JCI 2026

Journées du Campus Illkirch

May 21st-22nd
Pôle API - Illkirch

Abstract Book

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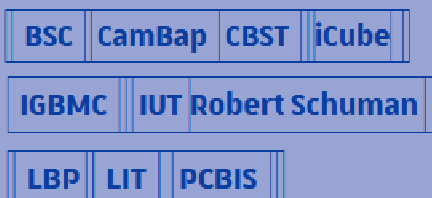

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	Thursday 21 May 2026		**Friday 22 May 2026**
08:45	Introduction by Pr. Claire GAVERIAUX	**08:45**	Welcome
09:00	Invited Young researcher **Dr. Guilhem Chaubet**, CBST	**09:00**	Invited Young researcher **Dr. Julie Karpenko**, LIT
09:30	Talk 1 Victorine ARTOT IGBMC Talk 2 Yelyzaveta DENYSIEVA LBP Talk3 Christos PASCHALIDIS BSC	**09:30**	Talk 8 Yamina BOUKENADEL LBP Talk 9 Sophie WALTER CBST Talk 10 Laura YEDIAGARYAN IGBMC
10:15	Metrohm, Cytiva, Opus	**10:15**	Pôle Appui 5 min
10:30	Coffee break	**10:20**	Coffee break
11:00	Talk 4 Yu QIU CBST Talk 5 Léa DENECHERE LBP Talk 6 Valeria BOIDE LBP Talk 7 Baptiste DUPOUY LIT	**10:50**	Talk 11 Maeva MARTIN LBP Talk 12 Mubarak OLAOLUWA Icube Talk 13 Shayan AHMED LBP Talk 14 Anthony AUGER LIT
12:00	Poster flash talks	**11:50**	Poster session Even
12:15	Lunch		
13:00	Poster session Odd	**12:50**	**Cocktail Tartes flambées** *Awards ceremony*
14:00	**Plenary Session-debate** ***"Science Together"*** ***Photo of all the participants*** **Pr. Jean-Louis Mandel** **& Dr. Maria-Victoria Hinckelmann,** IGBMC - Illkirch **Dr.Sandrine Glatron** MISHA-Strasbourg **Pr. Pascal Marchand**, IICiMed - Nantes	**14:15**	Ateliers HAL, Bases de données biblio
17:00 **19:00**	**Get-together Cocktail**		

POSTERS

Impact of diet-derived siderophores on the gut microbiota

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Résumé

The gut microbiome provides essential functions such as colonisation resistance against invading pathogens, but food-derived metabolites can disturb its homeostasis and cause dysbiosis–and therein, loss of function. Siderophores (iron-chelating molecules) are an example of metabolites present in some fermented foods–the utilisation of these exogenous siderophores by gut bacteria may shape colonisation resistance.
Within the broader aim of studying siderophore-mediated colonisation resistance, my project aims to determine whether gut bacteria can utilise siderophores present in fermented foods, focusing on those produced by cheese microorganisms.

Firstly, we aim to identify which siderophores are produced by key fungal species. This involves culturing cheese-derived fungi in iron-depleted medium to characterise the siderophores they produce using HPLC-MS/MS. Preliminary results confirmed metagenomic findings regarding the production of rhizoferrin, fusarinine, and coprogen by fungal strains.
Secondly, we aim to develop a qualitative spotting assay for the rapid screening of exogenous siderophore utilisation by gut bacteria. Two *Fusobacterium* strains tested seem able to utilise salmochelin, a siderophore produced by pathogenic Enterobacteriaceae. The optimisation of growth conditions in liquid minimal medium will allow us to confirm and quantify this initial result.

Mots-Clés: Siderophores, Microbiota, Colonisation resistance

*Intervenant

Mapping the molecular interactome of the human ATAC complex: uncovering its role in transcriptional regulation

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Résumé

In eukaryotes, DNA is packaged into chromatin, a dynamic structure that regulates transcription, replication, and DNA repair. Chromatin accessibility is finely modulated by coactivator complexes like SAGA (Spt-Ada-Gcn5 acetyltransferase) and ATAC (Ada-Two-A Containing), which promote transcription initiation through histone acetylation. Although they share a catalytic module, ATAC is metazoan-specific, structurally uncharacterized, and contains a unique core module, suggesting distinct regulatory roles compared to SAGA. ATAC is crucial for the expression of housekeeping genes (e.g., ribosomal protein genes), acetylates non-histone targets, and binds RNAs, suggesting a broader role in transcription regulation. However, how ATAC integrates these molecular interactions to coordinate transcription remains unknown. This project aims to bridge this gap by mapping the molecular interactome of the ATAC-specific core subunits: YEATS2, ZZZ3, ATAC2, and MBIP. To capture both stable and transient interactions within the nuclear environment, we are employing a proximity labelling strategy coupled with mass spectrometry. This approach enables the identification of proximal proteins in their endogenous environment, providing a comprehensive view of the ATAC interactome and its regulatory partners. By characterizing these subunit-specific networks, we aim to uncover how ATAC coordinates multiple molecular interactions to regulate gene expression, chromatin recruitment, and cellular homeostasis.

Mots-Clés: Transcriptional regulation, ATAC complex, Proximity labelling, Chromatin

*Intervenant

A chromogenic TLC bioautographic assay for the rapid detection of β-lactamase inhibitors

Fiorella De La Cruz Tito*[1] and Aurélie Urbain[1]

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Résumé

β-Lactam antibiotics, including penicillin derivatives, cephalosporins, and carbapenems, are among the most widely used treatments for bacterial infections. They are frequently co-administered with β-lactamase inhibitors to prevent enzymatic degradation by resistant bacteria. However, the few inhibitors currently available share closely related chemical structures, and resistance to these compounds is increasingly reported (1). This issue has been identified by the World Health Organization as a priority public health threat, highlighting the urgent need for new β-lactamase inhibitors.
While natural products constitute a rich source of bioactive molecules, their exploration remains challenging due to the high chemical complexity of natural extracts. To facilitate the detection of β-lactamase inhibitors in complex mixtures, we developed a thin-layer chromatography (TLC) bioautographic assay, a method combining chromatographic separation with an in situ enzymatic reaction (2,3). The method uses nitrocefin, a chromogenic cephalosporin that changes from yellow to red upon hydrolysis by β-lactamases (4). A key advantage of nitrocefin is its sensitivity to all known β-lactamases produced by both Gram-positive and Gram-negative bacteria. Using this approach, natural β-lactamase inhibitors can be directly visualized on the TLC plate as clear zones against a pink background.

Validation with the reference inhibitor sulbactam and clavulanic acid demonstrated the reliability repeatability and sensitivity of the assay, with clear dose and time dependent inhibition. This simple and rapid TLC-based method was adapted to the identification of potential beta-lactamase inhibitors present in fungal extracts, constituting a tool for screening complex natural extracts and for the discovery of new beta-lactamase inhibitors, and can be combined with antibacterial direct bioautography to identify multitarget compounds, thereby accelerating the discovery of new strategies to combat multidrug-resistant bacterial pathogens.

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Mots-Clés: thin, layer chromatography, bioautography, enzymatic inhibition assay, beta, lactamase, nitrocefin, fungal extracts

Enhanced drug delivery via antibody–drug conjugates and siRNA-linked nucleic-acid aptamers targeting EGFR in glioblastoma cells

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Résumé

Active targeting in drug delivery is based on the binding of ligands to receptors present on the surface of targeted cells in order to promote the internalization of ligand conjugated drugs. The most well-known conjugates are antibody-drug conjugates (ADCs), which combine the specificity of monoclonal antibodies with the cytotoxic of chemotherapeutic drugs. In addition to antibodies, nucleic acid aptamers, known as single stranded DNA or RNA oligonucleotides referring to chemical antibodies with high affinity and selectivity for their target (*Zhou et al, 2016*), are promising to deliver conjugated drugs or therapeutics nucleic acids such as siRNA by active targeting delivery (*Mercier et al, 2017*).
In our team, we are interested in developing an aptamer-siRNA chimera called AsiC targeting EGFR (epidermal growth factor receptor), a receptor, internalized by endocytosis (*Ivaska et al, 2011*) and often overexpressed in glioblastoma cells, the most aggressive tumour of the central nervous system. Our AsiC consists of a targeting part: a 2' fluoro modified RNA aptamer E07 targeting EGFR (Cruz da Silva, Foppolo et al, 2022) and a therapeutic part: a siRNA for gene silencing. The therapeutic efficacy of such conjugates not only depends on target specificity but also on efficient internalization into tumor cells. However, so far, no therapeutic approach to enhance endocytosis of conjugates is available.

