Young Scientists' Symposium

13th Young Scientists' *Symposium*

Book of Abstracts

16th May 2025 IECB, Bordeaux

Scientific program

08:30 - 09:00	Registration
09:00 - 09:15	Welcome Speech
09:15 - 10:00	**KL1: Prof. Gunnar von Heijne** University of Stockholm, Sweden Cotranslational membrane protein biogenesis
10:00 - 10:45	**Oral Communications: OC1 - OC3** **Rosario Mora:** Innovative Strategies to Guide Stem Cell Differentiation in Bone Tissue Engineering: Surface Immobilization of Polymetallic Complexes **Ana Alvarez-Mena**: Bacterial flotillins and their role in phospholipid membranes **Aline Makhloutah**: Synthesis of Photoswitches and Photoswitchable Lipids for Light-Controlled Therapeutic Applications
10:45 - 11:30	**Poster Session** Coffee Break
11:30 - 12:30	**Oral Communications: OC4 - OC7** **Clara Piersson**: Mechanisms of membrane-induced tau aggregation **Melissa Kosovari**: In Vitro Strategies for Bone Tissue Engineering: Biomaterial Functionalization with Mimetic Peptides and Silanization Approaches **Katharina Zimmeter**: A Bioinspired Cu2+-Responsive Magnetic Resonance Imaging Contrast Agent with High Selectivity and Relaxivity Response **Elio Gereige:** NanoPULSE: The First Micromixing Method Delivering Consistent Lipid Nanoparticle Formulations Seamlessly Across All Scales
12:30 - 14:00	Lunch Break
14:00 - 14:45	**KL2: Prof. Thomas Carell** LMU, Munich, Germany The prebiotic origin of the RNA nucleosides and translation
14:45 - 15:45	**Oral Communications: OC8 - OC11** **Pascale Sarkis**: Phosphorylation-driven modulation of eIF4B self-association and RNA binding **Ana Gorse**: Membrane partition and structural reorganization induced by antipsychotics with distinct clinical profiles **Razane El Annan**: Investigating the molecular effects of particulate matter on human bronchial epithelial cells using Confocal Raman Microscopy and ToF-SIMS Imaging **Anielle Villeronce**: Functional Selection of Molecular Aptamers Beacons
15:45 - 16:30	**Poster Session** Coffee Break
16:30 - 17:30	**Panel Discussion - Beyond the PhD: Exploring Career Pathways in Science** Denis Dupuy, Principal Investigator, ARNA Lab, Bordeaux Ruben Ragg, Editor-In-Chief, ChemBioChem Stéphanie Monzelun, Co-founder and COO, Aelis Farma
17:30 - 18:00	Closing Speech

Break | Speech | Keynote Lecture | Oral Communication | Poster Session | Panel Discussion

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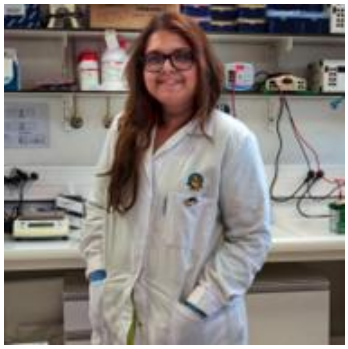

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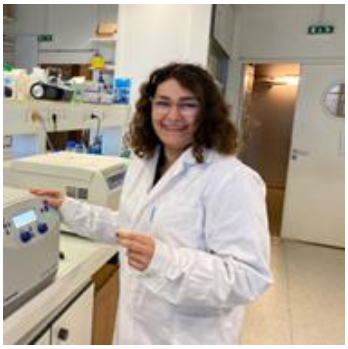

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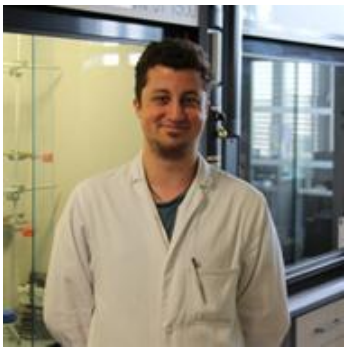

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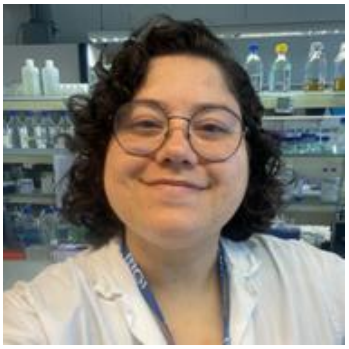

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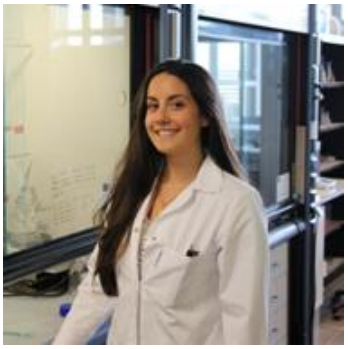

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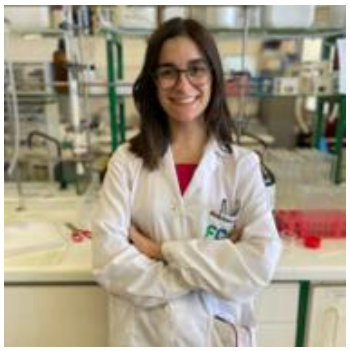

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Abstracts Keynote Lectures

KL1

Professor Gunnar von Heijne

University of Stockholm, Sweden

Cotranslational membrane protein biogenesis

Most integral membrane proteins are cotranslationally inserted into the bacterial inner membrane or the eukaryotic endoplasmic reticulum membrane, aided by translocon complexes (SecYEG-YidC in *E. coli*, Sec61-EMC in mammalian cells). Ongoing work is beginning to unravel the details of this process, and it is now possible to follow the membrane insertion of individual transmembrane helices with up to single-residue resolution.

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KL2

Professor Thomas Carell

Ludwig-Maximilians Universitat, Munich, Germany

The prebiotic origin of the RNA nucleosides and translation

The widely accepted RNA world hypothesis suggests that life first emerged from RNA, which is able to (self)-replicate and evolve. Replication of RNA requires formation of the complementary pyrimidine-purine Watson-Crick base pairs A:U and G:C, which are a prerequisite for accurate genetic information transfer. Although prebiotic pathways to RNA building blocks have been reported, no pathway has been able to generate all four constituents of RNA simultaneously.[1, 2] We recently reported a prebiotically plausible new pathway (FaPy-pathway) that is able to generate purine nucleosides.[3] The chemistry is driven exclusively by fluctuations of physicochemical parameters such as pH, temperature and concentration. These conditions allow in addition the parallel formation of a variety of non-canonical purine nucleosides as living molecular fossil of an early abiotic world.[4] Many of the formed non-canonical RNA building blocks are today assumed to have been part of the genetic system of the last universal common ancestor (LUCA).[5] In order to find a prebiotically plausible scenario for the parallel formation of purine and pyrimidine bases to create the fundamental Watson-Crick base pairing system, I will report about new prebiotically plausible chemistry route to pyrimidines. Because the new chemistry is compatible with the purine procedures it allows to simulate the formation of all four RNA building blocks in the same geochemical environment.[6]

Next to the formation of nucleosides, the emergence of life also required amino acids and the process of translation, in which RNA information encodes the formation of proteins. We were able to show that certain RNAs have the property to self-decorate with amino acids and that these amino acids can react directly attached to RNA to peptides. This so far unknown property of RNA forces us to extend the RNA world to an RNA-peptide world theory.[7] We now see an RNA-peptide world at the beginning of the emergence of life.[8]

References: [1] M. Powner et al. & J. Sutherland, *Nature* **2009**, *459*, 239.
[2] H.-J. Kim et al. & S. Benner, *Proc. Natl. Acad. Sci.* **2017**, *114*, 11315.
[3] S. Becker et al. & T. Carell, *Science* **2016**, *352*, 833.
[4] S. Becker et al., & T. Carell, *Nat. Commun.* **2018**, *9*, 163.
[5] M. C. Weiss et al. & W. F. Martin, *Nat. Microbiol.* **2016**, *1*, 16116.
[6] S. Becker et al. & T. Carell, *Science* **2019**, *366*, 86-78.
[7] W. Gilbert, *Nature* **1986**, *319*, 618.
[8] F. Müller, L. Escobar & T. Carell, *Nature* **2022**, *605*, 279–284.

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Abstracts Oral Communications

Innovative Strategies to Guide Stem Cell Differentiation in Bone Tissue Engineering: Surface Immobilization of Polymetallic Complexes

Rosario Moreno[a], Artem Zibarov[a], Murielle Rémy[a], Luc Vellutini[b], Marie-Christine Durrieu[a,*]

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In tissue engineering and regenerative medicine, promoting and controlling the differentiation of human mesenchymal stem cells (hMSCs) in vitro is crucial for obtaining a significant quantity of cells differentiated toward the desired lineage. This project aims to develop innovative chemical and biochemical strategies to guide hMSC differentiation into the osteogenic lineage. One of the proposed approaches involves synthesizing metal-organic complexes, particularly zinc-based, that can be anchored to surfaces to assess their influence on differentiation. Zinc has been widely recognized for its positive impact on osteogenic differentiation in solution (Ref. 1). Moreover, zinc-doped bioactive glasses have shown enhanced effects due to ion release (Ref. 2). However, the impact of immobilized zinc on cell differentiation has not been studied.

This project introduces the original concept of anchoring zinc to surfaces via coordination with an organic molecule, C4, which is subsequently grafted onto silicon substrates. A novel spin-coating silanization method using a phthalimide-terminated silylated coupling agent (Alk-Phtha) is employed, (Ref. 3) providing a versatile and efficient alternative to conventional protocols which refines surface engineering methodologies and offers tailored surface properties, addressing a variety of biomedical challenges. This strategy approach combines synthetic and biochemical tools to deepen our understanding of stem cell differentiation mechanisms, thereby advancing new materials and protocols for bone tissue engineering.

The synthesis of the organic molecule C4 was successfully achieved, as described previously (Ref. 4, Figure 1), and confirmed by Proton Nuclear Magnetic Resonance (1H-NMR) spectroscopy. To characterize the amount of Alk-Phtha grafted onto the surfaces, colorimetric assays, including Ninhydrin and Coomassie Blue, were tested and complemented by advanced characterization techniques. These included Water Contact Angle (WCA) measurements to validate surface modifications, X-ray Photoelectron Spectroscopy (XPS) to analyze the chemical composition of the surfaces, and Polarization-Modulation Infrared Reflection Absorption Spectroscopy (PM-IRRAS) to confirm the formation of self-assembled monolayers and evaluate the accessibility of amine groups. XPS analyses (Table 1) confirmed the successful silanization and subsequent functionalization of the surfaces with the C4 complex. Different concentrations of C4 were tested to determine the optimal conditions for surface modification. The observed Zn saturation at 0.02 mM suggests a sufficient concentration for achieving uniform distribution and a significant Zn presence on the surface, which is crucial for ensuring consistent biological responses.

The findings of this study demonstrate the feasibility of anchoring zinc to silicon substrates via an organic linker, providing a stable and homogeneous surface modification. Cell culture experiments using tomato human mesenchymal stem cells (hMSCs) have been conducted to

analyze the impact of our functionalized surfaces on hMSC behavior. These studies provide insights into cell adhesion, morphology, and potential cytotoxic effects of the immobilized zinc complex. To further investigate the biological response, ongoing immuno-cyto-fluorescent staining experiments aim to evaluate specific markers related to cell viability, proliferation, and potential differentiation pathways.

