LIVRET

20e RECOB

Aussois
22-26 mars 2026

REncontres de Chimie Organique Biologique

BIENVENUE AUX RECOB 20

C'est avec grand plaisir que le comité d'organisation des RECOB 20 vous accueille au centre Paul Langevin à Aussois. Cette édition marque une étape particulière dans l'histoire de ces rencontres scientifiques: 40 ans après leur lancement, les RECOB célèbrent leur vingtième édition, témoignant de la vitalité et de la continuité d'une communauté scientifique qui a su, au fil des années, faire vivre et évoluer cet événement.

Depuis leur création, les RECOB constituent un rendez-vous privilégié pour la communauté scientifique travaillant à l'interface de la chimie et de la biologie. Elles offrent un cadre propice à la présentation des avancées les plus récentes, aux échanges d'idées et à l'émergence de nouvelles collaborations.

Le cadre convivial du centre Paul Langevin constitue un environnement idéal pour ces échanges, qu'ils aient lieu lors des séances de posters ou dans les nombreux moments de discussion informelle qui accompagnent les pauses et les repas.

Dans l'esprit de cette édition anniversaire, le congrès s'ouvrira par une conférence historique, retraçant les origines des RECOB et leur évolution au fil du temps. Nous aurons également le plaisir d'accueillir sept conférenciers de renom. Fidèles à l'esprit des RECOB, nous avons souhaité laisser une large place aux contributions de la communauté, permettant aux chercheurs, jeunes comme plus expérimentés, de venir présenter leurs travaux lors des communications orales et des séances de posters.

Le comité d'organisation tient enfin à exprimer ses sincères remerciements à l'ensemble de celles et ceux qui contribuent à la réussite de ces rencontres – institutions publiques, partenaires industriels, exposants, conférenciers et participants – dont la présence, l'engagement et l'enthousiasme permettent de faire vivre les RECOB et d'en assurer la pérennité.

LE COMITÉ D'ORGANISATION DES RECOB 20

Karine Alvarez (*présidente*), Florence Mahuteau-Betzer (*secrétaire*), Nicolas Lebègue (*trésorier*), Sandy Desrat (*chargé de communication*), Alexandre Specht, Pierre-Yves Renard, Virgil Hélaine.

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ÉDITO : 20ÈME ÉDITION DES RECOB

par Pierre-Yves Renard, Professeur des universités, Université de Rouen Normandie

La chémobiologie est désormais une discipline à part entière, comme en atteste l'attribution du prix Nobel de Chimie 2022 à Carolyn Ruth Bertozzi (université de Stanford, États-Unis), Morten Peter Meldal (université de Copenhague, Danemark), et Karl Barry Sharpless (institut de recherche Scripps, La Jolla, États-Unis) pour le développement de la chimie click et de la chimie bio-orthogonale. Mais bien avant qu'elle ne trouve sa reconnaissance avec ce joli néologisme, des chercheurs et enseignants chercheurs ont compris l'importance de développer l'interface chimie-biologie en France, et de structurer la communauté s'intéressant à la chimie organique biologique. La chimie est à l'origine de tous les mécanismes biologiques. Seule la maîtrise de la synthèse organique, et les développements méthodologiques en chimie analytique permettent de créer des outils innovant pour sonder les mécanismes du vivant. Les contraintes liées à la manipulation des biomolécules, dans un solvant "inusuel" pour les organiciens, à des conditions de pH et de température bien précises, et la nécessité de développer des réactions chimio-sélectives en jouant sur la réactivité de la multitude des fonctions chimiques présentes dans les organismes vivants est un puissant moteur pour susciter l'imagination et la créativité des chercheurs.

L'organisation de la vingtième édition des RECOBs est l'occasion de rendre hommage à ces précurseurs, qui ont eu l'idée, en 1986, de réunir la communauté au centre Paul Langevin d'Aussois pour trois, puis quatre journées d'échanges et de conférences, à l'image des Gordon Conferences américaines. Andrée Marquet, Jean Lhomme, Françis, Schubert, Jean-Claude Chottard et Jean-Claude Depezay sont à l'origine de la première édition des RECOBs. On pourra retrouver l'histoire de l'émergence de la chemibiologie dans l'excellent article de Dominique Guianvarc'h (l'actualité chimique N° 468, 2021, 9 – 12). Une des originalités de ces rencontres est que leur organisation est confiée à un comité de 6 à 8 personnes, issus de toute la France et représentant les principales universités et centres de recherche où l'interface se développe. Le flambeau est donc continuellement transmis, et à chaque RECOB, les plus anciens membres du bureau cèdent leur place et l'apport de sang neuf, permet de renouveler la flamme. Tous les grands noms de la chémobiologie française sont passés par les RECOBs, au sein du comité d'organisation, en tant que conférencier invité.

Ces rencontres sont l'occasion de mettre en lumière toutes les sous-disciplines de cette chimie organique biologique, et de favoriser le mélange des genres (en tout bien tout honneur), terreau fertile pour initier de nouvelles collaborations. Conférenciers invités, doctorants, post doctorants, ingénieurs de recherche, chercheurs et enseignants chercheurs se retrouvent confinés dans une ambiance conviviale, propice aux échanges scientifiques, aux rapprochements (pas que thématiques, de solides amitiés se sont construites aux RECOBs), au montage de projets collaboratifs, et même au recrutement de chargés de recherche ou maître de conférences.

Les anecdotes sont nombreuses, et, entre fondue savoyarde, soirée dansante, et pistes noires, les personnalités se dévoilent, tel collègue qui semblait si austère (voire même un peu coincé…) enflamme la piste de danse. Les membres trop bavards des jurys de poster et les doctorants luttant contre le sommeil en attendant le passage du jury, avant d'être libérés au-delà de minuit. Le pèlerinage de Marcel Hibert au cimetière d'Aussois qui lui inspire une conférence lumineuse (et sa suite) sur la molécule de l'amour. Les calculs ab initio d'Odile Eisenstein sur la structure du centre métallique de l'oxy-hémocyanine mis à l'épreuve de celle qui venait d'être révélée par Karen Magnus. Un jeunot l'interroge : connait-elle cette structure ? Odile interloquée, reste bouche bée, silence glacial dans l'auditoire, vite remplacé par un tonnerre d'applaudissement, quand le jeunot, d'une voix chevrotante d'émotion conclue son intervention par "c'est bien votre proposition qui est la bonne structure". Les jeux de questions ping-pong entre Fréderic Taran et Sébastien Papot…

Pour autant que les archives (non numérisées) des RECOBs permettent de remonter le temps (pas de trace numérique, sauf la photo de groupe avant 1996, outre les pères (et mères fondateurs), se sont succédés au comité d'organisation, dans un ordre à peu près chronologique : Claude Benezera, Michel Gaudry , Marc Fontecave, Jean-Renaud Garel, Marcel Hibert, Bernard Badet, Michèle Reboud, Charles Danzin, Liliane Gorrichon, Marco Ciufolini, Maurice Goeldner, Jean-Baptiste Galay, Elisabeth Blee, Colette Demuynck, Marius Reglier, Laurence Hecquet, Olivier Ploux, Casimir Blonski, Jean-François Constant, Gilles Guichard, Ling Peng, François Morvan, Patricia Melnyk.

Edito

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Acteur majeur de la recherche fondamentale à l'échelle mondiale, le Centre national de la recherche scientifique (**CNRS**) est le seul organisme français actif dans tous les domaines scientifiques. Sa position singulière de multi-spécialiste lui permet d'associer les différentes disciplines scientifiques pour éclairer et appréhender les défis du monde contemporain, en lien avec les acteurs publics et socio-économiques. Ensemble, les sciences se mettent au service d'un progrès durable qui bénéficie à toute la société.

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Avec un effectif de près de 200 personnes, l'**ICSN** constitue le pôle chimie du campus CNRS de Gif-sur-Yvette. L'Institut est situé en bordure du futur campus Paris-Saclay, qui regroupera près de 10% de la recherche française, et fait partie intégrante de cette nouvelle Université. L'ICSN développe des activités à l'interface chimie-biologie, avec les substances naturelles comme objet d'étude et source principale d'inspiration. L'ICSN est organisée en quatre départements de recherche et dispose d'importantes plateformes analytiques.

La Gazette du LABORATOIRE est un point de rencontre et d'échange, accessible à l'ensemble des acteurs du monde du Laboratoire et des Sciences. Créée par un scientifique pour les scientifiques, La Gazette du LABORATOIRE accompagne depuis 1995, la vie des laboratoires francophones de Recherche, Développement, Analyse et Contrôle. Nous sommes une équipe à taille humaine, à votre écoute – pour toute question : contactez-nous ou appelez-nous au 04 77 72 09 65.

PROGRAMME DÉTAILLÉ

DIMANCHE 22 MARS 2026

18:30		**ACCUEIL DES PARTICIPANTS**
19:20		Apéritif de bienvenue
19:45		Dîner
20:45		**INTRODUCTION**

LUNDI 23 MARS 2026

SESSION 1 *Modération : A. Specht*

08:30	**CP1**	**Mimes structuraux et fonctionnels de domaines protéiques et de peptides pour des applications à visée thérapeutique - GUICHARD Gilles**
09:20	C01	Marquage chemoenzymatique des substrats protéiques d'une lysine méthyltransférase à l'aide d'analogues de S-adénosyl-L-méthionine - DAVID Charlène
09:40	C02	Développement de modulateurs originaux bio-inspirés des LXRs dans le potentiel traitement du cancer de la prostate métastasé - DELPORTE Norberta
10:00		Pause café
10:30	C03	La mal-aimée tagatose-1,6-bisphosphate aldolase : une enzyme finalement d'intérêt - GUILLETON Mathilde
10:50	C04	Engineering nucleophilic catalysis coupled to tandem electrostatic assistance enables native chemical ligation–based protein modification at nanomolar concentrations - DI ADAMO Julie
11:10	C05	Dynamic Combinatorial Library of Cyclopeptides for GAGs interaction - GARCIA COLL Jose
11:30	C06	Novel peptide bioprobes based on Ytterbium complexes for Near-Infrared cell imaging - DI SANTO Tom
11:50	C07	Photozyme strategies for enantioselective synthesis of chromanone derivatives - VINCHON Florian
12:30		Déjeuner - temps libre

PROGRAMME DÉTAILLÉ

LUNDI 23 MARS 2026 - SUITE

SESSION 2 *Modération : PY. Renard*

16:30	**CP2**	**Combining Chemical Biology and Mass Spectrometry to Decipher Bacterial Virulence - CHAMOT-ROOKE Julia**
17:20	C08	Copper-Chelating Probes Associated with Molecular Networks for the Discovery of New Polyacetylenic Natural Products - FRANCK Xavier
17:40	C09	Fluorogenic photocatalyzed proximity labeling with visible light to map the interactome in living cells - JOBIC Meven
18:00	C010	Engineering Robust Calixarene-Coated Nanoparticles for Next-Generation Therapeutic and Diagnostic Applications - BRUYLANTS Gilles
18:20	C011	Development of a novel fluorescence anisotropy assay for studying polyphenolic inhibitors of Tau fibrillation - DUPONT Cécile
19:30		Dîner
20:45		**CO Exposants**
21:15		**Session posters pairs**

MARDI 24 MARS 2026

SESSION 3 *Modération : S. Desrat*

08:30	**CP3**	**Réductases mitochondriales en cellules normoxiques : les observer et les exploiter - CHEVALIER Arnaud**
09:20	C012	Environmentally sensitive fluorescent molecular tools to study the local polarity of individual layers of the bacterial cell envelope - AUGÉ Anthony
09:40	C013	Genetically-targeted and red-emitting fluorescent indicator for subcellular zinc imaging - WITTWER Manon
10:00		Pause café
10:30	C014	A new, powerful fluorogenic click-and-release reaction - GOURVEST Malo
10:50	C015	Développement de nanobodies fluorogènes dans le proche infrarouge pour la détection de cellules cancéreuses - GRIESBAUM DUBOURG Sarah
11:10	C016	Optimized Fluorescent pH-Sensitive Dextran Conjugates Enable Ratiometric Measurement of Cerebral Blood pH In Vivo and In Situ - WALTER Sophie
11:30	C017	Synthesis and evaluation of the biological activity of photoswitchable monoamine oxidase inhibitors in the treatment of osteoarthritis - FABE Mélina
11:50	C018	Molecular engineering of the difluoro dipyridomethene boron complexes towards the development of heavy atom-free photosensitizers for PDT - FIGLIOLA Carlotta
12:30		Déjeuner - temps libre

PROGRAMME DÉTAILLÉ

MARDI 24 MARS 2026 - SUITE

SESSION 4 *Modération : K. Alvarez*

16:30	**CP4**	**Analogues de nucléotide et Paludisme, quand l'inattendu est au rendez-vous - PEYROTTES Suzanne**
17:20	C019	Kinase Inhibitors as host-targeting antivirals - KRIMM Isabelle
17:40	C020	Scaffold Hopping Strategy for the Discovery of Novel ACSL4 Inhibitors - LAFON Juliette
18:00	C021	Chemical synthesis and biological assessments of RhoGTPase inhibitors - TESSIER Arnaud
18:20	C022	Towards the next generation of antibiotics by targeting the IspH metalloenzyme - VIEIRA DE ALMEIDA Isabelle
19:30		Dîner
20:45		**CO Exposants**
21:15		**Session posters impairs**

MERCREDI 25 MARS 2026

SESSION 5 *Modération : F. Mahuteau*

08:30	**CP5**	**Design and synthesis of small-molecule binders targeting non-coding RNAs for anticancer and antimicrobial applications - DUCA Maria**
09:20	C023	Screening, Design, Synthesis and Evaluation of Macrocyclic Ligands for Stabilization of RNA Hairpins Implicated in Type 1 Myotonic Dystrophy - RICHAGNEUX Camille
09:40	C024	Discovery of Novel G-quadruplex Binding Peptidic Derivatives Using DNA Encoded Chemical Libraries - TRINCAS Massimo
10:00		Pause café
10:30	C025	Harnessing Nucleoside and Nucleotide Chemistry to Explore RNA Modifications ETHEVE-QUELQUEJEU Mélanie
10:50	C026	Design and Synthesis of Stable Antiviral Analogues of Macarangin B - ING Chea Julie
11:10	C027	"In situ" and "in crystals" click chemistry, a potent tool to accelerate antiviral drug discovery against Bunyaviricetes infections - DÉGARDIN Médéric
11:30	C028	Photocatalytic Strategies for Antibody Bioconjugation - LE STUM Marine
11:50	C029	Antiproliferative Activity of Bispidines and Their Copper Complexes: When the Ligand Outperforms the Metal Complexes - EL KADIRY Firas
12:30		Déjeuner - temps libre

PROGRAMME DÉTAILLÉ

MERCREDI 25 MARS 2026 - SUITE

SESSION 6 *Modération : N. Lebègue*

16:30	**CP6**	**Les sucres sous tension : bioconjugaison électrochimique de sucres complexes à la surface de protéines et cellule - GOUIN Sébastien**
17:20	C030	Deep-Tissue Molecular Activation: Ionizing Radiation-Driven theranostics to target cancer cells - BICHOT Marius
17:40	C031	Combination of metabolic glyco-engineering and disulfide rebridging for the grafting of antibody fragments on cell surface - toward new cell therapies - THOREAU Fabien
18:00	C032	AfKDNAse Inhibitors as Potential Antivirulence Agents against Aspergillus fumigatus - SCALABRINI Mathieu
18:45		**Assemblée générale**
19:30		Dîner : Fondue Savoyarde – Soirée dansante

JEUDI 26 MARS 2026

SESSION 6 *Modération : V. Hélaine*

08:30	**CP7**	**Unlocking the Potential of Untapped Chemical Spaces - ROCHE Didier**
09:20	C033	Synthesis of fluorescent probes targeting VGLUT3 for in vivo pharmacological studies - MAI Alexis
09:40	C034	Rewriting the tubulin code: Targeting α-tubulin detyrosination for therapeutic benefit - SIMON Matthieu
10:00	C035	Vectorization of pleuromutilin by a siderophore mycobactin analog: towards antibiotic Trojan horses against Pseudomonas aeruginosa - HAJEB Walid
10:20		**Clôture des RECOB20**
10:30		Pause café
11:00		Navette Bus Modane

CONFÉRENCES PLÉNIÈRES

CONFÉRENCIER INVITÉ

GILLES GUICHARD

Institut de Chimie & Biologie des Membranes et des Nano-objets

Gilles Guichard a obtenu son doctorat à l'Université Louis Pasteur à Strasbourg en 1996 pour des travaux en chimie des peptides. Après un stage post-doctoral à l'ETH Zürich (Suisse) sous la direction du Prof. Dieter Seebach au cours duquel il a étudié la synthèse et les propriétés de repliement des β-peptides, il a été recruté comme Chargé de Recherche CNRS à l'Institut de Biologie Moléculaire et Cellulaire (IBMC) à Strasbourg en 1998. Il est promu Directeur de Recherche en 2006, et rejoint en 2009 l'Institut de Chimie et Biologie des Membranes et Nanoobjets (CBMN) et l'Institut Européen de Chimie et Biologie (IECB) à Bordeaux ou il créé l'équipe de Chimie Peptidomimétique.

Il est aujourd'hui Directeur Adjoint de CBMN, et directeur du GIS-IECB, une structure hotel à projet sur le site de Bordeaux. Il a reçu le prix Grammaticakis-Neuman de l'Académie des sciences pour ses travaux dans le domaine des foldamères (2019) et le prix DCO de la SCF en 2021.

Ses recherches portent sur la chimie biomimétique des peptides et la chimie des foldamères. Ces dernières années, son groupe s'est particulièrement intéressé aux mimes structuraux et fonctionnels de domaines protéiques appliqués à la conception de modulateurs des interactions médiées par les protéines.

ABSTRACT

GILLES GUICHARD

Institut de Chimie & Biologie des Membranes et des Nano-objets

CP1 Mimes structuraux et fonctionnels de domaines protéiques et de peptides pour des applications à visée thérapeutique

Les interactions protéine-protéine (IPP) et protéine-acide nucléique sont au cœur de nombreux processus biologiques et représentent des cibles thérapeutiques majeures justifiant les efforts actuels pour identifier des modulateurs efficaces de ces interactions.

Différentes approches permettent de découvrir de tels modulateurs, notamment le criblage phénotypique, le criblage sur une cible d'intérêt ou encore la conception rationnelle guidée par la structure. Dans ce dernier registre, les éléments structuraux présents aux interfaces d'interaction offrent des points de départ pertinents pour concevoir des ligands à visée thérapeutique et explorer les fonctions biologiques des protéines ciblées.

La transformation de la séquence ou de la structure peptidique permet d'optimiser les propriétés des ligands : stabilisation de la conformation bioactive, amélioration de l'affinité et la sélectivité, résistance accrue à la protéolyse et meilleure perméabilité cellulaire. Parmi ces différentes transformations figurent la macrocyclisation («stapling»), l'incorporation d'acides aminés non canoniques, et la chimie des foldamères.

Au cours de cette présentation, nous illustrerons comment la combinaison de ces approches peut permettre de concevoir des ligands de haute affinité tout en atténuant le caractère peptidique des molécules. Nos travaux se sont focalisés sur plusieurs familles de cibles : des facteurs de transcription (récepteurs nucléaires, p53), des protéines impliquées dans la régulation épigénétique (chaperons d'histones) et la machinerie bactérienne de réplication de l'ADN (anneau de processivité). Plus récemment, nous avons exploré la notion de proximité moléculaire pour développer des inhibiteurs covalents dérivés de peptides.

Références :

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CONFÉRENCIÈRE INVITÉE

JULIA CHAMOT-ROOKE

Spectrométrie de Masse pour la Biologie, Institut Pasteur, CNRS UAR 2024

Julia Chamot-Rooke est chimiste analytique de formation et Directrice de recherche au CNRS (DR1). Depuis 2012, elle dirige le laboratoire Spectrométrie de Masse pour la Biologie (MSBio) à l'Institut Pasteur, à Paris. Elle a précédemment exercé au Département de chimie du Centre de recherche de l'École Polytechnique. Au sein de l'Institut Pasteur, son laboratoire mène des activités de recherche et de service en protéomique.

Ses travaux de recherche portent sur le développement de méthodes analytiques innovantes en protéomique dite top-down ainsi qu'en protéomique structurale (notamment via la spectrométrie de masse de réticulation, ou cross-linking MS), avec une attention particulière portée aux applications dans le domaine des maladies infectieuses.

Julia Chamot-Rooke a été présidente de la Société Française de Spectrométrie de Masse. Elle a représenté la France au sein de l'International Mass Spectrometry Foundation (IMSF) de 2014 à 2017, et siège depuis 2017 au comité exécutif de cette organisation en tant que représentante de la Région A (Europe/Afrique). Elle est également membre fondatrice et membre du comité exécutif du Consortium International pour la Protéomique Top-Down (CTDP).

En 2019, elle a co-organisé, en collaboration avec le CTDP, le tout premier symposium européen dédié à la protéomique top-down, qui s'est tenu à l'Institut Pasteur et a rencontré un franc succès.

Elle est partenaire de trois projets européens majeurs (EPIC-XS, TopSpec et ToxDetect), et coordonne également plusieurs projets multidisciplinaires financés par l'Agence Nationale de la Recherche (PathoTOP, T4PNanoAction) ainsi que par la Fondation pour la Recherche Médicale (PROTEO-SARS-CoV-2).

ABSTRACT

JULIA CHAMOT-ROOKE

Spectrométrie de Masse pour la Biologie, Institut Pasteur, CNRS UAR 2024

CP2 Combining Chemical Biology and Mass Spectrometry to Decipher Bacterial Virulence

In recent years, cross-linking mass spectrometry (XL-MS) has evolved from a technique mainly applied to purified proteins into a robust approach for large-scale studies of protein–protein interactions in complex samples, including whole bacterial cells. XL-MS enables the unbiased identification of interaction partners by circumventing purification steps that may disrupt transient or dynamic associations.

However, a persistent technical challenge is the inherently low abundance of cross-linked peptides after trypsin digestion, which necessitates enrichment prior to MS analysis. To this aim, our lab introduced a few years ago a novel bio-orthogonal enrichable cross-linker called NNP91. Building on this new reagent, we developed an in vivo XL-MS strategy to study bacterial protein-protein interactions with a focus on virulence systems. We used Neisseria meningitidis, a gram-negative bacterium which strictly infects humans, as our model organism2. Specifically, we were interested in gaining information on its type IV piliation (T4P) machinery, which is a large and highly dynamic complex spanning both the inner and outer membrane. Despite improvements in cross-linker chemistry and methodology, our results remained strongly biased toward abundant cytosolic proteins, limiting the coverage of membrane-associated pilus components. To overcome this, we developed a membrane enrichment protocol prior to XL-MS, which significantly increased the relative abundance and coverage of membrane complexes such as the T4P machinery, highlighting protein-protein interactions that were previously hidden.

We also introduced a simple approach using iBAQ protein abundance measurements to define a practical threshold for XL-MS success3. Our results, supported by comparison to published large-scale datasets, indicate that proteins of interest should be within the top 20% abundance range to expect robust detection of cross-links. This simple guideline now offers a predictive tool for researchers, helping to ensure that XL-MS experiments are optimally designed to capture even low-abundance but functionally crucial protein assemblies.

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CONFÉRENCIER INVITÉ

ARNAUD CHEVALIER

Institut de Chimie des Substances Naturelles

Arnaud Chevalier a obtenu son doctorat en chimie organique et bio-organique en 2014 à l'Université de Rouen sous la direction de Pierre-Yves RENARD et Anthony ROMIEU, où il a développé des outils pour l'imagerie par fluorescence. Il a ensuite poursuivi des recherches postdoctorales dans plusieurs domaines : d'abord à l'Université d'Arizona en chimie médicinale où il a principalement étudié les mitochondries, puis à l'Université de Rouen en synthèse totale et méthodologie, et enfin au CEA Saclay sur le radiomarquage et la bioconjugaison.

Depuis 2018, il est Chargé de Recherche CNRS au sein de département de Chémobiologie à l'Institut de Chimie des Substances Naturelles. Auteur d'une quarantaine de publications, A. Chevalier est lauréat du prix Jeune Chercheur 2025, décerné par la Division Transversale de Chimie Biologique de la SCF. Ses travaux actuels portent notamment sur le développement d'outils d'imagerie par fluorescence pour l'étude des processus intracellulaires et mitochondriaux en vue d'innovations thérapeutiques.

ABSTRACT

ARNAUD CHEVALIER
Institut de Chimie des Substances Naturelles

CP3 Réductases mitochondriales en cellules normoxiques : les observer et les exploiter

Fluorescence imaging is a powerful technique for visualizing living cells with high spatial resolution, enabling clear distinction between cellular compartments and organelles.[1] The strong correlation between the molecular structure of organic fluorophores and their photophysical properties allows the rational design of fluorogenic probes whose emission responds to specific chemical transformations.[2] These structural modifications can manifest as the onset of fluorescence or shifts in emission wavelength. In this presentation, we will see how this tight structure/property relationship can be exploited to study living cells, through examples ranging from fluorophore design[3] to enzyme activity sensing.[4]

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CONFÉRENCIÈRE INVITÉE

SUZANNE PEYROTTES

Institut des Biomolecules Max Mousseron (IBMM)

Suzanne Peyrottes est diplômée en chimie de l'Université de Montpellier (France) et a obtenu son doctorat en 1995 sous la direction du Dr J.J. Vasseur, où elle s'est consacrée à la synthèse et l'étude d'oligonucléotides modifiés. Elle a ensuite rejoint le groupe du Dr M.J. Gait au MRC (Cambridge, Royaume-Uni) en tant que postdoctorante, où elle a travaillé sur la synthèse en phase solide de conjugués oligonucléotides-peptides.

En 1999, elle a été nommée Chargée de Recherche par le CNRS et elle est actuellement directrice de recherche. Ses centres d'intérêt concernent la conception d'agents thérapeutiques potentiels pour traiter les infections et les cancers, le développement de nouvelles méthodologies de synthèse liées aux composants des acides nucléiques. Au sein de l'institut des biomolécules Max Mousseron (IBMM, Montpellier), elle dirige l'équipe Nucléosides & Effecteurs Phosphorylés depuis 2015.