In recent studies, we showed that gefitinib, a tyrosine kinase inhibitor directed against the EGFR, induces a massive, non-physiological endocytosis of EGFR, known as gefitinib-mediated endocytosis (GME), in different glioblastoma cell lines (*Blandin et al, 2021 ; Cruz Da Silva et al, 2021).* We thus hypothesized that besides promoting endocytosis of EGFR, gefitinib could also promote endocytosis of its ligands. In this study, we proved by quantitative fluorescence bioimaging, that gefitinib is indeed able to strengthen the endocytosis of

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fluorophore-conjugated EGFR-specific antibodies and aptamers. We also showed that the GME potentiates the toxicity of an ADC and the efficacy of an AsiC. Our results suggest the development of a new therapeutic combination with gefitinib, to potentiate the delivery of ADC, AsiC and likely other conjugates targeting EGFR in glioblastoma, while limiting side effects on non-targeted cells. Our results have been submitted for publication and are already available online as a preprint (https://www.biorxiv.org/content/10.1101/2024.10.22.617611v1).

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Mots-Clés: antibody, drug conjugates, aptamer, siRNA conjugates, bioimaging, epidermal growth factor receptor, gefitinib, glioblastoma, endocytosis, nucleic acid aptamers, RNAi

Not Just Appetite: Obesity in Down Syndrome is a Trisomy-Driven Inflammatory Stress State.

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Résumé

Introduction

Down syndrome (DS) is associated with a high prevalence of obesity from early life, yet the underlying biological mechanisms remain poorly understood. In the general population, obesity primarily arises from dysregulated hypothalamic control of appetite and energy balance. However, it's unclear whether obesity in DS follows similar neuronal pathways or results from trisomy-specific metabolic stress. Understanding obesity in DS is critical given the substantial variability in BMI and metabolic health among individuals.

In the brain, the hypothalamus stands as a central hub for the regulation of energy homeostasis. Unlike most other brain regions, it possesses a direct anatomical and functional connection with the systemic circulation. This strategic positioning enables the hypothalamus to integrate peripheral cues and orchestrate adaptive physiological responses, including appetite regulation, energy expenditure, and neuroendocrine signaling.

To elucidate the mechanisms driving obesity in DS, we modeled neuroinflammatory stress using iPSC-derived hypothalamic neurons from euploid individuals. By comparing transcriptomic profiles between DS and non-DS individuals across varying BMI and obesity statuses, we aim to identify trisomy-specific alterations in hypothalamic function and their potential contribution to metabolic dysregulation in DS.

Methods

iPSC lines (n=6) derived from euploid control individuals were differentiated into induced hypothalamic neurons (iHTNs) following a well-established 40-day protocol involving dual SMAD inhibition, Shh-mediated ventral diencephalic patterning, and DAPT-induced maturation. To model acute neuroinflammatory stress, Day 40 iHTNs were treated with IL-1β (10 ng/mL) for 3 hours and analyzed via bulk RNA sequencing. The resulting transcriptomic signatures were compared against two independent cohorts: (1) DS-iHTNs from the

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GO-DS21 project, stratified by donor BMI (high BMI: > 35 vs. low BMI), and (2) published transcriptomic profiles from super-obese and control iHTNs from non-DS euploid donors.

Results

Transcriptomic profiling of control iHTNs exposed to IL-1β revealed a robust induction of pro-inflammatory signaling, including TNF, IL-17, JAK-STAT, and NF-B pathways. Surprisingly, the transcriptomic signature of high-BMI DS iHTNs showed limited overlap with the signatures of non-DS ”super-obese” donors. Instead, high-BMI DS neurons exhibited a strong convergence with the IL-1β-treated state, characterized by the activation of cytokine, extracellular matrix, and hypoxia pathways, alongside suppressed neuroactive ligand and synaptic signaling. This inflammatory profile was further underscored by the consistent dysregulation of Human Chromosome 21 (HSA21) genes linked to immune responses, such as MX1 and MIR155HG.

Conclusions

Our findings demonstrate that obesity in DS represents a trisomy-conditioned metabolic stress state that is fundamentally distinct from canonical obesity. The striking similarity in transcriptomic signatures between high-BMI DS iHTNs and the IL-1β-treated inflammatory model rather than non-DS ”super-obese” profiles suggests that DS-related obesity is driven by chronic, HSA21-mediated inflammatory signaling. These results identify immune-mediated pathways as primary therapeutic targets for managing metabolic health in the Down syndrome population.
Funding: ANR GENESIF-DS21 and EU Horizon 2020 (Grant 848077 GO-DS21)

Mots-Clés: Down syndrome, Obesity, Hypothalamic neurons, Neuroinflammation, iPSC model, Transcriptomic analysis.

Synergism between Krameria lappacea root extracts and gentamicin against Gram-Positive bacteria.

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Résumé

Over the past years, one major public health priority is to develop new antibacterial drugs due to rising resistance and few viable alternatives exist. One promising strategy is enhancing existing antibiotics through combination therapy, by pairing them with plant-derived extracts, which has gained increasing attention in recent decades (1).
Previous research demonstrated that *Krameria lappacea* root extracts, rich in neolignans, exhibit strong antibacterial activity, with MIC values of 0.5–2 μg/mL against Gram-positive bacteria (2). This study explored the synergistic antibacterial potential of *K. lappacea* root supercritic fluid extracts combined with conventional antibiotics, building on *LickanAntay* traditional medicinal knowledge.

Extracts were prepared using C02 as supercritical fluid and ethanol as co-solvent with 5% (KL5), 10% (KL10), and 20% (KL20). Chemical analysis via HPLC-PDA-HRMS/MS and the GNPS platform revealed as expected a rich composition of polyphenolic compounds, including neolignans, but also methoxy-catechins, phenylethyl-hexosides, and flavonolignan derivatives, coherent with previus analyses reported for *K. lappacea* (3).

Notably, neolignans dominated the less polar KL5 extract, while flavonolignans and other polar compounds prevailed in the more polar KL20 extract, with nine phenolic compounds identified for the first time in this species. *In vitro* tests showed that the KL5/gentamicin combination exhibited synergistic effects against *Bacillus spp.*, *Listeria spp.*, and *Staphylococcus spp.*, with FICI values ranging from 0.27 to 0.48. The major neolignan compound in KL5 was isolated and tested with gentamicin on *Staphylococcus spp.*, demonstrating a slight synergistic effect with FICI values around 0.8. These findings highlight the potential of *K. lappacea* extracts to enhance antibiotic efficacy and combat bacterial resistance.

*Intervenant

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Mots-Clés: Dereplication, Synergism, Antibiotic

Efficient synthesis route toward lipopeptides with application to fluorescent antifungal echinocandins

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Résumé

Invasive fungal infections (IFIs) are increasing significantly in nosocomial settings and are responsible for 2.5 to 3.8 million deaths per year worldwide. Only four families of antifungal drugs are currently used to fight against IFIs and rising resistances are alarming. The present work belongs to a global project conducted at the Laboratoire d'Innovation Therapeutique in Illkirch, France, whose goal is to identify new antifungal candidates and understand their mode of action following a chemical biology approach.
Among the antifungal agents currently used, one family stands out. First proposed in the 2000s, Echinocandins (EC) are cyclic lipopeptides of natural origin that non-competitively inhibit ß-(1-3)-D-glucan synthase, an enzyme essential for the integrity of the fungal cell wall. Despite their great interest, their exact mechanism of action remains unclear. In addition, their intensive use has led to the emergence of resistances. All this results in a loss of sensitivity found in many fearsome fungi, especially those isolated from hospitalized and immune-compromised patients.

There is therefore a need for molecular probes to explore ECs' mechanism of action and resistance modalities. Due to their structural complexity, only few total syntheses and very limited fluorescent analogues have been reported yet.

Here, we present a versatile solid-phase strategy to readily access to cyclic lipopeptides derived from ECs. Using a safety-catch linker resin, a cyclization-release approach affords high-purity ECs azido-analogues that retain activity against *Candida albicans* following the EUCAST reference method. A subsequent click ligation with several alkyne-fluorophores, permitted to analyse the influence of diverse fluorophores and their linker on the antifungal

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activity. Thus this strategy was successfully applied to the synthesis of unprecedented fluorescent ECs to visualize their interaction with fungal cells by confocal microscopy.

This versatile methodology delivers the first fully synthetic fluorescent echinocandins, providing powerful tools to explore EC action and fungal resistance mechanisms.

Mots-Clés: echinocandins, lipopeptides, invasive fungal infections

High-resolution visualization of the architecture of invadopodes in melanoma

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Résumé

Cellular invasion is a complex process requiring the degradation of the extracellular matrix (ECM). In melanoma, as in many other cancers, this ECM degradation is carried out by specialized cellular structures called invadopodia.
Invadopodia are invasive, actin-rich membrane protrusions capable of degrading the ECM. They are highly organized cellular structures involving complex signaling mechanisms comprising various proteins such as actin, cortactin, Tks5, and Pyk2.

