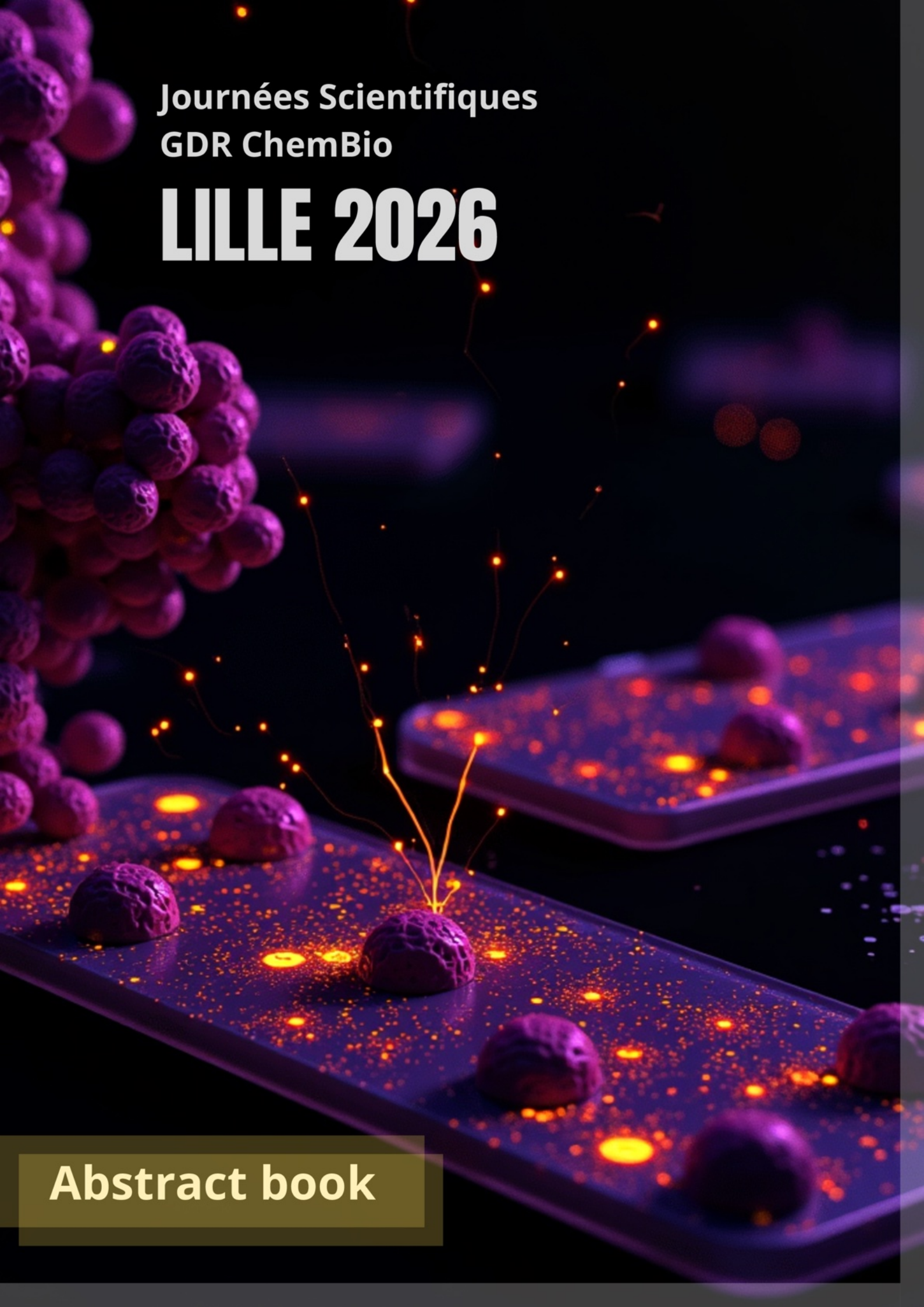
Journées Scientifiques
GDR ChemBio
LILLE 2026
Abstract book

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Plan d'exploration du gisement

L'interface au cœur du vivant et de la cité

Bienvenue à Lille.

Nous ouvrons ces journées dans le sillage d'une décision qui nous dépasse un peu et nous engage beaucoup : le renouvellement de notre **GDR ChemBio** pour une nouvelle mandature. Ce n'est pas qu'une simple reconduction administrative ; c'est la validation d'une persistance. Celle d'une communauté qui, depuis janvier 2021, refuse le cloisonnement pour habiter pleinement l'interface.

Nous sommes aujourd'hui **plus de 80 laboratoires et plus de 600 chercheurs**. Mais au-delà des chiffres, il y a une trajectoire. De Grenoble à Nantes, en passant par Toulouse, Strasbourg et Bordeaux, nous avons appris à faire de la science un lieu de rencontre. Nos sessions "DUO" ne sont pas des exercices de style ; elles sont la preuve par le geste que le dialogue entre le chimiste et le biologiste est l'unique voie pour appréhender la complexité du vivant dans sa globalité.

Cette exigence nous a naturellement conduits vers les **Arts et Sciences**. Ce n'est pas une coquetterie. C'est la conviction profonde que pour comprendre l'invisible, ce gisement moléculaire que nous explorons, il faut savoir décentrer notre regard et laisser la création redessiner nos propres représentations.

En entamant ce nouveau cycle, notre horizon est clair : **affirmer la chémobiologie comme un pilier stratégique de la recherche française**. Il ne s'agit plus seulement de marquer le terrain, mais de **transmettre**.

Si je regarde vers Calais pour évoquer cet art de l'engagement, c'est parce que notre science, ici à Lille, partage cette même exigence de révélation. Comme sur les côtes de la Manche, où l'art de **Banksy**, de **Vyrüs** ou de **Swed Oner** vient bousculer nos certitudes et forcer le regard sur l'invisible, apprenons nous aussi à « disrupter » nos propres modèles. Que nos outils chimiques ne soient pas de simples colorants, mais des vecteurs d'engagement scientifique. À l'instar de ces portraits d'anonymes qui reprennent vie sur les murs des gares, que nos travaux révèlent la complexité et la dignité du vivant là où il nous échappe encore.

Bienvenue à Lille, au cœur de ce gisement de savoirs à transmettre.

Christophe Biot
Directeur du GDR Chémobiologie

Oleg MELNYK

Center for Infection and Immunity of Lille
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Oleg Melnyk est Directeur de Recherche au CNRS à Lille. Expert en chémobiologie, il consacre ses recherches à la synthèse chimique des protéines et à leur modification. En s'appuyant sur des processus biomimétiques, son équipe développe des outils technologiques pour la recherche biomédicale et la conception de médicaments. Son expertise s'étend jusqu'au transfert de technologie, ayant co-fondé deux entreprises : Innobiochips et XProChem.

CI 001

Harnessing Protein Electrostatics to Enable Fast and Precise Protein Modification at Nanomolar Concentrations

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Résumé :

Chemical and biochemical methods that enable site-selective protein modification are central to the study of protein function and to their integration into diagnostic and therapeutic applications. While achieving high selectivity is essential to obtain homogeneous, well-defined products, the rate at which reactions occur on the protein surface is equally critical. Fast reactions help minimize by-product formation as well as protein aggregation or precipitation.

To meet these requirements, protein chemists rely on a limited set of intrinsically fast and selective reactions that are effective at the protein level. However, under the dilute conditions commonly used for handling protein reagents, the rate of protein modification can fall well below expectations based solely on the intrinsic rate constant of the underlying chemical transformation. In such regimes, additional factors become limiting, including the low frequency of productive encounters between reactants.

In this presentation, I will describe the strategies we are developing to accelerate protein modification under dilute conditions by exploiting protein electrostatics.[1-5]

Keywords: Selective protein modification; electrostatics; native chemical ligation, thioester

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Clotilde POLICAR

Laboratoire CPCV, dpt de chimie de l'ENS-PSL, Sorbonne université paris

Professeure au Département de Chimie de l'ENS-PSL, Clotilde Policar travaille en chémobiologie inorganique, à l'interface entre le biomimétisme et l'imagerie cellulaire. Ses recherches portent sur la conception de complexes métalliques capables de mimer l'activité de métalloprotéines (notamment pour la régulation du stress oxydant) ou servant de sondes pour la cartographie des métaux dans les systèmes biologiques. Engagée dans la médiation scientifique, elle développe des projets aux points de contact entre Arts et Sciences. Son intervention aux Journées du GDR à Lille portera sur l'apport de la créativité artistique dans la représentation et la compréhension des objets de la chémobiologie.

CI 002

Les métaux et la vie : du laboratoire à la scène de théâtre

Clotilde Policar, Laboratoire CPCV, dpt de chimie de l'ENS-PSL, Sorbonne université, CNRS UMR 8228

Les métaux sont des éléments essentiels à la vie et pourtant souvent les grands oubliés des études en chimie du vivant.[1,2] Le grand public connaît les oligoéléments mais s'inquiète de la toxicité des métaux. Le spectacle « les métaux et la vie », donné à la Reine Blanche et dans les établissements scolaires depuis 2018, discute de ces questions.
Notre savoir scientifique peut-il être transmis par ce media si particulier qu'est le spectacle vivant ?
Au-delà des pièces scientifiques destinées au grand public, peut-on mobiliser le théâtre pour former les publics étudiants ?
A travers différents exemples, autour de la mise en place de spectacles grand public dans le cadre d'un module universitaire (sur Pasteur[3,4] et sur la nouvelle Carbone de Primo Levi[5]), mais aussi dans celui d'un programme « des savants sur les planche » à la Reine Blanche, nous tenterons d'illustrer ce type de démarche.

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(4) *Quand Pasteur était chimiste*, version vulgarisée donnée à la Reine Blanche en 2016 : https://savoirs.ens.fr/expose.php?id=2607
(5) *Carbone de Primo Levi, projet Chimie et danse* : https://www.chimie.ens.fr/formation/activites-etudiantes-debouches/

Illustration : flyer de la Reine Blanche (2018)

Claire MOULIS

Toulouse Biotechnology Institute
Toulouse

Claire Moulis est professeure à l'INSA Toulouse et co-responsable de l'axe « Enzymes et Assemblages Moléculaires pour One Health » au sein du Toulouse Biotechnology Institute (TBI). Ses activités de recherche sont dédiées à l'ingénierie enzymatique pour la biotechnologie blanche et la chimie verte. Ses travaux portent sur l'étude des relations structure/activité, la résolution cinétique et l'évolution dirigée pour la synthèse de nouveaux poly- et oligosaccharides. Elle se concentre actuellement sur la génération d'enzymes aux spécificités inédites envers des substrats non naturels, visant leur intégration dans des cascades chémo-enzymatiques ou des procédés de production de biopolymères.

CI 003

Sucrose-active enzymes : Green tools for the synthesis of tailored oligosacharides or glucoconjugates

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Abstract:

Glycosylation is a major reaction in numerous biological processes, including cell communication, signaling and protection, and in energy storage. The demand for oligosaccharides and glycoconjugates has steadily increased over the last decades, because well-defined structures are needed to investigate the role of glycosylation in biological phenomena. In addition, there is a growing interest in the application of bioactive oligosaccharides and glycoconjugates in the food, health, and cosmetic industries. *In cellulo*, the transfer of a glycosyl unit from a donor substrate to an acceptor molecule is almost exclusively catalyzed by Leloir glycosyltransferases (GTs) [1]. But GTs are not ideal candidates for the *in vitro* and large-scale synthesis of glycoproducts, since they use nucleotide sugars as donors, which are expensive and in limited supply. But an alternative rely in the use of glycoside-hydrolases (GHs), especially retaining GHs that cleave the osidic bond and retain the anomeric configuration. These enzymes use abundant substrates, such as disaccharides, oligosaccharides, and polysaccharides, which is advantageous for bioeconomic development.

In this context, our group has a long-standing interest in very efficient bacterial alpha-transglucosylases that catalyze the production of high molar mass polysaccharides of glucosyl units from sucrose (our table sugar) such as dextran, the best known polysaccharide of this family. These enzymes are classified in the family 70 of Glycoside-Hydrolases, which comprises today around 1300 sequences for only about sixty enzymes biochemically characterized, that remains low. However, by combining bioinformatics, screening technologies and enzyme structure-function relationship studies, we recently discovered and/or engineered several enzymes dedicated to the production of tailor-made glucans of various sizes and structures, as well as well-defined oligosaccharides or glucoconjugates [2]. After a brief overview of these intriguing enzymes, the presentation will focus on our last developments regarding the functionalization of secondary metabolites such as polyphenols, terpenoids or mycosporine-like amino acids for improving their solubility and/or stability for pharmaceutical or cosmetic applications [3].

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Keywords: Transglycosylases, enzyme engineering, glycosides, oligosaccharides, glycoconjugates.

Plan d'exploration du gisement

DUO 001

Conception de nanobodies fluorogènes dans le proche infra-rouge pour la détection et l'imagerie de cellules cancéreuses

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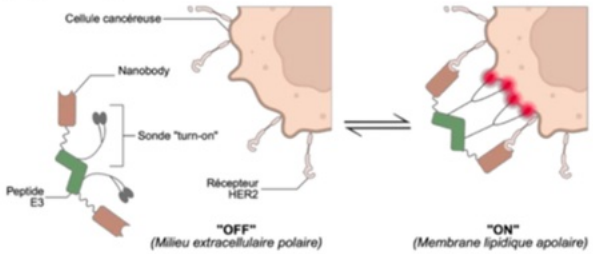
Résumé :

Les sondes fluorescentes constituent des outils majeurs pour la détection, l'imagerie et le suivi des cancers, en raison de leur caractère non invasif, leur forte sensibilité et leur excellente résolution spatiale et temporelle. Parmi ces sondes, on distingue les systèmes dits « *always-on* », qui émettent une fluorescence continue, et les sondes fluorogènes « *turn-on* » qui ne deviennent fluorescentes qu'après liaison à leur cible d'intérêt, améliorant ainsi le rapport signal/bruit et la sensibilité de détection. Récemment, nous avons démontré l'intérêt de ces sondes pour l'imagerie de récepteurs couplés aux protéines G à la surface de cellules vivantes, ainsi que dans des organismes entiers[1,2].

