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Abstract book

Innovative therapies Chantal Pichon

Cell Microenvironment and Cancer Giorgio Seano

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Innovative therapies

Messenger RNA vaccines and therapeutics: from design to in vivo applications

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Abstract

Messenger RNA (mRNA) has emerged as a transformative therapeutic platform, although its development initially faced major challenges related to molecular instability and scalable manufacturing. The success of mRNA vaccines during the COVID-19 pandemic established the clinical and technological relevance of this approach, demonstrating the capacity of mRNA platforms to support rapid, adaptable, and effective vaccine development. These advances were enabled by significant progress in mRNA engineering, production methods, and delivery systems. This breakthrough has opened new perspectives for the development of mRNA-based therapeutics and vaccines across a wide range of applications, including immunotherapy, regenerative medicine, and gene editing. In this presentation, I will review the major milestones that have shaped the field and discuss current knowledge on the critical determinants of mRNA efficacy, including molecular structure, stability, formulation, delivery technologies, tissue targeting, and their impact on translation and in vivo performance. I will also present our work as a showcase, illustrating how these concepts can be applied in practice to advance innovative mRNA therapeutic strategies.

Keywords: mRNA vaccines

*Speaker

Targeting bacterial trans-translation as a novel antimicrobial strategy

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Antimicrobial resistance is a major global health challenge, highlighting the urgent need for new therapeutic strategies. *Trans*-translation, a ribosome rescue mechanism mediated by tmRNA and SmpB, is essential for bacterial survival under stress conditions and absent in eukaryotes, making it an attractive antimicrobial target.
Here, we developed an integrated pipeline combining chemical screening, functional assays, and microbiological analyses to identify small-molecule inhibitors of trans-translation. Using *in vitro* and *in vivo* reporter systems, we screened chemical libraries and identified a family of compounds, including TTi-Ef and its derivatives, as effective inhibitors.

Functional characterization showed that TTi-Ef inhibits *trans*-translation in a dose-dependent manner and exhibits bacteriostatic activity against *Enterococcus faecium*, including multidrug-resistant clinical isolates with diverse genetic backgrounds. These results support the robustness of trans-translation inhibition across clinically relevant strains. Structure–activity relationship studies led to the identification of optimized analogues such as TTi-Ab, displaying improved antibacterial properties.

Importantly, TTi-Ab exhibited an extended spectrum of activity, including Gram-negative pathogens such as *Acinetobacter baumannii*, a critical priority pathogen. TTi-Ab inhibits trans-translation both *in vitro* and *in vivo*, as demonstrated using adapted reporter systems enabling quantification of target inhibition in bacterial cells. However, its antibacterial efficacy appears partially limited by permeability barriers.
Combination assays revealed synergistic effects with the LPS biosynthesis inhibitor CHIR-090, highlighting the potential of *trans*-translation inhibitors to enhance antibiotic activity. Altogether, this work demonstrates that *trans*-translation inhibitors represent a promising new class of antimicrobial agents that can be developed either as novel antibiotics or as adjuvants to improve existing therapies against multidrug-resistant bacteria.

Keywords: Antimicrobial resistance, ribosome, bacteria

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An optimized hiPSC model identifies holoprosencephaly molecular signatures

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Holoprosencephaly, or HPE, is a rare genetic disease characterized by incomplete separation of the cerebral hemispheres for severe cases, and microcephaly for minor forms. Multiple genes are involved in its etiology, with Sonic Hedgehog (SHH) being the most frequently implicated. SHH is a key morphogen essential for proper midline patterning of the developing brain. However, because of genetic heterogeneity, no causative mutation is identified in a large proportion of patients, with only ~30% receiving a molecular diagnosis. Human-induced pluripotent stem cells (hiPSCs) provide a powerful model to address this limitation, as they can be derived from patient cells and differentiated into disease-relevant human cell types. Our goal is to define omics signatures of HPE to deepen the understanding of disease mechanisms and improve diagnostic yield. Previous work of our team established a 12-day protocol to generate anterior neuroectodermal midline cells from hiPSCs using a combination of cytokines, including a 6-day SHH induction. These cells replicate early forebrain identity during the critical developmental window when HPE arises. At this early stage of the pathology, they are highly sensitive to reduced SHH signaling. To enhance the robustness and scalability of this model, we are optimizing the protocol by reducing both cytokine exposure and overall differentiation time. Here, we present our results demonstrating that modulation of cytokine treatment and culture duration improves protocol efficiency while preserving relevant cellular identity. This optimized system will be used for routine characterization of transcriptomic signatures in hiPSC-derived from patients with HPE, as well as in CRISPR-Cas9-engineered hiPSCs carrying SHH mutations of interest.

Keywords: Holoposencephaly, rare disease, neurodevelopment, SHH, diagnosis, hiPSC

*Speaker

Network based analyses of omics data to better understand mollecular mechanisms behind neuredevlopmental disorders

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Holoprosencephaly (HPE) is a rare neurodevelopmental disorder caused by reduced activity of the Sonic Hedgehog (*SHH*) signaling pathway. This disease is characterized by significant heterogeneity both in terms of phenotype and genetic causes. As *SHH* is the main gene involved, eighteen genes are known to play a role in HPE by reducing *SHH* morphogen activity. This genetic complexity leads to a low rate of precise molecular diagnosis (30%), which emphasizes the need to better understand the molecular interactions in HPE. However, the inaccessibility of the primary affected tissue in patients constitutes one of the main challenges in the study of HPE. To overcome this, we developed an in-vitro-based model of human developing neuroectoderm using induced pluripotent stem cells (iPSCs). We performed extensive transcriptomic analyses on this model to provide insight into the molecular consequences of *SHH* deficiency and identified sets of potential genes related to SHH activity. In order to get back to a clinical point of view, we integrated these transcriptomic data with exomic data from a cohort of 199 HPE patient. We then explored weighted gene network built from these integrated data using iterative random walk with restart approaches. With this systematic and patient specific approache we aim to detect distinct gene signatures and phenotypic landscapes that would help to better understand the consequence of *SHH* defect in neurodevlopement and enhance HPE diagnosis.