In this project, we use two-color 3D dSTORM (Stochastic Optical Reconstruction Microscopy) super-resolution microscopy to reveal the ultrastructural architecture of invadopodia with a lateral resolution of 20-30 nm and an axial resolution of 50-60 nm. The principle of this technique relies on stochastic fluorophore blinking within the sample, allowing the isolation of fluorescence events, the determination of their localization, and the reconstruction of a super-resolved image. A cylindrical lens, generating astigmatism, distorts the point spread function (PSF) along the Z-axis, thereby enabling three-dimensional imaging.
Visualization of the fine structure of invadopodia requires the optimization of several parameters. Resolving such a structure allows for a better understanding of the organization and architecture of invadopodia in relation to the degree of malignancy.

Mots-Clés: invadopodia, melanoma, STORM 3D, architecture

*Intervenant

Flow cytometry as a key tool in chemobiology, pharmacognosy, and bioremediation

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Introduction and objectives:

Over the past two decades, flow cytometry has undergone major technological advances, including miniaturization and the development of high-throughput screening (HTS) capabilities [1, 2]. These improvements have increased accessibility, sensitivity, and multiparametric analysis potential. As a result, flow cytometry is now widely used in fields ranging from eukaryotic cell biology to microbiology, pharmacology, and environmental sciences.

Since 2007, the eBioCyt UPS1401 platform (University of Strasbourg) has developed miniaturized fluorescence-based assays for both eukaryotic and prokaryotic cells [3–5]. This work highlights the role of flow cytometry in interdisciplinary projects aimed at developing tools for cellular and bacterial assays, including probe–bacteria interactions, antibacterial activity of natural compounds, cytotoxicity of pollutants, and oxidative stress in mammalian cells.

Materials and Methods:

Gram-positive and Gram-negative bacteria were incubated with fluorescent probes, including Nile Red-based antimicrobial peptides and the solvatochromic peptide UNR-1, enabling wash-free staining analyzed by flow cytometry. Antibacterial activity of natural compounds, such as sesquiterpene coumarins from *Ferula communis* L., was evaluated using dose–response experiments and propidium iodide staining to assess viability. For environmental applications, pollutant cytotoxicity, including asbestos-containing waste, was assessed on mammalian cell lines. Oxidative stress assays were performed to quantify reactive oxygen species (ROS) production and evaluate cytotoxicity after exposure to synthetic molecules.

Results and discussion:

Flow cytometry enabled rapid and sensitive characterization of cellular responses across all projects. Fluorescent probes showed differential bacterial labeling, with UNR-1 (bearing Alared) exhibiting the highest efficiency [6, 7]. Dose–response relationships were established for several bacteriotoxic compounds, and sesquiterpene coumarins demonstrated antibacterial activity [8].

In mammalian cell lines, flow cytometry allowed quantification of oxidative stress and cytotoxicity, supporting the development of HTS-compatible assays for drug evaluation. In environmental applications, a bioremediation strategy showed promising efficiency in removing iron from asbestos-containing waste.

Conclusion:

Overall, this work demonstrates the versatility of flow cytometry as a central tool for high throughput applied research in pharmacology and environmental sciences. Future work will focus on validating the bioremediation approach and assessing its impact on cytotoxicity reduction.

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doi: 10.1016/j.fitote.2025.106833. Epub2025 Aug 17.

Keywords: Flow cytometry, fluorescent probes, bacterial toxicity, bioremediation

Endoplasmic Reticulum-Targeted Polarity-Sensitive Fluorescent Probes for Live Cell Imaging

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Résumé

The Endoplasmic Reticulum (ER) is an essential and dynamic organelle involved in protein synthesis, lipid metabolism and calcium regulation. ER dysfunction is associated with numerous diseases, including neurodegenerative diseases, inflammation, and cancer1, creating a strong need for tools able to image and monitor its structure in living cells. In this regards, small-molecule fluorescent probes are particularly attractive for live cell imaging. Among them, environment-sensitive fluorophores such as solvatochromic dyes are valuable for sensing local polarity and lipid organization of biomembranes through changes in their fluorescence properties, enabling ratiometric fluorescence imaging and quantitative analysis of membrane properties2. Most reported ER probes are based on fluorophores such as BODIPY, Nile Red, naphthalimides, coumarins, or rhodamines, but often suffer from poor aqueous solubility, limited sensitivity to the environment polarity and photostability, small Stokes shifts, or demanding syntheses. In contrast, fluorene-based push–pull dyes offer attractive photophysical properties including outstanding solvatochromism, high extinction coefficients and fluorescence quantum yield, red-shifted emission, and high photostability3. Here, we present fluorene-based fluorescent probes functionalized with specific ER-targeting units such as propyl chloride, phenylsulfonamide, or glibenclamide enabling selective localization. The obtained fluorene-based probes display significant solvatochromism in organic solvents and in models of lipid membranes. Moreover, ratiometric fluorescence microscopy techniques were used to prove sensitivity of synthesized probes to polarity and lipid order of ER membranes of live cells.

Mots-Clés: Endoplasmic reticulum, fluorescent molecular probes, cellular imaging

*Intervenant

Synthesis, characterization and applications or thienoguanosine (thG) an outstanding isomorphic fluorescent analogue of guanosine

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Résumé

Thienoguanosine (thG) is an isomorphic fluorescent analogue of guanosine. Its structure is very close to guanosine and as a result it can be inserted in a DNA or RNA sequence without remarkably perturbing the structure. Moreover, it possesses a high quantum yield and two tautomers that can provide additional information on its environment. The fluorescence of thG remain significantly high even when incorporated in nucleic acids. All of this makes thG an outstanding probe for DNA and RNA study, as a recent study on G-quadruplexes (G4) has proven (Singh et al., 2026). G4 are non-canonical secondary structures resulting of the folding of G rich DNA or RNA sequences, in the presence of a cation. We focused on the telomeric sequence hTel22 G4, in which 9 of the 12 G residues have been substituted one by one by thG, in order to map the conformational dynamics of hTel22 G4. thG has been introduced into hTel22 thanks to solid-phase synthesis of oligonucleotides with the phosphoramidite method. Currently we are testing other kinds of functionalisation.

Mots-Clés: Fluorescent guanosine analogues, Nucleic acids, Fluorescence, G, quadruplexes

*Intervenant

Fourier-Based White-Light Interferometric Microscopy for Surface Topography and Spectral Imaging

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Résumé

White-light interferometric microscopy enables non-destructive, full-field measurement of surface topography and optical properties. Recording interference patterns while scanning the sample and calibrating, a hyperspectral reflectance map is generated. Using a Mirau-type interferometer with Fourier transform processing provides the spectral response of the sample with diffraction-limited lateral resolution of a few micrometers and axial sensitivity of around one nanometer. The method allows simultaneous acquisition of quantitative topography and spectral reflectance over small areas.

*Intervenant

Characterization of IKK–substrate interaction mechanisms

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Résumé

NF-B signaling (Nuclear Factor kappa-light-chain-enhancer of activated B cells) controls fundamental biological processes, including inflammation, immune responses, cell survival, and tissue repair (Mulero et al., 2019). There are two main NF-B signaling pathways: the canonical and the alternative pathways, both converge on the IKK (IB kinase) complexes. Those IKK complexes share a commun catalytic core composed of homo- or heterodimers of the homologous subunits IKKα and IKKβ. These proteins display a similar architecture consisting of a kinase domain, a ubiquitin-like domain, and a dimerization domain.
In both the canonical and alternative pathways, IKK complexes phosphorylate their substrates (IBα and p100), leading to their partial or complete degradation by the proteasome and the release of NF-B dimers, which then translocate into the nucleus to regulate gene expression. Dysregulation of these pathways results in severe outcomes, including complex and chronic diseases. Therefore, a comprehensive understanding of the molecular mechanisms, particularly the specific interactions of IKK complexes with their substrates, is essential to identify new therapeutic targets.
The recent identification of a conserved docking motif (YDDΦxΦ consensus with Φ : hydrophobic amino acid) located at the C-terminus of IBα has represented a significant breakthrough, providing the first insights into this interaction mechanism (Li C, Moro S et al., *Nat. Commun.*, 2024. Based on this discovery, an initial model of the interaction between an IKKβ homodimer and a peptide containing the docking motif has been established, paving the way for more comprehensive structural studies. Hence, this project aims to determine the structure of the IKK/IBα/NF-B complex by cryo-electron microscopy, in order to elucidate the mechanisms of substrate recognition and interaction.

