BIENVENUE AUX RECOB 19

C'est avec grand plaisir que le comité d'organisation des 19ièmes rencontres en chimie organique biologique vous accueille au centre Paul Langevin à Aussois.

Les RECOB demeurent un rendez-vous important pour tous les chercheurs travaillant à l'interface de la chimie et de la biologie, pour présenter leurs dernières avancées et échanger leurs idées, de sorte à mettre en place des collaborations fructueuses. Le cadre très convivial du centre Paul Langevin est propice à ces discussions, devant les séances de poster, mais aussi durant les pauses, les repas, les soirées…

En raison d'un nombre imporatnt de demandes de communications orales, nous avons ajouter une communication orale tous les jours en fin de matinée par rapport à l'édition précédente. Ainsi, nous vous proposons 35 communications orlaes en plus des 7 conférences plénières et des deux séances de posters.

L'organisation d'une telle manifestation ne peut se faire que grâce aux soutiens d'institutions publiques et d'entreprises ainsi que par la présence d'exposants. Le comité d'organisation tient à leur exprimer ses plus sincères remerciements

Le comité d'organisation tient également à remercier les conférenciers et tous les participants pour l'animation de ces journées.

Nous vous souhaitons un excellent séjour à Aussois.

Le comité d'organisation des RECOB 19

Florence Mahuteau-Betzer (présidente) ; Karine Alvarez (secrétaire), Jean-François Constant (trésorier), Alexandre Specht, Patricia Melnyk, Pierre-Yves Renard, Virgil Hélaine

19 REncontres Chimie Organique Biologique

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PROGRAMME

Dimanche 17 mars 2024

17h30-20h00	Accueil des participants
19h20-20h00	Apéritif de bienvenue
20h00	Dîner

Lundi 18 mars 2024

7h45	Petit déjeuner
8h30	Ouverture RECOB 19 : introduction

Session 1: Modératrice: Patricia MELNYK

8h30-9h20	CP1: "Copper nanoclusters as active agents for the treatment of Menkes' disease ", Ariane BOUDIER
9h20-9h40	CO1 : "Selecting nanobodies to disrupt the TSPYL5-USP7 protein-protein interaction" Marine ANCIA
9h40-10h00	CO2 : "Innovative NIR light responsive nanoparticles for enhanced antibacterial PDT and singlet oxygen mediated antibiotic release ", Maxime KLIMEZAK
10h00- 10h30	Pause café
10h30-10h50	CO3 : " Metal complexes in biological environments: a new frontier in inorganic chemistry ", Clotilde POLICAR
10h50-11h10	CO4: "Development of stimuli-responsive vectors modulating the redox balance of solid tumors", Elsa CANNONI
11h10-11h30	CO5: "Fingerprint approach using macrocyclic 'chemical nose' sensors-Application in prediction of outcomes in preeclampsia", Monica-Swetha BOSCO
11h30-11h50	CO6: "Original fluorescent probes for use in microscopy on a model organism: *Caenorhabditis elegans*", Marion LEROUX
11h50-12h10	CO7: "Scaffold-repurposing possibilities in the treatment of ovarian cancer: a first proof of concept with a PROTAC molecule", Marie CORNU
12h30	Déjeuner puis temps libre

Session 2: Modérateur: Virgil HELAINE

16h30-17h20	CP2: "Role of order and disorder in the interaction of Engrailed with membranes", Olivier LEQUIN
17h20-17h40	CO8: "Synthetic Cu^{+} transporters with potent anticancer activity", Hennie VALKENIER
17h40-18h00	CO9: "Synthesis of TMM analogs for the study of the outer membrane of mycobacteria", Paulin ROLLANDO
18h00-18h20	CO10: "Germination stimulant perception in *Phelipanche ramosa*; design of noncanonical strigolactone analogs", François-Didier BOYER
18h20-18h40	CO11: "Design and biological evaluation of alpha/beta interface-selective CK2 kinase inhibitor", Marine ORTILLON
19h30	Dîner
20h45-21h15	CO Industriel : Société Vacuubrand, Sébastien FAIVRE Société Anton Paar, Stéphane AIT-OUMEGHAR Société Huber, Philippe MURARO
21h15	Session posters pairs

Mardi 19 mars 2024

7h45	Petit déjeuner

Session 3: Modérateur: Pierre-Yves RENARD

8h30-9h20	CP3: "A Chemical Odyssey Toward Protein Drug Discovery", Oleg MELNYK
9h20-9h40	CO12: "Advantages and the limitations of synthetic antibacterial copolymers (SACs) over their natural inspiration models, the Antimicrobial Peptides (AMPs).", Marc MARESCA
9h40-10h00	CO13 : " Setting-up a combinatorial strategy to discover efficient catalystsmimicking antioxidant metalloenzymes", Nicolas DELSUC
10h00-10h30	Pause café
10h30-10h50	CO14 : "Resensibiliser HER2 au trastuzumab dans le cancer du pancréas : identification et activité biologique du premier peptide ligand de MUC4", Nicolas LEBEGUE
10h50-11h10	CO15 : "Phosphorylation toolbox to generate nucleosides 5'-triphosphates : development, application and interest", Aurélie CHAZOT
11h10-11h30	CO16 : "La protection supramoléculaire à l'aide de cavitants comme outil en synthèse organique", Ivan JABIN
11h30-11h50	CO17 : Design of new fluorinated peptides and fluorescent probes derived from spexin to study the implication of galanin receptors in pain modulation", Yann BERTHOMÉ
11h50-12h10	CO18: "Towards the identification of the binding site of new selective inhibitors of ACSL4 using a chemical biology approach", Darius MAZHARI DOROOEE
12h30	Déjeuner puis temps libre

Session 4: Modérateur: Jean-François Constant

16h30- 17h20	CP4 : " Interactive molecular visualization and simulation:examples with udock and vtx", Matthieu MONTES
17h20-17h40	CO19 : " LIT-002, a Highly Potent Nonpeptide Oxytocin Receptor Agonist as preclinical candidate for the treatment of autism", Marcel HIBERT
17h40-18h00	CO20 : "Fighting the resistance to aminoglycosides - design of bacterial enzyme inhibitors", Jean-François GUICHOU
18h00-18h20	CO21 : "Inhiber l'interaction protéique XIAP/RIPK2 pour obtenir des molécules anti-inflammatoires ", Charline KIEFFER
18h20-18h40	CO22 : "Synthèse, caractérisation et évaluation de l'activité anti-hyperlipidémiques des dérivés pyrimidiques obtenus par modification de la réaction de Biginelli", Mohammed EL MESKY
19h30	Dîner
20h45-21h15	CO Industriel: Société Buchi, Pierre DESHAYES Société Advion-Interchim, Sarah EDEL
21h15	Session posters impairs

Mercredi 20 mars 2024

7h45	Petit déjeuner

Session 5: Modératrice: Florence MAHUTEAU-BETZER

8h30-9h20	CP5 : "Bioorthogonal reactions with mesoionics", Frédéric TARAN
9h20-9h40	CO23: " Sondes fluorogéniques excitables à deux photons pour la délivrance de drogue via des réactions bioorthogonales ", Aurélie RODRIGUEZ
9h40-10h00	CO24 : " Enzyme-directed photoassembling of carbonic anhydrase inhibitors ", Cyrille SABOT
10h00-10h30	Pause café
10h30-10h50	CO25 : "The synthesis of N-acylsulfonamide-linked nucleosides via the Sulfo-Click reaction discloses new applications in the field of nucleic acid chemistry", Guillaume CLAVÉ
10h50-11h10	CO26 : "Bimodal PET/US imaging using ^{18}F radiolabelled lipid-shell microbubbles: synthesis, radiolabelling and in vivo studies", Julen ARIZTIA
11h10-11h30	CO27 : "Original radiotracers targeting P2Y12 receptors for neuroinflammation imaging: from synthesis to biological evaluation", Eugénie PINCEMAIL
11h30-11h50	CO28 : " An azo-based fluorogenic smart probe to visualize a mitochondrial azoreductase activity in live cells ", Laurane MICHEL
11h50-12h10	CO29: " Inhibiteurs de la réplication du VIH issus du criblage de la chimiothèque", Patricia BUSCA
12h30	Déjeuner puis temps libre

Session 6: Modératrice: Karine ALVAREZ

16h30-17h20	CP6 : " Les métabolites spécialisés de plantes, une source d'inspiration pour la chimie médicinale", Fanny ROUSSI
17h20-17h40	CO30 : " La délikine DAD3.473 : un nouveau modulateur/inhibiteur d'Orai1 pour la régulation SOCE dans le cancer du pancréas. Un aperçu ", Jean-Pierre BAZUREAU
17h40-18h00	CO31 : "N,N,N-triacylamines as promising inhibitors of kallikrein-8, an emergent biomarker of Alzheimer's disease.", Océane RONDOT
18h00-18h20	CO32 : "Unprecedented reactivity of polyamines with aldehydic DNA lesions", Laurent CATTIAUX
18h40-19h00	Assemblée générale
19h45	Dîner : fondue savoyarde

Jeudi 21 mars 2024

7h45	Petit déjeuner

Session 7: Modérateur: Alex SPECHT

8h30-9h20	CP7 : “Approches moléculaires émergentes en biodétection fluorogénique : assemblage et désassemblage covalent”, Anthony ROMIEU
9h20-9h40	CO33: “ Unprecedented perspectives on the application of CinNapht fluorophores obtained by a “late-stage” functionalization strategy”, Eléonore TACKE
9h40-10h00	CO34 : “ Thiovinyl-based coumarine derivatives : synthesis and fluorescence properties”, Isabelle TOUBIA
10h00-10h20	CO35 : “ Méthodes bioautographiques: sondes fluorescentes et HPTLC pour la détection d’inhibiteurs enzymatiques au sein de matrices complexes”, Elodie JAGU
10h20	Clôture des RECOB 18
10h25	Pause-café et panier repas
10h45	Bus pour Saint Michel Valloire

CONFÉRENCES PLÉNIÈRES (CP)

Copper nanoclusters as active agents for the treatment of Menkes' disease

Ariane Boudier[1,2,3], Audrey Malardé[4], Jean-Marc Alberto[4], Grégory Pourié[4], Benjamin Creusot[1,2], Alexa Courty[5], Bruno Madebène[5], Benoit Tremblay[5], Ali Ouadi[6], David Brasse[6], Igor Clarot[1,2], François Feillet[4,7]

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Menkes' disease is a very rare genetic disorder of copper metabolism with a life expectancy of 3 years [1]. This disease is linked to a deficiency of copper transporter (ATP7A) present in the intestine and in the blood-brain barrier (BBB) inducing a severe copper deficiency with a combined deficiency of essential cuproproteins. This leads to multisystem symptoms and as severe neurodegeneration. The only treatment using copper-histidine complex remains palliative with a poor biodistribution to the brain and unchanged fatal prognosis. Copper nanoclusters (CuNC) were synthetized, characterized and tested in Mo^{blo} mice (knock down model for ATPase7A transporter). They are characterized by a size of 0.7 nm in diameter, with a metallic core surrounded by biodegradable ligands and can be stored for a long time (>2 years). Subcutaneous injections of CuNC into Mo^{blo} mice from 5 days of life saw their life expectancy considerably increased, in correlation with a restoration of the activity of the cuproproteins. Indeed, tyrosinase, a cuproprotein responsible for the production of melanin, showed its activity restored by a darkening of the fur. Images obtained by positron emission tomography after injection of radiolabeled ^{64}CuNC suggested the biodistribution to the brain. The activity of cytochrome C oxidase in the brain showed a restoration of the activity of the brain mitochondrial respiratory chain. Neurobehavioral tests (horizontal scale, open field) showed a drastic improvement in locomotion and coordination of movements in mice, that received CuNC. All of these results allowed the obtention of orphan drug designation from the European Medicine Agency (EMA) and the establishment of a pharmaceutical form of the CuNC with the aim of launching clinical trials as soon as possible.

[1] K. Kodama, Y. Murata, Molecular genetics and pathophysiology of Menkes disease, Pediatr. Int. 41 (1999) 430–435. https://doi.org/10.1046/j.1442-200x.1999.01091.x.

Role of order and disorder in the interaction of Engrailed with membranes

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Homeoproteins are a family of transcription factors that have master roles in animal embryonic development and physiological processes. They are defined by the presence of a 60-residue DNA-binding domain, called homeodomain, which has the ability to cross plasma membranes through unconventional, non-endocytic mechanisms that involve direct membrane translocation. This property is mediated by the third helix of homeodomain, a discovery which has led to the emergence of penetratin and other homeodomain-derived peptides as a major class of cell-penetrating peptides.[1]

Despite their discovery more than 30 years ago, the mechanisms of membrane translocation are still not completely understood. Membrane crossing is involved in bidirectional transfers between the extracellular space and cytosol. These internalization and secretion pathways are modulated by a network of dynamic homeoprotein binding events to cell-surface glycosaminoglycans[2] and anionic lipids, in particular phosphatidyl-inositol-4,5-bisphosphate ($PI(4,5)P_2$)[3], depending on the side of the membrane.

We have carried out biophysical studies including solution-state NMR, circular dichroism and Trp fluorescence spectroscopies, in combination with molecular dynamics simulations at different scales (coarse-grained and all atom) to understand the consequences of homeodomain membrane binding in terms of lipid organization and homeodomain conformation.[4-6] Using an original NMR strategy based on chemical exchange saturation transfer (CEST), we were able to characterize the membrane-bound state of Engrailed homeodomain in $PI(4,5)P_2$-containing membranes, under conditions where it cannot be directly observed by NMR. The interaction with anionic phospholipids is shown to induce an unfolding of the homeodomain, enabling the third helix and a critical Trp residue to insert within the lipid bilayer. This conformational transition between ordered and disordered states helps understand how the homeodomain can bind a large variety of ligands such as DNA and membranes.

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A Chemical Odyssey Toward Protein Drug Discovery

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Finding practical methods for synthesizing proteins through chemical means while employing water as the primary solvent has guided our work for more than two decades. Drawing inspiration from natural chemical processes, our aim is to devise innovative reactions that facilitate high-yielding, chemoselective transformations at the protein level under exceedingly gentle conditions.

An hallmark of our approach is the development of robust methods for assembling peptide segments by engineering functional groups, with their reactivity modulated by disulfide, selenosulfide, or diselenide bonds functioning as redox switches.[1-5] These advancements have enabled us to overcome challenges in accessing complex proteins and lay the groundwork for the design of potential therapeutic proteins in the realm of regenerative medicine.[6]

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Interactive molecular visualization and simulation:examples with udock and vtx

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Interactive molecular visualization and simulation involve 1. the development of dedicated intuitive and ergonomic user interfaces and 2. the use of optimized representations and rendering/simulation engines for realtime performance. We will illustrate the different challenges we faced with our experience in developing UDock*, an interactive multibody protein docking software and VTX**, a high-performance molecular visualization software.

*UDock has been designed to take advantage of the possible solutions proposed interactively by the users, as a part of a protein–protein interactions exploration pipeline. In UDock, the users tackle simplified representations of protein structures and explore protein–protein interfaces' conformational space using a gamified interactive docking system with on the fly scoring. Udock is opensource and freely available at https://udock.fr and https://gitlab.com/Udock/Udock2

**VTX is a molecular visualization software that includes a real-time high-performance molecular graphics engine dedicated to the visualization of the structure and dynamics of massive molecular systems. VTX disposes of an interactive camera system controllable via the keyboard and/or mouse that includes different modes: 1. a classical trackball mode where the camera revolves around a fixed focus point and 2. a first-person free-fly navigation mode where the user fully controls the movement of the camera. VTX includes an intuitive and highly usable graphical user interface and tools designed for expert and non-expert users. It is opensource and free for non-commercial use at http://vtx.drugdesign.fr and https://github.com/VTX-Molecular-Visualization

[1] K. Kodama, Y. Murata, Molecular genetics and pathophysiology of Menkes disease, Pediatr. Int. 41 (1999) 430–435. https://doi.org/10.1046/j.1442-200x.1999.01091.x.

Bioorthogonal reactions with mesoionics

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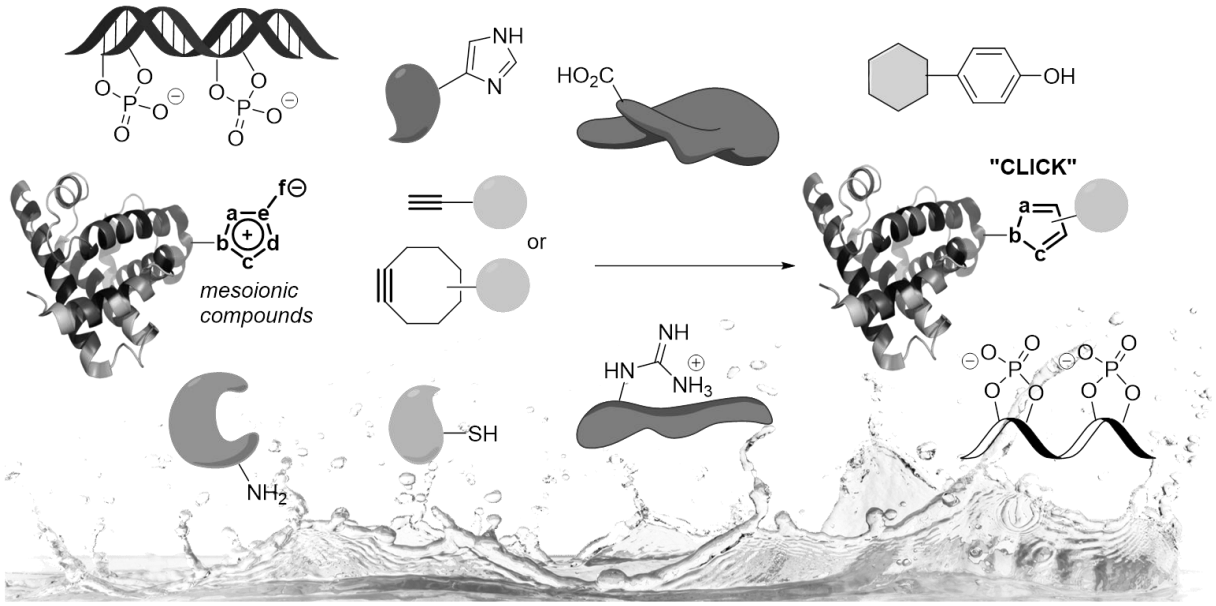
The development of chemical reactions that can be performed in living systems (i.e. cells, model organisms) has long held unique fascination in the field of chemical biology. A bio-orthogonal reaction is characterized by the reaction of two functionalities, which will react under mild physiological conditions and are inert towards the biological environment. On the other hand, the discovery of chemical reactions fulfilling the criteria of the click chemistry concept continue to have a huge impact in many research fields. Quintessential example is the copper-catalyzed azide-alkyne cycloadditions (CuAAC). Our laboratory is involved in the discovery and use of such reactions. Recent work from our team identified several mesoionic compounds as new efficient dipoles for click reactions with terminal alkynes[1] and for bioorthogonal reactions with cyclic alkynes.[2] These reactions were used for both ligation, imaging and drug release applications.



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Les métabolites spécialisés de plantes, une source d'inspiration pour la chimie médicinale

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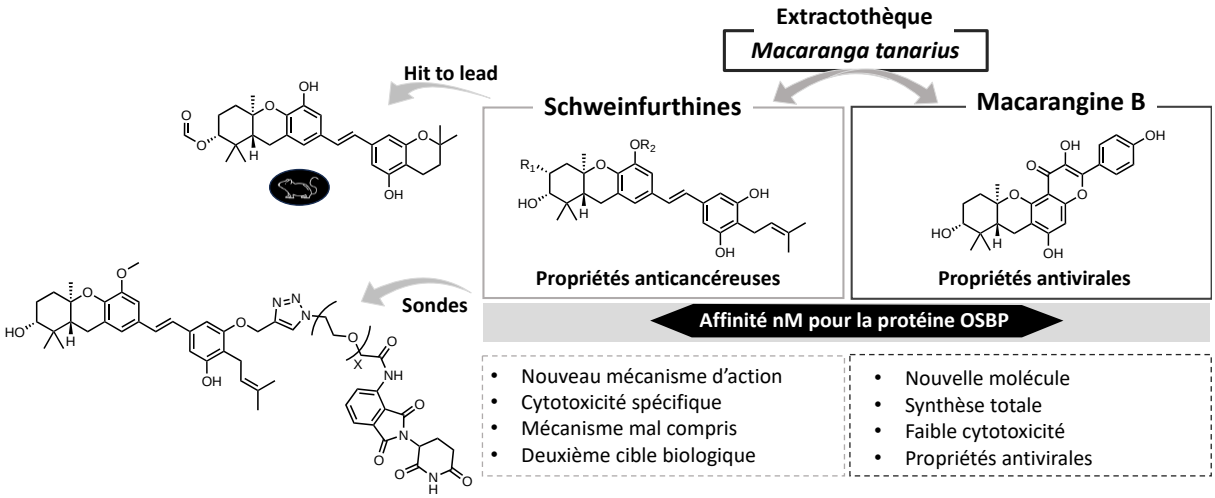
La Nature, par sa richesse impressionnante et sa complexité, est une source d'inspiration pour les chimistes médicinaux. Ainsi, alors que moins de 20% de la biodiversité mondiale ont été étudiés d'un point de vue chimique, plus de 60% des médicaments utilisés aujourd'hui sont inspirés de substances naturelles.[1] Les molécules naturelles qui présentent une activité biologique (ou métabolites spécialisés) sont très souvent originales, poly fonctionnalisées et complexes car elles ont été « prévalidées par la Nature ». Elles sont considérées comme des structures privilégiées.[2]

Notre équipe s'appuie sur des approches intégrées pour étudier et valoriser les métabolites spécialisés de plantes depuis leur isolement et leur identification jusqu'à leur synthèse et/ou leur pharmacomodulation afin d'améliorer leur activité biologique, leurs propriétés ADMET et/ou synthétiser des sondes originales. Cette présentation se focalisera sur deux familles de molécules isolées de plantes du genre *Macaranga* : les schweinfurthines[3] et la macarangine B.[4]



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Approches moléculaires émergentes en biodétection fluorogénique : assemblage et désassemblage covalent

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Au cours des deux dernières décennies, l'utilisation des sondes fluorescentes dites intelligentes (ou "'smart fluorescent probes") a bouleversé positivement le secteur de l'analyse (bio)chimique et a contribué à l'avènement de l'imagerie moléculaire *in vivo* et du photo-théranostique. Une des approches fréquemment employées pour concevoir ces sondes moléculaires exploite la réactivité chimique de l'analyte à détecter ; on parle alors de l'approche "activity-based sensing" (ABS)[1]. Elle permet souvent une détection hautement sélective de l'analyte cible. La conception des sondes ABS repose souvent sur la modulation de processus photophysiques bien connus (FRET, TBET, ICT, PeT, ...) et la mise en oeuvre de réactions fluorogéniques au sein de fluorophores conventionnels[2]. Afin d'accéder à des sondes moléculaires toujours plus performantes et de rélever des défis actuels et à venir en matière de bioanalyse, des travaux pionniers émanant des groupes d'Eric V. Anslyn et de Youjun Yang ont mis en lumière une approche de rupture connue sous l'anglicisme "covalent-assembly", particulièrement bien adaptée pour obtenir une sensibilité de détection optimale[3]. Elle est basée sur la conception et l'utilisation de précurseurs moléculaires "cagés" qui peuvent être convertis *in situ* en coeurs fluorescents, *via* des réactions domino, efficaces dans les milieux aqueux et déclenchées par l'analyte cible. Nos réalisations récentes dans ce domaine qui concernent la formation *in situ* de colorants de type xanthène sous l'action d'un stimulus enzymatique, seront présentées et l'accent sera mis à la fois sur des aspects méthodologiques et applicatifs[4]. Ce principe de sondes n'est toutefois applicable qu'à des analytes présentant une réactivité notable en chimie covalente. Afin de pouvoir détecter des anions d'intérêt, peu ou pas réactifs, nous avons exploré une approche alternative fondée sur des processus de décomplexation métallique et de désassemblage moléculaire récemment proposée par le groupe de Felix Zelder[5]. Son application à la détection fluorogénique des phosphates biologiques sera également présentée[6].

