Development
Adaptation
Ageing

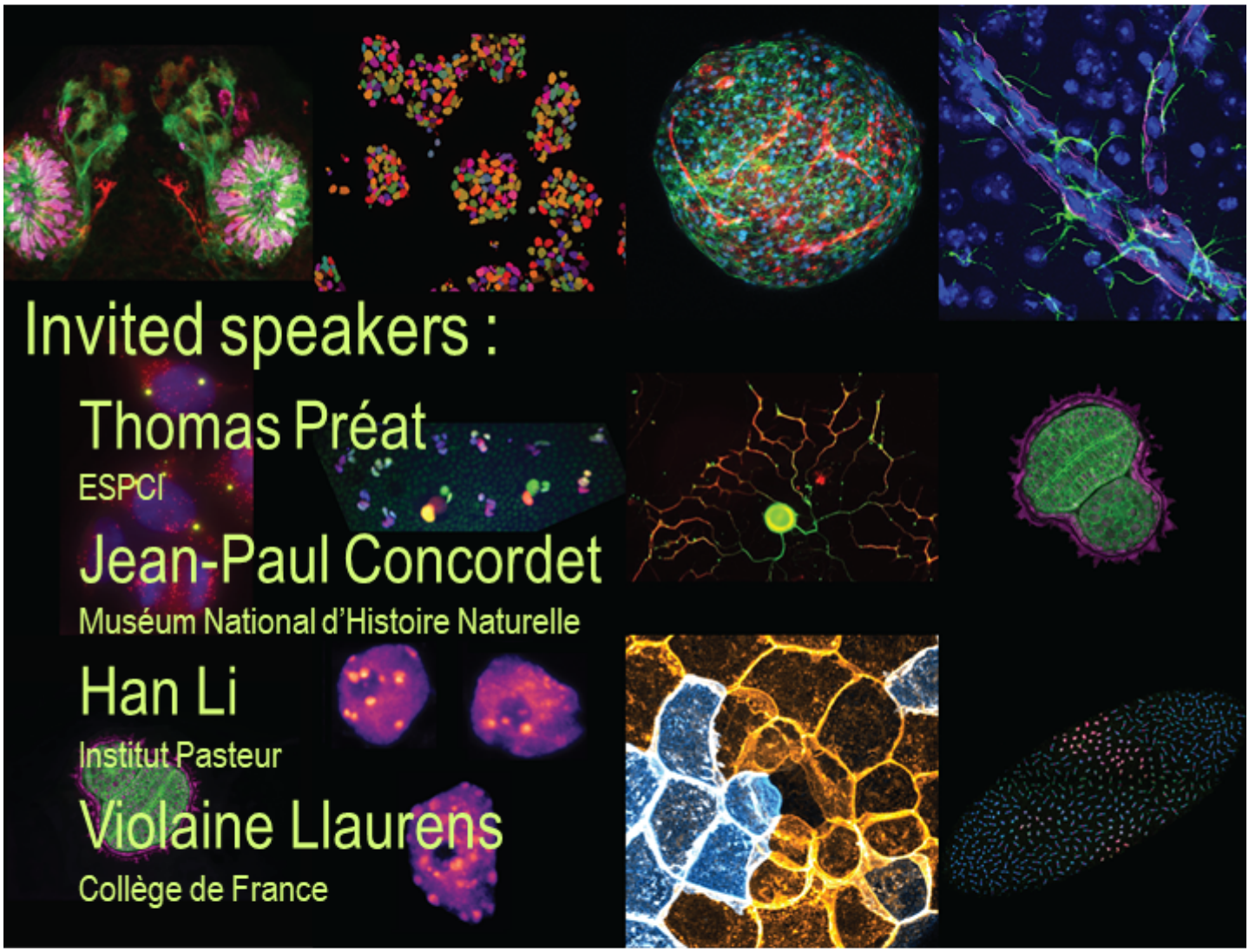
DeV2A

Annual Scientific Symposium

May 7th, 2026

Life in a changing environment

ADAPTATION & DEVELOPMENT | ADAPTATION & AGING | MECHANISMS OF ADAPTATION



Invited speakers :

Thomas Préat
ESPCI

Jean-Paul Concordet
Muséum National d'Histoire Naturelle

Han Li
Institut Pasteur

Violaine Llaurens
Collège de France

TALKS AND POSTERS SELECTED FROM ABSTRACTS

INSTITUT DE BIOLOGIE PARIS SEINE | SCIENCES SORBONNE UNIVERSITÉ | cnrs CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE | Inserm

4 Place Jussieu, 75005, PARIS | Campus Pierre et Marie Curie | Amphithéâtre 25

Dev2A Annual Scientific Symposium

« Life in a changing environment »

Organizer: Laboratory of Development, Adaptation and Ageing (Dev2A)

Date: 7 May 2026
Location: Sorbonne Université, campus Pierre et Marie Curie, amphi 25

9h20-9h30 – **Introduction**
Dominique Weil, Dev2A unit director

9h30-11h00 - **Session 1: Adaptation and Development** **Chair: Clément Carré**
9h30-10h00 – Invited talk
Jean-Paul Concordet, MNHN, Paris
Tardigrades, unique models of resistance to extreme environmental conditions

10h00-11h00
Talk 1 **Wenjin Xiao**, Dev2A, IBPS, Paris
From Development to Disease: Organ-on-a-Chip Models Uncover Mechanical Regulation of Liver Biology
Talk 2 **Aline Stedman**, Dev2A, IBPS, Paris
Primary cilia in neural development and adaptation to the cellular environment
Talk 3 **Lydie Naulé**, Dev2A, IBPS, Paris
Puberty, a critical period for the neuroendocrine organization of reproductive function

11h00-11h30 - Coffee break

11h30-13h00 - **Session 2: Adaptation and Ageing** **Chair: Charahzade El Amri**
11h30-12h00 – Invited talk
Han Li, Institut pasteur, Paris
A double-edged sword: cellular senescence in mammary gland development and breast cancer

12h00-13h00
Talk 1 **Onnik Agbulut,** Dev2A, IBPS, Paris
Combating cardiac fibrosis: fibroblast activation protein targeted engineered T cells
Talk 2 **Maria Victoria Gomez Roldan,** Dev2A, IBPS, Paris
Investigation of ROS molecular markers for the study of oxidative signaling during seed germination
Talk 3 **Aurore L'honoré,** Dev2A, IBPS, Paris
Targeting senescence cell surfaceome for selective senolysis: design and functional evaluation of a new senolytic compound in the context of muscle regeneration during ageing.