Dans le contexte d'un projet interdisciplinaire porté par l'Institut du Médicament de Strasbourg et soutenu par la Fondation Jean-Marie Lehn et AXA, permettant la réalisation d'une thèse en binôme, nous avons conçu les premiers nanobodies dimériques « *turn-on* » ciblant des cellules tumorales surexprimant le récepteur HER2. Ces sondes sont constituées de deux fluorophores dérivés de cyanines 5.5, capables d'émettre dans le proche infrarouge. En solution aqueuse ces fluorophores forment des H-agrégats non fluorescents (« *turn-off* »), qui se dissocient dans un environnement hydrophobe (« *turn-on* »). Afin d'assurer un ciblage spécifique, les sondes ont été conjuguées, via un espaceur, à un peptide (E3) porteur d'un fragment d'anticorps (VHH) ciblant le récepteur HER2 des cellules tumorales du cancer du sein[3]. Nous avons étudié l'influence de la longueur de l'espaceur et de la nature des cyanines sur les propriétés « *turn-on* » des sondes, leur brillance ainsi que leur affinité et spécificité vis-à-vis de leur cible. Ces études ont été menées à l'aide de mesures photophysiques, de cytométrie en flux et de microscopie confocale sur cellules vivantes. Les sondes développées présentent un fort potentiel pour l'imagerie de cellules tumorales, notamment dans des applications de diagnostic et de chirurgie guidée par la fluorescence.



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Keywords: Cancer, Nanobodies, Fluorescence

DUO 002

Chemistry with cells: bioorthogonal reconfiguration of intercellular interactions

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Résumé

Cell-to-cell contact signaling governs fundamental biological processes, ranging from tissue morphogenesis to neurotransmission and immune surveillance. Herein, we demonstrate that the bioorthogonal regulation of intercellular interactions enables spatiotemporal control over collective cell migration, thereby establishing a chemically programmed pathway for artificial cell communication. We engineered stimuli-responsive cell-surface markers **1** which incorporate three b-cyclodextrin (b-CD)-based recognition units, a sydnonimine (SI) trigger and a tetrazine (Tz) bioconjugation head (Figure 1C). Once functionalized, T lymphocytes acquire the ability to recognize tumor cells displaying complementary adamantyl moieties through non-covalent host-guest chemistry. However, upon activation by the dibenzocyclooctyne (DBCO) derivatives **2**, the membrane-bound markers **1** undergo a strain-promoted sydnonimine–alkyne cycloaddition (SPSIC). This 'click-to-release' reaction triggers the displacement of the surface β-CD units by the adamantyl groups. Therefore, the reshuffling of the immune cell membrane abrogates cell–cell adhesion by disrupting the initial host–guest framework, while simultaneously reconfiguring the T lymphocytes to target a secondary population of β-CD-functionalized cancer cells. Under these conditions, T-cells are transformed into programmable intercellular carriers, promoting the transport of small molecules from primary tumor targets to a distal cellular destination.

DUO 003

Identification et Ciblage par PROTACs de la Voie PI3Kγ-Akt, une Vulnérabilité Lignée-Spécifique dans les Leucémies Myéloïdes Aiguës.

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Résumé :

Les leucémies myéloïdes aiguës (LAM) sont les leucémies les plus fréquentes chez l'adulte et sont associées à un pronostic défavorable. Les traitements standards de la LAM, qu'ils soient intensifs (chimiothérapies) ou non (combinaisons à base de vénétoclax), sont souvent limités par leur toxicité envers les tissus sains. Il est donc crucial d'identifier des facteurs de survie qui soient hautement spécifiques du lignage myéloïde et pharmacologiquement actionnables afin d'ouvrir la voie à de nouvelles approches thérapeutiques avec une toxicité minimale.

La voie PI3K est l'une des voies de signalisation les plus fréquemment altérées dans les cancers et représente une cible oncogénique privilégiée pour les thérapies ciblées. Cependant, l'utilisation d'inhibiteurs pan-PI3K ou même sélectifs de certaines isoformes (α, β, δ) est entravée par une toxicité accrue en clinique, principalement due à l'inhibition de la signalisation PI3K dans les tissus non cancéreux.

Nous présenterons comment nous avons démontré,[1] de manière concomitante à deux autres équipes,[2,3] que la suppression de l'axe PI3Kγ (PIK3CG/PIK3R5) – dont l'expression est restreinte aux cellules myéloïdes – constitue une vulnérabilité majeure dans les LAM. Cette suppression inhibe la signalisation de la protéine kinase B/Akt et compromet la survie des cellules de LAM. De plus, l'extinction par approche génétique de l'unité catalytique PIK3CG ou de sa sous-unité régulatrice PIK3R5 sensibilise les cellules de LAM aux traitements déjà établis.

Ayant constaté que les inhibiteurs classiques de PIK3CG n'entraînent pas un effet anti-leucémique majeur, nous avons alors émis l'hypothèse que la dégradation pharmacologique sélective de PIK3CG pourrait constituer une alternative prometteuse pour circonvenir la prolifération leucémique. Nous avons ainsi synthétisé et caractérisé un PROTAC à partir d'un de ces inhibiteurs pharmacologiques. Ce PROTAC dégrade spécifiquement PIK3CG et démontre une efficacité remarquable, à la fois en monothérapie contre la progression de la LAM et en combinaison synergique avec le vénétoclax. Son action a été validée dans des lignées cellulaires humaines de LAM, des échantillons primaires de patients atteints de LAM et des modèles murins syngéniques.

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3. Gu, H. *et al. Blood* **2024**, *143*, 1965–1979. DOI : 10.1182/blood.2023022202

Keywords: Leucémies Myéloïdes Aiguës; PROTACs; PI3Kγ.

DUO 004

Multivalence to access HDAC inhibition selectivity and potent and selective antiplasmodial compounds

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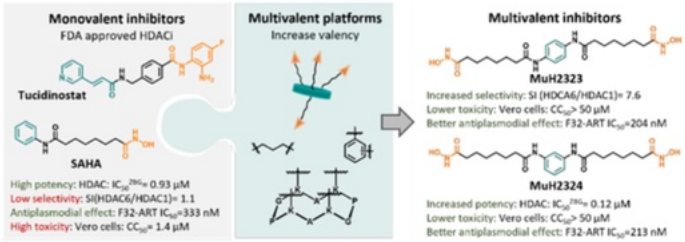
Context- Epigenetic enzymes, including histone deacetylases (HDACs), control gene expression and their deregulation is known to be involved in several diseases including cancer, cardiovascular, neurological and infectious diseases. To date five HDAC inhibitors (HDACi) were approved by the FDA against cancer. They all are pan-HDAC inhibitors and are used against cancer at low dose and in combination due to their toxicity. More recently, HDACi were also reported as an interesting strategy against parasites, in particular *Plasmodium falciparum*, responsible for malaria, especially against strains resistant to classical therapeutics.

Aim of the work- Given the importance of developing more potent and selective HDACi as novel antimalarial agents, we investigated a breakthrough strategy in HDAC inhibition: multivalence to target HDACs.

Results- From clinically approved or drug-candidate inhibitors such as SAHA or MS275, we designed and evaluated multivalent inhibitors for selective HDAC inhibition and antiplasmodial activity. Compounds MuH2323 and MuH2324, two divalent analogues of pan-HDACi SAHA, showed enhanced inhibition potency towards human HDACs. In particular HDAC6 emerged as the most susceptible enzyme to multivalent inhibition. Both compounds showed a potent antimalarial activity against artemisinin-susceptible and -resistant *P. falciparum* strains (IC_{50}= 204 and 213 nM, respectively), without toxicity for mammalian cell (CC_{50}> 50 µM). MuH2323 and MuH2324 are thus promising antiplasmodial candidate with improved safety profile compared to SAHA.



3. Gu, H. *et al. Blood* **2024,** *143,* 1965–1979. DOI : 10.1182/blood.2023022202

Keywords: Leucémies Myéloïdes Aiguës; PROTACs; PI3Kγ.

Plan d'exploration du gisement

CO 001

Solvatochromic fluorescent probes for assessing the local polarity of individual layers of the bacterial cell envelope

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The global spread of antibiotic resistance is widely recognized as one of the most significant threats to public health. While the development of new antibiotics remains crucial, there is also an urgent need for precise chemical biology tools to investigate bacterial physiology under antibiotic pressure.

In this study, we report the development of solvatochromic fluorescent conjugates designed to probe the local polarity of individual layers of the bacterial cell envelope. Using a recently established ratiometric flow cytometry approach with solvatochromic probes,[1,2] we monitored perturbations of the bacterial cell envelope in response to environmental stress, including antibiotic exposure. Our approach enables layer-specific analysis of envelope dynamics and provides a versatile platform for investigating bacterial stress responses at the molecular level.

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CO 002

Photoporation plasmonique en microfluidique pour la transfection cellulaire non virale

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Le transfert intracellulaire de biomolécules constitue une étape clé pour de nombreuses applications en biologie chimique, en thérapie génique et en ingénierie cellulaire. Les vecteurs viraux offrent généralement des rendements élevés mais présentent des limitations importantes liées aux risques immunogènes et oncogènes ainsi qu'à une capacité de chargement restreinte. Dans ce contexte, les approches **non virales basées sur la perméabilisation physique de la membrane cellulaire** constituent une alternative prometteuse.

La photoporation plasmonique exploite l'interaction entre impulsions laser nanosecondes et nanoparticules métalliques pour induire la formation de nanobulles de vapeur (Vapour NanoBubbles, VNB) via la résonance plasmon de surface. La dynamique d'expansion et de collapse de ces nanobulles génère des contraintes mécano-acoustiques locales capables de créer des nanopores transitoires dans la membrane plasmique, permettant l'entrée de macromolécules exogènes tout en préservant la viabilité cellulaire [1-2]. Cette approche offre un contrôle physico-chimique fin du processus de transfection à travers des paramètres tels que la concentration en nanoparticules, l'énergie laser ou encore la géométrie d'irradiation.

Dans ce travail, nous développons une approche optofluidique permettant de contrôler spatialement l'interaction entre cellules et nanoparticules plasmoniques. Une première configuration de photoporation en écoulement dans une puce microfluidique permet une transfection de cellules en suspension avec des rendements atteignant ~70 % pour des débits de (10^3–10^4) cellules·min^{-1} [3]. Dans un second temps, une stratégie de photoporation distante (remote photoporation) utilisant un focalisation hydrodynamique permet de contrôler précisément la distance cellule–nanoparticule, et donc l'intensité des contraintes mécano-acoustiques induites par les VNB, tout en évitant le contact direct avec les nanoparticules. Ces résultats illustrent l'intérêt de la photoporation plasmonique comme plateforme physico-chimique de transfection non virale, offrant un contrôle spatio-temporel du transport membranaire et ouvrant des perspectives pour l'administration intracellulaire de biomolécules et l'ingénierie de cellules thérapeutiques.

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Keywords: Photoporation; Non-viral intracellular delivery; Plasmonic nanobubbles

CO 003

Discovery and Binding Mode of LIBX-A401: A Potent and Selective ACSL4 Inhibitor to Block Ferroptosis.[1]

Abstract:

Acyl-coenzyme A synthetase long-chain family member 4 (ACSL4), a pivotal enzyme in lipid metabolism, has emerged as a therapeutic target for ferroptosis-related conditions and cancer.[2-5] However, its reference inhibitor, rosiglitazone, has off-target activity on peroxisome proliferator-activated receptor gamma (PPARγ), a key regulator of lipid homeostasis. Here, the discovery of LIBX-A401, a potent ACSL4 inhibitor derived from rosiglitazone devoid of PPARγ activity, is reported. Its binding to ACSL4 is ATP-dependent, stabilizing the C-terminal domain and altering the fatty acid gate region, as shown by Hydrogen-Deuterium Exchange Mass Spectrometry. Photoaffinity labeling identified A329 within the fatty acid binding site, while molecular dynamics and mutagenesis highlighted Q302 as critical for LIBX-A401 binding. LIBX-A401 exhibits anti-ferroptotic properties in cells, supported by target engagement. These findings establish LIBX-A401 as a valuable tool to study ACSL4 in ferroptosis and cancer, while its elucidated binding mode paves the way for the rational design of improved inhibitors.

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CO 004

Enzyme-directed photoassembling of carbonic anhydrase inhibitors

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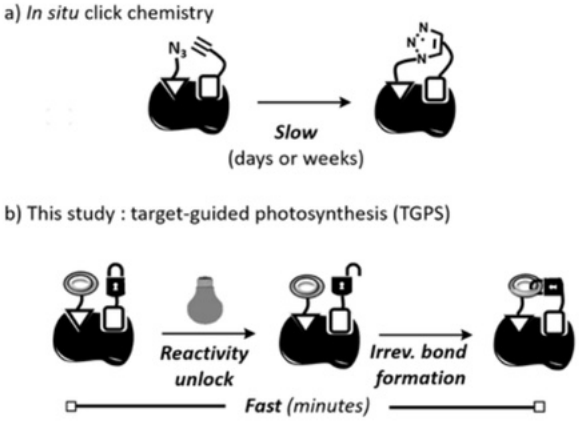
Kinetic target-guided synthesis (KTGS) is a fragment-based drug discovery (FBDD) approach in which the protein of interest (POI) is able to both select good binders and promote their linking through irreversible bond formation, in a single-step process.[1] *In situ* click chemistry, pioneered by Sharpless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

Based on this observation, we investigated for the first time the use of a photochemical transformation as a complementary ligation approach, to accelerate KTGS reactions to an unprecedented level (Scheme b). Carbonic anhydrase (CA-II), involved in a variety of physiological processes (pH regulation, gas exchange, ion transport…), was selected as a model enzyme to demonstrate this proof-of-concept.[4]



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CO 005

Exploiting disulfide-rich peptides as protein epitope mimics: development of a generalizable conjugation approach for immunogen preparation

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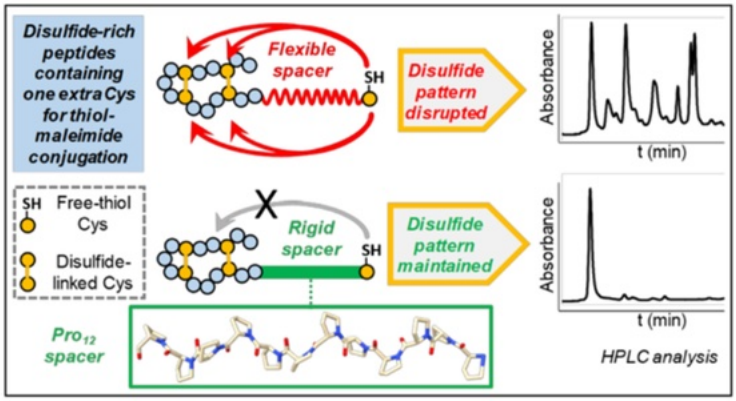
Generation of specific antibodies against peptides by immunization requires their covalent conjugation to protein carriers to override their inherently weak immunogenicity. The vast majority of bioconjugation approaches to achieve peptide-protein constructs rely on thiol-maleimide chemistry[1] and capitalize on a wide array of commercial maleimide-functionalized protein carriers. Disulfide-rich peptides[2] (DRPs) possess a rigid, constrained structure that makes them ideal for designing synthetic mimics of protein regions/domains. For bioconjugation purposes, the introduction of a single spare thiol moiety into a linear peptide antigen is straightforward, while DRPs' disulfide bonds are prone to intramolecular thiophilic attack by the reactive thiolate. This unintended reactivity competes with the desired Michael addition to the maleimide moiety, ultimately disrupting the native disulfide bridging framework. As a result, DRP's tertiary structure will be altered, affording an immunogen that is a poor mimic of the native target. Although a few studies have explored the late-stage introduction of thiol-containing cross-linkers onto DRP antigens for their conjugation onto protein carriers,[3,4] the stability of DRP's disulfide pattern in the presence of an extra thiol has never been examined. To address this, we systematically evaluated the influence of different spacers in "DRP-spacer-thiol" constructs, under thiol-maleimide reaction conditions.[5] Our results highlight how both linker length and flexibility are key to maintain DRP disulfides unaltered, providing a general approach to achieve DRP bioconjugation by thiol-maleimide chemistry. We have applied our approach to a small DRP predicted to closely mimic a surface-accessible epitope of the full LINGO-1 protein, and obtained a very specific antibody response upon immunization: the resulting polyclonal IgG was able to selectively bind the full-length protein in a cellular context, with stringent selectivity across its four homologs.