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COMMUNICATIONS ORALES (CO)

Selecting nanobodies to disrupt the TSPYL5-USP7 protein-protein interaction

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Cellular immortality is one of the hallmarks of cancer. Cancer cells achieve immortality by one of these two mechanisms: reactivation of the h*TERT* telomerase gene expression or activation of an alternative mechanism, dubbed ALT (Alternative Lengthening of Telomeres). The ALT mechanism enables telomere maintenance via homologous recombination processes. (1, 2)
Telomerase is reactivated in about 85% of all tumors. However, sarcomas, neuroblastomas, and tumors from the central nervous system display a preference for ALT activation (up to 50-60%). Paediatric tumors mostly belong to these categories of tumors and we estimate that about one-third of solid paediatric tumors may have activated the ALT mechanism (1). As ALT is repressed in healthy cells, it should represent a safe and very attractive target for new targeted anticancer therapies.
Our work focuses on the protein-protein interaction between TSPYL5 and USP7, two proteins involved in the ALT mechanism. Their interaction is required to maintain ALT^+ cell viability (3).
The objective of this project is to establish the proof of concept that TSPYL5-USP7 disruption can exert anticancer activity in ALT^+ tumor cells. To this end, new pharmacological tools against the ALT mechanism are under development.

Among these tools, nanobodies were developed (4). Nanobodies are small monodomain antibodies and are produced by the injection of the target protein into llamas. 39 nanobodies targeting TSPYL5 were selected. Nanobodies are classified following the sequence of their Complementary-Determining Region; we chose the most specific one from each group. Hence, 12 nanobodies were tested by Microscale Thermophoresis (MST), a biophysical approach, to determine their affinity for TSPYL5. Then, the 3 most potent (EC_{50} ranging from 60nM to 200nM) were selected to assess their ability to disrupt the interaction between TSPYL5 and USP7 in an MST competition assay. We identified one nanobody that was able to significantly prevent the assembly of our two targeted proteins. Following the success of these biophysical experiments, cellular viability assays will be performed to evaluate the ability of nanobodies to disrupt the interaction between the two proteins in cells and induce their apoptosis.
The nanobodies evaluation will help establish the proof of concept that targeting the TSPYL5-USP7 protein-protein interaction is a good strategy for anti-ALT therapy.

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Innovative NIR light responsive nanoparticles for enhanced antibacterial PDT and singlet oxygen mediated antibiotic release

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Abstract:

Antibiotics overuses, misuses and environmental factors led to a global increase in antimicrobial resistance. This poses a serious threat over human life worldwide, mainly because it allows the spread of nosocomial infections that have severe human and material costs every year. Therefore, there is an urgent need for new and efficient methods to reduce infection-related damages. Photodynamic Therapy (PDT) is a powerful tool allowing the formation of singlet oxygen upon light irradiation of a photosensitizer. As such, it has been widely used to treat various diseases, including infections. In this latter case, it is called Antimicrobial Photodynamic Therapy, or aPDT[1]. Recently, there has been reports of the synergistic potential of combining aPDT with antimicrobials[2]. This project aims at exploiting this potential in a more controlled and practical way by developing nanocarriers that allows both aPDT and the release of an antibiotic through breakage of a self-immolative linker. These nanocarriers would be linked to polyurethane catheters in order to allow their application in a medical context.

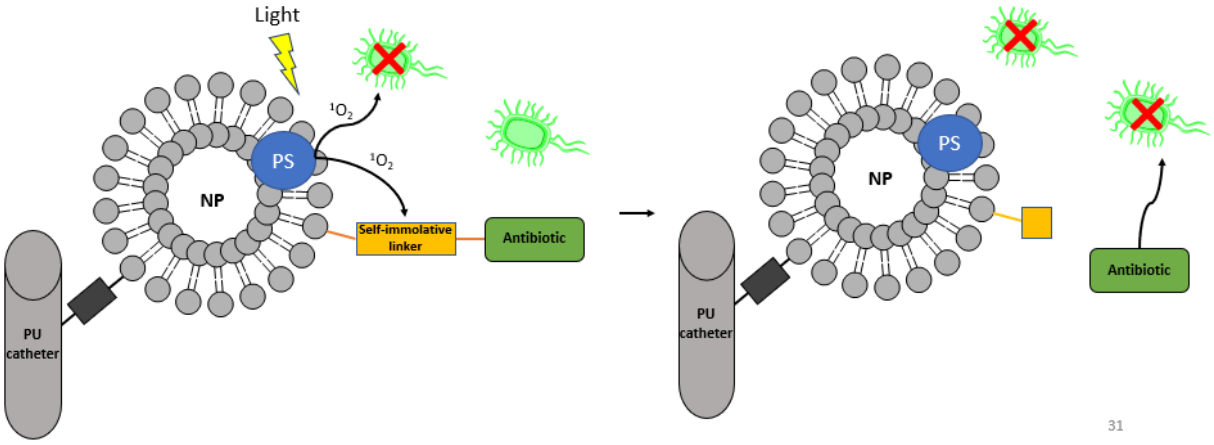

Figure 1. Schematic representation of the lipidic nanoparticle doped with a photosensitizer (blue) that, upon NIR light irradiation, would trigger the formation of singlet oxygen for a double effect: death of nearby bacteria (≈ 20 nm) and release of a caged antibiotic (green) through cleavage of a self-immolative linker (orange).

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Metal complexes in biological environments: a new frontier inorganic chemistry

Focuses on Mn-SOD mimics: from design to evaluation in cells

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Superoxide dismutases are redox metalloproteins that protect the cell against oxidative stress. These enzymes are highly efficient in catalysing the dismutation of superoxide, with several physico-chemical parameters that have been carved by evolution. We get bio-inspiration from these tremendously efficient enzymes to design low-molecular-weight Mn-based complexes with a catalytic anti-oxidant activity.[1] To better understand the bio-activity, and possibly rationalize the design of SOD-mimics, characterizing them directly in cells is key.[2,3] One of the cellular model consists of HT29-MD2, intestinal epithelial cells very sensitive to bacterial lipopolysaccharide that triggers a strong inflammatory response mediated by oxidative stress.[7] In this model, SOD-mimics have shown an anti-inflammatory activity.[3,5,6] The LPS-activation is associated with an over-expression of MnSOD that is partly reversed by co-incubation with SOD-mimic able to complement for SOD.
We have undertaken a work flow including determination of the bio-activity in HT29-MD2 cells, and analyses including quantification (EPR, IMS[4]…) and imaging (X-fluorescence imaging).[3,5,6] In particular, we have recently designed SOD mimics with an improved inertness, by rigidifying the 1,2-aminoethane central scaffold[6] in comparison with a previously non rigidified ligand.[3]

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Development of stimuli-responsive vectors modulating the redox balance of solid tumors

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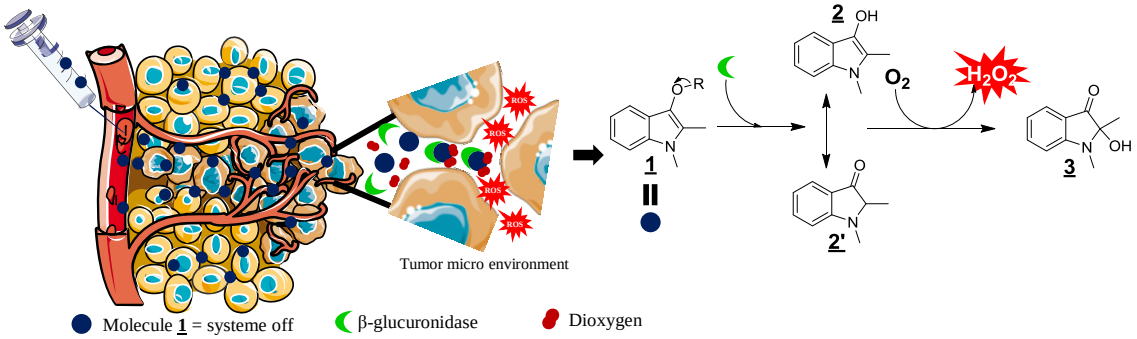
For a long time, reactive oxygen species (ROS) were considered harmful and responsible for numerous pathologies. However, many studies highlighted the major role of ROS in cell signaling as well as in the functioning of the whole organism[1]. When ROS, in particular hydrogen peroxide, concentrations are well regulated by antioxidant systems (glutathion, superoxide dismutase...), they can be beneficial for living processes. In contrast, a dysregulation of the red/ox balance can lead to a number of pathologies, including cancer. Within this framework, several strategies have been investigated to destroy tumor cells by targeting the red/ox balance: reducing the level of ROS in malignant tissues, inhibiting their production, or increasing their level until apoptosis activation. This latter approach was the most widely explored until now, via photodynamic therapy[2], development of molecules stimulating ROS production[3,4,5], or chemodynamic therapy[6] and ferroptosis[7]. In our team, we study a novel strategy based on the use of the 1,2-dimethyl-3-oxindole (**2**)[8] to mediated ROS production selectively in tumors through β-glucuronidase-catalyzed activation[9]. We demonstrated that **(2)** allowed the production of hydrogen peroxide through the transformation of atmospheric oxygen[10].Therefore, we developed different stimuli-responsive systems enabling to release hydrogen peroxide within the tumor microenvironment. The results of this study will be presente



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Fingerprint approach using macrocyclic 'chemical nose' sensors -Application in prediction of outcomes in preeclampsia

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Protein content, abundance and structures in human body fluids are meticulously regulated to maintain the physiological conditions of human beings. Abnormal protein expression levels serve as indicators of the onset of pathological conditions[1]. Therefore, strategies that enable holistic and untargeted analysis of global serum composition are being developed to provide insights into various pathological states

We have developed a non-specific, serum-based, "chemical nose" diagnostic strategy that mimics the selective array sensing of the human olfactory system[2-3]. This sensor array is constructed with cross-reactive synthetic receptors[4], leveraging the host- guest interaction of triphenylamine derivatives (TPA) with the macrocycle cucurbit[7]uril (CB[7]). The interaction of these receptors via non-specific binding modes (host/guest chemistry, electrostatic, hydrophobic, size exclusion) with biomolecules in serum creates a 'fluorescence-based fingerprint pattern' which can be tied back to the serum composition, representing specific diseased states. The optimized sensor array has been assessed with a diverse range of 14 protein analytes. Utilizing linear discriminant analysis (LDA), thee characteristic fluorescence fingerprints of these proteins were identified, achieving an accuracy of 98% in buffer and 100% in human serum. To establish a proof of concept for diagnostic applications, the array has been tested with a pre-existing cohort of 17 samples from healthy and preeclamptic patients, successfully discriminating between the two groups with 100% accuracy. Additionally, a dedicated droplet-based microfluidic platform with minimal utilization of sample volumes was developed for throughput analysis of larger sample cohorts. The fluorescence output signal detected on this platform was correlated with the initial droplet composition, providing 100% accuracy in discrimination of selected protein analytes.

The signatures obtained on this platform, along with available clinical/biological data, will be analysed further by suitable statistical approaches to derive classifiers for predicting preeclampsia outcomes[5] and exploring its complexity. The system's ability to detect changes in spectral signatures of serum presents a new diagnostic methodology for complex diseases like preeclampsia and will enable us to propose a strategy involving big data analysis based on chemical sensing and machine learning.

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Communication orale 6

Original fluorescent probes for use in microscopy on a model organism: *Caenorhabditis elegans*

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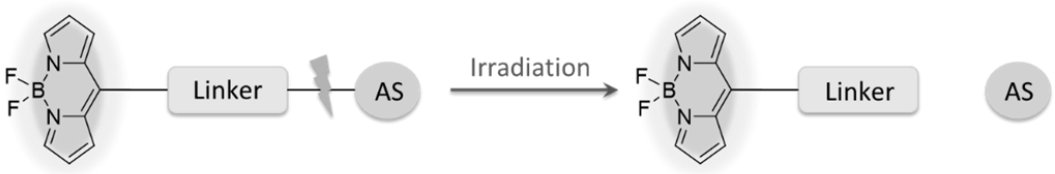
Following an active substance within an organism is a major stake. Indeed, this allows, among other things, to facilitate the discovery of new targets of interest. In order to do this, fluorescence microscopy is a particular well-suited tool.

The aim of this research work is to develop a novel fluorescent labelling technique to follow the fate of a molecule or a microorganism *in vivo*, in the intestine of the nematode *Caernorhabditis elegans* [1]. For this purpose, several fluorescent probes have been designed and synthetized to be coupled to an active substance or a microorganism of interest via a potentially cleavable link. The intent would be for the active substance to be released after an irradiation to a set wavelength.



Schematic depiction of a fluorescent probe

After ingestion, the vector's path can be followed thanks to the nematode's transparency at the bodipy's fluorescence wavelength [2]. Then, after an irradiation at another specific wavelength, the active substance will be released, allowing the study of its fate and impact *in vivo*. This approach will allow the following of the effect of a drug *in vivo* or could be used as an innovative screening process.

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Scaffold-repurposing possibilities in the treatment of ovarian cancer: a first proof of concept with a PROTAC molecule

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The escape of ovarian cancer cells from apoptosis is partly due to the overexpression of two anti-apoptotic proteins in particular: Mcl-1 and Bcl-x_L.[1] Inhibition of these proteins leads to cardiac and platelet toxicity. Also, inhibition of one of the two proteins induces overexpression of the other. Their concomitant degradation could therefore restore the balance in cancer cells and induce apoptosis. The aim of this project is to synthesise molecules with dual activity, i.e. the ability to degrade both Mcl-1 and Bcl-x_L simultaneously.[2] To achieve this, compounds have been synthesised using the PROTAC (PROteolysis Targeting Chimeras) approach, developed in 2001 by Prof. Crews *et al.*[3] In this way, PROTAC compounds are synthesised by 'recycling' pyridoclax, a known Mcl-1 inhibitor developed by CERMN,[4] as a ligand recruiting the target protein, and on the other hand a ligand capable of recruiting an E3 ligase. Using the PROTAC method to synthesise the degradants, which works catalytically, could make it possible to reduce the doses

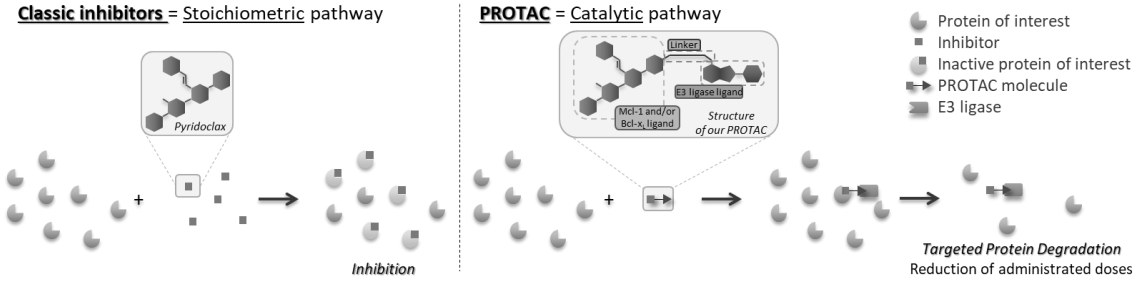

Figure 1. Recycling of pyridoclax (classic inhibitor) into PROTAC molecules and comparison of their modes of action.

administered and hence the side effects mentioned above.

After synthesis and biological evaluation by Dr Poulain's team, an initial compound named PBM1 provided proof of concept for the project, enabling Mcl-1 to be degraded at a dose 100 times lower than that of Pyridoclax to achieve the same effects.[5] The results of these tests are used to identify Structure-Activity Relationships (SARs) to guide the synthesis of new PROTAC molecules, and around thirty compounds have been synthesised so far. At the same time, thanks to a bibliographic exploration of pharmacokinetic parameters,[6] we decided to evaluate the synthesised compounds *in silico* to determine the appropriate theoretical physico-chemical parameters for pharmacokinetics and, ultimately, for oral bioavailability.

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Synthetic Cu^+ transporters with potent anticancer activity

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The resistance of certain cancers against current chemotherapies calls for radically new treatment strategies. An example of a novel strategy is the use of synthetic transmembrane transporters to disrupt homeostasis. Such transporters are small synthetic compounds that have a binding site for ions and sufficient lipophilicity to partition into lipid membranes. This allows them to extract ions into the membrane, carry them across, and release them on the other side. While many of such transporters have been developed for anions or Na^+ and K^+, we present here the first series of transporters for Cu^+ cations (Figure 1).[1,2]

Copper is an essential element in cells, as it is required by numerous enzymes, but high intracellular copper concentrations are toxic. Therefore, copper homeostasis is tightly controlled by different cellular processes. Furthermore, cancer cells were reported to have altered copper homeostasis mechanisms and compounds that impact copper subcellular distribution thus have a potential for cancer treatment.[3,4]

We will present a series of calix[4]arene-based structures with copper coordinating groups and their ability to efficiently transport Cu^+ cations across liposomal model membranes.[1,2] We will show that copper transport is also possible through membranes of living cells as demonstrated by the restoration of growth of a yeast mutant bearing a deletion of the *CTR1* gene encoding a plasma membrane copper transport protein. Furthermore, the most potent compound '*Cuphoralix'* has cytostatic effects on different cancer cell lines in the low µM range, including on lung cancer cells that are resistant against common treatments. When supplemented with copper, IC_{50} values decreased even further,[2] showing the high potential of these copper transporters for cancer treatment.

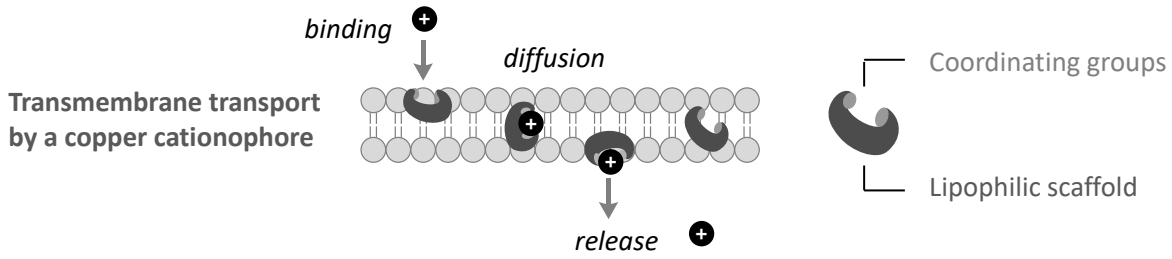

Figure 1. General representation of the mechanism of cation transport by copper transporters.

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Synthesis of TMM analogs for the study of the outer membrane of mycobacteria

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Corynebacteriales are a family of Gram-positive bacteria including *Mycobacterium tuberculosis*, the etiologic agent of human tuberculosis. *Corynebacteriales* are highly resistant towards chemotherapeutic molecules and this exceptional resistance might be due to their particular outer membrane, called mycomembrane. This rigid membrane is composed of specific fatty acids, the mycolic acids esterified to trehalose, a symmetrical disaccharide, leading to trehalose monomycolate (TMM). TMM is processed by enzymes called mycoloyltransferases (Myt) and acts as a donor of mycolate in the biogenesis of the mycomembrane. Recently one mycoloyltransferase (MytC) was identified to be responsible of mycoloylation of small membrane proteins (porins) in *Corynebacterium glutamicum*.[1] This is a unique post-translational modification in bacteria and its role remains to be clarified. In the recent years, our laboratory developed several molecular tools for the study of the biogenesis of the mycomembrane,[2] and one of our projects is to synthetize a large collection of TMM analogs in order to get insight in the mycoloylation mechanism of porins in *C. glutamicum*.[3] The synthesis of several TMM analogs including biorthogonal and/or photoactivatable compounds will be presented as well as biological results obtained with these new tools.

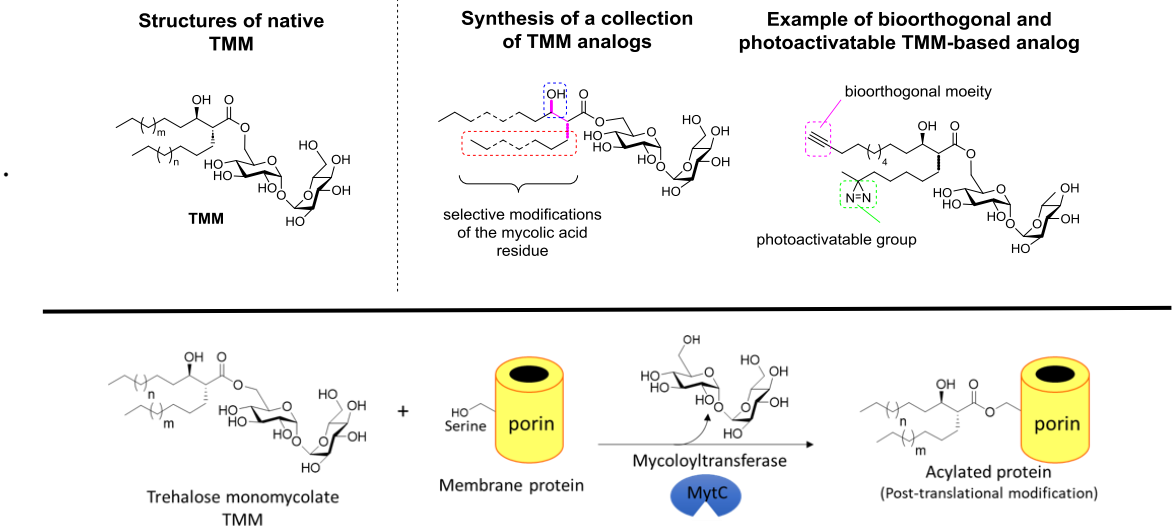

Figure 1- Mycoloylation reaction of porins catalyzed by MytC

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Germination stimulant perception in *Phelipanche ramosa*; design of noncanonical strigolactone analogs

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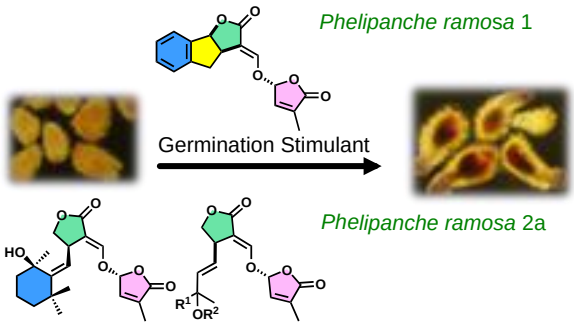
Strigolactones (SLs) are plant hormones exuded in the rhizosphere with a signaling role for the development of arbuscular mycorrhizal (AM) fungi and as stimulants of seed germination of the parasitic weeds *Orobanche*, *Phelipanche* and *Striga*, the most threatening weeds of major crops worldwide [1]. *Phelipanche ramosa* is present mainly on rape, hemp and tobacco. *P. ramosa* 2a preferentially attacks hemp while *P. ramosa* 1 attacks rapeseed. Cannalactone isolated recently from root exudates of hemp has been characterized as a non-canonical SL that selectively stimulates the germination of *P. ramosa* 2a seeds in comparison with *P. ramosa* 1 [2]. We developed novel chemical tools for understanding the SL perception based on the enzymatic properties of SL receptors [3]. We identified five putative SL receptors in *P. ramosa* 1 and showed that PrKAI2d3 is involved in the stimulation of seed germination [4]. We demonstrated the high plasticity of PrKAI2d3, which allows it to interact with different chemicals. The SL perception mechanism of PrKAI2d3 is similar to that of endogenous SLs in non-parasitic plants. We provided evidence that PrKAI2d3 enzymatic activity confers hypersensitivity to SLs. In addition, we synthesized cannalactone analogs (SdL) [2], which have an unsaturated acyclic carbon chain with a tertiary hydroxyl group and a methyl or a cyclopropyl group instead of a cyclohexane A-ring, respectively. (±)-SdL analogs are able to stimulate selectively *P. ramosa* 2a revealing that these minimal structural elements are keys for this selective bioactivity. We showed that a synthesized analog is able to inhibit shoot branching in pea and Arabidopsis, and induce hyphal branching in AM fungus *R. irregularis* as SLs.



