incubation. For salts, cells underwent varied pre-seeding incubation protocols. Regarding nanoparticles, pre-seeding incubation for late endosome/lysosome localization, and post-seeding incubation for early endosome localization, were employed. EV secretion was achieved for 4 hours upon high-speed stirring and EVs were purified through size exclusion chromatography. Quantitative analysis using nanotracking analysis and inductively coupled plasma determined the EV production yield and the iron load per EVs. Cryo-transmission electron microscopy and western blot assessed their integrity and biological content. Overall, we demonstrated a successful Fe transfer from mMSC to EVs for Fe stored in intracellular ferritins, but not in endosomes. These results provide information on Fe intra and extra-cellular transport, shaping the potential of Fe-engineered EVs for future therapeutic applications.



19 – Is mechanical constraint of single muscle cells promoting differentiation?

Van Der Spek Lorijn(1), Delivry Léa (2), Rancillac Armelle (3), Maire Pascal (2), Sotiropoulos Athanassia (2), Hénon Sylvie (1), Reffay Myriam (1)

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Understanding the interplay between electrical coupling, mechanical stimuli and transcription factors in the context of muscle cell differentiation is a challenge for mechanobiology and muscle tissue engineering. We aim to determine the correlation between mechanical and geometrical constraints and spatially resolved differentiation, focusing on single cell scale. I will present my research done on myoblast cells (C2C12) on square and rectangular adhesive micropatterns. Myoblast cells are specifically interesting as their shape changes from round to elongated in vivo during differentiation. While it has been shown that transcription factor expression of C2C12 depends on their shape, it remains unknown whether this results in a different differentiation fate. Therefore, the aim of our research is to correlate geometrical constraints with differentiation in 2D. The degree of differentiation can be measured along different types of markers, like expression of various transcription factors, proliferation rate, and myoblast membrane potential to shed light both on proteomics and on function. We focus on early differentiation (timespan of 3-18 hours). Even at such short time scales, our results point towards an important impact of geometric constraints on membrane potential and proliferation. I will also present our first results on mRNA expression.

20 – Mechanisms of T-cell acute lymphoblastic leukemia brain metastasis in a new humanized model of human vascularized brain organoids

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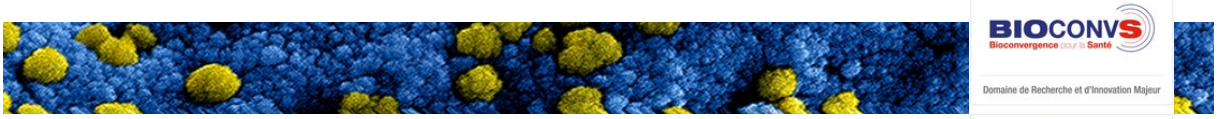
BACKGROUND: Central nervous system (CNS) involvement in T-cell acute lymphoblastic leukemia (T-ALL) indicates poor prognosis. Current models lack human-specific characteristics. We've developed human vascularized brain organoids (BO) and bone marrow organoids (BMO) xenografted in mice to study T-ALL's spread from BMO to BO. METHODS: BOs, derived from iPSCs, were vascularized using Matrigel containing



endothelial cells (E4ORF1) derived from HUVECs. Brain-specific endothelial cell markers were analyzed using confocal microscopy. Leukemic-BMOs were created using E4ORF1, bone-marrow stromal cells, and T-ALL patient cells in gelatin-scaffolds. After in vitro culture, BO and leukemic-BMO were grafted into NSG mice. T-ALL cell presence in BO was monitored via blood tests. RESULTS: By day 20, human vessels appeared, stabilizing over weeks and developing BBB characteristics in the neural environment. After 70 days in vitro, xenografted BOs remained stable in vivo, with their vessels connecting to mouse vasculature. Red blood cells circulated within BO, proving mouse bloodstream perfusion. Six weeks post-co-xenograft, T-ALL cells were found in BO, confirming hematogenous dissemination toward it. Effects of T-ALL on the BBB in BO are under characterization. CONCLUSION: Our model offers a novel approach to study leukemia's spread in the CNS. This method has potential applications in cancer, inflammation, and infection research.