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CO 006

Investigating the bacterial cell-penetrating and cargo capacity of cell-penetrating peptides by EPR spectroscopy and fluorescence microscopy

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Résumé

"Cellular structural biology" approaches, such as in-cell electron paramagnetic resonance (EPR), enable the study of biomolecules in physiological conditions. EPR with site-directed spin labeling (SDSL) is powerful for investigating protein dynamics, but usually requires protein delivery into cells, where conventional methods (e.g., electroporation) suffer from low efficiency and high toxicity. Cell-penetrating peptides (CPPs) provide a gentler alternative, crossing membranes and carrying diverse cargoes. While well established in mammalian cells, CPPs are poorly explored in bacteria. IMM-tag, an 80-residue, positively charged disordered region of a human protein, resembles known CPPs such as TAT. Notably, preliminary studies showed that IMM-tag penetrates E. coli cells without significant toxicity, supporting its potential as a CPP for in-cell structural biology in bacterial systems. In this talk, I will present in depth this promising tool, our recent results and the future directions.

CO 007

Mechanism-Based Inhibitors of the Bacterial Enzyme IspG to Probe Its Catalytic Mechanism

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Résumé

Isoprenoids are essential chemicals for the survival of all organisms as they fulfil a variety of crucial biological functions such as electron transport, membrane stabilisation, signalling. They are all derived from isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP). In most bacteria, IPP and DMAPP are synthesized according to the methylerythritol phosphate (MEP) pathway whereas humans utilize the mevalonate pathway to produce isoprenoids.

IspG catalyses the penultimate step of the MEP pathway by converting 2-*C*-methyl-D-erythritol 2,4-cyclodiphosphate into (E)-4-hydroxy-3-methylbut-2-enyl diphosphate. Since IspG is present in many pathogenic bacteria such as *Escherichia coli* or *Pseudomonas aeruginosa*, it is a potential enzymatic target for the development of unprecedented antibacterial agents to overcome resistance. Our goal is to design, synthesize and evaluate a series of substrate analogues to uncover the multistep molecular mechanism of IspG paving the way for future drugs. (1)

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CO 008

Development of RioK1 kinase inhibitors

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Résumé :

Ribosome biogenesis is a highly regulated, energy-intensive, and sequential process that enables the assembly of functional ribosomal subunits. This complex pathway initiates in the nucleolus and concludes in the cytoplasm, involving over 200 assembly factors. [1] Among these, the atypical kinase RioK1 plays a critical role during the final maturation steps of the 40S ribosomal subunit, facilitating its proper assembly and final maturation. Specifically, RioK1 contributes to the processing of pre-ribosomal RNA into mature ribosomal RNA through the action of the endonuclease Nob1. Following this cleavage, RioK1 is autophosphorylated, triggering conformational rearrangements within the small subunit that ultimately lead to the release of Nob1 and Pno1, finalizing 40S subunit maturation [2]. Previous studies have shown that RioK1 is overexpressed in cancer such as colorectal and prostate cancer. However, deletion of RioK1 results in reduced proliferation, migration and metastasis formation in various cancer cell lines. Therefore, RioK1 may represent a novel potential target for inhibiting ribosome biogenesis in cancer cells [3-5].

The aim of my PhD is to design and evaluate small molecules that inhibit ATP binding to RioK1, within an interdisciplinary chemistry–biology framework. The structure of RioK1 bound to ATP has been solved [4], revealing critical interactions in the active site. I therefore optimized expression and purification conditions to produce recombinant RioK1 for functional and structural studies. Using the purified protein, X-ray crystallography, tryptophan fluorescence quenching, and thermal shift assays (TSA) are used to explore protein–ligand interactions, binding affinities, and protein stability. ATP mimetics from two compound series were tested, and I actually synthetize derivatives of selected hit compounds to further evaluate their inhibitory activity. I just obtained structural data from protein–ligand complexes by X-Ray crystallography to initiate a rational drug design strategy.

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Keywords: Ribosome biogenesis, RioK1, enzyme inhibition

CO 009

Development of biomimetic surfaces to study the motility of *Toxoplasma gondii*

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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 move in the extracellular matrix of their host and invade their cells.[1] Recent studies performed on poly(L-lysine)-g-poly(ethylene glycol) (PLL-*g*-PEG), fibronectin and heparin-coated substrates have contributed to better understand the adhesion strategy and gliding mechanism of *T. gondii*.[2] In particular, it was demonstrated that heparan sulfate, a glycosaminoglycan (GAG) naturally present at the surface of our cells, is promotile. Building on these findings, the present study aims at understanding how parameters like the chemical nature of the ligand, the grafting density, the size and the lateral mobility of the surface influence the motility of *T. gondii*.

To answer this question, biomimetic surfaces are developed by attaching GAG ligands, either covalently or through biotin/streptavidin chemistry, onto anchoring polymers, which are laterally immobile, or supported lipid bilayers (SLB), which are laterally mobile (*Fig. 1*).[2,3] The build-up of these models is monitored with quartz crystal microbalance and further characterized with spectroscopic ellipsometry. Parasites are then introduced onto the functionalized surfaces and their behavior is recorded by confocal microscopy. The presentation will discuss the challenges involved in developing stable, specific, and tunable biomimetic model surfaces, together with our recent results on the role of GAG nature, size and grafting density in regulating *T. gondii* motility.

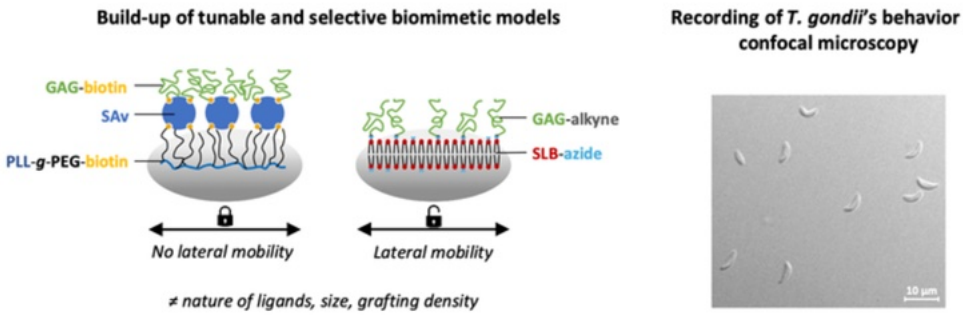

Figure 1: *Strategy for the study of the impact of ligand's nature, size, grafting density and lateral mobilty on T. gondii's motility.*

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Keywords: biomimetic surfaces, quartz crystal microbalance, toxoplasma gondii, parasite motility

CO 010

20 Years of Chemical Biology in France: Building a Community, Shaping a Discipline, Expanding Horizons

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Résumé :

Over the past two decades, chemical biology has progressively emerged in France through a series of complementary scientific, institutional, and community-driven initiatives. Early milestones include the integration of chemical biology within the Société de Chimie Thérapeutique, notably in preparation for the 2008 RICT meeting in Angers, which positioned the field at the interface of natural products and drug discovery. This momentum was reinforced by key structuring actions, including the Aviesan initiative in 2014, the CNRS "Actions de Convergence" in 2018, the PSL Chemical Biology Symposia, and the growing recognition of chemical biology within the SFBBM ecosystem, contributing to the progressive delineation of the discipline.

In parallel, sustained community-building efforts played a central role, with the creation of the SCF Chemical Biology group in 2020 (now a division since 2023), the development of a thematic school such as the École de Chémobiologie du Touquet (2021, 2023, and upcoming editions), and the organization of recurring national meetings fostering interdisciplinary exchanges. Editorial initiatives, including dedicated collections in journals such as *L'Actualité Chimique* and *ChemBioChem*, further contributed to structuring the field and increasing its visibility.

These converging efforts culminated in the establishment of the CNRS GDR ChemBio in 2021, now federating more than 600 researchers across more than 80 laboratories and providing a structured yet inclusive national framework. More recently, large-scale initiatives such as ChemBioParis have demonstrated the capacity of the French community to federate chemical biology at the European level. In parallel, sustained interactions with national funding agencies, particularly the ANR, have contributed to the recognition of chemical biology as a distinct interdisciplinary field.

Building on these achievements, these collective dynamics are now paving the way toward broader horizons, with initiatives such as ChemBioEurope aimed at strengthening integration, visibility, and impact of chemical biology across Europe and beyond.

Keywords: Chemical Biology; Scientific Community Building; Interdisciplinarity; Research Networks; European Integration

CO 011

Step-by-Step development of new fluorogenic probes for fluorescence-guided surgery

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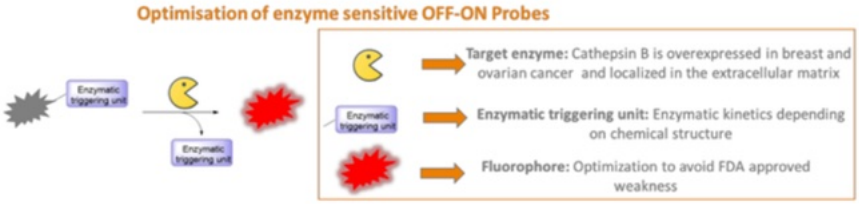
Surgery remains the primary treatment modality considered for cancer, with 63 to 98% of patients undergoing surgery.[1] However, traditional methods like naked-eye operations or palpation, offer low contrast between the target and healthy tissues, increasing the risk of not removing all cancer cells and recurrence rate.[2] in this context, alternative approaches to improve surgical precision are needed. One such advancement is Fluorescence Guided Surgery (FGS). FGS benefits from the inherent advantages of optical imaging modalities, namely excellent sensitivity, friendly user and modest cost.[3] This burgeoning field has been accompanied by an increase in the number of quality fluorescent probes approved by the Food and Drug Administration (FDA) like Indocyanine green (ICG) the most used to date. However, ICG is an "always ON" fluorophore, which limits the contrast and thus the accuracy of the images obtained with this fluorophore which conduct to high rate of false positive (62%).[4]

An ideal fluorescent probe for molecular imaging must deliver exceptional contrast, measured by the target-to-background ratio (TBR) between the target and healthy tissues. The disadvantage of the "always ON" conventional approach is that the probe emits a light signal indiscriminately, irrespective of its proximity or interaction with the target. This results in a strong background signal, which significantly reduces the TBR.[5] Therefore, the development of stimuli-responsive "OFF-ON" probes is gaining momentum.[6] These probes leverage physiological differences between healthy cells and target cells, such as enzyme overexpression such as cathepsin B (CatB).This allows these probes to exhibit increased TBR values.[7]



Here, the construction of OFF-ON probes for FGS will be presented step by step. First, the choice of target and the enzymatic triggering unit will be discussed and the impact of the choice of the peptide sequence and structural modifications on the recognition, the stability of the motif and the kinetics of enzymatic hydrolysis. In second time, the choice of fluorophores will be guided by the needs of the application. For applications in complex biological environments (*in vivo* imaging), the preference will be for high-performance fluorophores (exhibiting high brightness values) with absorption and emission maxima located in the near-infrared (NIR) range, particularly to overcome cellular autofluorescence. Thus, the development of new fluorophores meeting all this criterion will also be presented.

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CO 012

'S-GlyTag'- Enzymatic S-glycosylation as a selective protein labeling strategy

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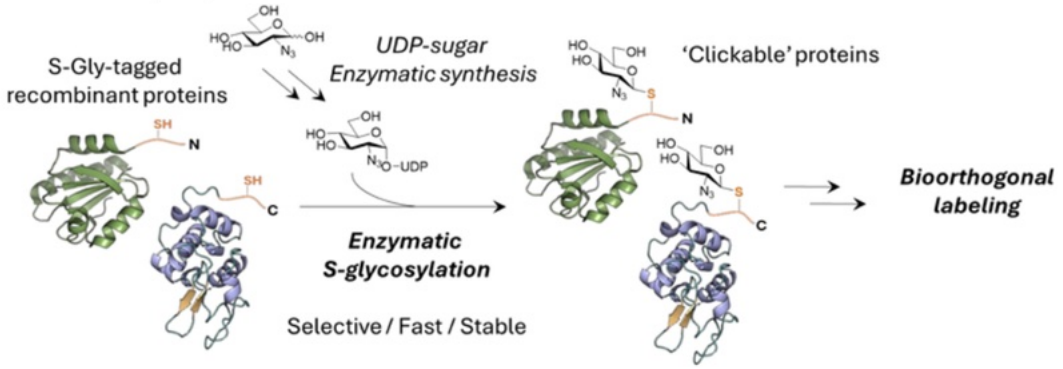
Résumé :

Protein bioconjugation has been used for many years has a powerful tool in many applications, ranging from diagnosis (cell imaging) to therapeutics (drug targeting). So far, several synthetic methodologies to label proteins with the desired compounds have been developed, mostly relying on the chemical reactivity of amino-acids side chains.[1] However, the availability of these residues is intrinsically dependent of the sequence and the 3D structure of the labeled protein. If other alternatives have been developed, based for instance on genetic engineering to incorporate non-canonical residues, they often require to adapt these strategies to each targeted protein.[2,3]

In this context, the *S*-GlyTag approach relies on the 'hijacking' of a bacterial peptide *S*-glycosylation mechanism, to selectively and simply grafting on a protein a modified sugar bearing an orthognal function.[4] This methodology involves 1) the production of the protein fused to the *S*-GlyTag peptide (like a His-Tag), 2) the use of a modified nucleotide sugar donor, obtained though enzymatic synthesis,[5] 3) a high versatility for sugar substrate of the bacterial *S*-glycosyltransferase, and 4) the selective labeling of the modified sugar on the S-GlyTag peptide though a *S*-glycosidic bond stable to enzymatic and chemical hydrolysis.



All these steps of this approach are genetically encoded, enabling its potential integration within a whole cell, leading to a 'clickable' recombinant protein production microbial cell.