The ability to functionalize surfaces with bioactive metals in a controlled and stable manner opens new perspectives in biomaterials design, offering a promising strategy for bone tissue engineering applications. Further optimization of surface chemistry and comprehensive biological assays will be necessary to elucidate the precise mechanisms by which immobilized zinc contributes to osteogenic differentiation.

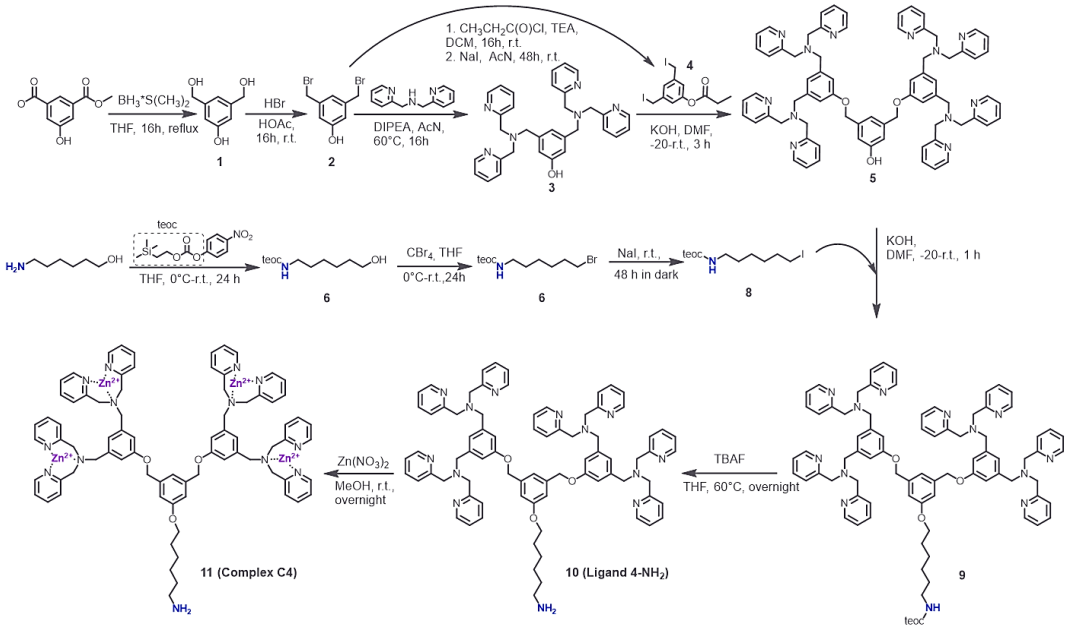

Figure 1: Synthetic Scheme for the Preparation of the C4 Molecule.

	%Si	%C	%N	%O	%Zn
Si wafer	53.8 ± 0.1	13.0 ± 0.8	0.6 ± 0.1	32.3 ± 0.3	0
Alk-Phtha	40.6 ± 0.3	20.8 ± 0.4	0.99 ± 0.04	37.6 ± 0.2	0
Alk-NH2	48.4 ± 0.8	17.9 ± 0.8	0.64 ± 0.05	33.1 ± 0.3	0
C4 0.02 mM	35 ± 1	33 ± 2	2.3 ± 0.1	29.6 ± 0.8	0.48 ± 0.03
C4 0.1 mM	39 ± 2	27 ± 2	2.3 ± 0.1	31.2 ± 0.4	0.51 ± 0.02
C4 0.5 mM	36 ± 1	29 ± 2	2.4 ± 0.1	31.4 ± 0.4	0.60 ± 0.05
C4 1 mM	34 ± 3	32 ± 4	2.7 ± 0.3	30 ± 2	0.64 ± 0.03
C4 2 mM	37.0 ± 0.7	31.5 ± 0.5	2.5 ± 0.2	28.44 ± 0.07	0.58 ± 0.02

Table 1: XPS Survey Analyses of Silicon Surfaces after Silanization, and C4 Functionalization Employing Different Concentrations.

References: [1] RSC Adv., **2020**, *10*, 14915-14927. [2] Materials, **2021**, *14*, 1864. [3] ACS Appl. Mater. Interfaces, **2024**, *16*, 29770-29782. [4] Iscience, **2019**, *21*, 110-123.

Bacterial flotillins and their role in phospholipid membranes

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Keywords: *Solid-state NMR; Flotillin; Membrane order; Membrane fluidity*

Flotillins are evolutionarily conserved scaffolding proteins, found from archaea to mammals, and are recognized for their ability to segregate nanodomains [1]. These proteins assemble into basket-like oligomeric structures on the membrane, driven by a conserved secondary structure arrangement that includes a membrane-binding region, an SPFH domain, and a coiled-coil flotillin domain. In *Bacillus subtilis*, a widely used model system, the flotillins FloT and FloA localize in distinct nanodomains and contribute to diverse cellular functions [2,3].

To better understand the mechanisms by which flotillins organize the bacterial membrane, we use deuterium and phosphorus solid-state NMR. We show how FloT, FloA, and their structural components - the SPFH and flotillin domains - influence membrane association and fluidity (Figure 1). Both bacterial flotillins destabilize the membranes, with FloT and FloA inducing distinct effects, and, surprisingly, the membrane-distant coiled-coil domains significantly impact membrane fluidity (Figure 1) [4].

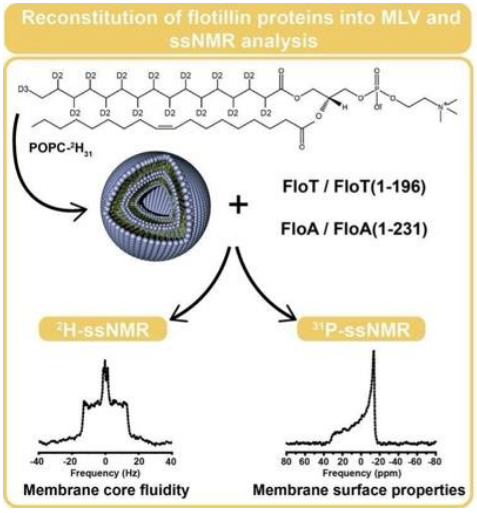

Figure 1: Schematic representation of the methodological approach.

References: [1] Microbiol. Mol. Biol. Rev., **2015**, *79*, 81-100. [2] PLoS Genet., **2016**, *12*, e1006116. [3] Elife, **2020**, *9*, e57179. [4] Biochim Biophys Acta Biomembr., **2025**, *1867(1)*, 184399.

Acknowledgments: This work was supported by ANR (grants ANR-19-CE13-0021, ANR-23-CE11-0005-01), CNRS Momentum, Fondation de la Maison de la Chimie, IECB Platform (CNRS UAR 3033, INSERM US001), and DFG (grant BR 2915/7-1).

Synthesis of Photoswitches and Photoswitchable Lipids for Light-Controlled Therapeutic Applications

Aline Makhloutah,[a]* Cédric Mittelheisser,[a] Ibrahim Abdellah,[a] Véronique Décot,[b] Antonio Monari,[c] Maxime Mourer,[a] Yann Bernhard,[a] Andreea Pasc[a]

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Keywords: *Phospholipids, Photoswitches, Photoimmunotherapy*

Photoswitchable lipids (photolipids) are emerging as a powerful tool for the precise, light-assisted manipulation and study of lipid function including membrane biophysics (permeability, fluidity…) and receptor activation.[1] In particular, a photolipid with a serine polar head can target TIM-3, a transmembrane receptor protein highly expressed on Natural killer (NK) cells, leading to a promising immunotherapeutic approach.[2] Herein, we will first present the synthesis of two photolipids featuring either a phosphatidylcholine polar head (Switch-PC) or a phosphatidylserine one (Switch-PS), designed for membrane-targeting application or TIM-3 activity modulation, respectively, and a photoswitchable unit in the lipid tail. As the photoswitch, we used a biomimetic 2,6-disubstituted-γ-pyrone analogue of cyclocurcumin,[3] [4] that undergoes reversible E/Z photoisomerization under UV light. Notably, this chromophore can theoretically be excited in the optical biological NIR-I window (650-900 nm) using a two-photon absorption approach (TPA), allowing for deeper tissue penetration. Second, we will describe the evaluation of the photoswitching properties of Switch-PC in Giant Unilamellar Vesicles (GUVs), serving as model membrane systems. Finally, we will discuss the development of new easily accessible styryl-heterocycle photoswitches with interesting properties expanding the limits of these systems (Figure 1).

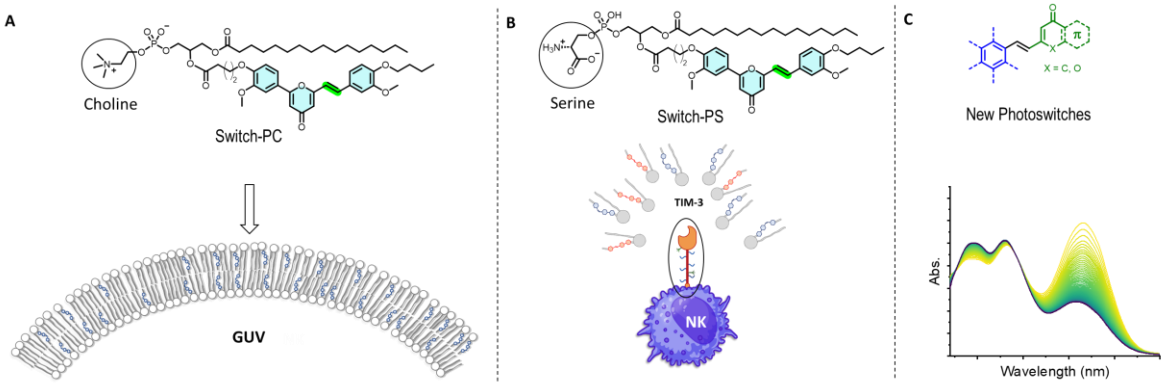

Figure 1: A- Switch-PC and its use in GUVs, B- Switch-PS targeting TIM-3 in NK cells, and C- General structure and properties of a new family of photoswitches.

References: [1] ChemBioChem, **2021**, *22*, 73-78; [2] J. Am. Chem. Soc, **2022**, *144*, 3863-3874; [3] J. Org. Chem, **2021**, *86*, 8112-8126; [4] Langmuir, **2022**, *38*, 15642-15655.

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Mechanisms of membrane-induced tau aggregation

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Keywords: *Tau aggregation, amyloid, mechanism*

Tau is a protein found in the brain where it regulates microtubule activity. It is an intrinsically disordered protein, which means that it does not have a unique three-dimensional structure. Tau can form highly-ordered aggregates that are directly involved in several neurodegenerative diseases, called tauopathies, including Alzheimer's disease. Recent research has shown that Tau protein can interact directly and indirectly with the neuronal membrane, mainly composed of lipids. Observations of Alzheimer's brain tissues show the association of Tau fibers with membrane lipids such as phosphatidylcholine, cholesterol, and sphingolipid. In addition, the interaction between Tau and lipids has been shown to promote Tau aggregation in vitro. Yet, how membranes modulate tau aggregation pathways remains poorly understood. We present a biochemical and biophysical characterization of tau amyloid filament formed in presence of different membrane models. In particular, we used Electron Paramagnetic Resonance (EPR) to directly quantify the population of tau bound to the membrane and to quantify the affinity between Tau and lipids. We show that the arrangement and the nature of anionic lipids at the membrane surface modulate the tau-membrane interaction, which in turn influence the aggregation of Tau into amyloid fibrils. The results suggest that a balance between free tau protein and tau bound to liposomes is necessary for efficient fiber formation, with charge density playing a key role in the interaction between tau and lipids. Together, our results show that cellular membranes might be an important modulator of tau aggregation.