ABSTRACT

SUZANNE PEYROTTES
Institut des Biomolecules Max Mousseron (IBMM)

CP4 Analogues de nucléotide et Paludisme, quand l'inattendu est au rendez-vous

Plasmodium falciparum (Pf) est responsable de la forme mortelle du paludisme, qui représente une menace sanitaire majeure dans les pays tropicaux et sub-tropicaux. Malgré la mise sur le marché d'un vaccin (RTS,S/AS01) en octobre 2021, son efficacité est limitée et le traitement de cette maladie reste compliqué en raison de l'émergence de parasites résistants. En particulier, la résistance du parasite aux médicaments les plus efficaces, tels que les combinaisons thérapeutiques à base d'artémisinine (ACT), est une vrai préoccupation. Le développement de nouveaux traitements basés sur des composés et des cibles thérapeutiques originaux est donc une priorité.

Récemment, nous avons rapporté deux familles de nucléotides en série phosphonate et appartenant aux analogues des carbonucléosides [1] et aux β-hydroxy-acyclonucléosides [2] comme nouveaux inhibiteurs de la croissance de Pf (souche 3D7) dans les globules rouges infectés. En série acyclonucléotides, nous avons identifié un composé très prometteur (UA2239), présentant une activité antipaludique sur les stades asexués in vitro (P. falciparum, IC50 = 76,6 ± 9 nM) ainsi qu'in vivo (P. berghei, ED50 = 0,5 mg/kg/jour).

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CONFÉRENCIÈRE INVITÉE

MARIA DUCA

Institut de Chimie de Nice

Maria DUCA est Directrice de recherche au CNRS et responsable de l'équipe Ciblage des Acides Nucléiques à l'Institut de Chimie de Nice (Université Côte d'Azur – CNRS). Après des études en pharmacie et chimie médicinale à la Faculté de Pharmacie de l'Université de Bologne (Italie), elle a obtenu un doctorat en biochimie moléculaire sous la direction de la Dr Paola B. Arimondo (Muséum national d'Histoire naturelle, Paris), portant sur les inhibiteurs de la topoisomérase II.

Elle a ensuite effectué un stage postdoctoral de deux ans dans le laboratoire de Sydney Hecht (Département de Chimie, Université de Virginie, États-Unis), où elle s'est spécialisée dans l'étude des acides nucléiques et la mutagenèse ciblée des protéines. Recrutée au CNRS en tant que chargée de recherche en 2008, elle est promue Directrice de recherche en 2022.

Ses travaux de recherche portent sur le ciblage des ARN non codants à l'aide de petites molécules synthétiques, avec pour objectif le développement d'approches thérapeutiques innovantes contre le cancer, les infections virales et les maladies infectieuses.

Elle a reçu plusieurs distinctions prestigieuses, dont le prix Michel Delalande de l'Académie de Pharmacie, le titre de Chemistry Europe Fellow en 2023, le prix Sanofi-iDEA-TECH en 2024, ainsi que le Grand Prix SCF-PACA en 2025. Elle est également lauréate de plusieurs financements nationaux et internationaux, notamment dans le cadre du programme H2020.

Dr Maria Duca est Associate Editor de la revue RSC Medicinal Chemistry et préside actuellement la Société de Chimie Thérapeutique (SCT), la société française de chimie médicinale.

ABSTRACT

MARIA DUCA
Institut de Chimie de Nice

CP5 Design and synthesis of small-molecule binders targeting non-coding RNAs for anticancer and antimicrobial applications

RNA is one of the most intriguing and promising biological targets for the discovery of innovative drugs in a large number of pathologies and various biologically relevant RNAs that could serve as drug targets have already been identified [1]. However, difficulties in the rational design of efficient and specific small-molecule ligands renders this kind of molecules relatively rare.

Our work focuses on the structure-based design of new RNA ligands targeting non-coding RNAs for the development of anticancer and antibiotic approaches. Thanks to a design strategy based on the combination of various RNA binding domains bringing both affinity and selectivity for the target, we obtained ligands selective for oncogenic microRNAs precursors with the ability to inhibit their biogenesis in vitro and in cancer cells [2]. The same approach has been applied to the development of chemical probes for the validation of original and innovative antibacterial targets. Finally, we are also developing new modalities involving RNA ligands able to induce covalent modifications in the target RNA thus opening the way for new applications in a near future.

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CONFÉRENCIER INVITÉ

SÉBASTIEN GOUIN

Laboratoire CEISAM - UMR CNRS 6230

Le Dr Sébastien G. Gouin a obtenu son doctorat en chimie organique à l'Université de Nantes en 2003, puis a effectué un stage postdoctoral auprès du Pr Paul V. Murphy à l'University College Dublin. En 2005, il a intégré le CNRS comme chargé de recherche à l'Université d'Amiens et a été promu directeur de recherche au CNRS à l'Université de Nantes en 2018.

Son équipe de recherche « Glycochimie et Bioconjugués » au laboratoire CEISAM, travail sur la conception de glyconjugués ciblant des lectines et glycosidases pathogènes, ainsi que sur le développement de méthodes de bioconjugaison chimiosélectives pour la fonctionnalisation de protéines, de virus et de surfaces cellulaires.

ABSTRACT

SÉBASTIEN GOUIN
Laboratoire CEISAM - UMR CNRS 6230

CP6 Les sucres sous tension : bioconjugaison électrochimique de sucres complexes à la surface de protéines et cellule

La modification chimiosélective des protéines natives est d'une importance fondamentale dans le développement de bioconjugués thérapeutiques. Nous avons développé la première méthode électrochimique spécifiquement conçue pour fonctionnaliser les résidus tyrosine (Y) des protéines dans des conditions biocompatibles [1]. Cette approche, nommée eY-click, repose sur un système à trois électrodes permettant l'oxydation sélective (activation) in situ d'une ancre diazodicarboxamide fonctionnalisée, pour le marquage efficace de peptides, d'enzymes et d'anticorps dans des tampons aqueux.

Cette présentation discutera de travaux plus récents ou des dérivés du N-méthylluminol (NML) [2], un groupe d'ancrage hautement sélectif de la tyrosine après oxydation monoélectronique [3], ont été utilisés pour la bioconjugaison de surfaces de bactéries vivantes, de vecteurs viraux utilisés en thérapie génique, et de cellules eucaryotes [4]. La stratégie de click-électrochimie permet en quelques minutes, de greffer des oligosaccharides biologiquement actifs sur ces surfaces, offrant une alternative à l'ingénierie métabolique pour les biothérapies ciblées.

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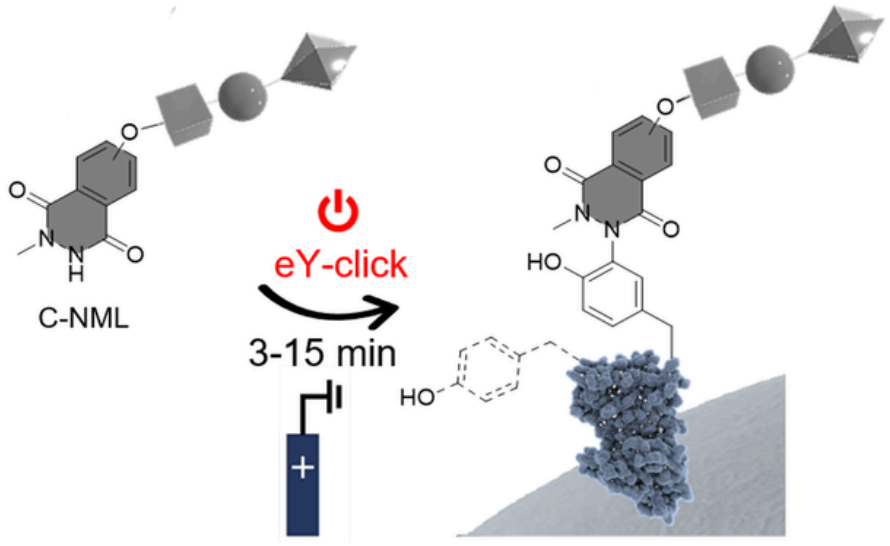

CONFÉRENCIER INVITÉ

DIDIER ROCHE

Société EDELRIS

Le Dr Didier Roche est directeur scientifique et cofondateur d'Edelris, société créée en 2005. Titulaire d'un doctorat de l'université de Strasbourg, il a débuté sa carrière par un poste de chercheur postdoctoral chez Novartis, où il a travaillé comme chimiste des procédés. Il est ensuite revenu à la chimie médicinale chez Merck KGaA, où il a dirigé une équipe de 25 chimistes dans la division diabète et contribué au développement clinique de trois candidats-médicaments.

Le Dr Didier Roche est le principal inventeur du Vonafexor, un agoniste du FXR qui achève actuellement son essai clinique de phase 2 pour le traitement du syndrome d'Alport. Il s'intéresse au développement de technologies innovantes dans le domaine de la découverte de médicaments.

Chez Edelris, il a dirigé la mise en place d'une plateforme de criblage basée sur la spectrométrie de masse par sélection d'affinité (ASMS) et organise depuis cinq ans un symposium annuel consacré à cette technologie.

Il est coauteur de plus de 60 publications et brevets tout au long de sa carrière.

ABSTRACT

DIDIER ROCHE
Société EDELRIS

CP7 Unlocking the Potential of Untapped Chemical Spaces

Over the last 20 years, drug discovery has undergone a major evolution. The field transitioned in the 1990s from phenotypic screening of natural products to target-based screening using large, Rule-of-Five–compliant libraries and high-throughput screening (HTS). Historically, HTS has aimed to identify compounds that modulate protein targets through inhibition or activation. Today, however, emerging therapeutic modalities are reshaping drug discovery and demanding new approaches to both molecular design and screening. Meanwhile, most of the possible chemical universe remains unexplored. Advances in computation, data science, and synthetic methods are now making it possible to navigate and leverage these vast, untapped chemical spaces.

COMMUNICATIONS ORALES

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CO1 Marquage chemoenzymatique des substrats protéiques d'une lysine méthyltransférase à l'aide d'analogues de S-adénosyl-L-méthionine
Charlène DAVID (*Université Paris-Saclay)*, R. MARGUERON, D. GUIANVARC'H

CO2 Développement de modulateurs originaux bio-inspirés des LXRs dans le potentiel traitement du cancer de la prostate métastasé
Norberta DELPORTE (*Université Clermont Auvergne)*, A. LAGARDE, S. BARON, J. LOBACCARO, I. ABRUNHOSA-THOMAS

CO3 La mal-aimée tagatose-1,6-bisphosphate aldolase : une enzyme finalement d'intérêt
Mathilde GUILLETON (*Université Clermont Auvergne)*, L. PAULAT, M. LEMAIRE, L. NAUTON, V. DE BERARDINIS, J. PETIT, V. HÉLAINE, C. GUÉRARD-HÉLAINE

CO4 Engineering nucleophilic catalysis coupled to tandem electrostatic assistance enables native chemical ligation–based protein modification at nanomolar concentrations
Julie DI ADAMO (*Université de Lille)*, V. DIEMER, O. MELNYK

CO5 Dynamic Combinatorial Library of Cyclopeptides for GAGs interaction
Jose GARCIA COLL (*Sorbonne Université)*, C. BOULIN, R. LOU, C. PERRIN, C. BICH, E. SACHON, R. MOUMNÉ

CO6 Novel peptide bioprobes based on Ytterbium complexes for Near-Infrared cell imaging
Tom DI SANTO (*Université Grenoble Alpes)*, O. SÉNÈQUE

CO7 Photozyme strategies for enantioselective synthesis of chromanone derivatives
Florian VINCHON (*Université Paris-Saclay)*, W. GHATTAS, A. URVOAS, J. DUWER, E. DESLIGNIERE, R. RICOUX

CO8 Copper-Chelating Probes Associated with Molecular Networks for the Discovery of New Polyacetylenic Natural Products
Xavier FRANCK (*Université de Rouen Normandie)*, C. PAVESI, S. PRADO

CO9 Fluorogenic photocatalyzed proximity labeling with visible light to map the interactome in living cells
Meven JOBIC (*CEA Grenoble)*, Y. WONG, A. ZAPUN

CO10 Engineering Robust Calixarene-Coated Nanoparticles for Next-Generation Therapeutic and Diagnostic Applications
Gilles BRUYLANTS (*Université Libre de Bruxelles)*, J. JANSSENS, I. JABIN

CO11 Development of a novel fluorescence anisotropy assay for studying polyphenolic inhibitors of Tau fibrillation
Cécile DUPONT (*Université Grenoble Alpes)*, B. BOUCHERLE, S. CHIERICI, M. PEUCHMAUR

CO12 Environmentally sensitive fluorescent molecular tools to study the local polarity of individual layers of the bacterial cell envelope
Anthony AUGÉ (*Université de Strasbourg)*, J. KARPENKO, V. REN, L. WEISS

CO13 Genetically-targeted and red-emitting fluorescent indicator for subcellular zinc imaging
Manon WITTWER (*Ecole Normale Supérieure, Paris)*, G. ROSATI, J. MALLET, B. DUMAT

CO14 A new, powerful fluorogenic click-and-release reaction
Malo GOURVEST (*Institut Curie, Orsay)*, K. RENAULT, G. CLAVIER, F. MAHUTEAU-BETZER

CO15 Développement de nanobodies fluorogènes dans le proche infrarouge pour la détection de cellules cancéreuses
Sarah GRIESBAUM DUBOURG (*Université de Strasbourg)*, E. BARBÉ, O. FLORÈS, M. VITTORIA SPANEDDA, A. DETAPPE, D. BONNET

CO16 Optimized Fluorescent pH-Sensitive Dextran Conjugates Enable Ratiometric Measurement of Cerebral Blood pH In Vivo and In Situ
Sophie WALTER (*Université de Strasbourg)*, M. COLLOT, M. TOURNISSAC, E. CHAIGNEAU, S. CHARPAK

CO17 Synthesis and evaluation of the biological activity of photoswitchable monoamine oxidase inhibitors in the treatment of osteoarthritis
Mélina FABE (*ICSN, Paris-Saclay)*, A. CHEVALIER, L. JEAN

CO18 Molecular engineering of the difluoro dipyridomethene boron complexes towards the development of heavy atom-free photosensitizers for PDT
Carlotta FIGLIOLA (*Université de Strasbourg)*

COMMUNICATIONS ORALES

CO19 Kinase Inhibitors as host-targeting antivirals
Isabelle KRIMM (*Université de Montpellier*), D. GRENIER, J. DELCROS, M. GELIN, J. GUICHOU

CO20 Scaffold Hopping Strategy for the Discovery of Novel ACSL4 Inhibitors
Juliette LAFON (*Université de Lille*), E. CHARNELLE, M. COEVOET, S. RAVEZ, J. EL BAKALI

CO21 Chemical synthesis and biological assessments of RhoGTPase inhibitors
Arnaud TESSIER (*Nantes Université*), C. TROUILLET, M. RIVIERE, A. QUÉMENER, M. ROUSSELLE, M. MAILLASSON, M. CROYAL, J. LEBRETON, S. COLLET, J. CHERFILS, G. LOIRAND, V. SAUZEAU

CO22 Towards the next generation of antibiotics by targeting the IspH metalloenzyme
Isabelle VIEIRA DE ALMEIDA (*Université de Strasbourg*), P. CHAIGNON, M. SEEMANN

CO23 Screening, Design, Synthesis and Evaluation of Macrocyclic Ligands for Stabilization of RNA Hairpins Implicated in Type 1 Myotonic Dystrophy
Camille RICHAGNEUX (*Institut Curie, Orsay*), A. MELIKOV, J. CHIARAVALLI, V. GABELICA, A. GRANZHAN

CO24 Discovery of Novel G-quadruplex Binding Peptidic Derivatives Using DNA Encoded Chemical Libraries
Massimo TRINCAS (*Université Grenoble Alpes*)

CO25 Harnessing Nucleoside and Nucleotide Chemistry to Explore RNA Modifications
Mélnie ETHEVE-QUELQUEJEU (*Université Paris Cité*)

CO26 Design and Synthesis of Stable Antiviral Analogues of Macarangin B
Chea Julie ING (*Institut Curie, Orsay*), C. GUIMARD, F. ROUSSI

CO27 “In situ” and “in crystals” click chemistry, a potent tool to accelerate antiviral drug discovery against Bunyaviricetes infections
Médéric DÉGARDIN (*Aix Marseille Université*), L. GARLATTI, M. FERACCI, B. CANARD, F. FERRON, K. ALVAREZ

CO28 Photocatalytic Strategies for Antibody Bioconjugation
Marine LE STUM (*CEA Paris-Saclay*), J. CINTRAT, E. ROMERO-LABOUREUR

CO29 Antiproliferative Activity of Bispidines and Their Copper Complexes: When the Ligand Outperforms the Metal Complexes
Firas EL KADIRY (*Aix Marseille Université*), A. BLANCO MEJÍAS, A. TCHOGHANDJIAN, P. COMBA, J. LUIS, O. IRANZO, M. MARESCA

CO30 Deep-Tissue Molecular Activation: Ionizing Radiation-Driven theranostics to target cancer cells
Marius BICHOT (*Institut Curie, Orsay*), G. BORT, G. MARCOU, H. HERLEM

CO31 Combination of metabolic glyco-engineering and disulfide rebridging for the grafting of antibody fragments on cell surface - toward new cell therapies
Fabien THOREAU (*Université de Poitiers*)

CO32 AfKDNAse Inhibitors as Potential Antivirulence Agents against Aspergillus fumigatus
Mathieu SCALABRINI (*Nantes Université*), D. LOQUET, C. ROCHARD, M. BAUDIN MARIE, C. ASSAILLY, F. DALIGAULT, A. LAMBERT, C. GRANDJEAN, D. DENIAUD, P. LOTTIN, S. PASCUAL, L. FONTAINE, V. BALLOY

CO33 Synthesis of fluorescent probes targeting VGLUT3 for in vivo pharmacological studies
Alexis MAI (*Sorbonne Université*)

CO34 Rewriting the tubulin code: Targeting α-tubulin detyrosination for therapeutic benefit
Matthieu SIMON (*Université de Montpellier*), A. FERAL, H. IMPHENG, G. GILLARD, M. AMBLARD, K. ROGOWSKI, L. VEZENKOV

CO35 Vectorization of pleuromutilin by a siderophore mycobactin analog: towards antibiotic Trojan horses against Pseudomonas aeruginosa
Walid HAJEB (*Université de Strasbourg*)

CO1

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

Charlène DAVID (Institut de Chimie Moléculaire et des Matériaux d'Orsay, Université Paris-Saclay) Raphaël MARGUERON (2 Institut Curie, INSERM U934, CNRS UMR 3215), Dominique GUIANVARC'H (Institut de Chimie Moléculaire et des Matériaux d'Orsay, Université Paris-Saclay)

La méthylation de la lysine des histones est une modification épigénétique clé qui module la compaction de la chromatine et est associée au statut de transcriptions des gènes. Catalysée par les histone lysine méthyltransférases (HKMT), cette modification implique le transfert du groupe méthyle de la S-adénosyl-L-méthionine (SAM) vers la fonction amine de résidus lysine. Alors que les histones sont considérées comme les principaux substrats de ces HKMT, les études s'accumulent et tendent à montrer que ces enzymes méthylent également d'autres protéines que les histones. La régulation de ce processus est cruciale pour les fonctions de ces protéines, et donc pour les fonctions cellulaires. Sa dérégulation est liée à des maladies telles que le cancer et les troubles neurodégénératifs, ce qui fait des HKMT des cibles intéressantes pour les agents antitumoraux.
Afin de caractériser le méthylome de PR-Set7, une HKMT d'intérêt, nous avons mis en place une approche dite «bump and hole»[1] qui combine des techniques chimiques et enzymatiques afin de marquer et identifier ses substrats. Nous avons synthétisé différents analogues de SAM avec des groupes bio-orthogonaux mais également leurs analogues de méthionine associés, qui permettent la biosynthèse du SAM à l'aide d'une méthionine adénosyl transférase (MAT)[2]. Ces analogues, imaginés pour s'adapter au site actif des mutants PR-Set7, seront incubés avec des extraits nucléaires ou dans des cellules, permettant ainsi le marquage des substrats. Les substrats marqués seront ensuite fonctionnalisés avec des marqueurs d'affinité via des réactions de chimie click et identifiés par spectrométrie de masse[3]. Cette stratégie permettant l'identification précise des substrats enzymatiques histones et non-histones de PR-Set7.

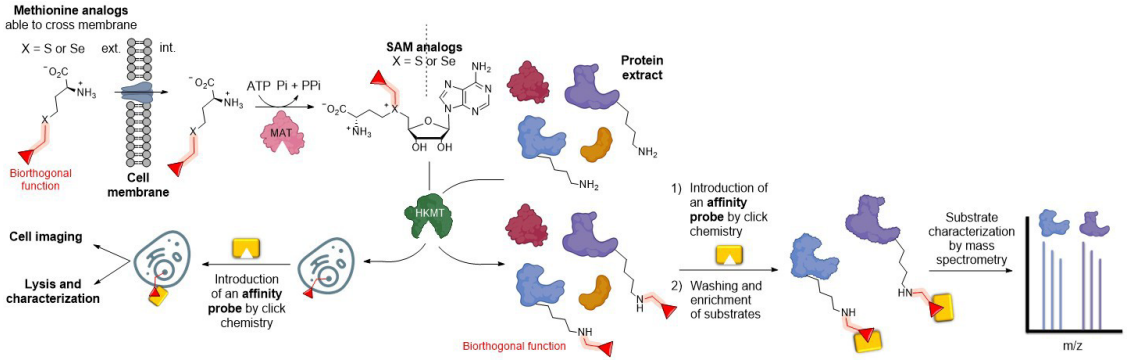

Figure: Schéma résumé de la stratégie mise en place afin de caractériser le méthylome d'une méthyltransférase d'intérêt.

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Développement de modulateurs originaux bio-inspirés des LXRs dans le potentiel traitement du cancer de la prostate métastasé

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Les récepteurs nucléaires LXRα (NR1H3) et LXRβ (NR1H2) jouent un rôle important dans la régulation de fonctions physiologiques telles que la croissance cellulaire, la réponse immunitaire et l'apoptose. Ils peuvent être activés par des oxystérols — dérivés oxydés du cholestérol (Janowski et al., 1996). Ce sont des cibles pharmacologiques potentielles pour le traitement des troubles métaboliques et des cancers (Buñay et al., 2021).
Cependant, les progrès cliniques dans le développement de médicaments ciblant les LXRs sont limités par la grande homologie de séquences entre LXRα et LXRβ au niveau de domaine LBD, ce qui rend difficile la sélectivité et entraîne des effets indésirables comme l'hypertriglycéridémie et des troubles neurologiques (Schultz et al., 2000 ; Wrobel et al., 2008).
Dans notre recherche, nous adoptons une double approche pour découvrir des modulateurs sélectifs de LXRβ dérivés de flavonoïdes naturels identifiés dans la propolis d'abeille. Tout d'abord, nous utilisons la modélisation moléculaire pour cartographier la poche de liaison du récepteur LXRβ. Cette analyse permet d'identifier les interactions importantes à établir entre nos molécules à synthétiser et le site actif afin d'activer sélectivement LXRβ. Ensuite, ces composés originaux obtenus sont évalués in vitro sur des cellules HeLa transfectées avec le récepteur LXRα ou β. À partir des résultats biologiques sur l'activité de LXRβ et la sélectivité des isoformes, une étude RQSA (Relation Quantitative Structure-Activité) est établie nous permettant d'optimiser notre modèle moléculaire et de concevoir les nouveaux ligands plus efficaces et sélectifs.
Les deux générations de ligands (31 molécules) ont ainsi été préparés selon un chemin de synthèse convergent, versatile et optimisé. Leur capacité à activer LXRα ou LXRβ a été évaluée par un test rapporteur à la luciférase. Trois composés ont présenté une affinité globale supérieure pour les récepteurs LXRs. L'un des composés a démontré une sélectivité plus importante vers LXRβ et fait actuellement l'objet d'une optimisation structurale en vue du développement d'une troisième génération de molécules plus sélectives et affines pour LXRβ. Cette étude contribue également à une meilleure compréhension des différences fonctionnelles entre LXRα et LXRβ.

Ce travail est financé par des subventions de la Ligue contre le Cancer (Nationale, Puy-de-Dôme, Haute-Loire).

CO3

La mal-aimée tagatose-1,6-bisphosphate aldolase : une enzyme finalement d'intérêt

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La réaction d'aldolisation constitue une étape clé dans la formation de liaisons carbone–carbone, permettant de construire des squelettes carbonés complexes et d'introduire de nouveaux groupements fonctionnels en une seule étape, par la création d'un ou deux centres asymétriques. Les aldolases jouent un rôle essentiel dans ce processus en assurant un contrôle précis de la stéréosélectivité, ainsi que de la régio- et chimiosélectivité, tout en étant respectueuses de l'environnement. Parmi les aldolases utilisant le dihydroxyacétone phosphate (DHAP) comme nucléophile, quatre enzymes ont été identifiées capables de générer les quatre stéréoisomères possibles résultant de la formation de deux centres asymétriques. Cependant, l'obtention de la configuration (S,S) demeure un défi, car l'enzyme correspondante, la tagatose-1,6-bisphosphate aldolase (TagA), est la seule DHAP-aldolase connue à ne pas présenter de stéréosélectivité.[1,2] Elle produit au mieux un mélange de D-tagatose-1,6-bisphosphate et de D- fructose-1,6-bisphosphate à partir de son substrat électrophile naturel : le D-glycéraldéhyde-3-phosphate (Figure1).
L'obtention de la stéréochimie (S,S) est un enjeu clé pour la synthèse de composés bioactifs comme le D-tagatose, reconnue comme édulcorant. Pourtant, l'enzyme TagA, seule capable de cette configuration, a été peu explorée et rapidement reléguée dans la catégorie des DHAP-aldolases présentant un intérêt limité.[3]
Dans cette étude, un criblage de 200 aldolases a permis d'identifier une nouvelle TagA produisant du D-tagatose-1,6-bisphosphate optiquement pur. L'analyse de son spectre de substrats électrophiles a conduit à la synthèse inédite de plusieurs composés (S,S) purs ou enrichis.