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Communication orale 11

Design and biological evaluation of alpha/beta interface-selective CK2 kinase inhibitor

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The protein kinase 2 (CK2) is a well described enzyme overexpressed in many different cancers, increasing cancer cell survival and proliferation[1]. Despite prior inhibition strategies focusing the protein's ATP-binding site, the lack of efficacy and selectivity of drug candidates has impeded clinical progresses[2]. To address these issues, we propose to target the protein-protein interaction between α and β subunits of CK2, allowing selectivity by leveraging the specificity of the targeted site.

Preliminary work in our team identified a series of molecules selectively binding to this α/β interface on CK2α, confirmed by X-ray co-crystallization studies[3]. Further modulations of these molecules led to nanomolar inhibitors but unfortunately, X-ray structures showed interaction with another binding site on CK2α[4]. Hence, molecular determinants favouring the α/β interface binding need to be clearly defined.

Using different site selective assays enabling early identification of ligand binding to the α/β interface of CK2α, the goal of the project is to assign the structural requirements to target specifically the protein-protein interaction between both subunits. We aim to identify the most promising molecules targeting this interface and evaluate them for their in vitro anti-cancer activities.

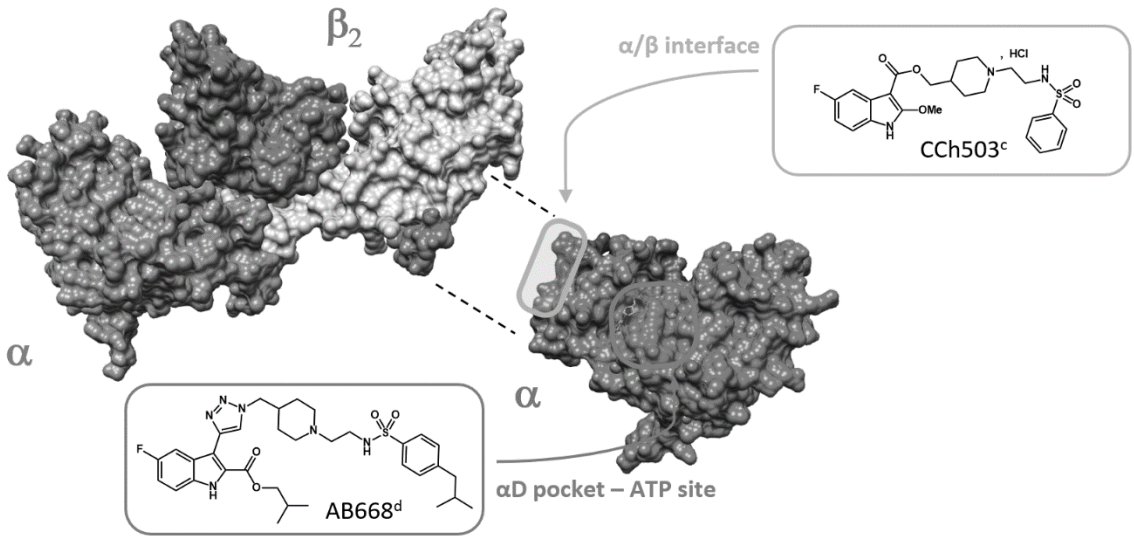

Figure 1: Three-dimensional structure of CK2α2β2 and its two hits candidates on two different binding sites

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Communication orale 12

Advantages and the limitations of synthetic antibacterial copolymers (SACs) over their natural inspiration models, the Antimicrobial Peptides (AMPs).

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Resistance to conventional antibiotics used in medicine is dangerously rising worldwide and may lead to more than 10 billion deaths per year by 2050 according to the World Health Organisation (WHO). New types of antibacterial molecules have to be developed and should be i) nontoxic to humans, ii) active against bacteria already resistant to conventional antibiotics, iii) not able or less prompt to cause resistance compared to conventional antibiotics. In that context, Antimicrobial Peptides (AMPs) and synthetic antimicrobial copolymers (SACs) showed promissing results against major bacteria infecting humans [1-4]. This presentation, focusing on the eradication of bacteria causing important infections in humans, will present the advantages and limitations of each class of molecules in term of spectrum of activity, mechanisms of action, innocuity, sensitivity to physiological factors (such as proteases, salts, or human serum), and production (time, price, scale). Overall, the presented data will demonstrate how AMPs and SACs can efficiently kill bacteria and limit the spread of resistance to antibiotics, a priority for the WHO.

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Setting-up a combinatorial strategy to discover efficient catalysts mimicking antioxidant metalloenzymes

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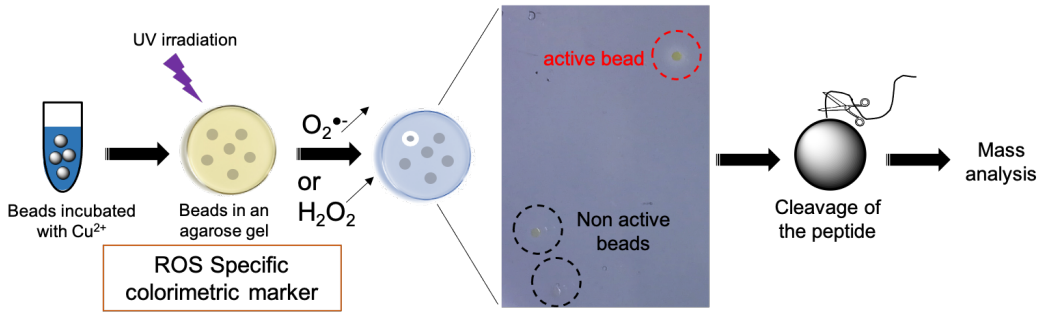
Superoxide dismutase and Catalase are metalloenzymes that catalyze the dismutation of the superoxide anion and hydrogen peroxide respectively, two deleterious reactive oxygen species (ROS) [1,2]. Overproduction of ROS leading to oxidative stress is involved in many pathologies. Consequently, the development of superoxide dismutase mimics (SOD mimics) or Catalase mimics (CAT mimics) to solve oxidative stress is of particular interest. Most of SOD and CAT mimics are complexes involving metal ions such as Fe, Mn or Cu. Peptide ligands are noteworthy as they are easily synthesized on solid support, afford a great versatility and are biocompatible [3]. Yet, the rational design of the sequence still remains a challenge as a single modification in the sequence can induce the total loss of activity. To circumvent this difficulty, a valuable alternative is the use of a one-bead-one-compound combinatorial approach [4]. Such approach has never been applied for the discovery of peptide-based redox active complexes. In this context, inspired by the work of B. Imperiali [5], we have designed a screening strategy of a peptide-based complexes library that relies on an activity-based assay with an easy-to-analyze read-out for the discovery of new SOD and CAT mimics (Fig) [6,7]. The selected hits have been studied in details using a panel of analytical techniques and more importantly on cellular model of oxidative stress [8]. Interestingly, they showed promising activities in cells highlighting the reliability of the screening strategy.



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Resensibiliser HER2 au trastuzumab dans le cancer du pancréas : identification et activité biologique du premier peptide ligand de MUC4

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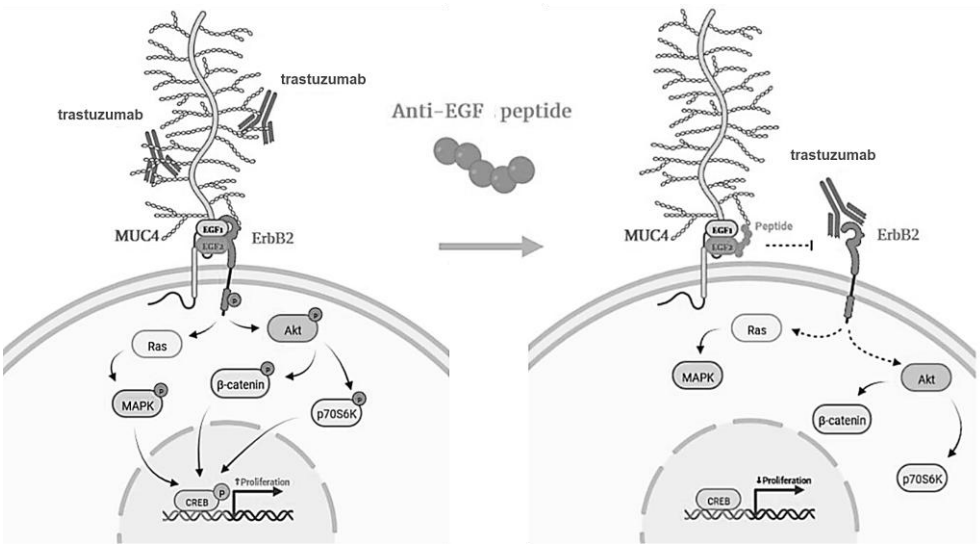
La mucine MUC4 est une O-glycoprotéine membranaire dont le rôle de senseur extracellulaire est d'assurer l'homéostasie épithéliale. MUC4 est l'un des partenaires privilégié d'HER2 avec lequel il forme un complexe qui participe à la transduction intracellulaire de nombreuses voies oncogéniques dont celles du cancer du pancréas.[1] La surexpression de MUC4 dans ce cancer, son interaction avec le récepteur ErbB2 via ses domaines de type EGF et les conséquences négatives de l'activité oncogénique du complexe font de MUC4 une cible thérapeutique très attractive.[2] Une des approches thérapeutiques ciblant le récepteur HER2 utilise des anticorps monoclonaux spécifiques, tel que le trastuzumab, se liant au domaine extracellulaire et inhibant les cascades de signalisation intracellulaire médiées par HER2. En plus de ses propriétés oncogéniques, la haute glycosylation de MUC4 crée un obstacle stérique qui empêche l'accès des molécules thérapeutiques/anticorps ciblant HER2, développant rapidement une résistance qui conduit inévitablement à la progression de la maladie et à la mort.[3]
Grace à une campagne de criblage virtuel basée sur la structure 3D de modèles d'homologie des domaines EGF de MUC4,[4] nous avons identifié le premier peptide ligand de MUC4 capable d'inhiber la formation du complexe avec HER2, de diminuer la prolifération et la migration de cellules cancéreuses du pancréas et surtout de resensibiliser HER2 au trastuzumab. Les méthodes bioinformatiques, biophysiques, biochimiques et biologiques permettant d'identifier, de caractériser et d'évaluer le peptide seront décrites dans cette présentation.



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Phosphorylation toolbox to generate nucleosides 5'-triphosphates : development, application and interest

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The current pandemic of SARS-CoV-2 has caused substantial health issues and emphasizes the immediate need of powerful antivirals. For several years, nucleos(t)ide analogues (NA) have been proving their efficiency as polymerase inhibitors against many viruses (HSV, HIV, HCV…) [1] and are a promising strategy against coronaviruses. [2] NAs are administered as prodrugs, metabolized intracellularly into their active 5'-triphosphate form and incorporated into the error-prone viral polymerase, by several mechanisms. [2]
Thus, to characterize these mechanisms and guide the synthesis of more powerful antivirals, *in vitro* studies require 5'-triphosphate substrates. Access to these phosphorylated forms is limited by chemical synthesis, which is hampered by low yields, poor selectivity and harsh purification conditions. [3] Therefore, the objective of this project is to develop potent and universal tools to phosphorylate nucleosides and NAs, by enzymatic catalysis.
To generate the "phosphorylation toolbox", appropriate enzymes have been selected, expressed and purified. Biophysical screening of experimental conditions provided an optimized test. An efficient HPLC monitoring method, transposable for sample recovery, was developed to quantify the substrate conversion. As an application example, an original and innovative enzymatic cascade synthesis has been applied to the production of ribavirin triphosphate, a broad-spectrum antiviral, and its α-thio-triphosphate analogue. Structural data shed light on the specificity of the enzymes used.

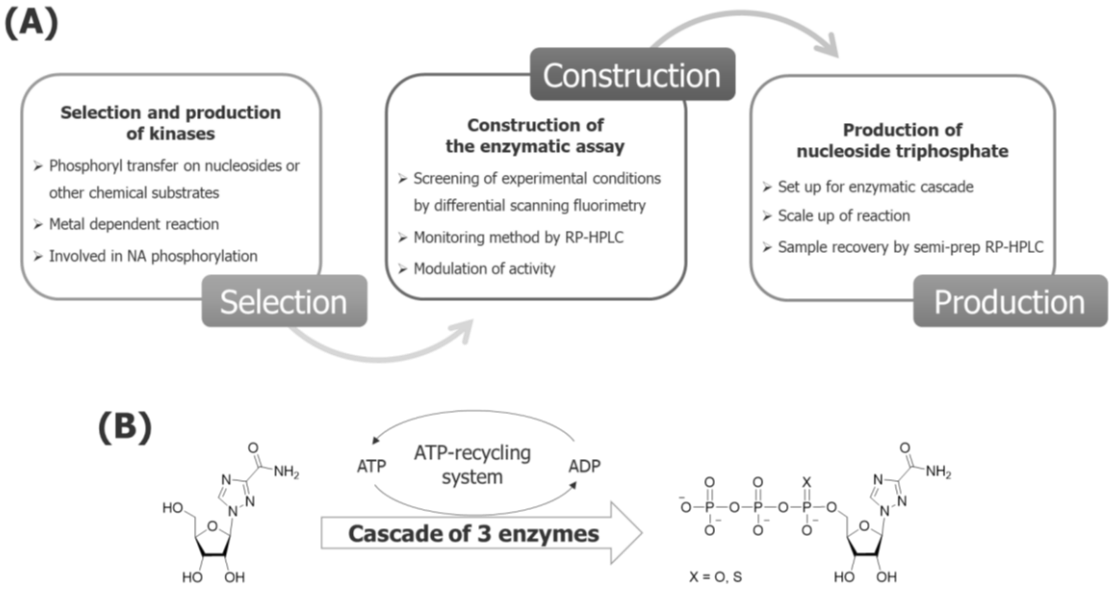

Figure 1 : (A) Strategy applied for the development of the enzymatic phosphorylation toolbox. (B) Application of the toolbox to the production of ribavirin triphosphate.

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La protection supramoléculaire à l'aide de cavitants comme outil en synthèse organique

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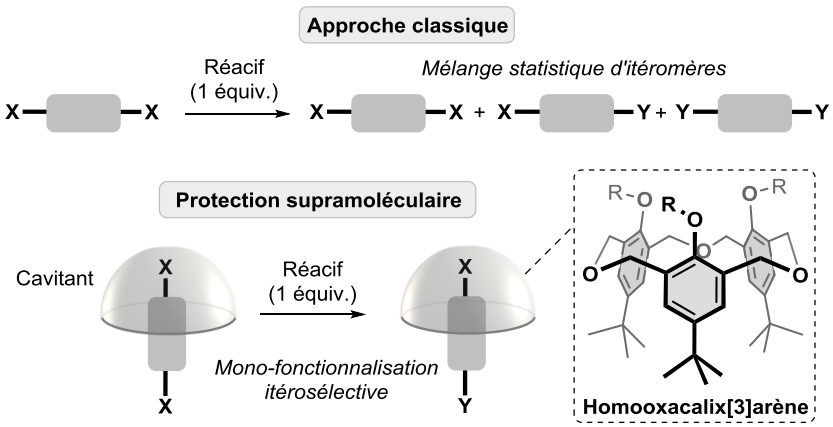
Une grande partie de la recherche en synthèse organique est consacrée au développement de réactions et de stratégies permettant la modification chimio-, régio- et/ou stéréosélective de composés polyfonctionnels. Dans la plupart des cas, les problèmes de chimio- et régiosélectivité sont surmontés en utilisant une séquence de protection/déprotection d'un ou de plusieurs des groupes fonctionnels présents sur le substrat. Cependant, cette stratégie n'est pas adaptée aux substrats portant des groupes identiques et distants, la transformation d'un groupe ayant peu ou pas d'influence sur la réactivité des autres. Le contrôle de l'itérosélectivité,[1] qui est la sélectivité qui régit le nombre de transformations chimiques répétées sur un substrat portant de multiples fonctions réactives identiques, reste donc un défi. Par exemple, une simple mono-fonctionnalisation de substrats symétriques présentant deux groupes réactifs identiques et indépendants conduit à un mélange statistique de trois itéromères (Figure ci-dessous). Une stratégie prometteuse consiste à utiliser des cavitants pour assurer une protection supramoléculaire.[2] Le concept repose sur la protection d'une partie d'un substrat polyfonctionnel enfoui dans la cavité d'un récepteur moléculaire, et sur la transformation sélective d'un de ses groupes fonctionnels restant accessible à l'extérieur de la cavité. Dans ce contexte, nous montrerons notamment comment l'emploi d'un homooxacalix[3]arène[3] (Figure ci-dessous) comme groupe protecteur supramoléculaire permet de réaliser des réactions de fonctionnalisation hautement sélectives de polyamines selon un processus monotope et cyclique.[4] Cette approche sera illustrée par la synthèse de composés sophistiqués et difficilement accessibles via l'utilisation de groupes protecteurs classiques.



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Design of new fluorinated peptides and fluorescent probes derived from spexin to study the implication of galanin receptors in pain modulation

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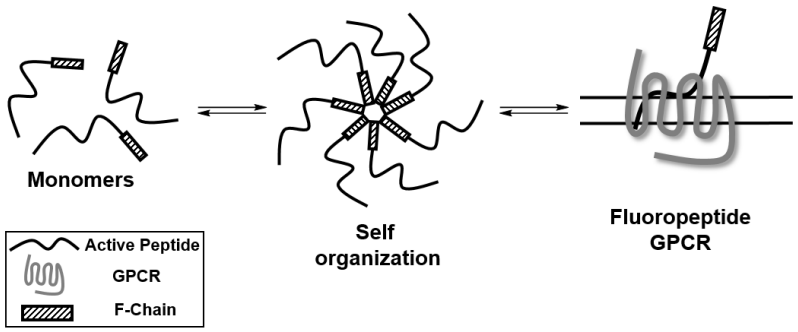
Chronic pain is a major public health issue, which has a huge impact on society. Approximately 40% adults worldwide suffer from chronic pain and its total cost has been estimated at 560-635 billion dollars/year in the United States.[1] In this field opioids still represent the gold standard analgesics. However, opioid treatments induce several adverse side effects among which analgesic tolerance and opioid-induced hyperalgesia (OIH) are of major importance. Hence, there is an urgent need to develop novel analgesics with fewer side effects. In this context, a promising neuropeptide, spexin (SPX), has been discovered using bioinformatic methods[2] and was recently deorphanized. Indeed, ligand-receptor interaction studies have shown that SPX specifically activates two subtypes of the G protein-coupled receptor GalaninR2 and R3 (GALR2/3).[3] Moreover, SPX was found to induce a dose-dependent and opioid-independent analgesic response when centrally injected in mice.[4]

To increase the metabolic stability and the *in vivo* efficacy of biologically active peptides, our team has recently developed a new approach named FluoroPEP. This is based on the introduction of a fluorinated carbon chain (F-chain) onto peptides to induce their self-organization in solution, resulting in the protection of the native peptides from enzymatic degradation.[5] This strategy was further extended to SPX giving rise to the first fluorospexin analogs. The introduction of the F-chain in SPX sequence induced a significant increase in plasma stability but also in efficacy towards GALR2. In this communication, we will present the design, the synthesis and the evaluation of fluorospexin conjugates as well as innovative fluorescent probes to investigate the mechanisms leading to the increase of efficacy and stability.



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Towards the identification of the binding site of new selective inhibitors of ACSL4 using a chemical biology approach

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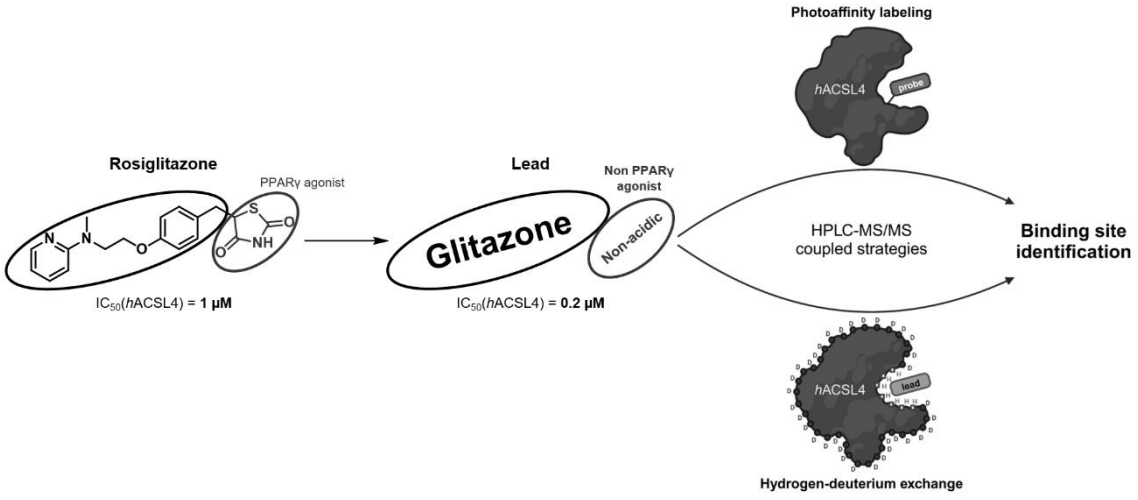
Ferroptosis is an iron-dependent form of regulated cell death characterized by the lethal accumulation of lipid peroxides. Unlike other cell death mechanisms, ferroptosis specifically involves the disruption of cellular membranes through the iron-catalyzed oxidation of polyunsaturated fatty acids. Evidence showed the implication of ferroptosis in neurodegenerative diseases such as Parkinson's disease, suggesting an interest for targeting this pathway to develop therapeutic strategies for neuroprotection.[1]

Inhibiting the acyl-CoA synthetase long chain 4 (ACSL4), a key enzyme in lipid metabolism, holds significant therapeutic interest as its inhibition by Rosiglitazone showed to prevent ferroptosis *in cellulo*[2], offering a novel avenue for intervention in various diseases characterized by this iron-dependent form of cell death. However, the lack of selectivity of Rosiglitazone for ACSL4 (vs PPARγ) hinders its use as a chemical tool.

