5èmes Journées Scientifiques du GDR ChemBio à Nantes

5-6 Juin 2025

Amphithéâtre Virginie FERRE, Faculté de Pharmacie de Nantes Université,
9 rue Bias, 44000 NANTES

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Jeudi		
9h-9h30	accueil	
9h30-9h50	présentation (C. Biot & S. Gouin)	
9h50-10h30	CI-1	**M. Mével**
10h30-11h	pause	
11h-12h	CO-1	Spyridon Katsakos
	CO-2	Ivan Jabin
Julie Pineau	CO-3	Timothé Antoine-Brunet
Ewen Bodio	CO-4	Saurav Yadav
12h-12h20	CF-1	Aurélien Pasturel
	CF-2	Mélyne Baudin-Marie
Julie Pineau	CF-3	Héloïse Delépée
Ewen Bodio	CF-4	Aurore Padox
12h20-14h	repas-posters	
14h-14h40	CI-2	**R. Dréan**
14h40-15h40	CO-5	Pierre-Yves Renard
	CO-6	Arnaud Chevalier
Cathy Charlier	CO-7	Arnaud Lehner
Cyrille Grandjean	CO-8	Emeline Richard-Millot
15h40-16h	CF-5	Inès Zerguine
	CF-6	Margaux Boutin
Cathy Charlier	CF-7	Maxime Henoc
Cyrille Grandjean	CF-8	E. Guca (MedChemExpress)
16h-16h30	Pause	
16h30-16h50	CD-1	M. Hinnebo & C. Biot
16h50-17h30	CI-3	**Zygophone**
17h30-19h	Table ronde	
Animation : Boris Vauzeilles		

Vendredi		
9h-9h40	CI-4	**A. Trézébré**
Christophe Biot		
9h40-10h40	CO-9	Mike Maillasson
David Deniaud	CO-10	Mélanie Laquembe
Monique	CO-11	Axia Marlin
Mathé-Allainmat	CO-12	Gatin Fraudet
10h40-11h10	Pause	
11h10-12h15	CO-13	Candice Botuha
Latifa Rbah-Vidal	CO-14	Roba Moumné
Marc-Antoine Bazin	CO-15	Mathieu Scalabrini
	CD-2	E. Defrancq & N. Scaramozzino
12h15-12h25	CF-9	Anthony Augé
Latifa Rbah-Vidal	CF-10	Sartorius
Marc-Antoine Bazin		
12h25-14h	Repas-Posters	
14h-14h40	CI-5	**A. Laurent**
14h40-15h40	CO-16	Lucas De Biasi
	CO-17	Paulin Rollando
Océane Baffroy	CO-18	Victor Goncalvez
Sébastien Gouin	CO-19	Meven Jobic
15h40-16h	Conclusions	

CI	Conférence Invitée	*40 min (questions comprises)*
CD/CO	Communication Duo / Communication Ora	*15 min (questions comprises)*
CF	Communication Flash	*5 min (pas de question mais possibilité d'associer un poster)*

Jeudi 5 Juin

Accueil à partir de 9h00

9h30 - 9H50 : Présentation des journées (Christophe Biot et Sébastien Gouin)

Session 1 ; Animateurs : Ewen Bodio et Julie Pineau
9h50 - 10h30 : **CI-1** Mathieu Mével (TaRGeT, Nantes)
Bioconjugated adeno-associated virus vectors: bridging organic chemistry and vectorology for enhanced gene therapy

10h30-11h00 : Pause café

11h00-11h15 : **CO-1** Spyridon Katsakos (Université de Poitiers)
Chemistry with Cells: A new innovative approach for manipulating cell-cell interactions
11h15-11h30 : **CO-2** Ivan Jabin (Université libre de Bruxelles)
Des nanomatériaux ultra-stables pour le développement de tests de diagnostic rapide
11h30-11H45 : **CO-3** Timothé Antoine-Brunet (Université Grenoble Alpes)
Stratégie antitumorale ciblée basée sur la surexpression du transporteur GLUT1 et l'utilisation de pro-substrats du glycométabolisme cellulaire
11H45-12H00 : **CO-4** Saurav Yadav (Université de Montpellier)
Synthesis and biological evaluation of new cyclic dinucleotide analogues having potential anti-bacterial activity
12H00-12H20 :
CF-1 Aurélien Pasturel (Idylle labs)
Idylle: Valoriser les innovations des chercheurs pour les chercheurs
CF-2 Mélyne Baudin-Marie (Nantes Université)
Multivalent Sialic Acid Derivatives as Potent Sialidases Inhibitors and Therapeutic Perspective against Intestinal Inflammation
CF-3 Héloïse Delépée (Nantes Université)
Bioconjugation of the capsid of adeno-associated viruses for osteoarthritis treatment by gene therapy
CF-4 Aurore Padox (CEA Saclay)
Synthèse de Bioconjugués Anticorps-Médicaments par chimie en flux continu

12h20-14h00 Pause déjeuner / Session Posters

Session 2 ; Animateurs : Cathy Charlier et Cyrille Grandjean
14h00-14h40 : CI-2 Raphaëlle Dréan (Affilogic Nantes)
Nanofitins®: how we can improve therapeutics with small affinity ligands as targeting vehicles
14h40-14h55 : **CO-5** Pierre-Yves Renard (Université de Rouen)
Access to Clickable glycerophospholipids mimics with untouched fatty acyl chains and polar head groups
14h55-15h10 : **CO-6** Arnaud Chevalier (ICSN)
Use of fluorogenic probes to visualize mitochondrial reductases in living cells: toward shuttling of active compounds
15h10-15h25 : **CO-7** Arnaud Lehner (Université de Rouen)

Glycans engineering for studying plant cell wall biosynthesis and functions
15h25-15h40 : **CO-8** Emeline Richard-Millot (CERMAV)
Biotechnological production of sialylated solid lipid microparticles as Influenza virus inhibitors
15h40-16h00 :
CF-5 Inès Zerguine (CEA Saclay)
Bioorthogonal Fluorogenic release of isocyanates in cells
CF-6 Margaux Boutin (Nantes Université)
Development of functionalized amidrazones as an original azaheterocycle for use in DEL Chemistry
CF-7 Maxime Henoc (Nantes Université)
Synthesis, modification and photophysical study of luminescent dipyridylmethene boron complexes
CF-8 Ewelina Guca (MedChemExpress, sponsor)

16h00-16h30 : Pause café

16h30-16h50: **CD-1** Marie Hinnebo et Christophe Biot (Université de Lille)
Collaborations Arts & Sciences : Croiser les regards, enrichir les savoirs
16h50 – 17h30 : **CI-3** Noémie Moal et Benjamin Dogona
Le zygophone- Dispositif musical et interactif - concerts botaniques
17h30-18h45 Table ronde animée par Boris Vauzeilles : La chémobiologie dans l'industrie (intervenants : François Autelitano-Evotec Toulouse ; Marie-Hélène Larraufie- Almirall Barcelone…)

Vendredi 6 Juin

Animateur : Christophe Biot
9h00 – 9h40 : **CI-4** Anthony Treizebré (Université de Lille 1)
Organes sur Puce : Une Révolution Technologique au Service de la Recherche Clinique

Session 3 ; Animateurs : David Deniaud et Monique Mathé-Allainmat
9h40-9h55 : **CO-9** Mike Maillasson (Nantes Université)
Generative Autoencoder-Driven Molecular Design for Virtual Screening and SAR Optimization
9h55-10H10 : **CO-10** Mélanie Laquembe (CEA Saclay)
Click-and-Release Formation of Urea Bonds in Living Cells Enabled by Micelle Nanoreactors
10h10-10h25 : **CO-11** Axia Marlin (ChimieparisTech)
Découverte des voies inhibitrices de croissance associées aux complexes de gallium-sidéromycines dans S. aureus.
10h25-10h40 : **CO-12** Gatin Fraudet (Université de Berlin)
Innovative Flurorophore Design for Spectroscopic high-resolution Techniques

10h40-11h10 : Pause café

Session 4 ; Animateurs : Latifa Rbah-vidal et Marc Antoine-Bazin
11h10-11h25 : **CO-13** Candice Botuha (Sorbonne Université)

Dérivés du Déférasirox comme agents duaux ciblant les kallikréines et la surcharge en fer dans les maladies neurodégénératives
11h25-11h40 : **CO-14** Roba Moumné (Sorbonne Université)
Dynamic Combinatorial Libraries of CycloPeptides For the Inhibition of Protein-Protein Interactions
11h40-11h55 : **CO-15** Mathieu Scalabrini (Nantes Université)
Electroclick-Driven Carbohydrate Vectorization: A Promising Glycocalyx Editing Strategy
11h55-12h15 : **CD-2** Eric Defrancq et Natale Scaramozzino (Université de Grenoble)
Chémobiologie des ADN G-Quadruplex : de la conception de l'outil chimique jusqu'à l'immunofluorescence sur cellules.
12H15-12H25 :
CF9 Anthony Augé (Université de Strasbourg)
New TURN-ON probes for the detection of bacteria in body fluids
CF10 Sartorius (Sponsor)

12h25-14h00 Pause déjeuner / Session Posters

Session 5 ; Animateurs : Océane Baffroy et Sébastien Gouin

14h00 – 14h40 : **CI-5** Adèle Laurent (Nantes Université)
14h40-14h55 : **CO-16** Lucas De Biasi (Nantes Université)
Development of a novel class of azaheterocyclic ligands to promote diversity in bioinorganic chemistry
14h55-15h10 : **CO-17** Paulin Rollando (Université Paris-Saclay)
Synthetic mycolates derivatives to decipher protein mycoloylation, a unique post-translational modification in bacteria
15h10-15h25 : **CO-18** Victor Goncalvez (Université de Bourgogne)
Chimie click supramoléculaire : un outil pour la préparation de radioimmunoconjugués
15h25-15h40 : **CO-19** Meven Jobic (Université Grenoble Alpes)
Fluorogenic photocatalyzed proximity labelling with visible light to map the interactome in living cells

15h40-16h00 Remise des prix et Conclusion

Conférences

Bioconjugated adeno-associated virus vectors: bridging organic chemistry and vectorology for enhanced gene therapy.

Mathieu Mével[a*], Mohammed Bouzelha[a], Dimitri Alvarez-Dorta[c], Karine Pavageau[a], Sarah Renault[a], Anthony Mellet[a], Audrey Bourdon[a], Mickaël Guilbaud[a], Therese Cronin[a], Caroline Le Guiner[a], Sébastien G. Gouin[b], Oumeya Adjali[a], David Deniaud[b].

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b. Nantes Université, CEISAM, CNRS UMR6230, Nantes, France.
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Résumé :

For our gene therapy projects, we employed innovative chemical bioconjugation techniques to enhance the efficiency of recombinant Adeno-Associated Virus (rAAV) vectors, termed BioAAV. This was achieved by selectively modifying lysine or tyrosine residues on rAAV capsids with ligands [1].

rAAV-based gene therapy is the result of decades of biological and clinical research aimed at treating diseases such as Duchenne muscular dystrophy, Alzheimer, and retinitis pigmentosa. However, overcoming key challenges - such as broad tissue distribution, high injected doses, and immunological complications - remains crucial to fully unlocking the potential of these vectors. Integrating chemical strategies with vectorology offers a promising approach to addressing these limitations. In our studies, we leveraged covalent coupling reactions, including the nucleophilic addition of lysine amino groups, the aromatic electrophilic substitution, and the electrochemical modification of tyrosine phenol groups using isothiocyanate, diazonium salt, or N-methylluminol ligands, respectively [2-3].

Following rigorous validation of the chemical modifications through a panel of analytical assays, we evaluated the *in vivo* efficacy of these BioAAV vectors, each carrying an enhanced Green Fluorescent Protein (eGFP) reporter gene expression cassette, in the retina and brain of rodent and non-human primate models. Our findings revealed that BioAAV2 significantly improved vector transduction efficiency and gene expression following both subretinal and intrastriatal injections. In rat and NHP retina, eGFP expression levels were an order of magnitude higher with BioAAV2 compared to unmodified rAAV2. In the mouse brain, BioAAV2 resulted in a broader eGFP expression area than unmodified rAAVrh10.

Overall, our study demonstrates that lysine and tyrosine bioconjugation on rAAV vectors represents a valuable strategy for enhancing protein expression in targeted tissues, complementing genetic engineering approaches. This innovative method holds significant potential for advancing gene therapy interventions for conditions such as glaucoma, optic neuropathies, and neurodegenerative disorders.

1. Mével, M. *et al*. *Chem. Sci.* **2020**, *11*, 1122−1131. DOI: 10.1039.C9SC04189C.
2. Depienne, S. et al. *Nat. Com.* **2023**, *14*, 5122-5131. DOI: 10.1038/s41467-023-40534-0.
3. Leray, A. et al. Biomed Pharmacother. 2024, 171, 116148-116158. DOI: 10.1016/j.biopha.2024.116148.

Keywords: Gene therapy, Adeno-associated virus, Bioconjugation

CI-2

Nanofitins®: how we can improve therapeutics with small affinity ligands as targeting vehicles

Dréan Raphaelle[a*], Sébastien Viollet[a], Simon Huet[a] and Mathieu Cinier[a]

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Résumé :

Small molecules remain a cornerstone of drug development, representing a major share of the pharmaceutical pipeline. However, their attrition rate remains higher than that observed for biologics, often due to challenges such as limited selectivity, which can lead to off-target effects and safety concerns, or issues with bioavailability[1]. To address these challenges, an emerging strategy is to harness the versatility of small molecules while incorporating the selectivity of biologics, thereby enhancing both efficacy and safety. This approach is particularly evident in the field of antibody-drug conjugates (ADCs), where antibodies serve as precise delivery vehicles for highly toxic payloads. More broadly, drug conjugates leverage targeting moieties to enable active accumulation in the brain or prolonged retention in the bloodstream, ultimately improving therapeutic outcomes.

At Affilogic, we leverage the intrinsic stability and customizability of Nanofitin® alternative scaffold technology to engineer binding domains with high selectivity for a target of interest while ensuring ease of conjugation with cargo molecules[2]. Nanofitins® are designed with a fully in vitro selection system, allowing fine-tuned specificity and affinity across a wide range of targets, including circulating and membrane proteins, cells, and viruses. Their exceptional resistance to high temperatures (above 80 °C) and extreme pH (1–13) makes them compatible with a broad range of chemical reactions. Moreover, Nanofitins are naturally free of cysteine, allowing for regioselective coupling through the introduction of a unique cysteine residue. The polarized structure of the Nanofitin scaffold, with its variable domain and terminal ends positioned on opposite faces, enables the anchoring of a cargo at either extremity without impairing intrinsic binding potential. This design also facilitates their assembly into multispecific molecules to further enhance pharmacological properties when needed. These unique features make Nanofitins® a powerful tool for improving existing therapeutics.

In this presentation, I will introduce the Nanofitin technology and highlight its potential for cargo vectorization, with proof-of-concept (PoC) cases in therapeutic areas such as CNS disorders and oncology.

1. Smietana, K., Siatkowski, M. & Møller, M. Trends in clinical success rates. *Nat Rev Drug Discov* **15**, 379–380 (2016). https://doi.org/10.1038/nrd.2016.85

2. Michot N, Guyochin A, Cinier M, Savignard C, Kitten O, Pascual MH, Pouzieux S, Ozoux ML, Verdier P, Vicat P, Dumas J. Albumin binding Nanofitins, a new scaffold to extend half-life of biologics - a case study with exenatide peptide. Peptides. 2022 Jun;152:170760. doi: 10.1016/j.peptides.2022.170760. Epub 2022 Feb 9. PMID: 35150805.

Keywords: affinity ligand proteins; therapeutic vectorization; Nanofitin

CI-3

Le Zygophone - Dispositif musical et interactif - concerts botaniques

Noémie Moal et Benjamin Dogona[a*]

a. Collectif L'Antithèse

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Résumé :

Le Zygophone est un dispositif floral musical, une jardinerie électronique pour musiciens en herbe. Sous la forme d'une pergola sonore, c'est le contact entre le musicien et la plante qui génère la note. En botaniste expérimental, l'interprète dissèque ce qu'il entend et sculpte les harmonies à l'aide d'effets intégrés à l'instrument. La pratique du Zygophone se fait en duo, face à face, de façon « zygomorphe », du terme botanique désignant les végétaux qui poussent en symétrie bilatérale.