13h00-15h00 – **Lunch and poster session**

15h00-16h30 - **Session 3: Mechanism of adaptation** **Chair: Fredy Barneche**
15h00-15h30 – Invited talk
Violaine Llaurens, Collège de France, Paris
Evolution of colour perception in the genus Morpho: from ecology to molecular mechanisms

15h30-16h30
Talk 1 **Jean-Michel Gibert,** Dev2A, IBPS, Paris
Bristle patterning is modulated by environmental changes in Drosophila: mechanisms and impact on cryptic genetic variation
Talk 2 **Jonathan Fouchard,** Dev2A, IBPS, Paris
Memory response of suspended microtissue to mechanical perturbation: role of collagen and cell-ECM networks
Talk 3 **Adham Safieddine ,** Dev2A, IBPS, Paris
Investigating the specificity of RNA localization in P-bodies

16h30-17h30 – **Keynote speaker** **Chair: Rachel Sherrard**
Thomas Préat, ESPCI, Paris
Astrocyte-to-neuron H2O2 signaling provides a new framework for investigating the origin of Alzheimer's disease
17h30-18h30 - **Drinks**

Oral communications

From Development to Disease: Organ-on-a-Chip Models Uncover Mechanical Regulation of Liver Biology

Brenda Nieto-Rivera[1], Brouna Safi[2,1], Dulanji Galappaththi[1], Dominique Baran[1], Audrey Saquet[1], Rafaele Attia[1], Valérie Bello[1], Mathieu Hautefeuille[1], and Wenjin Xiao*[1]

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[2]Centre de Recherche des Cordeliers, Inserm U1138 – Sorbonne Université, Institut National de la Santé et de la Recherche Médicale - INSERM – France

Abstract

The liver is a highly vascularized and mechanosensitive organ in which development, homeostasis, and disease progression are tightly regulated by dynamic mechanical cues. Blood flow–induced shear stress, matrix stiffness, and pressure gradients are critical regulators of cellular differentiation, function, and regeneration. Dysregulation of these mechanical signals is closely associated with liver pathologies such as fibrosis and cancer. However, mechanistic links between mechanical signaling and liver development remain poorly defined, largely due to the lack of physiologically relevant *in vitro* models that recapitulate physiologic mechanics. Microfluidic organ-on-a-chip (OoC) technologies provide a powerful platform to recapitulate the dynamic mechanical microenvironment of organs. By integrating controlled fluid flow, tunable extracellular matrix (ECM) properties, and multicellular architectures, these systems enable precise investigation of how mechanical forces coordinate cellular behavior across developmental and pathological contexts. Here, we present a suite of vascularized liver-on-a-chip models designed to dissect the role of mechanical cues such as flow in development, regeneration, and disease of the liver. (i) A liver sinusoid microvessel-on-a-chip model is employed to study how physicochemical signals guide the differentiation of liver sinusoidal endothelial cells from human induced pluripotent stem cells (iPSCs), addressing key questions in liver development. (ii) A perfusable vascularized liver-on-a-chip platform to investigate how physiological flow conditions act as early drivers of liver regeneration. (iii) A vascularized hepatocellular carcinoma-on-a-chip model reproduces the aberrant mechanical microenvironment of diseased tissue to study tumor angiogenesis, progression, and therapeutic response. Together, these platforms establish a mechanobiology-centered framework to understand how physical forces govern liver function across development and adaptation, and provide advanced tools for disease modeling and translational applications.

*Speaker

Primary cilia in neural development and adaptation to the cellular environment

Antonia Wiegering* , Ludovica Brunetti , Isabelle Anselme , Martin Catala , Sylvie Schneider-Maunoury[1,2], Christine Vesque , and Aline Stedman*

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[2]Dev2A unit, Sorbonne Université, Paris – Centre national de la recherche scientifique - CNRS (France), Sorbonne Université, IBPS, CNRS UMR 8263, Development, Adaptation and Aging (Dev2A), 75005 Paris, France – France

Abstract

The primary cilium is an antenna-like microtubular structure that receives, transduces and integrates multiple physical and chemical signals. As such, the primary cilium acts as a signalling hub for the cell to sense and adapt to changes in its environment. In the central nervous system (CNS), cilia are widely distributed, yet their dysfunction in humans leads to region-specific defects in neurodevelopmental "ciliopathies". This raises the question of how cilia diversity modulates cell fate and behavior, eventually impacting neural development and homeostasis.
In the lab we used mouse and zebrafish models as well as pluripotent stem cell (PSC)-derived organoid approaches to study the diversity of cilia content and function during CNS development. Doing so, we identified essential, region-specific functions of cilia and ciliary proteins in CNS development. We also showed that different organisms responded very differently to the loss of a same ciliary protein, thus emphasizing the importance of studying the developmental causes of ciliopathies in a human cellular context.

By generating spinal and cerebellar organoids derived from human induced PSCs, we uncovered progenitor type-specificity of cilia stability and function in the CNS. Depending on the progenitor type and differentiation stage, cilia responded differently to perturbations of the ciliary transition zone, a region at the base of the cilium involved in controlling ciliary content. We showed that cilia response adapted to the changing signaling environment of the neural progenitors. We also identified new functions of cilia and potential new pathways downstream of cilia in neural development.
Our results have important insight on the understanding of the role of primary cilia in the progenitor cell's adaption to its continuously changing environment during normal and pathological CNS development.

*Speaker

Puberty, a critical period for the neuroendocrine organization of reproductive function

Lydie Naulé*[1]

[1]Sorbonne Université, CNRS UMR8263, INSERM U1345, IBPS- Dev2A, Team Neuroplasticity of Reproductive Behaviors, Paris, France – Dev2A – France

Abstract

In mammals, fertility depends on the precise regulation of reproductive function throughout life. This includes the control of the gonadotropic axis and reproductive behaviors. The neural circuits controlling these neuroendocrine and behavioral functions are organized by sex steroid hormones during development. While the perinatal period has been extensively studied in males, the pubertal period has recently been suggested as a critical window and remains largely understudied. Puberty represents a critical transition from childhood to adulthood, enabling the attainment of sexual maturity. Defects in the regulation of pubertal onset can lead to reproductive disorders and infertility. This study aims to identify the neural mechanisms that regulate reproductive function during puberty in mice. To this end, we first identified sex-specific pubertal windows of neural plasticity in key hypothalamic regions controlling reproductive behavior. We examined the expression levels of sex steroid hormone receptors, and several markers of structural plasticity, glial activity, and mitochondrial function in the two integrative centers of sexual behavior, the preoptic area and the ventromedial hypothalamus, from early postnatal development to adulthood (postnatal days (PND)10 to 60) in male and female mice. The analyses revealed two distinct sex-specific pubertal windows around PND30-35 in males and PND40-45 in females. Second, neuronal activity of glutamatergic neurons assessed by calcium imaging has been performed in these hypothalamic areas. We are currently investigating the involvement of the estrogen receptor α expressed in glutamatergic neurons in the organization of sexual behavior during these critical pubertal windows. This work is ongoing using transgenic mouse models, chemogenetic, neuroendocrine, neuroanatomical, molecular, metabolic and behavioral approaches. The obtained data will allow progressing in the understanding of major neural modifications in key brain areas involved in the regulation of male and female reproduction. This could ultimately lead to the development of sex- and age-specific therapeutic strategies for fertility disorders.