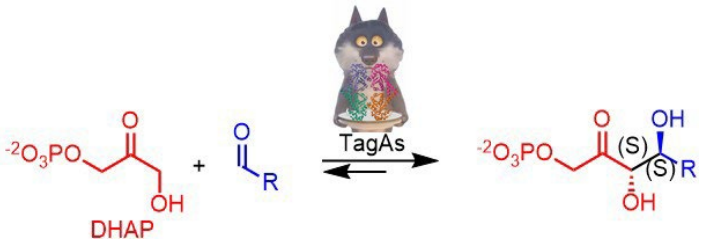

Figure Réaction d'aldolisation en présence de la TagA

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CO4

Engineering nucleophilic catalysis coupled to tandem electrostatic assistance enables native chemical ligation–based protein modification at nanomolar concentrations

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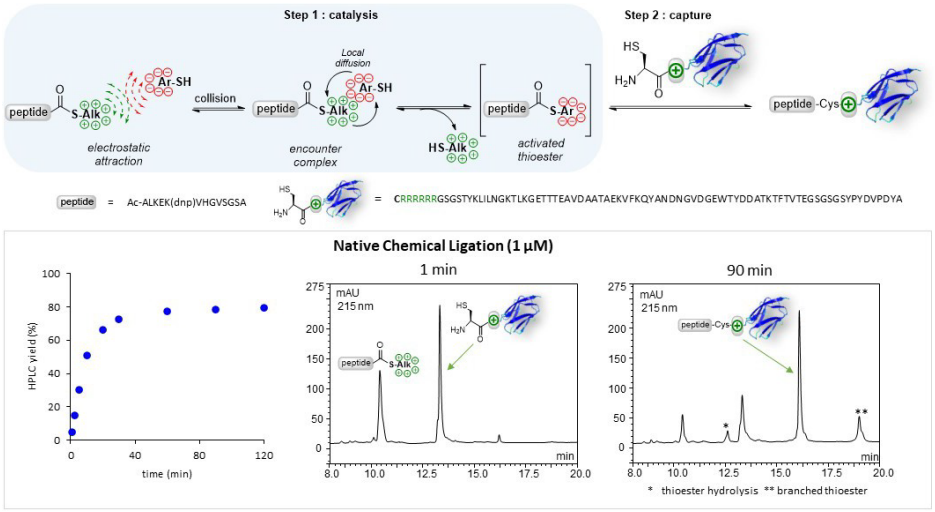
The native chemical ligation reaction (NCL) has considerably extended the size of polypeptides and proteins that can be produced by semi or total synthesis and has various applications.(1) NCL consist in reacting of a C-terminal peptide thioester with an N-terminal cysteinyl peptide to produce a native peptide bond between them.(2) Usually, the reaction first step is a nucleophilic catalysis that converts easily synthesizable alkyl thioesters (3) into more reactive aryl thioesters through a thiol-thioester exchange with an aryl thiol catalyst. Then, in a capture step, the intermediate thioester reacts with the cysteinyl peptide to produce a native peptide bond. However, even with the addition of a catalysis step this reaction is still slow at millimolar peptide concentration and in the most favourable cases (4), which promotes secondary reactions and leads to an efficiency loss at lower concentrations.

My PhD project focuses on engineering nucleophilic catalysis coupled to tandem electrostatic assistance to promote the above two essential steps of NCL reaction and overcome its limitations. An important objective has been to design a catalyst capable of providing electrostatic assistance during the catalysis step, and afterwards during the capture step thanks to the charges it imparts to the activated thioester intermediate. The significant rate enhancement of the NCL reaction achieved with this tandem electrostatic assistance enabled efficient and fast peptide and protein modifications at nanomolar concentrations.



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CO5

Dynamic Combinatorial Library of Cyclopeptides for GAGs interaction

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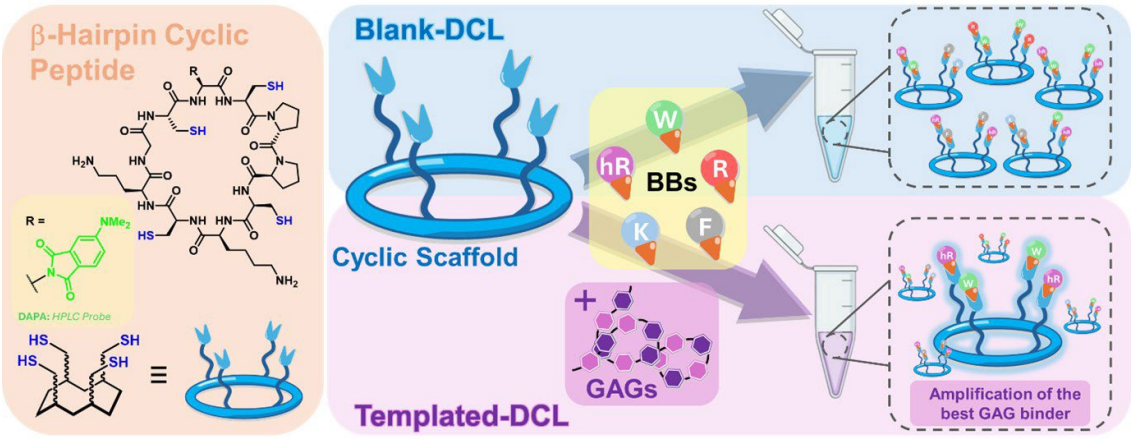
Peptides are attractive tools for targeting complex biological systems due to their unique position between small molecules and biologics. Their intermediate size offers favourable pharmacokinetics and membrane permeability, while maintaining high specificity and binding affinity. Cyclic peptide scaffolds (e.g. b-Hairpin, a-Helix), in particular, show enhanced stability and pharmacological performance compared to linear analogues, making them especially promising for therapeutic applications.

Traditional approaches to designing bioactive peptides are based on structure-guided rational design, relying on the mimicry of native binding motifs within a stable peptide scaffold. However, these approaches are limited by the availability of crystal or solution structures and often require labor-intensive optimization processes. To overcome these challenges, a novel strategy has been developed in our group utilizing dynamic combinatorial chemistry (DCC) to create peptide libraries with diverse side-chain combinations.[1] In this approach, a cyclic peptide scaffold is functionalized with reactive chemical groups, such as thiol groups present in cysteine residues, allowing dynamic exchange processes (e.g., thioester linkages) to generate a dynamic combinatorial library (DCL). This library can be selectively enriched in the presence of a biological target, enabling a target-directed DCC (td-DCC) approach for efficient drug discovery.

As a proof of concept, we present this strategy focusing on glycosaminoglycans (GAGs) templates, a family of complex extracellular biomolecules involved in cell-targeting therapies.[2] This innovative approach allowed the identification of heparin binding cyclic peptides.



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CO6

Novel peptide bioprobes based on Ytterbium complexes for Near-Infrared cell imaging

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Lanthanide (III) Ln3+ complexes have desirable luminescent properties for cell microscopy imaging; but cytosolic delivery of Ln3+ complexes and their use for two-photon (2P) imaging are still challenging, especially for NIR probes. To our knowledge, only one example of live cell microscopy imaging has been reported based on an Yb3+ probe. The advantage of this kind of probes are that they allow high spatial and temporal resolution. Our goal was to develop new Yb3+ probes for NIR cell-imaging. A series of Yb3+ complexes based on a DOTA-like ligand with novel push-pull antennas for good sensibilization of Yb3+ luminescence was synthsized. These antennas feature a coordinating picolinate moiety as electron accepting group and a dimethylamino moiety as an electron donating group. Electronic delocalisation has been modulated through aromatic groups of various size and conformational properties, in order to modulate the charge transfer within the antenna and find the antenna with the longest absorption wavelength, highest extinction coefficient and best and 2P absorption properties. Antenna-containing ligands were synthesised, that include a free carboxylate function for peptide conjugation to a Cell Penetrating Peptides (CPPs) capable of efficient cytosolic delivery. Several CPP /Yb3+ complexes conjugates were prepared and the most interesting luminescent complex was evaluated for 1P and 2P NIR cell microscopy.

CO7

Photozyme strategies for enantioselective synthesis of chromanone derivatives

Florian VINCHON (Paris Saclay - ICMMO) Wadih GHATTAS (ICMMO, Univ. Paris-Saclay) Agathe URVOAS (I2BC, Univ. Paris-Saclay) Justine DUWER (I2BC, Univ. Paris-Saclay) Evolene DESLIGNIERE (ICSN, CNRS Gif sur Yvette) Rémy RICOUX (ICMMO, Univ. Paris-Saclay)

Photochemistry is a key approach in green chemistry, as visible light serves as a clean and traceless energy source, enabling numerous catalytic transformations through photoinduced redox processes. Extending these reactions to enantioselective reactions is an intriguing challenge and an expanding field of investigation. Enantioselective reactions by photoredox catalysis are one of these hot topics. Biocatalysis has two main benefits: high chemo-, regio- and stereo-selectivity; and environmentally friendly conditions. Ultimately, the combination of biocatalysis and photoredox reactions has given rise to a new area of research, known as photozymes. These photozymes enable access to photochemical reactions while providing a high level of stereoselectivity.

The strong stereoselective potential of photozymes offers a promising strategy for the enantioselective construction of complex molecular scaffolds. Such approaches are particularly pertinent in medicinal chemistry for modulating structure–activity relationships. However, the asymmetric synthesis of chromanones requires multiple synthetic steps, and restricts functionalization to specific positions on the chromanone scaffold. Chromones are a class of heterocyclic compounds with significant biological activities and considerable interest due to their potential treatment of diseases especially 4-chromanone-derived compounds (2,3-dihydro-1-benzopyran-4-one) as versatile scaffolds for rational drug design. These molecules exhibit a wide range of biological and pharmacological properties, including antibiotic, antiparasitic, anticancer, and anti-HIV activities.

The objective of this work is the development of a one-step, enantioselective photoenzymatic strategy for the synthesis of chromanone derivatives.

CO8

Copper-Chelating Probes Associated with Molecular Networks for the Discovery of New Polyacetylenic Natural Products

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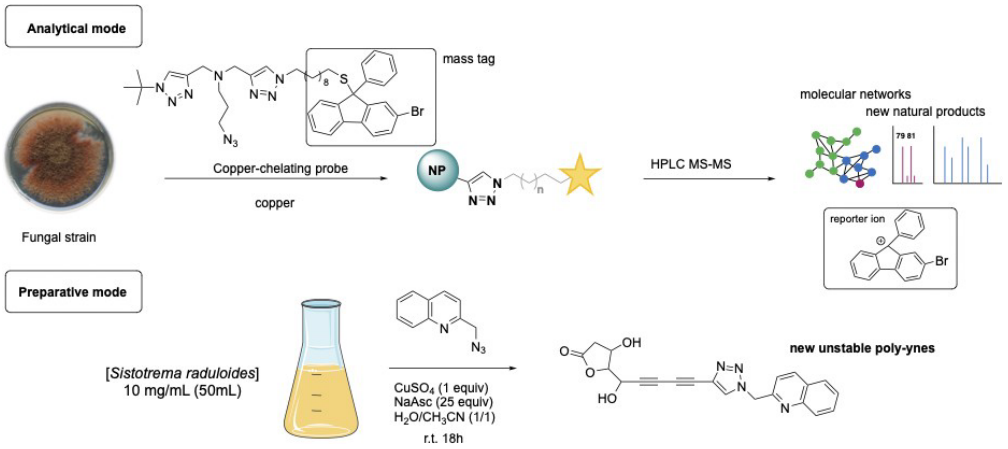
Chemical labeling is an innovative strategy for the identification of new natural products (NPs) in complex matrices such as plants and microorganisms where they are present in minute quantities that are difficult to detect using conventional purification methods. By leveraging bioconjugation tools, chemoselective labeling enhances the sensitivity of detection when combined with analytical techniques like HPLC and mass spectrometry. This proved very useful for identifying unstable poly-ynes, as their triazole derivatives are stable, which circumvents issues related to structure determination of the native compound.

We have developped a tetradentate copper-chelating azide probe bearing a mass-tag that has facilitated the labeling and identification of natural products containing a terminal alkyne group in the Sistotrema raduloides fungal strain, thanks to molecular networks. A preparative step performed with a bidentate azide allowed the isolation and structural determination of the previously identified new poly-ynes.



CO9

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

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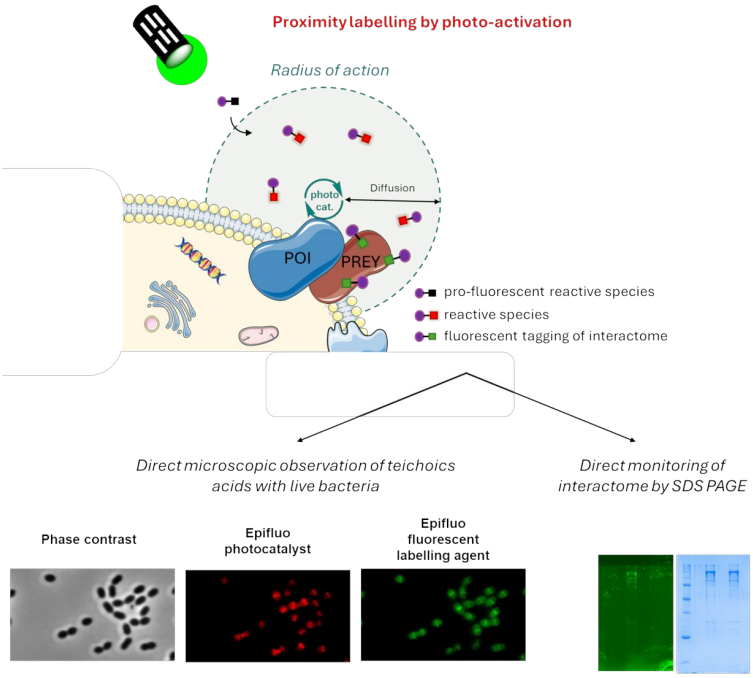
Living processes are primarily governed by transient and dynamic interactions between biomacromolecules and cells. Investigating these interactions is therefore essential to understand the molecular mechanisms they regulate. Proximity labeling techniques have emerged as powerful tools to map such interactions, typically relying on an enzyme genetically fused to a protein of interest (POI), as exemplified by the APEX approach. Despite their effectiveness, these methods may suffer from limitations related to labeling speed, cytotoxicity, and spatial precision.

More recently, photocatalytic proximity labeling has improved spatial and temporal control while operating under biocompatible wavelengths. In these systems, a photocatalyst acts as a molecular switch that, upon irradiation with low-energy visible light (e.g., green light), triggers the selective covalent tagging of biomolecules in the immediate vicinity. However, a major limitation shared by current proximity labeling strategies is their inability to directly visualize and monitor the evolution of dynamic interactions from the POI in living cells.

In this communication, we report the development of a fluorogenic photocatalyzed proximity labeling strategy that provides a straightforward solution to this challenge. This new approach relies on the combination of an organic photocatalyst with fluorogenic photo-crosslinking probes, enabling direct fluorescent readout of labeling events. Proof of concept was first established in living bacteria (*Streptococcus pneumoniae*) through spatiotemporally controlled fluorescent labeling of teichoic acids, key components of the Gram-positive bacterial cell wall, as monitored by fluorescence microscopy. We further demonstrate the selective fluorescent labeling of proteins interacting with teichoic acids, allowing direct visualization of the corresponding interactome.

Importantly, this fluorogenic readout significantly simplifies downstream characterization by eliminating the need for secondary detection or enrichment steps. In addition, we observed a labeling-associated toxic effect, highlighting the potential of this strategy as a foundation for the development of novel antimicrobial approaches.



CO10

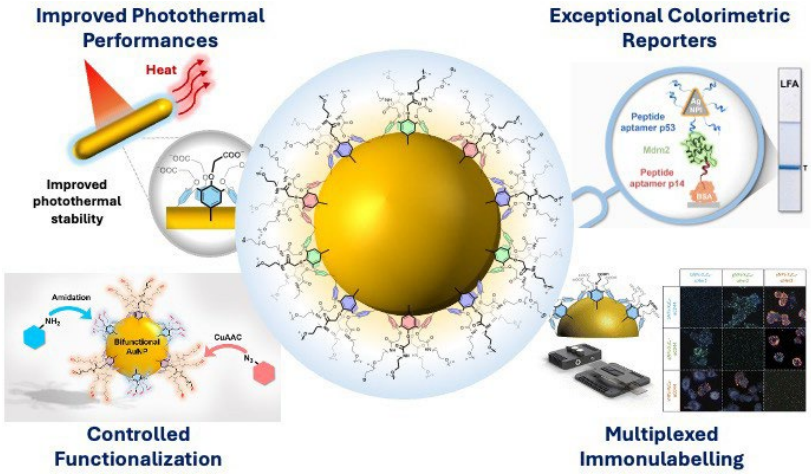
Engineering Robust Calixarene ? Coated Nanoparticles for Next?Generation Therapeutic and Diagnostic Applications

Victor LEPEINTRE (Université libre de Bruxelles) Julie JANSSENS (Université libre de Bruxelles) Ivan JABIN (Université libre de Bruxelles) **Gilles BRUYLANTS** (Université libre de Bruxelles)

Plasmonic nanoparticles, particularly gold nanoparticles (AuNPs), are widely studied in the biomedical field due to their exceptional chemical and optical properties. AuNPs have a localized surface plasmon resonance (LSPR) in the visible range and can be functionalized with a variety of (bio)molecules, making them ideal for applications such as drug delivery, photothermal therapy, imaging contrast agents, or as colorimetric reporters for in vitro diagnostics (IVD). For these applications, AuNPs must exhibit robust chemical and colloidal stability, as well as specific targeting capabilities. Traditionally, thiol chemistry has been used to functionalise AuNPs, but this approach faces limitations, including reduced chemical stability and challenges in controlling the density of surface-bound molecules.

To overcome these drawbacks, we have recently proposed a new strategy utilizing calix[4]arene-tetradiazonium salts. This approach enables the formation of thin and robust molecular coatings on nanoparticle surfaces through diazonium reduction, allowing for improved chemical stability and controlled grafting densities of different functional groups.[1] The calixarene-based method has shown compatibility with various plasmonic nanostructures, including anisotropic silver nanoplates.[2]

Recently, this calixarene functionalisation has been successfully applied to gold nanorods for photothermal therapy, allowing prolonged irradiation of the nanostructures without deformation.[3] In addition, calixarene-functionalised gold-silver core-shell and alloyed nanostructures have been used to enhance lateral flow assays [4] and multiplexed immunolabelling [5] respectively, demonstrating improved performance in IVD applications. Finally calixarene-coated AuNPs could be used for RNA delivery in cells, showing high biocompatibility and internalization efficiency. [6] These advances illustrate the potential of calixarene-functionalised nanostructures to drive new biomedical applications, by exploiting their robust chemical and colloidal stability, controlled bioconjugation, and adaptable surface properties.



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[5] Darviot et al. , Nanoscale Adv., 2024, 6, 4385-4393
[6] Darviot et al. , ACS Appl. Bio Mat., 2025, 8, 3040-3051

Development of a novel fluorescence anisotropy assay for studying polyphenolic inhibitors of Tau fibrillation

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Neurofibrillary tangles, which consist of intracellular fibrillar aggregates of the Tau protein, represent one of the major physiopathological hallmarks of Alzheimer's disease, alongside amyloid plaques. In this context, the identification of inhibitors of Tau protein aggregation constitutes a major challenge in therapeutic research.

In our previous work , several polyphenolic derivatives, notably aurones and indanones, were identified as *in vitro* inhibitors of Tau fibrillation. Structure–activity relationship studies were conducted on the A and B rings of these compounds, highlighting the key role of a pyrogallol moiety located on the B ring in the inhibition of Tau aggregation (Figure 1). Based on these findings, the present study aims to investigate the influence of the nature of the C ring, particularly the impact of the heteroatom and the overall aromaticity of the molecule, on inhibitory activity. To this end, a synthesis of a new series of polyphenol derivatives has been conducted, and the results will be presented.

Fibrillation is classically evaluated using the thioflavin T (ThT) assay, in which fluorescence increases in the presence of amyloid fibrils. However, this assay suffers from a major limitation related to the occurrence of false positives arising from the displacement of ThT by certain inhibitors. This phenomenon was confirmed by complementary analyses using circular dichroism and atomic force microscopy. These observations prompted the development of a new *in vitro* assay based on fluorescence anisotropy (FA).

In this framework, short peptide fragments, AcR3 and AcPHF6, derived from the R3 repeat region of the Tau protein involved in fibrillation process, are employed as models. The evaluation of inhibitors is performed in the presence of fluorescently labeled analogues of AcR3 or AcPHF6, which serve as reporters. Upon incorporation into fibrillar assemblies, the rotational mobility of these fluorescent probes is strongly restricted, resulting in a large FA signal (Figure 2).

Preliminary experiments performed using AcPHF6 model and its fluorescein-labeled analogue as probe revealed a significant FA signal. In addition, a decrease in this signal in the presence of myricetin, as well as the appearance of a lag phase in the presence of tlkivw peptide, two known fibrillation inhibitors, were observed. In order to minimize potential spectral interference between inhibitors and fluorescent probes, peptides labeled with BODIPY and rhodamine B, which exhibit absorption wavelengths distinct from that of fluorescein, are also under investigation.

The present study will ascertain the significance of the C-ring structural features in modulating the inhibitory activity of polyphenolic derivatives against Tau protein fibrillation. Furthermore, it will present fluorescence anisotropy as a robust complementary approach to ThT-based assays. This novel method will allow for a more reliable evaluation of Tau protein aggregation inhibitors by overcoming the limitations associated with false positives, and represents a valuable tool for screening and characterizing new series of compounds.

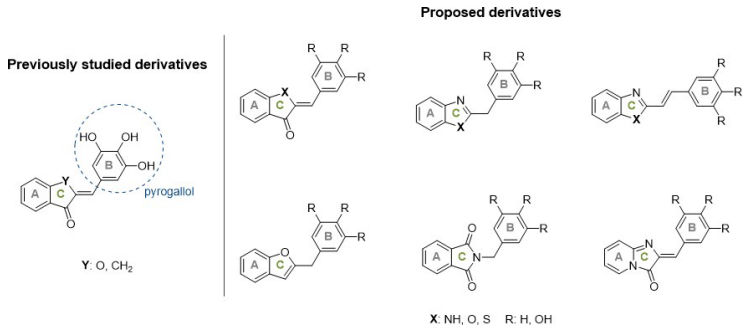


Figure 1: Polyphenolic derivatives

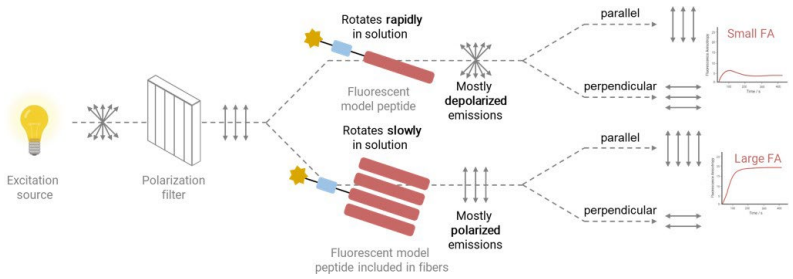


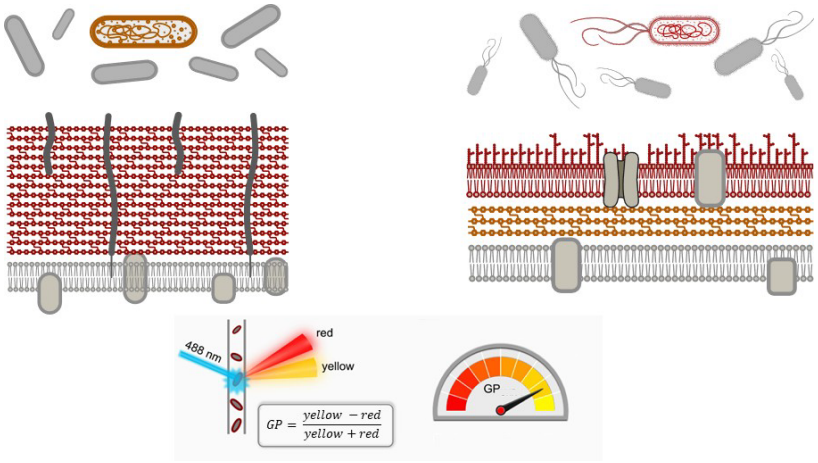
Figure 2: Principle of the FA assay based on the rotational constraint of labeled Tau-derived peptides

C012

Environmentally sensitive fluorescent molecular tools to study the local polarity of individual layers of the bacterial cell envelope

Anthony AUGÉ (UMR7200 - Equipe CPS) Julie KARPENKO (UMR7200 - Equipe CPS) Viviane REN (UMR7200 - Equipe CPS) Lucille WEISS (UMR7200 - Equipe CPS)

Due to the spread of antibiotic-resistant pathogens, bacterial infectious diseases became one of the first causes of mortality and morbidity in the world (1,2). Extensive efforts have been devoted to developing antibacterial therapies, ranging from small-molecule antibiotics to bacteriophage-based approaches (3). However, in the ongoing race against resistance, bacteria continue to stay a step ahead. The design of new therapeutic agents requires precise molecular tools to deepen our knowledge about bacterial physiology.
Previously, we have synthesized a conjugate of the antimicrobial peptide Ubiquicidin with the environment-sensitive fluorophore Nile Red (4). This new peptide-based probe UNR-1 displayed red fluorescence and enabled robust wash-free staining of both Gram-positive and Gram-negative bacteria with high selectivity over mammalian cells. Due to its solvatochromic properties, it was able to report on the subtle changes in the microenvironment of the bacterial membranes under environmental stress (5).
With the goal to develop environmentally sensitive fluorescent probes targeted to different layers of the bacterial cell envelope, we developed a new family of conjugates of Nile Red. Different vectors were used to target individual layers of the bacterial envelope. We also used bacteria-specific transporters to access to the cytoplasm. These probes can be used for studying polarity of different layers of the bacterial cell envelope, for evaluating behavior of bacteria under environmental stress or in the presence of antibiotics. Also, thanks to the fluorogenic behavior of Nile Red, these probes can be used for the diagnosis of bacterial infections directly in body fluids.



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CO13

Genetically-targeted and red-emitting fluorescent indicator for subcellular zinc imaging

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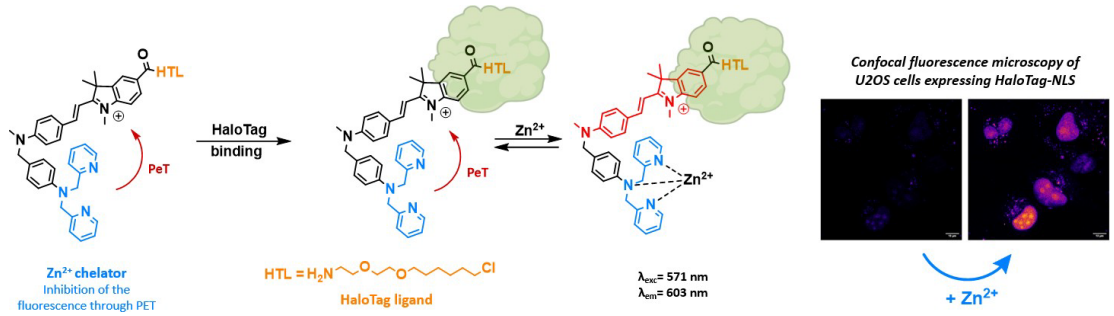
Chemogenetic reporters are a promising strategy that benefits from the precise targeting of recombinant proteins through genetics and from the structural diversity and versatility of organic fluorophores. They allow for specific labeling of proteins of interest, enabling the tracking of various biological processes in real-time. Among those systems, HaloTag proved to be one of the most powerful protein tag for covalently labeling with fast labeling kinetics and high labeling efficiency.