Mots-Clés: IKK complex, protein–protein interactions, NF, B signaling

*Intervenant

Role of the chaperone HSP90 on siderophore biosynthesis in Pseudomonas aeruginosa

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Résumé

As iron is an essential nutrient for almost all living organisms and is poorly bioavailable, its acquisition is a highly regulated process. To harvest iron from the environment, bacteria produce iron-chelating proteins called siderophores. In *Pseudomonas aeruginosa*, the biosynthesis of its main siderophore, pyoverdine, involves four non-ribosomal peptide synthetases (NRPSs) named PvdD, PvdI, PvdJ and PvdL and other enzymes such as PvdA, PvdF, PvdH and form together a multi-enzymatic complex located into the cytoplasm and anchored to the membrane called siderosome (Schalk, 2025). The heat-shock protein 90 (HSP90) is a chaperone protein well studied in eucaryotes and linked to pathogenicity and virulence in some bacteria (Grudniak *et al.*, 2018). Preliminary data showed that some NRPS are client protein of the HSP90, suggesting its implication in the formation of the siderosome and thus in siderophore synthesis. To study this question, a mutant DHSP90 deleted from the gene encoding the chaperone protein was constructed and tested for PVD production, confirming the reduction of pyoverdine production in the absence of the chaperone. Supernatants were analyzed by MALDI-TOF and showed no difference in the pyoverdine structure produced by the wt and DHSP90 strains. To investigate how the absence of the chaperone impacts the localization of the NPRS and siderosome, cellular fractionation was carried out on *P. aeruginosa* DHSP90 tagged-NRPS. In parallel, we also conducted cell free protein synthesis of NRPS to determine *in vitro*, if the chaperone has an effect on the folding on one of the NRPS. This combination of *in vivo* and *in vitro* approaches will highlight the role of HSP90 on pyoverdine synthesis and *P. aerignosa* virulence.

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Mots-Clés: Siderosome, HSP90, Pseudomonas aeruginosa, pyoverdine

*Intervenant

Innovative Microfluidic Solutions for Drug Discovery

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Résumé

The microfluidics department of the PCBIS platform develops innovative microfabrication tools for drug discovery, enabling the creation of high-precision, cost-effective and physiologically relevant *in vitro* models. Our workflow covers the entire process, from custom microchip design and mold fabrication to PDMS casting, surface coating, cell culture, and imaging. Here we present the versatility of our expertise through several examples: i) micropatterned microfluidic chips for reproducible cell assays and controlled neuronal network formation; ii) compartmentalized devices with microchannels to separate axons and soma for region-specific drug testing; iii) a human cell-based blood–brain barrier (BBB)-on-a-chip as a relevant complement to the existing *in vivo* BBB model on the platform; iv) fluorescence exclusion-based microfluidic assays to monitor sub-micrometric cell volume changes in living cells; v) droplet-based microfluidic screening for reduced reagent and cell consumption, enabling high-throughput assays and applications in personalized medicine. Together, these developments illustrate the ability of the PCBIS microfluidics department in addressing diverse challenges in drug discovery, ranging from physiologically relevant organ-on-a-chip models to the miniaturization of laboratory processes through lab-on-chip systems.

Mots-Clés: Microfluidic, Microfabrication, Micropatterning, Organ on a chip, Lab on chip, Screening

*Intervenant

Pin1-mediated modulation of p53 diffusion properties and impact on phase separation

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Résumé

The TP53 gene coding for the tumorsuppressor p53 protein is mutated in 50% of human cancers. Missense mutations in the DNA binding domain impair p53 binding to DNA response elements (loss-of-function). In addition, certain mutations, which are conserved in several types of cancers (hotspot mutations), induce the acquisition of oncogenic functions through new protein-protein interactions (gain-of-function). Both wt and mutant p53 (p53 mut) proteins undergo liquid-liquid phase separation (LLPS) in the nucleus. Notably, p53 mut proteins show an accelerated solid-like phase transition (SLPT) compared to wt p53.The peptidyl-prolyl cis-trans isomerase Pin1 binds to multiple P-Ser/Thr-Pro motifs located within the disordered regions of p53. Pin1 is overexpressed in cancer cells where it appears to enhance the oncogenic gain-of-function activities of p53 mutproteins. The aim of this study is to evaluate the effect of Pin1 activity on p53 diffusion and phase transition properties.

Mots-Clés: p53, liquid liquid phase separation, diffusion

*Intervenant

PACSI A new analytical service of PCBIS

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Résumé

PACSI (La Plateforme d'analyse chimique de Strasbourg Illkirch), a new analytical service of PCBIS (UAR 3286), joined the platform in 2024. The facility houses five instruments across three key analytical techniques: 400 MHz and 500 MHz NMR spectrometers, high-resolution LC-MS/MS, MALDI-TOF mass spectrometry, and FTIR spectroscopy.
Drawing on established expertise in NMR and mass spectrometry, PACSI provides comprehensive services for natural and synthetic organic molecules, including structural elucidation, spectral interpretation, accurate mass measurement, and molecular formula determination.

These services are open to all users, including undergraduate and graduate students, PhD candidates, postdoctoral researchers, and researchers from both public and private laboratories, regardless of their location on or off the Illkirch campus.
Self-service access to instruments is available following mandatory training, provided jointly by PACSI staff and the PCBIS prevention officer. Customized consulting and method development services are also available upon request.

Mots-Clés: NMR spectrometers, LC, MS/MS, MALDI, TOF mass spectrometry, FTIR spectroscopy, structural elucidation, spectral interpretation, accurate mass measurement, and molecular formula determination

*Intervenant

Fluorescent probes for the detection of bacteria in body fluids

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Résumé

Rapid diagnosis of bacterial infections is a major challenge in the fight against antimicrobial resistance, particularly to enable targeted antibiotic administration and to avoid antibiotic overuse. Current diagnostic methods are slow as they rely on bacterial culture (Váradi, Chem. Soc. Rev. 2017), leading to the widespread use of broad-spectrum antibiotics, which promotes resistance development and increases patient mortality. To address this critical challenge, we are developing an innovative strategy for bacterial detection in body fluids based on enzyme-activable "turn-on" fluorescent probe. These probes consist of two Nile Red fluorophores linked by a peptide substrate specific to an exoenzyme from Staphylococcus species. In aqueous environments, the fluorescence of the probes is quenched due to the formation of non-fluorescent H-aggregates (Karpenko, JACS 2015). Upon enzymatic cleavage, the fluorophores are separated, leading to the fluorescence "turn on". This approach may ultimately enable faster and more specific diagnosis, helping to limit the misuse of antibiotics and contributing to the fight against bacterial resistance.

Mots-Clés: Bacterial detection, Nile Red, Glutamyl endopeptidase

*Intervenant

Expanding peptide diversity: synthesis and incorporation of non-natural ornithine derivatives (NNODs)

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Résumé

Natural amino acids provide limited basicity, with lysine and arginine being the main naturally occurring cationic side chains. To expand the chemical space available for biomimetic peptide design, we developed a series of non-natural ornithine derivatives (NNODs) compatible with solid-phase peptide synthesis (SPPS). These building blocks were obtained through a scalable and efficient synthetic route, giving excellent yields without requiring purification, and were isolated as stable HCl salts.
We then investigated their incorporation into peptides, as standard SPPS conditions proved challenging due to the lower reactivity of NNODs and their sensitivity to base-promoted Fmoc deprotection, which can lead to side-product formation. To overcome these limitations, a systematic optimization of the coupling conditions in liquid-phase model studies was conducted. Our results showed that a preactivation step is unnecessary and may even reduce coupling efficiency. In contrast, the use of DIC/Oxyma, with repeated coupling cycles when needed, significantly improved NNOD incorporation.

The optimized conditions were defined as 1/2/1 stoichiometry for NNOD/DIC/Oxyma, with two to three coupling cycles and capping using acetic anhydride. This strategy enabled efficient assembly of tripeptides with very good yields and high purity.
Overall, this work provides a practical and robust method for the synthesis and incorporation of NNODs into peptides. By combining a scalable preparation of non-natural basic amino acids with optimized SPPS-compatible coupling conditions, this study opens new opportunities for expanding peptide diversity and designing biomimetic molecules with tailored properties.

Mots-Clés: Solide phase peptide synthesis, non, natural aminoacids

*Intervenant

Do bacterial pathogens exploit exogenous siderophores to proliferate within host cells?