*Speaker

Combating cardiac fibrosis: fibroblast activation protein targeted engineered T cells

Onnik Agbulut*[1]

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Abstract

Fibrosis is a hallmark of the aging in several tissues, characterized by the progressive and excessive accumulation of extracellular matrix components. While it initially occurs as a physiological reparative response to tissue injury, its uncontrolled development makes it a pathological entity which represents the final feature shared by several age-related diseases associated with chronic inflammation. Drugs targeting pathological fibrosis are constantly being developed, and most of them demonstrate promising anti-fibrotic effects in clinical trials. However, their side effects often lead to treatment discontinuation. Recently, engineered T cells targeting fibrosis-associated proteins have emerged as a novel therapeutic approach, offering the potential to selectively target and eliminate fibrogenic cells.
Engineered T cells "Chimeric Antigen Receptor (CAR)-T" therapy has revolutionized the treatment of hematological malignancies through its ability to recognize and kill targeted cancer cells, leading to several clinically approved products to date, with durable complete remissions in large patient populations. These successful outcomes have prompted numerous research teams to explore the potential of this therapy beyond hematological applications, particularly solid cancers, autoimmune diseases and fibrosis. In this context, we assessed the effects of targerting cardiac fibrosis by CAR-T cells directed against Fibroblast Activation Protein (FAP), a protein strongly expressed by activated fibroblasts. *In vitro* anti-FAP CAR-T cells were activated when co-cultured with FAP+ target cells. In a dystrophic murine model (D2.*mdx*) characterized by fibrosis, anti-FAP CAR-T cells, intravenously delivered following lymphodepletion, reached the heart and skeletal muscles, where they decreased FAP and fibrosis-associated genes. Single-cell RNA-sequencing linked these changes to a decrease in a definite cluster of fibrogenic fibroblasts. Concomitantly, anti-FAP CAR-T cells improved cardiac function compared to control mice injected with GFP-transduced T lymphocytes or serum albumin. These results suggest that anti-FAP CAR-T adoptive therapy could be efficient for mitigating fibrosis.

*Speaker

Investigation of ROS molecular markers for the study of oxidative signaling during seed germination

Maria-Victoria Gomez-Roldan*[1], Gaspard De Tournemire[1], Amandine Valat[1], and Chirstophe Bailly[1]

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Abstract

Reactive oxygen species (ROS) are one of the major regulators of seed germination. Their homeostasis is likely to play a role in the translation of environmental factors into molecular mechanisms associated with germination. The Radical-Induced Cell Death1 (RCD1) protein family of plant-specific proteins implicated in ROS responses. Members of this family are characterized by a conserved PARP-like (poly(ADP-ribose) polymerase) domain. The Arabidopsis genome encodes six plant-specific RCD proteins (called SIMILAR TO RCD-ONE). SRO proteins can be subdivided into two groups, group I (RCD1 and SRO1) and group II (SRO2 to SRO5). SRO5 is a seed-specific protein, transcriptionally induced by ROS in response to salt treatment and is required for the proper response to oxidative stress in seedlings.To better study the function of SRO5 during germination, assays were performed using *sro5* (t-DNA and CRISPR-edited) mutants. The mutants showed only slightly slower germination than WT under control conditions, but under osmotic and ionic stress (PEG, salt), a strong involvement of SRO5 was observed. Histochemical staining showed that *SRO5* is expressed in the embryo during early imbibition and more particularly in vascular tissues. The presence of a PARP-like domain in SRO5, combined with its seed-specific expression and stress-inducible regulation, positions it as a potential mediator linking redox signaling, DNA repair, and seed viability. Identifying the molecular regulatory network involving ROS signaling during seed germination will open new perspectives for genetically modified crops.

*Speaker

Targeting senescence cell surfaceome for selective senolysis: design and functional evaluation of a new senolytic compound in the context of muscle regeneration during ageing.

Mazzarine Dotou[1], José García Coll[2], Ariadna Anton[2], Benjamim Carvalho[1], Angel Letri[2], Feryel Soualmia[1], Dalila Darmoul[1], Nicolas Pietrancosta[2], Roba Moumné[3], Aurore L'honoré*[1], and Chahrazade El Amri[1]

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[3]Laboratoire chimie physique et chimie du vivant – Sorbonne Université, Ecole Normale Supérieure, PSL University CNRS – France

Abstract

Cellular senescence is a form of stress response characterized by a stable cell-cycle arrest, a robust senescence-associated secretory phenotype (SASP), and a marked resistance to apoptosis. It is associated with a variety of biological and pathological processes. While in young organisms it is critical for tissue regeneration and optimized wound healing, the accumulation of senescent cells in tissues of older organisms is known to trigger or exacerbate aging-associated diseases and declines, including regeneration processes. With these evidences, pharmacological depletion of senescent cells with a novel class of drugs called senolytics has gained attention in the past few years and has been identified as a new therapeutic approach to prolong both health- and life-span. While many senolytic compounds have been identified, their translational potential remains limited because of their lack of selectivity: they target common molecular pathways shared between senescent and non-senescent cells, which lead to severe off-targets effects. Senescent cell's surfaceome offers opportunities to design targeted senolytics with improved selectivity. The membrane serine protease DPP4, widely used in diabetes treatment, having been recently identified as a robust senescence marker, we took advantage of this protein to design and synthesize conjugates combining a DPP4-FDA approved inhibitor with Piperlongumine, a reference natural amide alkaloid senolytic, resulting in a conjugate named DPP4L-PL. Using myoblasts and MEFs cells as *in vitro* models of muscle regeneration, we demonstrate that the newly designed DPP4L-PL conjugate exerts enhanced selectivity while keeping the same IC50 towards senescent cells compared to Piperlongumine alone. We also bring new insights on the functional mechanism of both piperlongumine and DPP4L-PL, including combined effects on mitochondrial respiration and immunoproteasome's activity.