We have previously designed HaloTag probes based on push-pull viscosity-sensitive molecular rotors, where the formation of a covalent bond between the probe and HaloTag locks the molecule's excited-state conformation, thus enhancing fluorescence.[1] By coupling these fluorogens to sensing groups, we conceived dual-input probes with a fluorescence that is controlled by two distinct conditions: (i) reaction with HaloTag and (ii) analyte binding (Ca^{2+} or H^{+}).[2,3]

According to the same principle, two series of dual-responsive probes, combining genetic encoding through HaloTag and Zn^{2+} sensitivity, were developed. Zinc is metal ion with several key biological roles, including brain function and pathologies.[4] In particular, an indolenium-based Zn^{2+} probe series exhibited a red-shifted emission and high HaloTag responsiveness. It enabled the successful visualization of nuclear zinc in live cells. Ongoing work is now focused on optimizing other aspects of the probe's overall structure, such as modifying the Zn^{2+}-chelator to finely tune zinc affinity or modifying the fluorogen structure to improve its brightness.



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CO14

A new, powerful fluorogenic click-and-release reaction

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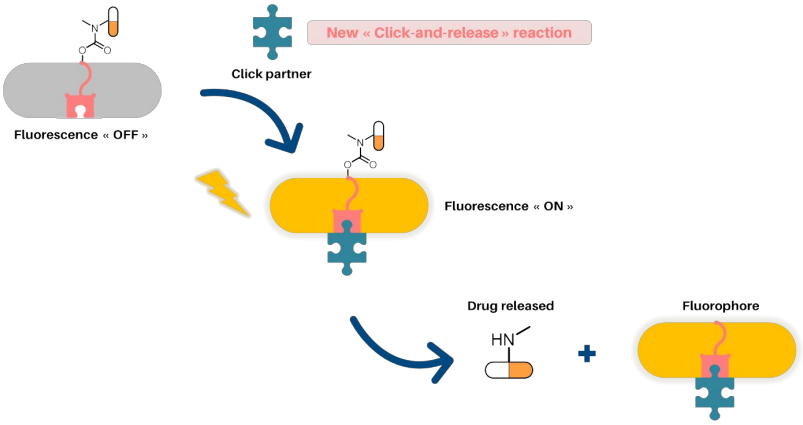
Fluorescent probes are powerful tools in bioimaging and diagnostics due to their ability to emit light in response to specific biological biomolecules or environmental changes. While conventional fluorescence techniques offer high sensitivity and resolution, they are limited by shallow tissue penetration 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 [3] reaction 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.



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CO15

Développement de nanobodies fluorogènes dans le proche infrarouge pour la détection de cellules cancéreuses

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Les sondes fluorescentes constituent aujourd'hui des outils majeurs pour la détection, l'imagerie et le suivi des cancers en raison de leur caractère non invasif, leur sensibilité, ainsi qu'une très haute résolution spatiale et temporelle. Parmi ces sondes, on distingue les systèmes dits « always-on », qui émettent une fluorescence continue, et les sondes fluorogènes ou « turn-on » qui s'éclairent uniquement après liaison à leur cible d'intérêt, permettant ainsi une amélioration de leur sensibilité de détection(1). Récemment, notre équipe a montré l'intérêt de ces sondes pour l'imagerie de récepteurs couplés aux protéines G à la surface de cellules vivantes mais également dans un organisme entier(2,3).
Dans le travail présenté ici, nous avons développé les premiers nanobodies « turn-on » dimériques ciblant des cellules tumorales qui surexpriment le récepteur HER2. Ces sondes sont constituées de deux fluorophores dérivés de cyanines 5.5 capables d'émettre dans le proche-infrarouge, de former des H-agrégats en solution aqueuse (turn-off) et de se dissocier dans un environnement hydrophobe (turn-on). Afin d'assurer un ciblage spécifique, ils ont été conjugués via un espaceur à un peptide (E3) porteur d'un fragment d'anticorps (VHH) ciblant HER2. Nous avons notamment étudié l'influence de la longueur de l'espaceur et de la nature des cyanines sur les propriétés « turn-on » des sondes, leur brillance mais également leur affinité et spécificité vis-à-vis de leur cible. Pour cela, des mesures photophysiques, de la cytométrie en flux et de la microscopie confocale sur cellules vivantes ont été effectuées. Ces sondes innovantes présentent un potentiel important pour l'imagerie de cellules tumorales pour le diagnostic et la chirurgie guidée par la fluorescence.

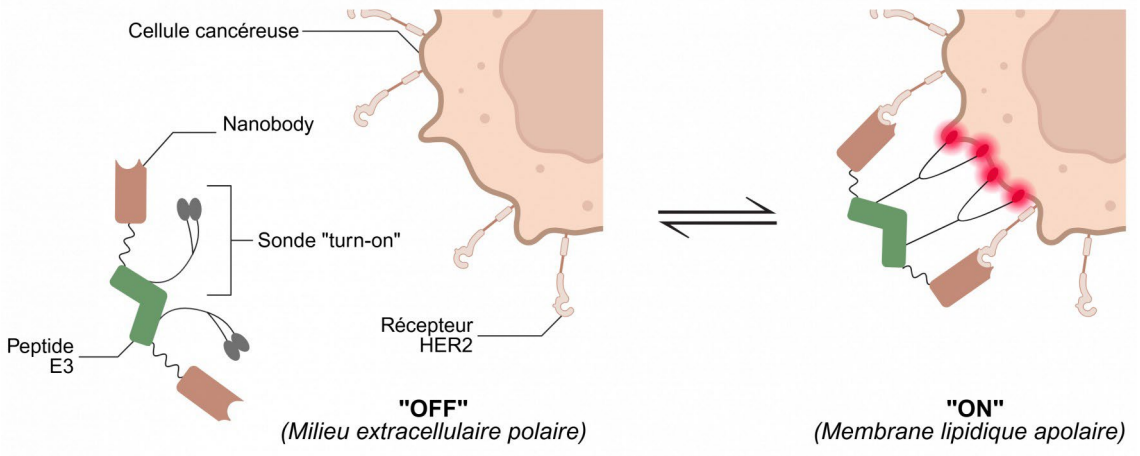

Figure : Schéma du fonctionnement des nanobodies fluorogènes

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C016

Optimized Fluorescent pH-Sensitive Dextran Conjugates Enable Ratiometric Measurement of Cerebral Blood pH In Vivo and In Situ

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Today, monitoring cerebrovascular acidification remains a challenge. The aim of this project is to develop fluorescent molecular tools compatible with blood circulation to provide a ratiometric readout of the pH. To achieve this objective, we started with the development of clickable probes compatible with two-photon (2P) imaging that will serve to functionalize dextran polymers for in vivo imaging applications. Indeed, dextran is a key element in our project as it reduces non-specific interactions and increases probe circulation time in the bloodstream. To reliably monitor pH variations in complex systems, ratiometric probes should be preferred over fluorogenic ones. We have thus synthesized and combined a pH-insensitive green-emitting dextran with a pH-sensitive red dextran based, H-Ruby probes developed by our team. Various parameters had to be considered for the structure of our fluorophore. Firstly, the pKa of the probe had to be finely tuned to fit with the physiological pH of resting blood (7.4), so that a small variation in blood pH would lead to a large signal amplitude. Secondly, the fluorophore/dextran ratio is of prior importance as a high loading will cause a loss of brightness due to staking of dyes within the dextran chains, a phenomenon known as aggregation caused quenching (ACQ). This aggregation phenomenon can also be reduced by modifying the rhodamine structure, in particular by making it more hydrophilic. This has been achieved by introducing PEG groups onto the H-Ruby fluorophore.
The synthesis of new fluorescent H-Ruby probe, different fluorophore/dextran loadings, their spectroscopic studies and in vivo cerebral microscopy will be presented to prove the use of these probes in pH monitoring for cerebrovascular imaging.

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CO17

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

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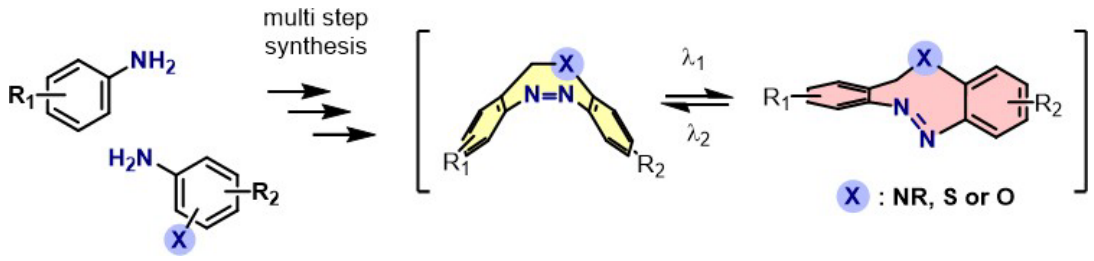
Osteoarthritis (OA) creates a growing public health burden yet lacks effective disease-modifying treatments. Recently, Monoamine oxidase B (MAO-B) emerged as a promising therapeutic target due to its overexpression and contribution to oxidative stress in OA-affected tissues.

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. 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.

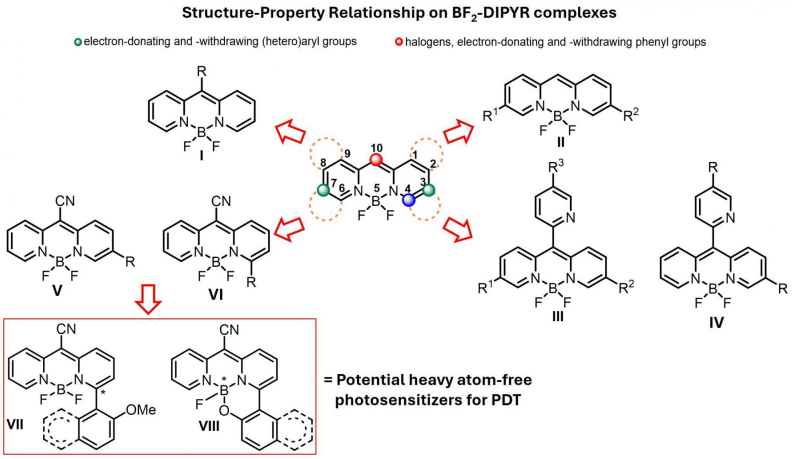


CO18

Molecular engineering of the difluoro dipyridomethene boron complexes towards the development of heavy atom-free photosensitizers for PDT

Carlotta FIGLIOLA (ICPEES)

Photodynamic therapy (PDT) is a medical treatment using the light in combination with a photosensitizer (PS) and molecular oxygen (3O2) against cancers and microbial infections.[1] The therapeutic effects of PDT derive from the absorption of the light by the PS, which reacts with 3O2 and produces singlet oxygen (1O2) and other reactive oxygen species (ROS) causing cell death, vessel damage and an inflammatory and immune response.[1] As part of the laboratory's research interest, difluoro dipyridomethene boron complexes, also known as BF2-DIPYRs, are proposed as potential heavy atom-free photosensitizing systems. In recent years, polycyclic aromatic systems have been used for the preparation of advanced fluorescent materials, optoelectronic devices, biological probes, and theranostic systems.2 The introduction into the structure of main group elements, such as boron and nitrogen, promotes the structure diversity conferring novel physical and chemical properties.[2] More specifically, nitrogen-chelated four-coordinated boron complexation is an effective strategy to obtain highly efficient photoluminescent compounds, because it increases molecular rigidity and planarity of their aromatic core.[3] Among them, 4,4-difluoro-4-bora-3a,4a-diaza-s-indacenes (BODIPYs) are by far the most developed,[4] and used in various areas, e.g. biological sensors, imaging agents, lasers, electroluminescent devices, as well as solar cells.[4] Compared to BODIPYs, BF2-DIPYR complexes have been scarcely investigated.[5] As a part of our molecular engineering of this scaffold to develop efficient PDT agents,[6] our study on the meso-CN BF2-DIPYR complexes via the introduction of electron-donating and withdrawing functional groups will be presented.[7] Furthermore, our strategy to induce a nonplanar molecular arrangement of the DIPYR core and favour the population of the nearest excited triplet state will be also described.[7] The synthesis as well as their detailed characterization, including the X-ray diffraction analysis, spectroscopic measurements and ab initio calculations, will be also provided.[7]



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Acknowledgements
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CO19

Kinase Inhibitors as host-targeting antivirals

Isabelle KRIMM (CBS) Dylan GRENIER (Université Lyon 1) Jean-Guy DELCROS (Université Lyon 1) Muriel GELIN (CBS), Jean-François GUICHOU (CBS)

Although only a limited number of host-targeting antivirals have been approved to date, this therapeutic strategy has recently gained significant attention as an alternative to direct-acting antivirals.
Host-targeted agents aim to disrupt essential cellular pathways that viruses hijack for their own replication. Notably, several human protein kinases have been identified as critical host factors exploited by the broad family of coronaviruses during their replication cycle.
In this context, we have developed a series of small-molecule inhibitors of protein kinase CK2. We characterized their biochemical properties, selectivity, and mechanism of inhibition at the molecular level using structural biology.
To assess their relevance as antiviral agents, we evaluated the compounds' ability to inhibit coronavirus replication in cellular models. These studies support the potential of host-targeted kinase inhibition as a promising strategy for combating coronavirus infections.

CO20

Scaffold Hopping Strategy for the Discovery of Novel ACSL4 Inhibitors

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Identified in 2012, ferroptosis is a regulated iron-dependent cell death characterized by excessive lipidic peroxidation.[1] 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 [2]. However, its reference inhibitor, rosiglitazone, has off-target activity on peroxisome proliferator-activated receptor gamma (PPARγ), a key regulator of lipid homeostasis. In this context, our lab recently described the discovery of LIBX-A401[3], a potent ACSL4 inhibitor derived from rosiglitazone lacking PPARγ activity and for which the binding mode has been elucidated. However, this molecule bears a methyl cinnamate motif that poses challenges for lead development.
In the present work, we address these issues by implementing a scaffold-hopping strategy that enabled the identification of potent ACSL4 inhibitors with improved drug-likeness.

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CO21

Chemical synthesis and biological assessments of RhoGTPase inhibitors

Camille TROUILLET (CEISAM Nantes Université / CNRS) Matthieu RIVIERE (CEISAM Nantes Université / CNRS) Agnès QUÉMENER (CRCI2NA INSERM/CNRS) Morgane ROUSSELLE (Institut du Thorax INSERM / CNRS) Mike MAILLASSON (CRCI2NA INSERM/CNRS) Mikael CROYAL (UMS BioCore (Inserm US16 et UAR CNRS 3556)) Jacques LEBRETON (CEISAM UMR CNRS 6230 / Nantes Université) Sylvain COLLET (CEISAM UMR CNRS 6230 / Nantes Université) Jacqueline CHERFILS (ENS Paris Saclay) Gervaise LOIRAND (Institut du Thorax INSERM / CNRS) Vincent SAUZEAU (Institut du Thorax INSERM / CNRS) **Arnaud TESSIER** (UMR CNRS 6230 - Laboratoire CEISAM)

Since the last fifteen years, the number of drugs allowed for marketing authorization has significantly stagnated despite all the funds invested by pharmaceutical companies. It seems to be clear that a renewal of approaches in drug discovery is required for more innovative discovery. In this context, protein-protein interactions (PPIs) are part of a promising field of research for new therapeutic issues.(1) In Human, between 130,000 and 650,000 PPIs(2,3) are implicated in numerous cellular processes and possibly in their dysfunction. The PIRAMID(4) collaborative consortium, involving several teams of biologists, chemists and bioinformaticians, was established in this field of research area in order to develop new tools or new drug candidates.
The Ras superfamily is comprised of five subfamilies especially Rho proteins (Rho homologous) which include 20 members in Human. Rho proteins are ubiquitous monomeric small GTPases (20-25 kDa) involved in the regulation of the cytoskeleton. Within this subfamily, the protein Rac1, RhoA and Cdc42 are the most studied. They are implied respectively in lamellipodia, actin stress fibers and filopodia formation with consequences on cell morphology, polarity, contraction, motility and adhesion. Each Rho protein presents a similar structure composed of 6 sheets β and 5 helix α. Between each sheets and helix, there are five loops noticed from G1 to G5 (Fig.1) These loops interact with GTP or GDP and the cation Mg^{2+}. These proteins are considered as molecular switches able to move from an inactive state associated with GDP to an active state associated with GTP to permit the activation of intracellular signaling pathways.(5)
In 2019, bronchial asthma affected around 262 millions of people over the world and caused 465 000 deaths. Over the years, asthma has become a major public health concern, while statistics show an annual increase of 6 to 10%.(7) Based on recent studies, signaling pathways involving Rac1 have been established as an attractive biological targets in asthma for development of new therapeutics.(8) Our communication will present our recent advances in this field based on the drug discovery and the synthesis of new designed PPI inhibitors toward this emerging area of research.(9)

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CO22

Towards the next generation of antibiotics by targeting the IspH metalloenzyme

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IspH is an oxygen-sensitive [4Fe-4S] enzyme that catalyzes the last step of the methylerythritol phosphate (MEP) pathway. It converts (*E*)-4-hydroxyl-3-methylbut-2-enyl diphosphate (HMBPP) into a mixture of isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), the two crucial building blocks needed for the biosynthesis of isoprenoids (Figure 1A).[1] This enzyme is essential for the survival of most bacteria, including several WHO priority pathogens, while being absent in humans.[2] As a consequence, IspH emerged as a promising therapeutic target for the development of novel antibiotics with new modes of action responding to the urgent need for innovative strategies to combat antimicrobial resistance.
Two HMBPP analogues were synthesized by the team by replacing the hydroxy group of HMBPP by a thiol or an amino moiety affording respectively TMBPP (Ki = 24 nM) and AMBPP (Ki = 54 nM), the two most potent IspH inhibitors.[3]
The crystal structure of IspH in complex with TMBPP or AMBPP prompted us to design and synthesize new inhibitors with potentially enhanced binding properties. Interestingly, the crystal structure of the IspH:TMBPP complex revealed TMBPP to adopt two conformations within the active site (Figure 1B).[4] To capture this structural flexibility, a cyclopentenyl motif was integrated in the structure of our candidates as a mimic of the superposition of these conformers (Figure 1C). This scaffold was further optimized *in silico* to better fill the active site in order to obtain more effective ligands for *E. coli* IspH. This design led to a series of molecules containing a thiol and an amino group predicted to bind respectively, to the apical iron of the $[4Fe\text{-}4S]^{2+}$ center and to glutamate 126 of *E. coli* IspH. Three molecules attracted our attention for further investigation: the first compound is inspired by this cyclopentenyl structure and the two others have a more flexible linear shape in case the first one would be too rigid to enter the active site (Figure 1D).
The multi-step synthesis of the candidate molecules as well as their preliminary biological evaluations on the oxygen sensitive *E. coli* IspH metalloenzyme will be presented.

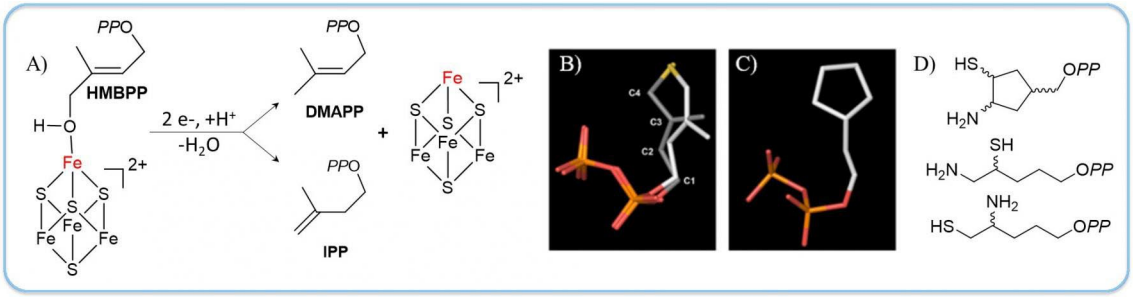

Figure : A) The enzymatic reaction catalyzed by IspH. B) Superposition of the two TMBPP conformers observed in E.coli IspH TMBPP complex. C) Cyclopentenyl scaffold that mimics the superposition of the two TMBPP conformers. D) Structure of potential

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Screening, Design, Synthesis and Evaluation of Macrocyclic Ligands for Stabilization of RNA Hairpins Implicated in Type 1 Myotonic Dystrophy

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Myotonic Dystrophy Type 1 (DM1) is an incurable neuromuscular disease affecting 1 in 8000–10000 people worldwide. This disease is due to the abnormal expansion of the CTG trinucleotide repeats in the *DMPK* gene. These repeats are transcribed into toxic mRNA whose 3'-UTR contains expanded repeats, r(CUG)^{exp}, which adopt two co-existing conformations: a hairpin form containing multiple U·U mismatches, and an open form. The latter sequesters MBNL splicing regulators, leading to abnormal splicing of multiple genes and the onset of DM1 symptoms.[1,2] A promising therapeutic strategy to treat DM1 relies on small RNA ligands able to stabilize the hairpin structure of r(CUG)^{exp}, thereby preventing MBNL sequestration and partially restoring normal splicing pattern (*Figure 1a*).[3]
To identify such ligands, we adapted the FRET-based melting assay[4] to evaluate stabilizing effect and selectivity of compounds on a r(CUG)$_{10}$ hairpin model sequence (*Figure 1b*). We screened a library of 51 polyazamacrocycles since some of them were previously known to target T·T mismatches in DNA.[5] In addition, we included in the assay 6 previously reported r(CUG)^{exp}-stabilizing drugs.[6] We identified eight macrocyclic hit compounds, highlighting the critical role of aromatic moieties in enhancing RNA hairpin stabilization. The affinity and selectivity of three selected hits were further assessed using orthogonal methods: native electrospray mass spectrometry with unmodified oligonucleotides, as well as isothermal fluorescence polarization assay, yielding K_d values in the low-micromolar range. In addition, their capacity to inhibit the sequestration of MBNL proteins is being evaluated using EMSA gels, fluorescence anisotropy and HTRF.
Based on the screening results, we designed and synthesized two new series of ligands by varying the linker lengths and incorporating selected aromatic groups, aiming to enhance the binding to a single U·U mismatch or to two consecutive U·U mismatches (*Figure 1c*). The capacity of novel macrocycles to stabilize the r(CUG)$_{10}$ hairpin form was assessed using the FRET-based melting assay.

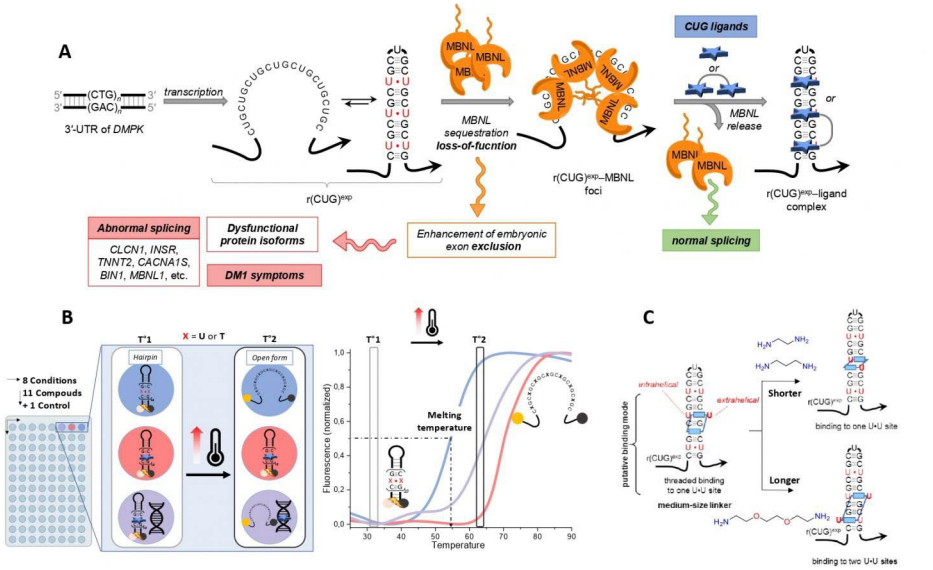

Figure A) DM1 molecular mechanism and ligand targeting strategy to overcome splicing defect.
B) FRET-based melting assay. ***C)*** Design of new polyazamacrocycles to better stabilize the r(CUG)^{exp} hairpin.