Keywords: bioinformatics, neurodevlopment, network, omics integration

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A new organoid model reveals the role of Celf1 in the lens development and transparency as an EMT Regulator

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In mice, the inactivation of the *Celf1* gene which encodes an RNA-BP leads to **cataract.** This is in part due to the disorganization of the lens structure which is linked to cytoskeletal alterations. The objective of my work was to characterize the changes affecting cytoskeletal dynamics and the signaling pathways induced by the loss of *Celf1* expression, combining classical cell-based approaches with a **lens organoid model** that we recently developed. This 3D model allows to **reproduce and study lens development and cataract pathology.**

My results, obtained from 21EM15 mouse lens cells, show that *Celf1* inactivation induces a loss of elongation, formation of large lamellipodia associated with actin rearrangement and reduced migratory capacity. While control 21EM15 cells display characteristics suggesting a mesenchymal state, *Celf1* inactivated cells seem to shift towards a more epithelial phenotype. Those results suggest an **epithelial to mesenchymal transition** (EMT) process regulated by **CELF1**. Experiments performed on our organoid model allowed us to show that an EMT process is necessary for lens development and transparency. Indeed, organoid treatment with several pro-EMT pathway inhibitors induced a cataract.

Furthermore, iCLIP and proteomic data, suggest the involvement of the **Wnt signaling pathway** in these processes. Treatment of organoids with Wnt pathway inhibitors partially rescued the cataract phenotype induced by CELF1 loss, demonstrating the **utility of the model for testing therapeutic approaches.**

Overall, our results suggest that **CELF1** may play a role in the differentiation of lens epithelial cells into lens fibers through an EMT process, by modulating Wnt pathway activity. The use of our **organoid model**, combined with a better understanding of the role played by **signaling pathways** in cataract development, could therefore lead us to **discover new drug treatments for cataracts**.

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Keywords: Cataract, CELF1, RNA binding protein, lens organoid, signaling pathway, EMT, drug treatments, therapeutic approaches

Seeing and knowing

Dynamics of the β-cardiac myosin auto-inhibited state explain cardiomyopathy pathogenesis

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Cardiac contractility requires precise regulation. An exciting, newly discovered form of regulation of cardiac contractility involves a β-cardiac myosin OFF-state, the Interacting-Heads Motif (*Car* IHM). Despite its central role in cardiac physiology and disease, *Car* IHM structural dynamics remain poorly understood. Here, we integrate near-atomic resolution cryo-EM with all-atom molecular dynamics to characterize *Car* IHM in solution and in the context of the filament. We describe its conformational ensembles maintained by dynamic interfaces, and the stabilizing effect of the dilated cardiomyopathy mutation E525K, which limits S2 coiled-coil flexibility and impairs myosin activation. Intrinsically disordered regions of *Car* IHM and MyBP-C further modulate these dynamics. Our findings provide evidence for how *Car* IHM ensembles balance OFF/ON states and anchor myosin heads in distinct thick filament environments. This integrated structural and dynamic approach significantly enhances the understanding of thick filament regulation and facilitates predictions of the effects of genetic variants in inherited cardiomyopathies.

Keywords: cardiomyopathies

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Centrosome identity drives asymmetric spindle positioning in neural stem cells

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The orientation and position of the mitotic spindle are critical determinants of organ development and tissue architecture. The prevailing model posits that cortical dynein motors generate pulling forces on astral microtubules and thereby play a central role in spindle orientation and positioning. In polarized *Drosophila* neural stem cells, we confirm that this canonical apical pulling model adequately accounts for spindle orientation but fails to explain spindle positioning along the apico–basal axis. By genetically and physically manipulating the mitotic spindle and centrosome nucleation capacity, we show that the number of astral microtubules nucleated by each centrosome is a key determinant of spindle position along the apico–basal axis. Our findings support a model in which asymmetric pushing forces, rather than cortical pulling, dominate spindle positioning along the apico–basal axis in neural stem cells.

Keywords: ASYMMETRIC CELL DIVISION / MITOTIC SPINDLE POSITIONING / CENTROSOME / TISSUE HOMEOSTASIS / TUMOR STEM CELL

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Computer-Aided Drug Design to develop trans-translation inhibitors

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The development of antibiotic-resistant microorganisms is one of the major public health issues of our century. In this context, the present project is to characterize the mechanism of action of antimicrobial molecules aimed at a new target: trans-translation. Trans-translation refers to a molecular process which allows for the release of ribosomes stalled on faulty mRNAs that lack stop codons as well as the elimination of these mRNAs and mistranslated peptides. The process is performed by the hybrid transfer-messenger RNA (tmRNA) and a small basic protein (SmpB). Essential for the survival and/or virulence of many pathogenic bacteria and absent in eukaryotes, trans-translation is a particularly attractive targets for new antibiotics. Starting from experimentally characterized structures of SmpB in complex with the ribosome and tmRNA , I will describe how we found then assessed the suitability of a binding site for drugs using *in-silico* approaches. As well as how we used Molecular Docking to explore the chemical space and find drug-candidates and then further refine their suitability with Molecular Dynamics.

Keywords: Antimicrobial resistance, Molecular Dynamics, Molecular Docking, antibiotics, ribosome

*Speaker

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Finding its target: Live cell imaging of RARγ nuclear exploration

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Cell identity and function are determined by the complex interplay of multiple molecular modulators. Among these, sequence-specific transcription factors (TFs) play a pivotal role in regulating gene-specific spatiotemporal expression patterns. This process involves the diffusion of TFs through the nucleus to locate and bind their specific DNA response elements, which are situated in cis-regulatory regions of their target genes. To elucidate this process, we investigated the target search dynamics of the retinoic acid receptor RARγ, a representative member of a large and essential family of TFs.