*Speaker

Bristle patterning is modulated by environmental changes in Drosophila: mechanisms and impact on cryptic genetic variation

Nicolas Doucet[1], Valérie Ribeiro[1], Michel Gho[1], Agnès Audibert[1], and Jean Michel Gibert*[1]

[1]Développement adaptation et vieillissement – Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique, Institut de Biologie Paris Seine – France

Abstract

How organisms respond to a changing environment during their development is a fundamental question. Using *Drosophila* bristle patterning as a model system, we observed that cold temperature and methotrexate, a medical drug that contaminates wastewaters, increase dorsocentral (DC) bristles number, a trait normally very robust (canalized). Bristle patterning involves the *achaete-scute (ac-sc)* proneural genes. Modular enhancers activate *ac-sc* expression in groups of cells, called proneural clusters, from which bristle precursors are selected. In addition, *ac-sc* basal expression is controlled by a cocktail of repressive factors. We observed that the deletion of the DC enhancer prevents the induction of ectopic DC bristles by methotrexate. Indeed, we show that methotrexate synergizes with factors that regulate the DC enhancer and extends the zone of activity of this enhancer. In contrast, temperature interferes with the repression of *ac-sc* basal expression. Thus, methotrexate and temperature affect DC bristle patterning by distinct mechanisms. We analysed whether these environmental perturbations can also reveal genetic variations that have no phenotypic impact in normal conditions. For this, we use the Drosophila Genetic Reference Panel, a set of fully sequenced isogenic lines established from a natural population. This allows to phenotype the same genotypes in distinct environments and to perform Genome Wide Association Studies. Using temperature changes, we find that most SNP associated to DC bristle number variation are not the same at distinct temperatures, which indicates that the environmental changes analysed decanalize development by revealing cryptic genetic variation. One promising region associated to DC bristle number variation at low temperature is an enhancer of the transcription factor *bric à brac 1*, previously shown to be involved in the thermal dependency of abdominal pigmentation, but not known previously to participate to bristle specification.

*Speaker

Memory response of suspended microtissue to mechanical perturbation: role of collagen and cell-ECM networks

Gowthamy Sivakuru[1], Charles Thomas[1,2], Olga Vasiljevic[1,2], Léa-Laetitia Pontani[2], Jocelyn Etienne[3], and Jonathan Fouchard[*1]

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[3]Laboratoire Interdisciplinaire de Physique [Saint Martin d'Hères] – Université Grenoble Alpes – France

Abstract

Living tissues live in complex and ever changing mechanical environments. Before performing complex biological functions, they need to maintain their physical integrity, which imply to resist against the mechanical challenges (stretch, compression, shear) they are subjected to. For that, one strategy is to adapt their mechanical properties, at a rate which correspond to the time-scale of the mechanical challenge. If transcription-dependent mechanosensitive pathways can adapt ECM or cytoskeletal content over the time scale of days, it is not well known whether and how tissues adapt their mechanical properties at shorter time-scales (minutes to hours).
In this talk, we will address this question using a novel system of suspended microtissue, composed of mesenchymal stem cells embedded in a type-I collagen network. We find that those tissue are able to stiffen after a period of uni-axial compression of few minutes. Importantly, this stiffening is conserved over the time-scale of the perturbation applied, indicating a memory response to compression. We demonstrate that the collagenous ECM is the substrate of this memory but that it also buffers against stiffening at short time-scales. In addition, we find that this effect is balanced by cell mechanical activity and the remodelling of the cell-ECM network since inhibition of integrins and myosin II activity tends to amplify stiffening.
Altogether, these findings emphasize the importance of the regulation of mechanical perturbation to maintain tissue homeostasis. Although the rapid remodelling of the collagenous ECM in response to compression could play a protective role for tissues, it could also be deleterious by triggering a fibrotic response

[*]Speaker

Investigating the specificity of RNA localization in P-bodies

Adham Safieddine*[1], Marie-Noëlle Benassy , Thomas Bonte , Michèle Ernoult-Lange , Maité Courel , Edouard Bertrand , Marianne Bénard , and Dominique Weil

[1]Développement adaptation et vieillissement – Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique, Institut de Biologie Paris Seine – France

Abstract

Understanding the dynamics of RNA targeting to condensates is essential to disentangle their functions. Notably, how the specificity of RNA localization to P-bodies (PBs) is determined remains unclear. Here, we tackle this question by (i) analysing the evolution of PB RNA content across the cell cycle, (ii) and investigating RNA isoform targeting to PBs. PB purification across the cell cycle uncovers widespread changes in their RNA content, which are partly uncoupled from cell cycle-dependent changes in RNA expression. Single molecule FISH shows various mRNA localization patterns in PBs peaking in G1, S, or G2, with examples illustrating the timely capture of mRNAs in PBs when their encoded protein becomes dispensable. Rather than directly reflecting absence of translation, cyclic mRNA localization in PBs is controlled by extrinsic (RNA binding proteins) and intrinsic (RNA features) factors. Moreover, by analysing the RNA content of purified PBs at the transcript level, we discover isoform-specific RNA localization to PBs. This is linked to 3'end processing events such as alternative poly(A) site selection which is sufficient to drive localization of a reporter in PBs. Altogether, our study supports a model where PBs are more than a default location for excess untranslated mRNAs.

*Speaker

Posters

A vascularized hepatocellular carcinoma-on-a-chip for studying angiogenesis in tumor progression

Dominique Baran*[1], Lynda Aoudjehane[2], Audrey Saquet[1], Rafaele Attia[1], Manon Allaire[3], Valérie Bello[1], and Wenjin Xiao[1]

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[2]IHU-ICAN Human Liver Biology, Hospital La Pitie Salpetriere, Paris, France. – Hôpital de la Pitié Salpêtrière – France

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and represents a major global health burden, with a five-year survival rate of approximately 20%, due to late diagnosis and limited therapeutic options. Tumor progression in HCC is associated with angiogenesis, the formation of new blood vessels from pre-existing ones to meet metabolic demands. However, tumor-induced vascular networks are often abnormal, contributing to hypoxia, immune evasion, metastasis, and therapy resistance. While the biochemical factors of this process, such as vascular endothelial growth factor (VEGF), are well documented, the influence of the mechanical microenvironment, including flow-induced shear stress, mechanical stretching, and extracellular matrix stiffness, remains poorly understood. Our primary objective is to develop a vascularized HCC-on-a-chip model to study how mechanical stimuli regulate angiogenic progression. By characterizing the underlying mechanotransduction pathways and key molecular mediators, this research aims to discover new therapeutic targets to improve clinical outcomes in patients with advanced HCC. Our preliminary results show the successful generation of _˜300 μm HCC spheroids from Huh7 cells, a HCC cell line, under low-attachment conditions, recapitulating physiological diffusion limits. Embedding in ECM-based hydrogel such as collagen I and fibrin showed that increased matrix density preserves spheroid integrity while restricting growth. Live/Dead imaging reveals a size-dependent hypoxic core surrounded by a viable proliferative edge, consistent with tumor-like organization. Ongoing work aims to optimize ECM composition to further support HCC spheroid viability, phenotype and function while promoting their integration with a perfusable vessel-on-chip platform. The goal is to develop a vascularized HCC spheroid-on-a-chip model and investigate angiogenesis under controlled mechanical cues.