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Keywords: bioconjugation, *S*-glycosylation, biocatalysis

CF 001

Design and Synthesis of Photolabeling Probes for Identification of Anti-Alzheimer Compounds

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Résumé

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder. Beyond its classical hallmarks-amyloid-beta deposition and Tau aggregation-AD is characterized by complex cellular dysfunctions, including neuroinflammation, and impaired proteostasis. To date, most small molecules in clinical development target a single pathological process and have shown limited disease-modifying efficacy.

Using a phenotypic screening strategy followed by a ligand-based pharmacophore approach, we identified several series of compounds capable of modulating APP metabolism, reducing Tau pathology in vivo, and improving cognitive deficits in transgenic mouse models combining amyloid and Tau lesions (1-4). Notably, some of these compounds also displayed beneficial effects on neuroinflammation and protein homeostasis, suggesting a multimodal mechanism of action.

However, the molecular target(s) and precise mechanism underlying these effects remain unknown. To address this limitation, we developed a bioorthogonal chemistry–based strategy aimed at target identification. Photoaffinity probes derived from the initial chemical scaffolds were rationally designed and synthesized through the introduction of diazirine photoactivatable groups and click-chemistry–compatible handles, guided by structure–activity relationships. These probes were first validated for their ability to modulate APP metabolism, and were then used in a workflow combining photocrosslinking performed by Dr. Catherine Baud, click chemistry–based enrichment, and proteomic analysis to identify candidate molecular targets (ref abstract Baud et al).

CF 002

VGF as a target for anti-alzheimer compounds

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Résumé

Alzheimer's disease (AD) is a progressive and incurable neurodegenerative disorder driven by the accumulation of misfolded and aggregated proteins, particulary amyloid precursor protein (APP)-derived species and Tau- in the central nervous system, along with neuroinflammation.
We have developed several families of small molecules that demonstrated robust *in vitro* and *in vivo* efficacy in AD models (1-6). These compounds reduce protein aggregation, modulate APP metabolism and Tau phosphorylation, improve cognition in APPxPS1 and Thy-Tau22 transgenic mice, and decrease microglial activation and astrogliosis.

Despite these encouraging results, two critical questions remained : **what is the molecular target of these compounds**, and **how do they act**? To address this, we implemented a two-component photoaffinity labeling (PAL) strategy combined with click chemistry. Four tailored probes, representative of our compound families and bearing diazirine and alkyne groups at distinct positions on the active scaffolds, were applied to the SY5Y-APPNSE1 cell line (poster Fina M. et al). Fluorescent click labeling revealed probe–target localization in lysosomes, endoplasmic reticulum, and late endosomes, while *in-cellulo* competition experiments confirmed that the probes and parent compounds share a common target.

Affinity-based mass spectrometry identified VGF, a neuropeptide precursor recently proposed as a Tau interactor in human AD brain, as the primary and shared target of all compound families (7). Higher VGF levels are associated with reduced cognitive decline in AD (8). Probe–VGF colocalization was confirmed by immunocytochemistry, and specific interactions were validated both *in cellulo* and *in vitro*.

In our cellular models, treatment with our compounds strongly increased VGF secretion, an effect further enhanced by APP expression. Importantly, VGF positively modulated APP metabolism under these conditions, establishing a functional link between VGF and APP. The effect on tau aggregation is still under evaluation.

Biophysical studies indicate that full-length recombinant VGF forms a hexameric assembly capable of binding the probes. Ongoing molecular docking and proteomic analyses aim to identify and confirm the precise compounds binding site.
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CF 003

Sugar/secondary alkoxyamine coupling: In-depth analysis of the reaction for bioconjugation

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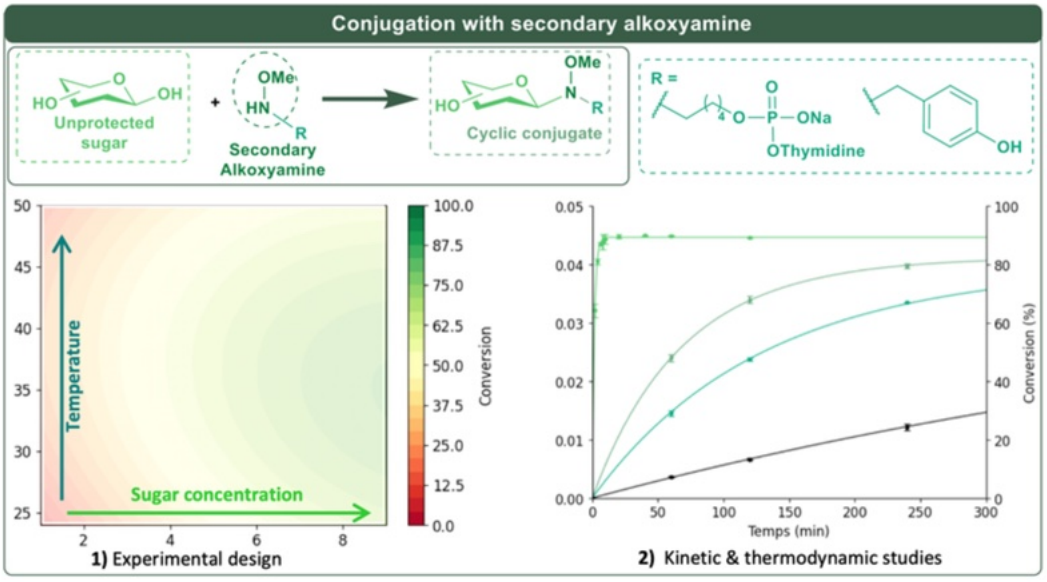
Résumé :

Glycoconjugates are an important class of molecules. As such, it is paramount for chemists to have a reliable toolbox of reactions that allows for the efficient preparation of such compounds [1]. In 1998, Peri, Dumy and Mutter introduced secondary alkoxyamine nucleophiles as a new method to prepare glycoconjugates from unprotected carbohydrates, leading to the formation of cyclic conjugates with high anomeric selectivity [2]. Yet, despite its popularity, few studies have analysed the parameters affecting the reaction or given a rational to explain the disparities between sugars.

In this work, we use experimental design, as well as kinetic and thermodynamic studies of the reaction with different sugars, to shed light on how temperature and concentration influence the reaction yield and propose a model to better understand (or predict) the reactivity of a given sugar. With this, we conclude on the advantages and caveats of using secondary alkoxyamine for glycoconjugation.



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Acknowledgements: This work was supported by the "Programme doctoral Blanc" from the Chemistry Graduate School of Université Paris-Saclay

Keywords: Sugar, Conjugation, Design of experiment, Kinetic study

CF 004

Synthesis of fluorinated oligonucleotides for miRNA therapeutic applications

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Nucleic acid-based therapeutics such as micro-RNA (miRNA), small interfering RNA (siRNA) and more recently messenger RNA (mRNA) vaccine have emerged as key tools for the tratment of a wide range of diseases[1]. However natural oligonucleotides (ONs) are rapidly metabolized in biological media by nucleases and suffer from a poor cellular uptake[2]. To overcome these limitations, several chemical modifications have been developed leading to ONs analogues with improved biological properties[3]. The project focuses on the design and synthesis of new ON series that would be able to counteract the main limitations of current therapeutic ONs. Given the importance of the fluorine atom in medicinal chemistry[4], we are particularly interested in the development of fluorinated nucleic acids which remain relatively underexplored.

In this work, we report the synthesis of RNA analogues bearing difluorophosphonylated modifications at the 2' position, including an allylic ether (2'-O-AllylCF$_2$P), as well as allyl (2'S-AllyCF$_2$P) or propyl (2'S-PrCF$_2$P) thioether moiety (figure). First, these phosphoramidites bulding blocks were successfully incorporated into oligonucleotides and evaluated[5]. UV-melting experiments and enzymatic degradation assays demonstrated that the 2'-O-AllylCF$_2$P modification enhances both thermal and metabolic stability of the RNA/RNA duplex while also increasing lipophilicity.In parallel, Oligonucleotides bearing 2'S-AllyCF$_2$P or 2'S-PrCF$_2$P adenosines were investigated. These modifications were found to destabilize RNA/RNA duplexes while improving metabolic stability and lipophilicity. Overall, these results highlight the potential of difluorophosphonylated group as promising candidates for improving the profile of therapeutic oligonucleotides.

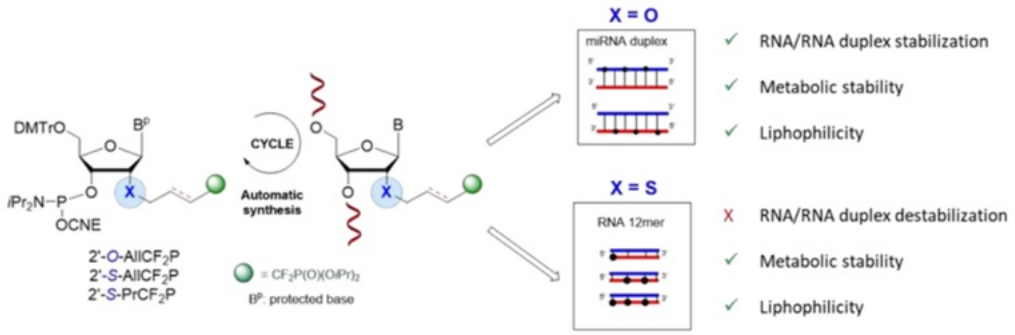

Figure : Synthesis of fluorinated oligonucleotides for miRNA therapeutic applications

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Keywords: oligonucleotides, 2'-modifications, RNA, lipophilicity

CF 005

Synthesis of photoactivatable molecules for the spatiotemporal control of cell motility with light

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Résumé

The actin cytoskeleton governs key cellular processes, making its regulatory proteins attractive targets for small molecules. CK-666 and (–)-blebbistatin are widely used inhibitors of Arp2/3 complex and non-muscle myosin II motors, but lack spatiotemporal precision. Thus, we are developing a synthetic toolbox of photo-responsive chemical inhibitors, enabling a light-controlled modulation of actin networks in cells. Photoswitchable CK-666 derivatives were synthesized and characterized, displaying remarkable photochemical properties. Using total internal reflection fluorescence microscopy assays, we demonstrated that these compounds selectively modulate Arp2/3-mediated branching with striking *(E)*/*(Z)* photoisomer-dependent activity (4- to 7- fold variation). Additionally, cell biology assays performed on B16-F1 cells revealed that the *(Z)* photoisomer induces a significant lamellipodial retraction, confirming its activity *in cellulo*. These results give a proof-of-concept for the photochemical control of Arp2/3 activity, providing a powerful means to decipher the interplay between actin cytoskeletal architecture and cell migration dynamics with unprecedented spatiotemporal resolution.

CF 006

Exploiting Electrostatic Landscapes for Powerful Sortase-Mediated Protein Modification

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Résumé :

Sortase A-mediated ligation (SML) has emerged as a powerful tool in protein engineering, enabling site-specific modifications under mild and biocompatible conditions. However, the intrinsic reversibility of SML results in poor conversions, significantly limiting its broader application.

We recently demonstrated that electrostatic interactions could be exploited to significantly improve SML by introducing short complementary charged peptide modules into both reaction partners. This electrostatically-assisted conjugation platform enables highly efficient and clean protein labeling at low micromolar concentrations.[1] The strategy is easily implementable, readily compatible with recombinant protein expression, although it introduces a charged ligation scar in the final product. To address this limitation, we developed a complementary electrostatically-assisted scavenging strategy that enables traceless SML.[2]

In parallel, ongoing mechanistic investigations supported by molecular dynamics simulations are uncovering the electrostatic design principles governing module composition and charge distribution enabling enhanced ligation efficiency while minimizing scar size and sequence dependence.[3] Altogether, electrostatic engineering establishes a versatile framework to expand the scope of SrtA-mediated protein modification, which will be discussed in this presentation.

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3. Wang, C.; Magalie, S.; Melnyk, O.; Agouridas, V. Manuscript under preparation.

Keywords: Sortase A; electrostatic; protein modification

CF 007

A new, powerful fluorogenic click-and-release reaction

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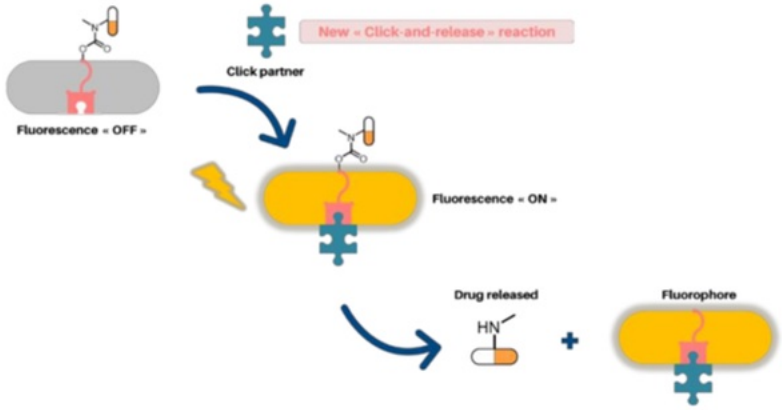
Fluorescent probes are powerful tools in bioimaging and diagnostics due to their ability to emit light in response to specific biological biomolecules or environmental changes. While conventional fluorescence techniques offer high sensitivity and resolution, they are limited by shallow tissue penetration and photodamage. Two-photon excitation (2PE) overcomes these issues by enabling deep tissue imaging with reduced phototoxicity[1]. However, most dyes are not optimized for 2PE, requiring high laser power due to low absorption cross-sections.

This project aims, among other objectives, to develop a new bioorthogonal fluorogenic click reaction[2] displaying a high fluorescence turn-on, alongside a novel click-and-release reaction[3] for controlled payload delivery. Notably, both fluorogenic activation and drug release are enabled on the same molecular scaffold, representing an unprecedented design in which imaging and therapeutic functions are directly linked. The model currently under development already shows fast click kinetics and promising preliminary results.



Keywords : Click, Flurophore, Drug

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CF 008

VOC-based probes: from cancer diagnosis to therapeutic guidance

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Résumé

VOC-based probes are emerging tools for disease diagnosis, including cancer(1). This study aims to evaluate their application in detecting glycosidase activity in biological systems, to indicate the early stages of cancer development directly from tissue or human plasma samples(2).
The objective of the first application was to highlight gastric preneoplasia following *H. pylori* infection. To achieve this, a longitudinal study was conducted on murine stomach tissues 24 hours, 3 days, 2 weeks, and 3 months post-infection. The tissues were incubated in DMEM medium for 30 minutes, followed by tissue removal and centrifugation. VOC-based probes were added to the medium, incubated for 4 hours, and VOCs were collected for 30 minutes using SPME fibres before analysis by GC-MS/MS. The volatolomics data were correlated with histological studies. In the murine model, infection marker enzymes β-galactosidase and α-mannosidase were detected at 24 hours, 3 days, and 2 weeks post-infection, while inflammation markers N-acetyl-β-D-glucosaminidase and β-glucuronidase were observed at 3 months. These enzymatic activities were strongly correlated with histological findings.