RARγ belongs to the nuclear receptor (NR) superfamily, which comprises 48 members in humans and 49 in mice. These evolutionarily conserved, ligand-responsive transcription factors regulate key processes such as development, reproduction, immunity, energy homeostasis, cell proliferation, differentiation, and metabolism.

We therefore developed a genetically engineered version of the RA-sensitive F9 embryonic carcinoma cell line to enable visualization of endogenous RARγ in living cells. Using fluorescence correlation spectroscopy (FCS), we investigated its nuclear dynamics in both unstimulated and ligand-stimulated conditions. This analysis revealed two distinct RARγ populations with different diffusion rates, whose relative abundances are modulated upon ligand stimulation. To assess the role of structure-dependent interactions between RARγ and the nuclear environment in partitioning between fast and slow populations, we employed CRISPR-assisted point mutagenesis to introduce specific mutations that selectively alter RARγ interactions with chromatin or with protein partners essential for its activity. Analysis of FCS data from these mutant forms enabled us to elucidate the contributions of the RARγ interactome to its target search process.

Keywords: transcription factor, nuclear dynamics, live cell imaging

*Speaker

Structural Characterisation of the Recipient Cell Detection Mechanism by the Bacterial Type IV Secretion System

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Bacterial conjugation is a biological process through which a donor cell transfers DNA to a recipient cell. It is the primary cause of the spread of antibiotic resistance genes among bacterial populations, significantly contributing to the global antibiotic resistance crisis (1). The DNA transfer is mediated by a large molecular machinery embedded in the donor cell membranes, called the conjugative Type IV Secretion System (T4SS) (2). To establish the first contact between the two bacteria, the donor cell produces a long extracellular filament – the conjugative pilus – essential for DNA transfer (3). Despite its importance, the structure and mechanism of the initial contact between the two bacteria during conjugation remain poorly studied.
In this context, our project aims to characterize the structure of the pilus tip and elucidate the molecular mechanisms involved in the interaction with the recipient cell using several cryo-Electron Microscopy approaches.

Firstly, we developed a specific protocol to purify native pili. Then, we identified the first conjugative distal protein complex by solving the pilus tip structure at an atomic resolution using Single Particle Analysis. This complex, composed of unexpected proteins, fundamentally reshapes our understanding of pilus biogenesis. Additionally, we point out a remarkable organisational and structural convergence among several independently evolved secretion systems, suggesting a potential case of functional convergence across these bacterial systems.
This study provides molecular-level insights into the key step of recipient cell recognition by the pilus tip and enables us to initiate the investigation of pilus-membrane interactions via Cryo-Electron Tomography.

Keywords: T4SS, Cryo, Electron Microscopy, Conjugative Pilus

*Speaker

Cellular microenvironment

Mechanisms of therapy-induced plasticity: Dissecting the impact of radiation, chemo, and surgery on the glioblastoma microenvironment

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Therapeutic resistance in glioblastoma (GBM) is driven by a complex interplay between intrinsic cellular plasticity and the tumor microenvironment. Crucially, the standard of care treatments themselves may serve as potent drivers of this adaptation, yet the extent to which chemotherapy, radiation, and surgical injury actively induce plastic cell state transitions remains a vital area of investigation. In this talk, Dr. Seano will examine how these conventional therapies actively reshape the GBM landscape. He will present published and unpublished data detailing how each therapeutic modality induces phenotypic switching, pushing tumor cells toward stem-like and mesenchymal states that are impervious to subsequent treatment. By dissecting the convergent pathways activated by radiotherapy, chemotherapy, and surgery, Dr. Seano will propose new strategies to target the dynamic adaptive mechanisms that sustain residual disease.

Keywords: cellular microenvironment

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A new and Integrin-independent function of Talin at the apical plane during cell junction remodeling

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Research thematic axis: Cell microenvironment and cancer

Epithelial tissues, which provide both mechanical strength and permeability barriers to organs, are composed of cohesive and polarized cells. These properties rely on intercellular junctions such as Adherens Junctions and Septate Junctions, which are localized at the apical and lateral planes, respectively. Moreover, at the basal side, cells are anchored to the tissue through Focal Adhesion points, which form links between cells and the extracellular matrix.

In response to cellular events such as division and intercalation, these junctions are dynamically remodeled. During these processes, epithelial integrity is preserved through a finely tuned balance between robustness and plasticity of intercellular junctions. In this context, the aim of my project is to understand how this integrity is maintained during junctional remodeling associated with cell intercalation, with a particular focus on the potential role of Focal Adhesion components that are transiently recruited to the plane of Adherens Junctions during these events.

Using the Drosophila model and live-imaging microscopy approaches, I investigated junctional remodeling occurring during cell intercalation events in the pupal notum. Preliminary results revealed that Talin, a Focal Adhesion component, is transiently recruited to the plane of Adherens Junctions during the formation of four-way junctions (junctions shared by four cells), and plays a key role in this process. Indeed, the loss of Talin induces an extension of these four-way junctions, suggesting an unknown function of Talin at the apical plane during junction remodeling and, consequently, in the maintenance of epithelial integrity.

Keywords: Epithalial tissue, Cell junction, Adherens Junctions, Focal Adhesion, Drosophila

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Deciphering the molecular function of dLsd1 in myogenesis.

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Myogenesis is a highly coordinated process involving specification, proliferation, migration, and differentiation of developing Muscle Stem Cells (MuSCs). While key transcriptional regulators of myogenesis have been identified, how chromatin-modifying enzymes regulate progenitors and MuSC fate decisions during development remains poorly understood. In this study, we focus on the conserved histone demethylase *dLsd1*. We use *Drosophila* as a model and study specifically developing MuSCs, known as adult muscle progenitors (AMPs). AMPs are closely associated with imaginal wing disc, which forms their niche and provides essential signalling cues for their development. AMPs give rise to two types of muscles: the Indirect and Direct Flight Muscles (IFMs and DFMs, respectively).
Using a *dLsd1::GFP* knock-in line we found that dLsd1 is expressed in the wing disc cells, including AMPs and epithelial niche. In the adult stages dLsd1 is detected in DFMs but not in IFMs. Consistently, loss of *dLsd1* function in AMPs does not affect IFM development; however, its depletion in niche cells and DFMs leads to severely impaired flight ability, along with subtle DFM fiber deformation, particularly at the muscle–tendon junctions. To further investigate this phenotype, we analyzed the distribution of Shot, a key regulator of muscle–tendon attachment and found that Shot localization is disrupted upon dLsd1 loss of function. Together, these results indicate that dLsd1 plays a critical role in regulating muscle–tendon attachment and structural integrity of DFMs, likely through modulation of cytoskeletal organization and niche-dependent signalling.