To address this need, we aim to design new selective inhibitors through chemical modulations. This led to the identification of more potent and selective ACSL4 inhibitors ($IC_{50} \approx 200$ nM). To get more insights into the binding site of designed compounds, we synthesized a diazirine chemical biology probe derived from our lead compound, and we identified the binding peptide by photoaffinity labeling and hydrogen-deuterium exchange coupled with HPLC-MS/MS.



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LIT-002, a Highly Potent Nonpeptide Oxytocin Receptor Agonist as preclinical candidate for the treatment of autism.

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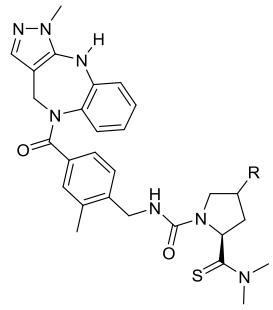
The objective of this project was to rationally design a preclinical candidate optimized for the treatment of autism spectrum disorder (ASD). ASD is a complex neurodevelopmental disorder diagnosed in presence of primary symptoms, namely impaired social communication and interaction together with a restricted, repetitive repertoire of behaviors (American Psychiatric Association, 2013). Numerous publications in animals and humans validate the oxytocin (OT) receptor (OTR) as a therapeutic target to develop a treatment for social interaction deficits in ASD. We have already developed and published the first non-peptide agonists of this receptor, active in a mouse model of the pathology.[1]

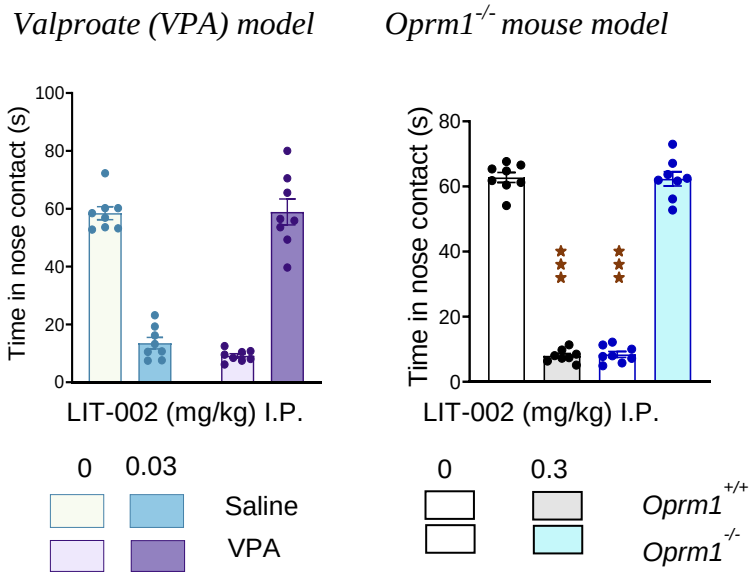
We report here the design and pharmacological activity of a second generation OT-R agonist, LIT-002, that is more potent and selective than OT itself both *in vitro* and *in vivo*, in two animal models of autism after peripheral administration.

It also displays activity in other disease models involving OT-R such as drug withdrawal, neuropathic pain, etc.

The preclinical candidate potential of this new lead compound has been evaluated and its patent has been out-licenced.



LIT-00X



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Fighting the resistance to aminoglycosides - design of bacterial enzyme inhibitors

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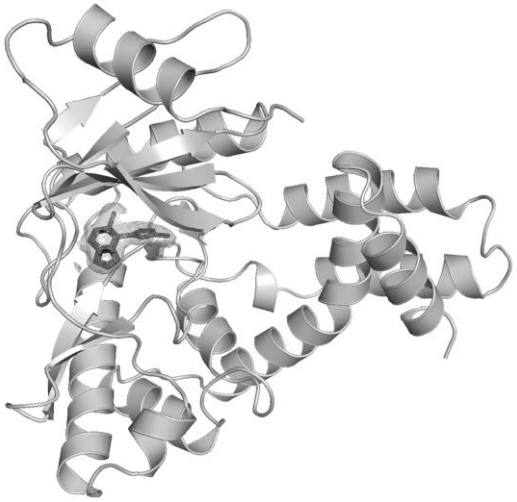
Multidrug resistance is a major health problem, the WHO highlighted the hurry to develop new treatments against Priority-1 pathogens (*P. aeruginosa*, *A. baumannii* and *Enterobacteriaceae*). Aminoglycosides antibiotics are used for severe infections but the development of resistance increase therapeutic difficulties. Aminoglycoside PHosphotransferases (APH) are bacterial enzymes responsible for resistance (*Ramirez and Tolmasky, 2010*) and the aim of this project is to design specific inhibitors of these proteins in order to restore sensitivity of bacteria to aminoglycosides (*Stogios et al., 2013*). A small molecules screening has been performed by in vitro activity measurements and thermal shift assay experiments on an APH model, this led us to the identification of interesting fragments. The selected fragments have been characterized in more details by IC50 and Kd measurements. Structures of APH-fragment complexes have been solved and allowed us to characterize at an atomic scale the interactions involved. These experiments have highlighted a chemical consensus motif and after optimization, we identified an interesting inhibitor capable of inhibit the activity of various APHs. This compound shows a sub-micromolar IC50 for two of these enzymes and a good affinity shown by micromolar Kd values. Structures of two APHs in complex with this inhibitor have been solved at a high resolution. Finally, MIC measurements show a capability of this molecule to restore sensitivity of bacterial strains to aminoglycosides. To conclude, in this work we have identified an interesting molecule with a high therapeutic potential to be further investigate. These results also guided the chemical synthesis of new derivates of this inhibitor. This work was supported by an ANR contract (SIAM, ANR-19-AMRB-0001-01) as well as associations Vaincre la Mucoviscidose and Grégory Lemarchal (project n°RF20220503015).



Inhiber l'interaction protéique XIAP/RIPK2 pour obtenir des molécules anti-inflammatoires

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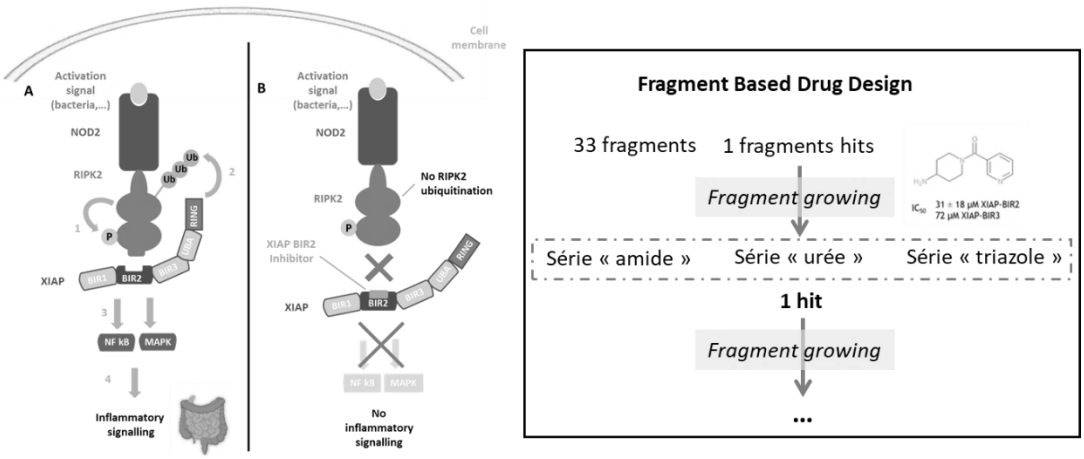
La protéine XIAP intervient dans de nombreuses voies de signalisation cellulaire, notamment celles impliquées dans la survie cellulaire et la réponse inflammatoire. Ses interactions avec ses partenaires protéiques impliquent différents domaines. Le motif XIAP-BIR2 interagit avec RIPK2 dans la voie inflammatoire NOD2, surexprimée dans certaines maladies inflammatoires telles que la maladie de Crohn. La découverte de molécules perturbant l'interaction XIAP-BIR2/RIPK2 offre une option thérapeutique prometteuse dans le traitement de ces pathologies.

Dans notre équipe, nous avons initié un projet interdisciplinaire pour développer des molécules affines et sélectives de XIAP-BIR2 via une démarche *fragment-based drug design* ». En partant de la structure co-cristallisée « XIAP-BIR2-ligand » nous avons conçu *de novo* puis synthétisé des fragments affins pour XIAP. L'évaluation biologique de la librairie de 33 fragments, nous a permis d'identifier 4 fragments hits. En s'appuyant sur les données *in silico*, les premières molécules affines ont été obtenues par fragment growing. Afin d'explorer un large espace chimique, 3 séries de composés ont été synthétisées, parmi lesquelles une molécule (MR37180) s'est montrée particulièrement intéressante. L'évaluation sur modèle cellulaire a confirmé la capacité du hit à perturber la voie NOD2.

A partir de données de dynamique moléculaire, nous poursuivons actuellement les travaux de pharmacomodulation de MR37180 pour augmenter l'affinité et la sélectivité en établissant des interactions avec les résidus spécifiques du domaine XIAP-BIR2.



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Communication orale 22

Synthèse, caractérisation et évaluation de l'activité anti hyperlipidémiques des dérivés pyrimidiques obtenus par modification de la réaction de Biginelli

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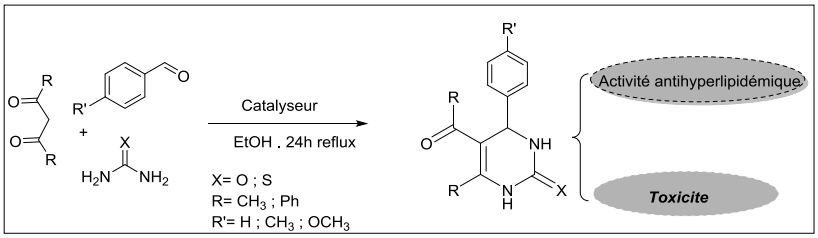
Résumé

Les composés hétérocycliques azotés mono ou polyfonctionnels continuent de plus en plus à être présents dans la structure de base des médicaments, et des composés naturels bioactifs [1,2]. Parmi ces composés, les dérivés pyrimidiques représentent une classe importante d'hétérocycles contenant deux atomes d'azote en position 1 et 3 de l'anneau à six membres. En effet, de nombreuses méthodes de synthèse de la pyrimidine et leurs diverses réactions offrent d'énormes possibilités dans le domaine de la chimie médicinale [3]. En raison de leur large éventail d'activités biologiques (anti-inflammatoires, antioxydants, antimicrobiens, antitumoraux, antiviraux, antidépresseurs, antiplaquettaires, antihypertenseurs et herbicides) [3,4] et d'applications cliniques, les hétérocycles contenant une fraction pyrimidine naturels et non naturels, sont très intéressants et sont de plus en plus prisés dans la recherche récente. L'objectif principal de cette étude est la synthèse et la caractérisation de nouveaux noyaux pyrimidiques. Notre approche se concentre sur l'utilisation des méthodes simples et respectueuses de l'environnement pour leur préparation ainsi l'évaluation de leurs activités anti hyperlipidémiques et de déterminer leurs niveaux de toxicité. Cette recherche pourrait potentiellement ouvrir de nouvelles perspectives dans le domaine de la santé et de la pharmacologie, en offrant des pistes pour le développement de traitements innovants.

Mots-clés : pyrimidines, anti hyperlipidémies, toxicité.



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Sondes fluorogéniques excitables à deux photons pour la délivrance de drogue via des réactions bioorthogonales

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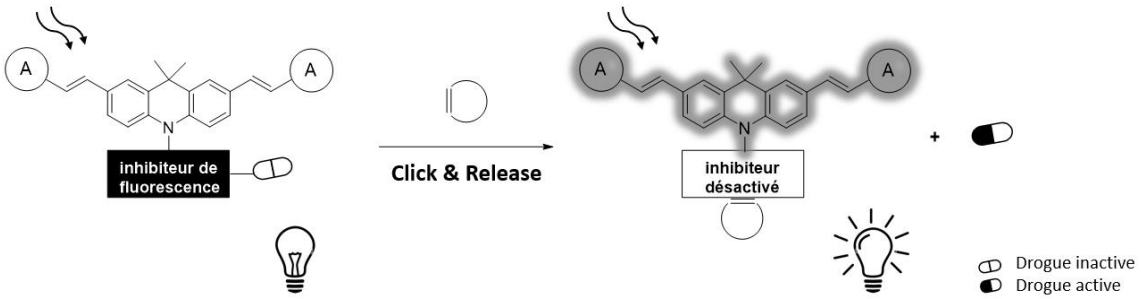
Les réactions bioorthogonales mettant en jeu des sondes fluorogéniques sont des outils prometteurs pour le marquage de petites molécules ou de biomolécules dans les organismes vivants.[1] Dans ce contexte, notre équipe a développé des sondes fluorogéniques excitables à deux photons.[2] L'excitation à deux photons, en déplaçant l'absorption vers le proche infrarouge idéalement, va permettre d'une part de minimiser les photo-dommages, et d'autre part de s'affranchir de l'auto-fluorescence cellulaire. De plus, l'absorption biphotonique présente l'avantage d'avoir une excitation localisée autour d'un point focal ce qui améliore la résolution spatiale et la pénétration dans les tissus.



Nous discuterons de nos actuelles recherches concernant le développement de nouvelles sondes OFF-ON à excitation biphotonique. Le design de ces sondes est inspiré des sondes à cœur acridane, développées au sein de l'équipe, qui ont présenté des propriétés spectrales satisfaisantes et un turn-on élevé.[2] Ces sondes représentent donc des candidats parfaits pour le développement d'objet théranostique de type « Click-to-Release ».[3,4] Les réactions « Click-to-Release » avec ces sondes permettraient à la fois de délivrer une drogue et de la localiser grâce à la fluorescence détectée après réaction click. Dans ce contexte, une sonde modèle porteuse d'un second fluorophore a été synthétisée. Cette dernière va permettre de contrôler par fluorescence à la fois la cinétique de la réaction bioorthogonale, mais également la cinétique de libération de la partie drogue.

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Enzyme-directed photoassembling of carbonic anhydrase inhibitors

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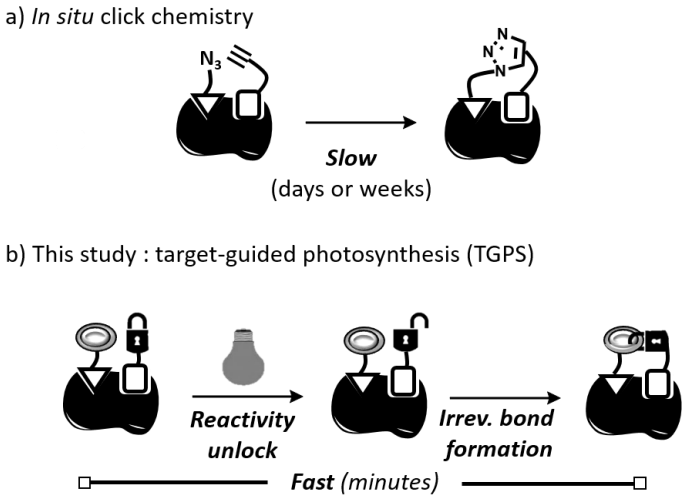
Kinetic target-guided synthesis (KTGS) is a fragment-based drug discovery (FBDD) approach in which the protein of interest (POI) is able to both select good binders and promote their linking through irreversible bond formation, in a single-step process.[1] *In situ* click chemistry, pioneered by Sharpless and colleagues,[2] is the most use KTGS reaction for the identification of multisite ligands (Scheme a). However, this strategy requires significant entropic contributions to overcome high activation barriers,[3] which can result in a long incubation time (up to several days), when tolerated by proteins, to counterbalance its low reactivity.

Based on this observation, we investigated for the first time the use of a photochemical transformation as a complementary ligation approach, to accelerate KTGS reactions to an unprecedented level (Scheme b). Carbonic anhydrase (CA-II), involved in a variety of physiological processes (pH regulation, gas exchange, ion transport…), was selected as a model enzyme to demonstrate this proof-of-concept.



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The synthesis of *N*-acylsulfonamide-linked nucleosides via the Sulfo-Click reaction discloses new applications in the field of nucleic acid chemistry

Guillaume Clavé, Romain Amador, Enes Dursun,
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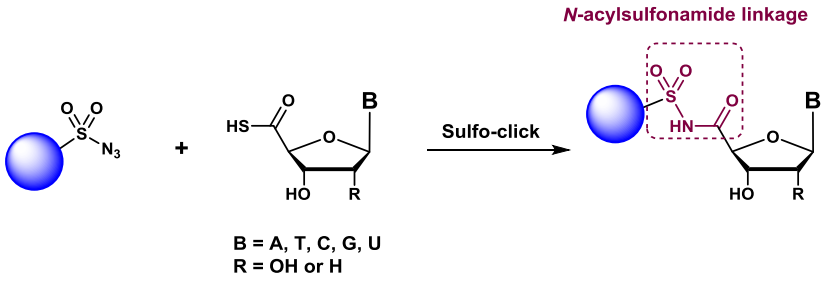
Click reactions are fast, chemoselective, and high-yielding covalent reactions between two reactive functions without generating armless byproducts.[1] Such ideal reactions have found a wide range of applications[2] in particular in the context of bioorthogonal chemistry.[3] Although the number of click reactions available has considerably grown over the past twenty years, the toolbox continues to rise and improvements are still required to achieve compatible reactions in a biological environment.[4]
The sulfo-click reaction is an emergent surrogate click reaction involving a thioacid that reacts specifically with a sulfonyl azide leading to the formation of a *N*-acylsulfonamide linkage. The sulfo-click reaction fulfills the criteria of click reactions, generates only sulfur and dinitrogen as byproducts and is compatible with aqueous conditions. These characteristics are of particular interest in the field of nucleic acid chemistry. We recently developed the synthesis of original 4′-thioacid nucleoside analogues that opened the way to new interesting applications of the sulfo-click reaction.



We will present our endeavor taking advantage of the biorthogonality of the sulfo-click reaction for bioconjugation.[5] Indeed, a variety of sulfonyl azide derivatives were successfully conjugated to 4'-thioacid nucleosides under aqueous biocompatible conditions. Then, the interesting properties of the *N*-acylsulfonamide linkage in the field of medicinal chemistry[6] were exploited to synthesize new cyclic dinucleotides for potential therapeutic applications by activating the native immune response.

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Bimodal PET/US imaging using ^{18}F radiolabelled lipid-shell microbubbles: synthesis, radiolabelling and *in vivo* studies

ARIZTIA, J.,[1] DAUBA, A.,[1] KERESELIDZE D.,[1] NOVELL, A.,[1] DELALANDE, A.,[2] GENNISSON, J-L.,[1] TRUILLET, C.,[1] KUHNAST, K.[1]

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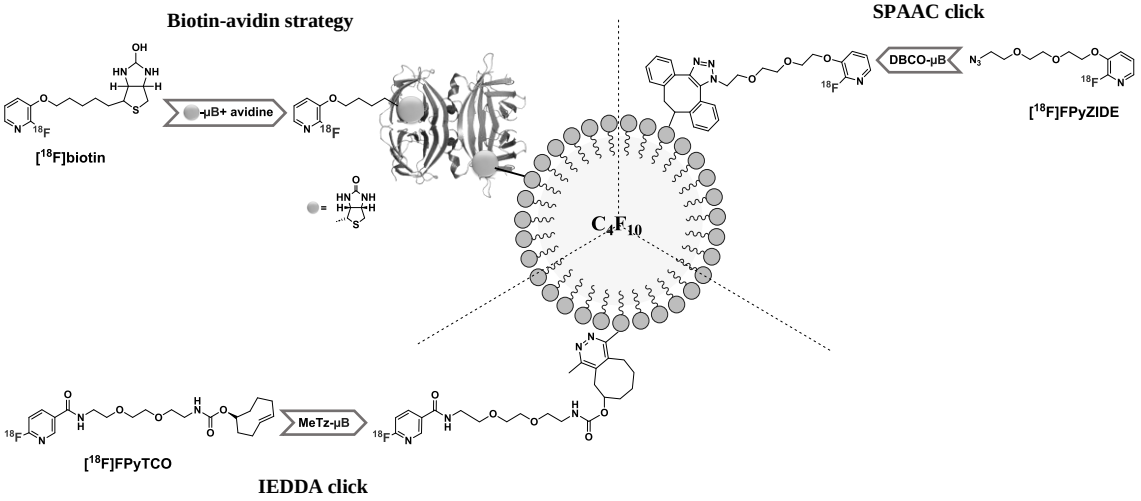
Positron Emission Tomography (PET) is a gold standard method for molecular, metabolic and quantitative imaging of relevant biomarkers.[1] Ultrasound (US) is a real-time imaging modality for anatomical and functional imaging. Their combination will allow studying the microbubble biodistribution and quantification. Additionally, the controlled cavitation of microbubble can be used to enhance radiopharmaceutical delivery in tissues.[2,3] To leverage the best profit of both modalities, lipid-shell microbubbles (µB) have been radiolabeled with fluorine-18.

Three approaches were studied for this propose: avidin-biotin coupling strategy[4] and two different click chemistry strategies (SPAAC and IEDDA).The different radiolabelling precursors and cold references have been synthetized and the fluorine-18 radiolabelling has been fully automated in a Trasis® All In One synthesizer. Lipid-shell-biotinylated microbubbles were successfully radiofluorinated with [^{18}F]biotine using avidin-biotin strategy (^{18}F-avidin-µB, 96% yield). The SPAAC reaction was optimized using DBCO-liposomes and [^{18}F]FPyZIDE tracer, an azide containing reagent amenable to react with strained cyclocotynes.[5] Then, the optimized conditions allowed us to obtain the ^{18}F-DBCO-µB with good yields (over 97%). For the IEEDA radiolabeling strategy, the [^{18}F]FPyTCO, a tracer containing the *trans*-cyclooctene moiety needed for the IEDDA reaction with tetrazine (Tz), was successfully obtained and the click reaction with the MeTz-µB was tested. Finally, in order to study the biodistribution of these PET/US dual tools, the simultaneous PET/US imaging was performed on healthy mice using the ^{18}F-avidin-µB.