21 – Optimization of umbilical cord mesenchymal stromal cell-derived evs production conditions using evs-free fetal bovine serum and vegetal peptone

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Mesenchymal stromal cells (MSCs) has been identified in the 60s and since then, well studied especially in the field of cellular therapy. MSCs are able to communicate with their microenvironment through both juxtracrine and paracrine pathways. Studies show that beneficial effects may mainly be due to the secretome and mostly the extracellular vesicles (EVs) cells derived. This opens the door to a new approach which can be named: acellular therapy. MSCs- derived EVs are classically obtained either in a chemically defined media or in a starved condition. Hence, we focus on the determination of better EVs production conditions compatible with therapeutic applications. Our approach is to work both on the media composition and on the culture platform. We first produce EVs-depleted fetal bovine serum (FBS) through tangential flow filtration. We combine this EVs-free FBS with the use of wheat peptone as coating while cultivating the MSCs. Our method led us to recover an increased EVs amount compared to more classical methods. EVs produced with our method exhibit better efficiency on two functional assays: a migration assay and a wound healing assay. Our technique may be useful for upscaling EVs production process which is a mandatory step for therapeutic EVs production.

22 – Pre-industrial production of lentiviral vectors. An exemple with a vector for CD28/4.1BB CD123 CAR T cells

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1 – ART-TG, US35, Inserm, Corbeil-Essonnes, France, 2 – UMR1098 RIGHT, . UMR1098 RIGHT, Université Franche Comté, EFS B/FC, CHRU de Besançon, France, 3 - . FC Innov', Bionovéo , Besançon, France

The Technological Research Accelerator in Genomic Therapy (ART-TG) is a public R&D innovation center that was established to promote excellence in gene therapy research. ART-TG is located within the Genopole campus, south of Paris, France. Our mission is to advance novel cell and gene therapy concepts towards clinical trials by bridging a gap between researchers/clinicians and industries. In this poster we illustrate one exemple of acceleration of translational research with manufacturing process development. Here, our aim was to support the development of CAR123 T cells that could efficiently and safely treat blastic plasmacytoid dendritic cell neoplasm (BPDCN) (Bôle-Richard et al. Leukemia, 2020). We have optimized the cassette of a self-inactivated HIV-1 derived VSV-G-pseudotyped LV for clinical use and produced the vector in pre-industrial conditions at medium scale (8L) using a GMP-compatible process. The purified CAR123 LV is stable and infectious for T cells, generating functional CAR123 T cells. Results support the feasibility of industrial manufacturing and warrant further development of the vector and of the protocol towards a clinical trial. ART-TG also develops LV specific analytics for this vector for quality control of the infused product and for monitoring patients in the trial.

23 – RNA-based synthetic organelles in bacteria

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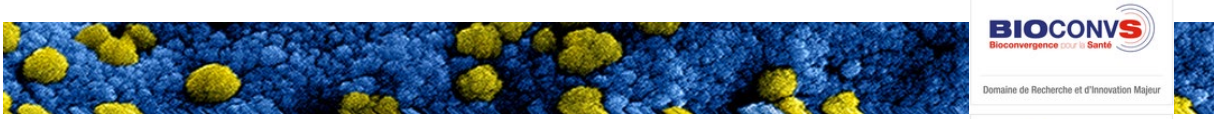
Intracellular compartmentalization is crucial for efficient biochemical processes in cells. The general lack of organelles in bacteria hinders their biotechnological applications. Compartmentalization through Liquid-Liquid Phase Separation (LLPS), based on proteins, DNA, or RNA interactions, is used to address this limitation. Our research focuses on RNA-based LLPS systems in bacteria with the development of Transcriptionally Engineered Addressable RNA Solvent (TEARS) droplets composed of repetitive CAG triple ribonucleotides. TEARS droplets form through the interaction of RNA repeats that can recruit multiple solutes via an RNA-aptamer binding adaptor protein, creating an isolated environment within the cell. Our main objective is to diversify the system by implementing orthogonal aptamers and their binding proteins and expanding the library of repetitive RNA triplet sequences, other than CAG, that can also confer phase separation in bacteria. Our results show proper condensate formation driven by diverse candidate triple repeat sequences with different phenotypes, suggesting potential biotechnological applications, including metabolic engineering.