To uncover the underlying molecular mechanisms, we aim to identify the direct genomic targets of dLsd1 using complementary genome-wide approaches. NanoDam, an in vivo profiling technique, will be employed to map the DNA-binding sites of GFP-tagged dLsd1, while single-cell RNA sequencing (scRNA-seq) will enable the assessment of transcriptional changes following dLsd1 depletion.
Together, this work reveals an unexpected role for *dLsd1* in regulating muscle function and attachment. Genomic experiments will provide a deeper understanding of the transcriptional and epigenetic mechanisms that shape muscle formation.

Keywords: Stem cells, Muscle, Drosophila, dLsd1, Genomic analysis

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Functional characterisation of de novo variants in the splicing factor SF3B1 associated with neurodevelopmental disorders

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The protein diversity depends largely on RNA splicing, which is a crucial process mediated by the spliceosome and required for the proper maturation of mRNA. Among the proteins of the spliceosome, SF3B1 plays a crucial role for the first steps of RNA splicing, within the U2 snRNP complex. While somatic missense variants in *SF3B1* are frequent in cancers, we recently reported the implication of *de novo SF3B1* variants in neurodevelopmental disorders (NDD) (Uguen, Bergot et al. Nat Commun. 2026). We assembled a cohort of 26 NDD patients harbouring constitutional *de novo SF3B1* variants, distinct from those found in cancers. The principal clinical signs are a global developmental delay and facial dysmorphic traits. Comparing predicted loss-of-function (9 patients) and missense variants (17 patients), a dichotomy may emerge with the missense variants contributing to a more syndromic phenotype. Functional complementation assay and genome-wide analysis of RNA splicing showed that the missense variants are not loss-of-function variants and they exert a milder effect on global splicing compared to somatic variants.

Regulation of SCFMet30 Ubiquitin Ligase Activity by Sulfur Availability

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Sulfur metabolism is central for cell proliferation, as it provides several key metabolites for cells. These include methionine and cysteine (sulfur containing amino acids), S-adenosyl-methionine (methyl donor), and glutathione (redox homeostasis). In budding yeast, sulfur metabolism is controled by the SCFMet30 complex, which regulates the activity of the Met4 transcription factor. Met4 activates the expression of genes encoding proteins involved in sulfur metabolism (enzymes, transporters...). Met4 is ubiquitylated by SCFMet30 when sulfur is available in the medium. How exactly SCFMet30 activity is regulated by fluctuations in sulfur concentration is not fully understood: we still do not know which metabolites are detected by the complex, nor which factors sense these metabolites.

To address these questions, we mapped the interactome of Met30 using NanoBiT, a method that enables probing protein-protein interactions dynamically in living cells. NanoBiT is a sensitive protein complementation assay based on the luciferase NanoLuc, which is split in two inactive fragments (SmBiT and LgBiT) having very low affinity for each other. Using this method, we identified several well-known interactors of Met30, including Met4. We also identified two interactors of Met30 never studied before: the cystathionine gamma synthase Str2 and its paralog YML082W (arising from whole genome duplication). Our objective is to understand what is the role of these two proteins on SCFMet30 activity and Met4 regulation.

Using NanoBiT, we observed that presence of sulfur in the culture medium influences Met30-Met4 interaction and Met30-YML082W in an opposite manner. Met30 interacts with Met4 when sulfur is present, while it interacts with YML082W when sulfur is depleted. We also observed that Str2 and YML082W are required for Met4 deubiquitylation upon sulfur depletion. Moreover, our results indicate that a surface of Met30 necessary for Met4 ubiquitylation is also required for its interaction with YML082W. Altogether, these results suggest that YML082W and Str2 are negative regulators of Met4 ubiquitylation and may promote its deubiquitylation.

Keywords: Ubiquitylation, Cullin RING Ligase, Sulfur metabolism, Protein Protein Interaction, Saccharomyces cerevisiae

*Speaker

Posters and flash talks

Beyond known cytoskeletal landscapes: a stunning microtubule diversity in Xenopus spermatids

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Microtubules are cytoskeletal filaments that play essential roles in cell division, intracellular organization, long-range transport, and specialized differentiation processes such as spermiogenesis. They are assembled from tubulin heterodimers, which interact longitudinally to form protofilaments and laterally to generate a cylindrical tube. During mammalian spermiogenesis, the manchette, a transient, microtubule-based structure, is crucial for sculpting the spermatid nucleus and ensuring the formation of functional spermatozoa (Dunleavy et al., 2019; Rattner & Brinkley, 1972; Russell et al., 1991). We revealed for the first time the presence of a manchette-like structure in Xenopus species, in which spermatid morphogenesis is expected to be particularly extreme to generate the characteristic corkscrew shape of the sperm head. Additionally, we discovered an undescribed helical internal organization within these microtubules never noticed in manchette microtubules of any species. Remarkably, we report an unexpectedly broad diversity of microtubule conformations coexisting within the same cells and never observed elsewhere.

Keywords: Microtubules, spermatogenesis, manchette, fertility

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Modeling cataracts using a unique lens organoid model

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Cataract, the opacification of the lens, is the leading cause of blindness worldwide1. It mainly occurs in ageing individuals, due to the accumulation of oxydative stress, UV exposure, or the use of certain drugs. But it can sometimes also arise in newborns due to inherited mutations (congenital cataracts).