A l'origine de ce projet, il y avait la volonté de réaliser un objet sonore poétique, qui puisse s'intégrer à divers environnements tout en étant vecteur de rencontres. Nous avons voulu faire ce qu'on aime, bidouiller, créer, faire sonner, sans autre moteur que le plaisir, et puis partager ce qui voudra bien sortir de ce labo. Après deux ans de développement, nous avons un dispositif stable, à haut potentiel artistique et poétique. Nous voilà devenus inventeurs d'un objet hybride qui associe musique électronique et organismes vivants dont il faut prendre soin au quotidien. Sa pratique nous fait nous questionner sur bien des sujets, de la botanique au digital, de la genèse du son à notre place dans la nature, et sur la place de la nature dans un monde peuplé d'humains. Symbiose ou antibiose ? A présent, nous sortons du laboratoire. Il est temps de pousser au grand air, la lumière y est plus directe et le CO^2 en abondance. On a envie de faire danser ou penser sur nos créations musicales et de partager les indéniables bienfaits d'utiliser la plante comme média sonore. On ne sait pas de manière empirique à quoi ça tient, le côté aléatoire, vivant, esthétique peut-être… En tout cas, ça fait un bien fou.

CI-4

Organes sur Puce : Une Révolution Technologique au Service de la Recherche Clinique

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Résumé :

Les organes sur puce représentent une avancée technologique majeure dans le domaine de la recherche clinique. Ces dispositifs microfluidiques, qui reproduisent les structures et les fonctions des tissus humains, permettent de simuler avec précision le comportement des organes in vitro. En intégrant des cellules vivantes, ils offrent une alternative prometteuse aux modèles animaux et aux cultures cellulaires traditionnelles. L'apport de la chimobiologie renforce encore davantage leur potentiel. En utilisant des sondes chimiques spécifiques et des molécules bioactives, la chimobiologie permet de suivre en temps réel les mécanismes biologiques, tels que la signalisation cellulaire, les interactions protéiques ou les réponses métaboliques. Cela ouvre la voie à une exploration fine des processus pathologiques complexes, tout en facilitant le criblage de nouveaux médicaments. Ces systèmes permettent ainsi d'étudier les mécanismes biologiques, de tester l'efficacité et la toxicité des traitements, et de développer des thérapies personnalisées dans des environnements biomimétiques. Bien que des défis subsistent, comme la standardisation et l'intégration dans les processus réglementaires, ces technologies promettent de transformer les pratiques de recherche clinique en favorisant une médecine plus éthique, précise et innovante.

CI-5

Turn on light on multiscaling simulation of ligand-protein biological system

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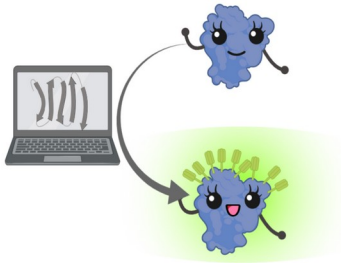
Résumé :

Ligand-protein interactions domain is extremely vast and is an ideal game for computational chemists. Indeed, independentaly of the applications a large set of methods are available going from low cost quantum mechanic methods to robust and accurate molecular mechanic approaches to deal with biological systems. In this talk, I will present results targetting various fields of chemobiology aligned with computational methods that are able to deal with the different scientific questions. Starting from photo(pharmaco)biology and going to the identification of specific biomarkers and protein-protein inhibitors, the goal is to travel accross a multi-scaling computational representation of the different system of interest. Such work will demonstrate the crucial interplay between computational chemists and biologists.



1. Tripathi, N.; Danger, R.; Chesneau, M.; Brouard, S.; Laurent, A.D. *J. Mol. Graph. Model.* **2022**, *114*, 108167. DOI:10.1016/j.jmgm.2022.108167.
2. Asad, M.; Laurent A. D. *Phys. Chem. Chem. Phys.* **2022**, *24*, 3816-3825. DOI:10.1039/D1CP04681K
3. Tripathi, N.; Leherte, L. ; Vercauteren, D.V.; Laurent A.D. *J. Comput. Aided Mol. Des.*, **2021**, *35*, 337-353. DOI: 10.1007/s10822-020-00369-z

Keywords: Molecular modeling; Docking; biomarkers; Photobiology

Communications Duo

CD-1

Collaborations Arts & Sciences : Croiser les regards, enrichir les savoirs

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Résumé :

Les collaborations entre arts et sciences ouvrent de nouvelles perspectives sur la recherche et la création. En mêlant approches scientifiques et pratiques artistiques, ces projets permettent d'explorer des concepts complexes sous un angle sensible et accessible, favorisant ainsi une nouvelle forme de médiation et de transmission des savoirs.
Dans cette dynamique, la notion d'art total prend tout son sens.[1] Héritée des avant-gardes, elle désigne une approche où différentes disciplines s'entrelacent pour donner naissance à des œuvres hybrides, intégrant autant les innovations technologiques que les expérimentations esthétiques. L'aboutissement entre chémobiologie et arts s'est entre autre concrétisé par une publication majeure.[2] Aux côtés de l'artiste Pierre Pauze, xSublimatio est une plateforme interactive où les molécules deviennent des œuvres d'art numériques sur la blockchain. En intégrant des outils comme AlphaFold et l'intelligence artificielle, ce projet associe rigueur scientifique et esthétique, tout en explorant les concepts de NFT et de science décentralisée. Proposant également une dimension ludique, il transforme l'interaction avec les données scientifiques en un jeu stratégique autour de la création et de l'échange de molécules. Sa publication dans un journal de l'Académie des Sciences confère à cette démarche une reconnaissance au-delà des critères traditionnels, affirmant son rôle pionnier à l'interface entre art et science.
Cette initiative illustre la richesse des interactions entre chercheurs et artistes, où la création artistique devient un vecteur de compréhension des phénomènes scientifiques et une porte d'entrée vers l'expérimentation et l'innovation. À travers cette conférence, nous partagerons des expériences concrètes et ouvrirons le débat sur les enjeux, méthodes et perspectives des collaborations entre arts et sciences.

Quels sont les leviers pour renforcer ces échanges interdisciplinaires ?
Comment l'art total prend son sens à l'heure actuelle dans les arts et sciences ?
Comment faire dialoguer efficacement la rigueur scientifique et la subjectivité artistique ?
Quelle place accorder aux images et aux dispositifs immersifs dans ces collaborations ?

Autant de questions qui guideront notre réflexion et inviteront à repenser ensemble les synergies possibles entre ces deux mondes.

1. Trahndorff Carl Friedrich Eusebius, Aesthetik oder Lehre van Westanschauung und Kunst, Aix-la-Chapelle, Mayersche Buchhandlung, 1827.
2. Gouspillou, N. et *al* C R Chim. 2025 (in press)

Keywords: chémobioogie ; arts ; sciences ; dialogue ; art total ; Gesamtkunstwerk

CD-2

Chémobiologie des ADN G-Quadruplex : de la conception de l'outil chimique jusqu'à l'immunofluorescence sur cellules.

Jérome Dejeu,[4] Dennis Gomez,[3] Natale Scaramozzino,[2*] Eric Defrancq[1*]

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3 Institut de Pharmacologie et Biologie Structurale (IPBS), CNRS UMR 5089, Université Toulouse III, Toulouse, France
4 Université Marie et Louis Pasteur, SUPMICROTECH, CNRS, institut FEMTO-ST, F-25000 Besançon, France

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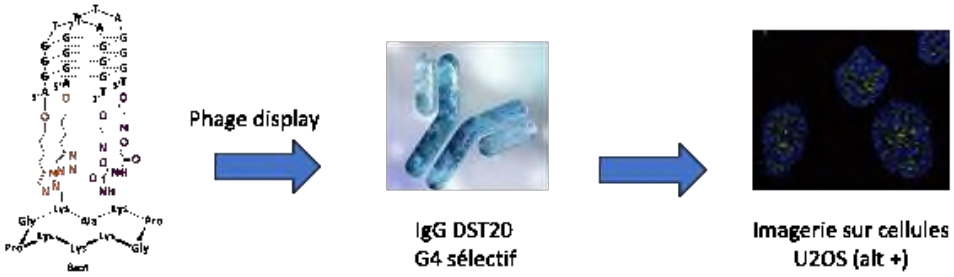
Résumé

Depuis plus de 20 ans, l'existence de structures plus élaborées d'acides nucléiques et leur pertinence biologique ont été démontrées. Parmi celles-ci, on trouve notamment des structures tétramériques telles que les G-quadruplexes (G4) formés avec des acides nucléiques riche en guanines suite à l'association, via des liaisons hydrogènes de type Hoogsteen, de tétrades de guanines et leur empilement. Ces motifs G4 possèdent également des bases non-appariées reliant les différentes guanines des tétrades et forment ainsi des boucles.

Pour étudier *in vitro* et *in vivo* ces ADN G4, il existe un certain nombre d'outils parmi lesquels on peut dénombrer les petites molécules (organiques ou inorganiques) et les anticorps. Toutefois, une caractéristique majeure des G-quadruplexes est leur nature polymorphique. En fonction de la concentration du milieu en cations, de la longueur et de la séquence, l'ADN G4 peut adopter différentes conformations dans lesquelles les brins sont parallèles ou antiparallèles, avec la présence de différents types de boucles (latérale, en diagonale ou en interne) et de longueur variable. Ce polymorphisme structural représente un sérieux inconvénient pour les études en biologie.
Dans ce contexte, nous avons développé des mimes d'ADN G-quadruplex contraints en une topologie unique (Fig. 1).[1] Grâce à ces constructions moléculaires, nous avons pu sélectionner par phage-display des anticorps hautement sélectif de la topologie antiparallèle de l'ADN G-quadruplex télomérique.[2] Ces anticorps ont ensuite été utilisé en imagerie cellulaire et nous avons pu par immunofluorescence détecter les séquences ADN G4 dans les cellules.[3] Suite à un projet de valorisation du CNRS, ces anticorps hautement spécifiques seront prochainement commercialisés par la société Idylle.



Keywords: ADN G-quadruplex, phage-display, imagerie cellulaire, anticorps

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Communications Solo

CO-1

Chemistry with Cells: A new innovative approach for manipulating cell-cell interactions

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The development of innovative strategies for cell membrane engineering is of prime interest to explore and manipulate cell-cell interactions. Herein, we report on innovative approach to form and break bonds between cells, using cells as chemical reactants. Artificial markers can be introduced at the cell membrane via biorthogonal chemistry, allowing the cells to assemble with cell partners bearing complementary markers through non-covalent click chemistry. With our recent design of an enzyme-responsive marker, we were able to conditionally trigger bond cleavage between cells and investigate cell attachment/detachment associated biological processes *(Fig. 1A)*. Herein, we report on markers that allow cells to form and break bonds only with the use of covalent and non-covalent click chemistry while the detachment of the cells lead to the formation of new communication *(Fig. 1B)*. Thus, our study shows that the ready-to-use complementary artificial surface markers are valuable tools for controlling the formation and the breaking of bonds between cells, offering an easy way to investigate biological processes associated with cell proximity.

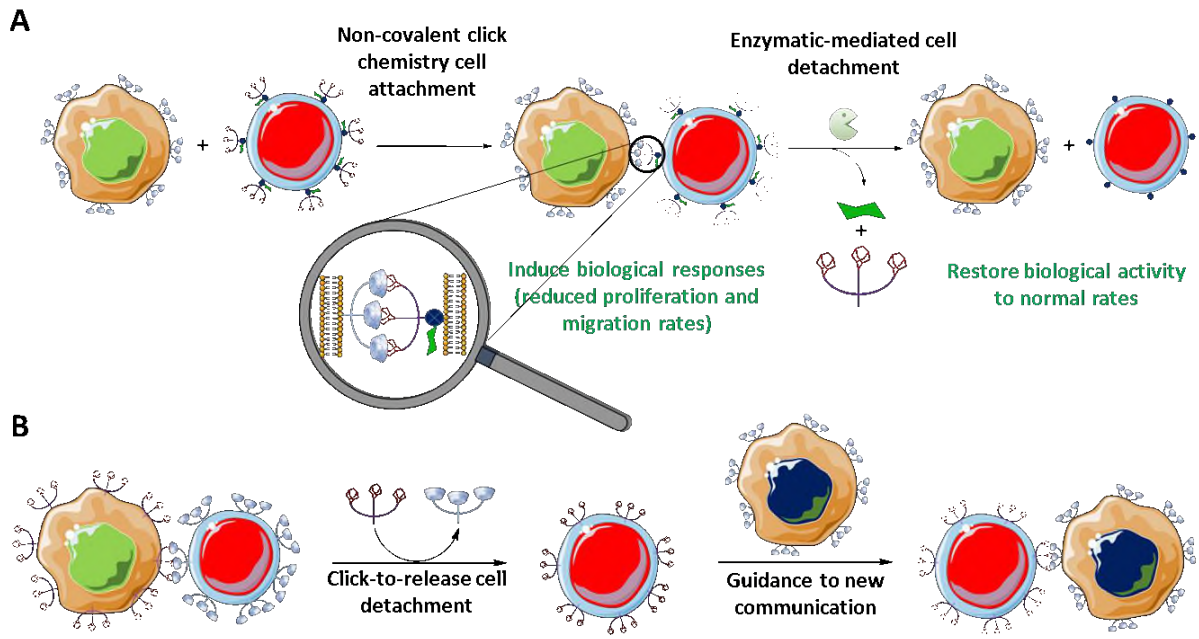

Figure 1A. *Previous work of enzyme-mediated cell detachment* ***B.*** *Current work of click-to-release cell detachment and guidance to new communication*

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Keywords: chemistry with cells, cell-cell communication, bioorthogonal chemistry, metabolic glycoengineering, non-covalent click chemistry, self-immolative linker, click-to-release reaction

CO-2

Des nanomatériaux ultra-stables pour le développement de tests de diagnostic rapide

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Résumé :

Les nanoparticules d'or présentent des propriétés optiques et (bio)chimiques qui en font d'excellents outils pour le développement de dispositifs de diagnostic rapide comme les tests à flux latéral (LFA). Les nanoparticules d'argent présentent de meilleures propriétés optiques que les nanoparticules d'or correspondantes,[1] leur utilisation devrait donc permettre d'améliorer la limite de détection et la sensibilité des LFAs. Les nanoparticules d'argent sont néanmoins très peu utilisées dans les applications de diagnostic médical rapide en raison de leur faible stabilité.[2] Nous avons récemment montré que des calix[4]arènes portant des groupes diazoniums sur leur grand col pouvaient être utilisés pour stabiliser des nanomatériaux.[3] Ces plateformes moléculaires peuvent en effet se greffer de manière covalente sur des surfaces variées et conduire à une fine couche organique (ca. 2 nm) extrêmement robuste.[4] Cette technologie a notamment été utilisée pour préparer des nanoparticules d'argent et d'or-argent ultra-stables de forme et de taille différentes.[5] Nous verrons comment cette famille de nouveaux nanomatériaux peut être utilisée pour concevoir des tests de diagnostic rapide efficaces.[6]

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Keywords: calixarènes; diazoniums; nanoparticules; argent; or ; tests à flux latéral

CO-3

Stratégie antitumorale ciblée basée sur la surexpression du transporteur GLUT1 et l'utilisation de pro-substrats du glycométabolisme cellulaire

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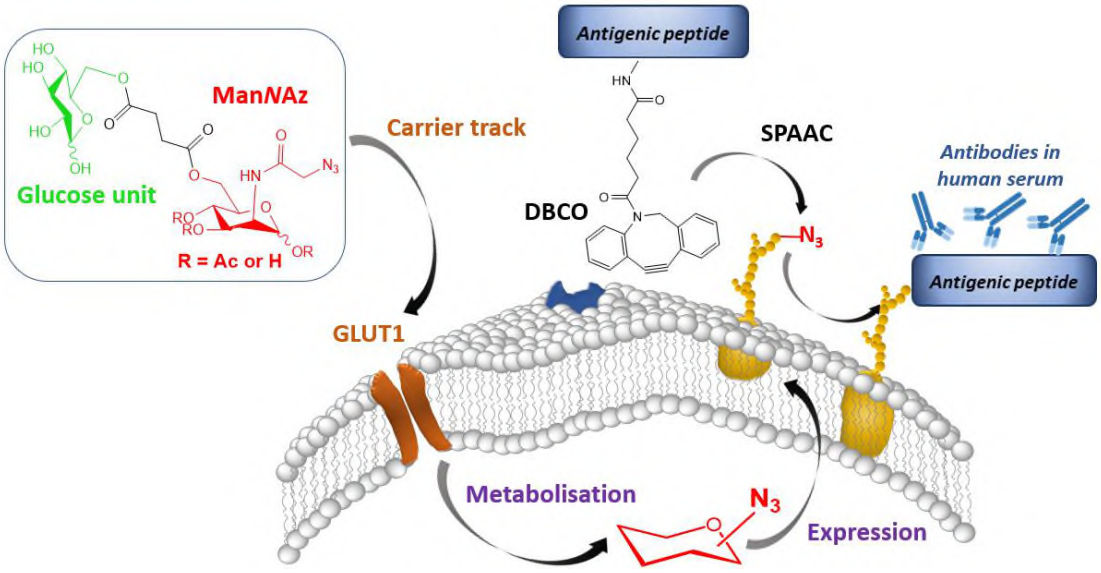
Résumé :

Ce projet de recherche à pour objectif de développer une nouvelle stratégie anticancéreuse sélective. Elle repose sur la modification spécifique de la surface des cellules cancéreuses via l'utilisation du glycométabolisme de sucre non-naturels et de chimie bioorthogonale pour induire leur reconnaissance et leur destruction sélective par les acteurs de l'immunité. Plusieurs études[1–3] ont été rapportées dans ce domaine, le plus souvent basées sur les travaux pionniers de Caroline Bertozzi. Cependant, les approches proposées jusque là souffrent encore d'un manque de sélectivité pour les cellules cancéreuses. Au laboratoire, de nouveaux pro-substrats du glycometabolisme cellulaire ont été élaborés, portant une fonction bioothogonale, ciblant les cellules cancéreuses. Ces composés possèdent une unité glucose liée à une unité mannosamine azoture (Man*N*Az). La surexpression du transporteur du glucose GLUT1 par les cellules cancéreuses, nommé l'effet Warburg, a été exploité pour délivrer spécifiquement les glycoconjugués dans les cellules cancéreuses. Par l'action des estérases intracéllulaires, l'unité Man*N*Az libérée est métabolisée et le groupement azoture exposé à la surface des cellules cancéreuses. Cet azoture est alors engagé dans une réaction de chimie-click : « Strain promoted Azide-Alkyne Cycloaddition (SPAAC) » pour fixer des peptides antigéniques à la surface des cellules cancéreuses. Leur reconnaissance par des anticorps spécifiques, présents dans le sérum humain, active alors une réponse immunitaire conduisant à la destruction des cellules cancéreuses.