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Original radiotracers targeting $P2Y_{12}$ receptors for neuroinflammation imaging: from synthesis to biological evaluation

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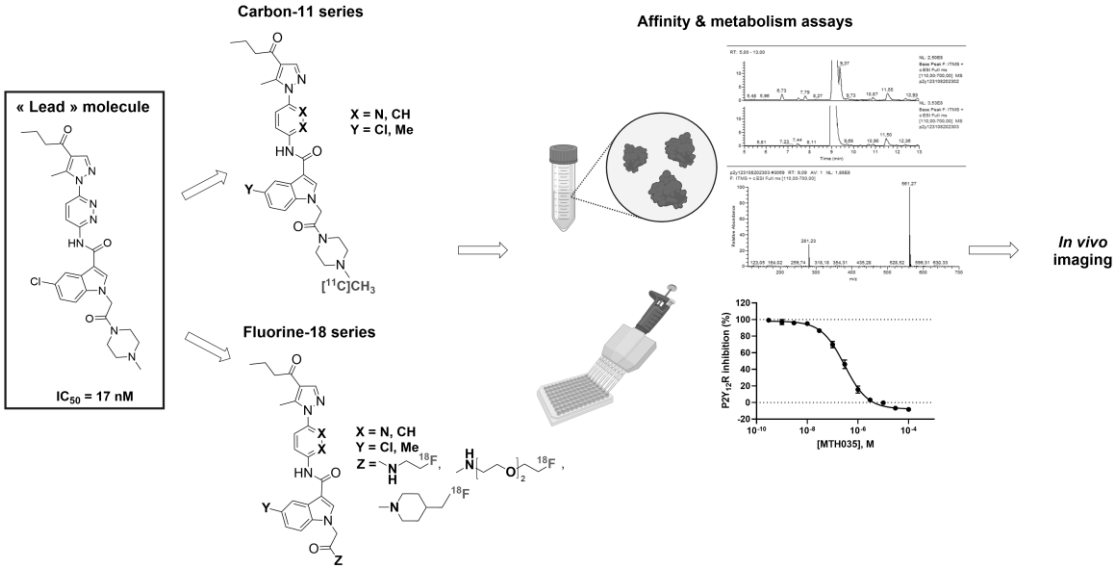
Neuroinflammation (NI) is a common phenomenon to all neurodegenerative diseases. One consequence of NI is the activation of microglia, the primary immune cells of the central nervous system. The expression of $P2Y_{12}$ receptors at the surface of microglia is modulated during neuroinflammation and these receptors could thus be used as biomarkers to monitor microglia state *in vivo* with positron emission tomography (PET) imaging.[1,2] To this end, we selected a pyrazolo-pyridazine scaffold presenting a high affinity for $P2Y_{12}$ receptors[3] and prepared precursor derivatives for radiolabeling with carbon-11 or fluorine-18 (Scheme 1). Eight reference compounds were synthesized and their affinity for $P2Y_{12}$ receptors was evaluated *in vitro* by two methods: a β-arrestin recruitment assay and a radioligand binding assay. Their metabolism was examined by *in vitro* experiments on mice and rat microsomes and mass spectrometry to predict their *in vivo* biotransformation. These *in vitro* experiments allowed us to select the best candidates and their radiolabeling was then implemented on an iPHASE C-11 Pro2 automate for carbon-11 and on a TRASIS AllInOne automate for fluorine-18. The purity of the radioligands (over 95 %) and the good radiochemical yields enabled their *in vivo* evaluation. One carbon-11 and one fluorine-18 radiotracer have thus been evaluated *in vitro* by autoradiography and *in vivo* by imaging of healthy rat and of a $P2Y_{12}$ rat model.

This work is supported by ANR-21-CE18-0067-01 and ANR-11-INBS-0006.



Scheme 1: Process of development of novels radiotracer for $P2Y_{12}$ receptors.

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An azo-based fluorogenic smart probe to visualize a mitochondrial azoreductase activity in live cells

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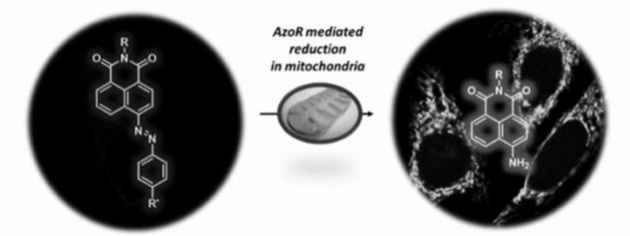
Mitochondria is the center of energy metabolism in the cell. Dysfunctions of this organelle have been related to many diseases, such as cancer, diabetes, cardiovascular or neurodegenerative diseases, and more.[1] In this context, the study of biological phenomena at the intramitochondrial level is particularly relevant. Fluorescence imaging, and more specifically fluorogenic smart probes, are potent tools to observe chemical transformations at the subcellular level. This approach has allowed the identification of an intramitochondrial nitroreductase activity.[2] Recently, this enzymatic activity has been exploited for the activation of prodrugs selectively inside mitochondria.[3]

Here, we describe our works on the design and utilization of fluorogenic probes thought for the observation of an intramitochondrial azoreductase activity in live cells. We have designed and synthesized azo-based probes derivated from 4-amino-1,8-Naphthalimides fluorophores. The particularity of these probes lies in their non-emissive structure, making them interesting OFF-ON probes. Their azo N=N double bond can be reduced by an AzoR activity, restoring a brightly emitting naphtalimide fluorophore. These sensors have been studied in vitro with multiple enzymes and were found to be stable under biological conditions, as well as highly sensitive and selective to AzoR. Confocal microscopy experiments conducted on different living cell lines showed the presence of a mitochondrial AzoR, expressed at different levels depending on the cell line. This interdisciplinary work involving organic chemistry, photophysics, and cell biology has provided convincing results making AzoR a plausible and promising alternative to NTR for specific drug delivery into mitochondria.



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Inhibiteurs de la réplication du VIH issus du criblage de la chimiothèque

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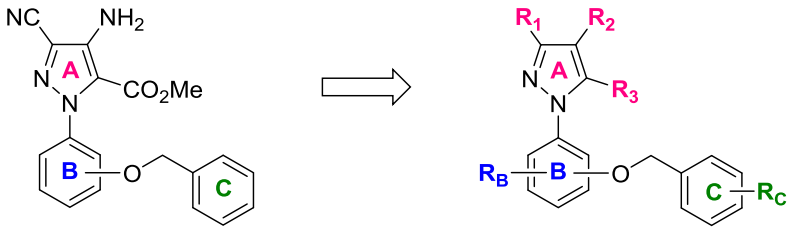
Le virus de l'immunodéficience humaine (VIH), et le syndrome d'immunodéficience acquise (SIDA) qui en résulte, représentent toujours une menace pour la santé publique. La thérapie antirétrovirale hautement active (HAART), introduite en 1996, a non seulement permis de réduire considérablement le nombre de personnes infectées par le VIH, mais aussi d'améliorer l'espérance de vie des patients qui se rapproche aujourd'hui de celle de la population générale.[1] Cependant, ces thérapies ne sont toujours pas curatives,[2] et ce traitement à vie souffre de plusieurs inconvénients tels que la toxicité inhérente aux médicaments,[3] l'émergence ou la transmission de souches résistantes [4] et le déclin de l'adhésion des patients.[5] En réponse à ces préoccupations, il est nécessaire de poursuivre le développement de nouveaux médicaments anti-VIH.[6]
Inspirés par l'activité antivirale de la Lersivirine, la chimiothèque de notre laboratoire a été criblée afin d'évaluer *in cellulo* l'activité de ces molécules en tant qu'inhibiteurs de la réplication du VIH-1. Deux composés, de structure très similaires, se sont révélés remarquablement actifs et non toxiques. La synthèse de plusieurs familles d'analogues a permis d'esquisser un pharmacophore et d'établir une relation structure-activité (SAR). L'évaluation des propriétés ADME et l'investigation du mode d'action ont permis d'identifier un composé puissant qui n'appartient pas aux trois principales classes de médicaments anti-VIH. Ces résultats sont prometteurs dans le cadre de la lutte contre la résistance virale.



2 Hits **80 Analogues**

Dans cette communication, nous décrirons la conception, la synthèse et les activités biologiques de ces composés.

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La *délikine* DAD3.473 : un nouveau modulateur/inhibiteur d'Orai1 pour la régulation SOCE dans le cancer du pancréas. Un aperçu

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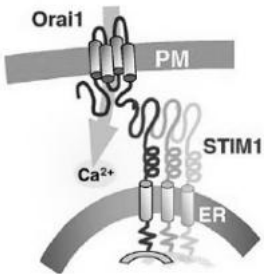

Le canal calcique Orai1 est considéré actuellement comme une cible émergente et pertinente dans le cancer en raison de sa contribution notamment dans la migration/invasion cellulaire et la propagation métastatique [1]. De ce fait, ce canal calcique Orai1 représente une piste thérapeutique prometteuse et l'accessibilité à un inhibiteur sélectif est un défi pour le traitement préventif des métastases. Les *délikines* constituent une nouvelle famille d'inhibiteurs sélectifs brevetés ciblant l'influx de calcium (SOCE, Store-Operated Calcium Entry) contrôlé par la protéine Orai1. Ainsi, la *délikine* DAD3-473 a été identifiée comme "hit" de 1ère génération particulièrement actif sur cellules du carcinome pancréatique PANC1 et sur cellules du carcinome du sein MDA-H321 lors d'une étude de Relation Structure Activité (RSA) de 1ère intention [2]. Ce projet a pour ambition d'aboutir à une stratégie anti-cancéreuse originale en ciblant le canal calcique Orai1 dont sa présence dans la membrane cellulaire en fait une cible privilégiée pour un développement thérapeutique. Au cours de cet exposé, nous présenterons successivement : i) les résultats majeurs de l'étude ''relation structure-activité RSA'' aboutissant à la famille des *délikines* et leurs activités biologiques, ii) les descripteurs pharmaco-chimiques [3] selon la règle RO5 de Lipinski [4] pour ce hit, iii) la pharmacocinétique *ex vivo* par HPLC-SM de la DAD3.473 à divers pH, iv) la toxicité aigüe de la DAD3.473 sur modèle animal selon le protocole « Acute oral toxicity : up-and-down procedure» OECD 425 [5], v) les résultats préliminaires de modélisation moléculaire d'Orai1 pour tenter de tenter de comprendre le mécanisme d'action de la *délikine* DAD3.473.

Remerciements : le Ministère de l'Enseignement Supérieure et de la Recherche, la Présidence de la République da la Côte d'Ivoire, la Fondation Benianh Internationale, Total Raffinage Africa, le District de la Région d'Abidjan et la Région de Moronou de la Côte d'Ivoire sont remerciés pour les financements doctoraux (C-D. D. ; L-A. V., A.A.). Les CD29, CD35 de La Ligue Contre le Cancer pour leurs soutiens à la recherche et la Satt Ouest Valorisation pour le programme de Prématuration 2021-23.

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N,N,N-triacylamines as promising inhibitors of kallikrein-8, an emergent biomarker of Alzheimer's disease.

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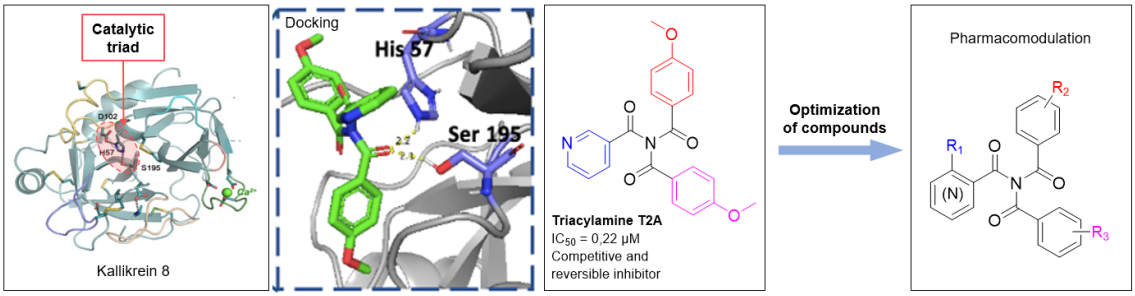
Alzheimer disease (AD) is the most common progressive neurodegenerative disease with devastating effects on cognition and memory. About 2 million people suffer from Alzheimer's disease type dementia and 55 million patients worldwide. Currently, there is no treatment nor pre-mortem diagnosis with specificity and selectivity.[1] One of the challenges of research on this disease is to diagnose it before the appearance of irreversible symptoms. Recently, studies underlined that kallikrein 8 (KLK-8),[2] a serine protease, would be involved in the development of different pathophysiologies associated with this disease.[3,4] Moreover, it has also been demonstrated that antibody mediated inhibition of KLK-8 restores a normal cognition activity in the mouse model of AD.[5,6] Despite a growing interest in this target, no potential therapeutic inhibitor has been identified to date.

The aim of this work is to design and synthetize the first organic KLK-8 inhibitors with high selectivity. We have recently discovered and characterized a series of molecules based on N,N,N triacylamines (T2A) as reversible and competitive inhibitors on KLK8 with IC_{50} in the range of submicromolar.

We present here a structure-activity relationship approach using pharmacomodulation on triacylamines to design structural analogues with improved activity and studied their selectivity towards other proteases.



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Unprecedented reactivity of polyamines with aldehydic DNA lesions

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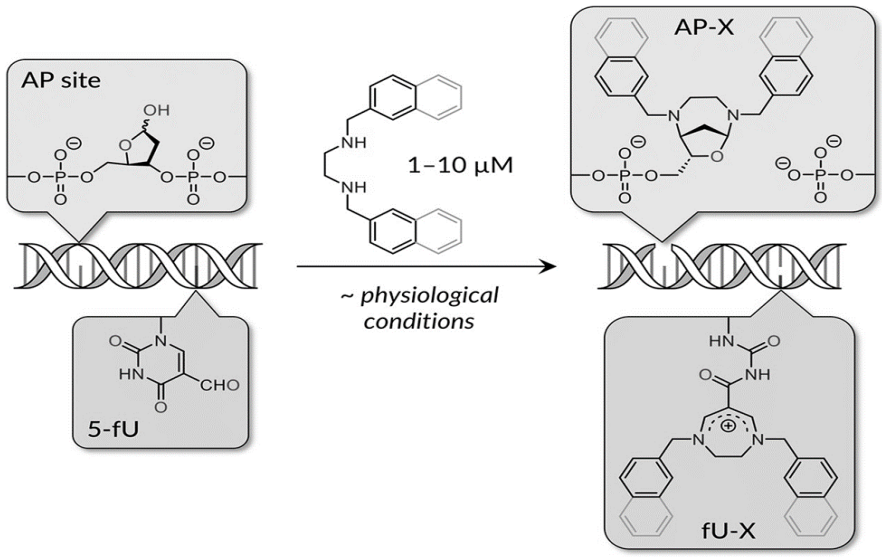
Deoxyribonucleic acid (DNA) contains the genetic information allowing cells to grow, function and reproduce. This biomolecule is constantly subjected to external attacks (UV, oxidative stress, metabolism of the cell itself, etc.) that induce DNA lesions (i.e., chemical modifications of nucleobases or of the sugar-phosphate backbone) and damage the genetic information. Apurinic/apyrimidinic (AP, or abasic) sites and 5-formyl-2′-deoxyuridine (5-fdU) represent examples of such DNA lesions, potentially leading to mutations and carcinogenesis. Previously, our lab developed polyazamacrocycles that showed a very strong non-covalent affinity *in vitro* with DNA strands presenting AP sites[1]. In addition, one of polyazamacrocycles was shown to chemically react with AP sites leading to the formation of a covalent adduct[2]; however, the chemical structure of this adduct was unclear. Moreover, it was not known whether a similar reaction could take place with 5-fdU. In this work, we synthesized small-molecule analogues of AP sites (or cleaved AP sites) and used 5-formyl-1-methyluracil (as a mimic of 5-fdU) and made them react with *N*,*N*′-DiBenzylEthyleneDiamine (DBED), the minimal common unit of synthesized polyazamacrocycles. The reaction products were isolated and characterized, revealing the formation of unprecedented tetrahydrofuro[2,3,4-ef]-1,4-diazepane (termed “ribodiazepane”) structure upon reaction with AP-site analogues on one hand, and a 1,4-diazepinium-type structure upon reaction with fdU, on the other hand. Knowledge of these reaction intermediates allowed us to synthesize new functionalized diamine ligands, with the aim to



label AP sites in the genome[3].

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Unprecedented perspectives on the application of CinNapht fluorophores obtained by a "late-stage" functionalization strategy

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(Times New Roman, 12)

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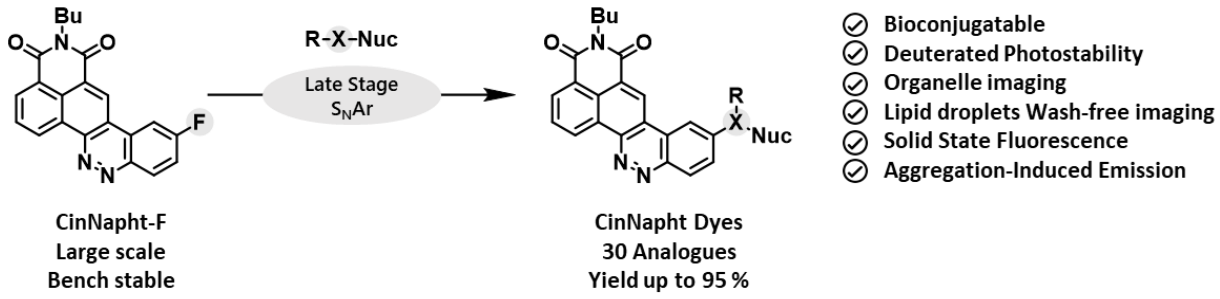
With the increasing interest of optical molecular imaging in medicine, fluorescence microscopy has seen constant development contributing to the emergence of new technologies and probes without discontinuity for the past decades. Fluorogenic probes are now considered as critical tools for the study of biological environments. [1] Therefore, there is definite interest in creating a new easily tunable chemical scaffold exhibiting fluorescent behavior that could later be used for the design of such probes. In this context, our group has investigated the synthesis of a fused ring cinnoline/naphthalimide hybrid here called "CinNapht" dyes. [2] The first generation of these new fluorophores exhibits original and promising properties in conventional fluorescence: a red emission, a large Stoke Shift, a strong solvatochromism, high chemo- and photostability and biocompatibility. [3] Here we present a an easy access to numerous analogues of CinNapht dyes by late-stage functionalization and a study of their photophysical properties. We have re-designed the synthesis via a fluorinated CinNapht-F intermediate that can react with a wide variety of amines in a SNAr type reaction. The reaction conditions and its scope have been investigated. We have now an easy access to new fluorophores with improved photophysical properties associated with a true utility for cell imaging applications such as organelle imaging. [4]



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Thiovinyl-based coumarine derivatives : synthesis and fluorescence properties

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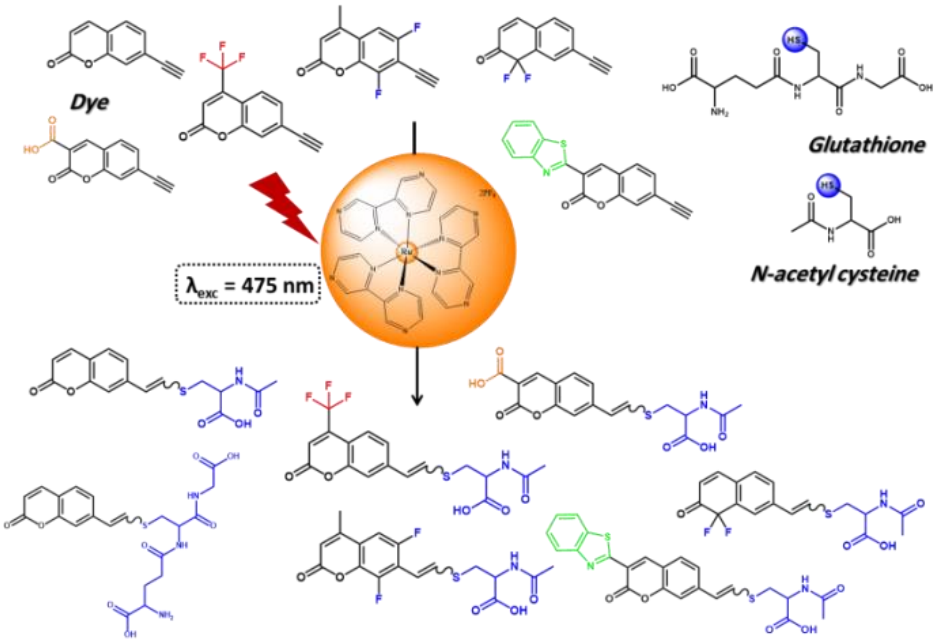
Thiol-Ene/Yne coupling reactions were established as a powerful tool for carbon-sulfur bond formations.[1–3] A way for thiol-Ene/Yne reaction involves a radical pathway to access the anti-Markovnikov type products, traditionally initiated by UV light or radical initiator.[4] Nowadays visible-light photoredox catalysis is used in the presence of organometallic photocatalyst (PC), such as ruthenium and iridium[5,6] complexes or metal-free PCs like acridinium, Fluorescein, Bengal rose and Eosin Y derivatives.[7]
We have recently highlighted a fluorescent photoisomerizable coumarin modified at position 7 by a thiovinyl function. This coumarin was obtained from corresponding 7-ethynylcoumarine and thiol through thiol-yne under basic conditions in organic medium.[8] Following this preliminary result, this project aims to further investigate coumarin derivatives with red-shifted photophysical properties. To achieve this, we developed a photoredox thiol-yne reaction methodology compatible with aqueous media and water-soluble thiols (such as glutathione, oligopeptide).



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Méthodes bioautographiques: sondes fluorescentes et HPTLC pour la détection d'inhibiteurs enzymatiques au sein de matrices complexes[1]

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La chromatographie sur couche mince haute performance (HPTLC) est un outil analytique sophistiqué pour l'identification de molécules biologiquement actives dans des matrices complexes telles que des extraits végétaux. La méthode dite de bioautographie permet une séparation et une identification facile et rapide de ces composés d'intérêt sur une plaque de chromatographie. Un des principaux développements de cette méthode consiste à évaluer l'inhibition de molécules sur l'activité enzymatique. Cependant, les méthodes existantes restent à ce jour rares et très spécifiques.

Cette présentation exposera le principe général de la méthode de bioautographie. Puis le développement d'une méthode spécifique pour la détection des inhibiteurs de l'acétylcholinestérase (AChE) à l'aide d'une sonde fluorescente dérivée de la coumarine, l'acétate de 4-méthylumbelliféryle. La découverte de nouveaux inhibiteurs de l'AChE pourrait être une cible principale pour le développement de nouveaux traitements de la maladie d'Alzheimer. Notre méthode combine les avantages de la bioautographie et de la détection à haute sensibilité d'une sonde fluorescente.