24 – Using bioprinting to develop a clinical-grade cardiac patch

Guesdon Rose (1), Guillemot Fabien (2), Menasché Philippe (3)

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Heart failure (HF) following myocardial infarction still requires the development of novel therapeutic strategies. One of them is cell therapy which likely works by paracrine mechanisms, largely mediated by extracellular vesicles (EV). We hypothesized that for surgical deliveries, using a carrier could protect the cells/EV and allows a longer release time. The aim is to compare the therapeutic effect of mesenchymal stromal cells (MSC) derived from iPSC (iMSC) or human muscle (mdMSC) to their EV and their incorporation into a bioprinted biomaterial. The MSC and their EV have been compared by different potency tests to assess their pro-angiogenic and anti-apoptotic properties. A bioprinted patch of collagen has been characterized. iMSC have a significant beneficial anti-apoptotic effect unlike mdMSC. However, mdMSC have a dose-dependent significant positive effect on angiogenesis. Rheology assays showed that the biomaterial has an elastic solid behavior that allows it to be manipulated and placed on the myocardium. Compared to MSC and EV, mdMSC yielded the best performances in the evaluation tests and will be printed on the collagen patch.

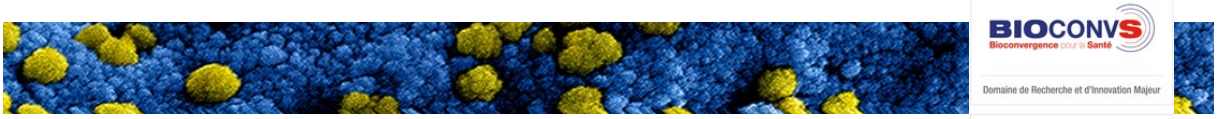
The next step will involve bioprinting the cells into the gel and testing its therapeutic potential in vivo using a rat model of ischemia/reperfusion.

25 – Variation of adhesion force in Drosophila species

Courtier-Orgogozo Virginie (1), Monier Manon (1), Borne Flora (1), Graner Francois (1), Lorenzi Jean-Noel (1), Mevel Louis (1)

1 - Courtier Team - Institut Jacques Monod (15 rue Helene Brion 75013 Paris France)

Bioadhesives display remarkable physico-chemical properties that have adapted to various subtrates and conditions across millions of years. The glue produced by Drosophila larvae to attach themselves for several days during metamorphosis constitutes a promising model for adhesion. This glue is mainly composed of 7 Salivary gland secretion (Sgs) proteins and Eig71Ee protein. We designed adhesion tests and measured adhesion of more than 20 species of Drosophila. Our work reveals differences in glue amount and also in glue adhesiveness between species. Ou work paves the way for a better understanding of the genetic basis of glue adhesion and for future industrial applications.



26 – Interferometry light microscopy for quality control of isolated mitochondria for biotherapy

Ribes Christopher (1), Aubertin Kelly (1), Berger Marie (2), Ayollo Dmitry (1), Florence Gazeau (1), Silva-Brun Amanda (1), Mozafari Sabah (1)

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Mitochondrial dysfunction is associated with various degenerative, inflammatory, and metabolic disorders. Mitochondrial transplantation has emerged as a promising biotherapeutic approach, inspired by intercellular mitochondrial transfer mechanisms. However, the rapid and accurate measurement of isolated mitochondrial size and count remains challenging. Here, we investigated an interferometry-based method using Videodrop to determine mitochondrial concentration and size. Human mesenchymal stromal cells (hMSCs) were used to isolate mitochondria, and their viability, structure, quality, and size were analyzed using fluorescence microscopy, transmission electron microscopy (TEM), Western blotting and protein concentration measurements. Videodrop measurements were compared to these techniques whenever applicable. We found that Videodrop measurements correlated with mitochondrial protein concentration and TEM analyses for count and size, respectively. Our data demonstrate the potential of Videodrop for rapid and reliable characterization of freshly isolated mitochondria. This technology has promising applications in clinical settings, facilitating mitochondrial research and translation into therapeutic interventions.