Although effective, cataract surgery is costly for countries with limited access to medical care and can lead to complications especially in children. Toward identifying alternate treatments, our team has developed a lens organoid model that recapitulates many aspects of lens organization and biology. More interestingly, these organoids are capable of mimicking cataract-like phenotypes when exposed to cataractogenic agents or genetically modified.

Our research hypothesis posits that clouding of lens organoid under cataractogenic conditions serves as a valuable phenotypic marker to understand dysregulated signalling pathways implicated in cataract development.

Keywords: cataract, lens organoid, deregulated pathways

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Development of ACSL4 inhibitors for the treatment of chronic kidney disease

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The acyl-CoA synthetase (ACS) family are a group of enzymes involved in fatty acid (FA) metabolism and lipid homeostasis. Many metabolic pathways require FA activation by reacting with Coenzyme A, and each ACS has its preferred substrate with variating chain length and saturation. Long-chain-fatty-acid CoA ligase 4 (ACSL4) is specialized in the metabolism of polyunsaturated fatty acids, and in particular arachidonic acid (AA). Activation of AA leads to its incorporation in the cell membrane, making it sensitive to ferroptosis, an iron-mediated form of cell death. On top of that, it regulates the renin angiotensin system, a hormone system regulating blood pressure and fluid / electrolyte balance. Both effects are hypothesized to drive chronic kidney disease, making ACSL4 an attractive target for a drug discovery campaign. Due to the lack of structural data, an AlphaFold model has been established in the presence of ACSL4's natural substrate. This model has been the basis for an *in silico* screen that identified a library of compounds with the potential to interact with its binding pocket. During this project, *in vitro* screening assays will be established to test the binding affinity of these compounds with ACSL4, as well as their potential to inhibit the enzyme. The project is part of a consortium in collaboration with the *Centre de Recherche des Cordeliers*, which includes two additional work packages to demonstrate I) the hypothesized effect of ACSL4 and AA on the kidney and II) that its activity progresses chronic kidney disease in murine models.

Keywords: Long, chain, fatty, acid CoA ligase 4, chronic kidney disease, drug discovery, screening

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Development of a panel of 15 genetically characterized canine mucosal melanoma cell lines as a relevant tool to test new therapies for human MM: example of anti-MDM2 targeted therapy

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Genetic characterization of cell lines is essential for understanding and predicting sensitivity to anti-tumoral targeted therapies. This study shows the development of a panel of 15 genetically characterized tumoral cell lines to test novel and repositioned anti-tumor therapies, focusing on mucosal melanoma (MM) models. Knowing that dog and human melanomas present strong clinical, histopathological and genetic similarities, we established a genetically diverse panel of MM canine cell lines, leveraging the ability to predict drug responses depending on the genetic background of the cell lines. Using long-read sequencing (Oxford Nanopore Technology, through the IGDRion platform), we performed a comprehensive genetic characterization of 15 canine MM cell lines, identifying single nucleotide variants, structural variations, and copy number alterations. We complemented our genomic analysis by RNA sequencing to assess gene expression profiles and potential fusion transcripts. Our methodology involved the following key steps: cell line establishment from dog mucosal melanoma samples (through the Cani-DNA BRC); phenotypic and histologic description, comprehensive genetic profiling; *in vitro* drug sensitivity screening and *in vivo* validation through mouse xenograft models.

We evaluated idasanutlin, an MDM2 inhibitor, across the 15 cell lines MM panel. We demonstrated a clear correlation between *TP53* mutational status and drug sensitivity: wild-type *TP53* cell lines were sensitive to the drug, while mutated *TP53* cell lines showed resistance. This result underscores the potential of genetic profiling to stratify patients and guide treatment decisions. Using this panel, we discovered genetic subgroups based on the structural variants (SV) content of each cell line linked to their expression data. Altogether, cell lines harboring a high SV content were more prone to respond to targeted therapies while those with a lower SV content were more likely to respond to immunotherapies, thus leading us to identify biomarkers for prognostic and to follow up drug response.

This 15 canine MM cell lines panel provides a relevant tool to test and validate therapeutic strategies tailored to specific genetic contexts. By integrating genomic, transcriptomic, and drug sensitivity data, we created a powerful research tool for both veterinary and human oncology, demonstrating the potential of comparative oncology in advancing cancer treatments. This genetically characterized 15 MM cell lines panel offers a comprehensive opportunity for drug screening and biomarker discovery, ultimately aiming to improve patient care and survival rates for challenging human MM in a one health perspective.

Keywords: dog, mucosal melanoma, cell lines, genetics, targeted therapies

*Speaker

Optimization of Sperm RNA Extraction for Molecular Analysis of Olfactory Receptors in Human Fertilization

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Sperm RNAs play a key role in fertilization and early embryonic development, but their study remains technically challenging due to low RNA abundance, chromatin compaction, and frequent contamination by somatic cells. Olfactory receptors, such as OR1D2, are involved in sperm chemotaxis and oocyte interaction. The aim of this study was to develop a robust protocol for high-quality RNA extraction from mammalian and human spermatozoa. We optimized a method combining density gradient purification, TRIzol pretreatment, DTT treatment, and NucleoSpin RNA II column extraction. This approach significantly improved RNA yield and purity compared to standard methods, as confirmed by spectrophotometry, RT-PCR of sperm-specific markers (PRM1, PRM2, HMGB4), and complete sequencing of the OR1D2 coding region. This work provides a reliable methodological framework for studying genetic variations of olfactory receptors and their potential involvement in male infertility.

Keywords: Sperm, RNA, Fertilization

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Accelerating genome-wide protein–protein interaction screening

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Artificial intelligence–based structure prediction methods such as AlphaFold, recognised by the 2024 Nobel Prize in Physics, have transformed our ability to model protein structures and, more recently, their interactions with other proteins, nucleic acids, and small molecules. These advances now enable the in silico prediction of protein–protein interactions (PPIs), offering a virtual analogue of experimental approaches such as pull-down assays. However, large-scale PPI screening remains computationally challenging due to the combinatorial explosion of possible interactions and the high cost of structure-based modelling.