In Vitro Strategies for Bone Tissue Engineering: Biomaterial Functionalization with Mimetic Peptides and Silanization Approaches

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Keywords: *Stem Cell Differentiation; Osteogenic Signaling Pathways; Cell-Material Interaction*

Engineering biomaterial surfaces with synergistic peptide combinations unlocks new possibilities for directing stem cell fate and advancing regenerative medicine[1]. This study explores a novel multi-peptide functionalization strategy to enhance the osteoinductive potential of biomaterial surfaces[2,3]. Accordingly, the existing synergy between RGD peptides and BMP-2 was leveraged by incorporating a third peptide designed to activate complementary signaling pathways[4], therefore enhancing the recruitment and differentiation of stem cells. This approach represents a paradigm shift in biomaterial design, taking advantage of the cooperative action of multiple ligands to optimize the cellular microenvironment. Surface functionalization was achieved using an optimized spin-coating method for controlled biomolecule grafting, ensuring a well-organized self-assembled monolayer. Surface characterization was performed by PM-IRRAS to confirm successful silanization and peptide immobilization. Human mesenchymal stem cells (hMSCs) were cultured on functionalized surfaces, and osteogenic differentiation was assessed through qPCR for key markers and immunofluorescence analysis. Experimental results demonstrated that multi-peptide functionalized surfaces significantly outperformed single peptide coatings in promoting osteogenic differentiation. This study highlights the transformative potential of multi-peptide functionalization to orchestrate complex biological processes at the cell-material interface paving the way for advancements in biomaterial design for tissue engineering applications by offering an efficient approach for bioactive surfaces.

References: [1] J. Pept. Sci., **2022**, *28*, e3335. [2] New J. Chem., **2023**, *47*, 9661. [3] ACS Appl. Mater. Interfaces, **2024**, *16*, 29770-29782. [4] ACS Biomater. Sci. Eng., **2017**, *3*, 2514-2523.

Acknowledgments: This work was supported by the Natural Science and Engineering Research Council of Canada (G.L) as well as the Centre Québécois sur les Matériaux Fonctionnels (G.L). M.K. is the recipient of a scholarship from the Fondation du CHU de Québec-Université Laval. M.-C.D. would like to thank the French National Research Agency (ANR-21-CE06-0031-02) for its support, as well as the Nouvelle Aquitaine Region (contract no. 2017-1R30109-00013176) and the Department of Health Sciences and Technologies from the University of Bordeaux for their support.

A Bioinspired Cu^{2+}-Responsive Magnetic Resonance Imaging Contrast Agent with High Selectivity and Relaxivity Response

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Keywords: Copper, MRI probe, contrast agent

Imaging extracellular Cu^{2+} *in vivo* is of great interest due to its biological importance in both physiological and pathological processes. Elevated levels of labile blood copper, primarily bound to human serum albumin (HSA), have been observed in conditions such as Wilson's disease and Alzheimer's disease.[1] Magnetic resonance imaging (MRI) is a powerful *in vivo* imaging technique with the potential to detect these biochemical changes through environment-responsive contrast agents.[2,3] We present the development of an innovative Cu^{2+}-responsive MRI contrast agent featuring a bioinspired Cu^{2+} binding site. This sensor exhibits a remarkable 400% increase in relaxivity upon Cu^{2+} binding, which can be attributed to an increase in the hydration number of the Gd^{3+} ion, triggered by the displacement of a pyridine subunit in the molecule (see Figure 1). The compound has been thoroughly characterized through spectroscopic and relaxometric studies, which have been supported by DFT calculations. Notably, it demonstrates unprecedented selectivity for Cu^{2+} over Zn^{2+}. However, while promising, the Cu^{2+} affinity is lower than predicted and requires further optimization.[4]

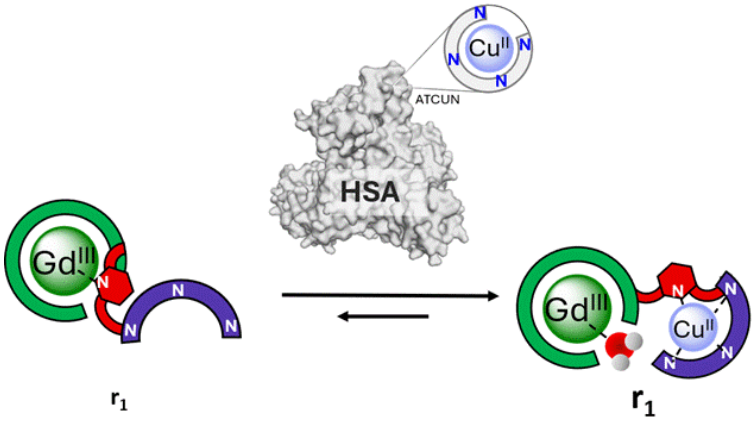

Figure 1: Schematic representation of a Cu^{II}-responsive MRI contrast agent with a pyridine switching arm. Green: MRI active Gd^{3+}-complex, Blue: Cu^{2+}-binding site, red: switching arm.

References: [1] Coord Chem Rev, **2020**, *433*, 213727. [2] Chem Rev, **2019**, *119*, 957–1057. [3] Future Med Chem, **2010**, *2 (3)*, 367-384. [4] Inorg Chem, **2024**, *63*, 23067–23076.

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NanoPULSE: The First Micromixing Method Delivering Consistent Lipid Nanoparticle Formulations Seamlessly Across All Scales

Elio Gereige[a,b*1], Claire Counil[a], Audrey Nsamela[a], Matthieu Kerhuel[a], Brice Calvignac[b], Marie Bonnin[b], Robin Oliveres[a], Thomas Guérinier[a]

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Keywords: Lipid Nanoparticles, Micromixing, Scale-Up

The development of RNA-based vaccines and therapies using lipid nanoparticles (LNPs) is hindered by the absence of a unified formulation technology that covers the entire development pipeline – from microliter-scale screening to tens-of-liters manufacturing. This gap requires transitions between different formulation techniques during scale-up, such as microfluidics, impingement jet mixing (IJM) or T-mixing, which can affect key LNP quality parameters, including size, polydispersity index (PDI), encapsulation efficiency (EE%), and morphology. Current approaches lead to prolonged, expensive, and sometimes unsuccessful LNP-based drug development. Here, we introduce NanoPULSE, a novel, patented active micromixing technology that ensures consistent LNP characteristics across all production volumes. Lagrangian numerical simulations are used to predict the impact of input parameters on particle characteristics and optimize the mixing channel's dimensions. Simulation results permitted the introduction of a novel index to quantify the mixing efficiency of NanoPULSE. Multi-angle dynamic light scattering (MADLS) measurements confirm that empty and RNA-loaded LNPs maintain constant sizes over production volumes ranging from 500 µL to 4 L, with PDIs remaining below 0.2, validating the seamless scalability of the technology. The EE%, yield and structural morphology of RNA-LNPs produced with NanoPULSE are characterized at different scales and benchmarked with standard microfluidic approaches. By modulating the solvents' injection periods, NanoPULSE can produce LNPs of variable sizes using the same formulation. The LNPs sizes and PDIs measured at different input parameters are correlated with simulations, linking the mixing performance to the nanoparticle characteristics. These findings underscore the promising repeatability, scalability, and efficiency of LNP synthesis via NanoPULSE.

References: [1] Hourdel, L., et al., *Int. J. Pharm.*, 2025. [2] Abu Dagga, I. & Abdelgawad, M., *Int. J. Thermofluids*, 2022.

Acknowledgments: We would like to express our sincere gratitude to BPI France for their support through the I-Lab Aware program, and to the Aquitaine Region for their invaluable support of the NanoPulse project.

Phosphorylation-driven modulation of eIF4B self-association and RNA binding

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Keywords: *Translation initiation, phosphorylation, phase separation*

Intrinsically disordered proteins (IDPs) lack a well-defined, unique, and stable three-dimensional structure but still remain functional under physiological conditions [1]. The eukaryotic translation initiation factor 4B (eIF4B) is a largely disordered protein that plays an important role in regulating translation initiation in eukaryotes [2] (**Figure 1**). The large intrinsically disordered region (IDR) of eIF4B facilitates a complex self-association transition from monomeric state to condensed phase, with large, dynamic, disordered oligomers forming prior to mesoscopic phase separation [3]. As a co-factor of RNA helicase eIF4A, eIF4B interacts with mRNAs containing long and structured 5' untranslated regions that is essential for efficient translation. Interestingly, eIF4B activity is regulated by phosphorylation, with Ser406 and Ser422 identified as functionally important sites [4,5,6]. To investigate the impact of phosphorylation on eIF4B self-association and RNA binding, we employed several phosphomimetic mutants alongside an integrative approach combining single-molecule Förster resonance energy transfer (smFRET) spectroscopy, nuclear magnetic resonance (NMR), and turbidity assays. Our results show that the S406E-S422E double-phosphomimetic mutant exhibits a substantially reduced propensity for mesoscopic self-association (i.e. phase separation) compared to the wild-type protein. Whereas, neither the S406E nor the S422E single-phosphomimetic mutants significantly alter eIF4B self-association. Similarly, different phosphomimetic variants affect RNA binding, accompanied by reduction of affinity to various degrees in an RNA sequence-dependent manner. These findings provide key foundational understanding for further studies exploring the functional implications of these interactions in physiologically relevant contexts.

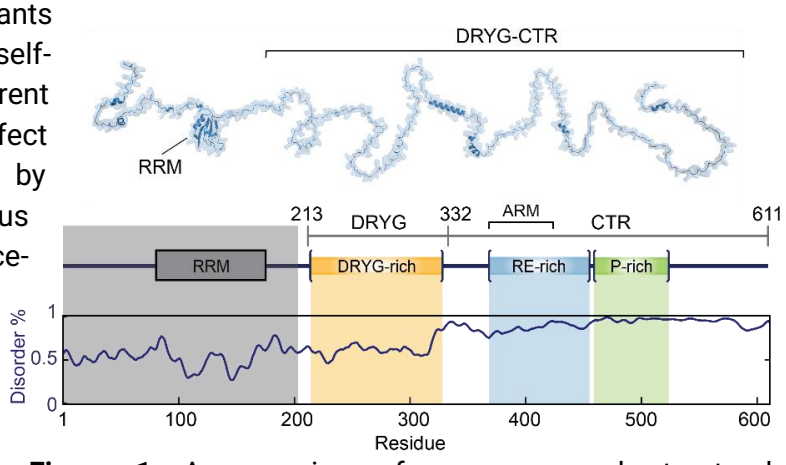

Figure 1: An overview of sequence and structural characteristics of eIF4B.

References: [1] Nat. Rev. Mol. Cell Biol., **2015**, *16* (1), 18-29. [2] Science, **2015**, *348* (6242), 1486-1488. [3] Nat. Commun., **2024**, *15*, 8766. [4] Nucleic Acids Res, **2015**, *43*, 512-520. [5] Embo j, **2006**, *25* (12), 2781-2791. [6] Embo j, **2004**, *23* (8), 1761-1769.