27 – A tri-dimensional multi-cellular model to study the crosstalk between adipocytes and adjacent cells in different pathophysiological context

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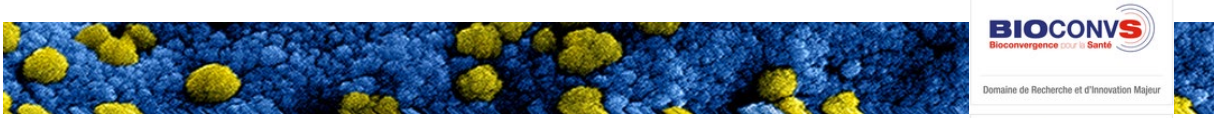
Adipose tissue (AT) is a complex tissue with metabolic, endocrine and immune functions. It is made up adipocytes, vascular cells and immune cells that contribute to its homeostasis. It is a sanctuary for certain persistent pathogens such as HIV-1. AT play a crucial role during the course of obesity and cancer. Finally, AT is the target of contamination by lipophilic molecules that can disrupt its functioning. Relevant in vitro models are needed to study the function of AT and to develop new therapeutic solutions. To this end, we have developed a 3D co-culture system made of adipospheres and T lymphocytes, to study their interplay in the context of HIV and obesity. Our aim is to understand the persistence of HIV in the AT, and measure the response to therapeutic molecules. In particular, we assessed



the secretion of biomarkers to characterize the molecular dialogue between adipocytes and T cells. Here we present an approach to assess the impact of adipocytes on the effectiveness of latency reversing agents, using the J-LAT reporter T cell model. We believe that our 3D co-culture model is sufficiently versatile to simulate other pathophysiological situations in which adipocytes play a decisive role (tumours and metabolic disease).

28 – PandaPure: Synthetic organelles enable protein purification with minimal operations

Guo Haotian (1)

1 - Ailurus Bio (Student Enterprise Hub, Appleton Tower 11 Crichton Street, Edinburgh, UK EH8 9LE Royaume-Uni)

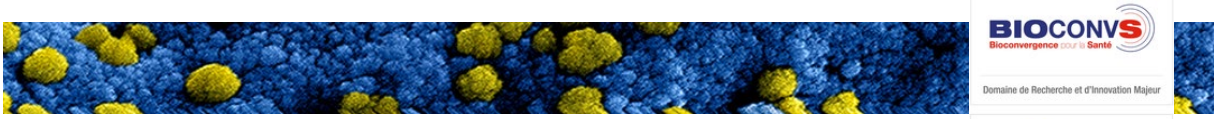
Purification of recombinant protein is a cornerstone in life science, supporting fundamental research and industrial applications. However, even the simplest 'one-step' purification involves a series of intricate and time-consuming steps. Furthermore, existing methods predominantly rely on chromatography over solid supports, and thereby are limited by their scalability and sustainability. Here we report a biological approach utilizing liquid-phase synthetic organelles to purify proteins at high yields and purity, termed PandaPure. PandaPure shortens the procedure to the minimum, including only two operations. We demonstrate its versatility for a range of proteins and applications, from high-throughput screening to large-scale protein production.

29 – Scalable Microbial Metabolite Discovery

Faussurier Baptiste (1), Libis Vincent (1)

1 - INSERM U1284 (8bis rue Charles V, 75004, Paris France)

Antimicrobial resistance is a major public health threat for human and animal health worldwide. Yet, the antibiotic discovery pipeline is drying. Very few novel antibiotics are currently in clinical trials. Hence, there is an urge to discover novel antibiotics. Antibiotics and other Natural Products are produced by specific biosynthetic pathways named Biosynthetic Gene Clusters (BGC) encoded in bacterial genomes. Genomic analysis revealed that bacterial genomes contain a large reservoir of unknown BGCs. However, accessing this reservoir remains challenging. Traditional strategies relying on the capture of single BGCs and transfer to an heterologous host remain expensive and time consuming. There is an urge to speed-up the capture and expression of BGCs by parallelizing multiple steps in the antibiotic discovery pipeline. Here we report a novel antibiotic discovery platform that holds promises to fasten the antibiotic discovery pipeline by mining and expressing BGC at scale from soil actinobacteria. Several steps of this platform could be implemented and scaled in the framework of a biofoundry. After a first cycle of our platform applied on a



novel strain collection, 38 complete clusters have been transferred to an efficient heterologous expression host and assessed for novel metabolites production using LC/MS.