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Keywords: Chimie bioorthogonale, Glycometabolisme, GLUT1, ManNAz, effet Warburg, peptides antigéniques, SPAAC.

CO-4

Synthesis and biological evaluation of new cyclic dinucleotide analogues having potential anti-bacterial activity

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Abstract: Cyclic dinucleotides (CDNs) are important second messenger molecules in various organisms. [(1)] Purine-containing CDNs have been extensively studied, but recent discoveries of pyrimidine nucleobase containing CDNs in *E. coli* suggests that CDNs containing pyrimidine nucleobases are also biosynthesized for functions that remains to be discovered. CDNs play key roles in bacteria, influencing processes such as quorum sensing, signal transduction or control of biofilm formation. Among the various cyclic dinucleotides (CDNs) identified in bacteria, cyclic di-GMP (c-di-GMP), synthesized by diguanylate cyclases (DGCs) and hydrolyzed by phosphodiesterases (PDEs), plays a crucial role in biofilm formation and growth. Therefore, the use of c-di-GMP analogues that inhibit DGC selectively over PDE could be used as an alternative to traditional antibiotics, especially given the rise of antibiotic resistance. [(2)] So far, several approaches depict the inhibition of biofilm formation *via* c-di-GMP pathways. These methods include screening small-molecule libraries *in vitro*, *in cellulo*, or *silico*. However, these inhibitors lack selectivity and also strongly inhibits PDEs (Figure 1A). [(3)] In 2015, Fernicola and co-workers published an interesting work concerning the synthesis of simplified analogues of the c-di-GMP that exhibited high bioactivity and selectivity *in vitro* by selectively inhibiting DGC but not PDE. However, bacteria tests on two bacterial strains *(i.e.*, *P. aeruginosa* and *E. coli*) these analogues depicted no activity, probably due to the excessive polarity of these molecules, which makes them unable to penetrate into the bacteria. [(4)]

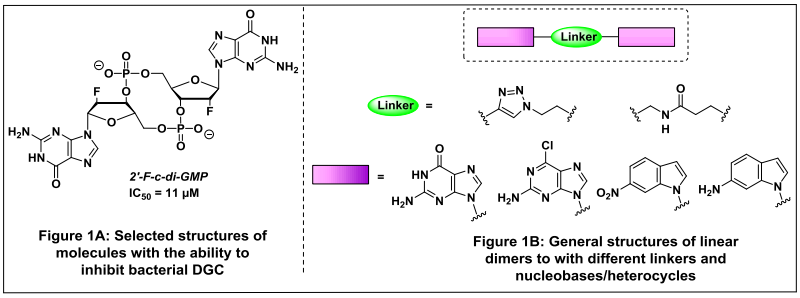

Figure 1A: Selected structures of molecules with the ability to inhibit bacterial DGC

Figure 1B: General structures of linear dimers to with different linkers and nucleobases/heterocycles

Following this pioneering work, we ambitioned synthesizing new selective analogues by designing alternative and more hydrophobic derivatives (Figure 1B). So far, 37 new molecules have been synthesized and their biological evaluation were performed on the planktonic cells of the *ESKAPEE* group of bacteria (MIC evaluation), and the biofilm formation and growth of *P. aeruginosa*, and promising activities were observed with several undescribed molecules with moderate to good activities. Key functional and structural features of these biological evaluations will be discussed.

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Keywords: Cyclic dinucleotide; Anti-bacterial; Biofilm growth inhibition.

CO-5

Access to Clickable glycerophospholipids mimics with untouched fatty acyl chains and polar head groups

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Résumé :

Glycerophospholipids (GPLs) play important roles in cellular compartmentalization and signaling. Among them, phosphatidic acids (PA) exist as many distinct species depending on acyl chain composition, each one potentially displaying unique signaling function.[1,2] Although the signaling functions of PA have already been demonstrated in multiple cellular processes, the specific roles of individual PA species remain obscure due to a lack of appropriate tools.[3] Indeed, current synthetic PA analogues fail to preserve all the functions of natural PA. To circumvent these limitations, grafting a clickable moiety on the glycerol moity seems promising,[4] but the current synthetic apporoach to such clickable GPL mimics is limited to PA bearing two identical fatty acyl chains. We developed a novel synthetic approach to produce these PA analogues without compromising structural integrity of acyl chains.[5] Moreover, addition of a clickable moiety allowed flexible grafting of different molecules to PA analogues for various biological applications*, in vitro* and *in cellulo*, and late stage esterification of PA allowed us to graft different head groups. Hence, this innovation also provides powerful tools to investigate specific biological activities of individual GPL species, with potential applications in unraveling complex GPL-mediated signaling pathways.

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Keywords: phosphatidic acid; glycerophospholipid; *in cellulo* click chemistry

CO-6

Use of fluorogenic probes to visualize mitochondrial reductases in living cells: toward shuttling of active compounds.

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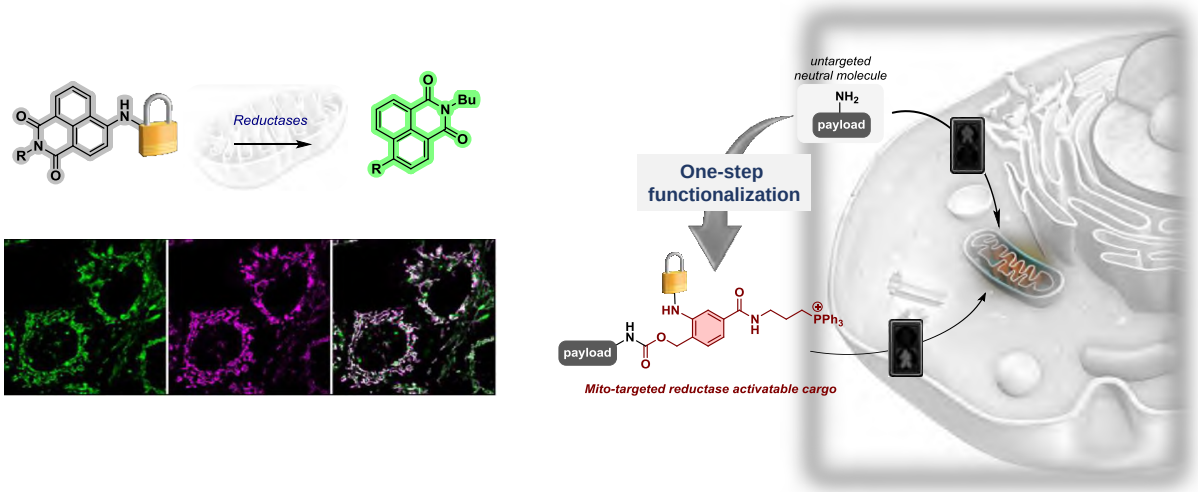
Abstract:



Fluorescence imaging is a wonderful tool to observe living cells. This technique provides a high level of resolution, making it possible to distinguish between the different cellular compartments or organelles.[1] The strong relationship between the structure of an organic fluorophore and its fluorescence properties offers the opportunity to observe chemical transformations impacting the chemical structure of the fluorophore, which are commonly reflected by the appearance of a fluorescent signal or by the modulation of the emission wavelength.[2] In this presentation, we will illustrate how we used this technique to demonstrate the metabolization of azobenzenes by an intra-mitochondrial azoreductase activity.[3] We will also discuss the possible use of mitochondrial reductases to design self-immolatve spacers that can be deployed for the shuttling of active compounds to the mitochondria.

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Keywords: Fluororescent probes • Mitochondria • Self-immolative spacer • Reductases

CO-7

Glycans metabolic engineering for studying plant cell wall biosynthesis and functions

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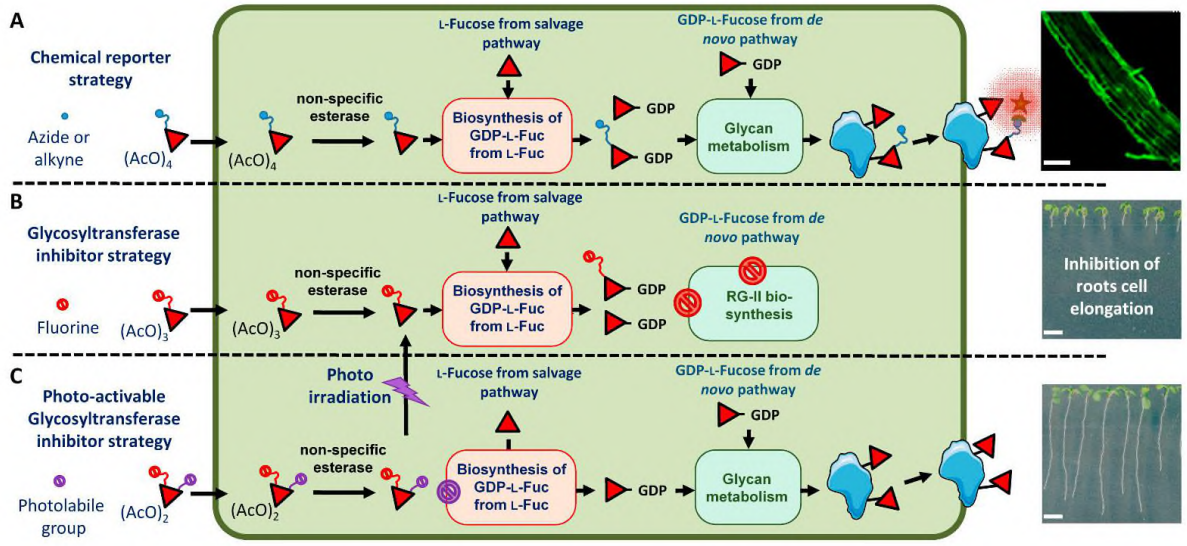
Glycans metabolic engineering is a powerful tool for studying the glycosylation of living cells [1, 2]. The use of modified monosaccharides, such as deoxy or fluorinated sugars, has been reported as a powerful pharmacological approach for studying carbohydrate metabolism and plant cell wall biosynthesis [3]. Moreover, non-natural metabolite derivatives that carry functions enabling bio-orthogonal ligations are now widely used for glycomolecules imaging in living organism. In both cases, these derivatives must cross the cell membrane and be accepted by the biosynthetic machinery of the cell to produce nucleotide-sugars that will be taken in charge by the enzymatic machinery to build complex glycomolecule such as cell wall polysaccharides in plant. Here, we illustrate the use of glycan metabolic engineering, photo release of caged monosaccharide derivative and click-chemistry, for studying the plant cell wall biosynthesis and function with an emphasis of the pectic domain rhamnogalacturonan II [4, 5].



Glycan metabolic engineering in plant cells using fucose derivatives.

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CO-8

Biotechnological production of sialylated solid lipid microparticles as Influenza virus inhibitors

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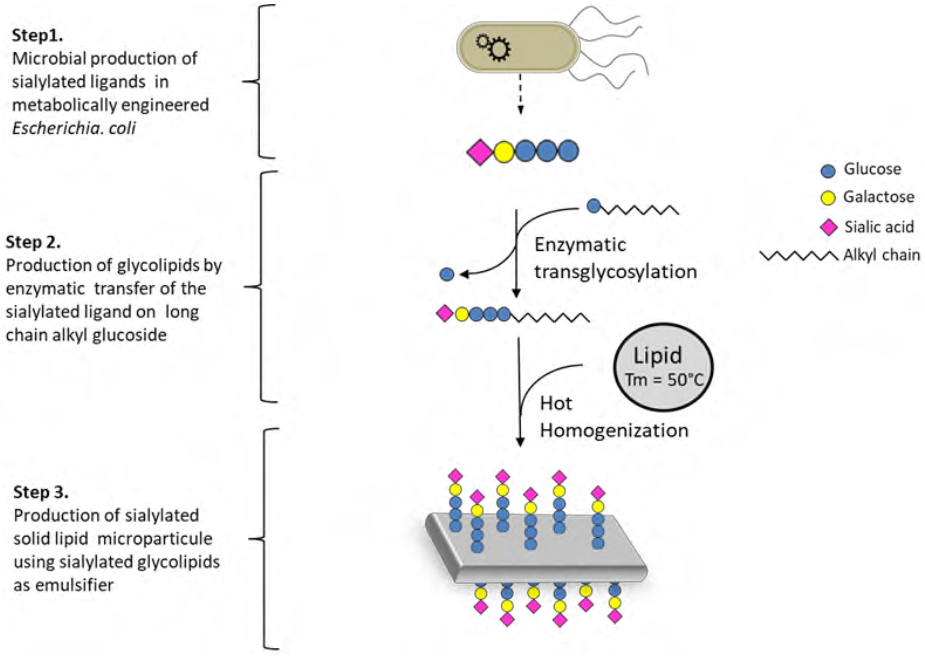
Résumé :

Influenza viruses bind to host cells via hemagglutinin proteins interacting with sialosides on the cell surface[1]. To block this, a therapeutic strategy involves developing multivalent sialylated structures to saturate viral hemagglutinins, preventing their attachment[2]. This study outlines the production of sialylated solid lipid microparticles (SSLMs) in three steps: (i) metabolic engineering of *E. coli* to produce sialylated maltodextrins, (ii) an in vitro glycosylation process using the enzyme MalQ to transfer sialosides from maltodextrins to long-chain alkyl glucosides, and (iii) formulation of SSLMs displaying multivalent sialic acid. The morphology and structure of SSLMs were characterized, showing well-defined spherical shapes with sialic acid ligands on their surface. These SSLMs demonstrated promising antiviral activity in hemagglutination inhibition and microneutralization assays, effectively inhibiting the A/H1N1 pdm09 virus. This approach offers a novel method for preventing influenza infections by blocking viral attachment and entry into host cells[3].



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Keywords: Metabolic engineering; Oligosaccharide synthesis; Multivalency; Influenza inhibition

CO-9

Generative Autoencoder-driven Molecular Design for Virtual Screening and SAR Optimization

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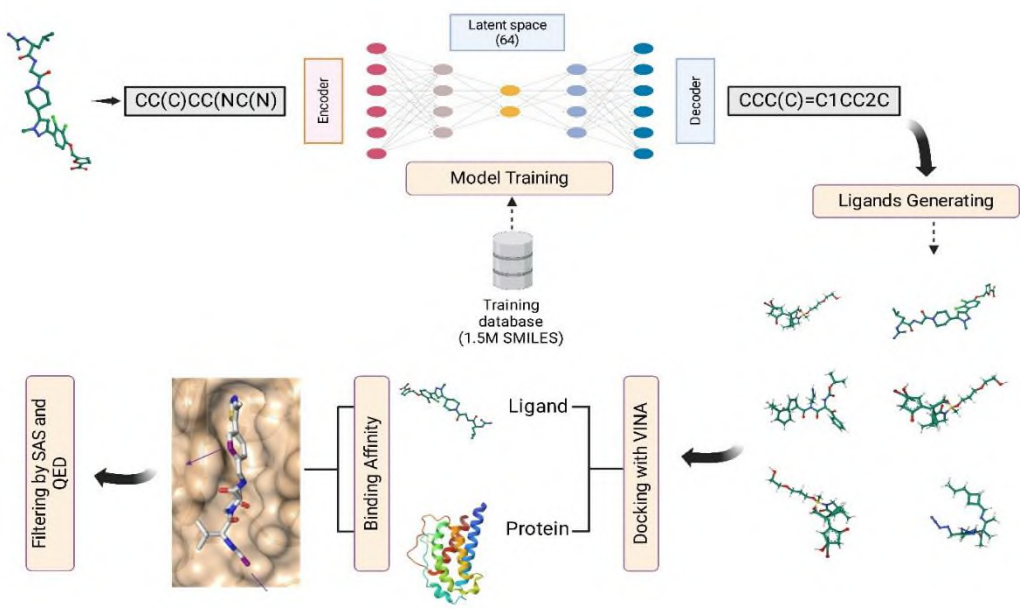
Résumé : In the search for novel bioactive molecules, deep learning and cheminformatics are increasingly converging to accelerate hit discovery and lead optimization. We present a generative autoencoder-based framework for molecular design, integrated with an automated virtual docking pipeline. This approach enables the exploration of chemical space by encoding molecular structures as latent vectors, generating novel compounds through slight perturbations, and screening them via docking simulations against a predefined biological target. The system iteratively refines molecular outputs based on docking scores, enabling de novo design with improved bioactivity potential. Additionally, the platform facilitates structure-activity relationship (SAR) analysis, aiding in the optimization of promising hits. This AI-assisted workflow provides valuable insights for drug discovery and chemical optimization, offering a scalable solution for hit expansion and ligand design.