Acknowledgments: University of Bordeaux, IECB, ARNA.

Membrane partition and structural reorganization induced by antipsychotics with distinct clinical profiles

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Antipsychotics (APs) are used in the treatment of severe mental disorders, such as schizophrenia. Their mechanism of action involves interaction with multiple brain targets, such as the dopamine D2 receptor (D2R). Due to their lipophilic nature, APs also partition and accumulate in lipid membranes, particularly around the D2R and in synaptic vesicles. When intercalated into brain membranes, APs slowly accumulate and act as a reservoir, allowing their rapid release on demand to modulate neurotransmitter signalling. They also modify the physicochemical and mechanical properties of the lipid bilayer, which can subsequently affect the conformational changes of embedded membrane proteins like the D2R.

We have investigated the effect of two major APs with different pharmacological and clinical profiles: chlorpromazine and clozapine, both commonly used in treatment. Surprisingly, although D2R antagonism is usually associated with AP potency, clozapine (with the weakest D2R potency) has repeatedly demonstrated clinical superior efficacy to all APs and is therefore recommended for treatment-resistant schizophrenia. We elucidated APs membrane remodelling properties by thoroughly comparing their partitioning and impact on the physicochemical properties of the lipid membrane by using a combination of several biophysical methods and look on their impact on phase transition, thickness, elasticity, phase separation, membrane integrity and charge.

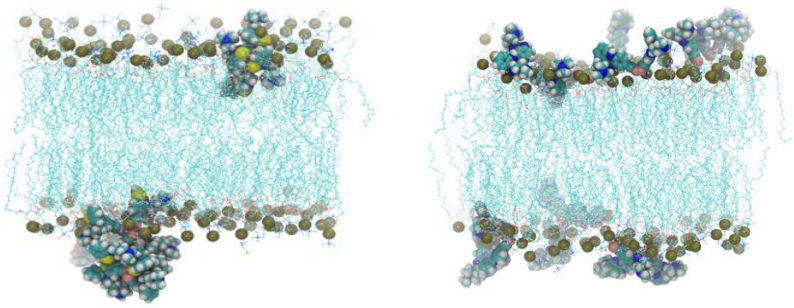

Figure 1: Chlorpromazine (left) and clozapine (right) interaction with a synaptic lipid membrane mimic – snapshot obtained by all-atom molecular dynamics simulation.

Acknowledgments: We would like to thank the financial support of ANR (polyFADO) and ANR Schizolip.

Investigating the molecular effects of particulate matter on human bronchial epithelial cells using Confocal Raman Microscopy and ToF-SIMS Imaging

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Keywords: Particulate Matter, BEAS-2B cells, Confocal Raman Microscopy, ToF-SIMS

Air pollution, is one of our era's greatest problem, not only in terms of its damaging impact on air quality, but also due to its impact on human health, potentially leading to death in the worst-case scenario. There are many air pollutants responsible for this premature death. Among them, particulate matter (PM) has attracted researchers' attention. It can easily penetrate the respiratory tract, causing an inflammatory response (e. g, secretion of IL-6, IL-8, TNF-α …) which triggers and exacerbates several respiratory diseases, such as asthma, and chronic respiratory disease (COPD)[1] [2]. The goal of our study is to analyze the effects of PM on lung cell models at the molecular level. To achieve this, human bronchial epithelial cells (BEAS-2B) were cultured under normal conditions and after 24 hours of exposure to PM to induce inflammation. Confocal Raman microscopy and Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) were used to identify particulate matter in cells and evaluate their impact. Additionally, various computational methods were applied to assess cellular responses. The outcomes of this study revealed significant morphological and spectral changes in cells following PM exposure compared to the control. This comprehensive approach provides insights into the cellular mechanisms triggered by PM exposure, contributing to a better understanding of its role in respiratory diseases.

References: [1] Environ. Pollut., **2020**, *263*, 114620. [2] Curr. Pollut. Rep., **2020**, *6* (4), 345-367.

Acknowledgments: This research is financially supported by the Francophone University Agency (AUF), the Institute of Chemistry & Biology of Membranes & Nanoobjects (CBMN) and the Lebanese Atomic Energy Commission of the National Council for Scientific Research of Lebanon (LEAC-CNRS-L). BEAS-2B sample cells were generously provided by Anthony Verdin at Univ. Littoral Côte d'Opale. Particulate matter sample used in this study was provided by the Lebanese Atomic Energy Commision (LEAC-CNRS-L).

Functional Selection of Molecular Aptamers Beacons

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Keywords: SELEX, Molecular Aptamer Beacon, DNA Aptamers

Designed for nucleic acid detection, Molecular Beacons (MB) are a powerful detection tool due to their ability to signal the presence of a target in real-time. To enhance their affinity and selectivity and extend their application for non-nucleic acid targets, Molecular Aptamer Beacons (MAB) were developed. Aptamers are small synthetic oligonucleotides obtained through Systematic Evolution of Ligands by EXponential enrichment (SELEX), a powerful combinatorial method leading to the identification of high affinity ligands for a specific target. SELEX allows the screening of libraries containing up to 10^{15} different candidates, either regular or chemically modified. MABs combine the recognition properties of aptamers with the switching ability of MBs, by triggering a fluorescence signal for imaging or drug release in a specific environment, with an improved signal/noise ratio. However, MABs designed from previous aptamers by trial-and-error or strand displacement can be tedious and do not ensure a successful candidate. Developing a SELEX method that can directly provide MABs without major post-SELEX modification is valuable.

In this project, we aim to develop a MAB SELEX method to detect Thrombospondin-1 (TSP1), a relevant biomarker of Glioblastoma, for theragnostic purposes. To reach that goal, we designed a library bearing FRET pair, and a two-step selection: first, 4 regular SELEX rounds were achieved using TSP1 immobilized on magnetic beads to reduce the diversity required for the next step. Then, 4 functional selection rounds were realized where monoclonal beads were produced by emulsion PCR and fluorophores grafted through NHS chemistry. The beads were incubated with TSP1; beads exhibiting fluorescence enhancement were sorted. A negative selection was used to discard sequences switching in absence of TSP1. After sequencing of all rounds, our method led to identification of Apta_1, which was synthesized and assessed by MST and fluorescence. Apta_1 exhibits moderate affinity (K_D = 1.8 µM) and its fluorescence is enhanced in the presence of TSP1, compared to non-specific binding, demonstrating its structure-switching ability. Although this candidate confirmed our experimental approach, we aim to improve affinity and fluorescence switch, through some protocol optimization: further selection rounds and a Doped-SELEX library.

Abstracts Poster Presentations

POST-TRANSCRIPTIONAL REGULATION OF KRAS GENE VIA 5 UTR RNA G-QUADRUPLEXES AND LONG NONCODING RNA

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Keywords: Cancer , KRAS, G4- quadruplex

In this work, we aim to elucidate the role of the hnRNPA1 protein in regulating both RNA and DNA G-quadruplexes (G4s) as a checkpoint modulator of KRAS gene expression. It is established, though not fully understood, that G4 structures in the KRAS promoter may facilitate transcription factor recruitment and also block histone modifiers that make inaccessible the transcription initiation site. On the other hand, rG4 structures within the untranslated region (5'UTR) of KRAS mRNA may act as steric barriers that regulate translation initiation while also maintaining the overall 5'UTR structure and stability required for translation. To investigate these mechanisms, we employed ChIP-seq and RIP-seq experiments, which confirmed the presence of folded G4 structures in vivo.

Furthermore, genome-editing using CRISPR/Cas9 allowed us to disrupt G4 structures, resulting in a significant increase in KRAS mRNA levels. Using biophysical techniques such as biolayer interferometry and NMR, we characterized the interaction of hnRNPA1 with both DNA and RNA G4s, in order to decipher its role in stabilizing their respective secondary structures. Our findings suggest that hnRNPA1 functions as a dual regulator, controlling two critical checkpoints in KRAS expression: transcriptional regulation via DNA G4s and post-transcriptional mRNA stability through rG4 formation in the 5'UTR.

References: Nucleic Acids Research. Submitted in 09/01/2025

Acknowledgments: This work is related to me (Zahraa Othman) and my director Gilmar Salgado as am a recipient of Excellence Eiffel fellowship. My Collaborations with Italian PhD students financed by Italian Ministry of Education.

DNA nanostructure based on an aptaswitch/aptakiss interaction

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Keywords: DNA, Aptamer, Kissing Complex

Thanks to its programmability, stability and accessible synthesis, DNA has been used as a biomaterial to detect molecules, treat diseases and produce nano-objects. Aptamers are single-stranded DNA (or RNA) molecules able to bind specific targets with high affinity and specificity. Among them, aptaswitches are dynamic aptamers which conformation change can enable a second interaction with a partner called aptakiss, through a well-described kissing interaction.[1] Moreover, the kissing interaction can be controlled by the presence or the absence of the aptaswitch target. Indeed, "positive" aptaswitch will engage a kissing complex with the aptakiss in the presence of its target; whereas, for "negative" aptaswitch, the kissing complex will be displaced upon target addition (Figure 1). In this work, we introduced such kissing interactions into DNA nanostructures. Depending on the presence of a trigger, our DNA nanostructure adopt different conformations or form different supramolecular assemblies.[2] In a first step, we have designed Holliday Junction-Like structures using 4 DNA helixes assembled in a cross. Each cross extremity was flanked with aptaswitches and aptakisses. Two aptaswitches responsive to adenosine were used: the "positive" aptaswitch realizes a kissing interaction in the presence of adenosine and the "negative" realizes kissing only in the absence of adenosine. We demonstrated that the supramolecular assembly is conditioned to the presence of adenosine, through native electrophoresis. In a second step, we have made a conditional nanomachine based on this aptaswitch/aptakiss interaction and we demonstrated its operation by native electrophoresis and FRET. As a perspective, this type of DNA nanostructure based on aptaswitches could be used to control the conformation of 2D or 3D assemblies, or to control the movements of nanomachines. In conclusion, this project aims to provide a proof of concept for the use of kissing aptaswitches in nanotechnology applications.

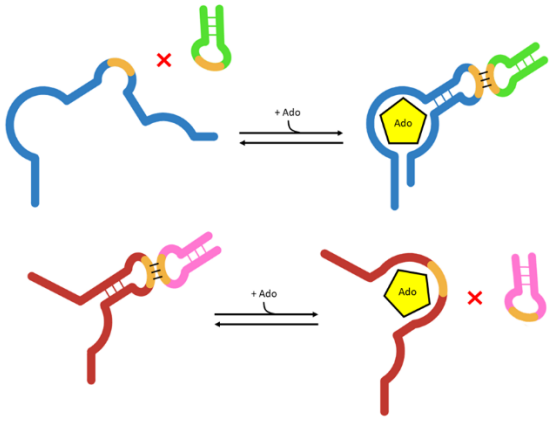

Figure 1: Schematic representation of aptaswitches. A positive aptaswitch (in blue) engages a kissing interaction in the presence of Adenosine (Ado) with its partner aptakiss. In the opposite way, the kissing interaction between the negative aptaswitch (in red) and its aptakiss is displaced upon Adenosine (Ado) addition.