Here, we present a novel computational pipeline for genome-scale, high-throughput PPI screening. The approach integrates biologically informed pre-filtering of candidates with efficient multiple sequence alignment generation and optimised structure-based modelling. By constraining the interaction search space and improving computational efficiency, this pipeline enables rapid and scalable prediction of protein complexes.

This new tool opens new avenues for in silico protein–protein interaction screening, with broad applications in biology, ranging from targeted studies to the identification of previously unrecognised homologues.

Keywords: AlphaFold, Protein, protein interaction

*Speaker

Anisotropy-Aware Strategy for Robust Deep Learning-Based Particle Picking in 3D Cellular Cryo-ET

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Particle picking in cryo-electron tomography (cryo-ET) remains challenging due to low signal-to-noise ratios, reconstruction artifacts such as the missing wedge, and anisotropic resolution along the Z-axis.

In this work, we investigate the impact of anisotropy-aware strategies within a standard two-stage deep learning pipeline. In particular, we propose a coherent framework for applying anisotropy-aware data augmentations, and extend this approach to inference through anisotropy-aware Test-Time Augmentation (TTA), which has not been explicitly studied in this context.

Through a controlled experimental evaluation, we show that consistently applying anisotropy-aware transformations during both training and inference leads to improved particle detection performance in terms of F4-score.

Overall, our results provide a clearer understanding of the role of anisotropy-aware strategies in cryo-ET particle picking and offer practical guidelines for their use.

Keywords: Cryo Electron Tomography, deep learning, anisotropy, Particle Picking, robustness

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Structural Characterisation of the Recipient Cell Detection Mechanism by the Bacterial Type IV Secretion System

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Bacterial conjugation is a biological process through which a donor cell transfers DNA to a recipient cell. It is the primary cause of the spread of antibiotic resistance genes among bacterial populations, significantly contributing to the global antibiotic resistance crisis (1). The DNA transfer is mediated by a large molecular machinery embedded in the donor cell membranes, called the conjugative Type IV Secretion System (T4SS) (2). To establish the first contact between the two bacteria, the donor cell produces a long extracellular filament – the conjugative pilus – essential for DNA transfer (3). Despite its importance, the structure and mechanism of the initial contact between the two bacteria during conjugation remain poorly studied.
In this context, our project aims to characterise the structure of the pilus tip and elucidate the molecular mechanisms involved in the interaction with the recipient cell using several cryo-Electron Microscopy approaches.

Firstly, we developed a specific protocol to purify native pili. Then, we identified the first conjugative distal protein complex by solving the pilus tip structure at an atomic resolution using Single Particle Analysis. This complex, composed of unexpected proteins, fundamentally reshapes our understanding of pilus biogenesis. Additionally, we point out a remarkable organisational and structural convergence among several independently evolved secretion systems, suggesting a potential case of functional convergence across these bacterial systems.

This study provides molecular-level insights into the key step of recipient cell recognition by the pilus tip and enables us to initiate the investigation of pilus-membrane interactions via Cryo-Electron Tomography.

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Keywords: T4SS, Cryo, Electron Microscopy, Conjugative Pilus

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Improved size and number of time gated detection for fast FRET by FLIM

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Fluorescence Lifetime Imaging Microscopy (FLIM) is an advanced imaging technique that measures the temporal properties of emitted photons and has emerged as a powerful quantitative tool in cellular biology. Unlike conventional fluorescence imaging based on intensity, FLIM relies on fluorescence lifetime, a parameter highly sensitive to the molecular environment of the probe. This enables the study of protein interactions and conformational changes through F ö rster Resonance Energy Transfer (FRET). We propose a method based on wide-field time-gated detection, called fastFLIM, which requires fewer photons than conventional Time Correlated Single Photon Counting (TCSPC) fitting-based approaches. However, as FLIM precision strongly depends on photon budget and living cells must be preserved from high excitation intensities, improvements in time-gated detection are still needed for fast measurements in dynamic samples.
In this work, we use a wide-field microscope to rapidly capture entire samples, reducing exposure time and phototoxicity. We address key limitations of fastFLIM by optimizing the number and width of temporal gates. Our strategy relies on wider gates to maximize photon collection while preserving measurement precision and FRET discrimination. We demonstrate that fastFLIM performed with fewer than five temporal gates remains accurate and can even improve efficiency. In particular, three gates of 4 ns over a 12 ns window outperform six gates of 2 ns, while two gates of 6 ns lead to insufficient FRET discrimination.

Experimental measurements of fluorescence lifetime, standard deviation, and FRET accuracy were combined into a score (StTR) for each gate configuration. Simulations across lifetimes ranging from 1 to 3.5 ns, together with experimental data and theoretical modeling, identify three gates of 4 ns as the optimal fastFLIM protocol.
This optimized and reproducible approach enables fast, quantitative FRET-FLIM measurements, opening the way to real-time protein dynamics studies and high-content screening of fluorescent biosensors.

Keywords: FLIM, FRET, Microscopy Technique, Fluorescent Protein

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Regeneration of the intestinal brush border

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The intestinal brush border at the apical surface of the enterocytes is critical for nutrient absorption. The microvilli that form the brush border may undergo atrophy in various conditions, including genetic disorders, infections, exposure to toxic substances in food, or chronic intestinal inflammation. This atrophy can lead to severe diarrhea and impaired nutrient absorption, causing a high number of deaths every year worldwide. In this context, identifying a way to correct microvilli atrophy is an important advance for public health. The objective of my PhD project is to determine if intestinal cells are able to regenerate their brush border after atrophy. Using an acute atrophy model I have established in the Caco-2 cell line, I have demonstrated that cells are indeed able to regenerate their brush border in 24 hours. With a pharmacological approach, I have also demonstrated that regeneration occurs through mechanisms partially similar to those involved in the initial formation of the brush border. I have additionally discovered that Villin, a microvilli actin-bundling protein, could have a critical role in regeneration.