30 – Galaxy-SynBioCAD

Hérisson Joan (1) (2)

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Here we introduce the Galaxy-SynBioCAD portal, a toolshed for synthetic biology, metabolic engineering, and industrial biotechnology. The tools and workflows currently shared on the portal enables one to build libraries of strains producing desired chemical targets covering an end-to-end metabolic pathway design and engineering process from the selection of strains and targets, the design of DNA parts to be assembled, to the generation of scripts driving liquid handlers for plasmid assembly and strain transformations. Standard formats like SBML and SBOL are used throughout to enforce the compatibility of the tools. In a study carried out at four different sites, we illustrate the link between pathway design and engineering with the building of a library of E. coli lycopene-producing strains. We also benchmark our workflows on literature and expert validated pathways. Overall, we find an 83% success rate in retrieving the validated pathways among the top 10 pathways generated by the workflows.

31 – Evaluation of information processing capacity of bacterial metabolism through regression problem solving

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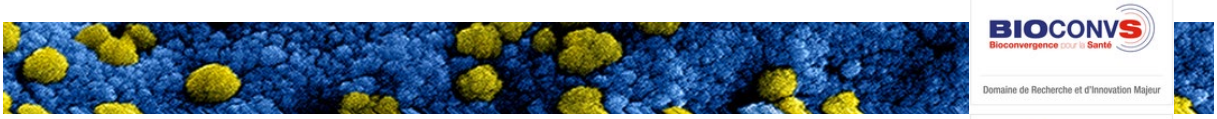
Throughout evolution, bacteria have acquired the ability to sense variations of the concentrations of nutrients in their growth medium. According to the medium composition, they adapt their metabolic behaviour by activating or repressing the appropriate metabolic pathways through a wide array of regulation mechanisms including transcriptional, translational or post-translational responses. Bacterial metabolism can therefore be compared to an algorithm taking as inputs the media composition and yielding as outputs metabolic fluxes describing its metabolic phenotype. Our work focuses on this perspective of the bacterial metabolism as an information processing unit. Our objective is to



demonstrate that E. coli's metabolism is capable of neural-like computation and to assess to what extend it can solve classical machine-learning problems (whether regression or classification). Our first step has been to generate an accurate model of E. coli's metabolism, using the AMN (Artificial Metabolic Network), a metabolic hybrid model previously developed in our lab. This model has then been used to solve machinelearning problems of different complexities in order to assess the capacity of our metabolic model.

32 – Printed Electronics for health and biomedical devices

Randriamahazaka Hyacinthe (1)

1 - Université Paris Cité (ITODYS UMR 7086 €“ UNIVERSITE DE PARIS CITE 15 rue Jean-Antoine de Baïf €“ Paris 75013 France)

PRINTUP Institute aims to structure an industrial sector for Printed Electronics for Health by creating the first network of R&D expertise in the field, based on the scientific skills (sensors, biosensors, flexible energy storage) of the ITODYS laboratory and the health laboratories of Université Paris Cité. The aim of this network is to initiate research collaborations and generate technological innovations that will then be transferred to the sector's industrialists. PRINT'UP is based on the multidisciplinary scientific expertise that characterises the Université Paris Cité. PRINT'UP, which is aimed at a myriad of industrial players, of all sizes, with complementary skills. This network between the academic and industrial worlds, innovative on the scale of the Ile-de-France region and nationally and even internationally, has the ambition to become a real engine for economic growth in the region.

33 – CellFromSpace: A versatile tool for spatial transcriptomic data analysis through reference-free deconvolution and guided cell type/activity annotation

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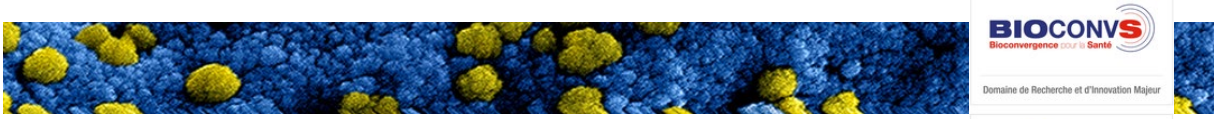
Spatial transcriptomics involves profiling millions of cells within their spatial context to interrogate tissue organization and cellular crosstalk. However, these new approaches present some analytical challenges, like signal deconvolution or cell segmentation. We present a novel analytical framework and tool called CellsFromSpace (CFS) allowing users to process outputs of commercially available technologies without single-cell reference datasets. With independent component analysis, CFS automatically decomposes spatial transcriptomic data into independent components (ICs) representing distinct cell types or activities. CFS includes a user-friendly graphical interface enabling anyone to perform a