Keywords: Machine Learning, Generative autoencoder, ChemoInformatics, Screening

CO-10

“Click-and-Release Formation of Urea Bonds in Living Cells Enabled by Micelle Nanoreactors”

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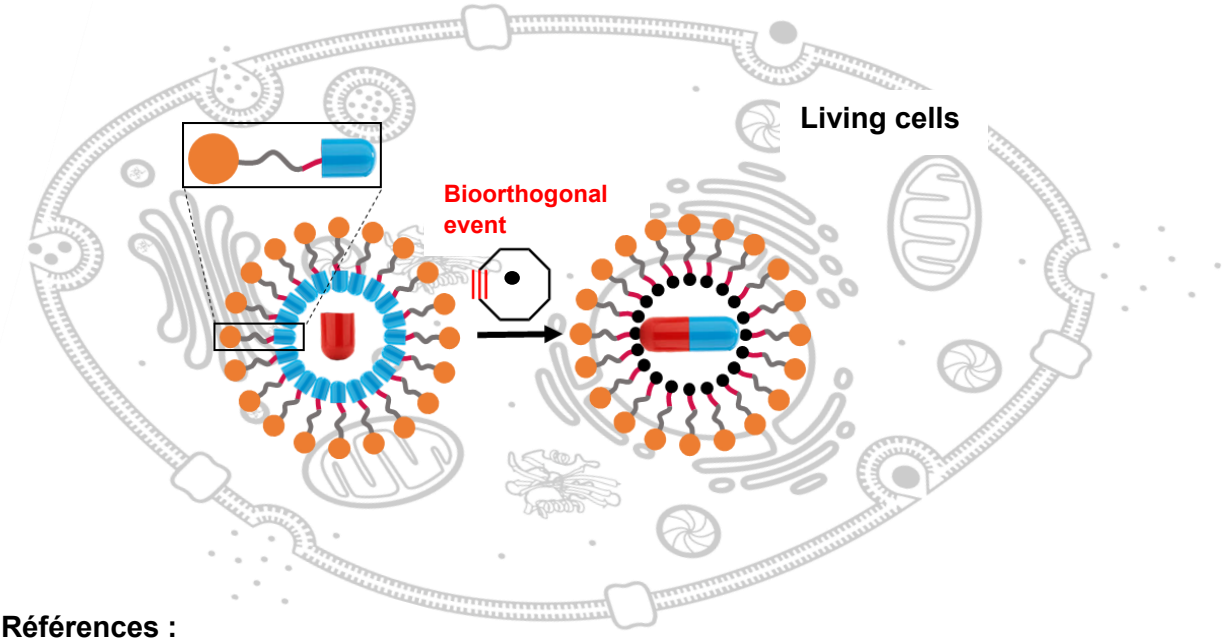
Résumé :

The development of innovative strategies enabling chemical reactions in living systems is of great interest for exploring and manipulating biological processes. Herein, we present a pioneering approach based on both biorthogonal[1] and confined chemistry for intracellular drug synthesis. Exploiting a click-to-release[2] reaction, we engineered nanoparticles[3] capable of synthesizing drugs within cellular environments through bioorthogonal reactions with cyclooctynes, areaction called Strain-Promoted SydnonImine-Cycloalkine cycloaddition reaction (SPSIC)[4]. Proof of concept experiments showed that this new approach could be successfully applied to the synthesis of the FDA approved Sorafenib within cancer cells. The integration of bioorthogonal and confined chemistry not only offers exciting prospects for advancing therapeutic strategies but also opens up new avenues for exploring non-natural reactions within living systems. This innovative approach represents a fundamental extension of the biorthogonal chemistry concept and holds great promise for pioneering developments in therapeutic applications[5].



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CO-11

Découverte des voies inhibitrices de croissance associées aux complexes de gallium-sidéromycines dans *S. aureus*.

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Résumé :

S. aureus (*SA*) est un agent pathogène Gram positif, responsable de la plupart des infections nosocomiales graves et mortelles dans les pays développés. Ces bactéries pathogènes ayant développé des mécanismes de résistance aux antibiotiques existants, nécessitent de nouvelles stratégies antimicrobiennes pour contourner ces résistances. Une approche prometteuse consiste à conjuguer les antibiotiques à des sidérophores. Ces derniers agissent comme des "chevaux de Troie", permettant aux antibiotiques d'atteindre efficacement le cytoplasme bactérien en exploitant les voies essentielles du transport du fer.[1] Plusieurs conjugués ont déjà été étudiés dont notamment, le céfidérocol, un conjugué formé par la liaison covalent d'un ligand catechol à un antibiotique de type bêta-lactame, s'est avéré particulièrement efficace et a récemment été approuvé par la FDA pour traiter les infections urinaires causées par des agents pathogènes Gram négatif.[2]

Notre équipe a précédemment développé des xénométallomomycines, des conjugués d'antibiotiques-sidérophores incorporant des ions métalliques non endogènes, comme le gallium (Ga^{3+}). Ce dernier peut remplacer efficacement le fer essentiel aux bactéries, renforçant ainsi l'efficacité des composés. En effet, les conjugués Ga^{3+}-sidérophore-antibiotique ont surpassé en efficacité le conjugué non-complexé et l'antibiotique seul, tant *in vitro* qu'*in vivo*.[3,4] Cependant, le mécanisme d'action et la source de cette efficacité demeuraient inconnu. À travers des analyses physicochimiques, synthétiques et transcriptomiques, nos travaux ont montré que les xénométallomomycines contenant du gallium, cinétiquement inertes, et ciblant des éléments cytoplasmiques bactériens, induisent des profils de résistance et des profils d'expression génique différents de ceux des antibiotiques parents dans *SA*. Les Ga-sidérophore-ciprofloxacine perturbent efficacement la biosynthèse et la machinerie d'absorption du fer-sidérophore dans les bactéries.[5]

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Keywords: *S. aureus*; gallium; sideromycines; RNA sequencing

CO-12

Innovative Flurorophore Design for Spectroscopic high-resolution Techniques

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Résumé :

Determining the dynamics of proteins is an unsolved challenge that slows down the identification of the specific function and molecular mechanisms of protein systems. Indeed, astonishing developments in cryo-EM or modern structure prediction algorithms (Alphafold) have failed to resolve the structures of highly dynamic proteins such as intrinsically disordered proteins (IDPs).[1,2] Among solution state techniques, single-molecule microscopy allows real-time observation of protein dynamics in solution (STED, smFRET, MINIFLUX). These technique relies on two crucial parameters: the label - ideally bright, photostable, soluble and small - and its covalent attachment to the protein. However, the background in the green spectral regime requests the use of red-emitting dyes, especially for samples with high background, such as the interior of the cell or liquid-liquid phase separating conditions which is oftenly observed for IPDs.[3] Unfortunately, red-emitting dyes are often less bright and more sticky.[4,5] We described deuterated and sulfonated fluorophores in the red and NIR spectrum with improved quantum yields, reduced bleaching rates.[6] Their improved characteristics warrant undiscovered potential to replace state-of-the-art fluorophores used in the field single molecule microscopy.

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Keywords: Biological chemistry – Molecular dynamics – Fluorescence Microscopy

CO-13

Dérivés du Déférasirox comme agents duaux ciblant les kallikréines et la surcharge en fer dans les maladies neurodégénératives

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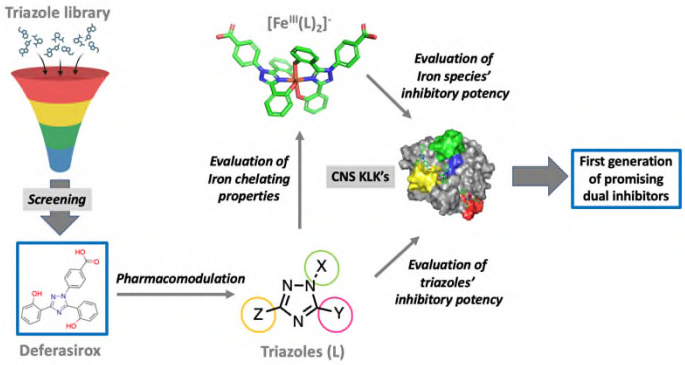
Résumé : Les peptidases apparentées aux kallikréines constituent une famille de protéases à sérine, dont la perte de régulation de l'activité est particulièrement associée aux maladies neurodégénératives.[1] Par ailleurs, la surcharge en fer joue également un rôle clé dans certaines de ces pathologies, en particulier la maladie d'Alzheimer.[2]

Dans ce contexte, nous avons identifié pour la première fois le **Déférasirox** (DFX), un **chélateur de fer** approuvé par la FDA,[3] comme un inhibiteur potentiel des kallikréines (KLK). Nous proposons ici la conception et la synthèse d'une petite bibliothèque de molécules utilisant le DFX comme squelette chimique.[4] Les sous-séries de composés obtenues ont été évaluées sur les kallikréines clés du système nerveux central (KLK1, KLK6 et KLK8) en appliquant des pharmacomodulations ciblées sur le DFX. Au-delà du DFX lui-même, plusieurs inhibiteurs réversibles de ces KLKs, avec des activités de l'ordre du micromolaire, ont été identifiés comme composés candidats et se sont révélés non cytotoxicité sur des lignées neuronales couramment utilisées dans l'étude des maladies neurodégénératives. Leur capacité de chélation du fer a également été évaluée en comparaison avec le DFX. Par ailleurs, les complexes préformés entre le fer et certains dérivés ont montré une légère amélioration de leur activité inhibitrice sur certaines kallikréines, de manière KLK-dépendante.



Ainsi, nous avons identifié plusieurs dérivés du DFX comme points de départ prometteurs pour le développement d'agents thérapeutiques doubles, ciblant à la fois la dérégulation de la protéolyse des KLKs et les déséquilibres du métabolisme du fer impliqués dans les maladies neurodégénératives.

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Mots clés: Kallikréines • 1,2,4-triazole • Déférasirox • maladie neurodégénératives • chélation du fer.

CO-14

Dynamic Combinatorial Libraries of CycloPeptides For the Inhibition of Protein-Protein Interactions

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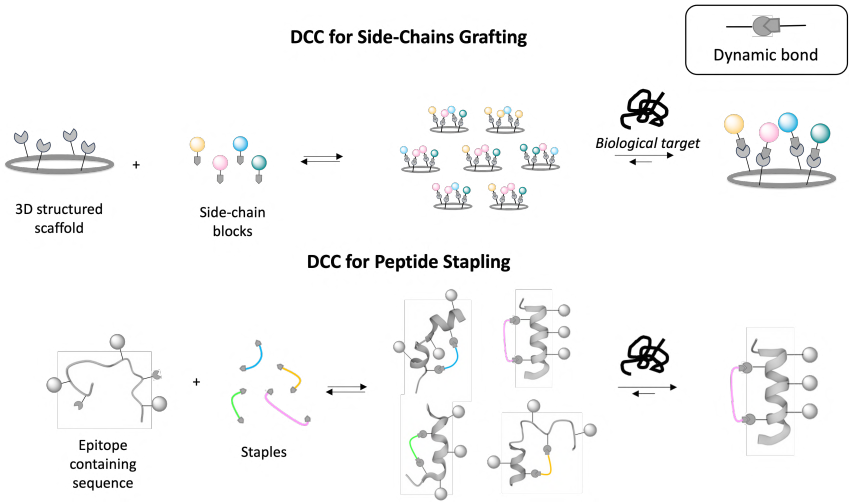
Cyclic peptides are promising candidates to tackle challenging large protein interfaces often referred to as undruggable.[1] In general, the discovery of bioactive compounds relies on the high throughput screening (HTS) of chemical libraries which is often quite difficult to apply to cyclopeptides.[2] Two conceptually different approaches, based on dynamic combinatorial chemistry (DCC),[3] are developed in our group, based on the **dynamic grafting** of amino acid's side-chains on 3D folded cyclic peptide scaffolds,[4,5] and the **dynamic stapling** of a flexible linear peptide, leading to a library of constrained cyclic candidates. The two strategies and their applications in the field of protein-protein interactions (PPIs) will be presented, using as a prototype of PPI, the interaction between the tumor suppressor p53 and the oncoprotein HDM2, involved in apoptosis and relevant for cancer therapy.[6]



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Keywords: Cyclopeptides; Dynamic Combinatorial Chemistry; Protein-Protein Interaction

CO-15

Electroclick-Driven Carbohydrate Vectorization: A Promising Glycocalyx Editing Strategy

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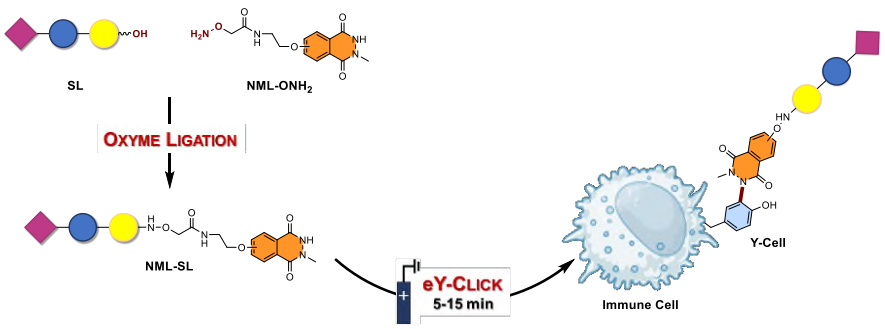
Abstract

Genetic or chemical modifications of cell membranes are revolutionary for advancing diverse therapeutic approaches and gaining deeper insights into biological processes. We recently introduced eY-Click, a biocompatible electrochemical method to functionalize native proteins.[1] Employing a *N*-methylluminol (NML), a fully tyrosine-selective protein anchoring group, we were able to functionalized cell surfaces from viruses, living bacteria and eukaryotic cells models, with simple molecules in just minutes.[2]

In this study, we extended this strategy to apply it to more complex biomolecules, especially by taking advantage of biological relevant oligosaccharides. To achieve this, we synthesized NML-glycoconjugates via oxime ligation between unprotected sugar and an aminoxy-functionalized NML. Our electro-bioconjugation method was successfully applied to a protein model, paving the way for the development of glycoproteins, which are widely explored for the study of biological process and vaccine applications. Finally, we vectorized the membrane surface of immune cells with NML-SialylLactose (NML-SL) conjugates, aiming to enhance their ability to recognize and target B-cell lymphoma, known to overexpress the siglec-2 receptor (CD22). This innovative solution offers a promising new strategy for advancing cancer immunotherapy beyond CAR-T or metabolic engineering, providing a streamlined and versatile approach to immune cell functionalization.



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Keywords: Bioconjugaison; Glycochemistry; Electrochemistry; Cell engeenering

CO-16

Development of a novel class of azaheterocyclic ligands to promote diversity in bioinorganic chemistry

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Coordination complexes are playing an increasing role in medicinal chemistry, particularly in the development of anticancer and diagnostic agents.[1,2] Their modularity and ability to interact with biologic target of interest make them promising therapeutic tools.

However, their development is hindered by the limited diversity of ligands, which are often restricted to well-established scaffolds such as terpyridine (tpy) and bipyridine (bpy). Any structural modification aiming at optimization of their pharmacological properties requires major chemical synthesis works to modify the ligand's core from the outset and to provide organometallic derivatives, allowing better functionalization and enhanced physico-chemico-pharmacological properties.

Exploring new ligands and more adaptable synthetic strategies is therefore crucial to expand the biomedical applications of such coordination complexes. Our approach is based on the substitution of one pyridine moiety and also on the functionalization of heteroaromatic compounds. The validation of this novel class of ligand have been achieved through complexation with a variety of metals (Figure 1A). According to previous works [1,2], further functionalization of these new ligands could proceed via a post-functionalization strategy, thus promoting vectorization, bioconjugation or the installation of a probe (Figure 1B).