*Speaker

Role of mutations on the RNA helicase DDX6 in a syndrome of intellectual deficiency associated to a P-body defect.

Altan Cornu[1], Sarah Baer[2], Michèle Ernoult-Lange[1], Dominique Weil[1], Amélie Piton[2], and Marianne Bénard*[1]

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Abstract

The DEAD box RNA helicase DDX6 is involved in various aspects of post-transcriptional regulation ranging from mRNA degradation to translational repression or RNA interference. DDX6 also plays a role in the storage of mRNAs into P-bodies (PB) as a factor key to PB assembly (1). Recent studies suggest that the storage and translational repression of mRNAs into P-bodies play a crucial role in the regulation of neurogenesis and stem cell expansion, a fine balance required for healthy brain development (2).
Our collaborators identified five patients with intellectual deficiency (ID) that bear *de novo* heterozygous missense mutations on DDX6 (3). We showed by functional studies a causative link between these pathogenic variants and the neurodevelopmental syndrome of the patients associated to RNA misregulation and PB assembly defects (3). Today, ten more patients have been identified with missense mutations in DDX6. What are the post-transcriptional regulatory functions of DDX6 the most affected by these mutations? What are the underlying mechanisms involved in neurodevelopmental defects?

We first investigated the impact of the mutations on PB assembly by immunofluorescence experiments performed on patient-derived fibroblasts and complementation assays of the variants in human cell line. Our results show strong defects in PB assembly. On the other hand, *in vitro* ATPase assays revealed a loss of function for a majority of variants while few of them maintain their enzymatic activity. Currently we investigate other biochemical activities of DDX6 variants, including interaction with partners. The characterization of molecular and cellular defects of DDX6 variants might shed light on the role of DDX6 and PBs in a context of neurodevelopmental delay.

*Speaker

(1) Standart, N. and Weil, D. (2018) Trends Genet. ***34****, 612-626.*

(2) Hoyle, M.L. and Silver, D.L. (2021) Curr Opin Neurobiol, 66, 93–102.
(3) Balak, C., et al. (2019) Am. J. Human Genet. ***105****, 3, 509-525*

Impact of a Mixture of Organic Pollutants on the Thyroid Axis

Manon Bonnelle*[1], Sebastien Le Mevel[1], Clémence Soulier[1], Chloé Wu[1], Stéphane Reynaud[2], and Jean-Baptiste Fini[1]

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Abstract

Endocrine disruptors are widely recognized for their adverse effects on human and environmental health. Their ubiquitous presence is suggested to impact amphibian metabolism, contributing to their decline over recent decades. In this context, a mixture of six obesogenic EDs (TBT (organotin compound), TCS (chlorophenol / antimicrobial agent), DDE (organochlorine pesticide metabolite of DDT), PBDE (brominated flame retardant), BaP (polycyclic aromatic hydrocarbon – PAH), and DEHP (phthalate plasticizer)) was assessed at concentrations corresponding to environmental quality standards (EQS) during short- and long-term exposure in Xenopus tropicalis at three developmental stages (NF47, 62, and 65). We hypothesized that liver metabolic dysregulation observed by our collaborators may partly originate in the brain and thyroid gland, given the central role of the thyroid system in metabolic regulation.
Regarding the F0 generation, short-term exposure (NF47) induced an increased cell proliferation and reduced cell mortality in the brains of exposed tadpoles. We assessed mobility of animals with light/dark stimulus. X. tropicalis eleutheroembryos were naturally more active in darkness, and exposure significantly intensified this mobility. At the molecular level, using RNAseq, exposure to the mixture led to deregulation of several genes involved in metabolism and thyroid function. In the long term (3 weeks), histological analyses on premetamorphic (NF62) and metamorphic (NF65) tadpoles revealed pronounced alterations in the thyroid glands, including increased colloid content, clusters of thyrocytes, and follicular disorganization, which were observed significantly in both sexes.

To investigate potential transgenerational impacts of this obesogenic mixture, the F1 generation which was not directly exposed was also examined. Long-term exposure resulted in a significant decrease in thyroid colloid in tadpoles (NF65), and the observed pattern suggests a possible maternal transmission of this impairment.
Overall, the obesogenic mixture is biologically active at EQS concentrations, supporting mixture-based risk assessment. Thyroid alterations in non-exposed offspring indicate transgenerational effects with potential long-term population health implications.

*Speaker

Effects of DEHP and BPA mixture through the food web on estrous cyclicity and associated neural processes in female mice

Elodie Desroziers*[1,2], Antoine Proost-Matencio[2], Juilie Garai-Memery[2], Muayad Hal Hafez[2], Annabelle Fuentes[3], Annick Maria[3], David Siaussat[3], and Sakina Mhaouty-Kodja[2]

[1]Sorbonne université - Faculté des Sciences et Ingénierie – Sorbonne Universite – France
[2]Neuroplasticity of reproductive behaviours – Sorbonne Université, IBPS, CNRS UMR 8263, Development, Adaptation and Aging (Dev2A), 75005 Paris, France – France
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Abstract

Phthalates, such as di-2-ethylhexyl-phthalate (DEHP), are widely found in the environment due to their use as additives in plastics, cosmetics, and herbicide adjuvants. Bisphenol A (BPA) was also massively used as an intermediate monomer in the manufacture of polycarbonate plastic (food containers) until it was banned in France (2015) and recently in Europe (2024). BPA and DEHP are endocrine disruptors meaning that they interfere with the endocrine system. Several studies have found DEHP and BPA within the agricultural soils and in edible plants. Here, this study aimed to **characterize the effect of a combined exposure through the food web to DEHP and BPA at environmentally relevant doses on reproductive function and associated hypothalamic neuroglial changes**.C57Bl6 adult female mice were fed for six weeks with a food mixture containing 50% standard chow diet, and 25% tomatoes plants (leaves and fruits) and 25% Spodoptera littoralis (crop pest) both either non-contaminated (vehicle, VEH) or contaminated with DEHP and BPA at environmentally relevant doses (contaminated food, CF). Interestingly, the number of female mice showing regular cycle in the CF group was significantly reduced (6/12; 50%) compared to the VEH group (12/13; 92%). Within the brain, the number of GnRH- and kisspeptin-immunoreactive (ir) neurons, both potent regulators of fertility, were similar in both groups. However, the number of kisspeptin-ir fibers within the rostral preoptic area was increased in exposed females (CF). We also observed an increase in astrocyte reactivity illustrated by increased GFAP-ir in the same brain region. To go further, we are currently studying the number of kisspeptin-ir fiber appositions onto GnRH-ir neurons. Our results suggest that a combined exposure to environmentally relevant doses of DEHP and BPA through the food web can lead to fertility disorders in female mice associated with neural changes.