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CO24

Discovery of Novel G-quadruplex Binding Peptidic Derivatives Using DNA Encoded Chemical Libraries

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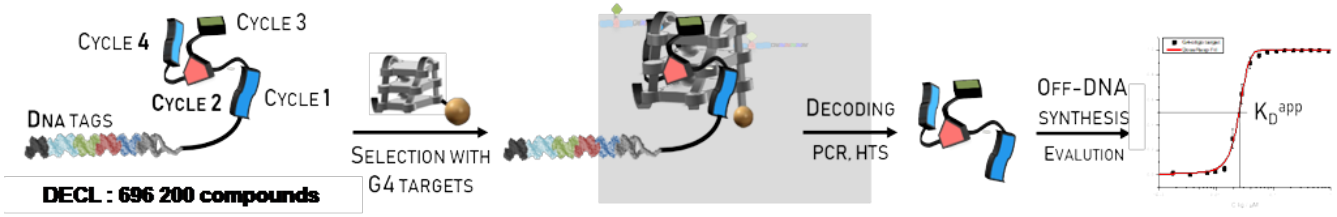
Beyond the canonical duplex DNA, there are now compelling evidences suggesting that nucleic acids can form secondary structures, including G-quadruplex (G4). G4 can arise through non-canonical nucleobase interactions within G-rich DNA and RNA sequences. Those structures, formed in key regulatory regions of genomes and transcriptomes, are involved in many biological processes, but also in the molecular mechanisms of several diseases, i.e., cancers or infections. Consequently, organic molecules specifically targeting and stabilizing G4 structures can provide a better understanding of their functions and possess significant therapeutic potentials.
Typical G4 ligands are synthetic small molecules, combining rigid aromatic heterocyclic architectures, able to act with external G-quartets, and cationic or protonable side chains, able to form additional interaction with negatively charged grooves and/or loops. The conventional chemical synthesis of ligands directed at G4 structures is typically demanding, thereby constraining the scope of structural diversity that can be explored.
To investigate alternative high-throughput approaches for identifying ligands with both high affinity and selectivity, capable of distinguishing among G4 topologies and against other DNA structures, we constructed two DNA-encoded combinatorial libraries (DEL-1 and DEL-2). DEL technology enables the rapid synthesis and screening of vast combinatorial libraries, where each compound is covalently linked to a unique DNA barcode, allowing simultaneous identification of ligands with high affinity and selectivity for specific targets. DEL-1, comprising roughly 200,000 compounds, was designed around a small rigid/flexible core and diversified through the attachment of pentapeptides flanking the core, combined with a range of heteroaromatic motifs known to engage G4 structures. DEL-2, a library of approximately 700,000 compounds, was constructed around trifunctional hydrophobic cores (aliphatic, aromatic, or heteroaromatic), functionalized at two positions with pentapeptides and at a third position with low-molecular-weight fragments bearing diverse molecular motifs.
Both DELs were engaged in selections against biologically relevant G4 targets, and high-throughput sequencing (HTS) of the enriched DNA-encoded binders revealed detailed structure-affinity relationships alongside clearly enriched molecular motifs and ligands. The most promising hits were resynthesized without their DNA tags and G4-binding affinity and stabilization potential were assessed using multiple biophysical methods (FRET-melting, G4-FID, CD, qPCR) confirming both their potency and the predictive value of the HTS-derived structure–affinity data. In select assays, several of these ligands demonstrated exceptional activity, in some cases exceeding that of established reference compounds.
For RECOB we would like to present the design, assembly, screening, deconvolution, and hit validation (with selected examples) of these DNA-encoded libraries aimed at identifying G4 binders, demonstrating the full potential of DEL technology for discovering novel ligands of structured nucleic acids.

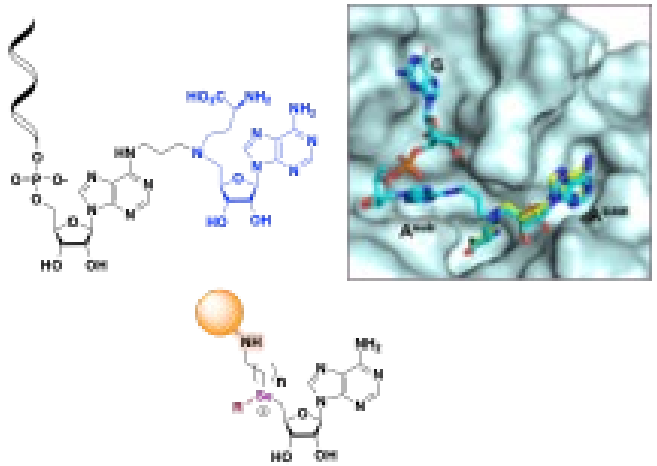


CO25

Harnessing Nucleoside and Nucleotide Chemistry to Explore RNA Modifications

Mélanie ETHEVE-QUELQUEJEU (Université Paris cite)

RNA methyltransferases (RNA MTases) are a family of enzymes that catalyze the methylation of RNA using the cofactor S-adenosyl-L-methionine. RNA MTases are promising drug targets, and new molecules are needed to fully understand their roles in disease and to develop effective drugs that can modulate their activity[1]. Here, we report original strategies for the synthesis of families of m6A MTase bisubstrate analogues. Our approaches are based on the synthesis of RNA conjugates containing a SAM cofactor analogue connected at the N6-atom of an adenosine using nucleophilic aromatic substitution[2,3] or by CuAAC[4] or iCuAAC reaction followed by a palladium-catalyzed cross-coupling[5]. Crystal structures of bacterial[6] and human MTases[7] in complex with our bisubstrate molecules were solved and revealed the RNA-specific recognition elements used by these enzymes to clamp the RNA substrate in their active site. This study demonstrates that bisubstrate analogues are potent molecular tools to explore the active site of RNA modification enzymes. We will also present SAM analogues that demonstrate interesting activity as inhibitors of m6A RNA methyltransferases.



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CO26

Design and Synthesis of Stable Antiviral Analogues of Macarangin B

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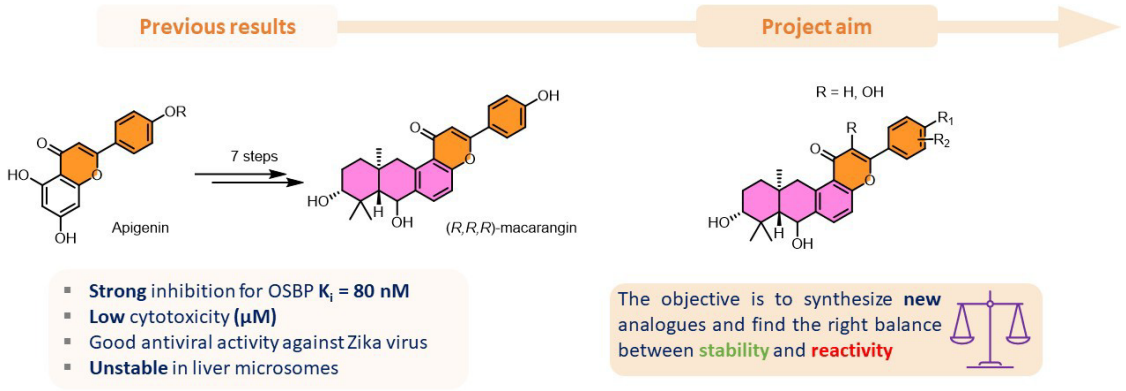
For decades, RNA viruses, particularly emerging or re-emerging ones, have posed a constant threat to global health and continue to present significant challenges. These viruses demand new and innovative antiviral strategies, particularly when vaccines are ineffective or non-existent.[1] (+)RNA viruses reach out to the host's own proteins, forging connections to enable replication.[2]
Studies have shown that the OSBP protein could be involved in many virus replications and thus can be used as a druggable broad spectrum medicine. In a healthy cell, OSBP transports cholesterol from the endoplasmic reticulum (ER) to the trans-Golgi network (TGN) via its OSBP-related domain (ORD) by counter-exchange and hydrolysis of phosphatidylinositol-4-phosphate[3]. This process is crucial for cell health and membrane stability. However, when a virus steps in, it hijacks OSBP, reroutes cholesterol and reorganizes lipids. This is why targeting these hijacked host mechanisms is currently one of the most promising strategies for combatting viral infections. Although inhibitors of the OSBP protein are already known, they are either too cytotoxic or not specific enough to OSBP to be used as an antiviral agent.
The aim of this project is to develop a new antiviral agent based on a natural compound called macarangin B. Previous work in the laboratory has shown that this compound inhibits OSBP in a dose-dependent manner (nM), exhibits interesting antiviral properties against Zika virus and is only slightly cytotoxic (µM).[4-5] However, although macarangin B is promising, it has low metabolic stability, which hinders its development. The aim is therefore to synthesize more stable antiviral analogues of macarangin B.



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CO27

"In situ" and "in crystals" click chemistry, a potent tool to accelerate antiviral drug discovery against *Bunyaviricetes* infections

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The *Bunyaviricetes* class currently groups together more than 600 (-)ssRNA species of viruses, including high-risk human pathogens. Three of these viruses are even mentioned in WHO's priority list, namely Lassa, Rift Valley Fever and Crimean-Congo Hemorrhagic Fever viruses. To make matters even worse, these viruses are gradually spreading throughout the world. Despite the growing global health threat posed by *Bunyaviricetes*, therapeutic options are still very limited. Developing effective and specific treatments against *Bunyaviricetes* is therefore a pressing issue.

Bunyaviricetes viruses have a specific replication machinery that considerably relies on the L-protein through its multiple enzymatic activities. In addition to the RNA-dependent RNA polymerase activity, the L-protein is responsible for an Endonuclease (EndoN) activity to perform host-RNA cap-snatching[1]. This activity, during which a host RNA cap is stolen – to be attached to a viral RNA strand – is detrimental to start the viral RNA replication machinery. Additionally, some of these viruses have a way of evading the host innate immune system thanks to their Nucleoprotein[2]. More specifically, Nucleoproteins of Mammarenaviruses possess an Exonuclease (ExoN) activity that hides and breaks down abnormal viral RNA strands to avoid recognition by host immune cells. Both viral EndoN and ExoN are Mg^{2+} and/or Mn^{2+}-dependent hydrolases, with their activities strictly relying on RNA chelation in their respective active sites. Thus, one strategy to design pan-genus antivirals against *Bunyaviricetes* is to develop EndoN and/or ExoN metal-chelating inhibitors with specific fitting properties.

Such inhibitors development can hopefully be accelerated with the help of a rational Kinetic Target-Guided-Synthesis approach, where the target enzymes will auto-assemble their "preferred ligands" from a pool of clickable fragments[3] via click azide-alkyne cycloaddition. Each enzyme will act as a mold, taking advantage of the metal-anchoring motif, and catalyze the cycloaddition between affine and specific fragments reaching defined pockets of the active site. This auto-assembly strategy can be applied in aqueous solutions containing the enzyme ("in situ")[4] and enrichment can be monitored by HPLC-MS. Originally, the same strategy could be applied in protein crystals ("in crystals")[5], where the fragment-linking event can be directly identified by X-ray diffraction.

We here report the development and results of the "in situ" click-based screening of fragments library. We observed clicked compounds formation auto-assembled by the La Crosse virus EndoN. We devised a simple and general three-step synthetic route for larger scale production. Some Hit compounds proved to be sub-micromolar binders and inhibitors, validating the "in situ" click strategy proof-of-concept. Additionally, we solved the crystallographic structure of one particular Hit in complex with its target, which in turn gave invaluable information regarding the ligand-target interactions and a starting point for the "in crystals" click strategy.

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CO28

Photocatalytic Strategies for Antibody Bioconjugation

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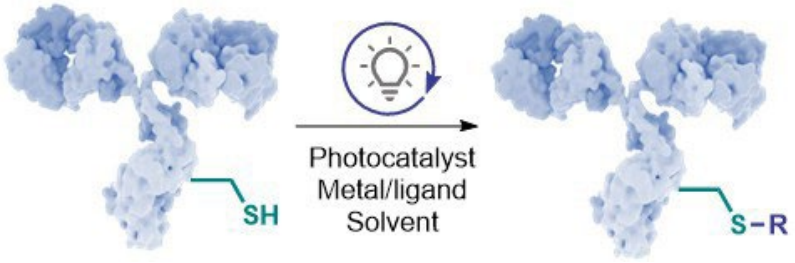
Antibody–drug conjugates (ADCs) have emerged as a powerful class of targeted therapeutics, combining the specificity of monoclonal antibodies with the potency of cytotoxic agents. Their clinical success relies on highly selective and stable conjugation strategies that preserve protein function. However, current chemical approaches often involve harsh conditions or lack sufficient site-selectivity, potentially compromising protein integrity. Therefore, developing mild, biocompatible strategies with high selectivity is critical to advance next-generation of ADCs and fully exploit their therapeutic potential.
By harnessing visible light, photocatalytic reactions enable the generation of reactive intermediates under mild conditions, leading to cleaner bond formation and greater control of the selectivity. Importantly, shifting to longer wavelengths reduces photodamage, allows for more controlled reactivity, and expands the range of compatible biomolecules.
Within this framework, our project focuses on cysteine-selective functionalization of IgG1 antibodies through photocatalytic strategies, explored under blue, green, and red light conditions, aiming to establish cleaner and more controlled methods for the preparation of ADCs.



CO29

Antiproliferative Activity of Bispidines and Their Copper Complexes: When the Ligand Outperforms the Metal Complexes

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Cancer remains one of the leading causes of mortality worldwide, with its burden expected to increase significantly in the coming decades, underscoring the urgent need for new therapeutic strategies. Metallodrugs have long been explored in this context, notably following the clinical success of cisplatin [1], which highlighted the therapeutic potential of metal-based compounds. Among these, copper complexes have gained increasing attention due to copper's biological relevance, redox activity, and favourable cost profile [2], [3].

In this work, we focused on a family of Bispidine ligands and their corresponding copper complexes [4], aiming to assess their antiproliferative activity against human cancer cell lines. Based on existing literature, metal coordination is generally considered essential for biological activity in copper-based systems. However, our results revealed that the Bispidine ligands displayed significant antiproliferative effects, with IC_{50} values down to 14.9 µM, whereas their copper complexes exhibited little to no activity under the same conditions.

These findings challenge the commonly accepted paradigm that copper coordination is the primary driver of cytotoxicity in many of systems and suggest that ligand-centered mechanisms can also play an important role.

Ongoing studies, including cellular uptake measurements, reactive oxygen species (ROS) assays, and flow cytometry analyses, aim to clarify the origin of this contrasting behaviour and to better understand the structure–activity relationships and mechanism(s) of action of this family of compounds.

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CO30

Deep-Tissue Molecular Activation: Ionizing Radiation- Driven theranostics to target cancer cells

Marius BICHOT (CNRS, Institut Curie) Guillaume BORT (CNRS, Institut Curie) Gilles MARCOU (Université de Strasbourg, UMR7140) Hadrien HERLEM (Institut Curie)

Photopharmacology allows for precise control of therapeutic agents, yet its clinical translation is severely hindered by the limited penetration depth of UV-visible light in biological tissues. To overcome this barrier, we propose a strategy utilizing clinical Ionizing Radiation (IR) such as X-rays and Gamma-ray which possesses unlimited depth penetration, to trigger molecular switches deep within the body.

We designed a theranostic Gadolinium-Azobenzene conjugate (GdAzo)[1] acting as a radioswitch. High-energy IR stimuli induces a specific cis-to-trans isomerization of the azobenzene moiety. Mechanistic investigations were conducted using complementary approaches, including computational chemistry, machine learning, steady-state experiments, and time-resolved spectroscopy. This activation leads to a drastic change in molecular polarity, inducing cell membrane permeabilization and cytotoxicity in cancer cells.

This work establishes Radioswitches as a breakthrough concept for deep tissue theranostics, successfully overcoming the depth penetration limit of traditional photopharmacology. By enabling the remote activation of cytotoxic drugs using standard radiotherapy equipment, this strategy offers a highly translatable approach for treating deep-seated or resistant tumors, with the added benefit of MRI-guided monitoring.

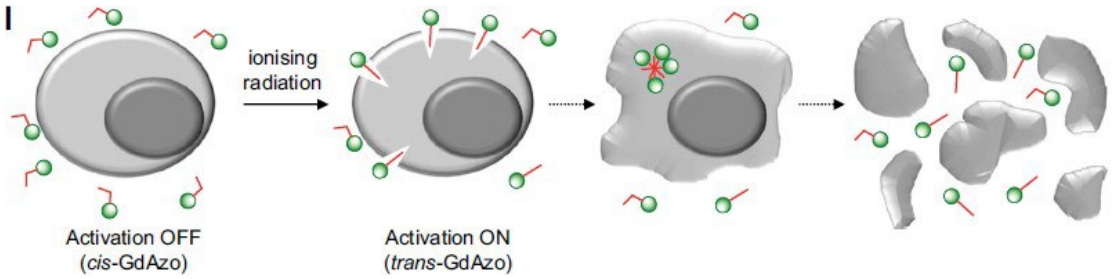

Figure 1: Assumed mecanism of permeabilisation of cancer cells after activation by ionising radiations

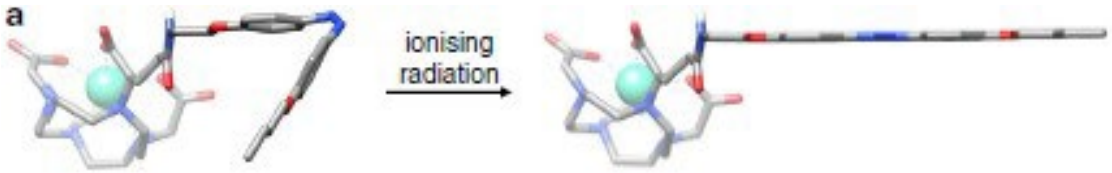

Figure 2: Structures of cis-GdAzo (left) and trans-GdAzo (right) calculated at the B3LYP/6-31 G* level of theory.

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CO31

Combination of metabolic glyco-engineering and disulfide rebridging for the grafting of antibody fragments on cell surface - toward new cell therapies

Fabien THOREAU (Université Poitiers)

Antibodies are Y-shaped proteins possessing two binding moieties termed Fragment Antigen Binding ("Fab"), which confer them a high affinity for their target antigen. Enzymatic digestion enables to generate and isolate Fab fragments, while disulfide rebridging method allows the selective installation of click handles (azide, tetrazine, BCN...) at their disulfide site, yielding "clickable Fabs".
In parallel, the metabolic glyco-engineering method, notably developped by Nobel prized Carolyn Bertozzi, consists in feeding cells with synthetic sugars which, once metabolised by the cell, will be incorporated in the glycans at their surface. Depending on the modified sugar design, click handles such as azide or cyclopropene can be displayed at the cell surface, yielding "clickable cells".
In a final step, a bioorthogonal click reaction is realised directly on the cell surface, between the clickable-Fab and the clickable-cell, to decorate the cells with Fab fragments, hence confering them a high affinity for a given antigen.
At this stage of the project, Fab_{HER2} and Fab_{CD3} fragments bearing a BCN function were reacted on azide-bearing Jurkat T cells (CD3+ immune cells) or azide-bearing A549 (HER+) cancer cells, to respectively generate Jurkat T cell displaying Fab_{HER2} or cancer cells displaying Fab_{CD3} at their surface.
The effect of such functionalisation on cell-cell association, cell viability and immune activation are currently assessed by microscopy, Elisa assays and flow cytometry. Preliminary results are really encouraging regarding the ability of the grafted $Fab_{HER2/CD3}$ to confer a targeting capacity to the modified tumour and/or immune cells, as well as inducing biological effects, paving the way to innovative cancer cell therapy.
Current developments in our lab include pursuing biological evaluation, adding a "selective immune activation module" to the construct, and extension of the concept to other cell types (macrophages, bacteria...)

CO32

AfKDNAse Inhibitors as Potential Antivirulence Agents against Aspergillus fumigatus

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Aspergillus fumigatus is a major opportunistic fungal pathogen responsible for life-threatening infections in immunocompromised patients. *Af*KDNAse, an exoglycosidase involved in the hydrolysis of the rare sugar 3-deoxy-D-galacto-D-glycero-nonulosonic acid (KDN), was recently identified as an important determinant of fungal cell wall architecture and virulence [1]. Despite this, the biological role of *Af*KDNAse remains poorly understood, highlighting the need for selective chemical tools to probe its function and evaluate its potential as an antivirulence target.

Here, we describe the rational design and synthesis of a new family of *Af*KDNAse inhibitors based on enzymatically stable thio-KDN scaffolds, engineered to interact with the enzyme's KDN-binding pocket. Two series of heterodi-KDN inhibitors, linked at either the C2 or C9 position, were developed, together with a multivalent polymer bearing an average of 54 KDN units, obtained via click chemistry. Enzymatic inhibition assays revealed moderate to high inhibitory activities across the series, with the multivalent poly-KDN displaying a remarkable enhancement in potency (IC_{50} = 1.52 ± 0.37 µM), corresponding to a >900-fold improvement compared to monovalent KDN (17-fold on a per-KDN basis).

Taken together, these findings demonstrate that multivalent thio-KDN inhibitors efficiently target AfKDNAse activity and translate into a marked inhibition of A. fumigatus filamentation. This work supports *Af*KDNAse as a promising antivirulence target and positions multivalent KDN-based inhibitors as attractive leads for the development of non-fungicidal antifungal strategies [2].

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CO33

Synthesis of fluorescent probes targeting VGLUT3 for in vivo pharmacological studies

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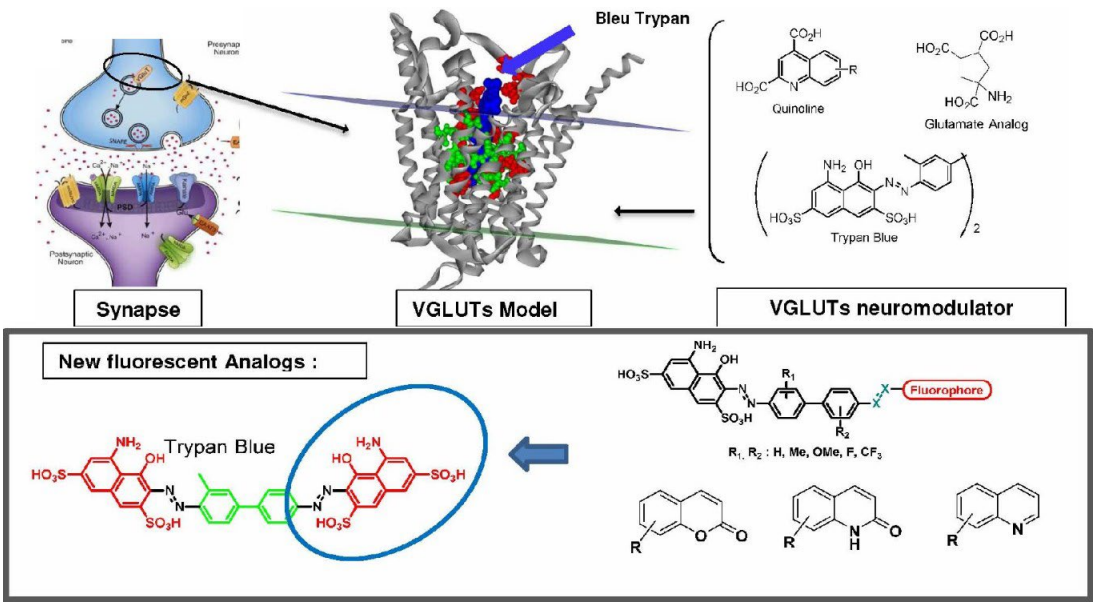
Vesicular glutamate transporters (VGLUTs) were once regarded as exclusive markers of glutamatergic excitatory transmission. However, the discovery of VGLUT3 two decades ago challenged this simplified view. VGLUT3 is strategically expressed in various populations of glutamatergic, cholinergic, serotonergic, and even GABAergic neurons.[1] These expressions in neurons initially characterized as "non-glutamatergic" reveal an unexpected complexity. Our team has shown that VGLUT3 has a dual function in these bilingual neurons: first, it enables these neurons to use glutamate as a neurotransmitter, and second, its colocalization with other vesicular transporters in synaptic vesicles induce a vesicular synergy. This process allows the regulation of neurotransmission through an overaccumulation of acetylcholine or monoamines in synaptic vesicles that co-express VGLUT3.[1]

Recent studies indicate the significant impact of VGLUT3-dependent glutamate co-transmission on brain functions and dysfunctions. Advances in the neuropharmacology of VGLUT3 have the potential to improve treatments for various conditions such as Parkinson's disease, addiction, eating disorders, anxiety, presbycusis, and pain.[2]

This work focuses on VGLUT3 and its vesicular mechanism, as well as potential approaches for targeting this unique transporter in future theranostic interventions. Additionally, fluorescent compounds mimicking glutamate will be used as imaging biomarkers to study glutamatergic co-neurotransmission in physiological and pathological contexts. [3]

Our work focuses on incorporating fluorophore scaffolds into our lead compounds, such as coumarin and quinoline, to replace the Trypan Blue naphthyl moiety and create fluorescent dye analogs. The synthesis involved various types of chemistry, including classical organocoupling reactions (such as Sonogashira, Suzuki or Huisgen coupling) as well as organic synthesis methods (such as protection and diazotization).[4] The next step will involve vectorizing the compounds into the brain to facilitate in vivo experiments.



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CO34

Rewriting the tubulin code: Targeting α-tubulin detyrosination for therapeutic benefit

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Microtubules (MTs) are essential cytoskeletal elements composed of α/β-tubulin heterodimers involved in key cellular processes such as cell division, migration, and intracellular transport. Their functional diversity is largely regulated by post translational modifications, among which detyrosination is the most abundant. This reversible modification, specific to α-tubulin, consists in the removal of the C-terminal tyrosine residue and has been implicated in numerous physiological and pathological processes.

We previously identified the two members of the vasohibin family, VASH1 and VASH2, as the first class of tubulin detyrosinating enzymes, representing a major breakthrough in the field[1]. Building on this discovery, we developed the first generation of selective covalent VASH inhibitors. Using a rational substrate-based medicinal chemistry approach combined with QSAR analysis, we identified LV80, an epoxide-based covalent inhibitor that efficiently blocks VASH-dependent tubulin detyrosination *in cellulo* with minimal off target effects. The favorable stability and safety profiles of the newly-developed inhibitor highlight its therapeutic potential[2].

In addition, using compounds which emerged from our inhibitor QSAR study, we demonstrate that tubulin detyrosination plays a central role in the maintenance of mesenchymal traits in lung cancer cell lines, regulating collective cell migration, three-dimensional spheroid formation, and epithelial to mesenchymal transition[3].

More recently, we identified Tubulin Metallocarboxypeptidase 1 (TMCP1) as a second class of tubulin detyrosinating enzymes, which is mechanistically distinct from VASHs[4]. To support inhibitor discovery against both types of enzymes, we developed a sensitive FRET based enzymatic assay enabling real time monitoring of VASH and TMCP1 activities5. This assay provides a robust platform for the discovery of selective inhibitors or pan detyrosinase inhibitors. The inhibitors identified through these studies will serve as powerful tools to investigate the biological functions of tubulin detyrosination in complex cellular contexts and represent promising leads for future therapeutic development.

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CO35

Vectorization of pleuromutilin by a siderophore mycobactin analog: towards antibiotic Trojan horses against Pseudomonas aeruginosa

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Iron is essential for various biological functions in eukaryotes and prokaryotes. This metal is involved in crucial biological processes (cellular respiration, DNA synthesis, etc.). However, under aerobic conditions, iron (III) is poorly soluble, and in the human body, iron is mainly sequestered by storage proteins, making it difficult for pathogenic bacteria to access this nutrient. To overcome this limitation, bacteria secrete siderophores, small chelating molecules capable of complexing iron(III) in the extracellular environment. Ferric siderophores are then recognized and transported into the bacterial cell by specific membrane transporters.
The design of siderophore analogues for the vectorization of antibiotics in Gram-negative bacteria is an innovative strategy for circumventing the low permeability of these bacteria to a large number of active molecules. Siderophores offer a unique opportunity to exploit these specific transport pathways to improve the penetration of certain antibiotics and enhance their effectiveness against problematic bacterial pathogens, such as Pseudomonas aeruginosa. Our approach consists of developing "Trojan horse" siderophore-antibiotic conjugates. The design of these conjugates requires preserving affinity for iron(III) and recognition by membrane transporters. The chemical functionalities of natural siderophores are often involved in both processes, and it is therefore necessary to develop functionalized analogues capable of mimicking siderophores to better hijack the corresponding iron transport system. In this context, we have developed Bis-AA, a compound that mimics the siderophore mycobactin and is capable of interacting with the dedicated outer membrane transporter called FemA in P. aeruginosa. This vector was used to vectorize pleuromutilin, an antibiotic specific to Gram-positive bacteria, whose spectrum of activity could be extended to P. aeruginosa thanks to our strategy.