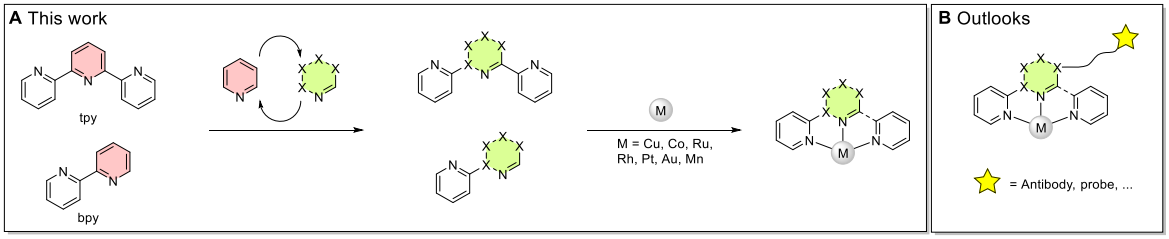

Figure 1: (A) Substitution of pyridine ring in terpyridine and bipyridine by an original azaheterocycle; (B) Possible post-functionalization of our new scaffold.

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Keywords: Azaheterocycle; coordination chemistry; bioinorganic chemistry

CO-17

Synthetic mycolates derivatives to decipher protein mycoloylation, a unique post-translational modification in bacteria

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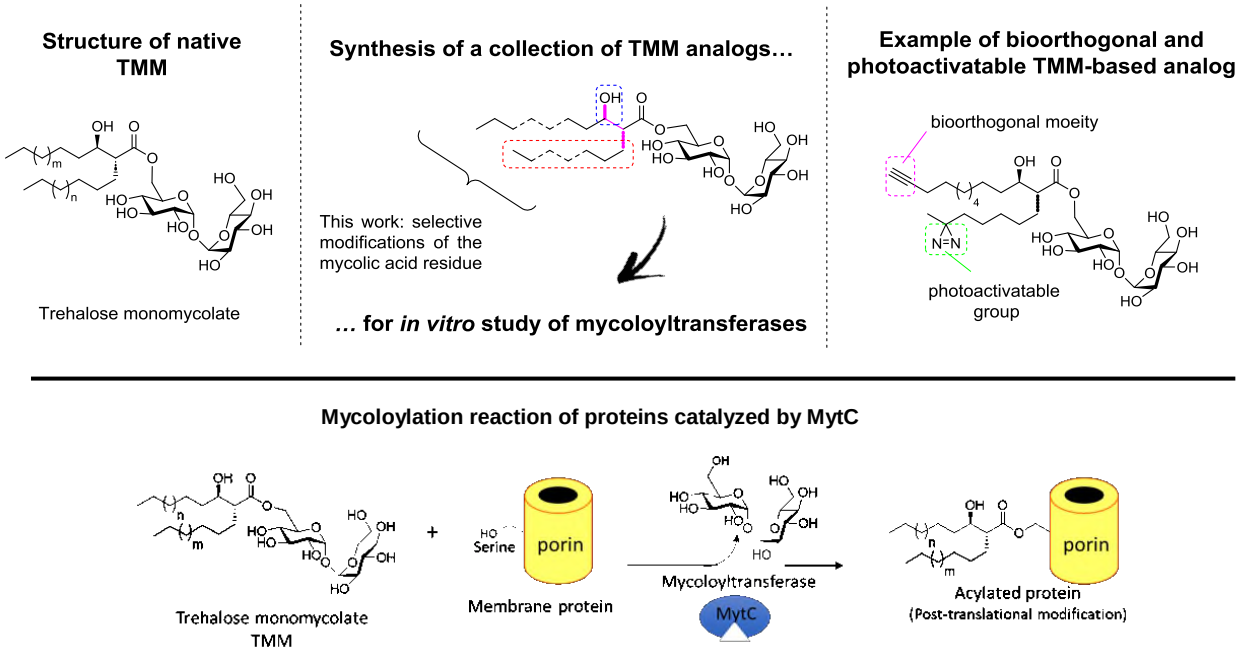
Résumé :

Corynebacteriales are a family of bacteria including *Mycobacterium tuberculosis*, the etiologic agent of human tuberculosis. *Corynebacteriales* possess a particular outer membrane, called mycomembrane. This rigid membrane is composed of mycolic acids esterified to trehalose leading to trehalose monomycolate (TMM). TMM is processed by enzymes called mycoloyltransferases (Myt) and acts as a donor of mycolates in the biogenesis of the mycomembrane. Recently one mycoloyltransferase (MytC) was identified to be responsible of mycoloylation of small membrane proteins in *Corynebacterium glutamicum*.[1] This is a unique post-translational modification in bacteria and its role remains to be clarified. In recent years, our laboratory developed several molecular tools for the study of the biogenesis of the mycomembrane.[2] One of our projects is to synthesize a large collection of TMM analogs to get insight in the mycoloylation mechanism of proteins 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.



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Keywords: Photoactivatable probe, Mycomembrane, Trehalose Monomycolate, Post-translational modification, Bioorthogonal probe.

CO-18

Chimie *click* supramoléculaire : un outil pour la préparation de radioimmunoconjugués

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Résumé :

Le couple biotine-streptavidine est devenu un outil essentiel en chémobiologie. Dotée d'une affinité et d'une sélectivité exceptionnelles, cette paire constitue une plateforme de choix pour de nombreuses applications *in vitro*. Cependant, la taille importante de la streptavidine ainsi que son immunogénicité limitent le potentiel de ce couple pour des applications *in vivo*, notamment chez l'Homme.

Récemment, la paire cucurbit[7]uril-adamantanamine a émergé comme une alternative prometteuse au couple biotine-streptavidine.[1] Ces deux partenaires sont des composés robustes et de faible poids moléculaire, capables de s'auto-assembler de manière sélective pour former un complexe stable, dont la constante d'association rivalise avec celle du système biotine/streptavidine. Dans cette communication, nous montrerons comment ce couple peut être exploité pour réaliser le radiomarquage d'anticorps par assemblage supramoléculaire, dans des conditions douces, biocompatibles.

Un anticorps anti-HER2 (trastuzumab) a été modifié de façon site-spécifique, par une approche chémoenzymatique (transglutaminase), afin d'introduire deux motifs adamatanamine sur ses résidus Q297. Parallèlement, le cucurbit[7]uril (CB[7]) a été couplé au chélateur de radiométaux DOTA et le précurseur DOTA-CB[7] a été radiomarqué à 90 °C avec différents radiométaux d'intérêt diagnostique ou thérapeutique : indium-111, gallium-68, zirconium-89, lutécium-177 et actinium-225.[2] L'incubation des deux partenaires a ensuite permis la formation du radioimmunoconjugué par autoassemblage, en l'espace de quelques secondes, à température ambiante dans le PBS.

Le radioconjugué marqué à l'indium-111 a finalement été évalué *in vivo* sur des souris xénogreffées avec la lignée tumorale SKOV3. Une accumulation sélective du traceur [^{111}In]In-DOTA-CB[7]⊂trastuzumab-adamantanamine a été observée dans la tumeur (40.5±2.4 %ID/g 72h post-injection) de manière analogue au conjugué obtenu par couplage covalent (SPAAC). Ces résultats illustrent la stabilité de l'assemblage supramoléculaire *in vivo*.

Des travaux sont en cours afin d'évaluer le potentiel de ces partenaires dans le cadre de stratégies dites de « préciblage », dans lesquelles l'assemblage du radioconjugué n'est pas réalisé *in vitro*, mais *in vivo*, une fois l'anticorps accumulé dans la tumeur.

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Keywords: Chimie supramoléculaire; Cucurbituril; SPECT/CT; Bioconjugaison; Anticorps

CO-19

Fluorogenic photocatalyzed proximity labelling with visible light to map the interactome in living cells

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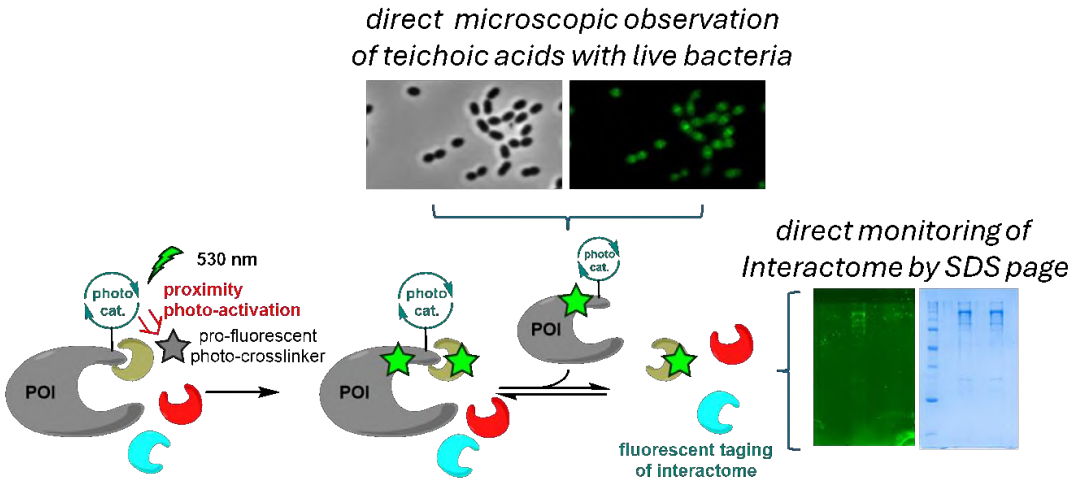
Abstract :

Living processes are primarily governed by transient and dynamic interactions between biomacromolecules or cells. It is therefore essential to study these interactions to understand the mechanisms they regulate. These are identified using proximity labeling techniques, where the labelling agent is usually a enzyme fused to the protein of interest (e.g. the APEX approach).[1,2] Although effective, this technique sometimes has limitations in terms of labelling speed, toxicity and precision. The use of photocatalytic proximity labelling has improved the spatial precision of proximity labelling, while using bio-compatible wavelengths.[3] A limitation common to all these methods is their inability to mark and follow the evolution of these dynamic interactions from the product of interest (POI) on living cells. In this communication, we will present our latest work on the development of a fluorogenic photocatalyzed proximity labelling that provides a simple solution to this problem. This new method is based on the use of organic photocatalyst and fluorogenic photo-crosslinking agents. Proof of concept was first demonstrated in living bacteria (*Streptococcus pneumoniae*) by spatiotemporally controlled fluorescent labelling of teichoic acids, a major component of the cell wall in Gram-positive bacteria, monitored by epifluorescent microscopy. We subsequently demonstrated that this method is effective for the selective fluorescent labelling of proteins that interact with teichoic acids. Once again, direct fluorescent labelling of the interactome simplifies characterization procedures.



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Communications Flash

CF-1

Idylle : Valoriser les innovations des chercheurs pour les chercheurs

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Résumé :

Depuis des années les chercheurs en chémobiologie redoublent d'inventivité pour proposer des molécules innovantes à même de répondre aux défis dans les sciences du vivant.

Pour les molécules à potentiel thérapeutique, le parcours de valorisation est assez clair : dépôt de brevet et création de start-up ou licence auprès d'un industriel. Cependant que faire si notre innovation est un outil pour la recherche qui s'adresse à une communauté réduite de chercheurs spécialistes ?

Filiale du CNRS [1], Idylle a pour mission de valoriser ces réactifs, consommables et autres petits dispositifs, à destination des usages en biologie en les transformant en produits prêts à l'emploi. Pour cela, Idylle identifie, évalue, et industrialise les inventions (notamment les sondes, tampons, et autre molécules) afin de les commercialiser partout dans le monde à destination des chercheurs les plus susceptibles d'en bénéficier. Plusieurs innovations issues de travaux de chercheurs chimistes ont déjà bénéficié du modèle[2-4] et d'autres sont à l'étude en ce moment.

Cette présentation reviendra sur la méthodologie, le déroulé ainsi que les succès et les défis de cette voie de valorisation.

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Keywords: Valorisation, Innovation; Outils de recherche; Savoir-faires

CF-2

Multivalent Sialic Acid Derivatives as Potent Sialidases Inhibitors and Therapeutic Perspective against Intestinal Inflammation

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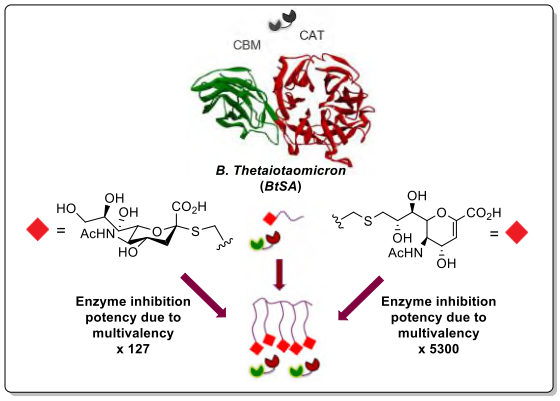
Résumé : Bacterial sialidases are enzymes produced by certain viruses, parasites and bacteria. Excessive activity of these glycosidases can lead to proliferation of *Enterobacteriaceae* such as AIEC (*Adherent & Invasive Escherichia Coli*), responsible for inflammation of the intestinal wall.[1]



Sialidases can have a single catalytic site (CAT) used to cleave sialosides present on intestinal wall mucins, while others can have a lectin site (CBM for Carbohydrate-Binding Module) in addition to this catalytic site. The CBM increases the catalytic efficiency of the enzyme by targeting the sialidases on the polymeric substrates through sugar-lectin interactions. Sialidases of both types represent potential therapeutic targets, and this project was dedicated to the design of selective and potent multivalent inhibitors of these enzymes.

In recent years, several inhibitors have been developed with the same goal but unfortunately have not shown sufficient selectivity and efficacy. For this new generation of inhibitors, we are interested in the synthesis of non-hydrolysable multivalent inhibitors based on thiosialoside[2] and DANA (2,3-dehydro-3-deoxy-N-acetylneuraminic acid) ligands grafted by click chemistry on poly azide scaffolds.

To study the dual targeting of the enzyme sites and to validate the concept of multivalency, different sialidases, like *Bacteroides Thetaiotaomicron* (*BtSA*) for example, were produced with a CBM. Promising results were first obtained on multivalent thiosialoside and DANA compounds which showed a much higher inhibition of the enzymatic activity compared to the monovalent references at equimolar ligand ratios. Polymeric DANA showed unprecedented Inhibitory values reaching the nano- to pico-molar range, and are therefore promising antivirulent factors of pathogens expressing sialidases.[3]

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Keywords: Multivalence; Enzymatic Inhibition; Sialidases; Sialic Acids; DANA-clusters; Glycochemistry; Click Chemistry.

CF-3

Bioconjugation of the capsid of adeno-associated viruses for osteoarthritis treatment by gene therapy

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Résumé :

This project focuses on chemically engineering adeno-associated viruses (AAV) through bioconjugation to enhance specificity toward cartilage tissue to treat osteoarthritis.

Cartilage is a non-vascularized tissue in which chondrocytes, the sole extracellular matrix (ECM) producing cells, generate a highly negatively charged matrix due to its major component, glycosaminoglycans. In osteoarthritis, chondrocyte dysfunction leads to cartilage degradation, affecting over 500 million people worldwide. Despite its prevalence, osteoarthritis remains incurable, due to the challenges of delivering therapeutic agents to chondrocytes embedded in the dense ECM.[1]

AAV are promising gene therapy vectors, as demonstrated by four ongoing clinical trials targeting cartilage. However, their broad tropism and limited ability to reach targeted cells reduce their efficiency. To address these limitations, our team developed a chemical modification strategy to enhance AAV specificity and efficacy for targeted cells or tissues.[2]

The AAV capsid is chemically modified in two steps: biotin ligands are bioconjugated to capsid lysines, followed by non-covalent binding of avidin, a positively charged protein. This modification exploits the strong biotin-avidin interaction and imparts an overall positive charge to the vector. This charges facilitates electrostatic interactions with the negatively charged ECM, enhancing vector retention, adhesion, and penetration into deeper cartilage layers.[3]

Preliminary results demonstrate that these modifications preserve AAV infectivity in human chondrocytes. Ongoing work assesses vector retention and penetration in cartilage explants, along with *in vivo* studies in a rat model to evaluate biodistribution and cartilage targeting. This approach presents a promising strategy to overcome challenges in cartilage-targeted gene therapy and develop osteoarthritis treatments.