*Speaker

Identification of sex-specific pubertal windows of plasticity in key hypothalamic regions controlling reproductive behavior in mice

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Abstract

Introduction: Puberty represents a crucial developmental transition from childhood to adulthood, marked by extensive physical, hormonal, neural, and behavioral changes. Sexual behavior in rodents relies on the organization of sexually dimorphic neural circuits modulated by the action of sex steroids during sensitive periods of development. These include the well-characterized perinatal period in males, and the postnatal/pubertal period, whose importance has recently emerged but remains poorly understood. In particular, the timing and underlying cellular processes are still unclear. This study aims to determine postnatal and pubertal sensitive windows of neuroplasticity in the hypothalamus while identifying sex differences.

Methods/results: To this end, we focused on two hypothalamic nuclei: the medial preoptic area (POA) and ventromedial hypothalamus (VMH), known to regulate male and female sexual behavior, respectively. Molecular and cellular changes were analyzed from postnatal day (PND) 10 to adulthood in C57Bl6/J mice. RT-qPCR analysis revealed two sex-specific windows of molecular changes. In the male POA, at PND30, we observed a transient downregulation of gene expression related to estrogen receptors α and β (*Esr1*/*Esr2*), androgen receptor (*Ar*), and glial markers (*Iba1, Gfap*), followed by a robust upregulation from PND35 onwards. In the female VMH, an upregulation of these markers occurred later, around PND40-45, that coincides with changes in dendritic spine density (Golgi-Cox staining). Interestingly, male testicular weight increased at PND30-35, while female ovarian and uterine weights rose at PND40-45, underscoring that these pubertal windows of hypothalamic changes align with gonadal maturation. To further elucidate cellular dynamics during these identified pubertal periods, analyses of microglia morphology and phagocytic activity, as well as neuronal activity through GCaMP calcium imaging are underway.

Conclusion: This study identified sex-specific pubertal windows of plasticity in key hypothalamic regions: around PND30-35 in males and PND40-45 in females. Further studies will clarify how hypothalamic plasticity during puberty shapes adult reproductive behavior.

*Speaker

Kdm3-mediated misdetermination of piRNA clusters depends on E(z) and kipferl at the beginning of oogenesis

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Abstract

Transposable Element (TE) activity in Drosophila's germline is controlled by small non-coding RNAs called piRNAs. They are produced from specific heterochromatic loci called piRNA clusters, enriched in H3K9me2/3 histone mark and containing fragments of TEs sequences. We showed earlier that a female germline knockdown (KD) of the H3K9me2/3 demethylase KDM3 disturbs piRNA production : about a hundred gene-containing regions become piRNA clusters, abnormally producing piRNAs. We seek now to better understand the determination of the piRNA producing state of these regions, from a chromatin perspective and an oogenesis developmental perspective. We found a H3K27me3 enrichment bias at abnormal piRNA producing loci, while functional assays showed that both, E(z) and Kipferl, are required for piRNA production from these regions. Timing of expression assays using different Gal4 drivers combined with Kdm3 KD showed that bam> Gal4 phenocopies nanos> Gal4, revealing an unexpected period of abnormal piRNA source loci determination at the early start of oogenesis, at the stages 1-2a in the germarium.

*Speaker

Barhl2 maintains a subpopulation of Granular Neurons progenitor in a low proliferative, low differentiated state thereby supporting GNP protracted proliferation period

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Abstract

Cerebellar granule neurons (GNs), which constitute the largest neuronal population in the brain, undergo a remarkably protracted period of proliferation, lasting approximately two weeks in mice and up to two years in humans. Owing to this extended developmental window, this population is particularly vulnerable to developmental abnormalities, including oncogenic events. However, the mechanisms that support and regulate this prolonged proliferative phase remain poorly understood.
The BARH-like homeodomain–containing transcription factors Barhl1 and Barhl2 are direct target genes of ATOH1, a master regulator of GN development. Both BARHL proteins act as transcriptional repressors and strongly inhibit TCF activity. Our previous work in amphibians demonstrated that Barhl1-mediated repression of TCF activity is required for granule neuron progenitors (GNPs) to exit the upper rhombic lip. In addition, we showed that the homeodomain-containing gene Barhl2 negatively regulates cell-cycle progression in the Xenopus diencephalon.
In the present study, using lentivirus-mediated knockdown and overexpression approaches combined with bulk transcriptomics, reanalysis of single-cell atlases of cerebellar development, and cell biological assays, we show that BARHL2 modulates GNP responses to WNT/TCF and Sonic Hedgehog (SHH) signaling and alters the expression of Hairy/ Enhancer of Split (*Hes/Hey*) genes. Our data indicate that BARHL2 is both necessary and sufficient to maintain a subpopulation of GNPs in a quiescent, early differentiated state that responds weakly to SHH-driven mitogenic stimulation. In this way BARHL2 supports the protracted proliferative period of GNPs. We are currently investigating the *in vivo* impact of *Barhl2* on GNP behavior, with a particular focus on its role in regulating proliferation.

*Speaker

A vascularized liver-on-chip model to study mechanical cues in liver regeneration

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Abstract

The liver possesses an exceptional capacity for regeneration following injury or surgical tissue removal (partial hepatectomy, PHx). However, this response is clinically variable and can fail to initiate, complicating patient recovery. While biochemical triggers are well-explored, mechanical triggers following rapid haemodynamic changes after PHx remain poorly understood. Investigating these forces in vivo is limited by the difficulty of precisely controlling mechanical cues, like shear stress, within living tissue. Meanwhile, current in vitro models often lack dynamic perfusion and physiological mechanical conditions. To bridge this gap, this project develops a vascularized liver-on-chip platform to establish functional intravascular perfusion within hepatic microtissues, mimicking post-PHx blood-flow dynamics and the hyper-perfused state of a regenerating liver.