In parallel, a clinical study involving 76 patients was performed to distinguish healthy individuals from cancer patients with elevated oncogenic markers (ACE, CA15-3, CA19-9). Plasma samples were incubated in acetate buffer (pH 5), followed by the addition of VOC-based probe cocktails and incubation for 7 hours. VOCs were collected for 30 minutes using SPME fibres and analysed by GC-MS/MS. In the clinical study, VOC-based probes successfully identified β-glucuronidase and β-N-acetylglucosaminidase activities, which distinguished healthy patients from cancer patients with elevated levels of ACE, CA15-3, and CA19-9.

In addition, a companion probe associated with a prodrug was developed to monitor therapeutic activation both *ex vivo* and *in vivo*, paving the way for applications in precision oncology.

Seven VOC-based probes were combined to evaluate their potential in two key applications: detecting early stages of stomach cancer development following *H. pylori* infection and diagnosing cancer through non-invasive blood sample analysis. In addition, the development of a companion probe associated with a prodrug highlights the potential of this approach to monitor therapeutic activation. Overall, these results demonstrate the promise of VOC-based strategies not only for early detection and disease monitoring, but also for advancing precision oncology through combined diagnostic and therapeutic applications(3).

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Keywords : VOC-based probes-cancer-glycosidase-precision oncology

CF 009

Groupe d'Echange Technique en RMN – GET-RMN : Un réseau collaboratif dédié à la technique de Résonance Magnétique Nucléaire

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Résumé :

Responsables ou utilisateurs d'appareils de Résonance Magnétique (RMN), nous sommes régulièrement confrontés à des problématiques : mise en place de nouvelles expériences, résolution de pannes, choix techniques, etc... Ces situations, souvent complexes, peuvent générer un sentiment d'impuissance et d'isolement, notamment en l'absence de collègues proches ou d'un réseau d'expertise accessible.

GET-RMN a pour objectif à un niveau national et plus largement francophone, de répondre à ce besoin en facilitant le partage des savoir-faire et des bonnes pratiques en RMN dans un esprit de bienveillance et sans a priori.

GET-RMN a d'abord mis en place une **liste de diffusion** ouverte à l'ensemble de la communauté francophone — couvrant la France, la Belgique, la Suisse et au-delà — dans les secteurs **académiques et privés**, à l'exclusion des fournisseurs.

Ses **quatorze membres fondateurs** poursuivent aujourd'hui leur mission en présentant ce réseau et ses objectifs. Ils invitent toutes les personnes intéressées à les rejoindre pour **échanger sur les actions en cours**, **proposer de nouvelles initiatives** et **s'engager collectivement** à les concrétiser.

Liste de diffusion : https://listes.services.cnrs.fr/wws/info/get-rmn

Keywords: réseau ; RMN ; partage ; échange ; entraide ; techniques

CF 010

Stapled peptides as new anti-influenza A viruses

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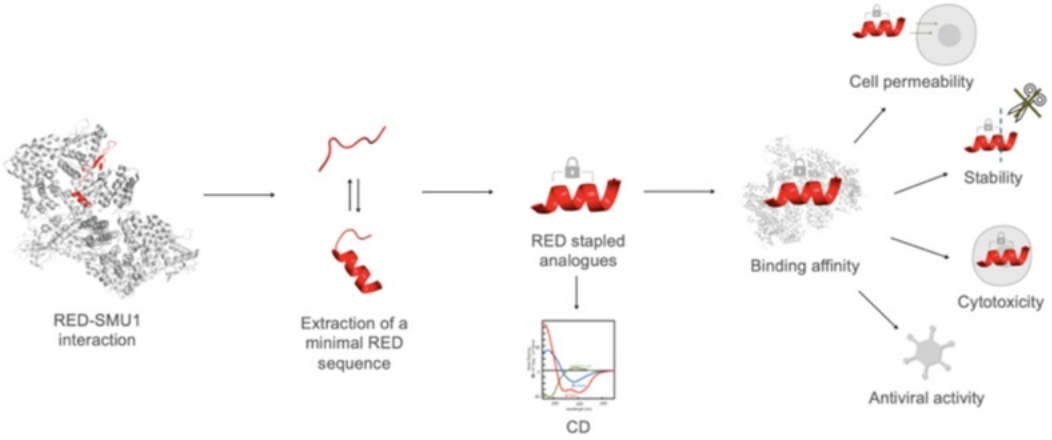

In recent years, host-directed therapies have emerged as a powerful paradigm in antiviral research.[1] Naffakh *et al.* identified the human splicing factor RED-SMU1 complex as a critical host dependency factor in the influenza A virus life cycle and established its tractability as a therapeutic target.[1] Disrupting this complex downregulates endogenous RED-SMU1 levels, inhibits viral mRNA splicing, and limits viral replication, without compromising cell viability, positioning it as a highly attractive target for antiviral intervention. Here, we leverage these findings to design a short, conformationally stabilized helical peptide derived from the RED protein that retains target affinity while acquiring drug-like properties compatible with *in vivo* application, including enhanced membrane permeability and proteolytic stability. We designed and synthesized a series of a-helical peptides incorporating a cross-turn staple to lock the bioactive conformation and optimize pharmacological properties. Biophysical characterization confirmed robust target affinity across several analogues. Notably, stapling translated into functional gains, enabling the recovery of antiviral activity, with one lead analogue displaying measurable efficacy at 10 µM. Taken together, these findings established peptide stapling as a powerful approach to convert protein-derived sequences into bioactive, cell-permeable antiviral agents and provide a strong foundation for the development of next-generation host-targeting therapeutics.

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Keywords: stapled peptides; host-directed therapies

CF 011

Target-directed stapled peptides through dynamic combinatorial chemistry for the inhibition of protein-protein interactions

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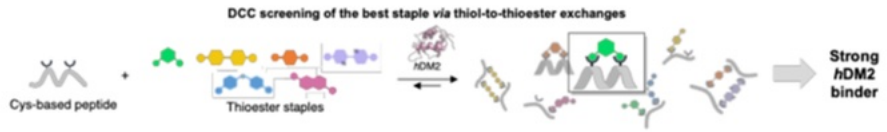
Résumé :

Target-directed dynamic combinatorial chemistry (tdDCC) offers a sophisticated self-assembly approach where biological targets actively select and amplify potent inhibitors from a library of interconverting moieties.[1] While tdDCC remains underexplored in peptide discovery[2], our group has been investigating its potential as a self-adaptive alternative to rational design. Using reversible thiol-to-thioester exchanges, we previously developed a platform to optimize side-chain residues on well-defined scaffolds.[3,4] More recently, we have been investigating the extension of this methodology to the structural optimization of stapled peptide linkers.[5] By mixing cysteine-functionalized peptides with thioester-based staples, a dynamic combinatorial library (DCL) was generated. When applied to the p53-*h*DM2 interaction—a prominent model for targeting challenging protein-protein interactions (PPIs)[6]—the dynamic system successfully shifts its equilibrium to selectively favor the formation of the most potent stapled peptide. This work validates tdDCC as a robust platform for the optimization of stapled peptides, offering a compelling and innovative strategy to address traditionally "undruggable" therapeutic targets, such as PPIs.



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Keywords: Dynamic combinatorial chemistry, stapled peptide, thiol-to-thioester exchange, p53-hDM2

CF 012

Novel fluorescent di-affibodies : modular synthesis of therapeutic constructs.

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Résumé :

The emergence of antibodies enabled the development of innovative therapeutic strategies based on the specific recognition of relevant biological targets. Their limitations (cost, size, affinity, tolerability) led to the development of advantageous alternatives, such as affibodies (AfBs). In this extension, we report the design of di-affibodies incororating a modular bivalent fluorescent platform for the covalent assembly of specific recognition motifs of relevant biological targets.

To this end, we developed versatile polyvalent fluorescent linkers (L1-L3, L1N) from a derivative of dimethoxyquinacridinium, emitting in the red, which served as the basis for the synthesis and characterization of the conjugates. Amine groups at the ends of the fluorophore allowed straightforward functionalization with bifunctional PEG linkers (NHS ester, maleimide) of variable length (n = 2 or 12). Affibodies, synthesized on solid support (SPPS), with a cystein at either the N-term (N-AfB) or C-term (C-AfB) position, enabled control over conjugation orientation. The assembly of the molecular components (affibody, linker, fluorophore) was achieved through rapid and simple bioconjugation reactions (NHS ester/amine, thiol/maleimide), ensuring high modularity of the platform.

Specific binding of the conjugates to SKOV3 cells overexpressing HER2 was demonstrated by flow cytometry (nanomolar affinities) and confirmed by confocal microscopy. Internalization of the constructs into this same cell line was monitored by flow cytometry following trypsin treatment.

In conclusion, the design of versatile linkers and polyvalent directional assemblies opens new perspectives for the development of advanced recognition platforms in chemical biology, particularly in contexts of complex targeting, or biomarker co-expression, whose activities remain to be explored.

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Keywords: Affibody; fluorescent plateform ; divalent construct; conjugation; receptor binding

CF 013

Iminosydnone-based probes for bioorthogonal cycloadditions with cyclooctyne as irreversible protein labeling in living cells

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CA 001

La chémobiologie comme outil de design moléculaire : du rapporteur bioorthogonal au geste artistique

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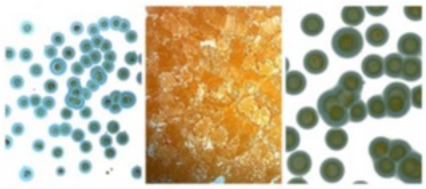
Historiquement cantonnée à l'analyse de l'œuvre d'art ou à la préparation de pigments, la chimie connaît aujourd'hui une mutation profonde au contact de la biologie. La chémobiologie, en permettant de sonder et de manipuler le vivant in vivo avec une précision moléculaire, ouvre un nouveau champ de recherche-création : le Chembioart. Ce travail présente une démarche où le chimiste n'est plus seulement un expert du matériau, mais un architecte capable de programmer des édifices moléculaires par design. Nous explorons l'utilisation de rapporteurs chimiques et de réactions de chimie click bioorthogonales pour cartographier des biopolymères au sein de systèmes complexes. Ici, le protocole expérimental s'affranchit de sa seule fonction analytique pour devenir un geste artistique à part entière.[1] En transformant la donnée chémobiologique en un matériau sensible, cette approche permet de révéler des structures invisibles et de proposer une nouvelle esthétique de la fonction moléculaire. Cette hybridation entre la rigueur du laboratoire et la liberté de l'atelier constitue un levier innovant pour la médiation scientifique et la réflexion sur notre rapport au vivant.

Du triple marquage métabolique du lin à la collection « LIN » pour Longchamp (Adèle Tilouine).



L'effacefer (Marie Hinnebo). Vulnérabilité d'un complexe organométallique en milieu hétérogène.

Le projet *xSublimatio* : de la structure moléculaire à l'expérience numérique (Pierre Pauze).

1. M. Hinnebo, C. Biot, Chembioart : quand le protocole moléculaire devient geste artistique, *L'Actualité Chimique*, 2026, n° 506 (Avril), sous presse.

Keywords: Chembioart; Chémobiologie; Esthétique Moléculaire; Recherche-Création

CA 002

Architectures du vivant et actifs numériques : une approche interdisciplinaire de la recherche-création en chémobiologie.

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Résumé :

La chémobiologie fournit des outils robustes pour la visualisation et la manipulation des processus biologiques *in vivo* avec une résolution subcellulaire. Au-delà de sa fonction strictement analytique, cette discipline permet l'émergence du « Chembioart » [1], une interface transdisciplinaire où le protocole chimique et la donnée structurale deviennent les vecteurs d'une expression plastique et d'une médiation scientifique renouvelée. Ce poster présente une synthèse de nos travaux récents articulés autour de deux axes de recherche-création .

La chémobiologie se distingue par l'utilisation d'une panoplie d'outils chimiques (sondes, modulateurs) pour imager, moduler et manipuler les processus biologiques *in vivo* avec une précision moléculaire. Au-delà de ses applications analytiques, cette discipline offre un terrain fertile à l'émergence du « Chembioart ». À l'interface de la recherche et de la création, cette approche transforme le protocole chimique et la donnée structurale en de nouveaux vecteurs d'expression plastique.

Notre poster présente deux axes de nos travaux récents de recherche-création.

Le premier volet expose l'implémentation de rapporteurs bioorthogonaux pour la cartographie spatio-temporelle des biopolymères pariétaux tels que les lignines et les glycanes [2]. Cette stratégie de triple marquage a permis le développement de la collection de porcelaines **LIN**, qui transpose les architectures du vivant dans le design d'objets quotidiens . Ce projet se poursuit par un projet d'arts contemporain, **Mythologie Cellulaire** qui s'accompagne d'extension pédagogique, les ateliers **Héros Cellulaires**, où le jeune public s'approprie ces images scientifiques pour créer des récits mythologiques, facilitant ainsi une compréhension intuitive des mécanismes biologiques .

CA 002

Le second volet explore la dimension numérique et spéculative de la donnée moléculaire à travers le projet **xSublimatio** [3]. En associant les prédictions de repliement protéique via AlphaFold et la technologie blockchain, les structures atomiques sont converties en actifs numériques certifiés . Cette démarche se prolonge aujourd'hui par l'installation immersive « **La Cuisine des Anomalies** ». À travers un dispositif associant IA et stimuli sensoriels, le public participe à la mutation de molécules gastronomiques en figures anthropomorphes, découvrant ainsi les principes de la chimie organique et de la certification numérique.

En décloisonnant la paillasse et l'atelier, ces initiatives démontrent que le dialogue entre chémobiologie et création artistique constitue un levier puissant pour rendre intelligible l'invisible moléculaire.

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Keywords : Chembioart; Click chemistry; Plant imaging; Artificial intelligence; Blockchain; Sci-art.