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Keywords: Gene therapy, Adeno-associated virus, Bioconjugation, Osteoarthritis, Cartilage

CF-4

Synthesis of Antibody-Drug Conjugates using continuous flow chemistry

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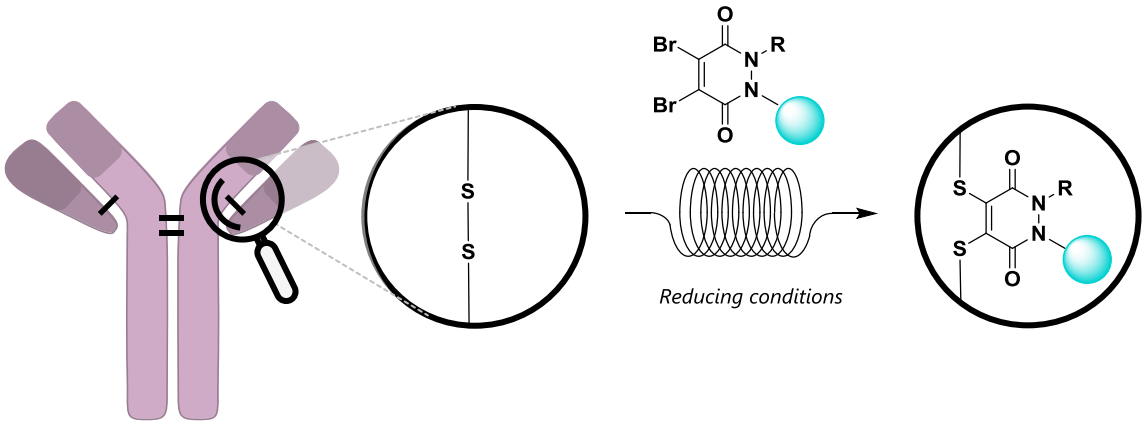
Résumé :

Antibody-drug conjugates (ADCs) are a class of innovative pharmaceutical compounds combining monoclonal antibodies with cytotoxic drugs. They are currently used in targeted therapy, particularly in the treatment of cancer. The controlled conjugation of the antibody with the cytotoxic agent, as well as their characterisation, analysis and production, remain one of the major challenges for their development. Current bioconjugation techniques mainly use the cysteine or lysine residues present on the antibody, but these do not allow effective control of the number of drug molecules attached to the antibody (DAR). As a result, ADCs are obtained in the form of heterogeneous statistical mixtures with differing efficiencies.

The development of effective and selective antibody functionalization methods is therefore essential.

The aim of the project is to adapt an existing bioconjugation method to flow chemistry to provide fast, safe and scalable processes for ADCs preparation while allowing a better control of the DAR. Our approach is based on the rebridging of disulfide bridges by a dibromopyridazinedione derivative coupled to the desired drug. This method enables bioconjugation via the 4 interchain disulfide bridges of the antibody (IgG1 type) while preserving the structure of the antibody, making it possible to develop homogeneous and stable ADCs with a maximum DAR of 4.[1] Continuous flow chemistry provides improved reproducibility, safety and reaction kinetics compared with conventional techniques. This process makes it easier to purify products and scale up. It also makes it possible to precisely control the DAR.[2]



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Keywords: Antibody-Drug Conjugate; Flow chemistry; DAR control.

CF-5

Bioorthogonal Fluorogenic release of isocyanates in cells

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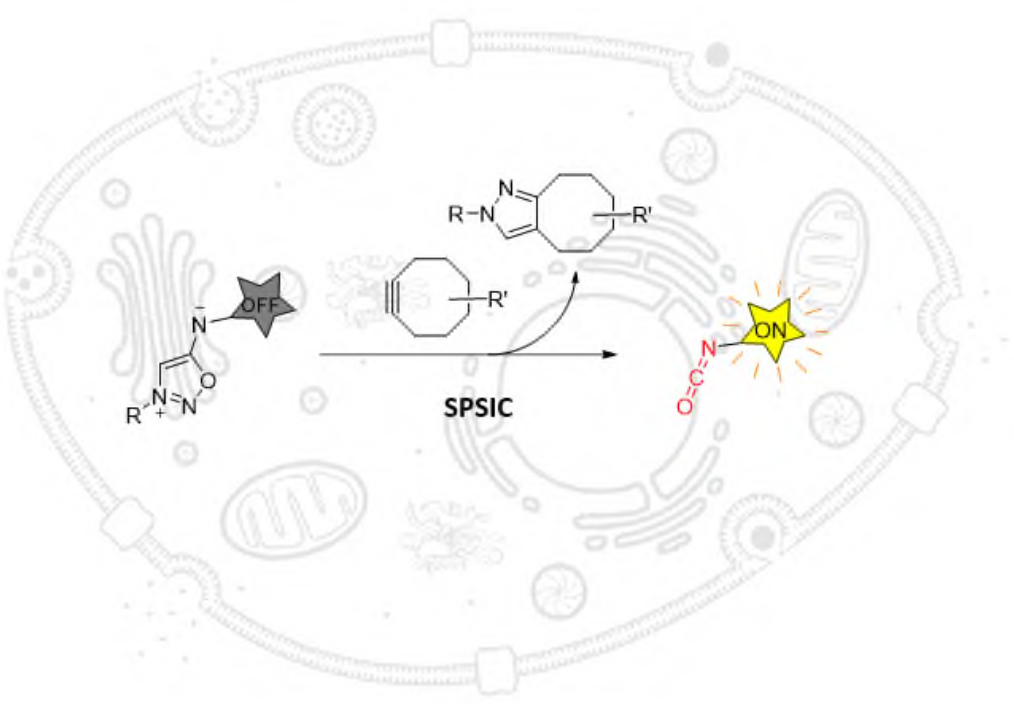
Résumé :

Sydnonimines belong to the mesoionic family, closely related to sydnones with the key distinction of containing a nitrogen atom at position 6. Discovered in the 1950s[1] and further developed in the 1970s for their biological properties, some of them have been approved as drugs.[2] Renewed interest in sydnonimines has recently emerged due to their ability to undergo chemoselective cycloaddition reactions with strained alkynes, termed SPSIC (for Strained Promoted SydnonImine Cyclooctyne Cycloaddition).[3] We developed sydnonimine probes allowing the release of fluorescent aromatic isocyanates inside living cells, upon addition of cyclooctynes.[4] These fluorogenic probes allowed the permanent, irreversible fluorescent labeling of cells which can be exploited in several cell imaging technologies.



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CF-6

Development of functionalized amidrazones as an original azaheterocycle for use in DEL Chemistry

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In the context of drug discovery, the need for greater structural diversity is prominent to address the identification of new molecular scaffolds to interact with a biological target of interest. Typical high-throughput screening (HTS) which uses such large chemical libraries and requires that each compound be individually synthesized, stored, and assayed in an automated facility is being revolutionised by DNA encoded libraries (DEL), where the power of genetic encoding overcomes the limitations of HTS. This method allows mixtures of compounds to be screened, as each molecule is tagged with a DNA 'barcode' that enables identification of the ligand that successfully binds to the target. This powerful technology represents a novel and robust approach in drug discovery for hit identification, rapid lead generation and the ability to diversify the chemical space. However, to further optimize this process, original building blocks are required. Based on the observation that 82% of FDA-approved small-molecule drugs contain a nitrogen heterocycle, but that pyridine, piperidine, and piperazine are the most common 6-membered azaheterocycles,[1] due to the numerous routes described to synthetize them, it seems necessary to expand the availability of synthetic methods to access original and underrepresented azaheterocycles with the aim of using them in the DEL process.

Our team's investigations focus on 1,4,5,6-tetrahydro-1,2,4-triazines also called cyclic amidrazones as bioisosters of classical heterocycles. Our first team works reported a novel synthetic access of functionalized amidrazones, but our results were only limited to the synthesis of amidrazones derivatives featuring aliphatic or aromatic groups (figure 1, a)).[2-3] In order to use the cyclic amidrazone as an original building block in the DEL technology, we now report the synthesis of new multifunctionalized amidrazones (figure 1, b)), with reactive groups that will serve as anchors to attach other building blocks for the development of new DELs.

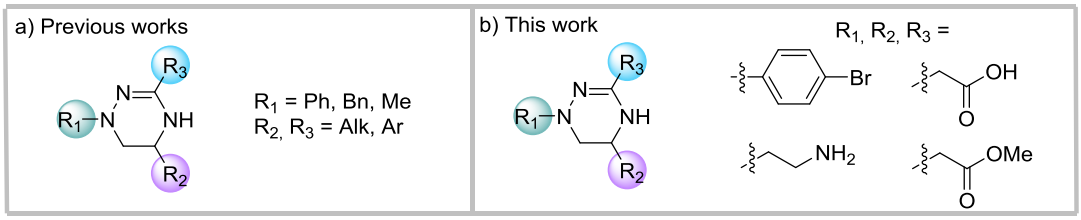

Figure 1. New advances in the synthesis of functionalized amidrazones for use as DNA encoded library building blocks

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Keywords: azaheterocycle, amidrazone, DNA encoded librairy, functionalization

CF-7

Synthesis, modification and photophysical study of luminescent dipyridylmethene boron complexes

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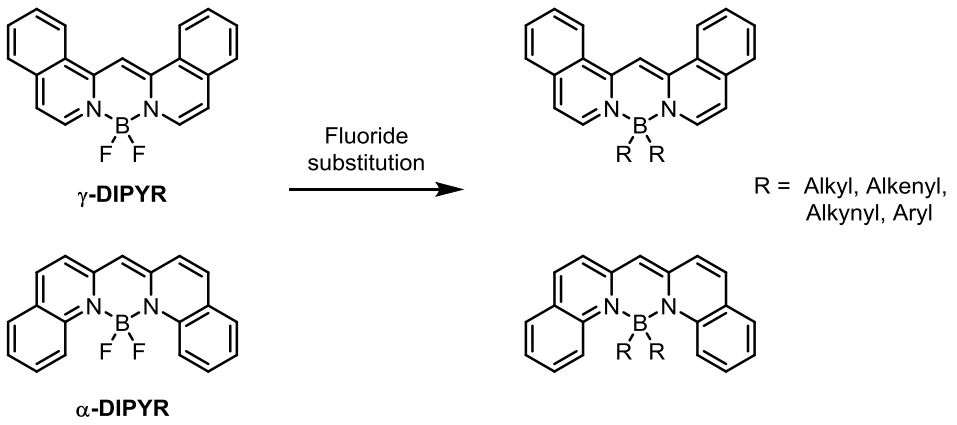
Molecular bioimaging is an important and still growing field of research and the development of new fluorescent scaffolds is a key feature to be able to adapt the fluorophore for a specific application. Among all the organic fluorophores one successful strategy consist of transforming a flexible cyanine type heteroaryl compound into a fluorophore by complexation with a boron atom [1]. The archetypal example is the BODIPY scaffold in which a BIII 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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Keywords: DIPYR, boron complexe, fluorescence

Favoriser l'innovation en biologie chimique grâce à des outils de recherche de haute qualité

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CF-9

New TURN-ON probes for the detection of bacteria in body fluids

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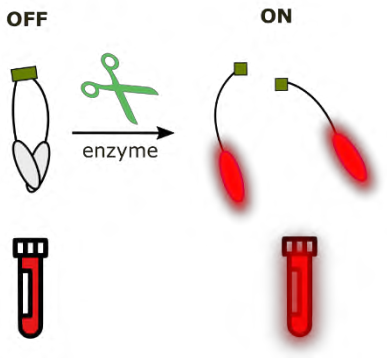
Résumé :

Due to the spread of antibiotic-resistant pathogens, bacterial infectious diseases became one of the first causes of mortality and morbidity in the world[1],[2]. An early administration of an appropriate antibiotic considerably reduces the risk of mortality[3]. However, the current methods of clinical detection and identification of bacteria in body fluids (urine, blood…) are insensitive and time-consuming due to the bacterial culture step. In our team, we aim at developing rapid and direct next-generation methods for clinical diagnostics of bacterial infections.

We have recently developed a new concept of targeted fluorescent turn-on probes for bacteria, based on aggregation-caused quenching (ACQ)[4]. The probes are composed of bacteria-targeting vectors (antimicrobial peptides) and covalent dimers of far-red squaraine dyes. In an aqueous medium, the probes exist in the form of non-fluorescent π-stacked H-aggregates, whereas in an apolar medium (cell membrane), the fluorescence is restored. We have successfully applied dimeric squaraine probes for the detection of bacteria in patient urine samples. However, the squaraine probes were not suited for the analysis of blood, as they displayed strong fluorescence in the presence of serum albumins.

To reduce the non-specific opening of the dimer in the presence of albumins, we turned our attention to the hydrophobic planar dye Nile Red, which was expected to form strong intracellular dimers. We demonstrated that Nile Red dimers were characterized by an excellent fluorescence turn-on between aqueous and apolar media, and a highly reduced off-target fluorescence in the presence of serum. To increase the efficiency of the opening of the dimers upon bacterial labeling, we inserted bacterial enzyme-cleavable peptide sequences between two Nile Red fluorophores. The new probes, combining the ACQ principle and the bacterial activation, are expected to selectively recognize the presence of *S. aureus*, one of the emergent pathogens, in body fluids.



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Keywords: fluorescent probes; fluorogenic detection; Nile Red; bacterial detection.

Communications par Poster

CP-1

CHEM-Symbiose : **A custom synthesis platform of organic compounds for chemical-biology program**

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Abstract :

Open to new collaboration/opportunities ?

Located at CEISAM laboratory (Nantes Université, UMR CNRS 6230), CHEM-Symbiose is a fully equipped platform dedicated to the elaboration of simple or advanced organic molecules (milligram to gram preparation scale) for academic research programs in life sciences and health[1], food and nutrition[2], and agriculture and environment, including marine environment. Thanks to its expertise in lots of chemistry fields, beyond its role as a supplier of organic molecules based on the state of the art, CHEM-Symbiose platform also supports collaborative works with biologist partners for establishing proof of concept of innovative research projects. CHEM-Symbiose is labeled by regional and national scientific networks Biogenouest and IBiSA. This platform is also a member of ChemBioFrance.

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Polyphenols-plant proteins interaction : effect on polyphenol antioxydant activity

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Résumé :

Secondary plant metabolites, such as natural phenolic compounds are well-known for their biological activities (antioxidant, antimicrobial, antifungal,…) but they often show low stability or solubility limiting their applications[1]. Encapsulation in sustainable drug delivery systems could overcome some limitations of these natural compounds, enhance their stability and efficiency to make them suitable for agrochemical, food or pharmaceutical applications. Finding a suitable matrix for encapsulation of natural compounds is often challenging. For food application, food-grade matrices such as polysaccharides or proteins are required. Among them, plant protein isolates are now currently used in food product and for encapsulation of various bioactive compounds.

Herein, we study the interaction between several polyphenols and plant protein isolates (pea, soy, hemp, rice) or BSA as model protein by several spectroscopic methods (fluorimetry, FTIR, ITC…) to select the most suitable biopolymer for their encapsulation. The affinity contant, the thermodynamic parameters and the number of binding site were determined for resveratrol and differents plant protein isolates. The effects of polyphenol structure (aglycon/glycosylated, free or methylated phenolic groups) on the interaction were as well evaluated. Finally, the interaction of resveratrol with plant protein isolates affects its antioxidant activity as determined by DPPH and FRAP assays. A correlation between the affinity constant and the antioxidant activity modification has been observed.

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Keywords: resveratrol, plant isolate proteins, interaction

CP-3

Imp@ct Platform :
Innovative technologies specializing in functional proteomic analysis

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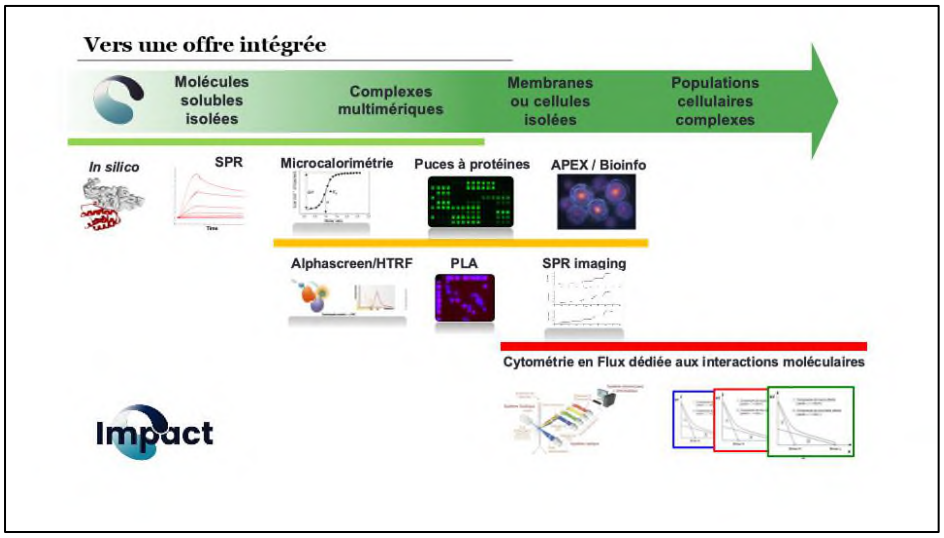
Résumé :

The Imp@ct platform takes place in the proteomic area and is dedicated to functional proteomic in order to meet the needs of academic and private laboratories, mainly in the field of biotechnology. The Imp@ct platform offers a unique set of technologies dedicated to the global study of biomolecular interactions, from screening to the characterization of molecules. Recently, we developed bioinformatics tools (AI-assisted workflow) for molecular design and structure-activity relationship (SAR) analysis.