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Résumé

Iron is an essential nutrient for bacterial growth but is tightly restricted in the host during infection by nutritional immunity and competition with the microbiota1,2. To overcome this limitation, many enteric pathogens rely on siderophores, small molecules that bind iron with high affinity. Pathogens can either produce their own siderophores or exploit those produced by other microorganisms present in their environment. Comparative genomic analyses performed in this work show that most antibiotic-resistant enteric pathogens encode multiple siderophore uptake systems, suggesting flexible iron acquisition strategies depending on environmental conditions. Consistently, we previously observed that under acidic conditions mimicking the intestinal environment, *Salmonella enterica* shifts iron acquisition toward the exploitation of exogenous siderophores, largely because endogenous siderophore production decreases3.
Despite the widespread ability of bacterial pathogens to utilize multiple siderophores, it remains unclear whether exogenous siderophore exploitation contributes to iron acquisition during intracellular infection. This project aims to determine if intracellular *Salmonella* can sense and exploit exogenous siderophores and whether this strategy supports bacterial proliferation within host cells. We further investigate how iron availability and iron acquisition strategies vary across distinct intracellular niches, including vacuolar and cytosolic environments, using infection models in epithelial cells and macrophages. Understanding how pathogens acquire iron across different infection environments is essential to better predict their behavior within the host and may help identify new therapeutic targets.

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Mots-Clés: iron, nutritional immunity, enteric pathogens, siderophores, intracellular infection

*Intervenant

Transitions in the RNA polymerase II machinery during oocyte growth and zygotic genome activation

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Résumé

Folliculogenesis and the initiation of embryonic development require precise regulation of gene expression, particularly at the level of transcription initiation by RNA polymerase II (RNA Pol II), which transcribes all protein-coding genes. In somatic cells, the initiation of transcription by RNA Pol II results from the sequential assembly of the pre-initiation complex (PIC) at a basal promoter. The PIC comprises six general transcription factors (GTFs) and RNA Pol II. The first GTF to be recruited is TFIID, composed of the TATA-binding protein (TBP) and thirteen TBP-associated factors (TAFs).
During oocyte growth, an intense transcriptional activity is required for the establishment of the maternal transcriptome. This process relies on a change in the RNA Pol II transcription initiation machinery. The TBP-TFIID complex is replaced by the specific TBPL2-TFIIA complex, which allows the accumulation of maternal reserves essential from oocyte maturation through the onset of embryonic development, a period during which transcription is inactive. At the onset of development, the maternal-to-zygotic transition (MZT) occurs, during which the maternal transcriptome is progressively replaced by the zygotic transcriptome, notably through zygotic genome activation (ZGA).

At this stage, a new mechanism for RNA Pol II transcription initiation is established. Although its composition remains largely unknown, TBP has been shown to be re-expressed, while TBPL2 disappears suggesting that the TBP–TFIID complex is required for ZGA. However, although zygotic deletion of *Tbp* is lethal in mice, it does not result in a defect in RNA polymerase II activity, indicating that the mechanism of transcription initiation during ZGA remains to be elucidated.
Thus, my thesis project aims to identify the protein complexes that govern Pol II transcription initiation during these transitions. The central question of my project is therefore: what is the composition of the RNA polymerase II transcription initiation machinery during oocyte growth and early embryonic development?

*Intervenant

Indolenine Oxazaborinine Styryl Dyes as a New Fluorescent Scaffold to Assess the Effect of Furan Position on Directed Photooxidation-Induced Conversion

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Résumé

Photomodulable fluorescent probes have many applications in advanced bioimaging and microscopy. Upon light irradiation, these molecules can undergo various modifications affecting their photophysical properties and leading to photoconversion or photoactivation. Recently, our group established a new mechanism called "Directed Photooxidation Induced Conversion" (DPIC)1–3. When exposed to light, a fluorophore produces singlet oxygen which can then react with the fluorophore, often leading to photobleaching. In the DPIC mechanism, the oxidation is directed towards an Aromatic Singlet Oxygen Reactive Moiety (ASORM) such as furan, which disrupts its conjugation with the fluorophore.
These chemical transformations lead to photophysical variations, namely hypsochromic shifts and fluorescence enhancement. The DPIC concept has already been demonstrated with several fluorophores such as BODIPYs1,2 and styryl coumarins3 . In this work, we extend the scope of this mechanism by providing a new class of photoresponsive fluorophores, the Indolenine Oxazaborinine Styryl Dyes (IOS). Based on this new scaffold, we synthesized a total of five fluorescent probes in which the furan was introduced at different positions. Here we show that depending on its location, the conjugation of the furan moiety influences both the photophysical properties of the fluorophore and its photomodulation properties. Overall, this work provides new insights into the DPIC mechanism through a comprehensive structure/properties relationship study on a new class of photomodulable fluorophores.

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Mots-Clés: Fluorescent probe, photoconversion, Borondifluoro Indolenine

*Intervenant

Nitrogen-Assisted Decarbonylative Fukuyama Coupling for Amine Synthesis

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Résumé

The Fukuyama coupling is a well-established method for the synthesis of ketones from thioesters and organozinc reagents. However, its application to the direct synthesis of amines remains limited. In 2019, Bihel and co-workers introduced POxAP as an efficient palladium precatalyst for Fukuyama cross-coupling, enabling mild and practical conditions.
Herein, we report a nitrogen-assisted decarbonylative variant that provides direct access to substituted amines from amino-thioesters. The transformation proceeds via a palladium intermediate in which the proximal nitrogen functionality promotes decarbonylation, diverting the classical pathway from ketone formation toward C–C bond formation at the amine center.

The method operates under mild conditions and exhibits broad scope, tolerating secondary, tertiary and quaternary carbon centers. More than 25 examples were obtained with moderate to excellent yields. In addition, the use of flow conditions for the preparation of organozinc reagents improves scalability and reproducibility.
This work expands the reactivity of Fukuyama-type couplings and provides a practical approach to structurally diverse amines.

Mots-Clés: Fukuyama Coupling, Decarbonylation, Flow Chemistry

*Intervenant

Combinatorial Search for Artificial Receptors of Neurotransmitters based on Lipid Nanoemulsions

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Résumé

Neurotransmitters (NTs) are chemical messengers responsible for the communication between neurons throughout the human body. NTs are essential to the proper function of the nervous system as well as the communication of organs with the nervous system. Abnormal levels of NTs can therefore be tied to a variety of physiological and neurological disorders, so that the detection of such imbalances is of high interest. However, the recognition of small molecules in complex mixtures remains a challenging endeavor. In nature, the recognition of NTs is performed by protein receptors containing highly structured and functionalized binding sites selective to their target. Lipid nanoemulsions (LNEs) have shown to be promising artificial receptors for dopamine when loaded with a boronic acid as recognition ligand (RL) selective to catechol moieties. Following this line of research, we intend to mimic natural biding sites by incorporating hydrophobic analogues of common amino acid side chains as RLs, where the capture of the hydrophilic analytes in the lipid nanoreactors is performed through supramolecular interactions with the RLs such as hydrogen bonding, electrostatic interactions or π-π stacking. Inspired by biological protein receptors, we developed a library of lipophilic decarboxylated amino-acid derivatives (AAs). A combinatorial strategy and high throughput spectroscopy methods, based on the emission shift of an aldehyde dye sensitive to primary amines, were used to find AA mixtures with an emergent affinity and selectivity towards the following NTs: dopamine, histamine, noradrenaline and serotonin. Using this approach, we first discovered that LNEs loaded with our glutamic acid analogue (EC16) showed higher capture of NTs than other RLs. Secondly, mixtures of EC16 with the glutamine analogue (GC16) and EC16 with the methionine analogue (MC16) displayed a higher capture of NTs than EC16 alone and an emergent selectivity towards dopamine. To further improve the sensitivity of our probe and to emulate the 3D structure of biological protein receptors, we intend to add hydrogen-binding groups to the RLs. Thus, causing them to pre-organize in the LNEs, which adds structural recognition to the already demonstrated functional recognition of our probe.

Mots-Clés: nanoemulsions, neurotransmitters, artificial receptors, molecular recognition, supramolecular chemistry, combinatorial chemistry

*Intervenant

Investigation of biobased compounds derived from Hypholoma genus for the formulation of phytotoxic biocontrol products

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Résumé

Long-term overuse of chemical herbicides has caused weed resistance, environmental pollution, and harm to non-target organisms. There is an urgent need for eco-friendly and sustainable alternative as bioherbicides to support green agricultural development. *Hypholoma* fungi are widely distributed saprotrophic macrofungi that grow on decaying wood. They produce diverse bioactive secondary metabolites including terpenoids, sesquiterpenoids, sterols, phenolic derivatives, and fatty acids, some of which have reported biological activity. Preliminary data generated in our laboratory revealed that the aqueous extract of *Hypholoma fasciculare* exhibited promising phytotoxic activity. This observation leads to the hypothesis that other macrofungi species within the same genus may possess similar bioactive properties. In this study, a preliminary herbicidal activity screening was conducted on 12 extracts obtained from 4 *Hypholoma* species of which 2 are synonyms: *Hypholoma fasciculare*, *Hypholoma capnoides* and *Hypholoma lateritium*, using garden cress (*Lepidium sativum* L.) seeds as the model target plant. The results indicate that three ethyl acetate extracts and one water extract exhibited interesting herbicidal activity reducing both germination rates and radicle length. The same results also show that the three investigated species exhibit moderate phytotoxic activity towards cress seeds. In order to identify the active phytotoxic compounds, a first HPLC-UV method was developed to separate the targeted compounds from the active extracts. This step will be followed by an online fractionation and the implementation of the *in-vitro* herbicidal assay. These final steps will allow highlighting the more active fractions and the corresponding active molecules.