POSTERS


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P01 A NEW THERAPEUTIC APPROACH TARGETING LIM KINASES VIA INNOVATIVE PROTACS
Sylvain ROUTIER (*Université d'Orléans)*, A. SERRANO, S. ACI-SECHE, P. BONNET, H. BENEDETTI, B. VALLEE, K. PLE

P02 A straightforward synthetic route toward lipocyclopeptides. Application to antifungal fluorescent echinocandins
Clémentine LEGER (*Université de Strasbourg)*, S. RICHE, D. BONNET, R. HANY, H. ANTON, A.M. SABOU, L. BOUREL, L. BRENDEL

P03 Artificial DNAzymes for asymmetric oxidations
Quentin FREMI (*Université Grenoble Alpes)*, N. SPINELLI, C. MARCHI-DELAPIERRE

P04 Association synergique antibiotique-inhibiteurs de biofilm pour une antibiothérapie contre Pseudomonas Aeruginosa
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P05 Bioorthogonal Fluorogenic release of isocyanates in cells
Ines ZERGUINE (*CEA Paris-Saclay)*, J. BAUDET

P06 Carbon Dots pour la délivrance de siARN et la PDT améliorée : Application à la Dermatite Atopique
Elise CHERASSE (*Université de Strasbourg)*, F. BURGER, L. GARCENOT, J. FATH, L. LEBEAU, F. BOLZE, F. PONS, A. SPECHT

P07 Click-and-Release Formation of Urea Bonds in Living Cells Enabled by Micelle Nanoreactors
Mélanie LAQUEMBE (*CEA Paris-Saclay)*, L. MADEGARD

P08 Combining gold and visible light in catalysis: a new route for heterocycle skeletons
Virginie MANSUY (*Sorbonne Université)*

P09 Désassemblage moléculaire pour la détection fluorogénique des phosphates biologiques
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P10 Design and synthesis of RED-SMU1 disruptors as new antiviral agents against Influenza A virus
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P11 Design of acridan based NIR fluorophores for imaging
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P12 Design of antiviral prodrugs targeting the central nervous system to treat neurotropic viruses.
Alexandre PEREZ (*Aix Marseille Université)*, K. ALVAREZ

P13 Design of Artificial Peptide Helices via Heterocycle-Editing
Baptiste LEGRAND (*Universite de Montpellier)*, C. DIDIERJEAN, A. GACOGNE, M. FILLAUDEAU, Y.K. KANG, A. LEBRUN, J. BANTIGNIES, D. HOUSSET, M. AMBLARD, L. MAILLARD

P14 Design of new N-substituted-4-hydrazino-7-nitrobenzofurazan as fluorescent probes and active reagent for colon cancer diagnostic and prevention
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P15 Design of photolabeling probes to identify the target of anti-Alzheimer compounds
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P16 Development of a Peptide Receptor Radionuclide Therapy (PRRT) strategy for Poor-Prognosis Cancers
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P17 Development of Bifunctionnal & Bioorthogonal Nanoplatforms Based on Calix[4]arenes-Coated Gold Nanoparticles for Advanced Bioconjugation
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P18 Development of biphotonic fluorogenic probes for the detection of enzymes overexpressed in tumour environment
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P20 Développement de sondes fluorogéniques basées sur des fluorophores à phénol rigidifiés pour des applications FGS
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P21 Elucidation des relations structure-fonction des complexes LRRK2/Phosphatases dans la maladie de Parkinson.
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P22 Engineering of near infra-red bioluminescent reporters for in vivo bioimaging and biosensing
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P23 Evaluation of the binding characteristics of [18F]FBVM in non-human primates, a new radiotracer for imaging the vesicular acetylcholine transporter in vivo using positron emission tomography
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P24 Exploration of biodiversity for the discovery and design of antiviral cyclopeptides
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P25 Exploring the IspG mechanism with innovative substrate analogues as a source of inspiration for new antibacterial strategies
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P26 Fluorescent probes for the detection of bacteria in body fluids
Viviane REN (*Université de Strasbourg)*, A. AUGÉ, J. KARPENKO

P27 Greffage de fragments d'anticorps à la surface de cellules par combinaison de glyco-ingénierie métabolique etchimie click bioorthogonale : vers des thérapies cellulaires innovantes
Lucie CAILLET (*Université de Poitiers)*

P28 Identification of new MASTL inhibitors for cancer therapy from a promising chemical scaffold
Amine BOUIDDER (*Institut Curie, Orsay)*, F. MAHUTEAU-BETZER, C. BEAUVINEAU, A. CASTRO

P29 Iminosydnone-based probes for bioorthogonal cycloadditions with cyclooctyne as irreversible protein labeling in living cells
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P30 L'arachidonyl-CoA dicte la spécificité de substrat de l'acyl CoA synthétase à longue chaîne 4 (ACSL4)
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P31 Ligation of oligonucleotides induced by Charge-Transfer interactions
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P32 Luminescent Lanthanide Bioprobes as tools for biology
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P33 MANNOSE-SPECIFIC BORONOLECTINS: DESIGN AND SYNTHESIS OF BIS-BORONIC ACIDS
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P34 Marquage de la capsule K1 : Optimisation du marquage en MOE et mise au point d'une stratégie marquage utilisant la SEEL
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P35 Modification sélective d'anticorps par une approche de "re-bridging" supporté - vers des conjugués drogue-anticorps originaux et homogènes
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P36 Nanoréacteurs activables par chimie bioorthogonale pour la synthèse organique dans les systèmes vivants
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P37 Nouveaux PROTACs ciblant PI3Kγ, une vulnérabilité lignée-spécifique dans les leucémies myéloïdes aiguës.
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P38 Nouvelles amidoximes comme donneurs potentielles de NO.
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P41 Quinoline based luminescent imidazolium salts as vector for gene therapy
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P42 Rational drug design strategy against Bunyaviricetes class viruses
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P44 Styryl Borondifluoro Indolenines as new photomodulable fluorescent probes based on Directed Photooxidation Induced Conversion
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P45 Synthèse de prodrogues azobenzènes dérivées d'un produit naturel cytotoxique original
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P46 Synthesis and characterization of radiation-activated PROTAC for cancer treatment
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P47 Synthesis and photo-electrochemical characterization of reversible RedOx-responsive metallocene-based fluorescent probes
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P48 Synthesis of bioorthogonal trehalose monomycolate analogs for probing the membrane of Mycobacteria
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P49 Synthesis of Fluorescent Probes Targeting VGLUT3 for in vivo Pharmacological Studies
Nicolas PIETRANCOSTA (*Sorbonne Université)*

P50 Targeted Release of Drugs using Photolabile Groups and Photoactivatable Nanoparticles : Application to Neovascular Diseases of the Retina
Léa GARCENOT (*Université de Strasbourg)*, F. BOLZE, A. KICHLER, A. SPECHT

P51 Tetracyclic pyrazinotriazapentalene (PyTAP) a new family of red emitting fluorescent scaffold for cellular imaging
Franck SUZENET (*Université d'Orléans)*, R. DELATOUCHE, N. CHOPIN, R. LAMARE, J. LE BESCONT, P. DEMAY-DROUARD, M. HIEBEL

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P52 Thiazolium-Based ⍰-Aminoacids as Precursors of NHC-Supported gamma-Peptide Foldamers
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P53 Total Synthesis and Biological Evaluation of Cannalactone, a Noncanonical Strigolactone from Hemp
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P54 Towards new inhibitors of the IspD enzyme of Bacillus anthracis
Philippe CHAIGNON (*Université de Strasbourg)*, B. LABORIE, F. BOREL, M. SEEMANN

P55 Tuning Photophysical Properties of Cyanine-7 Dyes through Dimerization: Toward Theranostic Applications
Khaoula CHERKANI EL HASSANI (*Université de Lorraine)*, K. JOUAD, N. ILLI, T. GULON, M. BOUCHÉ, K. SELMECZI, S. LAMANDÉ-LANGLE, N. PELLEGRINI MOÏSE

P56 Two-photon excitable fluorogenic probes for Click-to-Release bioorthogonal reactions
Juichi BAINVEL-SATO (*Institut Curie, Orsay)*, A. RODRIGUEZ, D. NAUD-MARTIN, G. FONTAINE, K. RENAULT, F. MAHUTEAU-BETZER

P57 Development of a hyphenated LC-MS method to characterize N- glycan structures of recombinant glycoproteins produced in microalgae
Elodie MATHIEU-RIVET (*Université de Rouen Normandie)*, R. XAVIER, O. PERRUCHON, P. LEROUG, O. SIMON, C. AFONSO, C. LOUTELIER-BOURHIS

P58 Developing xenonucleic acid-based ligands for biodetection
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P01

A NEW THERAPEUTIC APPROACH TARGETING LIM KINASES VIA INNOVATIVE PROTACS

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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 cytoskeleton polymerization and microtubule dynamics. The molecular mechanisms involved for actin filament turnover are well known, as LIMKs phosphorylate and inactivate cofilin, an actin depolymerization factor.
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).
For the past several years, ICOA and CBM have been working together to develop LIMK inhibitors. We have a database of over 200 molecules. Robust structure-activity relationships have been established, and some of our inhibitors have very good activities on purified enzymes in the nanomolar range, and are also highly active in cellulo on different cell lines.
To capitalize on our expertise in the design and synthesis of LIMK kinase inhibitors, we have begun to develop tools for chemical biology based on these active compounds. Several fluorescent probes have been synthesized and evaluated in our laboratory. In addition, we wish to design PROTACs (PROteolysis TArgeting Chimeras) to induce the targeted degradation of LIMKs.
Briefly, PROTACs are hetero-bifunctional molecules that induce the targeted degradation of a protein of interest (POI) directly inside the cell. They consist of three distinct parts: (i) a POI ligand, (ii) a linker arm and (iii) an E3 ubiquitin ligase ligand. When PROTAC binds to its POI and to ubiquitin E3 ligase, a ternary complex is formed, resulting in ubiquitination of the POI and its degradation by the proteasome. PROTAC technology is rapidly gaining ground in therapeutic areas such as oncology, neurodegenerative and viral diseases.[1,2] PROTACs are structurally diverse molecules, and the most promising involve fine optimization of the linker arm between the two respective ligands (POI and E3 ligase).
Several original PROTACs from our compound library have been prepared and tested in cellulo ith very promising results. Some of our PROTACs induce significant LIMK silencing in two cell lines. The synthesis of these bifunctional molecules, in cellulo degradation studies and their functional implications will be discussed in this poster.

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P02

A straightforward synthetic route toward lipocyclopeptides. Application to antifungal fluorescent echinocandins

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Invasive fungal infections (IFIs) are increasing significantly in nosocomial settings and are responsible for 2.5 to 3.8 million deaths per year worldwide. Only four families of antifungal drugs are currently used to fight against IFIs and rising resistances are alarming. The present work belongs to a global project conducted at the Laboratoire d'Innovation Therapeutique in Illkirch, France, whose goal is to identify new antifungal candidates and understand their mode of action following a chemical biology approach.
Among the antifungal agents currently used, one family stands out. First proposed in the 2000s, Echinocandins (EC) are cyclic lipopeptides of natural origin that non-competitively inhibit ß-(1-3)-D-glucan synthase, an enzyme essential for the integrity of the fungal cell wall. Despite their great interest, their exact mechanism of action remains unclear. In addition, their intensive use has led to the emergence of resistances. All this results in a loss of sensitivity found in many fearsome fungi, especially those isolated from hospitalized and immune-compromised patients.
There is therefore a need for molecular probes to explore ECs' mechanism of action and resistance modalities. Due to their structural complexity, only few total syntheses and very limited fluorescent analogues have been reported yet.
Here, we present a versatile solid-phase strategy to readily access to cyclic lipopeptides derived from ECs. Using a safety-catch linker resin, a cyclization-release approach affords high-purity ECs azido-analogues that retain activity against Candida albicans following the EUCAST reference method. A subsequent click ligation with several alkyne-fluorophores, permitted to analyse the influence of diverse fluorophores and their linker on the antifungal activity. Thus this strategy was successfully applied to the synthesis of unprecedented fluorescent ECs to visualize their interaction with fungal cells by confocal microscopy.
This versatile methodology delivers the first fully synthetic fluorescent echinocandins, providing powerful tools to explore EC action and fungal resistance mechanisms.

P03

Artificial DNAzymes for asymmetric oxidations

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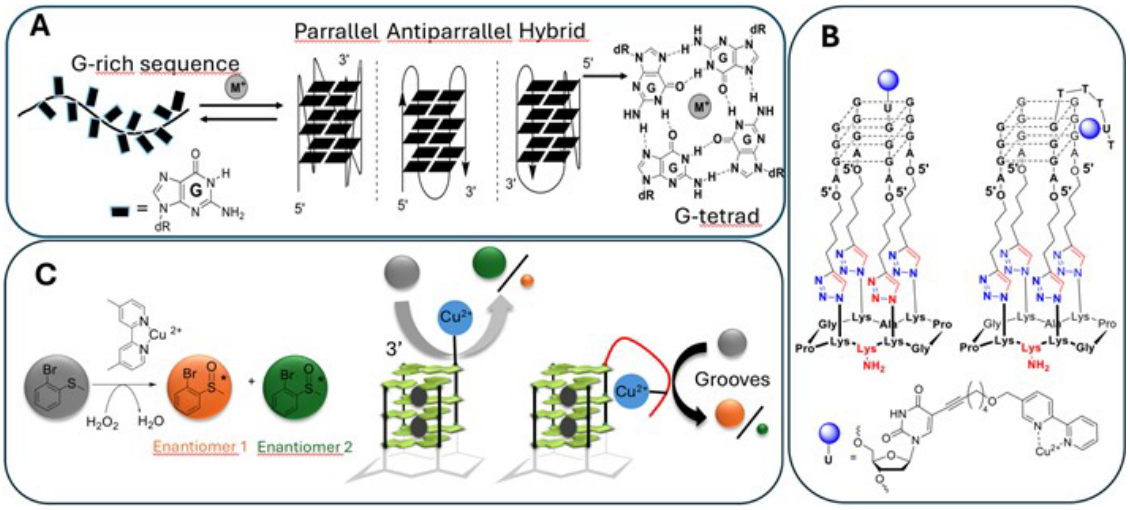
The development of artificial metalloenzymes (ArMs) represents a promising frontier in sustainable chemistry, aiming to combine the versatility of transition metal catalysis with the unparalleled selectivity of biological scaffolds. In this context, nucleic acids—specifically G-quadruplexes (G4)—have emerged as attractive, eco-compatible alternatives to protein-based scaffolds. Their unique, definable three-dimensional architectures offer a chiral microenvironment capable of inducing asymmetry in catalytic transformations.[1] However, the application of DNA-based catalysis is frequently hampered by the structural polymorphism of G4s. These structures often exist in a dynamic equilibrium of coexisting topologies,[2] a heterogeneity that negatively impacts the reproducibility, catalytic activity, and stereoselectivity of the resulting hybrid catalyst (Fig 1, A).
To address this structural ambiguity, recent strategies have employed peptide templates designed to immobilize guanine-rich oligonucleotides. These scaffolds force the DNA into stable, specific G4 topologies (G4 mimics). Previous studies have demonstrated that combining these constrained G4 structures with copper(II) complexes allows for the enantioselective oxidation of thioethers.[3] Despite these advances, the enantiomeric excesses (ee) obtained to date remain moderate. This is largely attributed to the non-covalent nature of the catalyst assembly; the insufficient interaction between the external metal complex and the DNA scaffold results in a poorly defined second coordination sphere, allowing the cofactor too much conformational freedom relative to the substrate. Furthermore, the stereoselectivity is strongly dependent on the precise location of the catalytic center within the G4 groove.
This PhD project, a collaborative effort between the Département de Chimie Moléculaire (DCM) and the Laboratoire de Chimie et Biologie des Métaux (LCBM), addresses these limitations through a novel strategy: the covalent conjugation of the copper complex to specific, pre-determined regions of the G4 mimic (Fig 1, B). By transitioning from supramolecular assembly to covalent anchoring, we aim to rigidly position the active metal center within the chiral environment of the DNA.
This poster presents the design and synthesis of these new covalent artificial metalloenzymes. We describe the specific synthetic pathway developed to introduce a copper(II) 4,4'-dimethyl-2,2'-bipyridine cofactor directly onto the oligonucleotide backbone. This site-specific functionalization is achieved via solid-phase synthesis using a custom-designed modified phosphoramidite building block. The structural integrity and topology of the resulting conjugates are subsequently validated using Circular Dichroism (CD) and UV-melting experiments to ensure the G4 architecture is preserved after conjugation.
The core objective of this strategy is threefold: (i) to eliminate non-enantioselective background reactions by preventing metal leakage, (ii) to strictly control the reaction orientation by targeting specific attachment sites (Fig 1, C), and (iii) to expand the catalytic scope. We report preliminary results comparing the activity of these covalent systems against non-covalent analogues in sulfoxidation reactions. Furthermore, we explore the versatility of these metalloenzymes in more challenging transformations, specifically the enantioselective epoxidation of olefins.



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

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P04

Association synergique antibiotique-inhibiteurs de biofilm pour une antibiothérapie contre Pseudomonas Aeruginosa

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Pseudomonas aeruginosa (PA), bactérie à Gram négatif largement répandue en milieu hospitalier, est responsable d'infections chroniques graves et parfois fatales chez les patients atteints de mucoviscidose. Résistante à de nombreux antibiotiques conventionnels, PA est classée comme pathogène prioritaire par l'Organisation mondiale de la santé en 2024.[1] Le mécanisme de résistance le plus redoutable de cet agent opportuniste repose sur la formation de biofilms,[2] un mode de vie multicellulaire qui protège la bactérie à la fois de l'action des antibiotiques et du système immunitaire de l'hôte.
Le fer,[3] en tant que nutriment essentiel, et les lectines (LecA et LecB), impliquées dans la reconnaissance protéine–glycane des cellules hôtes,[4] jouent un rôle clé et concerté dans le contrôle de la formation du biofilm. Sur la base de résultats préliminaires obtenus au sein du laboratoire LG2A UR7378,[5] nous avons développé à la fois de petites molécules et des glycoclusters spécifiquement conçus pour interagir avec la structure du biofilm et inhiber de manière synergique la reconnaissance lectine–glycane ainsi que l'acquisition du fer.
Par ailleurs, ce travail portera également sur la modulation de l'antibiotique utilisé dans l'antibiothérapie contre Pseudomonas aeruginosa, dans le but d'optimiser son efficacité en combinaison avec ces nouvelles approches anti-virulence. Cette stratégie thérapeutique est innovante car elle cible des systèmes de virulence extracellulaires, ce qui pourrait limiter l'émergence de résistances, un inconvénient majeur des thérapies antibiotiques conventionnelles.

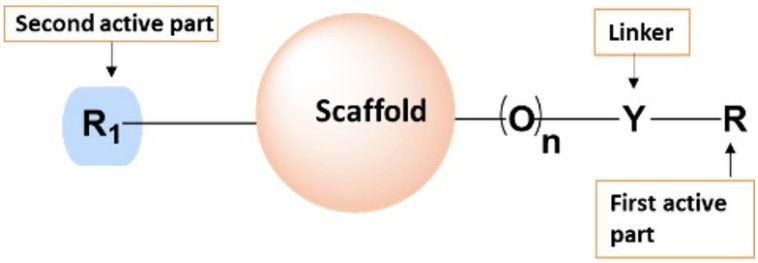

Figure 1: Modèle structural de glycoclusters doubles

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P05

Bioorthogonal Fluorogenic release of isocyanates in cells

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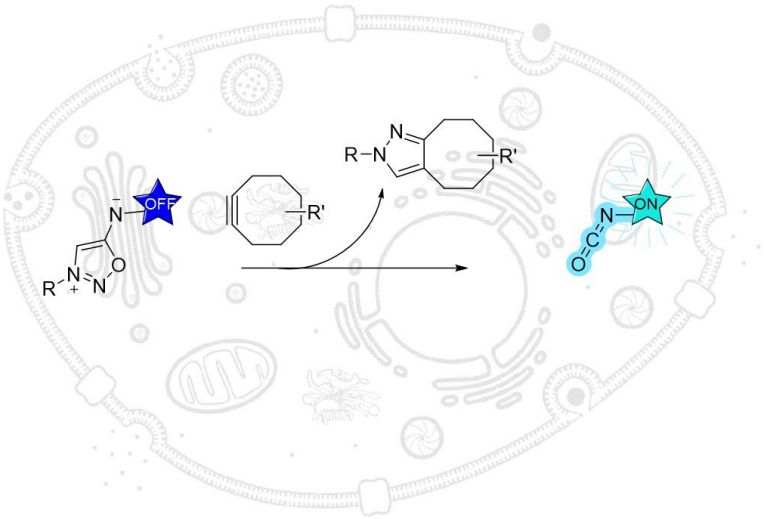
Sydnonimines belong to the mesoionic family, closely related to sydnones with the key distinction of containing a nitrogen atom at position 6. Discovered in the 1950s[1] and further developed in the 1970s for their biological properties, some of them have been approved as drugs.[2] Renewed interest in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



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P06

Carbon Dots pour la délivrance de siARN et la PDT améliorée : Application à la Dermatite Atopique

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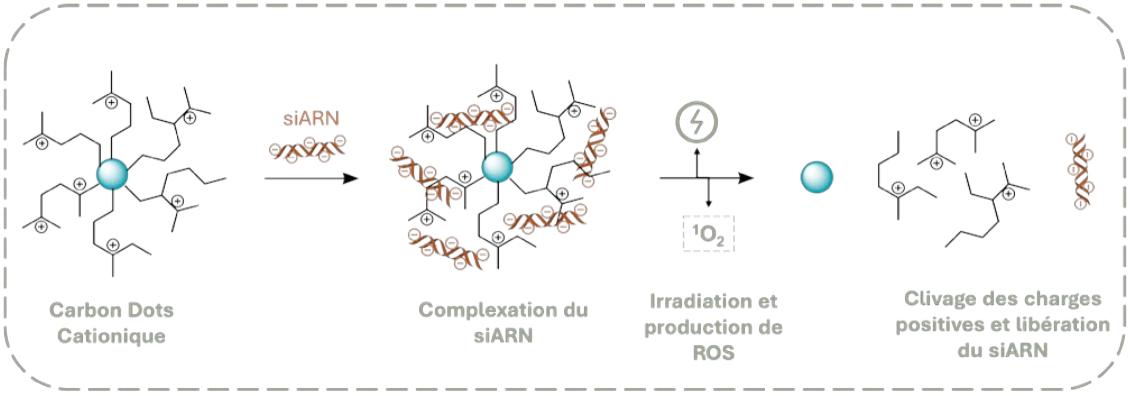
La Dermatite Atopique (DA) est une maladie inflammatoire de la peau qui affecte 15 à 20% des enfants et environ 3% des adultes.[1] L'objectif est de fournir une alternative non-invasive aux traitements actuels, qui sont souvent chers, nécessitent des doses régulières et peuvent provoquer des effets indésirables.[1]
La stratégie adoptée est de moduler la réponse immunitaire mise en cause dans la DA par l'action de siARN.[2] Le siARN libre pouvant être rapidement dégradé par les nucléases ayant des difficultés à traverser la membrane cellulaire il est nécessaire de vectoriser le siARN grâce à des nanoparticules.[3]
Les nanoparticules utilisées dans ce projet sont des « Carbon Dots » (CD), préparées à partir de polymères de polythiophène cationiques. Ce type de nanoparticule peut être utilisée dans certains traitement comme la thérapie photo-dynamique (PDT)[4] Ce qui est rendu possible de par leur haute stabilité, leur bonne solubilité en milieux aqueux, leur biocompatibilité, leur faible toxicité et leur propriétés photophysiques.[5] Les polymères de base sont obtenu à partir de blocs de base aromatiques contenant des fonctions permettant une post-fonctionnalisation.
Après avoir synthétisé les nanoparticules, les tailles des objets sont analysées par Dynamic Light Scattering (DLS) et STEM (Scanning Transmission Electron Microscopy) et le potentiel Zeta est déterminer par Zetasizer. Les propriétés photophysiques ont également été évaluées : les spectres d'absorbance, d'émission et d'excitation, ainsi que les rendements quantiques de fluorescence et de génération d'oxygène singulet. Les propriétés de complexations de ces nanoobjets avec des siARN thérapeutiques seront étudiés dans un second temps ainsi que leur application au traitement de la DA par PDT combinée à la libération de siARN thérapeutiques.