complete sample processing and IC annotation. Signal interpretation through the annotation of latent space ICs allows users to isolate cell-specific signal, despite the mixed nature of the signal, resulting in direct signal deconvolution. Downstream spatial subsetting and reanalysis using ICs of choice then allows for the isolation of specific cell populations within complex tissues and the study of proximity or interactions between populations. Additionally, the CFS workflow supports integrated analysis of multiple samples and allows for noise or artifact reduction in data by IC selection. We also demonstrate the efficiency of CFS to identify spatially confined as well as diffuse cell populations on datasets from the Visium, Slide-seq, MERSCOPE, and CosMX technologies.

34 – IROC, the personnal agent of the researcher

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Considering, the huge amount of publications per search on databases, the excess of unnecessary data and the lack of disruptivity, leading to spend a lot of time on sorting & searching data, overwork to keep being updated and the risk of missing a relevant paper, we have developped a AI tools bringing efficiency in the daily tasks of researchers/clinicians, including literature review.

IROC is a personal agent for the researcher/clinician, it will automate the literature review thanks to AI.

This way, the user will be able to sort, compare, analyse and summarize all the literature, from any scientific field, they may found in their usual database(s). There is also a personalized recommendation system based on their profile, able to find interesting & relevant publications through wide and various databases selected by the user.

The data the user is using are securized on Health Data Hosting servers, and you have precise information, sourced in scientific databases and you keep having the control on your data, unlike other tools.

Thus we allow the researcher/clinician to optimize their research and gain 25% of their time, helping them to optimize their research, increasing their efficiency, visibility and well-being.

35 – Dorsal root ganglia cultured on a soft thermoplastic elastomer neurofluidic chip: proof of concept of an alternative to PDMS material

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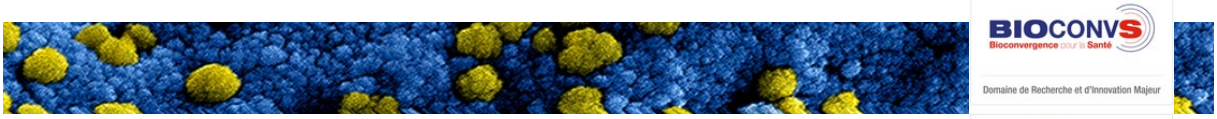

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Microfluidic contributes to augment in vitro neurobiological models. They allow a compartmentalized screened on well-controlled neural networks, are commercially available and keep diversifying in terms of network design and cell types involved. These devices are exploited to reproduce neuronal networks and to study the myelination process of the peripheral and the central nervous systems.[1] Most of the neurofluidic chips are made of polydimethylsiloxane (PDMS), yet it presents limitation in terms of manufacturing, industrial translation and biological modeling itself. Easy to prototype and to translate, soft thermoplastic elastomers (sTPE) have emerged as an alternative material for on chip biology with a potential for cell biology to explore.[2]

Here, we develop the first sTPE compartmentalized device and compare it to a standard, PDMS, for growing of embryonic Dorsal Root Ganglia (DRG) explants. We emboss a FDA approved copolymer of polystyrene and ethylene/butylene. We exploit its bulk properties for fast prototyping (less than 10 min/chip) and reversible adhesive bonding. It allows easy assembly of two-level architectures and direct analysis using atomic force or scanning electron microscopy. We demonstrate its capacities on DRG cultures from mouse embryos in a well suited axisymmetrical design compatible with high content screening microscopy. We cultured dissociated and DRG explants for more than 1 month in our devices with controlled convection, diffusion and evaporation. We compartmentalized soma from the axons in ≤ 5 days. The chips can be re-used up to five times without impacting the viability of the cells after a simple wash and sterilization procedure. The sTPE neurofluidic chip paves the way to an alternative way of modeling complex neural systems on chip, widening its field of applications and making its manufacturing more accessible and sustainable.