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PO26 « FRET-Sensing of Multivalent Protein Binding at the Interface of Biomimetic Microparticles Functionalized with Fluorescent Glycolipids»
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Poster 1

Lead-Oriented Synthesis of Epigenetic-Relevant Scaffolds

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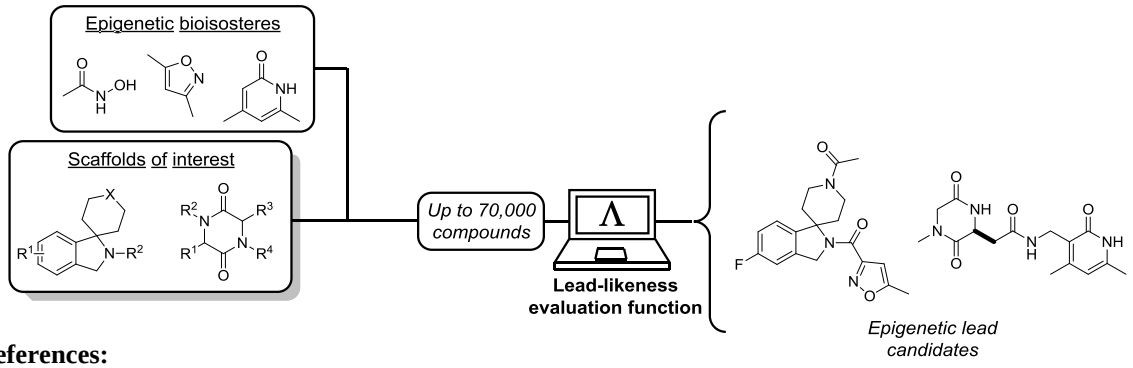
Post-Translational Modifications (PTMs) have a major impact on gene expression[1], enzymes activity[2] and protein homeostasis'[3]. These PTMs can be installed, recognised, or removed through enzymatic processes performed by specific proteins known as writers, readers and erasers respectively. In the last decades, those proteins and their respective PTMs have proved to play a primary part in various biological disorders like cancers,[4] inflammation responses[5] or cardiovascular diseases[6] making them targets of choice for the control and the study of epigenetic processes. In 2021, our group showed the importance of particular isosteres of interest (e.g. hydroxamic acids, isoxazoles, pyridin-2-ones), that are still scarcely represented in chemical libraries, to facilitate the discovery of novel epigenetic small molecules inhibitors.[7] However, to efficiently accelerate the discovery of epigenetic drugs, the introduction of these isosteres must be paired with a careful control of the molecular properties of candidates.

We thus herein describe the development of a simple, modular and open-source workflow to drive synthetic efforts towards lead-like compounds of interest for epigenetically enriched chemical libraries. To do so we designed tunable continuous evaluation sub-functions derived from acoustic or electronic filters to score molecules over a set of nine molecular properties (MW, HBA, HBD, Fsp^3…) which were all included in a global evaluation function **Λ**. Our evaluation function was then validated and benchmarked against known metrics and finally incorporated in a pipeline for the discovery of epigenetic lead candidates. By combining docking experiments and our evaluation function, we selected and synthesised candidate compounds, identifying lead molecules with biological activity for epigenetic targets of interest.



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Poster 2

Catalyst-Free Thia-Diels-Alder Click Reaction for the Labelling of Peptides

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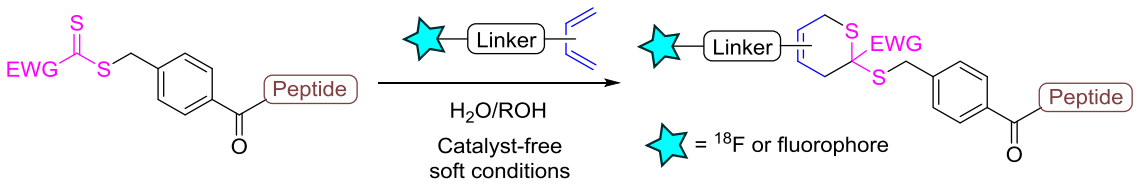
Click reactions represent an efficient method for the chemoselective modifications of peptides of proteins in mild conditions. Amongst these reactions, the Cu-Catalysed Alkyne-Azide cycloaddition (CuAAC) remains the most used system despite the *in vivo* toxicity of the Cu(I) catalyst that may get trapped by the peptide at the end of the reaction [1]. Alternatives such as the Strain-promoted Azide-Alkyne cycloaddition (SPAAC) or the Inverse Electron Demand Diels-Alder reaction (IEDDA) have been developed [2] to overcome this issue but still remain scarcely represented in the literature mostly due to poor accessibility and high cost of the reactive partners.
Herein, we report the use of a thia-Diels-Alder reaction between a dithioester and a diene [3] for the chemoselective labeling of peptides under catalyst-free mild conditions. While this cycloaddition had already been used as a click reaction to functionalise the Bovine Serum Albumin (BSA) with polymers [4], it had never been applied to the chemoselective labeling of peptides for imaging applications. Thus, we developed a practical method to introduce for the first time the phosphonodithioester moiety into a model peptide. Then, the diene was designed to combine good stability and high reactivity towards the dithioester partner while keeping mild reaction conditions. Finally, bioactive peptides were labelled with either fluorine-18 for *in vivo* Positon Emission Tomography (PET) or fluorophores for *in cellulo* optical imaging.



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Marquage chemoenzymatique des substrats protéiques d'une lysine méthyltransférase à l'aide d'analogues de *S*-adénosyl-L-méthionine

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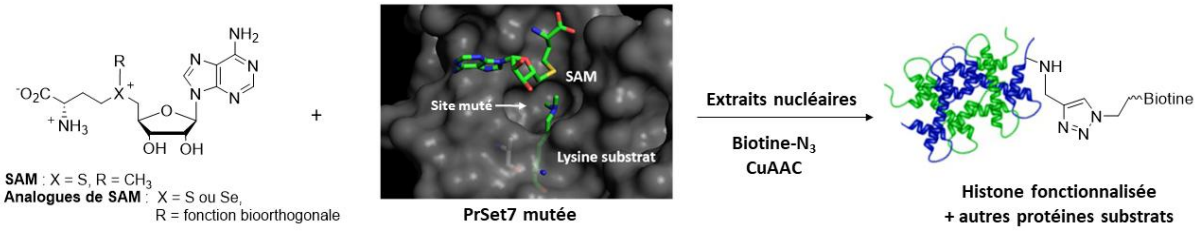
La méthylation des histones sur leurs lysines est une modification post-traductionnelle qui joue un rôle crucial dans de nombreux processus biologiques. Cette marque, qualifiée comme épigénétique, module la structure de la chromatine et est associée au statut de transcription des gènes. Les enzymes responsables de cette méthylation, appelées histone lysine méthyltransférases (HKMT), catalysent le transfert du groupement méthyle provenant d'un cofacteur, la *S*-adénosyl-L-méthionine (SAM), sur la fonction amine en position ε de la chaîne latérale d'une lysine de leur substrat. Alors que les histones sont considérées comme les principaux substrats de ces HKMT, les études s'accumulent et tendent à montrer que ces enzymes méthylent également d'autres protéines que les histones, ces modifications entraînant des changements dans la fonction des protéines méthylées.
Dans ce contexte et dans l'objectif de caractériser de façon exhaustive le méthylome d'une HKMT cruciale nommée PR-Set7, nous avons mis en œuvre une approche dite « bump and hole » [1,2] basée sur l'utilisation d'outils chimiques et enzymatiques pour étiqueter et identifier les substrats protéiques de cette enzyme. Dans cette approche nous avons synthétisé différents analogues séléniés et soufrés de la SAM et nous avons produits des mutants de PR-Set7 susceptibles d'accommoder ces molécules pour introduire sur les substrats une fonction chimique bioorthogonale. Les protéines étiquetées à l'aide du couple cofacteur bioorthogonal/mutant de PR-Set7 peuvent alors être enrichies à l'aide d'une sonde d'affinité et caractérisées par spectrométrie de masse[3].



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A new type of nitrogen containing cyclotriveratrylenes: synthesis and NMR characterization

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Magnetic Resonance Imaging is a technology frequently used in the medical imaging field because of its high resolution and the excellent tissue contrast it provides. Despite its several benefits, in various cases, the use of contrast agents is needed in order to enhance image resolution among different tissues. Among the promising contrast agents, hyper-polarized xenon-129 (HP-^{129}Xe) has attracted much interest. Thanks to its hyperpolarization using optical pumping, the signal can be improved and detected at low concentration with high signal to noise ratio. To date, the use of HP-^{129}Xe as contrast agent allows to acquire image of the human pulmonary system[1] and brain.[2] However, HP-^{129}Xe is not specific of a biological target and needs to be vectorized with the use of a molecular host. The aim of combining these two parts is to synthesize a biosensor usable in MRI. One promising host is the spherical cryptophane molecule which shows very good xenon encapsulation properties,[3] but its poor water solubility precludes its use as biosensor. It is therefore necessary to improve its physico-chemical properties.

In our project, we focus on the synthesis of a cryptophane including pyridines cores and nitrogen atoms in place of carbon on the methylene bridge. In this communication, we will present the synthesis of a new type of cyclotriveratrylenes (CTV), which are key intermediates in the preparation of cryptophanes, using Burchwald-Hartwig amination,[4] according to the methodology described by our group. [5] In another part we will focus on the characterization in NMR of two functionalized CTV in order to study the behavior of two conformers the crown or saddle CTV.[6]

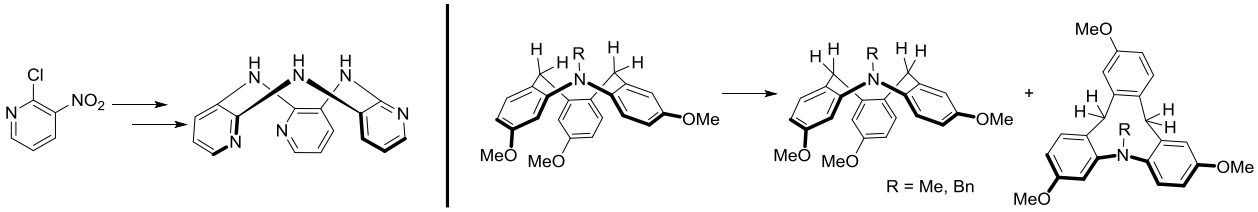

Figure 1 : Synthesis of two new nitrogen containing CTVs

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Robust Calixarene-Coated Gold Nanorods for Photothermal Therapy

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Gold nanorods (AuNRs) have emerged as highly promising materials for advancing biomedical *in vivo* applications.[1],[2] They exhibit two distinctive Localized Surface Plasmon Resonance (LSPR) bands: transverse and longitudinal. The maximum absorption wavelength of the latter can be tuned by altering the aspect ratio of the rods. For high aspect ratios, it falls within the near-infrared (NIR) region where minimal absorption by endogenous molecules enhances light penetration into tissues.[2]

Photothermal therapy (PTT) is a promising non-invasive cancer treatment strategy exploiting the conversion of light to heat by photothermal agents for thermal ablation of cancer cells.[3-5] AuNRs possess several qualities that make them excellent photothermal agents: high biocompatibility, long circulation times, ease in functionalization, and intense optical extinction coefficients in the NIR region.[3-5] However, one limitation is their anisotropic structure that is susceptible to deformation under laser irradiation leading to a rapid decrease of their NIR extinction and photothermal efficiency.[6],[7] To address this challenge, we have employed an effective approach involving the use of calix[4]arene-tetradiazonium salts, which can be irreversibly and strongly grafted onto surfaces through the reduction of their diazonium groups.[8-11] We have adapted this calixarene-based coating strategy to fabricate ultrastable AuNRs which exhibit superior stability compared to conventional AuNRs, notably under laser irradiation in the context of PTT. Enhancing the stability and efficiency of AuNRs in the context of PTT has the potential to drive significant advancements in the field.

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Novel LC-MS based method to measure trypanothione and ROS levels in *Leishmania*

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Keywords: *Leishmania*, LC-MS, trypanothione, ROS, molecular probes, fluorescence

Leishmaniasis is one of the major neglected parasitical diseases that affects each year millions of people worldwide, particularly in poor southern countries. Current treatments, such as antimony, are limited by their toxicity, their lack of efficiency, and the emergence of resistance. Therefore, there is an urgent need to develop new, safe, effective and affordable treatments against leishmaniasis. Most of these new treatments are metal complexes that inhibit *Leishmania* antioxidant enzymes that are essential for maintaining redox homeostasis. Indeed, their inhibition allows an oxidative cascade, ultimately leading to the death of the parasite. Since the antioxidant defences of the parasite relie on the highly specific trypanothione system, it is critical to better understand *Leishmania* trypanothione-based enzymatic systems, their interactions with molecular treatments, and to analyse other redox dysregulations that are induced by such treatments.

For this purpose, an LC-MS method has been developed for measuring trypanothione in parasite extracts, and its modulation in presence of gold-complexes such as auranofin. Moreover, different methods have been implemented to measure the oxidative cascade through the quantification of ROS induced by the treatment such as LC-MS using ROS-specific probes, flow cytometry and confocal microscopy. In the same manner, an original method based on the fluorescence of a DNA intercalant associated to a controlled illumination on living parasite cells has been used to highlight redox homeostasis dysregulations. The first results have revealed that the effect of the redox effectors on the parasites depends strongly on the parasite stages *i.e.* amastigote or promastigote.

Poster 7

Conception, synthèse et efficacités *in vitro* et *in vivo* de nouveaux composés antipaludiques ciblant une phosphatase de *P. falciparum*

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Le paludisme est l'une des maladies infectieuses les plus répandues dans le monde en raison de ses fortes morbidité (247 millions de malades) et mortalité (619 000 décès) chaque année.[1] Malgré les nombreux traitements existants, le nombre de cas de multirésistance aux médicaments augmente, faisant du paludisme un problème de santé majeur.[2] Chez *Plasmodium falciparum* (*Pf*), l'espèce pathogène causant la plus forte mortalité, les kinases et les phosphatases ont montré une importance cruciale pour sa survie.[3] Ainsi, après la caractérisation moléculaire et fonctionnelle d'une sérine/thréonine phosphatase métallo-dépendante (PPM) et le criblage *in silico* de son site catalytique construit en 3D par homologie comparative, nous avons procédé à l'optimisation d'un hit thérapeutique.

Les composés sont synthétisés et testés *in vitro* pour déterminer leur CI_{50} contre *Pf* (souche 3D7 chloroquino-sensible et souche Dd2 multirésistante), et pour leur cytotoxicité sur les cellules humaines HFF et HepG2 afin de calculer leur indice de sélectivité (IS). Les modulations chimiques et les relations structure-activité correspondantes contribuent à améliorer l'inhibition de la survie de *Pf*. Ensuite, les paramètres pharmacocinétiques des meilleurs composés (CI_{50} sur Pf < 100 nM et IS > 100) sont déterminées. Enfin, des études d'efficacité sur des animaux infectés par *Plasmodium berghei*, modèle de référence pour les études *in vivo*, sont réalisées.

Environ 90 molécules ont été synthétisées et testées depuis le début du projet, parmi lesquelles douze ont une CI_{50} sur *Pf* inférieure à 100 nM et un IS supérieur à 100. Des études pharmacocinétiques *in vivo* chez la souris pour quatre d'entre elles ont donné des paramètres pharmacocinétiques satisfaisants.

Notre meilleur hit à ce jour comporte une CI_{50} de 25 nM sur la souche sensible 3D7 et de 40 nM sur la souche multirésistante Dd2, avec un indice de sélectivité sur cellules HFF et HepG2 supérieur à 400, et pour lequel les études *in vivo* ont montré 100% d'efficacité à la dose de 30 mg/kg, deux fois par jour par voie intra-péritonéale.

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SYNTHESIS AND VALIDATION OF DUAL PI3K/mTOR INHIBITORS AND PROBES FOR THE TREATMENT OF CANCER

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Kinases are enzymes that catalyze reactions in the cell, and are essential to cellular mechanisms such as cell proliferation, survival, growth and angiogenesis. According to various studies, activating mutations of enzyme genes that lead to elevated pathway activities has been observed in cancer patients. In efforts to cure cancer, research on combined therapies (radio and chemo) has been strongly developed within the last years as it has proven to be much more beneficial for the patient. We chose to inhibit the PI3K/Akt/mTOR pathway in particular, as it is often mutated in various types of cancers, thus making it a promising target in therapeutic research. [1-5]
The design, synthesis and screening of pyridopyrimidines as dual PI3K/mTOR inhibitors is described giving derivatives with nanomolar enzymatic and cellular activities on both targets, with an acceptable kinase selectivity profile. [6-8]
A docking study was performed to understand the binding mode of the compounds and to explain the differences in biological activity. In addition, cellular effects of the best dual inhibitors were determined on six cancer cell lines and compared to a healthy diploid cell line for cellular cytotoxicity. Two compounds were highly potent on cancer cells in the submicromolar range without any toxicity on healthy cells. A more detailed analysis of the cellular effect of these PI3K/mTOR dual inhibitors demonstrated that they induce G1-phase cell cycle arrest in breast cancer cells and trigger apoptosis.

These compounds show interesting kinase profiles as dual PI3K/mTOR tool compounds or as a chemical series for further optimization to progress into in vivo experiments. Our progress towards the discovery of PI3K inhibitors prompted us to develop chemical biology tools used to probe mechanisms and demonstrate feasibility and consequences of pathway inhibition.

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Novel Acyl-CoA synthetase long chain family member 4 (ACSL4) inhibitors as anti-ferroptotic agents

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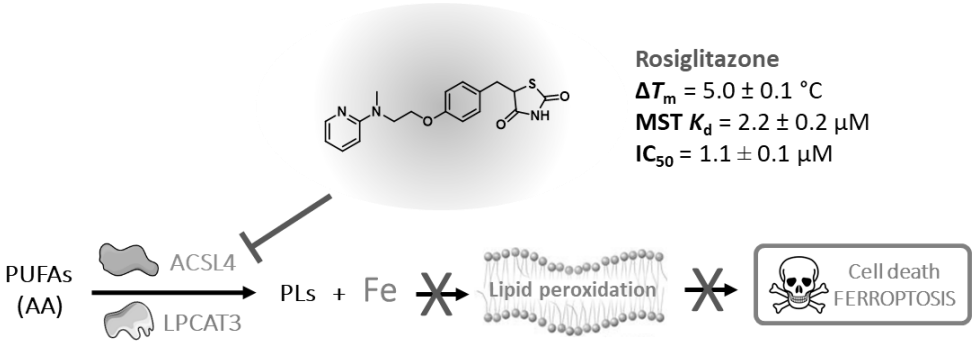
The regulation of cell death is essential for the development of the organism and the maintenance of tissue homeostasis. Thus, a dysfunction of this process contributes to the progression of many diseases. In recent decades, several forms of regulated cell death (RCD) have been identified. Among these new RCDs, the Brain Biology & Chemistry team (BBC, UMR-S1172) is particularly interested in ferroptosis, an iron-dependent RCD characterized by the accumulation of lipid peroxides to toxic levels.[1] Several studies have highlighted the important contribution of ferroptosis in neurodegenerative diseases such as Parkinson's disease, opening new therapeutic perspectives in the potential treatment of these pathologies. Acyl-CoA synthetase long chain family member 4 is a key enzyme in ferroptosis execution. In this context, our objective is to develop new anti-ferroptotic agents targeting ACSL4.



To date, the reference inhibitor of ACSL4 is Rosiglitazone, evaluated *in vitro* and *in vivo* in the Doll et al. study,[2] which demonstrated a powerful anti-ferroptotic effect. However, its lack of selectivity for ACSL4 (vs PPARγ) and its low affinity for the enzyme (IC_{50} in the micromolar range) hinder its therapeutic use. Current work focuses on improving both ACSL4 inhibitory activity and anti-ferroptotic potential of identified hits, while moving away from their initial pharmacological activity.

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MoloVol: An Easy-to-Use Tool for Calculating Volumes, Surfaces Areas, and Cavities

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Cavities are a ubiquitous feature of chemical structures encountered in various fields ranging from supramolecular chemistry to molecular biology. They are involved in the encapsulation, transport, and transformation of guest molecules, thus necessitating a precise and accessible tool for estimating and visualizing their size and shape. MoloVol is a free, open-source software parametrizable through a user-friendly graphic interface developed for calculating a range of geometric features of chemical structures. MoloVol utilizes up to two spherical probes to define cavities, surfaces, and volumes. The general scope of the program utility and its algorithms were previously reported.[1] This poster presents the utility of MoloVol for the characterization of cavities in macrocyclic and cage compounds (Fig. 1). MoloVol is available on Windows, macOS, and Linux distributions at https://molovol.com

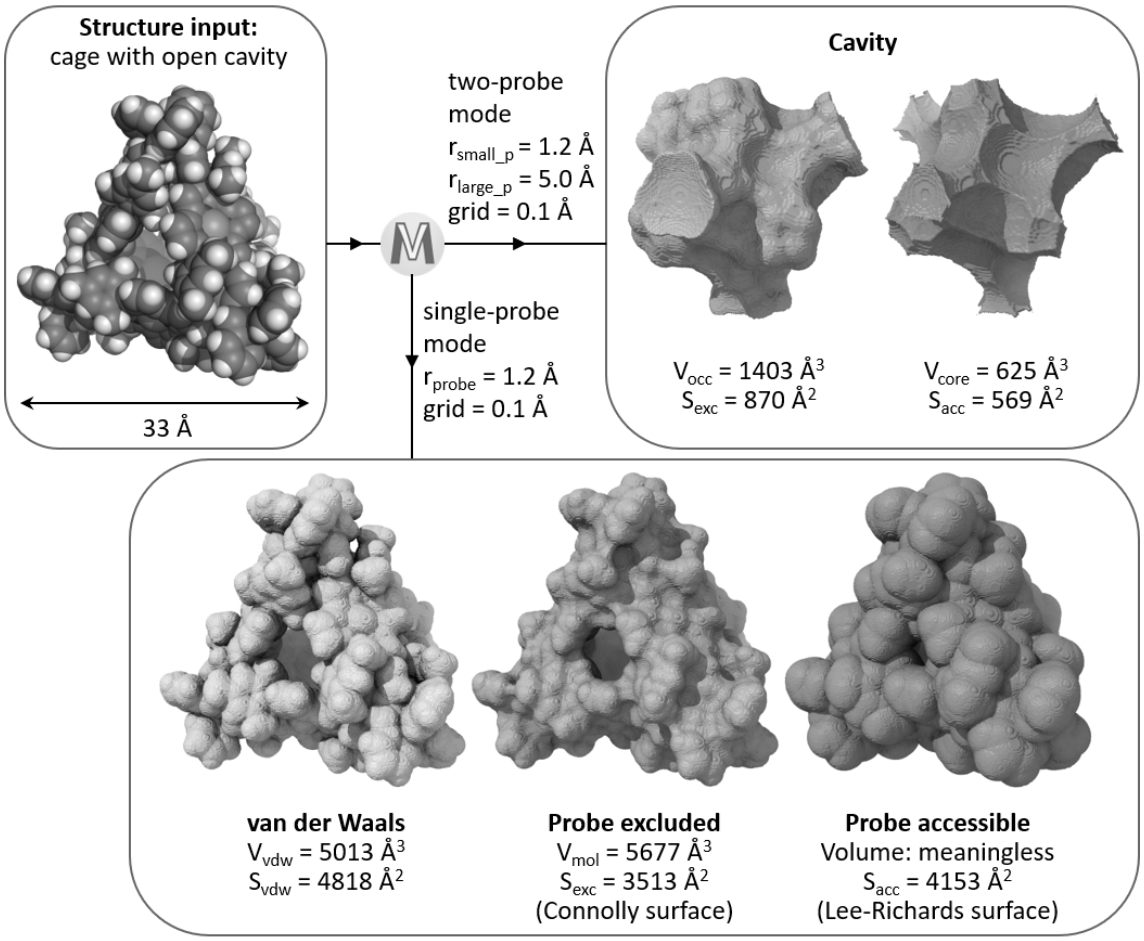

Figure 1. Example of calculation output from MoloVol with an open cage compound.