References: [1] Angew. Chem. Int. Ed., **2014**, *53* (27), 6942-6945. [2] Nucleic Acids Res., **2017**, *46* (3), 1052-1058.

Condensation of translation initiation factor eIF4B: from *in vitro* to *in-cell*

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Keywords: Intrinsically disordered proteins, Phase Separation, Single-molecule FRET

Emerging research suggests that the formation of biomolecular condensates, often mediated by phase separation of intrinsically disordered proteins (IDPs) and nucleic acids, is essential for regulating fundamental physiological processes and is also implicated in neurodegenerative diseases. To discern the molecular mechanisms behind the formation of biomolecular condensates, a deep understanding of condensation at mesoscale and underlying molecular processes at nanoscale is highly important both *in vitro* and ultimately in living cells.

My project focuses on *in vitro* and *in-cell* characterization of condensation of eukaryotic translation initiation factor 4B (eIF4B), an intrinsically disordered translation factor implicated in regulation of protein synthesis [1] and formation of stress granules [2]. In this work, the co-localization of endogenous eIF4B in stress granules (SGs), along with G3BP1, a SG marker protein, is first confirmed using an immunofluorescence (IF) assay. Nonetheless, U2OS eIF4B knockout cells still show the formation of G3BP1-positive SGs in the absence of endogenous eIF4B, highlighting the role of eIF4B as cargo rather than a scaffold in SG assembly within cells. Our group has previously shown that DRYG region of eIF4B with its large fraction of tyrosine residues, is essential for eIF4B condensation *in vitro* [3]. In line with this observation, my preliminary results show that SG induction in cells expressing eIF4B variants exhibits a significant reduction in SG accumulation propensity for eIF4B variant, where tyrosine residues are replaced by serine residues in the DRYG region. Furthermore, my single-molecule experiments enable characterizing the distinct intra- and inter-molecular dynamics of eIF4B and in the presence of RNA, which can help in rationalizing the condensation behavior of the protein.

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Acknowledgments: Frontiers of Life (RRI)-University of Bordeaux, ANR, INSERM.

NMR SPECTROSCOPY TO STUDY PROTEIN ASSEMBLIES ON BACTERIAL MEMBRANE

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Keywords: Antimicrobial resistance, ZipA protein, NMR Spectroscopy

Antimicrobial resistance in bacteria is an escalating public health threat, making it crucial to identify new therapeutic targets [1]. Understanding the atomic mechanisms behind protein-membrane interactions in bacteria offers a promising strategy to discover novel drug targets. Our research focuses on the ZipA protein, which plays a vital role in bacterial cell division [2], controlling the initial molecular steps during set-up of the division site in certain bacterial pathogens such as Escherichia coli.

Using both solution and solid-state Nuclear Magnetic Resonance (NMR) spectroscopy, we investigate the molecular structure of ZipA in a membrane-mimicking environment. By targeting the protein structure in a native-like setting, this study aims to uncover insights into the structures and the interactions with the membrane at the atomic level, providing crucial information for the development of new antimicrobial agents.

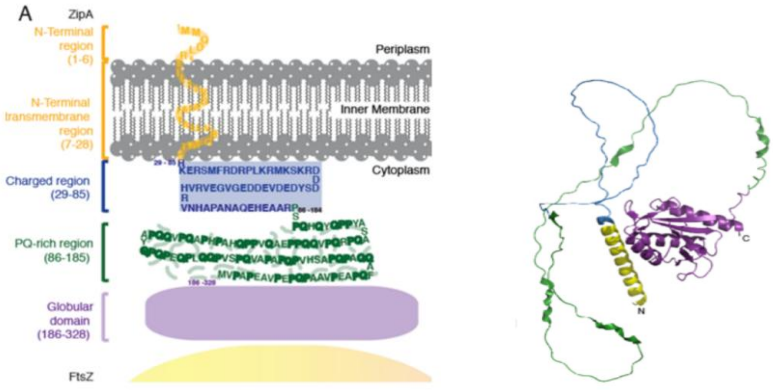

Figure 1: Structural domains of ZipA [3].

References: [1] C. Jariremombe R., **2023**, Escherichia coli - Old and New Insights, IntechOpen, DOI: 10.5772/intechopen.101671. [2] Sci. Rep., **2019**, *9* (1), 18712. [3] Tawani A. et al., *in preparation*.

Acknowledgments: The work is supported by CNRS Momentum and ANR BACDOMAIN. This work has benefited from the facilities and expertise of the Biophysical and Structural Chemistry platform (BPCS) at IECB, CNRS UAR3033, INSERM US001, and Bordeaux University. We thank INFRANALYTICS CNRS.

Impact of membrane polyunsaturated fatty acids on cannabinoid type 1 receptor pharmacology

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Keywords: Polyunsaturated fatty acids; G-protein; cannabinoid receptor; GPCR

The cannabinoid type 1 receptor (CB1R) is one of the most abundant GPCR in the central nervous system, where it plays a crucial role in modulating physiological processes including motor control, cognition, or pain regulation[1]. CB1R dysregulation, either at the level of its expression or activity at the plasma membrane, has been linked to various pathological conditions, including neurodegenerative diseases such as Alzheimer's disease. These pathological conditions are also associated with alterations in the levels of polyunsaturated fatty acids (PUFAs) in brain lipids, one of the regions where CB1R is highly expressed[2]. Membrane lipid environment is known to influence GPCR pharmacology, including receptor conformation, ligand binding, and downstream signaling[3] as demonstrated for several GPCRs previously studied by our team and others[4, 5]. We hypothesize that PUFAs influence CB1R pharmacology. To test this, we aim to investigate PUFAs impact on CB1R ligand/lipid interaction as well as receptor conformational states, and intracellular signaling pathways.

To test how PUFAs could affect receptor conformational changes, we use a CB1R FRET conformational sensor and we integrate molecular dynamics approaches to analyze these structural changes. Using BRET-based G protein biosensors, we assess PUFA modulation of CB1R G-protein dependent signaling[6]. Our results show that PUFAs impact CB1R conformation and G-protein dependent signaling. Their impact depends on their nature and degree of polyunsaturation but also varies depending on the ligand used and the effectors they interact with, such as different G proteins subtypes.

References: [1] Front Neurosci, **2013**, *7*, 256. [2] Lipids Health Dis, **2016**, *15*, 25. [3] Biophys Chem, **2022**, *285*, 106794. [4] Mol Psychiatry, **2023**, *28* (5), 1960-1969. [5] Sci Rep, **2016**, *6*, 19839. [6] Science Signaling, **2021**, *14*, 699.

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sRAGE, A Potential Therapeutic Approach to hIAPP Amyloid Fibrillation and Toxicity

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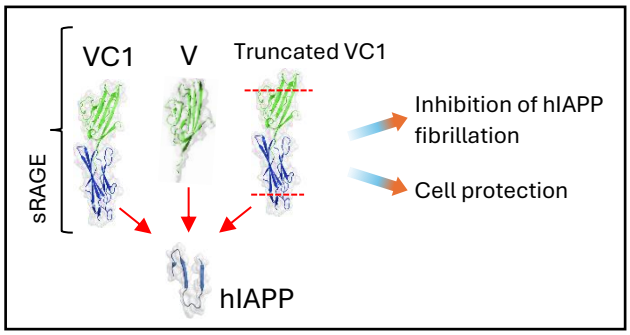

The receptor for advanced glycation end products (RAGE) is a multi-ligand receptor capable of binding amyloid proteins such as amyloid β, α-synuclein, and human islet amyloid polypeptide (hIAPP). It promotes both amyloid fibril formation and cellular toxicity[2,5,6] observed in amyloid-associated pathologies[1-4]. However, recent studies on hIAPP have shown that the soluble extracellular domain of RAGE receptor, known as sRAGE, can trap hIAPP, preventing its fibrillation and toxic effects on cells[1]. Therefore, sRAGE may serve as a model for the development of bio-mimetic peptides to reduce amyloid proteins toxicity[7].

To explore the inhibitory effect of this receptor on fibril formation, fragments of sRAGE, including the VC1 domain, the V domain, and a truncated VC1 domain, were produced and purified. The presence and the structural integrity of these proteins were determined using mass spectrometry and circular dichroism. Our results indicate successful production of the three sRAGE fragments, with well-structured proteins observed except for the isolated V domain, which exhibits comparatively lower structural integrity, in agreement with previous study that indicate a low stability for this V domain[8].

Then, the aggregation kinetics of hIAPP in the presence and absence of sRAGE fragments, at varying ratios, was assessed through Thioflavin T fluorescence assays. Additionally, Transmission Electron Microscopy (TEM) was used to obtain structural insights of the sRAGE/hIAPP complexes. Thioflavin T assays reveal that both VC1 and truncated VC1 domains exhibit identical inhibition of hIAPP fibrillation, whereas the V domain shows a weaker inhibitory effect, possibly due to its weaker structural integrity or the necessity of the C1, domain for the proper inhibition of hIAPP fibrillation. These findings are supported by TEM images, which show the absence of amyloid fibrils in the presence of VC1 and truncated VC1 domains at a ratio of 1:1 (c/c). Furthermore, hIAPP fibrillation was studied by adding the VC1 domain at different time points to identify the forms in which hIAPP interacts with the VC1 domain. The results indicate that the VC1 domain exerts its inhibitory activity by binding to hIAPP monomers and oligomers. Following that, the cytoprotective efficacy of both the full-length VC1 and its truncated form was assessed on neuronal SH-SY5Y cells via the MTT cell viability assay. The findings demonstrate that both domains effectively safeguard SH-SY5Y cells from hIAPP-induced cell death.

Altogether, our results validate the hypothesis on the inhibitory effect of sRAGE and highlight its potential therapeutic significance in amyloid-related disorders. Further biophysical

investigations are underway to identify the specific amino acids of the sRAGE constructs involved in sRAGE/hIAPP binding, characterize the thermodynamic parameters of the interaction, and assess the cytoprotective effects of these constructs on hepatic and pancreatic cell models.

References: [1] J Clin Invest, **2018**, 128. [2] Cell Reports, **2022**, *40*, 111401. [3] Exp Rev Neuro, **2009**, *9*, 1635. [4] IJMS, **2022**, *23*, 11816. [5] J Alzh Dis, **2019**, *16*, 833. [6] Chem Rev, **2021**, *121*,1845. [7] Mech Ageing Dev, **2015**, *145*, 18. [8] Biochem, **2007,** *46*, 6957.

Biofuel production from microalgae

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One of the most important challenges facing humanity in this century is to stabilize CO_2 concentrations in the atmosphere in order to limit the global increase of Earth's temperature. To reduce CO_2 emissions, countries worldwide are implementing a number of strategic actions to reduce the use of fossil fuels in transports, including the production of biofuels. For this purpose, microalgae have been identified as a promising biomass resource because of their rapid growth and high oil yields. However, at present, large-scale production of microalgae-based biofuels faces a number of challenges that have made its development economically unviable, including the challenge of producing large quantities of biomass. A promising strategy to tackle this problem is to grow microalgae in mixed cultures with yeast cells. In these consortia, microalgae and yeast establish a mutualistic relationship based on gas exchange in situ resulting in increased biomass and lipid production. In such setting however, stability between the two microorganisms' sub-populations is key to maintain the mixed culture over long period of time. Understand these interactions between yeast and microalgae is of primary importance to delineate the stability between microorganism's sub-populations. We propose to develop a strategy to investigate the molecular organization of the cell surface of yeast cells, microalgae and their mixed co-culture. The first objective is to scrutinize the molecular organization of various microorganism's cell wall using advanced solid-state NMR techniques. The second is to understand homotypic polysaccharide interaction by molecular dynamics simulation combined with experimental NMR data.