Keywords: Caco2, Regeneration, MVID, Intestinal brush border

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Single particle tracking

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Understanding how nuclear factors dynamically interact with chromatin is essential to understand genome regulation and maintenance mechanisms. However, their behavior in the complex nuclear environment remains difficult to characterize in living cells. We investigate the intracellular dynamics of nuclear proteins using single-particle tracking in live cells. Proteins of interest were fluorescently labeled using a HaloTag-based system and imaged by widefield fluorescence microscopy under HILO illumination, allowing detection of individual molecules at high temporal resolution. Time-lapse image sequences are acquired at the microscope and subsequently processed for particle localization and trajectory reconstruction using the FreeTrace computational pipeline. Due to the three-dimensional motion of proteins in the nucleus, trajectories are often short and fragmented. To address this limitation, FreeTrace combines probabilistic particle detection, sub-pixel localization, and trajectory reconstruction based on fractional Brownian motion modeling. This approach enables robust extraction of dynamic parameters from noisy and incomplete trajectories. By quantitatively analyzing these trajectories, we can classify different diffusion regimes, reflecting transitions between free diffusion and chromatin-bound states. These analyses provide insights into how nuclear proteins explore the nuclear space and interact with chromatin. We applied this approach to a DNA repair protein, PARP1, and show that mutations affecting a DNA-binding region significantly alter its mobility, highlighting the role of chromatin interactions in regulating its dynamics. This work demonstrates the power of combining advanced microscopy and computational analysis to study nuclear protein dynamics at the single-molecule level in living cells.

Keywords: single molecule fluorescence microscopy

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Understanding the Regulation of Microtubule Structural Instability and Dynamics by the EB1 Protein

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Microtubules are key cytoskeletal elements that are involved in a variety of functions, including cell motility, compartmentalization, and division. They ensure these functions thanks to their characteristic dynamic instability, a phenomenon described as the rapid and stochastic switches between growth and shrinkage phases. In the light of our recent findings, we propose that the basis of microtubule dynamic instability is intimately tied to its structural heterogeneity. Besides, in contrast to microtubules assembled *in vitro,* which show high structural heterogeneity, cytoplasmic microtubules are strikingly much more structurally regular, yet with a certain degree of heterogeneity. Cells could therefore regulate microtubule structure to control their dynamics. In this context, we aim to unravel the mechanisms by which microtubule structure is regulated in cells and how it influences their dynamic behavior. We propose that microtubule-associated proteins could be a perfect mean for this cellular regulation. One candidate is the end-binding protein 1 (EB1), which interacts with the tip of growing microtubules with a comet-like pattern and could proofread the lattice during assembly.

Taking advantage of TIRF microscopy, we first investigated the regulation of dynamics by EB1 on microtubules assembled from purified porcine tubulin, *Xenopus* tubulin, and in *Xenopus* egg cytoplasmic extracts. Our preliminary results show that adding EB1 to both porcine and *Xenopus* tubulin increases microtubule growth speed and catastrophe rate. On the contrary, depleting EB1 from *Xenopus* egg extract leads to the assembly of structures of much decreased size, likely due to dysregulation of microtubule dynamics. Having set up suitable experimental conditions to assess the effect of EB1 on microtubule dynamics *in vitro* and egg extracts, we will then evaluate, using cryo-electron microscopy, its importance for the regulation of lattice structure.

Keywords: microtubule, EB1 protein, dynamic instability, Xenopus

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Innovative Biomarkers in Liquid biopsies to improve precision oncology

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This PhD research project ties in the ”seeing and knowing” theme. It aims to develop machine learning approaches to predict cancer presence from epigenetic signals obtained through liquid biopsies. Following apoptosis, cells' DNA is released into the bloodstream. For patients with cancer, a fraction of circulating free DNA comes from tumors. However, this fraction is small, making single sequence alterations challenging to detect. Retrotransposons are repeated elements, which facilitate the detection of signals they carry. They are also rich in CpG sites, which methylation patterns are known to be altered in cancer. Therefore, epigenetic alterations in retrotransposons are interesting targets.

Previous work demonstrated that global hypomethylation of LINE-1 elements can serve as a non-specific multi-cancer biomarker using the DIAMOND multiplex PCR assay (PMID: 39620930). An improved version of this assay now enables the capture of approximately three times more CpG sites.

Our overarching goal is to improve the downstream analysis for higher accuracy and detection of tumor content. Models based on average methylation at single CpG sites showed limited predictive performance due to strong feature correlations. We hence investigate whether the information at CpG sites can be combined.

Overall, this work aims to define more robust and biologically meaningful feature representations for improved cancer detection from liquid biopsy methylation data.

We focus on identifying robust and informative genomic regions using healthy plasma samples and validating them on independent public datasets. Beyond correlation-based segmentation, we explore autocorrelation, partial correlation, and mutual information to better capture dependencies between CpG sites and consider their precise localizations.

Keywords: LINE, 1, epigenetic, hypomethylation, Liquid Biopsy, cancer

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Super-resolution microscopy reveals mitochondrial subclassification in breast cancer driven by AURKA and P5CS

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Breast cancer cells exploit two main metabolic pathways to generate their energy. Oxidative phosphorylation (OXPHOS) relies on the mitochondrial respiratory chain to produce ATP. Glycolysis, a cytoplasmic process, yields less ATP than OXPHOS but enables rapid energy production under hypoxic conditions. For decades, the Warburg effect dominated our understanding of cancer metabolism, suggesting that tumor cells preferentially use glycolysis. However, recent research reveals a more complex reality in which breast cancer cells appear to favour OXPHOS, linked to Aurora A kinase (AURKA) overexpression. Beyond its classic role in cell cycle regulation, AURKA acts as a key mitochondrial dynamics regulator. It has also been reported that this kinase can be directly imported into the mitochondrial matrix, where it interacts with ATP synthase subunits (ATP5A/ATP5B). Disrupting AURKA's binding to these subunits impairs OXPHOS-dependent energy production, triggering apoptosis in glycolytic cells but inducing quiescence in oxidative cells.