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Evaluation of the binding characteristics of [^{18}F]FBVM in non-human primates, a new radiotracer for imaging the vesicular acetylcholine transporter in vivo using positron emission tomography

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Age-related neurodegenerative diseases have in common the occurrence of cognitive impairment, a highly incapacitating process that involves the cholinergic neurotransmission system.[1] The vesicular acetylcholine transporter (VAChT) positron emission tomography (PET) tracer [^{18}F]fluoroethoxybenzovesamicol ((-)-[^{18}F]FEOBV) has recently demonstrated its high value to detect alterations of the cholinergic system in Alzheimer's disease, Parkinson's disease and dementia with Lewy body. [2-3]

Herein, we present the development of the new vesamicol derivative tracer (-)-(R,R)-5-[^{18}F]fluorobenzovesamicol ((-)-[^{18}F]FBVM) that we compared to (-)[^{18}F]FEOBV in the same experimental conditions.[4-5] We show that: i) in vitro affinity for the VAChT was 50-fold higher for (-)FBVM (Ki=0.9±0.3 nM) than for (-)FEOBV (Ki=61±2.8 nM); ii) in vivo in rats, a higher signal-to-noise specific brain uptake and a lower binding to plasma proteins and peripheral defluorination were obtained for (-)[^{18}F]FBVM compared to (-)[^{18}F]FEOBV.Our findings demonstrate that (-)[^{18}F]FBVM is a highly promising PET imaging tracer which could be sufficiently sensitive to detect in humans the cholinergic denervation that occurs in brain areas having a low density of VAChT such as the cortex and hippocampus.

We next investigated the brain distribution, kinetics, and selectivity of [^{18}F]FBVM in non-human primates (NHP) compared to (-)-[^{18}F]FEOBV, another radioligand for the VAchT. The in vivo kinetics of [^{18}F]FBVM and higher signal to noise ratio when compared to the (-)-[^{18}F]FEOBV suggest that [^{18}F]FBVM has highly suitable characteristics for probing the vesicular acetylcholine transporter with PET.

All the results will be presented in this communication.

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Poster 12

Design de fluorophores et de photosensibilisateurs pour l'absorption biphotonique

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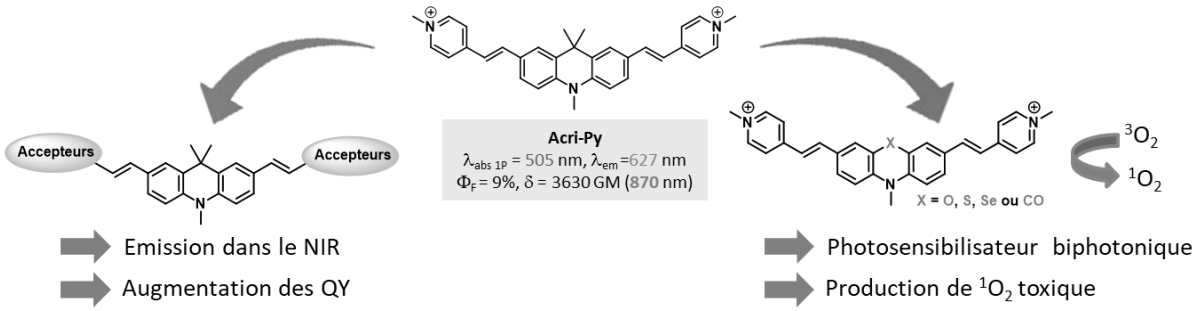
Depuis deux décennies, le développement de molécules fluorescentes toujours plus performantes est devenue un aspect important de la chemo-biologie. En effet, ces fluorophores sont utilisés comme outils de visualisation du vivant *in cellulo* dans de nombreuses applications comme le développement d'outils de diagnostic. C'est dans cet optique qu'ont été développés des fluorophores capables d'absorber simultanément 2 photons de plus basse énergie. Les avantages de l'absorption biphotonique (2PA) sont une absorption dans le proche Infra-Rouge, une limitation des photo-dommages et une meilleure résolution spatiale[1]. Ainsi, le développement de fluorophores optimisées pour le 2PA est en plein essor. Il a été mis en évidence que les structures conjuguées possédant de forts groupements donneurs et accepteurs, c'est-à-dire présentant une forte polarisabilité présentaient des sections efficaces élevées [2]. Cependant, ces structures du type A-π-D à la conjugaison étendue sont souvent de taille importante et peu solubles en milieu aqueux[3-4]. Ainsi, notre équipe a développé une première génération de fluorophores 2PA de petite taille, soluble dans l'eau et présentant des sections efficaces très élevées jusqu'à 3630 GM pour le composé Acri-Py [5]. Le premier objectif de nos recherches est de modifier la structure de l'Acri-Py pour en améliorer les propriétés photophysiques. Ainsi, notre stratégie consiste à modifier les accepteurs tout en gardant le cœur Acridane préalablement optimisé pour la fluorescence. Le second objectif est de modifier chimiquement l'Acri-Py pour obtenir un photosensibilisateur 2PA capable de générer l'oxygène singulet sous excitation biphotonique. Pour ce faire, l'introduction d'atomes lourds (S et Se), connus pour transformer les fluorophores en photosensibilisateur est réalisée.[6]



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Synthesis, modification and photophysical study of luminescent dipyridylmethene boron complexes

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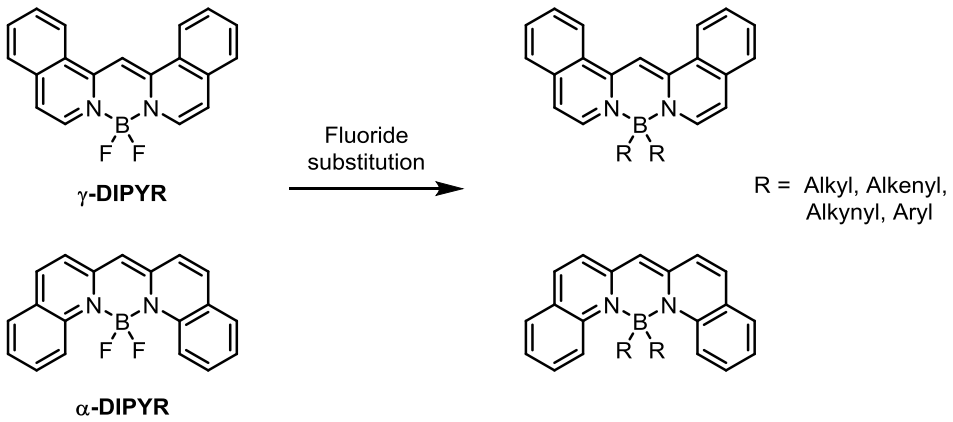
Molecular bioimaging is an important and still growing field of research and the development of new fluorescent scaffolds is a key feature to be able to adapt the fluorophore for a specific application. Among all the organic fluorophores one successful strategy consist of transforming a flexible cyanine type heteroaryl compound into a fluorophore by complexation with a boron atom [1]. The archetypal example is the BODIPY scaffold in which a B^{III} atom is complexed by a dipyrrin ligand. By replacing pyrrole units by pyridines, DIPYR (Dipyridylmethene boron complexes) were synthetized for the first time in 1973 [2] and falsely described as non-fluorescent [3]. In 2017 [4], two quinoline and isoquinoline based structures, the α-DIPYR and the γ-DIPYR, were studied in details showing promising characteristics but very few functionnalization methods have been described so far.
Herein, we describe the replacement of the fluorine on the boron atom and the photophysical properties of those new compounds. No such functionalization has been yet reported.



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Poster 14

Ligand-tailored Divergence of Copper-catalyzed Aerobic Oxidation of Cyclopropanols. Application to the practical synthesis of β-aminoketones and β-enaminones

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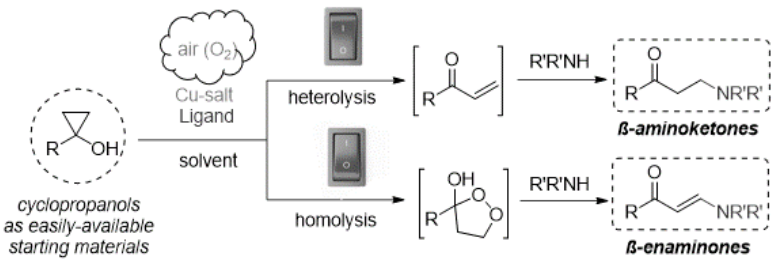
Aerobic ring-opening oxidation of cyclopropanols catalyzed by copper complexes has been systematically investigated, focusing on the effect of nitrogen ligands on product distribution in the oxidation of 1-(2-phenylethyl)cyclopropanol. The nature of the ligand has been found to significantly influence product outcomes, with σ-donor ligands (DABCO, quinuclidine) predominantly yielding vinyl ketone, while π-acceptor ligands (phen, bipy, imidazole) favor the generation of 1,2-dioxolane product. This divergence is attributed to switching the mechanism from heterolytic (via copper homoenolate) to homolytic (via β-keto radical) fragmentation of the cyclopropane C–C bond, with the latter pathway also facilitated by changing the solvent from methanol to acetonitrile. The study offers an adaptable platform for developing cascade transformations, with ring-opening product specificity tuned through ligand and solvent selection, as illustrated by the development of a new practical synthesis of β-aminoketones and enaminones from cyclopropanols. Thus, copper(II) acetate-catalyzed aerobic oxidation of cyclopropanols in the presence of nucleophilic secondary aliphatic amines results in the generation of β-aminoketones in 34–99% yields via aza-Michael reaction of vinyl ketone intermediates. On the other hand, using bipyridine-ligated copper catalysts results in the generation of β-enaminones in 62–77% yields, presumably via the Kornblum-DeLaMare rearrangement of intermediate 1,2-dioxolanes.



- Readily available catalyst, ligand and starting materials
- Green, divergent ring opening (en)amination strategy
- Ligand-tailored mechanistic switch
- 21 examples, yields up to 99%

Poster 15

Synthesis and characterization of radiation-activated, MRI-detectable theranostic prodrugs for cancer treatment

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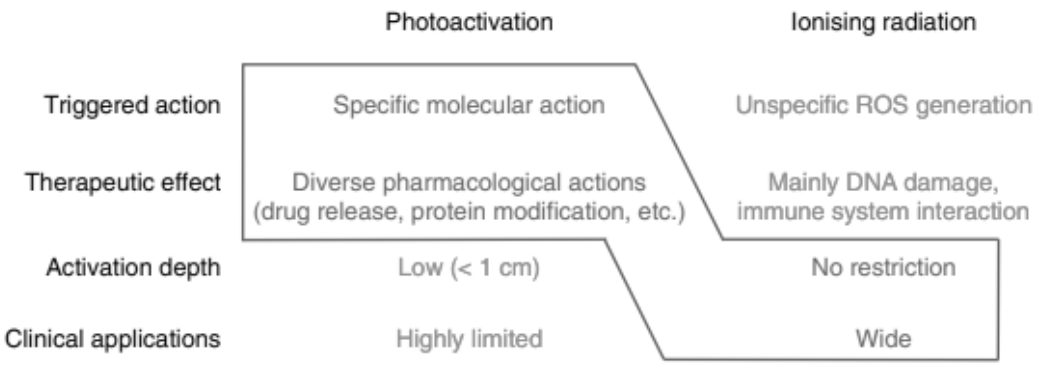
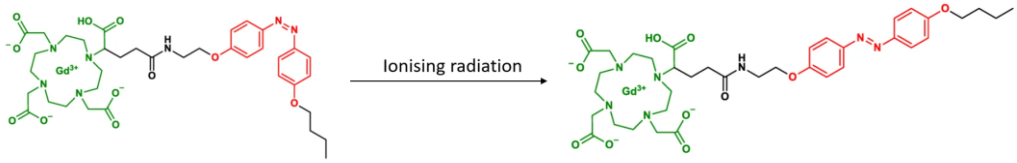
Cancer therapy is limited by the off-target toxicity of current treatments, often induced by the non-specificity of drugs towards tumor environment. To solve this issue, photoactivable molecules were developed but they are limited to shallow activation under the skin. The strategy developed by our team to overcome this difficulty is to use theranostic prodrugs that can be activated by highly-penetrating stimuli such as those used in radiotherapy. The accumulation of the prodrugs in the tumor can be monitored by MRI after intravenous injection, thanks to the presence of a gadolinium chelate. The compounds developed here comprise an azobenzene group that can be switched from *cis* to *trans* configuration upon radiotherapy, activating their cytotoxicity. Therefore, we designed "radioswitches" that can be activated at high spatiotemporal resolution at any depth in biological tissues, able to reach deep-seated tumors and with limited impact on healthy tissues.





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Nanoémulsions de perfluorocarbures, du diagnostic au traitement du SNC

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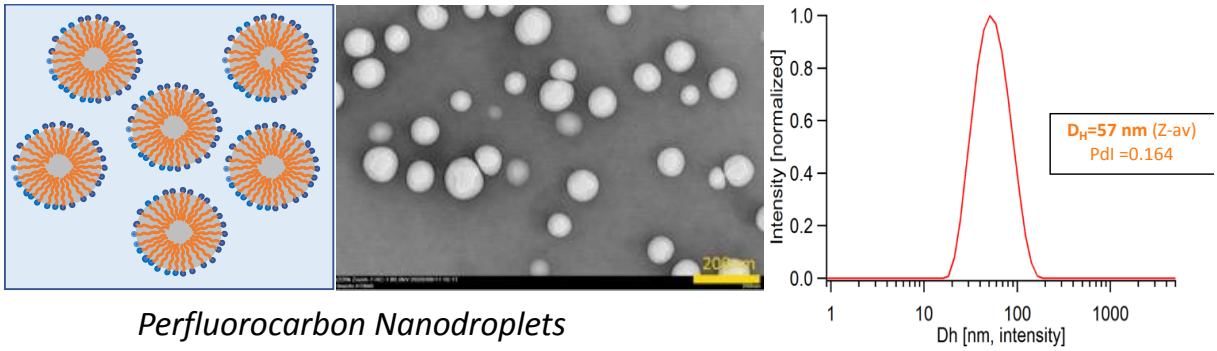
Longtemps utilisés comme agents de contraste en imagerie médicale, les perfluorocarbures (PFC), sous forme de microbulles (MBs) ou de nanogouttes (NanoDroplets) sont de plus en plus appliqués en thérapeutique.[1] Dans ce domaine, notre équipe a mis au point des formulations de PFC, sous forme de nanogouttes stabilisées par des tensioactifs fluorés biocompatibles synthétisés par nos soins.[2] Ces nanoémulsions ont été optimisées en termes de taille, de polydispersité et de charge en principe actif afin de pouvoir transporter un principe actif en concentration optimale vers le système nerveux central (SNC). Une attention particulière a été portée à la taille des nanogouttes (moins de 100 nm pour pouvoir traverser la barrière hémato-encéphalique) ainsi qu'à leur stabilisation sous forme de formulations sèches prêtes à l'emploi par simple addition d'eau.
Cette présentation montrera la synthèse des tensioactifs ainsi que la préparation et caractérisation des formulations de PFC (de la distribution en taille des nanogouttes à l'efficacité d'encapsulation en principe actif). Le potentiel thérapeutique de ces nanogouttes de PFC pour le traitement des maladies du cerveau sera démontré grâce aux derniers résultats obtenus *in vitro* et *in vivo* sur un modèle de Glioblastome.[3]



Perfluorocarbon Nanodroplets

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Poster 17

Synthèse et valorisation de nouveaux composés à activités antimicrobiennes

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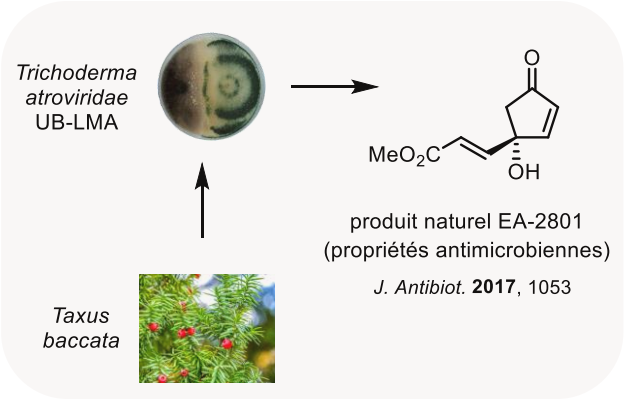
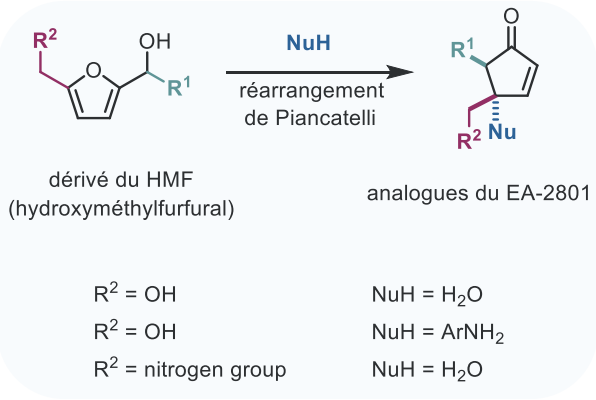
En 2017, dans nos laboratoires, est identifié un nouveau produit naturel EA-2801, isolé à partir d'un extrait de champignon (*Trichoderma atroviridae UB-LMA*) vivant en symbiose avec l'arbre *Taxus Baccata*. Ce nouveau composé s'est révélé avoir des activités antimicrobiennes intéressantes, notamment vis-à-vis des bactéries à Gram-négatif. [1][2] Ces premiers résultats ainsi que la structure relativement simple de ce composé ont encouragé à développer de nouvelles méthodes synthétiques pour former cette cyclopenténone substituée. Des études préliminaires ont permis de montrer que ce motif cible pouvait être obtenu en une seule étape par un réarrangement de Piancatelli à partir de furan-2,5,-dicarbinols non symétriques, catalysé par un acide de Lewis et sous irradiations micro-ondes. [3][4] Cette méthodologie a permis de développer une voie d'accès générale au motif cible cyclopenténone substitué du produit naturel, et en particulier à la synthèse d'analogues azotés à partir de substrats 2-5-furyldicarbinol non-symétriques, fonctionnalisés par des groupements aminométhyle (-CH_2-NR_1R_2) en position C-5, et en utilisant comme matière première biosourcée le hydroxymehylfurfural (HMF). En parallèle de ces travaux synthétiques, l'évaluation des activités antimicrobiennes et cytotoxiques sont réalisées sur l'ensemble des composés synthétisés.





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Click Chemistry *In Situ* and *In Crystals* for drug discovery against *Bunyavirales* : A method to study auto-assembled ligands by viral enzymes

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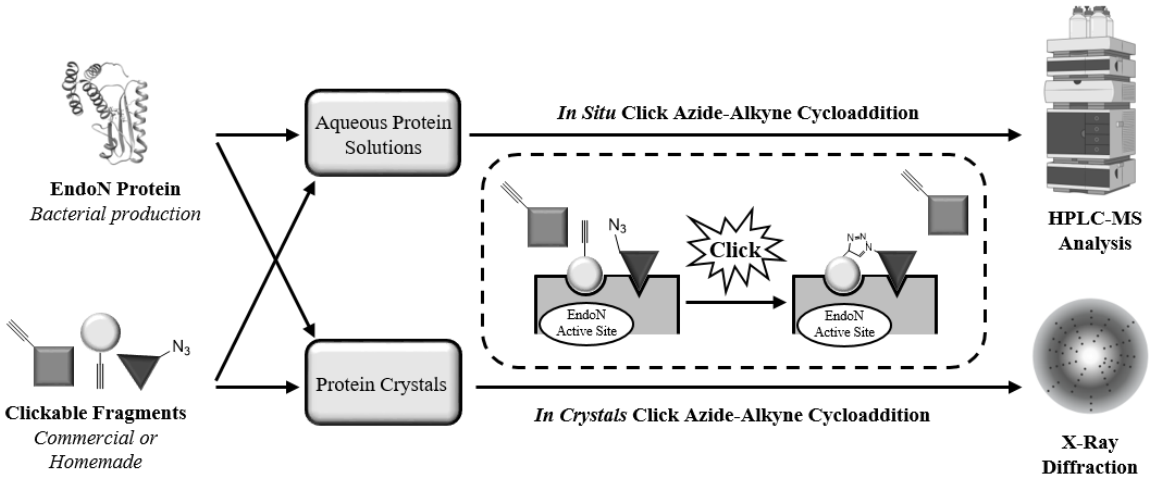
A number of viruses from the *Bunyavirales* order are currently included in WHO's priority list since they represent a public health threat worldwide[1]. The very limited therapeutic options available against these viruses make it urgent to develop effective and specific treatments in view of the seriousness and growing number of infections

The replication machinery of these viruses heavily relies on the Endonuclease activity (EndoN) of the L-protein, responsible for the host RNA cap-snatching *via* Mg^{2+} and/or Mn^{2+}-mediated RNA hydrolysis[2]. Thus, one strategy to design *pan-genus* antivirals against *Bunyavirales* is to develop EndoN inhibitors with specific metal-chelating properties.

Such inhibitors can hopefully be designed thanks to rational Kinetic Target-Guided-Synthesis approaches, where EndoN will assemble its own ligands from a pool of clickable fragments[3]. Here, we use azide- or alkyne-containing fragments to ensure their covalent assembly in aqueous media *via* click azide-alkyne cycloaddition. The EndoN, as a reaction mold, will catalyze the cycloaddition between fragments showing affinity and specificity for the active site, by taking advantage of a metal-anchoring motif and one or more specificity motifs to reach pockets of the active site

This auto-assembly strategy can be applied in aqueous solutions containing the soluble EndoN (« *in situ* »)[4] and enrichment can be monitored and validated by HPLC-MS, after identification with authentic samples. Even better, the same strategy could be applied in protein crystals (« *in crystals* »)[5], where the assembly of fragments in the EndoN active site can be directly identified by X-ray diffraction.



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Poster 19

Development of a sustainable process to increase the bioavailability of xanthophyll-loaded nanoemulsions

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With the current ecological challenges, there is a great societal interest for natural products. It is important to develop alternatives to organic solvents for the extraction of natural products because of their toxicity and environmental concern. Our laboratory has worked on the extraction of curcumin from turmeric and its encapsulation in oil/water (O/W) nanoemulsions for therapeutic purposes, using the "extremulsion" technology (1). This is a new process combining extraction and emulsification in a single step without organic solvents use, which results in nanoemulsions so-called extremulsions. It reduces the environmental impact and is in line with the requirements of green chemistry (2).