The Imp@ct platform is a member of the Scientific Interest Group Biogenouest, a network of 37 technology platforms in life and environmental sciences.

Keywords: interactions, proteins, structure-function, screening

CP-4

Criblage et Identification de Nouveaux Inhibiteurs des Facteurs de Réparation de l'ADN à Visée Thérapeutique par une Approche Nanotechnologique basée sur les Quantum Dots

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Résumé :

Les thérapies anticancéreuses se heurtent fréquemment aux résistances des cellules cancéreuses et le mécanisme de réparation des cassures doubles brin (CDB) de l'ADN par la recombinaison homologue (RH), est apparue comme une cible thérapeutique pour sensibiliser les tumeurs et ainsi optimiser les traitements anti-cancéreux. La surexpression de la protéine clef de la RH, RAD51, est à l'origine de certaines chimiorésistances des cancers et il est décrit que son inhibition potentialise les traitements anticancéreux. RAD51 constitue donc une cible thérapeutique pertinente.[1] Le développement d'outils de détection apparaît nécessaire pour mieux comprendre le fonctionnement de RAD51 et pour le criblage et l'identification de nouvelle molécules capables d'inhiber son activité mais aussi ses interactions avec ses partenaires. Les méthodes de détection sensibles et spécifiques basées sur des conjugués de biomolécules et des nanocristaux « quantum dots » (QDs) fluorescents constituent un avantage important pour le criblage de chimiothèques. Les QDs ont bénéficié d'une perspective d'application remarquable dans le domaine de la biomédecine et présentent des avantages considérables par rapport à leurs homologues organiques : plus photostables, spectre d'émission plus étroit, photoluminescence excitable dans une large gamme spectrale et surtout la dépendance des transitions optiques par rapport à la taille physique des QD, ce qui a permis d'utiliser les QD dans la biodétection multiplexe. Hypothèses et questions posées : La détection sensible et spécifique basées sur des conjugués de biomolécules et des nanocristaux « quantum dots » (QDs) fluorescents, constitue un avantage pour le criblage de chimiothèques. L'objectif est d'utiliser des peptides spécifiques des domaines fonctionnels de la protéine RAD51 conjugués à des QDs pour développer des outils de criblage en multiplex et ainsi identifier de nouvelles molécules thérapeutiques et pour suivre le trafic intracellulaire des partenaires de RAD51 dans des contextes pathologiques et normaux.

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Keywords: Réparation d'ADN; Cancer; Thérapies anti-cancéreux; Quantum dots.

CP-5

Development of biomimetic surfaces for the study of the adhesion, motility and invasive behavior of *Toxoplasma gondii*

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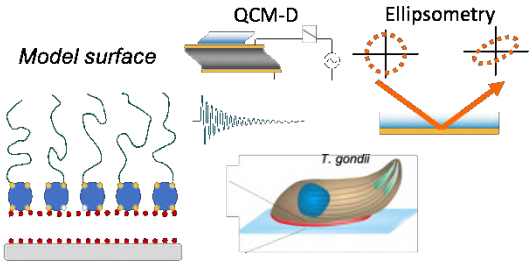
Résumé :

Toxoplasma gondii is a single-celled eukaryotic microbe responsible for toxoplasmosis, a disease that can be particularly dangerous in immunocompromised people or if contracted during pregnancy. The tachyzoite morphotype of this parasite, known to be highly motile, invasive and fast-cycling, is used as a model to better understand how apicomplexan protozoans are able to evolve in the extracellular matrix of their host and invade their cells.[1] Recent studies performed on poly(L-lysine)-g-poly(ethylene glycol), fibronectin and heparin-coated substrates have contributed to better understand the adhesion strategy and gliding mechanism of *T. gondii*.[2] However, the biophysical and biochemical conditions necessary for the parasite to invade a host cell remain poorly understood.

In our project ("MiniToxoAd", ANR-23-CE44-0024-02), that is at the interface of cell biology, biophysics and surface chemistry, we use biotinylated supported lipid bilayers and self-assembled monolayers, functionalized with streptavidin, to develop tunable biomimetic surfaces.[3] We use these models for the study of *T. gondii*'s adhesion, motility and invasion properties. In particular, we investigate how these processes depend on the nature, density and mobility of surface ligands. Here we present our results, focusing on the surface characterization with quartz crystal microbalance with dissipation monitoring and spectroscopic ellipsometry, completed by the examples of *in vitro* fluorescence microscopy imaging.



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Keywords: biomimetic surfaces, quartz crystal microbalance, toxoplasma gondii

WazaGay, an innovative bimodal probe for PET imaging and Near Infrared fluorescence guided surgery

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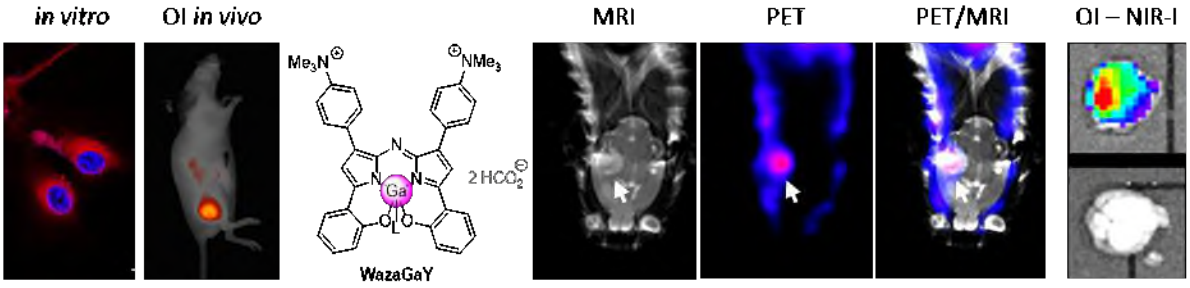
Résumé :

Aza-boron-dipyrromethenes (aza-BODIPYs) have emerged as a class of highly promising fluorophores, comparable to rhodamines and cyanines, due to their ease of synthesis, high stability, and strong fluorescence in the near-infrared (NIR-I, 700–900 nm). These properties make them ideal candidates for *in vivo* fluorescence imaging and surgical guidance. Some of our developed aza-BODIPYs extend emission into the NIR-II window (1000–1700 nm),[1] enhancing imaging resolution.

While structural modifications have focused on tuning the substituents and conjugation of aza-BODIPYs, little attention has been given to the boron center itself. In this work, we explore the impact of replacing boron with metal centers, leading to the synthesis and characterization of novel aza-Metal-DIPY complexes. [2] Special emphasis will be placed on a gallium derivative that has been water-solubilized and designed as a bimodal probe for both NIR fluorescence and PET imaging. We will present its biodistribution in tumor-bearing mice (U87MG, IGROV1, A375), its application in fluorescence-guided surgery, [3] and its potential for PET imaging through radiolabeling with [^{68}Ga]. These results highlight the promise of metal-substituted aza-BODIPYs for advanced bioimaging applications.



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Keywords: Bimodal imaging; fluorescence guided surgery; NIR-fluorescence

CP-7

CLICKABLE FLUORESCENT PROBES FOR BIOLOGICAL APPLICATION

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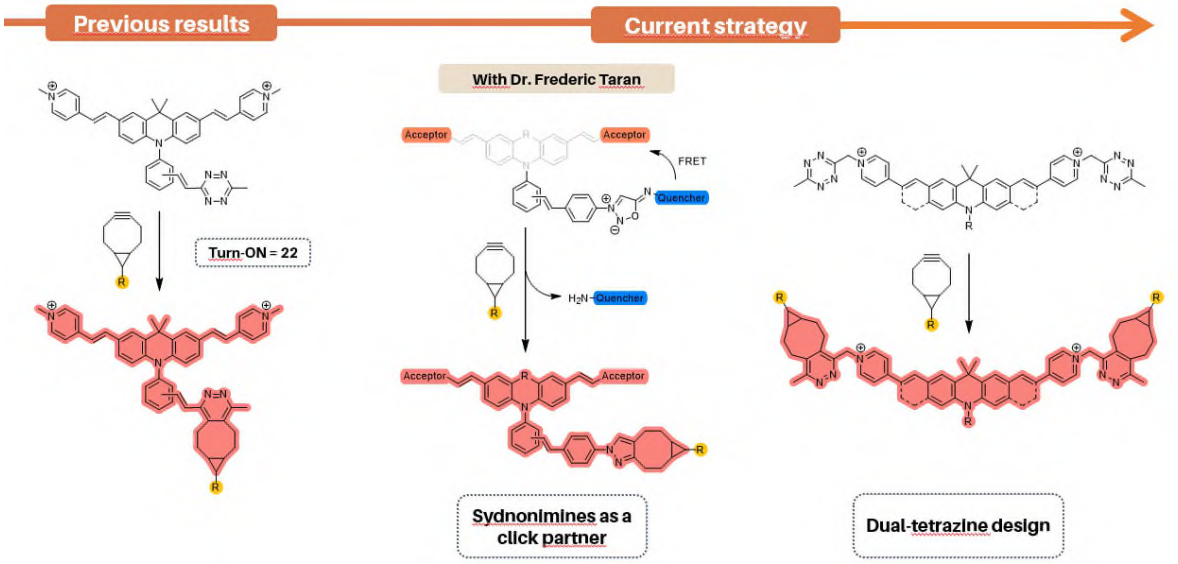
Fluorescent probes are powerful tools in bioimaging and diagnostics due to their ability to emit light in response to specific biological biomolecules or environmental changes. While conventional fluorescence techniques offer high sensitivity and resolution, they are limited by shallow tissue penetration and photodamage. Two-photon excitation (2PE) overcomes these issues by enabling deep tissue imaging with reduced phototoxicity. However, most dyes are not optimized for 2PE, requiring high laser power due to low absorption cross-sections.

This project aims to develop red-emissive, water-soluble fluorophores with strong two-photon absorption[1], combining efficient photophysical properties and biocompatibility for advanced imaging applications.In the laboratory, several fluorophores with promising two-photon photophysical properties have already been developed [2]. However, a major limitation remains their low fluorescence quantum yield in water, which drastically reduces their brightness and overall imaging efficiency. To address this, one of the strategies under investigation is molecular rigidification. Indeed, it is well established in the literature that restricting bond rotations within the fluorophore's structure reduces non-radiative energy loss, thereby enhancing fluorescence emission [3]. Another goal of this project is to develop fluorogenic systems that turn on their fluorescence upon a bioorthogonal click reaction. In previous work in the laboratory, tetrazine-based systems have demonstrated efficient turn-on properties [4]. The current goal is to expand the scope of click partners, notably by exploring sydnonimines[5], or by introducing two tetrazine units within the same probe to potentially enhance the fluorescence turn-on effect.



Alongside this, Density Functional Theory (DFT) calculations are carried out to predict the photophysical properties of the developed probes. These theoretical studies help guide the synthetic efforts toward the most promising structures by identifying candidates with the best predicted performance.

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Design moléculaire, développement *in synthetico* de dérivés de 3-amino-4-imino-3,5-dihydro-4*H*-chromeno[2,3-*d*]pyrimidine et leurs biologies *in silico*, *in vitro* et *in vivo*

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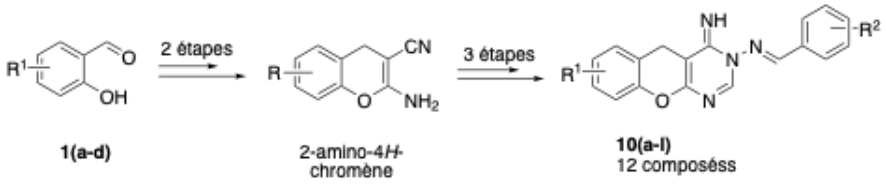
Abstract : Depuis cette dernière décennie, la plateforme 2-amino-4*H*-[1]-chromène suscite l'engouement de la communauté des pharmaco-chimistes car plusieurs de leurs dérivés comme le HA14-1 [1] (inhibiteur de Bcl2) et l'EPC2407[2] ou *crolibuline* (inhibiteur de microtubuline, NTC 01240590) ont été respectivement l'objet d'essais pré-cliniques pour le lymphome folliculaire et d'essais cliniques phase I/II pour le traitement de tumeurs solides du cancer anaplasique de la thyroïde.



Dans ce contexte, la mise en place d'une séquence synthétique courte, simple, robuste, impliquant 2 étapes sous chauffage diélectrique d'irradiation micro-onde a permis de générer de la diversité moléculaire autour de la plateforme 2-amino-4*H*-[1]-chromène[3] privilégiant l'émergence de nouveaux dérivés **10(a-l)**[4]. Les propriétés physicochimiques *in silico* de ces composés **10(a-l)** ont été déterminées selon la règle des cinq de Lipinski (RO5) associée à la prédiction de leur biodisponibilité *in silico*. Ces nouveaux composés **10(a-l)** ont été testés *in vitro* pour leurs activités antiprolifératives sur des lignées cellulaires tumorales humaines représentatives (Huh7 D12, Caco2, MDA-MB231, MDA-MB468, HCT116, PC3, MCF7 et PANC1) et sur fibroblastes. Des tests de régulation calcique SOCE (Store-Operated Calcium Entry) de **10h** sur lignée cellulaire cancéreuse HEK293 ont montré que ce composé agit de manière dose dépendante. L'embryo-toxicité et l'angiogenèse *in vitro* sur lignée de poisson Zebrafish *danio rerio* transgénique mCherry ont montré que ce composé **10h** ne présente aucun effet toxique ni aucun effet angiogénique sur les embryons avec une dose de 5 mM à 72 hpf.

Remerciements : Campus France et le Comité Mixte pour la Coopération Universitaire (CMCU) du Programme Hubert Curien Utique « Synérèse » sont remerciés pour leurs soutiens à la mobilité internationale entre les équipes de Sfax (SK, MD, HA) et de Rennes (EL, LP, JPB). Contrat 2021-23 Campus France : 46156NL, CMCU : 21G202

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Keywords: 2-amino-4*H*-[1]-chromène; micro-onde, cytotoxicté ; SOCE ; Zebrafish ; angiogénèse

Fluorescent molecular rotors as probes for RNA-based biomolecular condensates

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Biomolecular condensates (BCs) are microscopic fluid bodies formed by proteins and nucleic acids through a process known as liquid-liquid phase separation (LLPS). Cells exploit LLPS to organize certain proteins, RNAs, and other molecules in space and time in a regulated way. Phase-separated cellular bodies and organelles (such as the nucleolus, RNP granules, and others) are crucial for several fundamental cellular processes, including ribosome biogenesis, mRNA metabolism, nuclear transport, and stress response [1–2]. Studying the material properties of BCs, such as internal viscosity and surface tension, is essential because these properties determine the mobility of the droplet-embedded biomolecules and the dynamics of interphase exchange, which ultimately influence the biological functions of BCs. However, the current methods used to investigate the material properties of BCs are both time-consuming and invasive.

We hypothesized that environmentally sensitive fluorophores known as fluorescent molecular rotors (FMRs) could serve as non-invasive optical probes for investigating the internal viscosity of RNA-based BCs. The fluorescence lifetime of FMRs is highly responsive to the local viscosity. Hence, measuring the fluorescence lifetimes of FMRs covalently linked to biomolecules can infer the internal viscosity of BCs by using appropriately prepared calibration curves as references. To test our hypothesis, we synthesized FMR probes based on the BODIPY scaffold in the form of hydrazides suitable for covalent 3'-end labeling of RNAs. This labeling method will be applied to RNAs containing trinucleotide repeats known to undergo LLPS in vitro and in vivo [3]. Time-correlated single-photon counting and fluorescence lifetime imaging will be employed to measure the fluorescence lifetimes of the condensate-embedded FMR reporter, enabling non-invasive analysis of the internal viscosity of RNA-based BCs with high spatial and temporal resolution.

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Keywords: Fluorescence, RNA labelling, Molecular rotors

CP-10

Artificial DNAzymes for Asymmetric Oxidation

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Résumé :

As part of the development of artificial metalloenzymes as eco-compatible catalysts, nucleic acids, particularly G-quadruplexes (G4), offer an alternative to proteins for asymmetric catalysis due to their unique structures.[1] However, G4 structures exhibit coexisting topologies in dynamic equilibrium,[2] which can significantly influence their catalytic activity and selectivity (Fig. 1, A).
Consequently, controlling the G4 topology can be a way to tune the catalyst.

Peptide templates have been used to immobilize guanine-rich oligonucleotides and block G4 in a specific topology. These structures have been shown to catalyze the enantioselective oxidation of thioethers in combination with a copper(II) complex.[3] However, the obtained enantiomeric excesses remain moderate due to insufficient interaction between the G4 and copper complex. Additionally, it has been shown that stereoselectivity is strongly influenced by the position of the reaction site within the G4 structure.