Mots-Clés: Macrofungi, Hypholoma, phytotoxic activity, bioherbicides, bioguided fractionation.

*Intervenant

Multi-omics network integration across disease progression in myotubular myopathy

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Résumé

X-linked myotubular myopathy (XLMTM) is a rare and severe form of centronuclear myopathy (CNM) caused by loss-of-function mutations in Myotubularin 1 (MTM1). Previous studies have used network-based integration to combine different layers of omics with public knowledge bases into a multilayer network, revealing both pathogenic and protective pathways in XLMTM. However, the analyses overlooked the temporal dynamics of disease progression across developmental stages. Moreover, the coordinated impact of transcriptomic and proteomic changes on downstream metabolic alterations remains poorly understood. To address this, we performed longitudinal transcriptomic and proteomic analyses in the tibialis anterior muscle of Mtm1-/y mice at embryonic, early, and late developmental stages. These analyses revealed temporal dysregulation at the pathway level, with coordinated changes in gene and protein expression across stages. Notably, pathway-level overlap between transcriptomic and proteomic layers highlighted convergent molecular alterations, emphasizing the need for time-resolved integrative approaches to capture disease progression. Building on these findings, we propose a temporal multi-omics network framework that integrates transcriptomic, proteomic, metabolomic, and lipidomic datasets across developmental stages. Transcriptomic and proteomic profiles are modelled as a time-resolved multiplex network, in which each stage represents a distinct layer and is connected by directed temporal edges. Metabolomic and lipidomic data collected at the late stage are incorporated via pathway-based bipartite connections linking genes, proteins, and metabolites. Network propagation using Random Walk with Restart (MultiXRank), seeded from Mtm1 in the early stage, enables the topological and functional prioritization of molecular features and pathways and potentially captures the dynamic disease trajectories. Overall, this provides a comprehensive view of disease progression, facilitates identification of candidate biomarkers, and highlights potential therapeutic targets for XLMTM.

Mots-Clés: Centronuclear myopathy, MTM1, Multi, omics integration, Temporal dynamics, MultixRank, Metabolomics, Lipidomics, Transcriptomics, Proteomics

*Intervenant

Structuring and Analysing Oral and Dental Data from the GenIDA Database in Rare Diseases with Intellectual Disability

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Résumé

Rare genetic disorders associated with intellectual disability, with or without autism spectrum disorders or epilepsy, may present with oral and dental abnormalities that have a significant impact on patients' health and quality of life. However, these manifestations remain insufficiently described due to the rarity of these conditions. Oral and dental features nonetheless represent clinically relevant signs that may contribute to diagnosis, follow-up and patient management, particularly in connection with rare oral and dental diseases monitored by the O-Rares network https://www.o-rares.com/. The international GenIDA database is a participatory registry that collects clinical information through online questionnaires completed by families of patients with rare neurodevelopmental disorders. This approach enables the creation of international and longitudinal cohorts and improves the characterization of the clinical spectrum and natural history of these diseases. However, oral and dental data within GenIDA are often scattered throughout the questionnaire, organized as interdependent questions and frequently described using non-medical language, sometimes in multiple languages. This organization makes direct data exploitation complex and limits their value for clinical research. The objective of this project is to structure oral and dental data extracted from GenIDA in order to make them more readable, usable and reusable. A reproducible methodology is proposed to identify relevant information, group responses related to the same clinical issue and organize the data in a coherent manner. Koolen-de Vries syndrome is used as a case study, as it is sufficiently represented in the GenIDA database, with 257 patients included. It allows the development and testing of a robust methodology intended to be subsequently applied to the analysis of oral and dental data reported by families in other rare conditions.

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Mots-Clés: Base de données, GenIDA, Maladies rares, Anomalies bucco, dentaires, Structuration des données.

Measuring the membrane order of the inner leaflet in the HIV-1 Gag assembly site

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Résumé

Human immunodeficiency virus type 1 (HIV-1) is an enveloped virus that acquires host lipid during budding from the host plasma membrane (PM). Lipidomics studies have shown that virions have a different lipid composition from PM, characterized by enrichment in sphingomyelin (SM), cholesterol (Chol), phosphatidylinositol-(4,5)-bisphosphate (PIP(4,5)P2), and phosphatidylserine (PS). During the late phase of the viral replication cycle, Gag is targeted to the PM via myristoylation and positive charges within the matrix (MA) domain. Subsequently, Gag multimerizes to form a Gag lattice with membrane curvature as a platform for viral assembly. Notably, Gag expression alone is sufficient to drive the formation of virus-like particles (VLPs).
In the PM, lipids are asymmetrically distributed across the bilayer. SM is mainly found in the outer leaflet, whereas PI(4,5)P2 and PS are in the inner leaflet. Saturated lipids, such as SM, together with Chol, tend to form tightly packed (liquid-ordered, Lo) domains, also called "lipid rafts", creating lateral heterogeneity in the outer leaflet. In contrast, most inner leaflet lipids are (poly)unsaturated and form more loosely packed (liquid-disordered, Ld) membranes.

A major question in HIV-1 assembly is how inner leaflet Gag proteins enrich outer leaflet lipids, such as SM, into virions without direct contact. Our previous work showed that Gag brings SM-rich and Chol-rich domains into close proximity in a multimerization- and curvature-dependent manner(1). However, in living cells, the local physical properties (lipid order, polarity, and viscosity) around the Gag are largely unknown. Therefore, it is essential to determine the physical properties of the inner leaflet at Gag assemblies to understand the mechanism of Gag-induced lipid enrichment.
Here, we employed a combination of fluorescence lifetime imaging microscopy (FLIM) and a recently developed solvatochromic probe, NR12-Halo(2), alongside Halo-tagged Gag proteins (Gag-Halo) to quantitatively assess membrane order in the inner leaflet of Gag assemblies. We first confirmed that Halo tagging did not impair Gag expression and VLP production by Western blotting. We also confirmed that NR12-Halo labeling specifically localized Gag-Halo to the PM by confocal microscopy. FLIM measurements were then performed on HeLa cells expressing wild-type Gag (Gag WT) and the multimerization-deficient Gag-WM and Gag-NC mutants, in addition to controls that are preferentially partitioned in Lo and Ld domains. The fluorescence lifetimes of NR12-Halo conjugated proteins revealed that Gag WT significantly increased membrane order compared to Gag-WM and the Ld domain control. Next, to investigate the influence of membrane curvature on membrane order at the assembly, we performed FLIM imaging of cells expressing Gag mutants (Gag-P99A and Gag-EE),

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which are defective in curvature formation. The results showed that Gag-P99A and Gag-EE increased membrane order compared to Gag-WM, but not as much as Gag WT. Together, these findings suggest that both multimerization and membrane curvature are necessary to increase membrane order in the inner leaflet at Gag assembly. This study provides new insight into how Gag reorganizes the PM during HIV-1 assembly.

Mots-Clés: Virology, HIV, 1 assembly, Plasma membrane order, Environment sensitive dye, FLIM

Development of an immunogenic integrin-targeted photodynamic therapy in head and neck tumoroids to re-sensitize patients to immunotherapy

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Résumé

Cancers of the upper aerodigestive tract, including head and neck squamous cell carcinoma (HNSCC), represent a major public health challenge due to their high morbidity and mortality rates. Immune checkpoint inhibitors are currently used as first-line treatments in recurrent or metastatic HNSCC. However, only about 20% of patients respond, highlighting the need for strategies to re-sensitize tumors to immunotherapy. In this context, stimulating anti-tumor immune responses is of particular interest. Photodynamic therapy (PDT), which relies on the activation of photosensitizers (PS) by light to generate reactive oxygen species (ROS) and singlet oxygen (^1O), induces oxidative damage and cell death including immunogenic cell death know to stimulate anti-tumor immune responses.
The aim of this project is to develop and validate, in collaboration with Dr. Figliola's team (ICPEES), an optimized PDT strategy for HNSCC by integrating innovative, tumor-targeted photosensitizers with 3D tumor models. Specifically, we seek to (i) optimize key PDT parameters such as PS concentration, light dose, and oxygenation conditions; (ii) characterize the diffusion and localization of PS within different cellular compartments of tumor organoids; and (iii) investigate post-treatment cellular responses, including immunogenic cell death.