We have established liver spheroids by co-culturing hepatocytes and non-parenchymal cells, including liver sinusoidal endothelial cells and hepatic stellate cells, utilizing both cell lines and primary cells derived from patient biopsies under low-attachment conditions. Our preliminary results demonstrate that applying external flow, mimicking physiological shear stress, enhances cell viability and upregulates genes associated with regeneration and mechanotransduction. These findings support the hypothesis that flow-dependent mechanical cues may act as early triggers of liver regeneration following PHx. Moreover, endothelial cells self-organize into early vascular-like structures with open lumens. To further optimize the spheroid culture microenvironment and promote integration with an external vascular network, we embedded the spheroids in a pro-angiogenic ECM hydrogel, collagen I, at varying concentrations. Collagen I greatly supports liver cell viability, phenotype, and function, while enabling hepatic stellate cell activation and the formation of outward-growing sprouts. Next, we aim to connect these spheroids to an external vascular network of HUVECs to achieve a fully perfusable system. This platform provides a new approach to investigate the mechanobiology of liver repair, supporting the development of improved therapeutic strategies.

*Speaker

Synergistic effect of a combined strategy for spinal cord injury repair

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Abstract

Spinal cord injury (SCI) triggers a complex cascade of secondary events, including inflammation, neurodegeneration, and vascular dysfunction, which together limit tissue repair and functional recovery. Given this multifactorial pathophysiology, single therapeutic approaches have shown limited efficacy, highlighting the need for combinatorial strategies targeting complementary mechanisms.
In this context, we investigated two distinct but potentially synergistic approaches: a pharmacological neuroprotective treatment and a chitosan-based biomaterial. Independently, both strategies demonstrated significant beneficial effects in a rat model of thoracic SCI. Neuroprotective treatment promoted locomotor recovery, prevented the development of mechanical hypersensitivity, and contributed to tissue preservation. Similarly, implantation of the chitosan-based biomaterial improved functional outcomes, reduced pain-related behaviors, supported axonal regrowth associated with astrocytic processes, and preserved functional vascularization within the lesion site.

These findings indicate that each approach effectively targets different aspects of SCI pathophysiology, suggesting that their combination may provide enhanced therapeutic benefit. Building on these results, the objective of the present work is to determine the optimal combinatorial strategy by defining the appropriate duration of neuroprotective treatment and the most relevant timing of biomaterial implantation. Specifically, we aim to assess whether simultaneous or sequential administration of these therapies can maximize tissue repair and functional recovery.
This study provides a rationale for the development of temporally optimized combinatorial therapies for SCI, with potential implications for translational applications.

*Speaker

Deciphering the Effects of Cold Atmospheric Plasma (CAP) on the Differentiation and Functionality of induced Pluripotent Stem Cell- Derived Cardiomyocytes (iPSC-CMs)

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Abstract

The generation of mature iPSC-derived cardiomyocytes (iPSC-CMs) is of particular interest to cardiac biologists and clinical researchers. iPSC-CMs serve as a human-specific platform for cardiac disease modeling, pharmaceutical screening, and developmental studies. Unfortunately, iPSC-CM differentiation protocols often yield heterogeneous cell populations displaying incomplete maturation (e.g. disorganized sarcomeres, reduced contractile force, incomplete mitochondrial maturation). Researchers have explored numerous methods to improve differentiation, but these strategies still fail to fully restore adult-like phenotypes.

Throughout this study, we postulate that cold atmospheric plasmas (or CAP) low-temperature, weakly ionized gases generated by electrical discharges within ambient air could present a novel approach. Notably, CAP contains a mixture of reactive oxygen and nitrogen species (RONS) and possesses varying radiative, chemical, thermal and fluid-mechanical properties depending on the parameters of generation (e.g. electrical potential difference, reactive gas). Given the positive implication of low levels of RONS on cardiomyocyte maturation in vivo, we postulate that CAP could be used to improve current iPSC-CM generation protocols. By provoking an intracellular accumulation of RONS to induce a minor stress response, CAP treatment of iPSCs may stimulate adaptive, RONS-sensitive cellular mechanisms in order to generate more mechanically robust iPSC-CMs.

Post-CAP treatment, changes in iPSC-CM differentiation were analyzed by evaluating changes in their contractility, calcium handling, oxygen consumption, and transcriptomics. Early data indicates that brief CAP treatment coinciding with WNT antagonist application during early differentiation results in improved differentiation and contractility, but additional troubleshooting is necessary to identify optimal treatment conditions. Once CAP treatment has been refined, we intend to characterize the nature of the RONS generated within CAP and CAP-treated liquid, to better characterize the influence of these species on iPSC-CMs at the molecular layer.

Key words: Cold Atmospheric Plasma (CAP), Induced Pluripotent Stem Cell-Derived Cardiomyocytes (iPSC-CMs)

*Speaker

Disruption of embryonic development in Paracentrotus lividus by chemicals leached from plastics

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Abstract

Chemicals associated with plastics are an increasing environmental concern, with approximately 917 tonnes of plastic additives entering the marine environment annually. Therefore, developmental defects induced by plastic-associated chemicals were investigated using a standardized toxicity assay with the sea urchin (*Paracentrotus lividus*).

Different leaching times (1 day, 10 days, 1 month, 2 months, 4 months and 8 months) were applied to four types of polyethylene (supposedly additive-free, recycled, bubble wrap and oxodegradable). The effects on *Paracentrotus lividus* larval development were assessed using a standardized assay and larval size was measured to detect subtle effects. In addition, inorganic and organic compounds released from plastics were analyzed to investigate the origins of developmental alterations.

Effects on the embryo-to-larval development test were observed after 1 month of leaching for oxodegradable polyethylene (PE-oxo) and only after 8 months for supposedly additive-free polyethylene (PE-pure). An increase in developmental defects was observed with increasing leaching time. No effects were detected for bubble wrap and recycled polyethylene due to low or negligible leaching from these materials. For the first time, the kinetics of leaching toxicity were described by an exponential decrease of EC50 values with increasing leaching time. Larval size was affected after 1 and 10 days of leaching for all plastics, except recycled

*Speaker

polyethylene, which showed significant effects only after 10 days. These effects were partially explained by a link between certain metals in the leachates and developmental alterations. A progressive increase in organic compounds released from PE-oxo was observed between 1 and 8 months of leaching. Many of these compounds were not identified in the original material, suggesting the formation of degradation products. Overall, this study highlights the kinetics and developmental impacts of plastic leaching on the embryogenesis of *Paracentrotus lividus*.