This PhD project, conducted in collaboration between the Département de Chimie Moléculaire (DCM) and the Laboratoire de Chimie et Biologie des Métaux (LCBM), aims to enhance the enantiomeric excesses by covalently conjugating the copper complex to a specific region of the G4 mimic (Fig. 1, B). Our strategy seeks to (i) prevent off-structure reactions, (ii) control reaction orientation by targeting a specific site (Fig. 1, C), and (iii) expand the scope of enantioselective oxidation reactions to other transformations, such as olefin epoxidation.

This poster will present the development of artificial metalloenzymes based on G4 for asymmetric catalysis. It will highlight the use of peptide templates to stabilize specific G4 topologies and their role in the enantioselective oxidation of thioethers. Different covalent conjugation methods for the copper complex will be explored to select the reaction site and thus control stereoselectivity.

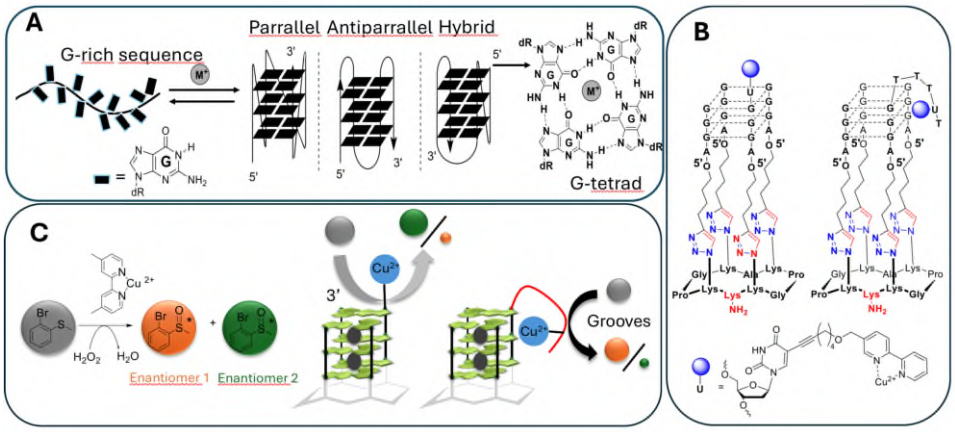

Fig. 1 : A - Conformational equilibrium of G4, examples of topologies, and guanine tetrad. B - Examples of G-quadruplex mimics with a covalently conjugated copper complex. C - Asymmetric sulfoxidation using G-quadruplex mimics as chiral inducers.

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Keywords: G-quadruplex, asymmetric catalysis, sulfoxidation

CP-11

Biophysical Evaluation of IRE1α Inhibitors with Blood-Brain Barrier Permeability for Glioblastoma Adjuvant Therapy

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Résumé :

Glioblastoma (GB) is the most aggressive primitive cancer of the central nervous system (CNS). The current standard of care, the Stupp protocol, combines surgical resection when possible (~70 % of patients), radiotherapy and temozolomide (TMZ)-based chemotherapy. However, cancer cells rapidly develop resistance to TMZ and tumor relapse, resulting in an average survival time of 12 to 18 months post-treatment.[1]

Recent studies have highlighted the role of the unfolded protein response (UPR), an adaptive signaling pathway associated with the endoplasmic reticulum (ER) stress, in promoting cancer cell survival. This signaling pathway offers to cancer cells a mechanism to cope with cellular stress, notably through the main UPR sensor: the inositol-requiring enzyme type 1 α (IRE1).[2] IRE1 is a highly conserved protein, which presents a dual serine/threonine kinase and endoribonuclease (RNase) activity. Inhibition of IRE1 activities has shown significant potential in resensitizing cancer cells to TMZ, making it a promising therapeutic target to overcome resistance in GB.[2,3] However, no IRE1 kinase inhibitor capable of crossing the blood-brain barrier (BBB) is currently available on the pharmaceutical market, partly due to the need for high membrane permeability—a critical requirement for effective drug delivery to the CNS.

In a previous study, our laboratories discovered and characterized Z4P as a first promising hit and first-in-kind BBB-permeable IRE1 inhibitor.[4] This compound demonstrated IRE1 inhibition in the micromolar range in vitro, prompted target engagement in vivo and most notably had a real impact as adjuvant with TMZ in an orthoptic xenograft murine GB model.[4] Chemical diversification around the Z4P scaffold was performed. However, in-house biological assays hindered the establishment of a clear mode of action and structure-activity relationships (SAR). We are currently focusing on developing complementary biophysical and biochemical assays applied to IRE1 to (1) provide insights into its binding mode and (2) support the development of a quantitative SAR (QSAR) model, guiding the access to early lead based-Z4P analogs.

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Keywords: Glioblastoma; IRE1; kinase inhibitor; biophysical assays.

CP-12

Molecularly imprinted polymer (MIP) particles for specific capture of Vascular Endothelial Growth Factor

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Résumé :

Vascular Endothelial Growth Factor or VEGF is a secreted protein which, upon binding to its designated receptor VEGFR, plays an important role to form new blood vessels during embryonic development, wound healing, and vascular permeability. VEGF is found to be a key mediator of tumour-associated neo-angiogenesis and progression. Angiogenesis is regulated by pro- and anti-angiogenic modulators. During tumour progression, the angiogenesis process is turned on by upregulation of pro-angiogenic factors, such as VEGF which is indeed found overexpressed in most human cancers. This process of new blood vessel proliferation is fundamental for tumour growth, invasion, and metastasis formation since these tumoral mass growth is limited by nutrient requests[1]. Indeed, the formation of new blood vessels that bring oxygen and nutrients inside the new tumour results in sustaining the progression and growth of tumoral mass. VEGF is therefore an important drug target. The purpose of this project is to rely on molecular imprinting technology to bind and sequester VEGF to impar its associated angiogenic pathway. Molecular imprinting technology aims at producing synthetic antibodies with specific and selective recognition proprieties towards a target molecule, here VEGF. These synthetic antibodies (molecularly imprinted polymers, MIPs), are 3D polymer networks with cavities generated by the use of molecular templates. The cavities are complementary in terms of size, shape, and position of chemical groups to the template molecule[2]. In this PhD project, MIPs are synthetised as polyacrylamide nanogels by relying on solid-phase synthesis.[3]

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Keywords: Molecularly imprinted polymer (MIP) – synthetic antibody – solid-phase synthesis – Vascular endothelial growth factor (VEGF)

CP-13

DNA origami for tunable spatiotemporal control over IRE1 assemblies

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Abstract:

The inositol-requiring enzyme 1 (IRE1) is considered to be a "master regulator" of the Unfolded Protein Response (UPR), an adaptive signalling pathway to protect cells against endoplasmic reticulum (ER) stress.[1] Although IRE1 has been demonstrated to be a key player in severe diseases like cancer or degenerative diseases, the structural bases underlying its activation mechanism remain unclear and even if recent publications[2,3] have attempted to document those aspects, they are still unclear. These mechanistic details have important implications for the biological understanding of adaptive signalling outputs as well as for better therapeutic targeting of IRE1.

My project focuses on using a programmable DNA origami where the nanoscale organisation and nature of the complexes formed by the cytosolic domain of IRE1 can be controlled, notably their oligomeric state and phosphorylation status. With this approach, I will be able to shed light on key questions such as assembly requirements (*e.g.* dimers or dimers-of-dimers) and *trans*-autophosphorylation impact of IRE1 on its oligomeric status and activities.

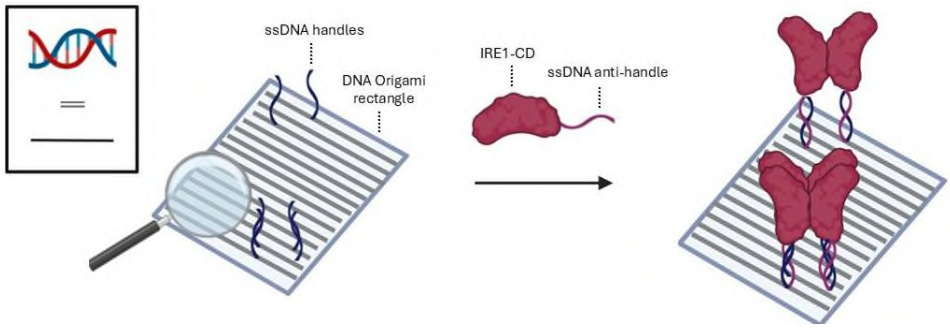

Figure 1: DNA Origami Model for IRE1 activation mechanism investigation.

The first year of my PhD focuses on the expression of the recombinant cytosolic domain of IRE1 (IRE1-CD) in insect cells. This purified recombinant protein will be modified at its *N*-terminus *via* a site-specific chemical approach with a single-stranded DNA sequence. This will allow for hybridisation of the protein with a complementary sequence of the DNA origami. In parallel, a DNA origami rectangle with protruding ssDNA handles at its surface will be designed *in silico* and assembled using the M13mp18 scaffold molecule DNA and hundreds of purpose-made "staple strands".[4]

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Keywords: IRE1, DNA Origami, Molecular Mechanisms, Protein Complex

CP-14

New Aptamer Conjugates Mimicking Monoclonal Antibody Activity

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Résumé :

Monoclonal antibodies (mAbs) are widely used for diagnostic, research, and therapeutic applications, but several limitations related to their nature limit their extensive clinical use. Developing new molecular systems that integrate the advantages of mAbs while circumventing their limitations is then highly advantageous. In this context, nucleic acid aptamers are a special class of biomolecules that are currently investigated for clinical use.

Herein, we are interested by the development of DNA aptamers that target the CD20 (Cluster of Differentiation 20) antigen. Among the key target of mAbs, the recognition of CD20 antigen, exclusively expressed on B cells, is used for the treatment of several pathologies including lymphoma and autoimmune diseases, by using for example the mAb Rituximab. Recently, the interaction between CD20 and Rituximab was shown to involve a dimerization of CD20 at the cell surface, which we have been able to recapitulate on a synthetic biomimetic surface.[1]

Based on this result, we selected DNA aptamers from a dimeric version of CD20 by using CE-SELEX (Capillary electrophoresis-systematic evolution of ligands by exponential enrichment)[2] and characterized them *in vitro* by various physico-chemical methods. The best aptamer candidates will then be integrated into multivalent systems by grafting several aptamers onto a molecular scaffold in combination with a fluorophore. The proof of concept in hands, this project may lead to the design of a therapeutic candidate.

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Keywords: aptamers; biomimetic surfaces; biomolecular assembly

CP-15

Understanding the activation of radiation-actuable, MRI-detectable theranostic prodrugs for cancer treatment

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Résumé :

Chemotherapy is limited by the off-target toxicity of current treatments, largely due to the lack of specificity of drugs for the tumour environment. To address this limitation, photoactuatableivable prodrugs have been developed; however, their activation remains confined to superficial tissues due to the low-energy photon (UV to near-IR) required for their activation. Our team has devised a strategy based on theranostic prodrugs that can be activated by deeply penetrating stimuli such as those used in radiotherapy. The compounds developed contain an azobenzene moiety that switches from cis to trans configuration upon irradiation, thereby triggering cytotoxicity.

We observed an activation efficiency ranging from 33 to 69% (2 to 20 Gy) for cis-GdAzo, leading to significant cytotoxic effects on cancer cells after activation at clinically relevant radiation doses.

As a result, we have developed “radioswitches” that can be selectively activated with high spatiotemporal precision at any depth within biological tissues, allowing the treatment of deep-seated tumours while sparing healthy tissues. Additionally, the presence of a gadolinium chelate enables monitoring of prodrug accumulation in tumours by magnetic resonance imaging following intravenous administration, supporting early patient stratification.

Understanding the activation mechanism is a key aspect of this project, and experimental results have shown that the metal ion in the chelate influences the activation efficiencypotential of the prodrug. We are therefore investigating, through DFT calculations and machine learning approaches, the various parameters that could highlight the relation between the nature of the metal ion and the activation behavior.

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Keywords: radioactivation, DFT calculation, theranostics, prodrugs, cancer treatment.

CP-16

New soluble supports for synthesis: Cap-4 analogues to study cap-4 interaction mechanism with the *T. cruzi* EIF4E homologues 5mCpG dinucleotides to interfere with DNA methylation reader proteins

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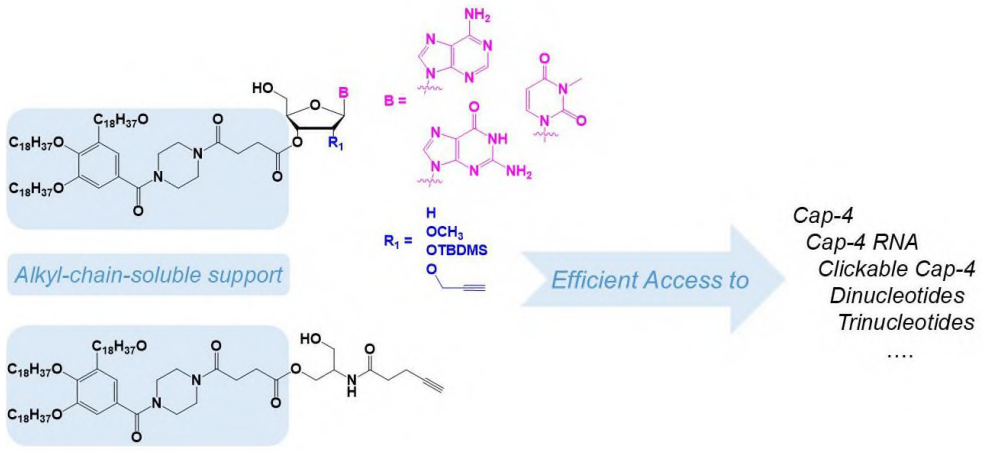
Résumé :

Taking advantage of an alkyl-chain soluble support described by Kim *et al.*[1], we developed and optimized the synthesis of various supported nucleosides. This opens the path to the synthesis of nucleotides and oligonucleotides on a rapid and large scale for various applications without time-consuming and costly purification steps. The desired products are recovered easily by precipitation and centrifugation while the synthesis steps are carried out in homogeneous media. Here we described the preparation of the alkyl-chain soluble support, five soluble support attached nucleosides, and their use to access Cap-4[2], Cap-4 RNA, for study cap-4 interaction mechanism. Also, a library of dinucleotides or trinucleotides was obtained through this approach and evaluated on DNA methylation reader proteins[3]. More recently, a new supported clickable linker was prepared to obtain large scale clickable Cap-4 and develop new affinity resins.



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Keywords: Alkyl-chain-soluble support; Cap-4; convertible nucleoside phosphoramidites; CpG dinucleotide analogs

Modulation of positions 2 or 8 of the imidazo[1,2-*a*]pyrazine lead CTN1122 influences its antileishmanial properties, L-CK1.2 kinase inhibition and its safety profile

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Leishmaniasis is a parasitic disease classified as a neglected tropical disease by the WHO.[1] It manifests in various forms—cutaneous, mucocutaneous, and visceral—and poses a serious public health issue, with 12 million people infected globally and over 40,000 deaths annually. The disease is endemic in many regions worldwide, with its emergence in Europe attributed to global warming. Current treatments are far from ideal due to their high toxicity, significant costs, and administration methods that limit accessibility for disadvantaged populations. Additionally, increasing parasite resistance to these treatments is diminishing their effectiveness in some areas. Consequently, there is an urgent need to develop new treatments that are safer, more effective, and target novel proteins to overcome these resistances. A promising recent discovery is CTN1122,[2,3] which targets a specific *Leishmania* Casein Kinase 1 protein (L-CK1.2) and demonstrates strong antileishmanial properties. In this context, we have decided to synthesize **CTN1122** analogues to enhance the pharmacological activity profile (**Figure 1**).

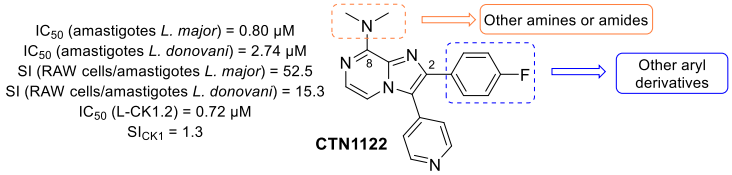

Figure 1: Modulations from the lead compound **CTN1122**

Two types of pharmacomodulation on the imidazo[1,2-*a*]pyrazine ring of the lead compound **CTN1122** will be presented and compared: one by modifying the substituent in position 8 with various amines and amides, and the other by modifying the substituent in position 2 with different substituted aryls. The study of these analogues will allow us to discuss the structure-activity relationship concerning their antileishmanial properties, their ability to inhibit the target protein L-CK1.2 and to consider their toxicity profile.

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Keywords: antileishmanial activity; imidazo[1,2-*a*]pyrazine; casein kinase 1; L-CK1.2 inhibitors