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P07

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

Mélanie LAQUEMBE (CEA Paris-Saclay) Léa MADEGARD (CEA Paris-Saclay)

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

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P08

Combining gold and visible light in catalysis: a new route for heterocycle skeletons

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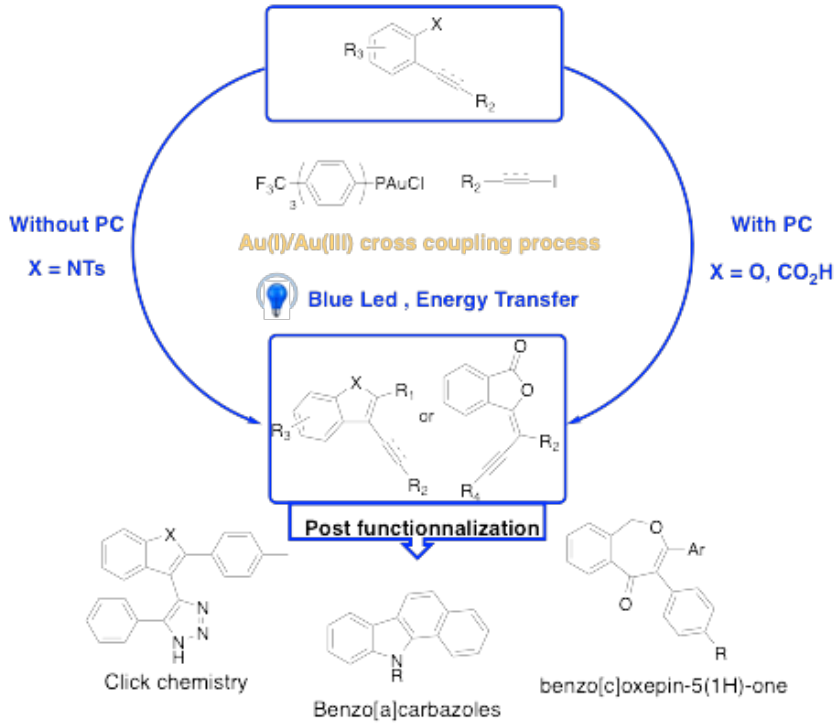
Over the past few decades, homogeneous gold catalysis has become a powerful and versatile tool for forming C–C and C–heteroatom bonds and for obtaining compounds of interest.[1] In most cases, the gold catalyst acts as a soft π-Lewis acid and selectively activates a carbon–carbon multiple bond of the substrate, followed by intramolecular or intermolecular addition of a nucleophile. The final step consists of protodeauration of the resulting gold intermediate to form the reduced product.[2] One method of post-functionalizing this intermediate is to engage it in a cross-coupling reaction. Unlike Pd(0) complexes, gold(I) complexes have shown some reluctance to undergo oxidative addition,[3] unless special ligands on gold(I), reagents, or reaction conditions are used. We have developed a new approach to overcome this obstacle. Under visible light irradiation, with or without a photocatalyst, we were able to excite a vinyl–gold intermediate complex to its triplet state, thus allowing the oxidative addition of an iodinated electrophile to afford Csp^2–Csp coupling products after reductive elimination. This enabled us to obtain a wide range of indoles, furans, and lactones which, after post-functionalization, allowed the synthesis of the core of biologically interesting compounds.[4]`



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P09

Désassemblage moléculaire pour la détection fluorogénique des phosphates biologiques

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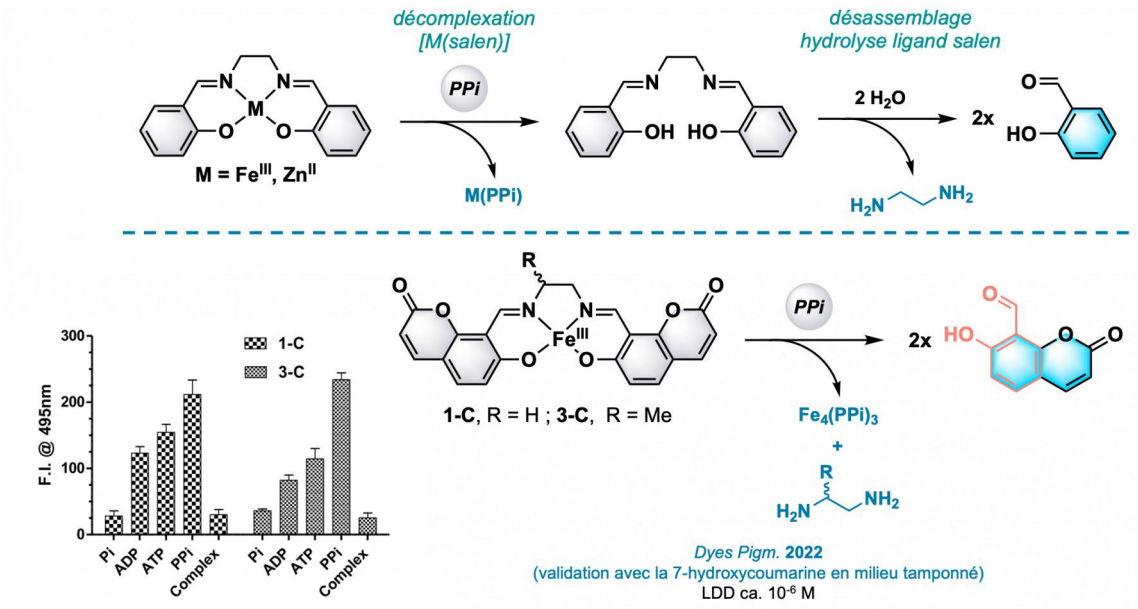
La détection efficace et sélective des phosphates biologiques (principalement les anions phosphate (Pi) et pyrophosphate (PPi)) est un sujet d'importance du fait de son large spectre d'applications : (1) bioanalyse des acides nucléiques (e.g., séquençage de l'ADN, PCR, ...), (2) biomarqueurs pour le suivi/diagnostic de certaines pathologies osseuses (e.g., hypophosphatémie et arthropathie familiale à cristaux de pyrophosphate de calcium (CPPD)), et (3) essais enzymatiques dans les domaines des biotechnologies ou du diagnostic. Comme c'est souvent le cas avec beaucoup d'autres analytes biologiques, une attention toute particulière a été portée aux approches de détection moléculaire capitalisant sur les caractéristiques avantageuses de la fluorescence. Ainsi, de nombreux senseurs fluorogéniques plus ou moins sélectifs de l'anion Pi ou PPi ont été développés[1] ; les processus de reconnaissance sont toujours fondés sur des interactions non-covalentes et potentiellement réversibles (approche dite "chemosensor") ce qui peut impacter la qualité des résultats pour des applications réalisées dans des milieux biologiques complexes (interférences biologiques possibles, problèmes de sélectivité)[2]. Idéalement, la mise au point d'une approche de type ABS ("activity-based sensing")[3] exploitant la réactivité chimique de l'analyte à détecter dans le contexte d'une sonde fluorogénique de type "chemodosimeter", activée selon des processus chimiques non réversibles, permettrait d'accéder à des outils de détection plus performants. Toutefois, il faut surmonter l'écueil lié à la très faible réactivité nucléophile des phosphates, en particulier en milieu aqueux. Ainsi, nous avons mis en œuvre une approche de type ABS fondée sur des processus de décomplexation métallique et de désassemblage moléculaire, et inspirée de celle proposée par le groupe du Prof. Felix H. Zelder[4]. Ainsi des complexes métallo-salen originaux ont été envisagés pour la détection fluorogénique de l'anion PPi via leur désassemblage conduisant au final à la libération d'un fluorophore à phénol ortho-formylé (i.e., fluorophores à motif ortho-salicylaléhyde)[5]. Une étude de la relation structure/réactivité fluorogénique a été réalisée afin d'identifier les meilleurs candidats (complexes salen de Fe(III)). La synthèse, les propriétés spectrales et les performances en détection (PPi) de ces "chemodosimeters" non usuels seront présentées ainsi que les pistes d'amélioration actuellement envisagées.



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P10

Design and synthesis of RED-SMU1 disruptors as new antiviral agents against Influenza A virus

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Influenza-A virus (IAV) is an infectious respiratory disease affecting annually billions of people across the globe and causing more than 300,000 deaths. Various therapies are currently being used for the treatment of IAV, but resistant strains have already been found against most of them. Host Directed Therapy, an emerging therapeutic strategy consisting in targeting a host protein complex instead of the virus itself, represents a promising avenue for the development of broad-spectrum antiviral drugs and an innovative approach to face the ongoing challenge posed by IAV.

In this context, our team focused on the Red-SMU1 complex, a human protein complex involved in splicing of pre-mRNA, which appeared to be essential for the replication of the virus and therefore representing a valuable target. Indeed, by disrupting this complex, the replication of Influenza-A can be reduced, thereby limiting its pathogenicity. In silico screening of more than 4,000 compounds followed by biological evaluation of the best candidates, allowed the identification of the compound ALG61 (Figure 1), a "hit" capable of inhibiting not only the formation of the Red-SMU1 complex but also the replication of the virus in cellulo. Starting from this compound, our aim is to design and synthesize RED-SMU1 disruptors. Several analogues were synthesized, either in the pyridopyrimidine family or in the naphthyridine family derived from it. These candidates were evaluated as antivirals against Influenza-A virus.

This work presents our latest results regarding the synthesis and the biological activity of these Red-SMU1 disruptors.

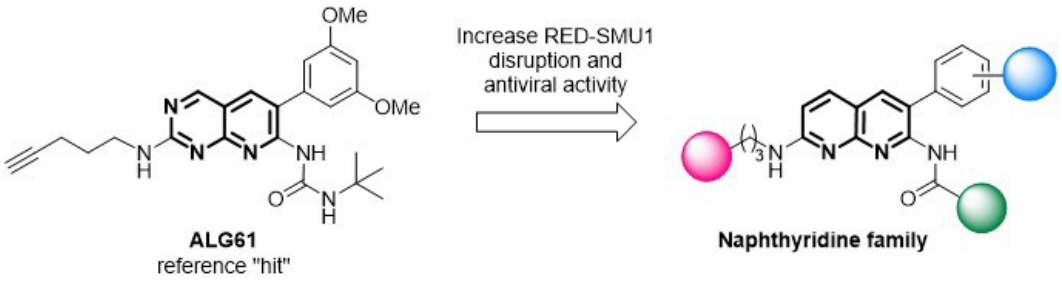

Figure : Structure of ALG61 and targeted compounds

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P11

Design of acridan based NIR fluorophores for imaging

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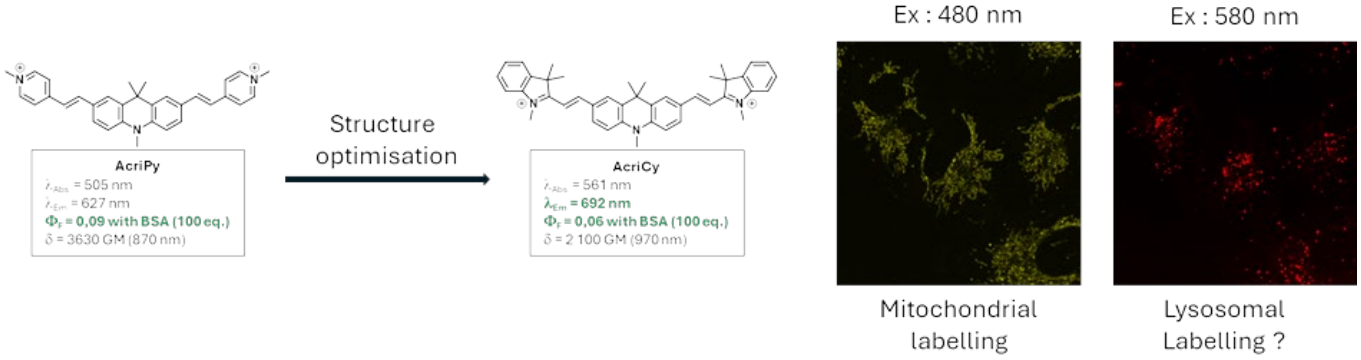
Over the past two decades, the development of increasingly efficient fluorescent molecules has become a key aspect of chemical biology. Indeed, these fluorophores are used as visualization tools for living systems in cellulo and in vivo in numerous applications, such as the development of diagnostic tools. In this context, fluorophores capable of simultaneously absorbing two lower-energy photons have been developed. The advantages of two-photon absorption (2PA) include near-infrared (NIR) excitation, reduced photodamage, and improved spatial resolution [1]. As a result, the development of fluorophores optimized for 2PA has been rapidly expanding.

It has been shown that conjugated structures bearing strong donor and acceptor groups and therefore displaying high polarizability, exhibit large two-photon absorption cross-sections [2]. However, such extended conjugated A-π-D type structures are often large and poorly soluble in aqueous media [3–4]. To address this, our team developed a first generation of small-sized, water-soluble 2PA fluorophores with remarkably high cross-sections, reaching up to 3630 GM for the compound Acri-Py [5].

The primary objective of our research is to modify the structure of Acri-Py to further improve its photophysical properties. Our strategy involves modifying the fluorescent core while preserving the Acridane core, which has already been optimized for fluorescence. In this regard, we have obtained new compounds exhibiting remarkable fluorescence properties in the NIR region, with excellent two-photon absorption cross-sections. Moreover, these compounds have proven to be powerful tools for confocal microscopy.



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P12

Design of antiviral prodrugs targeting the central nervous system to treat neurotropic viruses.

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Les Flavivirus constituent l'un des principaux groupes de virus responsables d'atteintes neurotropiques, c'est-à-dire d'infections du système nerveux central (SNC). Les Flavivirus sont des zoonoses transmises à l'homme directement par un vecteur arthropode (moustiques, tiques, vers, mouches) ou par l'intermédiaire d'un hôte-réservoir infecté (bétail). Le réchauffement climatique accroît les contacts entre les vecteurs infectieux, humains et bétails en favorisant l'activité saisonnière prolongée et l'expansion géographique des vecteurs. Parmi eux, l'encéphalite japonaise (JEV) est responsable de 30 000 à 50 000 cas par an, entraînant des séquelles neurologiques graves dans 30 à 50% des cas, avec un taux de mortalité pouvant atteindre 30%. A cela s'ajoute l'absence de traitements efficaces, faisant des infections aux Flavivirus un enjeu de santé publique majeur.

En effet, les analogues de nucléotides constituent une classe thérapeutique validée pour bloquer la réplication des flavivirus via l'inhibition de la polymérase virale, mais leur efficacité dans un contexte neurotropique est limitée par la barrière hématoencéphalique (BHE), qui restreint l'accès au SNC. Cette barrière se caractérise à la fois par une forte imperméabilité, liée à la présence de jonctions serrées entre ses cellules endothéliales, et par l'activité de transport dynamique assurant l'efflux de nombreuses molécules exogènes via des transporteurs spécialisés (SLC).

L'enjeu des infections neurotropes réside donc dans l'adressage ciblé du traitement au système nerveux central et le franchissement de la BHE. Le développement d'un système d'adressage spécifique au SNC, compatible avec les analogues de nucléotides, s'avère donc nécessaire car aucun système de ce type n'existe à ce jour.

Pour répondre à cet enjeu, nous développons d'une part un nouveau type de prodrogues ciblées d'analogues de nucléotides détournant à nôtre avantage les transporteurs (SLC) surexprimés à la BHE. D'autres part, nous concevons les outils nécessaires à leur étude et caractérisation : analyses HPLC et LC-MS in vitro, évaluation du clivage enzymatique et du devenir métabolique des analogues de nucléotides, modèles cellulaires 3D de la BHE et modèles murins infectés.

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P13

Design of Artificial Peptide Helices via Heterocycle- Editing

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Five-membered heterocycles are ubiquitous motifs found in both natural products and synthetic compounds, including catalysts, dyes, and pharmaceuticals. Their conformational rigidity and ability to engage in various non-covalent interactions enable fine control over local geometry and strongly influence molecular properties and biological activity.

In this context, we previously introduced heterocyclic γ-amino acids based on a thiazole core, termed ATCs, which stabilize an artificial γ-peptide fold mimicking the rarely populated 3_{10}-helix in proteins plays critical roles in molecular recognition and is found in enzyme active sites including serine proteases and kinases. The ATC oligomers adopt a left-handed 9-helix, stabilized by thiazole cyclic constraints, regular nine-membered hydrogen bonds, and attractive 1,4-S···O stereoelectronic interactions involving the thiazole ring.

Seeking simple strategies to switch γ-peptide architectures, we introduce here "heterocycle-editing" as a simple yet powerful approach for programming peptide folding. By selectively modifying heteroatoms within the five-membered aromatic rings, first through sulfur/nitrogen permutation in the thiazole, and subsequently by nitrogen-to-oxygen substitution to generate oxazole-based γ- peptides, we tune key local stereoelectronic interactions between the heterocycle and the peptide backbone. These subtle modifications unwind the canonical 9-helix and ultimately give rise to a straight and stable 7-helix featuring a unique spatial rearrangement of functional groups, with no known natural counterpart. These first examples demonstrate that fine stereoelectronic tuning through judicious heterocycle selection can unlock previously inaccessible peptide secondary structures.

P14

Design of new N-substituted-4-hydrazino-7-nitrobenzofurazan as fluorescent probes and active reagent for colon cancer diagnostic and prevention

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Colorectal cancer is a major public health concern for which dietary factors such as red and processed meat consumption seem to play a prominent role. Heme iron, which is present in high concentration in these food products, has been reported to play a role in colorectal cancer promotion in animal studies. Its role in colorectal cancer initiation has also been established in our previous work [1]. Heme iron is involved in several biological mechanisms which lead to the formation of reactive oxygen species such as superoxide ion and hydroxyl radical and cell damage as a consequence of oxidative stress.
At the cellular level, an increase in oxygen and nitrogen species can cause protein oxidation resulting in formation of protein carbonyls. Protein carbonylation results in irreversible modifications of amino acid side chains and leads to alterations in protein expression and turnover and modulation of cell signaling. Thus, the quantification of carbonyl content in cell proteins is a useful indicator of oxidative damage that occurs during pathological processes such as colorectal cancer.
More recently, our group showed that the probe 7-hydrazino-4-nitrobenzofurazan (NBDH) can be used as a rapid, sensitive, and accurate fluorimetric method for the assessment of protein carbonyl levels in biological samples under oxidative stress. This method is based on the reaction of protein carbonyls with NBDH to form highly fluorescent derivatives via hydrazone formation.[2]
In addition to this, previous work showed that NBDH skeleton shows promising abilities for selective binding to toxic metal ions such as nickel and copper to form complex structures. [3] The binding properties express spectroscopic and visual responses that can be studied by UV-Vis titration. The aim of this project is to develop NBDH-based probes able to bind with heme iron in colorectal cancer cells to prevent oxidative stress.
In this context, we will present here the synthesis of various N-substituted-4-hydrazino-7-nitrobenzofurazan derivatives (R-NBDH). Here, we report the first results about the development of molecular probes and the chelating abilities. We believe that this new series of reagents could be useful for the rapid determination of relevant carbonyls in pathophysiological conditions and the prevention of colorectal cancer development thanks to iron chelating and oxidative stress inhibition.

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P15

Design of photolabeling probes to identify the target of anti-Alzheimer compounds

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A phenotypic screening was performed in our laboratory to uncover compounds targeting the two main pathological hallmarks of Alzheimer's disease: amyloid deposits and neurofibrillary tangles. Several molecules showed a significant decrease in the secretion of Aβ peptide, involved in amyloid deposits formation, as well as in Tau protein phosphorylation, both in vitro and in vivo. From these initial hits, a pharmacophore was identified, guiding the synthesis of additional compounds. Despite these advances, the molecular target and mechanism of action of these compounds remain to be elucidated in order to better understand their activity. Our approach aims to identify this target using a strategy based on bioorthogonal chemistry, which employs a photoaffinity group to form a covalent bond with the target. To this end, we designed and synthesized several probes derived from the initial chemical scaffold, functionalized by introducing a photoactivatable group of the diazirine type, as well as moieties compatible with click chemistry. The bioorthogonal functions were positioned at different locations on the chemical structures, in accordance with structure-activity relationships (SAR). Various types of diazirines were explored to optimize the photocoupling yield, and a photochemical study was conducted to determine the most effective wavelength for generating the reactive species. Each probe was then tested to assess its activity on APP metabolism before being used in the protocol combining photocoupling, click chemistry, and proteomic analysis to identify the molecular target.

P16

Development of a Peptide Receptor Radionuclide Therapy (PRRT) strategy for Poor-Prognosis Cancers

M Valisoa Niaina RABENANDRASANA (Sorbonne Université) Philippe KAROYAN (Sorbonne Université)

Currently, the standard treatment for cancer includes surgery, external radiotherapy and chemo- and/or immunotherapy. With the need to offer more personalized approaches, tumor-targeting strategies have emerged. Among these, internal radiotherapy enables the delivery of a cytotoxic dose of radiation directly to tumor cells, sparing healthy tissues. This requires vectors capable of selectively addressing cancer cells. Peptides are powerful tools in this context, as they are easy to synthesize, engineer, and functionalize, notably to construct radiopharmaceuticals targeting specific receptors.

With this aim, CD47 is an ideal target. It is a transmembrane protein involved in immune evasion through interaction with SIRPα, and is overexpressed in numerous tumors such as triple-negative breast and pancreatic cancers. Its high expression, associated with poor prognosis, makes it an attractive candidate for Peptide Receptor Radionuclide Therapy (PRRT). Indeed, compared to monoclonal antibodies, peptides offer better tumor tissue diffusion, lower immunogenicity, and pharmacokinetic profiles that are particularly well suited for theranostic applications. Their rapid clearance and shorter half-lives align with the temporal dynamics required for effective imaging and therapy using radiometals such as ^{68}Ga or ^{177}Lu.

To develop high-affinity peptides targeting CD47, we draw inspiration from its known ligands - SIRPα, monoclonal antibody B6H12, and thrombospondin-1 (TSP-1): we designed libraries of peptide mimics that are optimized through structure-activity relationship studies and molecular modeling. These peptides are functionalized with bifunctional chelators to enable radiometal complexation and subsequent evaluation as imaging and therapeutic agents.

This presentation will highlight the rational design strategy and pharmacological evaluation of novel CD47-targeted peptides as part of the PanCaIKS (Pan-Cancer Imaging and Killing Strategy) project, with a focus on their potential for clinical translation in the PRRT field.

Acknowledgments: ANR and χ-PHARMA for funding this project

P17

Development of Bifunctionnal & Bioorthogonal Nanoplatforms Based on Calix[4]arenes-Coated Gold Nanoparticles for Advanced Bioconjugation

Julie JANSSENS (Université libre de Bruxelles) Gilles BRUYLANTS (Université libre de Bruxelles) Ivan JABIN (Université libre de Bruxelles)

Gold nanoparticles (AuNPs) have been extensively investigated for biomedical applications due to their unique optical properties, biocompatibility, and ease of surface functionalization. Their high surface-area-to-volume ratio enables dense ligand grafting, rendering them particularly attractive for theragnostic applications. Conventional AuNP functionalization strategies rely on thiolated ligands; however, the inherent lability of the Au–S bond complicates the formation of stable and well-defined mixed monolayers for further conjugation and use in biological media.

To address these limitations, our group has developed an alternative surface functionalization strategy based on calix[4]arene derivatives, which can form a robust and compact monolayer stabilized by multiple covalent anchoring points onto the AuNP surface. In addition, the small rim of the calix[4]arenes can bear different reactive groups, including carboxylic acids, azides, and alkynes, enabling easy post-functionalization with (bio)molecules.

In parallel, the growing interest in multifunctional nanoplatforms has highlighted the need for orthogonal reactions that proceed without cross-reactivity. In this context, bioorthogonal reactions are particularly attractive because of their high specificity, rapid kinetics and compatibility with complex biological environments. Among them, the strain-promoted alkyne–azide cycloaddition (SPAAC) and the inverse electron demand Diels Alder (iEDDA), the fastest bioorthogonal reaction, have shown high potential for biomedical applications.

Despite these advances, few studies report bifunctional AuNPs able to perform orthogonal reactions, including bioorthogonal chemistries. It often remains limited to a single reaction type and rely on conventional coupling reactions with a poor control over surface composition.

Here, we present a versatile nanoplatform capable of performing bioorthogonal reactions, such as SPAAC or iEDDA, with precise control over the ratio of functional groups, overcoming the limitations of thiol-based approaches. We developed the successful synthesis of bifunctional AuNPs bearing two different molecules coupled through orthogonal reactions while preserving the activity of both biomolecules. These results highlight the strong potential of this strategy for the design of advanced multimodal AuNP systems for targeted imaging and therapy applications.

P18

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

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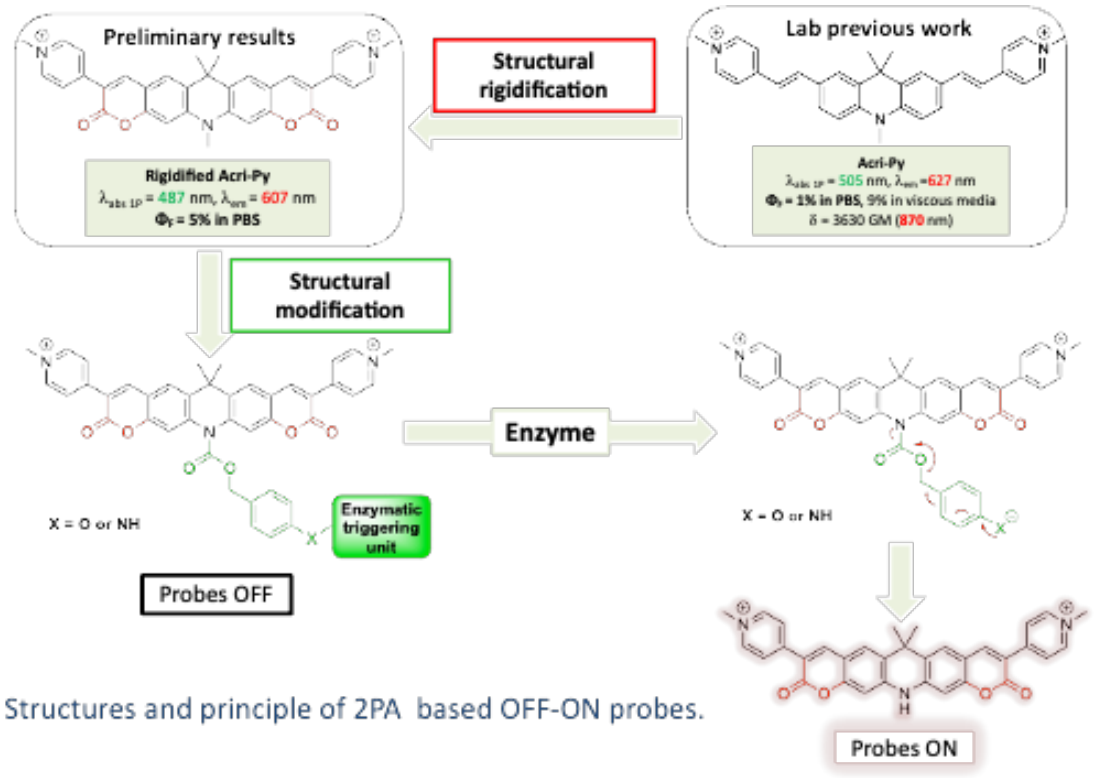
Surgery is the main treatment for most cancers. However, conventional surgical techniques often suffer from low contrast between cancer and healthy tissues, which increases the risk of leaving residual tumour cells and leads to cancer recurrence. To overcome this limitation, fluorescence-guided surgery 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].



Structures and principle of 2PA based OFF-ON probes.