FP-iTP-Seq: a novel high-throughput method to study co-translational protein folding

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Keywords: Co-translational folding, Arrest peptides, Ribosomes, Force profile analysis, iTP-Seq

Force Profile Analysis (FPA) is a widely used technique for studying co-translational protein folding. It is based on the principle that the free energy released by protein folding on the ribosome exerts a pulling force on a nascent polypeptide sufficient to resolve translational arrest induced by a force-sensing arrest sequence fused to its C-terminus. A map of such co-translational force-generating events for multiple N-terminal truncations of a protein of interest is called a force profile (FP) and can reach single-amino acid resolution if sufficient constructs of such truncations are analyzed. In its current form, FPA relies on the low-throughput generation of up to ~100 individual constructs and the subsequent quantification of their translation products on polyacrylamide gels. Here, we present a novel high-throughput technique called FP-iTP-Seq (Force Profile coupled to iTP-Seq), which multiplexes FPA of protein fragments translated in vitro using inverse toeprinting coupled to next-generation sequencing (iTP-Seq). A typical DNA library for FP-iTP-Seq contains one or several protein-coding ORFs fragmented to generate every possible N-terminal truncation, followed by one of several arrest peptides of varying strengths. Ultimately, this approach should make it possible to study the in vitro co-translational folding of hundreds of soluble proteins in a highly parallel fashion.

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Acknowledgments: A.B. and C.A.I. have received funding for this project from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement no. 724040). A.B. has also received funding from the Agence Nationale de la Recherche, France (ANR-22-CE11-0012-01). G.v.H., A.M., and J.M.W. have received funding from the Knut and Alice Wallenberg Foundation (2017.0323), the Novo Nordisk Fund (NNF18OC0032828), and the Swedish Research Council (2020-03238).

Structure of the type IV pilus from *Streptococcus sanguinis*

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Keywords: *Streptococcus sanguinis,* Type IV pilus, Cryo-electron microscopy

Type IV filaments (T4F) represent a ubiquitous superfamily of nanomachines found in Bacteria and Archaea, comprised mainly of filamentous polymers of type IV pilins. These filaments play pivotal roles in adhesion, motility (both swimming and twitching), DNA uptake, bacterial community formation and protein secretion, making them significant virulence factors in various bacterial pathogens. Cryo-electron microscopy (cryo-EM) has unveiled conserved helical architectures of T4F of Gram-negative bacteria, revealing intriguing "melted" segments within the α1N portion of pilins during filament polymerization. Our research investigate the T4F architecture in phylogenetically distant Gram-positive species. Here, we present a 3.7 Å resolution cryo-EM structure of *Streptococcus sanguinis* (S. sanguinis) heteropolymeric T4F, providing a comprehensive atomic model encompassing all minor pilins.

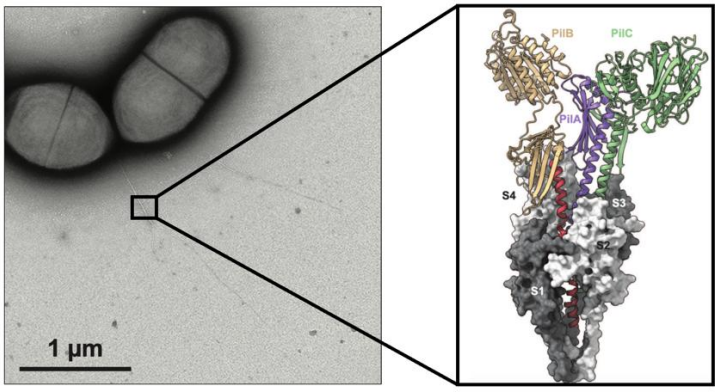

Figure 1: Atomic model of the heteropolymeric type IV pilus in *S. sanguinis*.

References: [1] Microbiol. Rev., **2015**, 39, 134–154. [2] Mol. Microbiol., **2008**, *68*, 827–837.

Acknowledgments: This work was funded by the Agence Nationale de la Recherche and the Medical Research Council.

A ubiquitin-like protein controls assembly of a bacterial Type VIIb secretion system

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Keywords: Type VII secretion systems (T7SS), Cryo-EM, interbacterial competition

Type VII secretion systems (T7SS) are crucial bacterial nanomachines that mediate interbacterial competition and hostpathogen interactions in Gram-positive bacteria. Despite their importance, the structural basis for assembly and substrate transport in T7SSb, a widely distributed T7SS variant, remains poorly understood. Here, we present the cryo-EM structure of the T7SSb core complex from Bacillus subtilis, revealing how a ubiquitin-like protein, YukD, coordinates assembly of the secretion machinery. YukD forms extensive interactions with the central channel component YukB and promotes its association with the pseudokinase YukC, creating a stable building block for channel assembly. Using microscopy and competition assays, we demonstrate that YukD is essential for proper T7SSb complex formation and contact-dependent bacterial killing. Structural modeling suggests this YukD-dependent assembly mechanism is conserved across diverse Gram-positive bacteria. Our findings reveal how bacteria have adapted a ubiquitin-like protein as a structural regulator for assembling a large secretion complex.

RNase S engineering using ligand-directed bioconjugation

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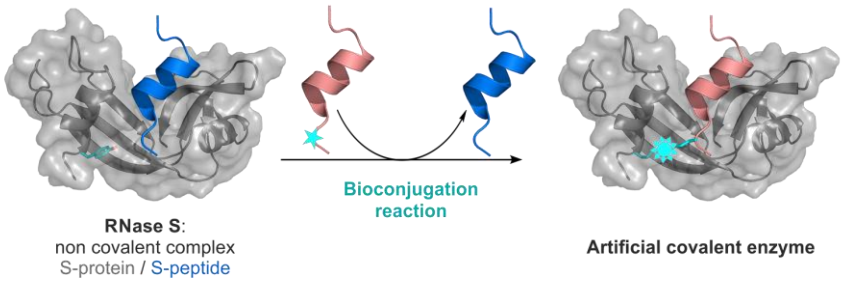
Keywords: Protein engineering; ligand-directed bioconjugation; SuFEx; RNase S.

Protein engineering resulting from the recombination of natural and synthetic protein fragments (i.e., protein semi-synthesis) is a valuable tool in chemical biology for modulating protein activity or introducing non-native chemical functions.[Erro! A origem da referência não foi encontrada.] Despite significant advances in synthetic biology, chemical synthesis remains the most sequence-specific and flexible method to alter protein sequences, including side chain modifications as well as alterations to the peptide backbone and chirality.

In this work we use the protein scaffold of the non-covalent RNase S complex to develop a ligand-directed bioconjugation reaction that would enable efficient semi-synthesis of RNase S conjugates. The proximity between the Tyr-25 side chain of the S-protein fragment and the C-terminus of the S-peptide helix led us to explore site-selective tyrosine bioconjugation using ligand-directed strategies.[Erro! A origem da referência não foi encontrada.] We report here the results obtained with the Sulfur Fluoride Exchange (SuFEx) reaction,[Erro! A origem da referência não foi encontrada.] that enables efficient cross-linking of S-peptide variants to S-protein.



References: [1] Chem. Rev., **2020**, *120* (6), 3051-3126. [2] Organic & Biomolecular Chemistry, **2020**, *18* (44), 9018-9028. [3] Angew. Chem. Int. Ed, **2014**, *53* (36), 9130-9448.

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Aromatic Oligoamide Foldamers as Tools for Selective Carbohydrate Recognition

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Keywords: Carbohydrate Recognition, Cone-shaped Aromatic Oligoamide, Supramolecular Protecting Groups.

Carbohydrates play a crucial role in life, serving as essential building blocks and mediators of intercellular communication. However, their recognition (whether by natural or artificial receptors) remains a significant challenge due to their complex structural diversity[1]. Saccharides exist as isomers with various tautomeric and anomeric forms that closely resemble one another[2], making selective binding difficult.

To address this, we draw inspiration from protein-based molecular recognition and employ a class of synthetic molecules known for their predictable folding behavior: **aromatic oligoamide foldamers**. By adjusting the type of monomers used, it is possible to generate molecular containers such as capsules or cones. These cavities, lined with multiple hydrogen bond donors and acceptors, can interact with and encapsulate guest molecules, including carbohydrates, through non-covalent interactions.

Our group has shown that foldamer capsules can achieve selective recognition of mono- and di-saccharides in polar organic solvents[3]. However, this encapsulation approach becomes less effective with larger saccharide targets. To overcome this limitation, we developed open-cavity receptors, specifically **Cone-shaped Foldamer** architectures, which offer a more accessible binding interface.

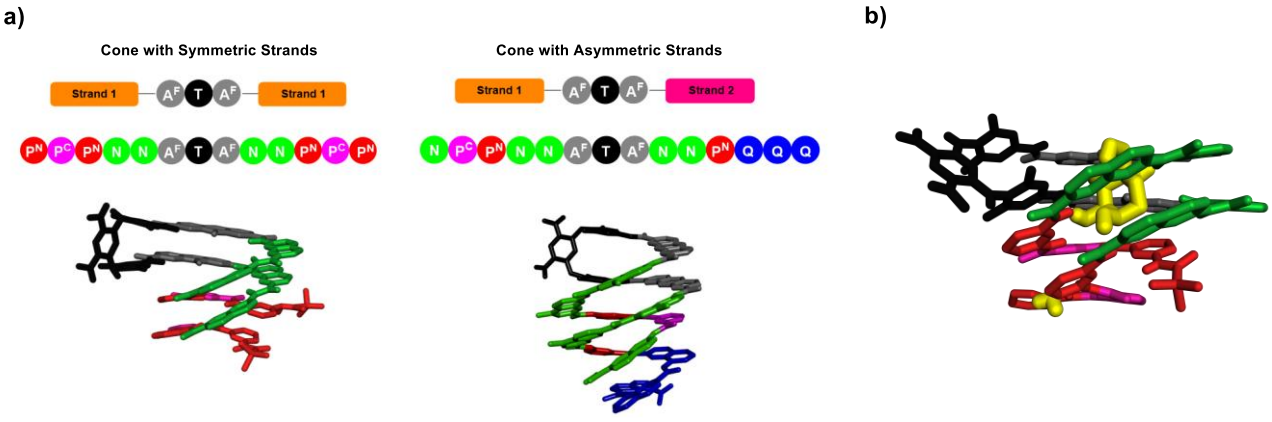

Figure 1: a) two different strategies adopted for the synthesis of cones, the models are calculated with MMFFs, b) X-Ray structure that show interaction of a cone with β-D-Fructopyranose.

Herein, we present two different strategies (**Fig 1.a**) to construct foldamer-based cone-like receptors for carbohydrate recognition, and we focus on the interaction of one such cone with various saccharides (**Fig 1.b**). Beyond recognition, these foldamers also show promise as **Supramolecular Protecting Groups**, capable of shielding multiple reactive sites and enabling controlled functionalization. In both cases, these foldamers emulate the first crucial step of enzymatic processes: precise molecular recognition.

References: [1] Science, **2001**, 291, 2357, [2] Angew. Chem. Int. Ed., **2008**, 47, [3] *Nature Chemistry*, **2015**, *7*, 334.