We use patient-derived tumor organoids (PDTOs), which faithfully recapitulate the histological, molecular, and functional features of native tumors. In this study, we compared four BODIPY-based PS designed to assess how structural modifications affect phototoxic potency under both normoxic and hypoxic conditions, intracellular trafficking, and cell death mechanisms. The series includes: a BODIPY core (BOD), a BODIPY conjugated with a RGD peptide for integrin targeting (BOD-RGD), a BODIPY bearing a pH-responsive group activated in acidic organelles (BOD-pH), and a dual-functional construct combining RGD targeting with pH sensitivity (BOD-pH-RGD). Cell viability was assessed using standard colorimetric assays, while confocal microscopy, flow cytometry, western blotting, and immunofluorescence were used to evaluate PS uptake, subcellular distribution, and the expression of hallmarks of immunogenic cell death.

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Across the series, BOD showed the highest phototoxicity at low concentrations, whereas the addition of targeting or pH-responsive groups modestly reduced potency, likely due to increased specificity. Regarding localization, BOD and BOD-pH showed a rather diffuse distribution, whereas RGD functionalization promoted a plasma membrane localization. For all PS, IC values decreased with increasing light dose, and phototoxic effects were maintained under hypoxic conditions, highlighting their potential to efficiently target hypoxic tumors. Post-illumination analysis revealed the activation of damage-associated molecular patterns, together with the activation of apoptotic and autophagic pathways, indicating an immunogenic cell death.
Future work will further investigate cell death mechanisms in more detail and explore the induction of anti-tumor immune responses, in order to determine whether this strategy can re-sensitize HNSCC tumors to immunotherapy.

Mots-Clés: tumoroids, photodynamic therapy, head and neck cancer

Development of a fluorogenic assay for high-throughput screening and identification of ABHD6 modulators in metabolic liver disease

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Résumé

Metabolic liver diseases, including Metabolic-Associated Steatotic Liver Disease (MASLD), have emerged as a major global health concern due to their rising prevalence and their strong association with metabolic disorders. In addition, MASLD progression can lead to advanced liver pathologies such as fibrosis, cirrhosis, and ultimately Hepatocellular Carcinoma (HCC), a malignancy characterized by poor clinical outcomes and limited therapeutic options. Identifying and addressing novel molecular targets involved in early lipid dysregulation is thus essential for potent therapeutic intervention in this domain.

In this context, the alpha/beta hydrolase domain-containing protein 6 (ABHD6) has gained a growing interest as a key regulator of lipid homeostasis. Indeed, this plasma membrane enzyme that was initially described for its role in the degradation of the endocannabinoid 2-Arachidonoylglycerol in the CNS, was recently highlighted for its key implication in hepatic lipid metabolism and metabolic disease progression. Moreover, recent studies reported its contribution to MASLD-associated hepatocarcinogenesis, positioning ABHD6 as a promising therapeutic target. Up to now, the discovery and fine characterization of ABHD6 modulators remains however limited by the lack of robust, scalable, and high-throughput-compatible screening methodologies.

To address this limitation, we established an original and global procedure, including a robust and tailored methodology for producing and purifying ABHD6 in membrane-mimicking environments, as well as a fluorogenic enzymatic assay relying on the hydrolysis of a methylumbelliferyl-based substrate enabling a direct monitoring of ABHD6 activity. The activity assay has been optimized for ABHD6 isolated in detergent micelles and is compatible with quantitative and kinetic analyses. It was further miniaturized, demonstrating its compatibility with high-throughput screening formats. In addition, preliminary validation using reference inhibitors confirmed its suitability for identifying ABHD6 modulators.

Altogether, this study aims to establish a robust platform for the systematic identification of ABHD6-targeting compounds and to provide a valuable tool for drug discovery efforts in metabolic liver diseases.

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Mots-Clés: ABHD6, ABHD6 modulators, fluorogenic enzymatic assay, high throughput screening, Metabolic Associated Steatotic Liver Disease (MASLD)

A metabolically resistant spexin analogue, LIT-01-144, induces potent non-opioid peripheral antinociception in persistent pain via activation of GALR2

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Résumé

Chronic pain affects a significant proportion of the population, with substantial clinical and socioeconomic burdens. Current management largely relies on opioids, which pose risks of dependence and misuse, underscoring the need for alternative therapies. Galanin receptors (GALR1–3) are implicated in pain modulation, but their specific roles remain unclear due to a lack of selective ligands. Recent discoveries identified spexin, a peptide that selectively activates GALR2 and GALR3, offering a novel way to develop pharmacological tools that selectively target these two receptor subtypes. In this study, a modified spexin analog, LIT-01-144, was designed by attaching a fluorocarbon chain to enhance metabolic stability without altering receptor selectivity. In vitro, LIT-01-144 demonstrated high potency toward GALR2 and GALR3 and poor activity at GALR1. Pharmacokinetic studies in mice showed that LIT-01-144 has a significantly longer plasma half-life than native spexin and does not cross the blood-brain barrier. In vivo, LIT-01-144 exhibited potent antinociceptive effects at much lower doses than spexin when administered intracerebroventricularly. While systemic administration had no effect in naïve mice, LIT-01-144 significantly alleviated pain in a model of persistent inflammation induced by CFA. This antinociceptive effect was mediated through GALR2 rather than GALR3 and was independent of opioid pathways. In situ hybridization revealed increased GALR2 expression in dorsal root ganglia of inflamed mice. These results highlight GALR2 as a promising peripheral target for non-opioid pain therapies and establish LIT-01-144 as a valuable pharmacological tool for investigating GALR2-mediated antinociception.

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Mots-Clés: Pain, GPCRs, neuropeptide, pharmacological tool, fluoropeptide

Ancient Arabic Formulations as a Source of Antibiofilm Biomaterials: Synergistic Metal–Plant Combinations Against Multidrug-Resistant Bacteria

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Résumé

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The rapid emergence of multidrug-resistant bacteria, particularly in the context of biofilm-associated infections, highlights the urgent need for alternative anti-infective strategies beyond conventional antibiotics. In this context, ancient pharmacopoeias represent a largely underexplored reservoir of therapeutic knowledge, built on centuries of empirical observations and combining plant, mineral, and animal-derived ingredients.

Unlike modern pharmacology, which often focuses on single active compounds, historical preparations frequently rely on complex combinations of ingredients, suggesting complementary or synergistic mechanisms of action. Among these, plant–metal associations appear recurrently in treatments for skin infections, a field in which topical applications allowed the use of otherwise toxic substances such as metals.

To rationally explore this chemical and biological diversity, we conducted an ethnopharmacological survey of Arabic medical manuscripts dating from the 9th to the 13th century. From more than 300 recorded formulations, 14 preparations targeting infection-related symptoms were identified, of which the majority included metallic components. A preparation described by Al-Kindī1, combining copper with recurrent plant ingredients such as Aloe vera, myrrh and gum ammoniac, was selected based on the frequency and consistency of its components across sources. This selection provided a robust framework to investigate the biological relevance of ancient plant–metal combinations.

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Mots-Clés: Bacterial multidrug resistance, alternative strategies, ancient pharmacopoeias, reservoir of potential therapeutic agents, IRGAP, Interdisciplinary Research Group on Ancient Pharmacopoeias

SOLVENT-FREE BUCHWALD-HARTWIG AMINATION: TOWARDS SUSTAINABLE CATALYSIS FOR SYNTHESIS

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Résumé

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Amines are an integral part of biologically active molecules. The pharmaceutical industry heavily relies on robust and reproducible reactions for the formation of aryl amine moieties, with the Buchwald-Hartwig (BH) amination playing a central role. Its widespread use is spans various stages of drug discovery and process development.1 Traditionally, BH amination is performed in organic solvents such as THF and toluene. Unfortunately, at multi-kg scale pharmaceutical manufacturing, these conditions become extremely costly for the environment, with the solvents accounting for up to 80% of mass use.2 To address this environmental concern and to provide efficient and safe methodology, our aim was to develop eco-compatible conditions for this crucial chemical transformation. We tackled this issue using mechanochemical ball milling.3 By eliminating the need for bulk solvent use, this strategy provides cleaner and ecological synthesis alternatives. While many cross-coupling reactions have been explored under mechanochemical conditions, research on solvent-free BH amination conditions in the literature remains limited.4–7 Building on our previous work developing a novel precatalytic system featuring (Pd(π-allyl)tBuXPhos)Cl in green alcoholic solvents,8 in this study, we demonstrate the application of the same precatalyst in mechanochemical solvent-free reaction conditions.9 We have demonstrated the coupling of aryl halides with various nitrogen-containing substrates including amines, amides, carbamates, ureas, among others. This expansion of reaction scope underscores the potential of our approach in facilitating sustainable and atom-efficient synthesis for synthesis of biologically active molecules.