CA 003

Bioorthogonal Imaging of Lignin via Thio-Glycosylated Monolignol Probes

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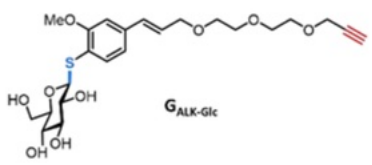
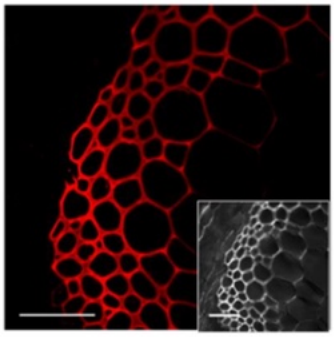
Lignin biosynthesis is a vital yet complex process that significantly contributes to the structural integrity and defense mechanisms of plant cell walls. Despite its importance, the role of monolignol glucosides (MLGs) as intermediates in this pathway has been debated. To elucidate MLGs' involvement, we developed thioglycosylated monolignol probes compatible with click chemistry for in situ visualization of lignin biosynthesis. These probes incorporate glycosyl thiols into MLGs, creating stable thioacetal bonds to enhance both metabolic stability and tracking precision. The unique chemistry of these probes allows for incorporation within the lignification pathway, enabling specific visualization of MLG involvement in lignin formation. Our strategy leverages bioorthogonal click chemistry (strain-promoted or copper-catalyzed) combined with confocal microscopy to achieve detailed tracking of MLG incorporation into cell walls.
Our findings provide new insights into lignification dynamics, underscoring the metabolic roles of MLGs and demonstrating their potential as metabolic intermediates in lignin polymerization [1]. This approach offers a novel chemical biology toolset to dissect plant cell wall biosynthesis and will help elucidate the molecular roles of MLGs in the context of plant biochemistry and resilience.





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CA 004

Synthesis and evaluation of the biological activity of photoswitchable monoamine oxidase inhibitors in the treatment of osteoarthritis

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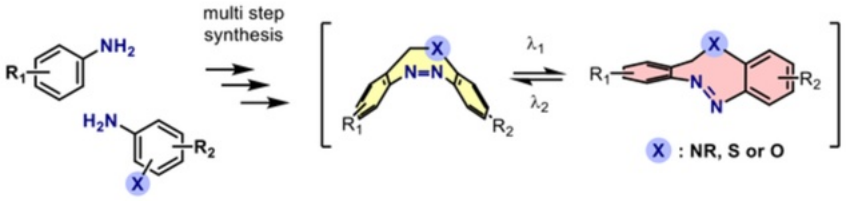
Osteoarthritis (OA) creates a growing public health burden yet lacks effective disease-modifying treatments. [1] Recently, Monoamine oxidase B (MAO-B) emerged as a promising therapeutic target due to its overexpression and contribution to oxidative stress in OA-affected tissues. [2]

To address this, we applied a photopharmacological approach centered on heteroatom-bridged diazocines whose synthesis has only been poorly described in the literature. While synthetically more challenging than standard azobenzenes, these bridged analogues were selected for their ability to operate under biocompatible visible light, avoiding the tissue-damaging UV irradiation typically required by conventional switches.[3] Consequently, we developed synthetic strategies to access a library of O-, S-, and N-bridged scaffolds, exploring diazonium coupling, intramolecular cyclization, and substitution-based routes. Beyond seeking bathochromic shifts, we incorporated specific donor–acceptor patterns to fundamentally investigate the structure-reactivity relationships of these switches.



The impact of these structural modulations on optical properties were assessed through extensive photochemical measurements, supported by preliminary Density Functional Theory (DFT) calculations. This work establishes a robust foundation for the next stage of the project: grafting inhibitor pharmacophores onto our optimized scaffolds. These insights guide our current design of functionalized inhibitors aimed at establishing precise optical control over MAO-B in osteoarthritis.

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CA 005

Two-photon excitable fluorogenic probes for Click-to-Release bioorthogonal reactions

Juichi Bainvel-Sato*[1], Aurélie Rodriguez[1], Delphine Naud-Martin[1], Gaëlle Fontaine[1], Kévin Renault[1], and Florence Mahuteau-Betzer[1]

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Résumé

Fluorogenic bioorthogonal chemistry offers a compelling way to visualize small molecules or biomolecules within living systems.1 In this context, our group has developed two-photon excitable fluorogenic probes activable through a bioorthogonal reaction.2 By shifting the excitation toward the red, twophoton absorption moves the imaging into the biological optical window, enabling more precise images, reducing photodamage, and permitting imaging about tenfold deeper than conventional fluorescence imagery. The probes designed in our team display satisfactory spectral behaviour, a high fluorescence turnon factor, and an excellent twophoton absorption crosssection.
In this work we present our ongoing research to develop a new class of theranostic tools: twophoton excitable fluorogenic probes for clicktorelease bioorthogonal reactions.3,4 These clicktorelease systems simultaneously liberate a therapeutic or cytotoxic agent and activate fluorescence, thereby revealing the localisation of the released drug and enabling evaluation of the release efficiency. The efficiency of drug release was evaluated with a range of click partners, and a first proofofconcept experiment in living cells validated the approach. This represents a novel theranostic platform that couples precise drug delivery with realtime imaging.

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CA 006

Conformational complexity of the disordered N-terminal region in biological function of tumor suppressor p53 protein

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Tumor suppressor p53 is a transcriptional activator, involved in a majority of cancers. It contains various regions, N-terminal transactivation domain (NTAD), proline-rich domain (PRD), DNA-binding domain (DBD), nuclear localization signal (NLS), tetramerization domain (TET), and C-terminal regulatory domain (CTD).[1] Transactivation domain (TAD) is an intrinsically disordered region and can adopt multiple conformations that are responsible for binding to other various proteins like CREB-binding protein (CBP/p300), Double minute 2 protein (HDM2) and many others.[2] To modify its interactions, TAD variants were synthesized with α-methylated leucine and fluorinated amino acids. They were obtained using native chemical ligation of two peptides segments.

The LXXLL motif of TAD was targeted for the modifications because it is known to mediate many protein-protein interactions. This conserved modification sequence mediates specific interactions with nuclear receptors and their coactivators, making it a reliable choice for motif to target.[3] We used α-methylated leucine to conformationally constrain the backbone and stabilize helical conformations.[4] 4,4-difluoro-2-aminobutyric acid (DfAbu) was chosen as an isosteric fluorinated analogue of leucine, while its fluorine atoms also make it as a valuable ^{19}F NMR probe.[5] With this modifications, the purpose is to understand how distinct conformations of intrinsically multi-structured N-terminal region of p53 affect its biological function. To evaluate the impact of these modifications, we studied their binding interactions with nuclear coactivator binding domain (NCBD) of CBP/p300 using well-established biophysical techniques, such as circular dichroism (CD), biolayer interferometry (BLI) and NMR spectroscopy.

Acknowledgements

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CA 007

Kinetic Target-Guided Synthesis (KTGS): From Concept to MedChem Applications

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Résumé

Kinetic target-guided synthesis (KTGS) is an elegant drug discovery strategy in which a biological target catalyzes the irreversible formation of its own ligands from a set of precursors bearing compatible reactive groups.(1) First introduced in 2001 with carbonic anhydrase II,(2) its development has been closely linked to the rise of click chemistry, particularly the azide–alkyne cycloaddition, which was awarded the Nobel Prize in Chemistry in 2022.
Initially applied to enzymes, KTGS has since been extended to a broader range of biological targets, including receptors and ion channels.(3) This poster outlines the fundamental principles of this strategy, as well as the design of precursors and the reactions employed, highlighting both the potential and the key challenges associated with this approach.

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CA 008

A Bioorthogonal approach for controlled Fluorogenic isocyanate release in living cells

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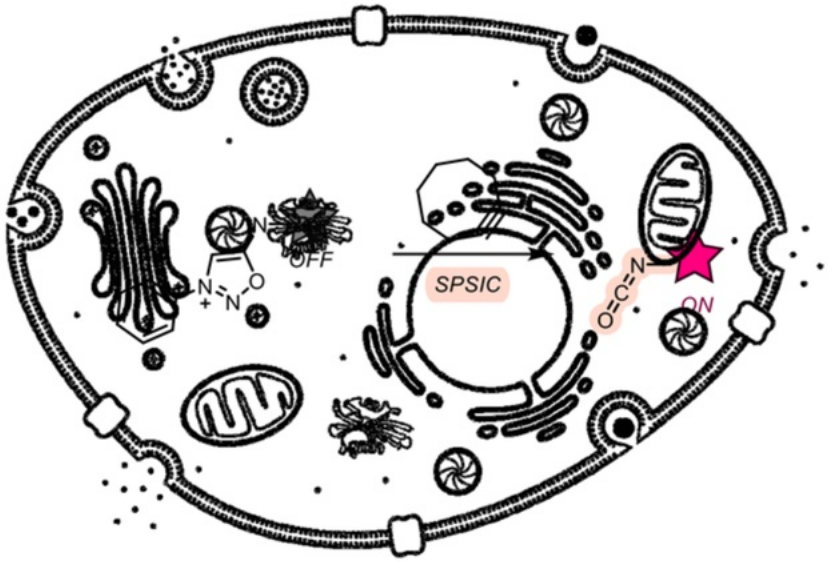
Keywords: biorthogonal reactions, sydnonimines, fluorogenic, probes.

Abstract:
Sydnonimines belong to the mesoionic family and are closely related to sydnones, differing primarily by the presence of a nitrogen atom at the 6-position. First discovered in the 1950s[1] and further developed in the 1970s for their biological properties, several sydnonimines have since been approved as therapeutic agents.[2] Recently, renewed interest has arisen from their ability to undergo chemoselective cycloaddition reactions with strained alkynes, known as SPSIC (Strain-Promoted SydnonImine–Cyclooctyne Cycloaddition).[3] We developed sydnonimine-based probes enabling the intracellular release of fluorescent aromatic isocyanates upon reaction with cyclooctynes.[4] These fluorogenic probes allow permanent and irreversible fluorescent labeling of cells, which can be exploited in a variety of cell imaging applications.



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CA 009

Development of biphotonic fluorogenic probes for the detection of enzymes overexpressed in tumour environment

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Résumé

Surgery is the main treatment for most cancers. However, conventional surgical techniques often suffer from low contrast between cancer and healthy tissues, which increases the risk of leaving residual tumour cells and leads to cancer recurrence. To overcome this limitation, fluorescence-guided surgery is being developed to improve the visualisation of tumours during operations (1).
The aim of this project is to develop new fluorogenic probes that significantly enhance the contrast between cancer and healthy cells. These probes are designed to exploit differences in enzyme expression between tumour and normal tissues.

Furthermore, these fluorogenic probes are based on two-photon absorbing fluorophores previously developed in the laboratory (2). This enables a near-infrared excitation, deep tissue penetration, and high spatial resolution. They will be chemically modified to incorporate a self-immolative spacer arm that allows the quenching of the fluorophore while conferring reactivity and specificity towards the target enzyme. After enzymatic activation, the fluorophore is released and its fluorescence is restored, allowing real-time imaging without long accumulation times. Finally, the probe design will be further optimized through a rigidification strategy aimed at limiting non-radiative pathways and enhancing photophysical properties (3).

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CA 010

Leveraging Sortase A Electrostatics for Powerful Transpeptidation Reactions

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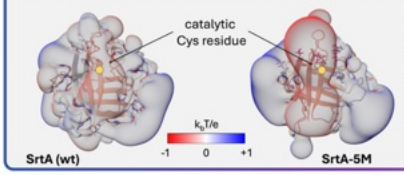
<<<<<< Full details in *Angew. Chem. Int. Ed.* **2025**, e202507236 (10.1002/anie.202507236)

Introduction

Sortase A (SrtA)-mediated transpeptidation has emerged as a powerful tool in protein engineering, enabling site-specific modifications under mild, biocompatible conditions.[1,2] Over the years, numerous SrtA variants have been engineered to enhance catalytic performance and expand the scope of this technique. Among these, **the pentamutant variant (SrtA-5M)** is one of the most widely used for sortase-mediated ligations (SML).[3] Despite these advances, a fundamental limitation persists across all variants used for SML and regards the **intrinsic reversibility** of the transpeptidation reaction, which constrains overall efficiency and yield.

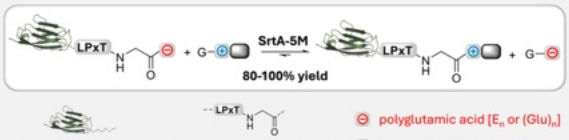
In this work, we leverage the unique electrostatic profile of SrtA-5M (1) to overcome this limitation. By introducing short, charged peptidic modules into the reactants, we enhance reaction directionality and efficiency (2). Notably, this strategy enables **rapid and high-yielding ligations at low micromolar substrate concentrations, using only minimal excess of the nucleophile**. Electrostatic assistance obviates the need for additives or elaborate substrate engineering strategies, is fully recombinant-compatible, thereby offering a broadly applicable approach to SML.[4]

(1) SrtA and SrtA-5M exhibit markedly distinct electrostatic potentials.



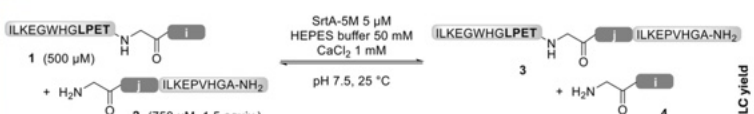
Given SrtA-5M well-marked surface charge distribution, substrates should experience significant affinity and/or reactivity differences toward the enzyme based on their own charge.

(2) Principle of the electrostatically-assisted SrtA-5M-mediated ligation

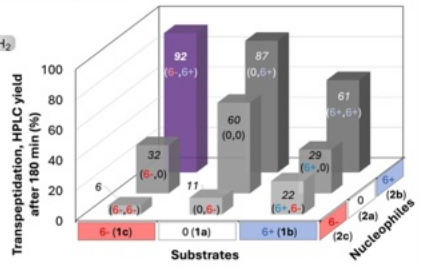


Proof of concept & optimization

• **Influence of charged peptidic modules on SML**

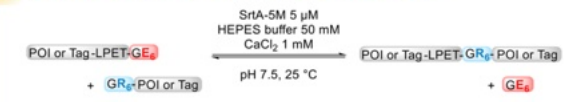


1 i =	2 j =	3 j =	4 i =
1a = SGSGSL-NH_2 (0)	2a = GG (0)	3a = GG (0)	4a = SGSGSL-NH_2 (0)
1b = R_6L-NH_2 (6⊕)	2b = R_6 (6⊕)	3b = R_6 (6⊕)	4b = R_6L-NH_2 (6⊕)
1c = E_6L-NH_2 (6⊖)	2c = E_6 (6⊖)	3c = E_6 (6⊖)	4c = E_6L-NH_2 (6⊖)

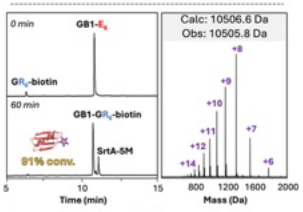


SrtA-5M efficiently promotes the ligation of an N-terminal Gly peptide containing the positively charged R_6 module with an acyl donor peptide containing the negatively charged E_6 module. The conversion reaches **92%** at a 1:1.5 stoichiometry and **achieves complete conversion (100%)** at a 1:5 stoichiometry or higher. In addition, the reaction is tolerant to the size of the R_6 module (can be reduced to 4 Arg) and to its positioning. It is also **highly efficient over a broad concentration range with minimal hydrolysis side reaction** (from mM to low µM).