Acknowledgments: This project has received funding from the European Union's Horizon Research and Innovation programme under the Marie Sklodowska-Curie (HORIZON-MSCA-2022-DN) grant agreement No. 101119492.

Lipid modulation of the β-arrestin signaling pathway following activation of Dopamine D2 receptor by ligands

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Dopamine D2 receptor (D2R) signaling, the primary target of antipsychotics (APs), is influenced by the lipid composition of cellular membranes. In schizophrenia, lipid imbalances observed in patients, such as omega-3 polyunsaturated fatty acid (PUFA) deficits, may further alter these signaling pathways as shown in pioneer work by the team.[1] Undesired AP side effects have been associated in part with their lack of specificity in activating particular pathways. Understanding the β-arrestin signaling pathway is particularly important as this pathway is often linked to better therapeutic outcomes with antipsychotics. Preliminary data by the team suggests that the lipid membrane environment, namely PUFAs, modulate this pathway.[2] However, the molecular mechanisms by which membrane lipids exert such effect remain poorly understood. In addition to the inherent lipid imbalance observed in patients with psychiatric disorders, AP treatment also changes their lipidomic profiles and differ depending on the AP class (typical, atypical). Levels of the anionic lipid phosphatidylserine (PS) are altered in patients with a decrease being associated with a poor AP treatment outcome.[3] Our project focuses on understanding if and how lipids (PUFA and anionic lipids as PS) modulate β-arrestin recruitment at the D2R, its activity and structure. To address this we will use a combination of biochemical and biophysical approaches like *in cellulo* FRET biosensors, *in vitro* techniques such as hydrogen/deuterium exchange mass spectrometry and *in silico* simulations. Understanding how membrane lipids influence β-arrestin interaction with the D2R and subsequent signaling could could help identifying new therapeutic targets for schizophrenia, which is especially relevant given that current antipsychotics often lead to significant side effects and treatment resistance.

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Implementing Sequence Selective Hybridization in Artificial Double Helices

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Molecular self-sorting is a phenomenon where molecules spontaneously organize into distinct, well-defined structures, even in the presence of similar species. This process is driven by precise molecular recognition, facilitated by complementary shapes and non-covalent interactions. Heteromeric self-sorting, which involves the selective association of different molecules, enables information encoding at the molecular level as seen in nature with nucleic acids (DNA duplexes) and proteins (coiled-coil peptides). In a recent study, we demonstrated that different artificial helical aromatic oligoamide sequences, which typically form homomeric double helices in water, quantitatively produced a heterodimer when combined (Fig. 1, left). Building on this observation, our current work aims to establish a general sequence complementarity pattern by combining F and O monomers (Fig. 1, right). Ultimately, this project seeks to develop a novel, artificial sequence-complementarity code distinct from that of nucleic acids.

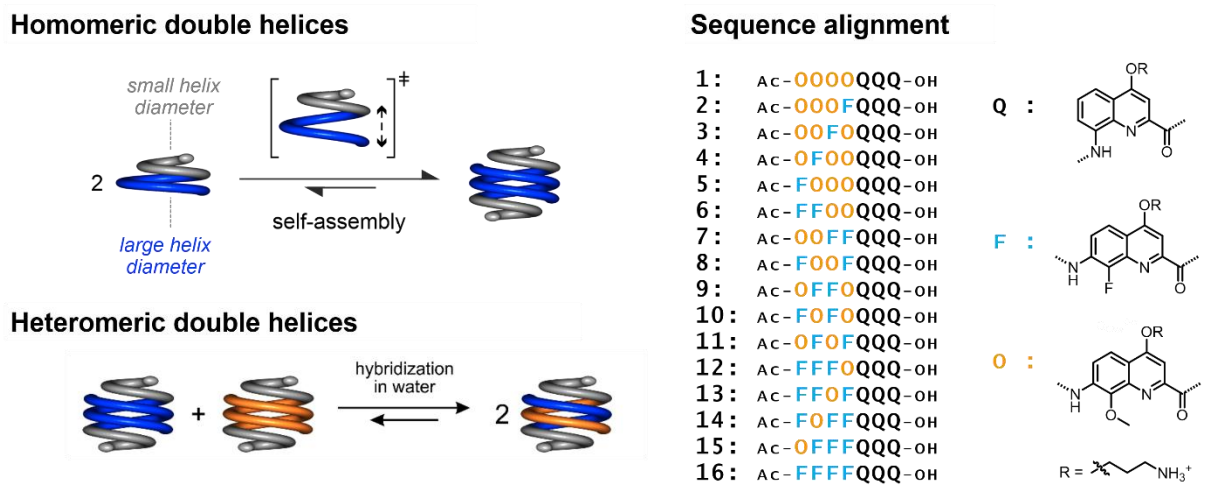

Figure 1. (left) Cartoon representations of: i) the self-assembly of identical helical strands forming a homomeric double helix and ii) the hybridization of two different strands in water. (right) Aromatic oligoamide sequences prepared to decipher the artificial sequence-complementary code.

References: [1] *Angew. Chem. Int. Ed.*, **2023**, *135*, e202311639.

In situ prevascularization and mineralization using Laser-Assisted Bioprinting for personalized maxillofacial bone regeneration

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Keywords: biofabrication; laser-assisted bioprinting; bone tissue engineering; vascularization; dental stem cells; personalized medicine.

Oral cancer affects approximately 275,000 patients annually, leading to significant functional impairments and a reduced quality of life. The management of maxillofacial defects remains a major clinical challenge [1]. Bone tissue engineering combines functional scaffolds with bioactive molecules and stem cells to promote bone regeneration. Laser-assisted bioprinting (LAB) has emerged as a promising technique for scaffold fabrication, offering precise bioink deposition and high spatial resolution [2]. Previous studies suggest that endothelial and dental stem cells enhance bone regeneration, although they do not achieve bone formation ad integrum [3]. Meanwhile, MRI has proven effective for tracking printed cells in 3D construct [4]. This thesis aims to address current challenges by formulating bioinks incorporating biopolymers and mineral particles to promote both mineralization and vascularization, while also improving MRI resolution. Initial qualitative analysis identified nine formulations with excellent spreadability, evaporation, and printability. Quantitative assessments of circularity and reproducibility demonstrated that 2% PGU with 0.1% nanohydroxyapatite exhibited the best performance (circularity=0.985±0.027, area=0.248±0.041). MRI evaluations confirmed the ability to track printed cells over time with high spatial resolution, reproducible image analysis, and sustained retention of the internalized contrast agent. This research contributes to the advancement of tissue engineering by integrating cutting-edge technologies such as LAB and cell-MRI into personalized medicine approaches.

References: [1] Regen Eng Transl Med., **2016**; *2* (2), 55-68. [2] Biomaterials., **2010**, *31*(28), 7250-7256. [3] Biofabrication., **2019**, *11* (4), 045002. [4] Sci Rep., **2018**, *8* (1), 15777.

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Nanocarriers in Drug Delivery: Innovations in Light-Responsive Liposomes

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Keywords: light responsive liposomes; drug delivery; diazirine.

The advantages of liposomes as drug delivery vehicles are confirmed by the enhanced therapeutic index of many FDA approved formulations. The benefits of these nanocarriers are further enhanced by developing stimulus-responsive versions that ensure controlled release at target sites.[1] Taking advantage of the small photo-reactive diazirine moiety, we have developed and patented stable light-responsive nanoparticles that released their cargo upon irradiation. [2,3] Phosphatidyl cholines (PCs) in C_{14}, C_{16} and C_{18} series incorporating diazirine moiety were synthesized and formulated into SUVs encapsulating the hydrophilic fluorescent probe calcein. Formulations were prepared with cholesterol and DSPE-PEG to enhance their plasma stability. Analysis of the irradiation products showed that the light triggered release is a result of diazirine conversion to the corresponding ketone and unsaturated derivatives, which increase the liposomal membrane permeability. *In-vitro* toxicity studies showed that diazirine-PCs had a similar profile to the natural PC. Additionally, *in-vivo* biodistribution tests proved their biocompatibility and accumulation in tumors (Figure). We are currently optimizing formulations that are stable and photo-responsive to test the therapeutic advantage of the light triggered release in vivo, using Doxorubicin as the therapeutic agent.

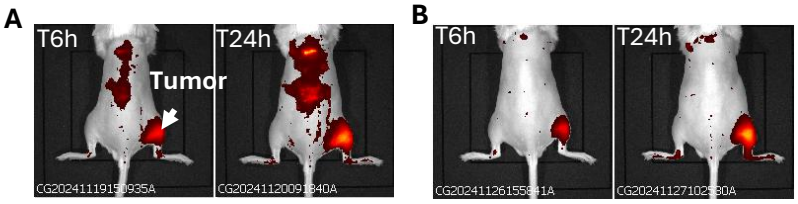

Figure: Accumulation of Lipodox (control, A) and photo-sensitive Lipodox (B) in tumors.

References: [1] Leung SJ, Romanowski M, *Theranostics*, **2012**, 1020-36. [2] Saryeddine L et al, *J Colloid Interface Sci*, **2024**, 1792-1804. [3] Badarau E et al, WO2024084096A1, **2024.**

Acknowledgments: This work is supported by the grants from: Initiative of Excellence of the University of Bordeaux (LiRLi 2023) and Ligue contre le cancer (PhotoSENSEI 2023).

GLUT1 Deficiency Syndrome: New Horizon

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Keywords: GLUT1 deficiency syndrome, Rare disease, Cerebral energy metabolism, CRISPR-Cas9

The glucose transporter type 1 deficiency syndrome (GLUT1-DS) is a rare systemic condition with a pediatric onset, leading to drug-resistant epilepsy, neurodevelopmental and complex movement disorders. The GLUT1 transporter facilitates the transport of glucose from the bloodstream to the central nervous system (CNS). The brain accounts for only 2% of body mass but consumes about 25% of the body's total energy in the form of glucose. Therefore, this transport is essential for the development of the CNS. Patients with GLUT1-DS experience a significant reduction in cerebral energy supply. The only currently available therapy involves following a ketogenic diet, which is proportionally low in carbohydrates and high in lipids. However, this diet does not alleviate all symptoms. Neurodevelopmental disorders that emerge during childhood generally persist throughout life. Furthermore, this diet is ineffective for about 25% of patients and represents a major challenge for many families. Implementing such a ketogenic diet is difficult to manage and tolerate for children.

To explore new therapeutic avenues, our team has developed a new rodent model of GLUT1-DS. This innovative and promising model features GLUT1 deficiency ($GLUT1^{+/-}$), generated by CRISPR-Cas9, in rats. It represents a valuable tool for identifying innovative therapies aimed at improving therapeutic management and the quality of life for patients. The multimodal characterization of this new model is currently underway.

Finally, in conjugation with this preclinical phase, a retrospective, observational clinical study (collecting and analysing data from GLUT1-DS patients) is being conducted. This study will provide scientific evidence to support the implementation of a future therapeutic clinical trial.

Acknowledgments: Fondation Maladies Rares et Fonds de Dotation Neuroglia.

Formulation of novel tripolar bolalipids for sustained drug release

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Keywords: bolalipids, sustained drug delivery, controlled release.