A key emerging question is how these cells survive despite reduced energy production. Under energetic stress, the Δ1-pyrroline-5-carboxylate synthase (P5CS) pathway may act as an alternative energy source, sustaining metabolic homeostasis and cell survival. Mass spectrometry studies identified P5CS as a top 10 interactor of AURKA, confirmed by protein-protein interaction analyses using FRET-FLIM. Colocalization studies showed that AURKA activation reduces P5CS cluster formation in mitochondria, suggesting metabolically distinct mitochondrial subpopulations. Spinning disk microscopy coupled with SRRF (Super-Resolution Radial Fluctuations) allowed the extraction of three parameters: mitochondrial mass, cluster intensity and number of clusters. Combining SRRF with the mitoGO-ATeam2 FRET biosensor revealed two mitochondrial subtypes. These were named class 1 (OXPHOS-dependent) and class 2 (P5CS-driven). ATP5B depletion abolishes AURKA's effect on class 1 mitochondria, while enhancing the abundance of class 2.

These results reveal that AURKA dynamically balances OXPHOS and P5CS metabolism, providing mechanistic insight into breast cancer metabolic plasticity and the existence of distinct mitochondrial subclasses.

Keywords: Super-resolution, FRET FLIM, Metabolism, Mitochondrial heterogeneity

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Dissecting the Mitotic Roles of DCLK1 Isoforms: Insights into Cancer Cell Division.

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Cancer progression is often driven by defects in cell division, leading to aneuploidy and uncontrolled proliferation. DCLK1 (Doublecortin-like kinase 1), a microtubule-associated protein (MAP) with kinase activity, is a biomarker in multiple cancers, where its overexpression correlates with poor prognosis and therapy resistance. DCLK1 exists in four isoforms: DCLK1-αS/αL (with both kinase and MAP domains) and DCLK1-βS/βL (kinase domain only). Isoform deregulation varies across tumour types: renal tumours typically upregulate both DCLK1-α and DCLK1-β, while colorectal tumors overexpress DCLK1-β and downregulate DCLK1-α. Our aim is to uncover how DCLK1 isoforms differentially affect cell division, which could inform more precise, patient tailored cancer therapies. In the present work, we used CAKI2 renal cancer cells, which overexpress DCLK1-α and DCLK1 β compared to healthy HK2 cells, mirroring renal tumor profiles. Using siRNA, we depleted DCLK1-α alone or in combination with DCLK1-β, then compared mitotic phenotypes with those of control cells. DCLK1-α depletion caused chromosome segregation defects and spindle shape abnormalities whereas DCLK1-α/-β co-depletion attenuated these effects. By contrast, co-depleting DCLK1-α/-β seemed to increase astral microtubule curvatures and spindle misorientation, more so than depleting DCLK1α alone. These findings suggest that DCLK1 isoforms may distinctly influence mitotic spindle organization, orientation and chromosome alignment. Further work will determine whether these effects depend on DCLK1's kinase activity, MAP function, or both.

Keywords: Cancer, Cell division, Microtubule, associated protein, Spindle, Isoforms, Confocal microscopy

*Speaker

My PhD work aims at deciphering the consequences of both loss-of-function and missense variants on the function of the SF3B1 protein, in particular through analysis of RNA splicing and gene expression profiles both in patient blood samples and in cellular models under development. As SF3B1 interacts with numerous proteins, we will also investigate whether splicing defects result from a loss or a reduction of protein-protein interactions

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Keywords: SF3B1, neurodevelopmental disorders

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The cancer-related kinase Aurora A/AURKA shapes mitochondrial import efficiency

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Breast cancer (BC) is characterized by an abnormal and uncontrolled growth of mammary cells leading to a tumor. These cells need a large quantity of energy produced by mitochondria. Its efficiency depends on the importation of 99% mitochondrial protein synthesized in cytosol. Aurora kinase A/AURKA is also overexpressed in breast cancer models. In BC models, import is perturbed, and some key AURKA partners involved in protein import are also overexpressed: TOMM70, TIMM9, TIMM17, and TIMM50. AURKA is crucial for mitochondrial shape maintenance, energy production, and mitophagy of defective mitochondria. Therefore, cancerous cells may conserve hyperfunctional mitochondria to support their fast growth.
We hypothesized that AURKA overexpression induces mitophagy by lowering mitochondrial import efficiency. To test this hypothesis, we rely on F ¨o rster resonance energy transfer via Fluorescence Lifetime Imaging Microscopy (FRET/FLIM). My host team developed a biosensor for mitochondrial protein import, called mitoPort. Associated with confocal microscopy, the biosensor offers an unparalleled spatiotemporal resolution of the import efficiency in cells. We used MCF-7 BC cells, expressing the mitoPort biosensor with or without AURKA overexpression.

To test the performance of mitoPort, we benchmarked it with the alternative probe Su9-GFP, well-characterized for mitochondrial protein import studies. MitoPort shows a greater sensitivity than Su9-GFP in detecting import alterations. Our probe revealed that AURKA overexpression leads to a loss of inner membrane integrity and a thorough mitochondrial import block.
In the near future, we will identify the key partners of AURKA involved in mitochondrial import regulation. Through gene downregulation approaches, we will deplete AURKA partners to evaluate their impact on import efficiency. Third, we will determine if the presence or absence of import-related AURKA partners can block or slow down AURKA-dependent mitophagy. Finally, we will explore pharmacological strategies targeting stress-response pathways (UPRmt, ISR, ...) to overcome AURKA-dependent import deficiency and loss of subcompartmental integrity.

Keywords: mitochondrial protein import, subcompartmental integrity, mitoPort, AURKA, breast cancer

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