This process can be applied to human nutrition to allow food fortification or supplementation of scarce molecules such as carotenoids, and more particularly xanthophylls: lutein and zeaxanthin. Indeed, they possess many health benefits, such as neuroprotective and ophthalmological effects, protection against UV or anti-allergic activity (3). Due to their hydrophobic nature, they make good candidates to be encapsulated in the oily phase of extremulsions in order to increase their supply and bioavailability.

This poster discusses the results of different phases of the project. First, the choice of food sources and the quantification of lutein and zeaxanthin rates using the reference extraction method (Soxhlet in refluxing organic solvents). Second, we screen different oils, which constitute the dispersed phase of the nanoemulsions (O/W), in order to determine the best ones to solubilize our active ingredients. Finally, we show the results of xanthophyll-loaded nanoemulsions, obtained by applying our best “blank-emulsion” conditions to the chosen matrix, *i.e.* broccoli and paprika.

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Synthesis and study of new calix[6]arene-based complexes and their application for molecular recognition

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Calixarenes are macrocyclic polyphenolic compounds that have been extensively studied for several decades and have found numerous applications in various fields of chemistry.[1] Their success can be attributed, in large part, to the numerous synthetic methods developed for their itero[2] - and regioselective modification, both at the small rim and the large rim.[3]

Few synthetic methodologies yielding tris-functionalized C_{3v}-symmetrical calix[6]arenes are reported. In this work, three allyl protecting groups are selectively placed in 1,3,5 alternate positions of calix[6]arenes Removal of the protecting allylic groups gives access to sophisticated calix[6]arenes that can be further modified. The potential of these new C_{3v}-symmetrical molecular platforms is notably exemplified through the development of a new family of calix[6]arene-based N-ligands (Figure 1).

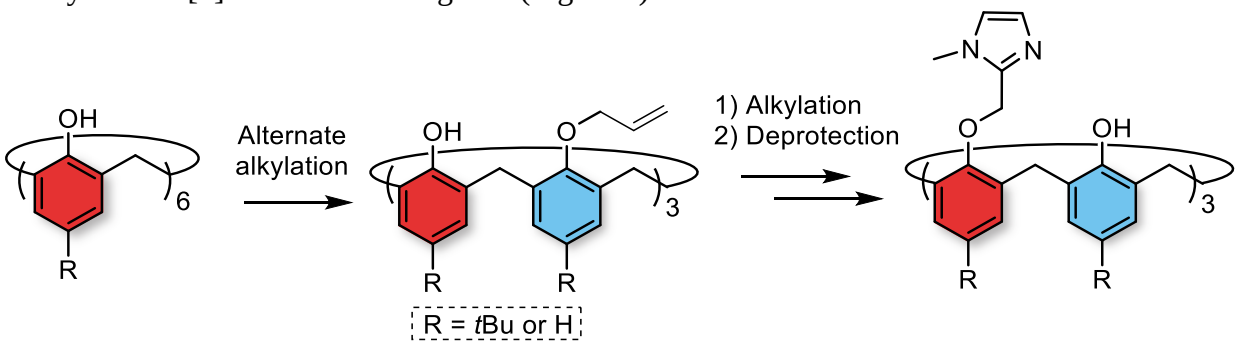

Figure 1. Synthesis of calix[6]arene-based ligands via "alternate alkylation" strategy.

The derived zinc complexes were investigated in host-guest chemistry, and the results were compared with those of previous calixarene-based zinc complexes.[4] Interestingly, the presence of the phenol units makes them suitable to recognize anions, which was rarely observed in previous complexes.[5] Moreover, the presence of hindered tert-butyl groups has a strong influence on the recognition outcome.

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Design and synthesis of original fluorescent probes for use in microscopy on a model organism: *Caenorhabditis elegans*

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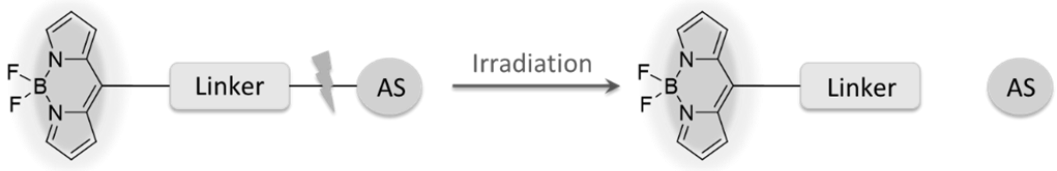
Following an active substance within an organism is a major stake. Indeed, this allows, among other things, to facilitate the discovery of new targets of interest. In order to do this, fluorescence microscopy is a particular well-suited tool.

The aim of this research work is to develop a novel fluorescent labelling technique to follow the fate of a molecule or a microorganism *in vivo*, in the intestine of the nematode *Caenorhabditis elegans* [1]. For this purpose, several fluorescent probes have been designed and synthetized to be coupled to an active substance or a microorganism of interest via a potentially cleavable link. The intent would be for the active substance to be released after an irradiation to a set wavelength.



Schematic depiction of a fluorescent probe

After ingestion, the vector's path can be followed thanks to the nematode's transparency at the bodipy's fluorescence wavelength [2]. Then, after an irradiation at another specific wavelength, the active substance will be released, allowing the study of its fate and impact *in vivo*. This approach will allow the following of the effect of a drug *in vivo* or could be used as an innovative screening process.

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Synthèse de monomères/polymères pour l'extraction/recyclage des ions métalliques des terres rares

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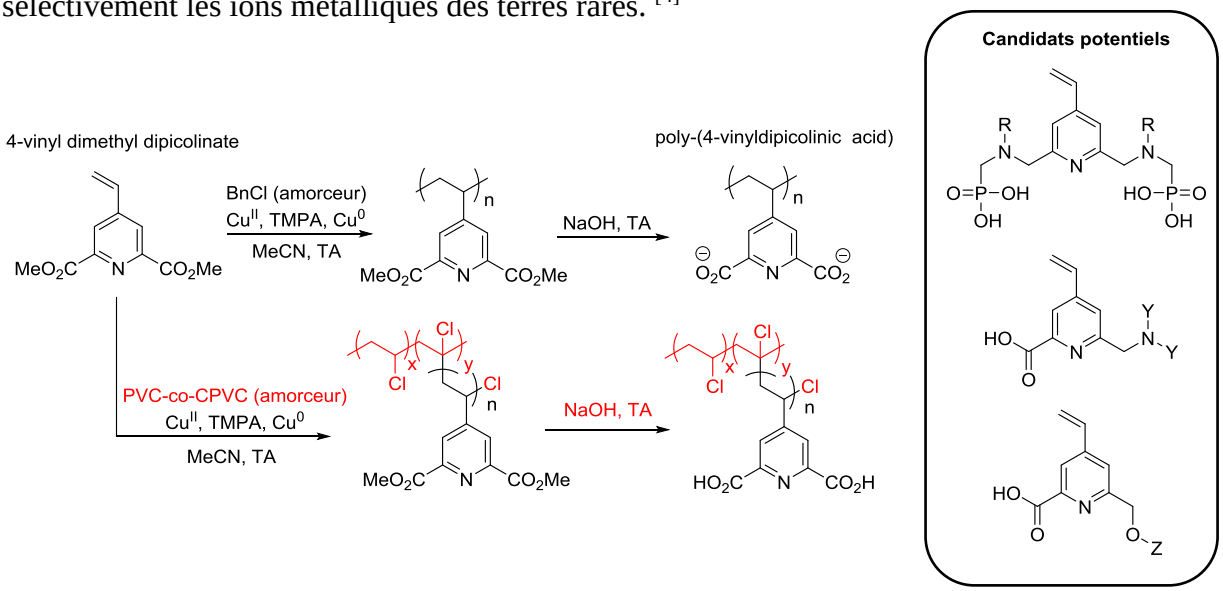
Les terres rares sont un ensemble de métaux constitués des éléments des lanthanides ainsi que de l'Yttrium. Ils sont très convoités pour produire des objets de haute technologie : ordinateurs, téléphones portables, batteries, etc. Plus précisément, l'Europium (Eu), le Dysprosium (Dy) et le Lanthane (La) sont utilisés dans les complexes luminescents permettant d'afficher les couleurs des pixels, alors que le Néodyme (Nd) et Praséodyme (Pr) sont massivement exploités pour construire des aimants du secteur éolien. Le processus d'extraction et de purification des terres rares à partir des minerais correspondant est complexe et coûteux en ressources. Actuellement, l'enrichissement se fait par extraction liquide-liquide, et les usines de productions voient défiler en moyenne 1500 cycles d'extraction pour avoir une pureté correcte en un élément des terres rares [1]. Vu l'exploitation croissante de ces ressources et le monopole de la Chine sur l'exportation de ces dernières, explorer de nouvelles voies d'extraction et de recyclage de ces éléments semble indispensable.

Une alternative intéressante est l'extraction solide-liquide avec des molécules organiques ou des polymères greffés sur surface [2]. Les polymères présentent l'avantage d'avoir un grand nombre d'unité de répétition pouvant complexer les ions métalliques. Il a été montré que la polymérisation de l'acide 4-vinyldipicolinique, monomère complexant l'Uranium et l'Europium, peut être initiée sur des surfaces de poly(chlorure de vinyle) (PVC) et de manière contrôlée par Atom Transfert Radical Polymerization (SI SARA - ATRP) [3]. Notre projet consiste à concevoir de nouveaux monomères de seconde génération permettant de complexer sélectivement les ions métalliques des terres rares. [4]



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Optimisation chimique d'inducteurs de l'interleukine IL-10 à visée thérapeutique

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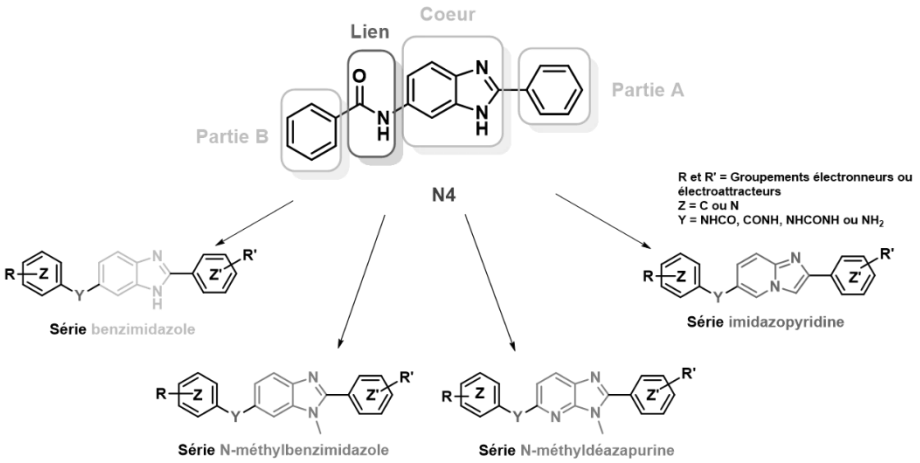
Les maladies inflammatoires auto-immunes touchent 5 à 10% de la population mondiale. Leur traitement repose sur des médicaments immunosuppresseurs ou soulageant les symptômes, qui ralentissent la progression de la maladie mais permettent rarement de la guérir. L'importance de cellules B productrices d'IL-10 a été démontrée dans les maladies auto-immunes, allergiques, infectieuses et malignes[1]. Elle a été largement étudiée dans la sclérose en plaques (SEP)[2]. La différenciation des cellules B productrices d'IL-10 et leur développement pour la thérapie cellulaire ont été limités par l'absence d'un protocole permettant de générer efficacement ces cellules. Pour surmonter cette limitation, un criblage à haut débit a été réalisé pour identifier de petites molécules permettant l'induction de cellules B productrices d'IL-10 presque pures et stables. Ces cellules B ont guéri des souris receveuses de l'encéphalomyélite auto-immune expérimentale (EAE), modèle de SEP, dans les jours qui ont suivi leur administration au pic de la maladie[3]. En parallèle, différents composés ont été identifiés comme inducteurs de l'expression de l'IL-10 dans les cellules B humaines, en particulier N4.

Aux vues des résultats de la POC, une optimisation structurelle a alors été envisagée pour obtenir des analogues brevetables et biologiquement actifs de N4. L'objectif était alors de modifier le squelette central en conservant ou en améliorant l'induction de l'IL-10 dans les cellules B à des fins de thérapie cellulaire visant à réduire les symptômes de la SEP. Des modifications du cœur, des groupements fonctionnels et du lien du composé N4 ont été réalisées pour établir une relation structure-activité.



Une chimiothèque ciblée et variée de 340 composés a été obtenue à l'aide d'un robot de synthèse en parallèle. Dans ce poster, les voies de synthèse et les résultats biologiques seront discutés[4].

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SYNTHESIS AND EVALUATION OF ANTIVIRAL CYCLOPEPTIDES ISOLATED FROM A TROPICAL PLANT

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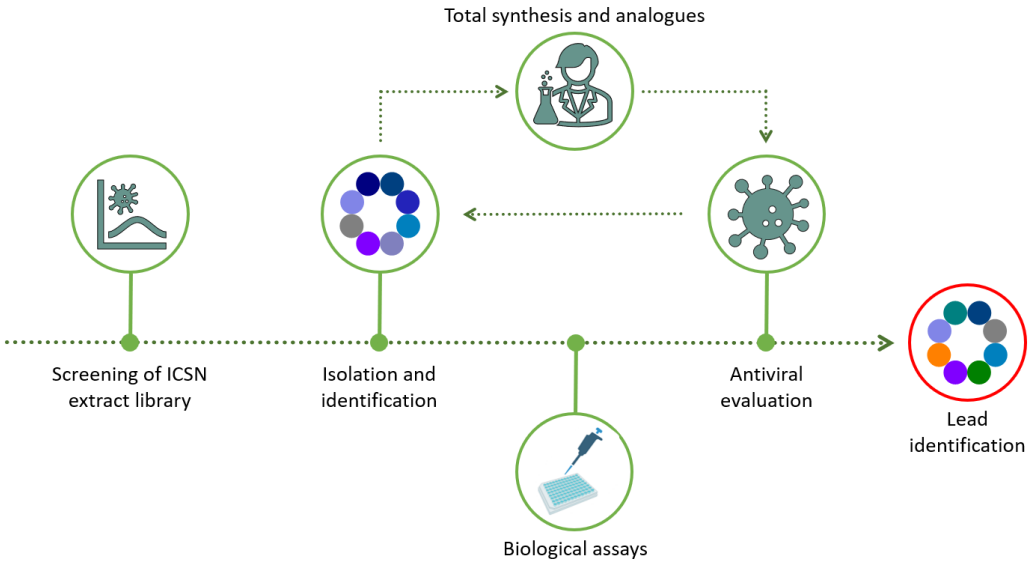
Arboviruses are viruses that are transmitted to humans and other animals through the bites of infected arthropods, such as mosquitoes, ticks, and sandflies. The most well-known viruses from this family are Dengue, Zika, and Chikungunya. These viruses can lead to significant epidemics with the potential for high human death rates[1]. In this context, a screening of 824 extracts of the ICSN extract library on the Zika virus replication inhibition was performed. From plant extract hits, we were able to isolate and identify a series of novel natural cyclopeptides bearing uncommon non-canonical amino acids (nCAA). This peptide family has shown low toxicity to cells and strong antiviral activity against a panel of positive-sense single-stranded RNA viruses such as the Chikungunya, Dengue, Zika, Ross River, and SARS-CoV-2 viruses.

To further develop antiviral compounds, we have designed a synthetic strategy using solid phase peptide synthesis (SPPS). This method was reliable enough to incorporate nCAAs to access not only the isolated natural cyclopeptides but also a library of analogues[2,3]. The natural cyclopeptides synthesised allowed us to confirm the great potential of this series of compounds but also the target involved and the associated mechanism of action. These experiments aimed to observe the impact of peptides on target degradation as well as on RNA transcription or replication in arboviruses.



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Poster 25

Design and biological evaluation of antiviral cyclopeptides

Lagardère, P.[1]; Grisel, C.[1]; Apel, C.[1]; Litaudon, M.[1]; Girard, J.[2]; El Kalamouni, C.[2]; Roussi, F.[1]; Desrat, S.[1]

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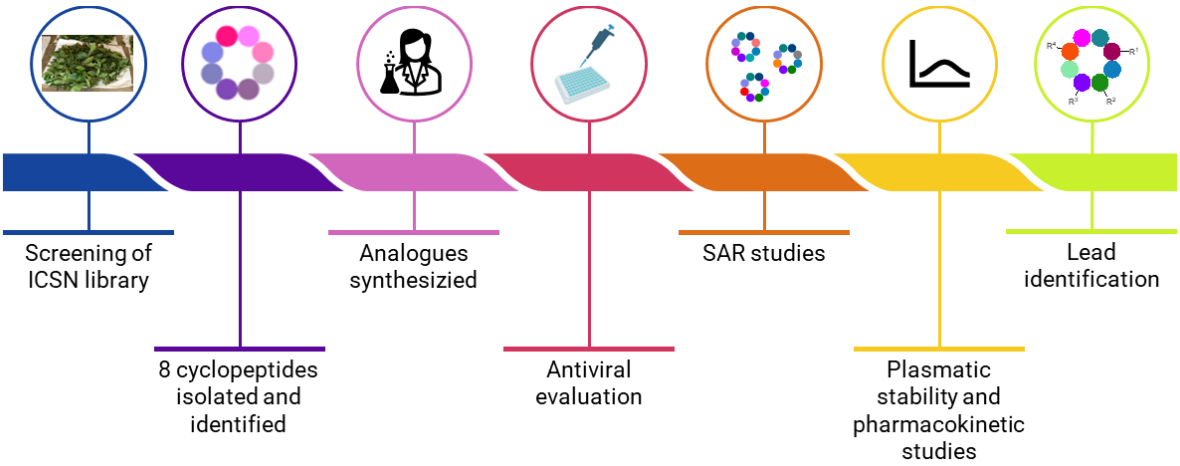
Arboviruses can be transmitted to humans through the bite of infected arthropods such as mosquitoes, ticks, or sandflies. This family of viruses mainly includes dengue fever (DENV), Chikungunya (CHIKV) and Zika (ZIKV). They represent a major scourge for tropical and subtropical populations[1] and pose a threat to the European Region, with the appearance of several indigenous cases in 2023[2]. After a screening of 824 plant extracts from ICSN extract library, our research team identified a family of 8 antiviral cyclopeptides with activity ranging from micromolar to nanomolar. Among them, a hit was identified and showed broad-spectrum antiviral activity against DENV, CHIKV, ZIKV, SARS-CoV-2 and Ross River (RRV) viruses.

With the aim of developing new antiviral compounds, we design a series of synthetic analogues. Several structural modifications on the R^1, R^2, R^3 and R^4 side chains were performed and the insertion of non-canonical amino acids was considered. We synthesized more than thirty analogues which were evaluated *in vitro* against ZIKV on VERO-E6 cell lines, 48 h post-infection. Preliminary ADME experiments together with the structure-activity relationships study allow us to envisage the synthesis of new analogues in order to obtain a lead compound.



[1] Pan American Health Organization. Epidemiological Update Dengue, Chikungunya and Zika, 2023.
[2] Dengue Global situation. https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON498 (accessed 2024-02-27).

FRET-Sensing of Multivalent Protein Binding at the Interface of Biomimetic Microparticles Functionalized with Fluorescent Glycolipids

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Cell adhesion is a fundamental phenomenon involved in stimulating signals that regulates cell differentiation, cell cycle, cell migration, and cell survival. In immunity processes, such as phagocytosis, it allows the detection of pathogens and their internalization by immune cells. Adhesion sites are triggered by specific ligand-receptor interactions inducing the clustering of both partners at the contact point. Investigating cell adhesion using microscopy techniques requires targeted fluorescent particles with a signal sensitive to the clustering of receptors and ligands at the interface. We have previously shown that glycosylated particles based on oil in water (O/W) lipid droplets are simple cell or bacterial mimics that are specifically recognized by lectin membrane receptors and internalized by macrophages.[1] To further study cell adhesion and the role of lectin receptors in phagocytosis, we have developed glycosylated droplets functionalized with a FRET pair of lipids on their surface to study receptor binding using nano-scale energy transfer. These lipids are targeted towards lectins or biotin membrane receptors and the resulting particles can be specifically identified and internalized by primary macrophages. We evidence the possibility to sense the binding of a multivalent lectin, concanavalin A, in solution by monitoring the energy transfer on the surface of the particles by fluorescence lifetime imaging (FLIM). We anticipate that these liquid particle-based sensors, able to report via FRET on the movement of ligands on their interface upon protein binding, will provide a useful tool to study receptor binding and cooperation during adhesion processes such as phagocytosis.

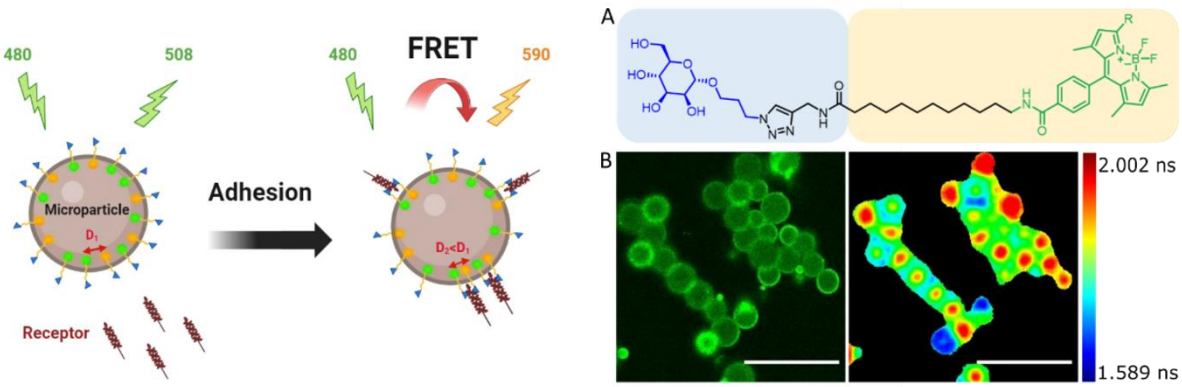

Figure. (left): General principle of the detection of multivalent protein binding on microparticles using FRET. (right): (A) General structure of the glycolipids. (B) Fluorescence lifetime imaging of the droplets in presence of conA.

(1) Dumat, B.; Montel, L.; Pinon, L. L.; Matton, P.; Cattiaux, L.; Fattaccioli, J.; Mallet, J.-M. M. Mannose-Coated Fluorescent Lipid Microparticles for Specific Cellular Targeting and Internalization via Glycoreceptor-Induced Phagocytosis. *ACS Appl. Bio Mater.* **2019**, *2* (11), 5118–5126.
(2) Michelis S, Pompili C, Niedergang F, Fattaccioli J, Dumat B,* Mallet JM*: FRET-sensing of multivalent protein binding at the interface of targeted biomimetic microparticles functionalized with tunable fluorescent lipids. *ChemRxiv* 2023, doi: 10.26434/chemrxiv-2023-7cfwq-v2.

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