Neural effects of developmental exposure to human breastmilk contaminants in male and female mice

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Abstract

Human populations are exposed to a wide variety of environmental chemical substances. However, risk assessment of such exposure for human health is still carried out substance by substance. In this context, the team has contributed to the development of a new methodological approach for assessing the chemical risk of heterogeneous contaminants mixtures (*Crépet et al., 2022*). This methodology was applied to the contaminants measured in human breastmilk collected in French lactariums (*Rigourd 2015*). This initial theoretical assessment of combined risks suggested a high risk for neurodevelopment related to cognitive and motor processes and thyroid hormone system. Thus, our study aims to generate experimental data to establish and improve this methodology by analyzing the effects of this human breast milk contaminants mixture on neurodevelopmental and cognitive processes. Eight-week-old C57BL6/J dams were orally exposed to a mixture of breast milk organic persistent pollutants containing either 9 substances or the 5 drivers of effects identified by the theoretical approach at the environmental dose and at two higher doses. Exposure was carried out two weeks before mating, and during gestation and lactation. Our results show that, whatever the dose, the mixture had no effect on maternal weight, litter size or pup survival. A treatment effect was observed on body weight, developmental landmarks such as fur apparition, eye opening and age at puberty in male and female offspring born from exposed dams. Behavioral analyses conducted in adult males exposed developmentally to the human breast milk mixture at different doses, showed increased basal anxiety level, and temporal and spatial memory impairments. The specific effects in females are under analysis. Further investigation will decipher the hippocampal cellular and molecular mechanisms implicated in the observed cognitive impairment following developmental exposure to real life mixture of men-made chemicals.

*Speaker

Low-intensity magnetic stimulation exerts pattern-dependent effects on tissue repair after spinal cord injury

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Abstract

Spinal cord injury (SCI) is a devastating condition leading to permanent sensorimotor deficits below the lesion site, associated with fibroglial scar formation, neural network disruption, and a chronic inflammatory environment. Effective treatments remain limited; nevertheless, neuromodulation has emerged as a promising strategy to enhance functional recovery and promote tissue repair after SCI. Among these approaches, repetitive magnetic stimulation (rMS) is a widely used therapy in humans that non-invasively modulates neural excitability and plasticity at both cortical and spinal levels. Previous studies have shown that trans-spinal rMS at high-intensity improves motor function and tissue remodeling in rodents. In this context, our study focuses on low-intensity rMS (LIrMS) and investigates how focal spinal stimulation patterns influence spinal cord repair after injury. Wild-type mice underwent SCI, followed by two weeks of either sham or trans-spinal LIrMS with three stimulation patterns. Locomotor recovery was assessed using the Basso Mouse Scale, and spinal cord samples were collected for immunohistochemistry and RNA sequencing. Our results indicate that LIrMS induces pattern-dependent effects on fibroglial scar reorganization, inflammatory processes, and myelin debris clearance. These data are further corroborated by transcriptomic profiling, revealing distinct molecular signatures depending on the stimulation pattern including pathways related to fibrosis, immune and inflammatory regulation, vascular dynamics, and apoptotic processes. These data identify focal trans-spinal LIrMS as a promising neuromodulatory strategy to promote spinal cord repair, and pave the way for future investigations, including validation in a rat model whose pathophysiology after SCI is closer to humans. Grant : Fondation pour la Recherche Médical (FRM).

*Speaker

Effect of physicochemical environments on the differentiation of Liver-Specific Endothelial Cells from iPSCs

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Abstract

The liver is a major metabolic organ whose cells are organized into hepatic lobules around a central vein, forming hepatocyte cords vascularized by specialised capillaries called sinusoids. These sinusoids are characterized by their high permeability and a metabolic gradient that allows efficient nutrient and waste exchange. However, studying these microvessels remains challenging since replicating their native microenvironment in vitro requires the integration of complex cues, including paracrine signaling from neighboring hepatic cells, matrix composition and stiffness, and shear stress induced by blood flow. To address this challenge, this project leverages human induced pluripotent stem cells (hiPSCs) and combines specific mechanical and chemical signals to enhance the specification of endothelial cells toward liver sinusoidal endothelial cells (LSECs). The goal is to generate LSECs with a more mature phenotype than those obtained using conventional growth factor-based differentiation protocols.

hiPSCs were differentiated to CD34+ progenitor cells over a seven-day period, followed by subsequent expansion and integration into both 2D and 3D co-culture configurations alongside hepatocytes and other non-parenchymal cells. Furthermore, we employed a microfluidic platform to introduce physiological flow conditions, mimicking the shear stress induced by blood flow. The influence of both mechanical and chemical cues on LSEC maturation is

*Speaker

assessed through molecular identification (e.g., key endothelial marker expression), together with functional and morphological characterization.
By integrating shear stress and multicellular signaling, this study aims to establish a more physiologically relevant in vitro model that could advance liver disease modeling, improve drug toxicity screening, and deepen our understanding of hepatic development and regeneration.

Accumulation of PFAS in the myelin sheath: Long-term consequences on myelin stability physiology and functional remyelination stability

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Abstract

Over the past 30 years, an unexplained increase in the incidence of multiple sclerosis has been observed in developed countries, with a suspected contribution from environmental factors. We wondered whether exposure to some endocrine-disrupting chemicals, in particular fluorinated surfactants (PFAS) such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), could interfere with myelin formation and remyelination. We hypothesize that PFAS could accumulate in lipid-rich structures such as myelin, thereby disrupting myelin sheath integrity.

Accordingly, we have recently demonstrated that PFAS accumulate in the myelin sheath of offspring exposed via maternal drinking water during late gestation and lactation. Furthermore, using ex vivo and in vivo approaches, we have shown that PFOS, but not PFOA, impaired functional remyelination. Here, we investigated the long-term effects of perinatal PFOS exposure on oligodendrogenesis, myelination, and remyelination. First, we showed that perinatal PFOS exposure blocked oligodendroglial maturation in the corpus callosum. Transmission electron microscopy studies in the corpus callosum showed that PFOS permanently reduced myelin sheath thickness and altered myelin sheath ultrastructure, suggesting permanent changes in myelin integrity and stability. To analyse this hypothesis, we developed an in vitro system based on the production of myelin-like giant unilamellar vesicles, which allows us to assess how PFOS exposure might affect the mechanical and biophysical properties of myelin. By using this method, we showed that the addition of PFOS led to a weaker and more fragile myelin lipidic bilayer. This result was also confirmed by in silico membrane dynamics simulations.

In conclusion, our data show that perinatal exposure to PFOS, and to a lesser extent to PFOA, results in permanent changes in myelin physiology that may increase susceptibility to myelin disorders such as multiple sclerosis.

*Speaker

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