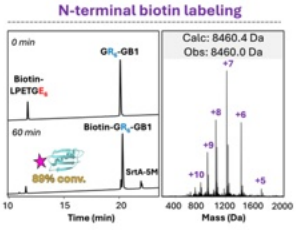
Application to protein modifications



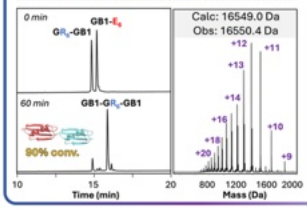
C-terminal biotin labeling



N-terminal biotin labeling

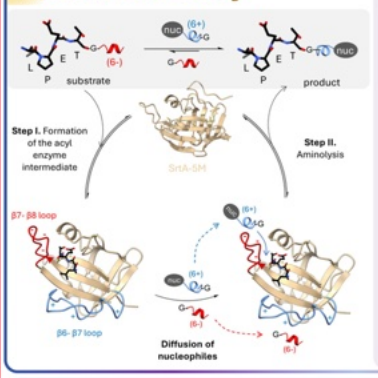


Protein-protein coupling



The approach has been successfully applied to model proteins or protein domains other than GB1 (including ubiquitin, titin I27 domain). The obtained results consistently demonstrate the robustness and versatility of the charge-assisted SrtA-5M-mediated SML for protein engineering applications, offering efficient solutions for labeling and coupling at both protein termini.

Mechanistic study



Molecular dynamic simulations reveal that the positively charged peptide consistently and exclusively contacts the highly negatively charged β7/β8 loop of SrtA-5M.

Such repeated and directional contacts may significantly increase the local concentration of the nucleophile near the catalytic site, **thereby enhancing aminolysis rates of the acyl enzyme intermediate**.

Conclusion

SrtA-5M-mediated ligations are improved by incorporating short charged peptidic modules into reaction partners. This method is **compatible with recombinant protein expression**, and **enables remarkably clean protein labeling and protein-protein coupling**. Overall, the high conversions, combined with the method's cleanliness, underscore its potential for broader implementation in protein modification workflows.

This research was supported by the ANR (**ANR-21-CE44-0031**).
CW gratefully acknowledges the GFPP committee for the grant.

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CA 011

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

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

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

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

All the results will be presented in this communication.

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CA 012

PROTACs as a new promising therapeutic strategy to target LIM kinases, proteins involved in cytoskeleton remodelling

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Résumé

LIM kinases (LIMKs) are a family of serine/threonine and tyrosine kinases comprising two highly homologous members: LIMK1 and LIMK2. They play a crucial role in cytoskeleton dynamics by independently regulating both actin filament and microtubule remodeling. Due to their role in cytoskeleton remodeling, LIMKs are involved in many physiological processes such as cell motility, morphogenesis, division, differentiation, apoptosis, neuronal morphology and neuritogenesis. Consequently, they are also implicated in multiple pathologies: cancers, viral infections (HIV, herpes), ocular diseases (glaucoma), Neurofibromatosis type 1 and 2, and neuronal diseases (Amyotrophic Lateral Sclerosis, Alzheimer and Parkinson diseases, Williams-Beuren syndrome). LIMKs have therefore emerged as promising therapeutic targets. Furthermore, they are interesting therapeutic alternative compared to usual chemotherapies targeting microtubules known for their deleterious side-effects, morbidity, and increasing resistances. Although many small molecules inhibiting LIMK kinase activity have been developed these past 15 years, none has successfully reached the stage of clinical assay. It is thus vital to develop alternative strategies to target LIMKs. We propose such an alternative by taking advantage of a PROTAC strategy (PROteolysis-TArgeting Chimeras). PROTACs are engineered as a three-part molecule: (i) a ligand of the Protein of Interest, POI, LIMKs in our case, (ii) a linker, (ii) a ligand of an ubiquitin E3 ligase. The PROTAC binds simultaneously to the POI and the ubiquitin E3 ligase, creating a physical proximity between these two proteins, leading to the ubiquitination of the POI and its subsequent degradation by the proteasome. The chemistry team of our consortium has developed a set of PROTACs based on the same LIMK ligand but carrying various linkers and ubiquitin E3 ligase ligands. These different PROTACs were then evaluated by the biology team. Their degradation potency against LIMK1 and LIMK2 was tested in different cell lines, at different concentrations and times of incubation. Their physiological impact has also been assessed via cytoskeleton imaging and migration evaluation. We have shown that the nature and length of the linker as well as the choice of the ligand of the ubiquitin E3 ligase are crucial in PROTAC efficiency. Two PROTACs appeared particularly promising with highly potent efficiency on LIMKs, opening the path towards a promising new therapeutic approach to targeting LIMKs.

CA 013

Design and synthesis of TEAD inhibitors conjugated to GnRH peptide for vectorization within tanycytes for application in the treatment of metabolic diseases

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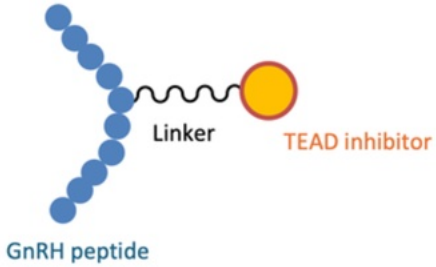
Tanycytes are ependymoglial cells in the hypothalamus that act as metabolic signal sensors at the interface between blood, cerebrospinal fluid (CSF), and the mediobasal hypothalamus parenchyma (MBH).[1, 2] Recently, Dr. Ariane Sharif's team demonstrated that the Hippo pathway, via the YAP/TAZ-TEAD transcriptional complex, regulates the proliferation of these cells and energy homeostasis. Furthermore, it has been shown that excessive activation of this pathway induces weight gain and increased adiposity, while its inhibition improves metabolic parameters in obese mice. Therefore, the strategy consists of selectively targeting tanycytes using peptide-drug conjugates (PDC) to restore energy homeostasis while minimizing off-target effects related to the ubiquitous expression of the Hippo pathway throughout the rest of the body. Other studies identified the gonadotropin-releasing hormone peptide (GnRH) as a candidate for vectorization. Consequently, the strategy consists of selectively targeting tanycytes using peptide-drug conjugates (PDC)[3] to restore energy homeostasis while minimizing off-target effects related to the ubiquitous expression of the Hippo pathway in the rest of the body. Other studies identified the gonadotropin-releasing hormone peptide (GnRH) as a candidate for vectorization. Indeed, GnRH receptors (GnRHr) are highly expressed in tanycytes, whereas they are minimally present in peripheral tissues, except for pituitary gonadotroph cells.[4] Therefore, the design and synthesis of bimodal probes (TEAD inhibitor-linker-GnRH[^{6}-D-Lys]) were undertaken to inhibit the TEAD proteins specifically within tanycytes This approach could represent a new therapeutic strategy for treating obesity and could be extended to certain cancers overexpressing GnRHr.



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Keywords: Tanycytes, Hypothalamus, Hippo pathway, TEAD, vectorization, PDC, GnRH, metabolic diseases.

CA 014

Methodological innovation in bioorthogonal chemistry for the study of sialylation

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Résumé

Glycobiology research requires cutting-edge chemical tools to overcome the challenges inherent in studying glycans *in vivo*. This work relies on the chemical reporter strategy and click chemistry-pillars of bioorthogonal chemistry-to study sialylation, an essential glycosylation process. The developed approaches aim to extend the scope of labeling and imaging methods, focusing on two main axes:

The development of a strategy for the labeling and visualization of the K1 polysialic capsule of *Escherichia coli*, thereby facilitating the understanding of this important virulence factor.

The design of new clickable iridium-based organometallic probes for bioorthogonal ligation. These compounds enable the use of high-performance imaging techniques, such as time-resolved photoluminescence and elemental nano-imaging, offering more sensitive and versatile detection of glycans.

These results constitute an advancement in the chemobiology toolkit, offering new tools to explore the role of sialylation in various biological systems.

Keywords: Bioorthogonal Chemistry, Sialylation, Metabolic Engineering, Click Chemistry, *E. coli*, Organometallic Probes.

CA 015

VOC-based probes: from cancer diagnosis to therapeutic guidance

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Résumé

VOC-based probes are emerging tools for disease diagnosis, including cancer. This study aims to evaluate their application in detecting glycosidase activity in biological systems, to indicate the early stages of cancer development directly from tissue or human plasma samples.
The objective of the first application was to highlight gastric preneoplasia following *H. pylori* infection. To achieve this, a longitudinal study was conducted on murine stomach tissues 24 hours, 3 days, 2 weeks, and 3 months post-infection. The tissues were incubated in DMEM medium for 30 minutes, followed by tissue removal and centrifugation. VOC-based probes were added to the medium, incubated for 4 hours, and VOCs were collected for 30 minutes using SPME fibres before analysis by GC-MS/MS. The volatolomics data were correlated with histological studies. In the murine model, infection marker enzymes β-galactosidase and α-mannosidase were detected at 24 hours, 3 days, and 2 weeks post-infection, while inflammation markers N-acetyl-β-D-glucosaminidase and β-glucuronidase were observed at 3 months. These enzymatic activities were strongly correlated with histological findings.

In parallel, a clinical study involving 76 patients was performed to distinguish healthy individuals from cancer patients with elevated oncogenic markers (ACE, CA15-3, CA19-9). Plasma samples were incubated in acetate buffer (pH 5), followed by the addition of VOC-based probe cocktails and incubation for 7 hours. VOCs were collected for 30 minutes using SPME fibres and analysed by GC-MS/MS. In the clinical study, VOC-based probes successfully identified β-glucuronidase and β-N-acetylglucosaminidase activities, which distinguished healthy patients from cancer patients with elevated levels of ACE, CA15-3, and CA19-9.

In addition, a companion probe associated with a prodrug was developed to monitor therapeutic activation both *ex vivo* and *in vivo*, paving the way for applications in precision oncology.

Seven VOC-based probes were combined to evaluate their potential in two key applications: detecting early stages of stomach cancer development following *H. pylori* infection and diagnosing cancer through non-invasive blood sample analysis. In addition, the development of a companion probe associated with a prodrug highlights the potential of this approach to monitor therapeutic activation. Overall, these results demonstrate the promise of VOC-based strategies not only for early detection and disease monitoring, but also for advancing precision oncology through combined diagnostic and therapeutic applications.

CA 016

Fluorescent probes for the detection of bacteria in body fluids

Viviane REN, Anthony AUGÉ, Julie KARPENKO

Keywords : Bacterial detection, Nile Red, Glutamyl endopeptidase

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

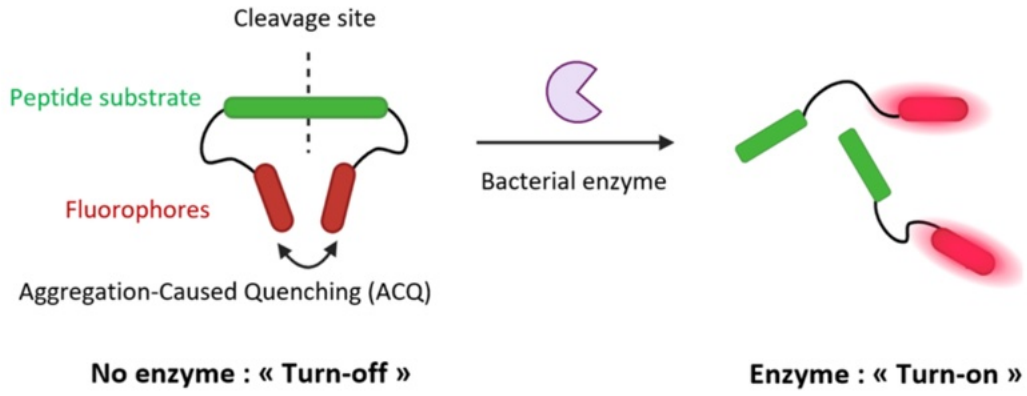

Figure 1. Principle of bacterial detection using fluorogenic dimeric probes

CA 017

Development of new fluorescent probes for fluorescence-guided surgery

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Résumé

To treat cancers, surgery is one of the most used method to remove tumoral cells. For example, 63 to 98% of patients affected by lung, breast, bladder or colorectal cancer have been treated by surgery.(1) However, traditional methods such as naked-eye operations, palpation or intraoperative histopathology are limited by low contrast between tumors and background tissues.(2) The visualization and localization of the surgical site is crucial during the incision process. For instance, residual cancer cells after resection is a strong predictor of tumor recurrence.(3) Imaging-guided surgery facilitates the distinction of cancer cells and healthy tissues and especially fluorescent-guided surgery (FGS) has been developed showing multiple advantages - high sensitivity, specificity and real-time visualisation - improving precision of tumor resection.(4,5)

In FGS, near-infrared (NIR) fluorophores are used for deeper imaging and improving tissue penetration by reducing cellular autofluorescence.(6) Nowadays, the indocyaninice green (ICG) fluorophore is the most used in FGS thanks to its fluorescence properties (quantum yield and molar extinction coefficient) but it is very sensitive to photobleaching, not easily functionnalizable and can give false positive (62%) due to low contrast.(7)

This project focused on the development of new functionnalizable family of fluorophores with competitive and modulable fluorescence properties, better chemical stability and solubility compared to ICG. Therefore, these compounds are synthesized through a practical and efficient one-step synthetic route.(8) (1) C. E. DeSantis et al., CA: Cancer J. Clin. 2014, 64, 252–271.
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(3) R. Liu, Y. Xu, K. Xu, Z. Dai, Aggregate 2021, 2, e23.
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(7) S. Kashiwagi, H. S. Choi, Ann. Transl. Med. 2023, 11, 274.
(8) European Patent Application number EP 25 306 895.1, filed on November 13th, 2025, and entitled "NEW COMPOUNDS, PROCESS AND USES THEREOF".

CA 018

Design and synthesis of anti-malarial compounds targeting PRDX6 to combat the emergence of resistance

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1 Aim of the study

Malaria is an infectious disease caused by a parasite of the Plasmodium species. In 2023, Plasmodium falciparum was responsible for nearly **263 million cases of malaria**, resulting in approximately 597 000 deaths according to the WHO[1]. Furthermore, the ***development of resistance to first-line antimalarial drugs***, including artemisinin[2], makes the development of new antimalarial treatments a major public health issue.

Our approach is to target **PRDX6**, a human enzyme that has been identified to be **essential for the plasmodium growth**. Indeed, targeting a host enzyme that is essential for the parasite's survival is an approach to develop drugs with **minimal risk of resistance.** Our study aims to optimise PRDX6 inhibitors capable of inhibiting the parasite growth in vivo, with pharmacokinetic and pharmacodynamic properties suitable for proof of concept in animals

2 PLA_2 is rescuing oxidized membrane of the parasite

To fight oxydative stress, the parasite needs a PLA_2 enzyme to specifically cleave its oxidized membrane phospholipids and replace them with non-oxidized fatty acids (fig. 1). Until now, no protein involved in repairing damage caused by lipid peroxidation had been identified in Plasmodium.