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Mots-Clés: mecanochimie, buchwald, chimie verte

A Metabolic Rescue Index for Monitoring Therapeutic Response in Centronuclear Myopathies

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Résumé

Centronuclear myopathies (CNM) are a clinically and genetically heterogeneous group of rare
congenital muscle disorders characterized by myober hypotrophy and progressive muscle weak-
ness. Three principal genetic subtypes are recognized: mutations in MTM1 cause X-linked
myotubular myopathy, the most severe form, presenting at birth with profound hypotonia and
respiratory failure and frequently fatal in infancy; mutations in BIN1 underlie autosomal re-
cessive CNM of intermediate severity with childhood onset; and mutations in DNM2 cause
autosomal dominant CNM, the mildest form, with later onset and a more favorable progno-
sis.
While therapies targeting DNM2 reduction or BIN1 modulation show promise in murine mod-
els, clinical transition is hindered by a lack of non-invasive biomarkers to track muscle re-
covery
without repetitive biopsies. This study identies a serum-based metabolic Rescue Index to mon-
itor disease progression and therapeutic response across these CNM subtypes. By integrating
dierential abundance metabolomics from skeletal muscle and serum with transcriptomic and
proteomic datasets from wild-type, disease-model, and rescued mice, we applied a reverse ma-
trix analysis to map systemic metabolite shifts back to upstream genetic drivers and enzy-
matic
complexes.
We identify a convergent biomarker pair with robust cross-model reproducibility: N,N,N-
trimethyl-alanylproline betaine (TMAP) and trans-4-hydroxyproline. TMAP, a byproduct of
MuRF1-mediated myosin degradation, was signicantly elevated in disease states (log2 FC $\approx$
0.83) and fully reversed upon rescue. Conversely, trans-4-hydroxyproline was markedly sup-
pressed in disease and rose signicantly during recovery (r = –0.85 correlation with muscle
mass), reecting P4H-mediated extracellular matrix remodeling. Proteomic proling enabled
identication of P4HB (PDI) overexpression as the chaperone-driven mechanism underlying
this

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anabolic surge. Our ndings demonstrate that the TMAP/4-hydroxyproline ratio provides a robust, biopsy-free surrogate for muscle structural integrity and metabolic normalization. This
Rescue Index aligns with the common therapeutic signatures of DNM2 reduction and BIN1 overexpression, oering a scalable diagnostic tool for human clinical trials to track real-time pharmacological ecacy.
Overall, this work establishes a metabolomics-driven framework for non-invasive monitoring of therapeutic response in CNM, with the TMAP/4-hydroxyproline ratio serving as a cross-genotype metabolic indicator of structural muscle recovery. The convergent dysregulation of these metabolites across MTM1, BIN1, and DNM2 models positions this Rescue Index as a translationally relevant endpoint for upcoming gene therapy and antisense oligonucleotide trials
in centronuclear myopathies.

Mots-Clés: Centronuclear myopathy, MTM1, BIN1, DNM2, Metabolomics, Biomarkers, Ther, apeutic Rescue, Proteomics.

How do GGC repeat expansions located in a ”non-coding” 5UTR region lead to a myopathy?

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Résumé

Oculo-Pharyngo-Distal Myopathy type 1 (OPDM1, OMIM #164310) is a rare adult-onset genetic neuromuscular disorder characterized by progressive weakness and atrophy of

facial, pharyngeal, and distal limbs skeletal muscles. At the histopathological level,

OPDM muscle fibers are characterized by the presence of typical intranuclear inclusions,

which are p62-positive, but of unknown origin. Thanks to progress in whole genome and

long read sequencing, the genetic cause of OPDM1 was recently identified as an abnormal

expansion of 50 to 200 GGC repeats in the 5 untranslated region (5UTR) of the LRP12

gene.

Here, we found that these GGC repeats lie within a previously unrecognized small open

reading frame (sORF), resulting in their translation into a novel polyGlycine-containing

protein. Mass-spectrometry analysis indicates that translation initiation occurs at two near

cognate CTG and GTG start codons located upstream of the GGC repeats. Near-cognate

start codons are codons differing from the cognate AUG start codon by one nucleotide, but

that can nonetheless initiate translation through mispairing with the initiator methionine

tRNA. Imporatntly, expression of this novel polyGlycine protein forms p62-positive

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intranuclear inclusions in muscle cells, thus, recapitulating a key feature of this disease.

We are now in the process of determining the toxicity of this polyGlycine protein in cell culture, and future studies will focus on developing antibodies to test its expression in patient tissues, as well as developing an animal model for this disease.

Overall, these findings suggest that OPDM1 is as a repeat expansion disorder caused by expression of a novel and potentially toxic polyGlycine protein.

Mots-Clés: OPDM1, LRP12, GGC repeat expansion, 5UTR, near, cognate start codon, polyGlycine protein, p62, positive intranuclear inclusions, repeat expansion disorder, skeletal muscle weakness, translational initiation

Investigating the cellular and molecular mechanisms impacting striatal development in a mouse knockout model of Dyrk1a

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Résumé

DYRK1A (Dual-specificity Tyrosine-phosphorylation Regulated Kinase 1A) is a kinase with a prevalent function in neuronal development and involved in numerous cellular processes including cell cycle control and cell viability. While DYRK1A overexpression leads to the neurodevelopmental defects in Down syndrome, its heterozygous loss of function leads to DYRK1A syndrome characterised by intellectual disability, microcephaly, developmental delay, autism spectrum disorders and epilepsy. Homozygous knockout (KO) of Dyrk1a in the mouse leads to early embryonic mortality, precluding studies of Dyrk1a function during later development. My internship laboratory generated a conditional KO mouse model for Dyrk1a to study its role in GABAergic neurons development. Conditional homozygous KO mice die shortly after birth. Furthermore, these mice exhibit striatal agenesis. Previous analyses have shown that postmitotic GABAergic neurons undergo apoptosis at the onset of neurogenesis in the conditional KO embryos. Additionally, the size of the progenitor proliferation zone is increased from the E16.5 stage onwards. The aim of my internship project is to identify the molecular and cellular mechanisms involved in neuronal cell apoptosis and in the impact on progenitor cell proliferation observed in the embryos. I have performed Western blot quantifications of proteins from different pathways leading to cell apoptosis, survival and cycle regulation to identify which pathway(s) is/are affected by Dyrk1a loss-of-function. I will also analyse the cell cycle via immunohistochemistry to investigate how the proliferation of neural progenitor cells is affected.

Mots-Clés: DYRK1A, GABAergic neurons, apoptosis, cell cycle, striatum

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The importance of the citrate mediated iron import pathway in Pseudomonas aeruginosa

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Résumé

Pseudomonas aeruginosa poses a significant threat to both animals and plants, particularly in the context of hospital-acquired infections. This bacterium engages in a crucial struggle with the host for iron, an essential nutrient in both human and bacterial physiology. To enhance iron acquisition, *Pseudomonas aeruginosa* employs siderophores which are small molecules adept at sequestering and importing iron into the cell. It can produce its own siderophores like pyoverdine and pyochelin, as well as utilizing siderophores produced by other microorganisms called xenosiderophores or molecules like citrate, a naturally abundant iron chelator.
Ferric citrate uptake is mediated by the TonB-dependent transporter (TBDT) FecA, yet the regulatory conditions controlling this pathway remain incompletely understood.

This work aims to unravel the mechanisms underlying citrate-dependent iron uptake in *P. aeruginosa* and to determine how this pathway integrates within the broader network of iron acquisition strategies. We combine differential proteomics, targeted gene expression analyses, mutant strains deficient in specific TBDTs, and fluorescent transcriptional reporters to monitor *fecA* expression under varying iron and citrate concentrations.

These approaches allow us to investigate the contribution of FecA, to explore potential alternative transport systems involved in ferric citrate utilization, and examine how ferric citrate uptake competes with endogenous siderophores and various xenosiderophores under iron-limited conditions.
Altogether, this study provides new insights into the regulation and hierarchy of iron acquisition pathways in *P. aeruginosa*, highlighting the adaptability of this pathogen to fluctuating environmental conditions and providing essential knowledge for targeted intervention.

Mots-Clés: iron, Pseudomonas aeruginosa, citrate

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