Liposome-based drug delivery systems have shown undeniable advantages (*e.g.*, increased biocompatibility, modularity, versatility of payloads, etc.), and are therefore the most clinically successful drug delivery system (DDS) described to date.[1]

The group developped atypical bola-amphiphiles[2] that modulates the membrane's properties because of their unique conformational behaviour.[3]

The current Nano-Sure project addresses the optimization of the previously identified bola-amphiphiles, with a focus on improving the stability of the resulting bolasomes. Several formulations were screened by mixing natural phospholipids with the bolalipid synthesized in-house. Among them, an ester as central polar moiety (**Figure 1**) gave the most promising results : compared to highly leaky control *DMPC-liposomes* (cargo loss within 30 min) a *DMPC/Bola : 5/5* mixture was able to conserve the cargo for at least 2 weeks.

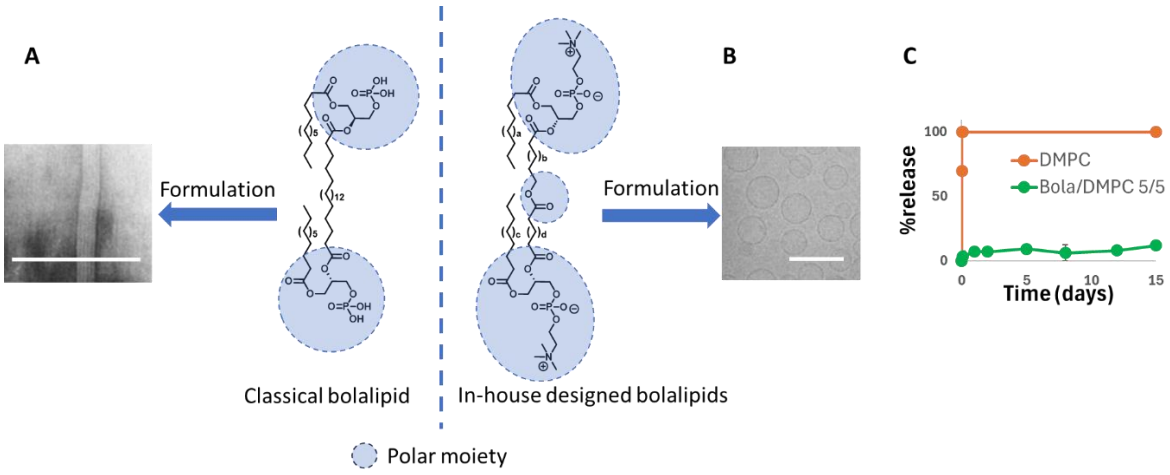

Figure 1: (A) Filaments obtained from classical bolalipids (scale bar 100 nm, adapted from Ref[4]). (B) Vesicles obtained from DMPC/Bola 5/5 (scale bar 200 nm, adapted from Ref[3]). (C) Release profile of DMPC/Bola 5/5.

References: [1] Cancer Nano, **2019**, *10 (1)*, 11. [2] Chem. Rev, **2004**, *104 (6)*, 2901. [3] Bioconjug Chem, **2024**, *35 (12)*, 1900. [4] Langmuir, **1992**, *8* (2), 637.

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Innovative hydrogels for post-surgical glioblastoma treatment

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Keywords: hydrogels, cancer treatment, radiotherapy, drug delivery, glioblastoma.

Glioblastoma (GB) remains highly aggressive and recurrent due to deep tumor infiltration and limited treatment efficacy. Conventional post-surgical therapies, such as Gliadel® implants, often cause severe side effects and struggle to adapt to brain tissue. This study presents the development of a hydrogel (HG)-based implant designed to improve post-surgical GB treatment by addressing the limitations of current options and offering enhanced brain adaptability and therapeutic efficacy. The HG will be formulated using ε-poly-L-lysine (ε-PL), chosen for its antimicrobial properties, biocompatibility, and ease of functionalization. Functionalization with tyrosine residues enables enzymatic crosslinking, avoiding the use of harsh conditions. This implant incorporates a multifaceted therapeutic approach by integrating chemotherapy (CT), radiotherapy (RT), and nanocatalytic therapy (NCT) to surpass the limitations of monotherapy. The incorporation of metal nanoparticles (NPs) enhances RT efficiency by acting as radiosensitizers, while simultaneously generating oxygen to mitigate tumor hypoxia and amplify RT efficacy through reactive oxygen species (ROS) production upon X-ray activation. *In vitro* and *in vivo* assessments will evaluate the therapeutic performance, recurrence suppression, and safety profile of this system. This innovative HG-based implant holds promise for advancing post-surgical GB treatment, improving patient outcomes, and enhancing quality of life.

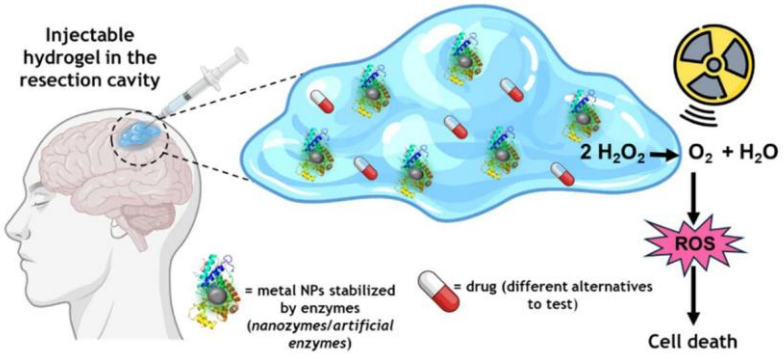

Figure 1: The combination of the different therapies (CT, RT, NCT) will kill the residual GB cells.

References: ACS Nano, **2023**, *17* (6), 5435‑5447.

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Aza-Helicene Derivatives: Synthesis and Chiroptical Properties for Potential Biological Use

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Keywords: Helicene, Azahelicene, Optical properties, PDT.

A modular synthesis of π-extended aza-helicenium was developed from simple triarylamine precursors.[1] Under Vilsmeier–Haack conditions, via intramolecular cycloaromatization and subsequent nitrogen quaternization yielded an acridinium intermediate, followed by cyclodehydrogenation to form a benzo[ghi]perylene motif. This double cyclization gave the dissymmetrical aza-helicenium **1** with ten fused aromatic rings.

Azahelicenium **1** showed multi-band ECD and strong long-wavelength CPL with high dissymmetry factors in both organic and aqueous media, indicating potential for biological applications. An extended derivative **2** was synthesized. It efficiently generated singlet oxygen, making it a promising agent for photodynamic therapy.[2]

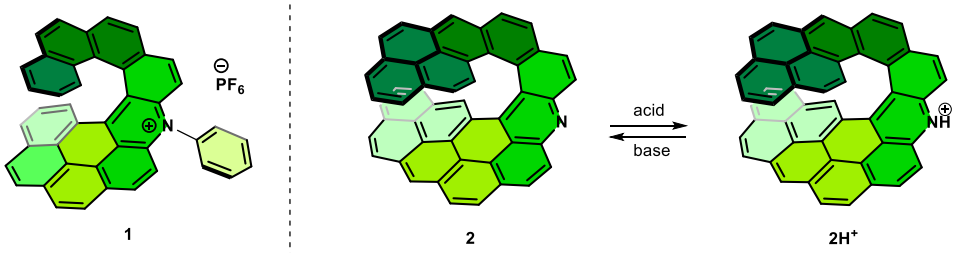

Figure 1: Synthesis of π-extended azahelicenium.

References: [1] Org. Chem. Front., **2023**, *10*, 752–758. [2] Nanoscale, **2024**,*16*, 3243–3268.

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Hetero-helicenes with multi-state emission for singlet oxygen generation

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Keywords: Helicenes, NIR emission, Singlet Oxygen Generation.

Compounds capable of populating the triplet excited state (T_1) can generate singlet oxygen ($^1O_2$) through interaction with ground-state triplet oxygen ($^3O_2$).[1] These properties are particularly relevant in photodynamic therapy, a promising approach for antitumoral cancer treatment.[1,2] Molecules with non-planar conformations, such as helicenes, exhibit favorable properties for such applications due to their ability to enhance intersystem crossing (ISC), thereby populating and stabilizing triplet excited states and enabling the photoconversion of $^3O_2$ into $^1O_2$.[2] In this context, we propose a novel series of donor-acceptor-donor compounds featuring acridine as the acceptor and aromatic arms with heteroatoms forming a helicene-like structure. This design leverages steric hindrance to induce distortion from planarity in a multi-aromatic system, making it a promising candidate for singlet oxygen generation. The compounds also display acid/base switch, enabling protonation and consequent redshifts in absorption and emission bands. Unexpectedly, the molecules exhibit near-infrared (NIR) phosphorescence. The compounds demonstrate a singlet oxygen quantum yield up to 78%, highlighting their potential for applications in photodynamic therapy.

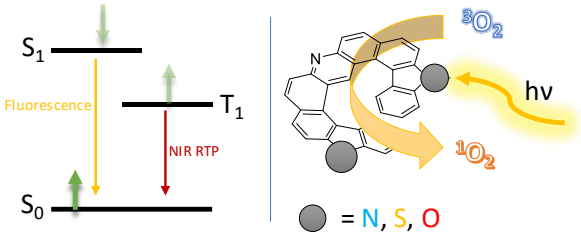

Figure 1: Simplified Jablonski diagram and singlet oxygen generation after excitation of helicenes.

References: [1] J. Phys. Chem. A, **2024**, *128*, 2273–2285. [2] Angew. Chem. Int. Ed., **2024**, *63*, e202412681.

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Exploring the Role of Maternal Nutrition and Gut Microbiota in Neuroprotection Against Neonatal Hypoxia-Ischemia – A Study in Rats

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Keywords: Neonatal hypoxia-ischemia, Polyphenols, Microbiota.

Neonatal hypoxia-ischemia (NHI) remains a leading cause of perinatal mortality and long-term neurological impairment. While therapeutic hypothermia is currently the only approved treatment, it fails to protect nearly 50% of treated newborns, highlighting the urgent need for alternative neuroprotective strategies. Our team has previously demonstrated that maternal dietary supplementation with resveratrol (RSV), a polyphenol derived from grapes, offers neuroprotection in a rat model of NHI, characterized by reduced brain lesion volumes and preserved sensorimotor functions. To enhance the bioavailability and translational potential of this strategy, we evaluated two complementary approaches: (i) maternal supplementation with piceatannol, a hydroxylated analogue of RSV with improved pharmacokinetic properties, and (ii) a polyphenolic cocktail (RSV + ε-viniferin + pterostilbene), combining compounds with distinct mechanisms of action and half-lives to maximize synergy. Both interventions exhibited greater neuroprotective effects than RSV alone. Given the potential role of the gut–brain axis, we investigated whether these effects might be mediated through modulation of the neonatal gut microbiota. To test this hypothesis, we conducted fecal microbiota transplantation (FMT) from pregnant dams supplemented with the polyphenolic cocktail to pups born to non-supplemented dams, from postnatal day 0 (P0) to day 7 (P7), the day of NHI induction. Preliminary results indicated that microbiota modulation via FMT significantly reduced brain lesion volumes in the short term. Furthermore, behavioral assessment revealed that NHI-pups receiving FMT from cocktail-supplemented dams maintained better behavioral abilities compared to untreated NHI control. These findings suggest that part of the neuroprotective effects of maternal polyphenol supplementation may be mediated through gut microbiota modulation.

References: [1] Front Neurosci. **2021**, *14*, 616824. [2] Nutrients. **2022**, *14*, 773.