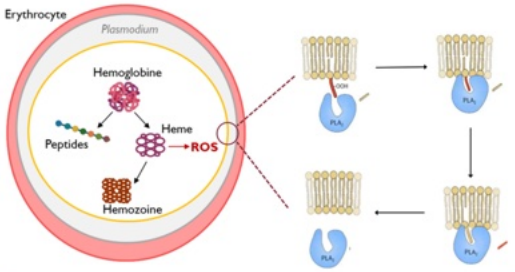


Fig 1. Formation of reactive oxygen species in P. falciparum and membrane renewal by PLA_2 enzyme

3 *P. falciparum* highjacks human PRDX6-PLA_2

P. falciparum internalises the human enzyme peroxiredoxin 6 (PRDX6) simultaneously with haemoglobin and uses the PLA_2 activity of PRDX6 to replace its peroxydated phospholipids (fig.2&3).

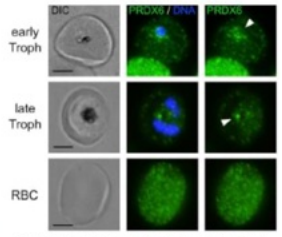
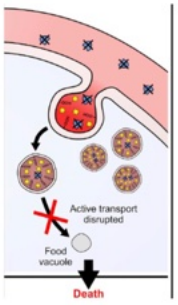


Fig 2. Immunofluorescence microscopy of cytosolic PRDX6 in RBCs[3]



4 Identification of a first inhibitor of PRDX6

Darapladib, a PLA_2 inhibitor, has been shown to inhibit PRDX6-PLA_2 activity (IC_{50} = 0.5 µM). Treatment of *P. falciparum* in the blood stage with darapladib inhibits parasite growth and progression through its life cycle with sub-micromolar potency (fig.3).

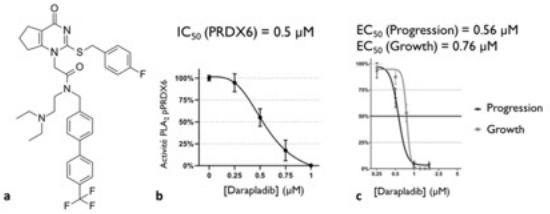
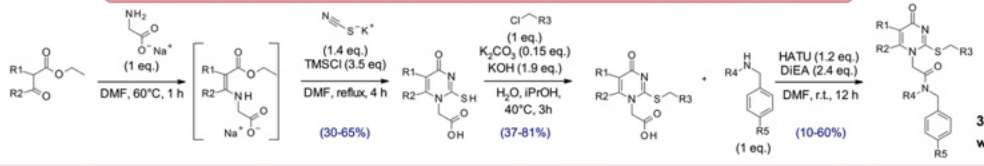


Fig 3. (a) Structure of darapladib (b) Radioactive PLA_2 activity assay[3] (c) Inhibition of P. falciparum ring-to-schizont progression[3]

5 Study of the structure-activity relationships in the darapladib series



35 compounds were synthesized

6 Biological results

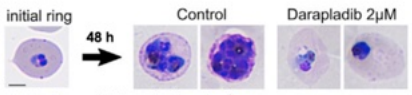
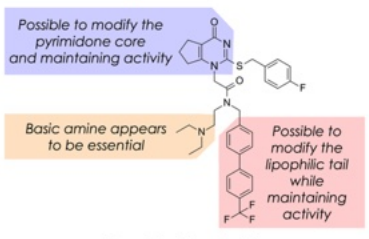


Fig 4. Light microscopy of P. falciparum blood-stage cultures[3]

Growth inhibition were assessed on tightly Percoll-synchronised culture (2% parasitemia and 2% hematocrit) treated with different inhibitors at ring stage. After 48 h incubation, the overall growth and development of next generation rings was measured with flow cytometry (fig 4.).



EC_{50} = 0.8 µM to > 5 µM

Conclusions and next steps

- Differents **darapladib analogues** were synthesized and **evaluated** against ***P. falciparum.***
- *First structure-activity results were obtained, enabling us to notice the importance of the* ***basic amine*** *or the* ***lipophilic chain****.*
- *Other PLA_2 inhibitors were synthesized and will be tested.*
- *Enzymatic assay will be develop to validate target engagement.*

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CA 019

Chelation assisted click-and-release chemistry for efficient bioconjugation

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Résumé :

Sydnonimines are mesoionic compounds that have recently emerged as valuable partners in click chemistry and bioorthogonal reactions[1]. Here, we report the development of a new generation of chelation-assisted "click-and-release" reactions enabling efficient bioconjugation in biological media. Our strategy relies on copper-chelating dipoles based on sydnonimine scaffolds, specifically designed to enhance catalytic efficiency. A scope study was conducted on a series of sydnonimines reacting with terminal alkynes under copper catalysis. This approach is based on the concept of internal chelation, which strongly activates copper complexes, significantly increasing reaction rates while minimizing metal toxicity. The newly developed reactions will enable both bioorthogonal ligation and the controlled release of active compounds, opening major prospects in cellular imaging, drug delivery, and chemical biology.

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Keywords: click chemistry, bioconjugation, copper, sydnones, azides

CA 020

Halogenated Sydnonimines For Fast Click & Realease Reactions

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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 Strain-Promoted Sydnonimines-Cyclooctyne Cycloaddition).[3]

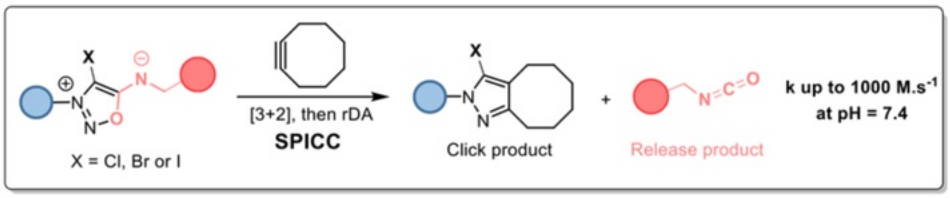

Figure 1. Strain-Promoted Sydnonimines-Cyclooctyne Cycloaddition with Halogenated Sydnonimines

In this work, we demonstrated that functionalization in C4 position of sydnonimines with halogen atom increases up to 120-fold the speed of SPSIC, leading to kinetic constant up to 1070 $L.mol^{-1}.s^{-1}$ with DBCO and 580 $L.mol^{-1}.s^{-1}$ with BCN. Thanks to their enhanced reactivity, halogenated sydnonimines were afterwards used for ultrafast radiolabelling of biologics.

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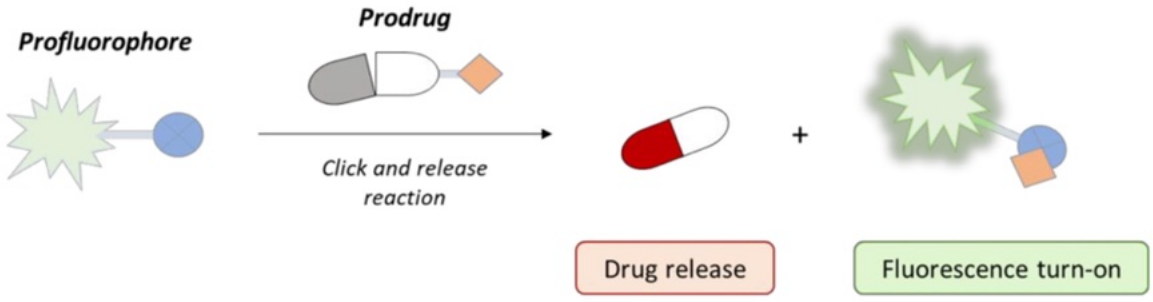
Keywords: biorthogonal reaction; mesoionic compounds; radiolabelling

CA 021

Widening the scope of tetrazine based biorthogonal click and release reactions for the development of theranostic tools

Dr. Alexis Truchon, Dr. Karine Porte

The development of targeted and effective therapeutic strategies, particularly against cancer, remains a major research priority. Bioorthogonal chemistry has gained interest in this field through the design of biocompatible chemical transformations [*Angew. Chem. Int. Ed. Engl*. **2021,** *60*, 43, 23084–23105]. These reactions involve two reactive partners that interact exclusively with each other within complex biological environments, thereby avoiding interference with native biomolecules. Such bioorthogonal processes enable precise applications in imaging and drug delivery *in vivo* [*ChemBioChem* **2021**, *22*, 100–113]. In this context, our work focuses on the development of new "click-and-release" bioorthogonal reaction involving tetrazine partners with the aim to creating an efficient theranostic platform. The product resulting from this transformation will enable both imaging, through turn-on fluorescence effect ("click"), and therapy, through on demand intramolecular drug delivery ("release"). In this communication, we will illustrate our first efforts targeting a [4+1] click and release reaction.



CA 022

Design and Synthesis of Photolabeling Probes for Identification of Anti-Alzheimer Compounds

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Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder. Beyond its classical hallmarks—amyloid-beta deposition and Tau aggregation—AD is characterized by complex cellular dysfunctions, including neuroinflammation, and impaired proteostasis. To date, most small molecules in clinical development target a single pathological process and have shown limited disease-modifying efficacy.

Using a phenotypic screening strategy followed by a ligand-based pharmacophore approach, we identified several series of compounds capable of modulating APP metabolism, reducing Tau pathology in vivo, and improving cognitive deficits in transgenic mouse models combining amyloid and Tau lesions (1-4). Notably, some of these compounds also displayed beneficial effects on neuroinflammation and protein homeostasis, suggesting a multimodal mechanism of action.

However, the molecular target(s) and precise mechanism underlying these effects remain unknown. To address this limitation, we developed a bioorthogonal chemistry–based strategy aimed at target identification. Photoaffinity probes derived from the initial chemical scaffolds were rationally designed and synthesized through the introduction of diazirine photoactivatable groups and click-chemistry–compatible handles, guided by structure–activity relationships. These probes were first validated for their ability to modulate APP metabolism, then applied in a workflow combining photocrosslinking, click chemistry-based enrichment, and proteomic analysis to identify candidate molecular targets.

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CA 023

VGF as a target for anti-alzheimer compounds

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Alzheimer's disease (AD) is a progressive and incurable neurodegenerative disorder driven by the accumulation of misfolded and aggregated proteins, particulary amyloid precursor protein (APP)-derived species and Tau- in the central nervous system, along with neuroinflammation.
We have developed several families of small molecules that demonstrated robust *in vitro* and *in vivo* efficacy in AD models (1-6). These compounds reduce protein aggregation, modulate APP metabolism and Tau phosphorylation, improve cognition in APPxPS1 and Thy-Tau22 transgenic mice, and decrease microglial activation and astrogliosis.
Despite these encouraging results, two critical questions remained : **what is the molecular target of these compounds**, and **how do they act**? To address this, we implemented a two-component photoaffinity labeling (PAL) strategy combined with click chemistry. Four tailored probes, representative of our compound families and bearing diazirine and alkyne groups at distinct positions on the active scaffolds, were applied to the SY5Y-APPNSE1 cell line (poster Fina M. et al). Fluorescent click labeling revealed probe–target localization in lysosomes, endoplasmic reticulum, and late endosomes, while *in-cellulo* competition experiments confirmed that the probes and parent compounds share a common target.
Affinity-based mass spectrometry identified VGF, a neuropeptide precursor recently proposed as a Tau interactor in human AD brain, as the primary and shared target of all compound families (7). Higher VGF levels are associated with reduced cognitive decline in AD (8). Probe–VGF colocalization was confirmed by immunocytochemistry, and specific interactions were validated both *in cellulo* and *in vitro*.

In our cellular models, treatment with our compounds strongly increased VGF secretion, an effect further enhanced by APP expression. Importantly, VGF positively modulated APP metabolism under these conditions, establishing a functional link between VGF and APP. The effect on tau aggregation is still under evaluation.
Biophysical studies indicate that full-length recombinant VGF forms a hexameric assembly capable of binding the probes. Ongoing molecular docking and proteomic analyses aim to identify and confirm the precise compounds binding site.

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Keywords: Alzheimer's desease; VGF; click chemistry; APP metabolism.

Plan d'exploration du gisement

Nos soutiens précieux

Carnet de bord

Jeudi 4 Juin 2026

09h00	*Accueil*	
09h30	**Christophe Biot**	*Introduction*
09h50	**Oleg Melnyk**	*Conférence Invitée*
10h35	**Julie Karpenko**	*Comm. Orale*
10h55	*Pause Café*	
11h25	**S. Griesbaum & E. Barbé**	*Comm. DUO*
11h45	**Emmanuel Courtade**	*Comm. Orale*
12h05	**Jamal El Bakali**	*Comm. Orale*
12h25	**Fina Maureen**	*Flash A1*
12h30	**Catherine Baud**	*Flash A2*
12h35	**Guillaume Blondy**	*Flash A3*
12h40	*Repas / Posters*	
14h15	**Cyrille Sabot**	*Comm. Orale*
14h35	**S. Katsakos & S. Papot**	*Comm. DUO*
14h55	**Robin Fournier**	*Flash B1*
15h00	**Morane Lucas**	*Flash B2*
15h05	**Chen Wang**	*Flash B3*
15h10	**Carlo Pifferi**	*Comm. Orale*
15h30	**Matteo Crespi**	*Comm. Orale*
15h50	**Malo Gourvest**	*Flash C1*
15h55	**Rony Eid**	*Flash C2*
16h00	**Xavier Trivelli**	*Flash C3*
16h05	*Pause / Posters*	
16h45	**Clotilde Policar**	*Conférence Invitée*
17h25	**D. Guianvarc'h**	*Table ronde: L'importance du réseau GDR ChemBio pour les jeunes recrues*

Vendredi 5 Juin 2026

09h00	**Claire Moulis**	*Conférence Invitée*
09h45	**Jean-Bernard Behr**	*Comm. Orale*
10h05	*Pause Café*	
10h35	**A. Martin & A. Puissant**	*Comm. DUO*
10h55	**Sarah Mehdi**	*Flash D1*
11h00	**Asmi Rodrigues**	*Flash D2*
11h05	**Eric Kaya**	*Flash D3*
11h10	**Narjis Ouazzani**	*Flash D4*
11h15	**Emilie Nguyen**	*Comm. Orale*
11h35	**Quentin Gaudillat**	*Comm. Orale*
11h55	**Boris Vauzeilles**	*Comm. Orale*
12h15	*Repas / Posters*	
14h00	**Marie Lopez & Flore Nardella**	*Comm. DUO*
14h20	**Kevin Renault**	*Comm. Orale*
14h40	**Pierre Lafite**	*Comm. Orale*
15h00	**MCE**	*Sponsors*
15h05	**Optimus**	*Sponsors*
15h10	*Échanges libres*	
16h00	*Conclusion*	

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