Figure : Structures and principle of 2PA based OFF-ON probes

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P19

Development of new copper ionophores: Variation of coordinating groups

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To combat the resistance of certain cancers to current treatments, the search for new and innovative therapeutic agents is essential. One of the solutions being considered is the use of ionophores, i.e. molecules capable of binding and selectively transporting an ion across a lipid bilayer. These compounds would disrupt homeostasis and thus leading to cell death. Many Cu^{2+} ionophores have been tested as cytotoxic agents. However, in the intracellular environment, copper is present in the form of Cu^{+} and copper transport proteins also transport copper as Cu^{+}. The use of Cu^{+} ionophores could therefore impact cells differently compared to Cu^{2+} ionophores. Recently, the very first synthetic Cu^{+} ionophores were developed in our laboratories. They are based on a calixarene structure with two methyl-imidazole groups capable of coordinating Cu^{+} in a linear geometry. However, the selectivity of these ionophores for Cu^{+} compared to Cu^{2+} was still to be investigated, which is also the case for the optimal affinity. Therefore, the nature and number of coordinating groups on the calixarene platform will be varied, which will impact the coordination strength and geometry, and potentially the selectivity. Several compounds have been synthesized and ^{1}H NMR titrations were used to study the complexation of Cu^{+} by these compounds. Studies in liposomes using specific fluorescent probes for Cu^{+} and Cu^{2+} allowed to study the transport activity and selectivity. Next, the transport activity by the ionophores will also be studied in cellular models such as yeast cells and their biological activity will be studied in cancer cells.

P20

Développement de sondes fluorogéniques basées sur des fluorophores à phénol rigidifiés pour des applications FGS

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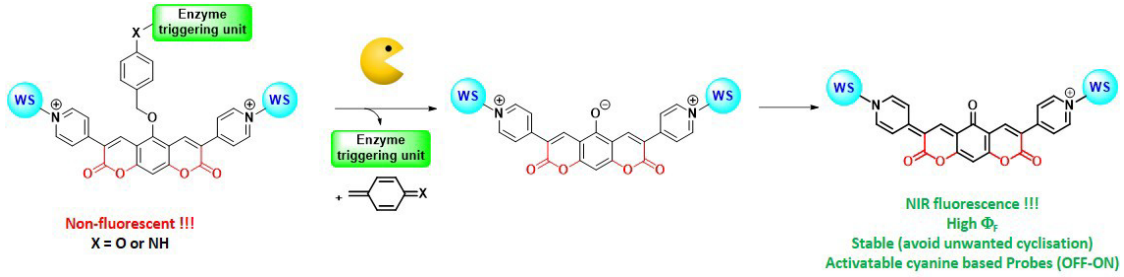
La chirurgie guidée par fluorescence (Fluorescence-Guided Surgery, FGS) constitue une approche prometteuse pour améliorer la détection peropératoire des tissus pathologiques et la précision des gestes chirurgicaux [1]. Cette technique repose sur le développement de sondes moléculaires capables de générer un signal fluorescent spécifique des tissus pathologiques. Les sondes fluorogéniques activables, capables de générer un signal fluorescent uniquement en présence d'une activité enzymatique spécifique, représente ainsi un levier majeur pour accroître la spécificité du contraste tumoral.
Dans ce contexte, nous nous intéressons à améliorer les propriétés spectrales de fluorophores connus en utilisant une stratégie de rigidification [2], [3]. Ces fluorophores seront ensuite modifiés afin de les rendre fluorogéniques et sensibles dans certains contextes pathologiques à la nitro-réductase, utilisée comme cible enzymatique pour la FGS.
Nous avons ainsi développé à partir d'un dérivé salisaldéhyde une voie de synthèse convergente permettant l'accès à une librairie de molécules. Une première sonde fluorogénique a été ainsi obtenue puis validée in vitro en présence de la nitro-réductase, ce qui a permis d'établir la preuve de principe.



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P21

Elucidation des relations structure-fonction des complexes LRRK2/Phosphatases dans la maladie de Parkinson

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La Leucine Rich Repeat Kinase 2 (LRRK2) apparaît comme un déterminant crucial de la maladie de Parkinson (MP) et constitue donc une cible intéressante. Son état de phosphorylation est fortement corrélé à la progression de la maladie, régulée à la fois par elle-même (sites autologues) et par des kinases en amont (sites hétérologues). Nos collaborateurs et notre équipe ont montré que la déphosphorylation de LRRK2 au niveau des clusters de sérine (S935 et S910) dans la P-loop contribue à la pathogenèse de la MP, comme le montrent les échantillons cérébraux post-mortem. L'équipe a identifié plusieurs sous-unités des protéines phosphatases Ser/Thr (PP1 et PP2A) comme régulateurs clés de la déphosphorylation de LRRK2, mais les mécanismes d'interaction précis restent difficiles à cerner. Nous émettons l'hypothèse que la modulation de ces interactions pourrait préserver son état de phosphorylation basal neuroprotecteur. Notre projet vise à élucider les relations structure-fonction au sein des complexes LRRK2:Phosphatases et à étudier l'impact des mutations associées à la MP sur ces interactions. À l'aide de tests de liaison protéine-protéine (NanoDSF, thermophorèse à micro-échelle, pull-down, Co-immunoprécipitation), nous cherchons à caractériser le mode de liaison entre LRRK2 et les phosphatases. Cette approche globale dévoile les mécanismes moléculaires des interactions LRRK2:PP1/PP2A, fournissant des informations sur leur rôle dans la pathogenèse de la MP. Ces résultats jettent les bases du développement d'outils thérapeutiques permettant de comprendre et d'identifier plus précisément les interfaces de ces complexes, mais aussi de mettre en place une campagne de criblage afin d'identifier des modulateurs potentiels.

Dans cette étude, nous avons optimisé et développé la production et la purification de LRRK2, ses domaines et les sous-unités catalytiques des phosphatases (PP1 et PP2A). La caractérisation de leur liaison a été réalisée grâce au développement du GST-pull down puis validée par co-immunoprécipitation (Co-Ip). Un test enzymatique a également été développé afin d'évaluer la capacité de certains peptides à moduler la phosphorylation de LRRK.

Plusieurs peptides de PPP1CA et PPP2CA ont été identifiés comme interagissant avec LRRK2 par Pepscan. L'interaction entre la protéine purifiée LRRK2 et PPP1CA ou PPP2CA a été démontrée par GST-Pull down, puis confirmée par Co-Ip. Les peptides identifiés par Pepscan ont ensuite été utilisés pour déplacer les complexes LRRK2:Phosphatases. Un déplacement de 40% du complexe LRRK2:PPP2CA pour l'un des peptides de PPP2CA à 1mM. Un effet similaire de 70%, sur le complexe LRRK2:PPP1CA a été observé avec l'un des peptides de PPP1CA à 1mM. La caractérisation de l'interaction des domaines de LRRK2 avec PPP1CA et PPP2CA a été réalisé par le Pull down et la Co-IP afin d'identifier les hotspots d'interaction des complexes LRRK2:Phosphatases.

Ces résultats montrent qu'il est possible de moduler les complexes LRRK2:Phosphtases. Ces peptides constituent des outils intéressants pour identifier plus précisément les hotspots d'interaction sur PPP1CA ou PPP2CA via la modulation, l'alascanning et la mutagenèse. Ils seront également utilisés dans un test enzymatique afin d'évaluer leur capacité à moduler la phosphorylation de LRRK2 et dans le but de développer une campagne de criblage.

P22

Engineering of near infra-red bioluminescent reporters for in vivo bioimaging and biosensing

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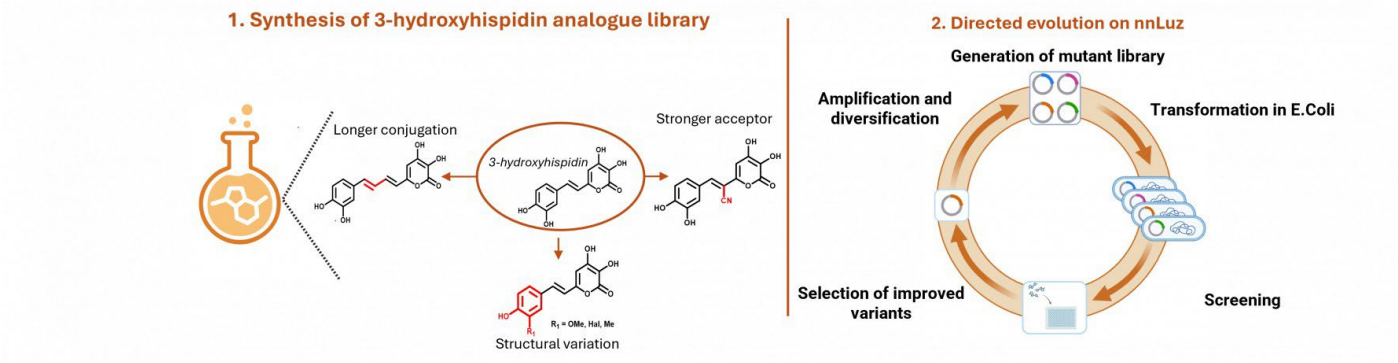
Bioluminescence is the production of light by living organisms via a chemical reaction between an enzyme (luciferase) and its substrate (luciferin). This natural phenomenon has been turned into a powerful laboratory technique to report on biological processes in cellular and animal models [1]. However, natural luciferins emit below 600 nm, a wavelength range where light is strongly absorbed by biological tissues. Hence the importance to develop far-red or NIR-emitting bioluminescent reporters which can be obtained by engineering the luciferin to tune its emission wavelength, combined with the engineering of the luciferase to ensure the compatibility between the enzyme and its modified substrate. In this project, we propose to explore a bioluminescent system from the N. nambi fungus, because of the small size (28.5 kDa) of its luciferase nnLuz and the simple structure of its luciferin, 3-hydroxyhispidin, which gives a green luminescence centered around 525 nm and shows potential for tunability. A small palette of 3-hydroxyhispidine derivatives with tunable colors has also been developed, suggesting some level of promiscuity for the luciferase if the 3-hydroxy-α-pyrone ring is conserved [2]. The first part of the project consists in synthesizing a library of luciferin analogs. The structure is that of a dipolar chromophore, and the luminescence can be red-shifted by applying known strategies: increase of the strength of the electron donor and of the length of π-conjugation. To obtain bright bioluminescent reporters, we will thus perform directed protein evolution of the nnLuz enzyme to optimize the binding and the reaction with the most promising new substrates. Libraries of protein mutants can be generated by random or saturation mutagenesis. As colony screening can allow high-throughput evaluation and screening of bioluminescence properties using camera-based imager [3], the constructed libraries will be expressed in bacteria. Camera-assisted colony screening allows the identification of variants with high bioluminescence efficiency. In addition to enhancing the brightness, the evolution of nnLuz may also lead to the discovery of orthogonal luciferases useful for multiplexing experiments.



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P23

Evaluation of the binding characteristics of [18F] 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 [18F]fluoroethoxybenzovesamicol ((-)-[18F]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-[18F]fluorobenzovesamicol ((-)-[18F]FBVM) that we compared to (-)[18F]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 (-)[18F]FBVM compared to (-)[18F]FEOBV.Our findings demonstrate that (-)[18F]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 [18F]FBVM in non-human primates (NHP) compared to (-)-[18F]FEOBV, another radioligand for the VAchT. The in vivo kinetics of [18F]FBVM and higher signal to noise ratio when compared to the (-)-[18F]FEOBV suggest that [18F]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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P24

Exploration of biodiversity for the discovery and design of antiviral cyclopeptides

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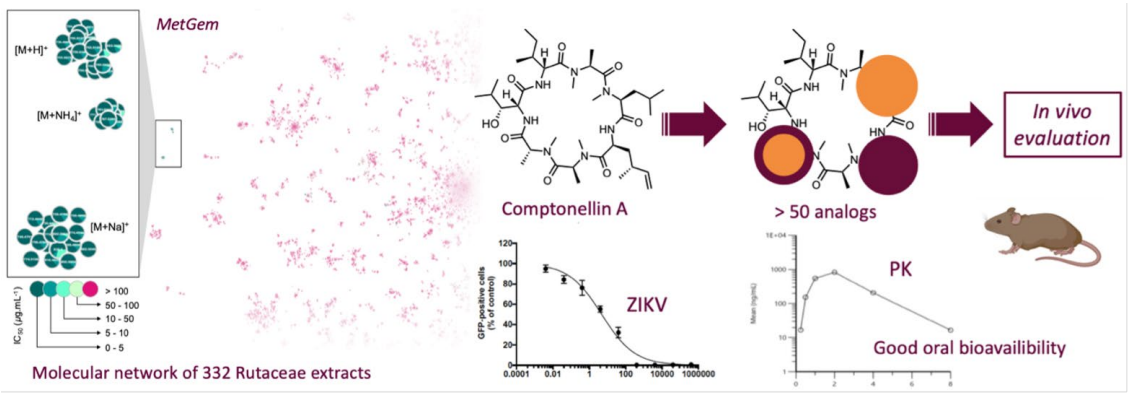
Viral diseases represent a major public health concern. The emergence of new viruses, such as coronaviruses, and the re-emergence of pathogens like dengue and Zika viruses underline the urgent need to develop effective treatments. For decades, the chemical diversity of plant metabolites has generated significant interest, particularly in medicinal chemistry, but it requires the development and application of innovative approaches.
In this context, a screening of 824 plant extracts from the ICSN extract library was conducted to evaluate their ability to inhibit the Zika virus, in collaboration with C. El Kalamouni (UMR PIMIT). Among these, eight extracts from phylogenetically related species demonstrated remarkable inhibitory activities. These extracts were analyzed using LC-HRMS/MS, and their metabolite content was organized and visualized as molecular networks using MetGem. This analysis revealed a group of ions specific to the eight active extracts. Targeted isolation of these compounds led to the identification of eight novel cyclopeptides, named comptonellins. Some of these cyclopeptides exhibited remarkable antiviral activities, in the nanomolar range, and were active against several viruses. Supported by SATT Paris-Saclay, over 50 analogs were designed to identify a lead candidate that is orally bioavailable.



P25

Exploring the IspG mechanism with innovative substrate analogues as a source of inspiration for new antibacterial strategies

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Antibiotics save millions of lives each year. However, antibiotic resistance is one of the biggest threats to public health as some bacterial infections impossible to treat with the existing therapeutic repertoire are emerging everywhere.[1] As a consequence, there is increasing urgency to discover new drugs with innovative modes of action, acting on new bacterial targets, to avoid entering into a 'post-antibiotic era'.

Targets that could be explored to combat antibacterial resistance are unstable and difficult-to-isolate essential bacterial enzymes, including certain metalloenzymes, that were not previously discovered due to lack of knowledge and technology to characterise them. IspG is such an enzyme. It is a [4Fe-4S] oxygen-sensitive metalloenzyme that is essential for the survival of numerous disease-causing microbes, including those posing a major challenge for new drug development. It is involved in the methylerythritol phosphate pathway that provide Isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP, Figure 1), key compounds for the synthesis of terpenoids. Importantly, IspG does not exist in humans and is therefore valuable targets for the development of new specific antibacterial drugs. IspG catalyses the conversion of 2-*C*-methyl-D-erythritol-2,4-cyclo-diphosphate (MEcPP) into (*E*)-4-hydroxy-3-methyl-but-2-enyl-1-diphosphate (HMBPP, Figure 1). This reaction is unprecedented and involves two one-electron transfers and a water elimination.

To address gaps in our understanding of the IspG catalytic mechanism, innovative substrate analogues were designed and evaluated in combination with the IspG metalloenzyme. These studies provided new mechanistic insights and, more importantly, led to the identification of highly potent and specific mechanism-based inhibitors. [2,3,4] The latter represent promising starting points for the development of novel antibacterial agents.

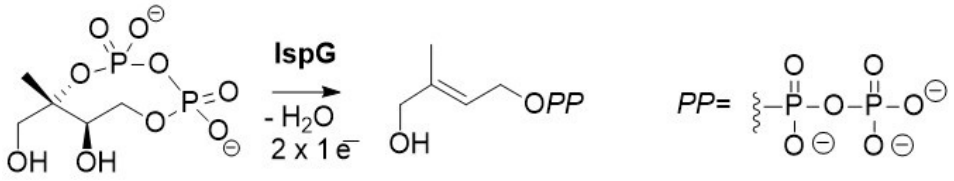

Figure : Reaction catalysed by IspG

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P26

Fluorescent probes for the detection of bacteria in body fluids

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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.

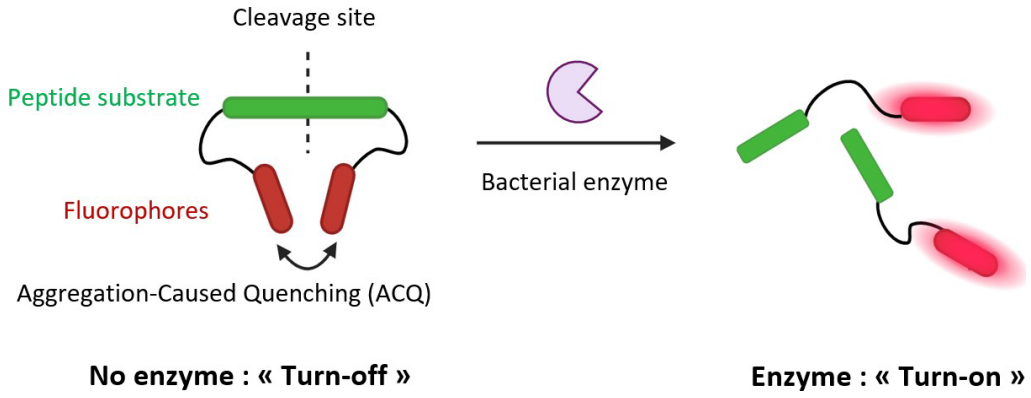

Figure : Principle of bacterial detection using fluorogenic dimeric probes

P27

Greffage de fragments d'anticorps à la surface de cellules par combinaison de glyco-ingénierie métabolique etchimie click bioorthogonale : vers des thérapies cellulaires innovantes

Lucie CAILLET (IC2MP)

Ce projet de thèse vise à développer une nouvelle méthode combinant chimie organique et chemobiologie pour ouvrir la voie à de nouvelles thérapies cellulaires anti-cancéreuses. Elle consiste notamment à greffer chimiquement des fragments d'anticorps à la surface de cellules immunitaires pour booster ou réactiver leurs propriétés thérapeutiques. Pour ce faire, des cellules seront modifiées par glyco-ingénierie métabolique, permettant ainsi l'expression d'une fonction click bioorthogonale à leur surface. Parallèlement, des anticorps seront digérés afin d'obtenir leurs fragments Fab, ceux-ci seront ensuite réduits puis modifiés par rebridging des ponts disulfures accessibles. En effet, des plateformes chimiques de type dibromopyridazinediones seront synthétisées et porteront une fonction click. L'introduction de ces plateformes au sein des Fab permettra leur greffage sur cellules modifiées, par réaction de click bioorthogonale. De plus, certaines plateformes seront synthétisées pour porter à la fois une fonction click et un agent immunomodulateur prévu pour ne se libérer que dans le micro-environnement tumoral. Cette stratégie permettra donc de créer des cellules immunitaires munies d'un agent de ciblage et dont l'activation sera spécifiquement restreinte à l'environnement tumoral, permettant une meilleure efficacité et une réduction des effets secondaires.

P28

Identification of new MASTL inhibitors for cancer therapy from a promising chemical scaffold

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Cancer remains one of the most lethal diseases known to Man1. Although numerous anticancer drugs have been developed and introduced into clinical use over the past decade, many of them present significant limitations, including complex side effects resulting from off-target interactions2. This has led medicinal chemists to develop new drugs that would bear a safer profile for patients. Herein, we describe the discovery of new Benzopyridoindoles, using high throughput screening against a nucleus located kinase, overexpressed in breast and prostate cancer. Our compounds exhibited high selectivity toward the target protein while demonstrating no detectable toxicity against healthy cells. This profile can be attributed to their specific binding mode to the kinase. However, given the complexity of the biomolecular structure, we first designed photoreactive probes to map the binding or docking site of our compounds3, thereby guiding our ligand optimization process from initial hits to lead compounds. A new chemical synthesis of these compounds is also described, using safer methodologies for scale up and hit to lead optimization purposes.

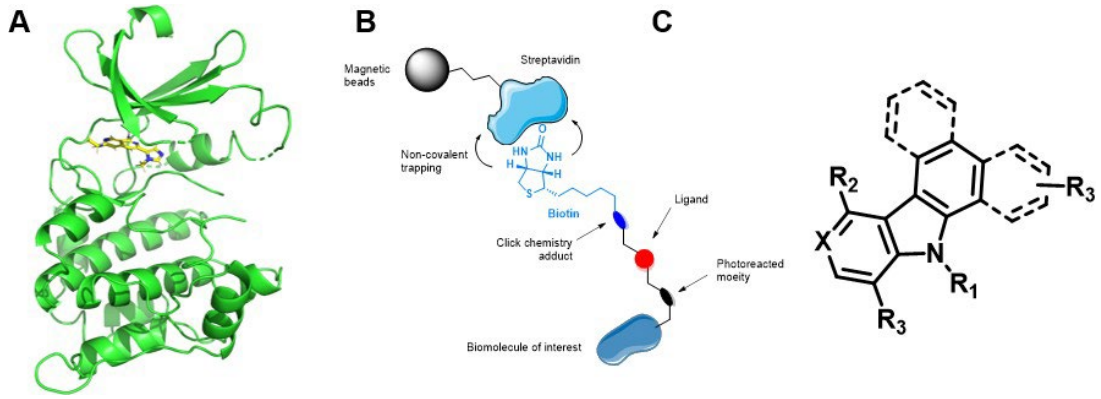

Figure : (A) PDB : 8V5H (B) Concept of photocrosslinking and pulldown strategy (C) Structure of our hit compound from HTS

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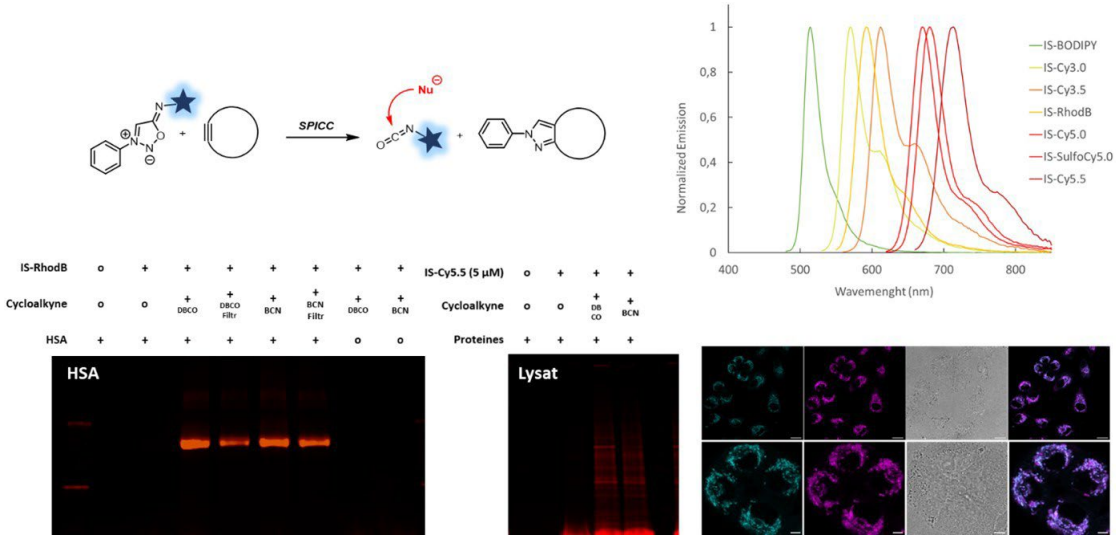
P29

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

Narjis OUAZZANI (ICSN, CNRS) Arnaud CHEVALIER (ICSN, CNRS) Frederic TARAN (CEA Paris Saclay)

Sydnonimines are a class of mesoionic dipoles that can undergo bioorthogonal cycloadditions with cyclooctynes, releasing reactive electrophiles (isocyanates). This unique reactivity positions them as promising tools for fluorogenic scavenging of endogenous cellular nucleophiles, including protein thiols and amines residues(1). The aim of this projet is therefore to develop, synthetize and use highly reactive sydnonimine-based probes for irreversible protein labeling in living cells. Among the possible applications of this strategy, we intend to explore permanent fluorescence labeling for advanced cell imaging.
A library of probes featuring various fluorophores was developed, spanning a broad spectrum of absorption and emission wavelengths. These chemical modifications were designed not only to modulate the optical properties but also to allow the targeting of specific subcellular compartments. Ex cellulo preliminary experiment conducted on Human Serum Albumin (HSA) and subsequentel ectrophoresis gel analysis (SDS-PAGE) have validated the labeling efficiency and selectivity of our probes thus confirming the covalent adduct formation and the robustness of the bioconjugation process. Additional experiments on A549 live cells including confocal microscopy experiments, and lysate analysis by SDS-PAGE demonstrated the biocompatibility of the IS-based probes and their ability to perform site-specific labeling in a cellular environment. The finalization of this work will provide a highly efficient, fluorogenic platform for site-specific protein labeling and the investigation of protein dynamics in living systems.



P30

L'arachidonyl-CoA dicte la spécificité de substrat de l'acyl CoA synthétase à longue chaîne 4 (ACSL4)

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La ferroptose est une forme de mort cellulaire régulée qui dépend de l'incorporation préférentielle d'acides gras polyinsaturés (AGPI) dans les membranes. L'acyl-CoA synthétase ACSL4 joue un rôle clé dans ce processus en activant préférentiellement certains AGPI, comme l'arachidonate (AA, 20:4ω-6). Pourtant, les paramètres enzymatiques décrits dans la littérature s'avèrent insuffisants pour rendre compte de cette spécificité.

Nous avons donc combiné des approches biochimiques, biophysiques et analytiques pour comprendre comment ACSL4 sélectionne ses substrats. Les mesures issues du suivi enzymatique (Km, Vmax, Kcat) n'ont révélé que de faibles différences entre les substrats, tandis que les mesures d'affinité de liaison ont permis de distinguer clairement les acides gras en fonction de leur longueur de chaîne et de leur degré d'insaturation.

Afin de refléter plus fidèlement la complexité biologique, nous avons développé un test de compétition par LC-MS permettant de suivre l'activité d'ACSL4 au sein d'un mélange contenant simultanément plusieurs acides gras. Cette approche a confirmé la hiérarchie établie grâce aux tests biophysiques, et a montré que l'arachidonyl-CoA, produit issu de la conversion de l'AA par ACSL4, inhibe l'enzyme vis-à-vis de la prise en charge de substrats de moindre priorité, comme notamment les acides gras saturés et monoinsaturés.

Dans leur ensemble, ces résultats fournissent une explication moléculaire à la spécificité d'ACSL4 pour les acides gras polyinsaturés, en mettant en évidence un mécanisme d'inhibition par le produit.

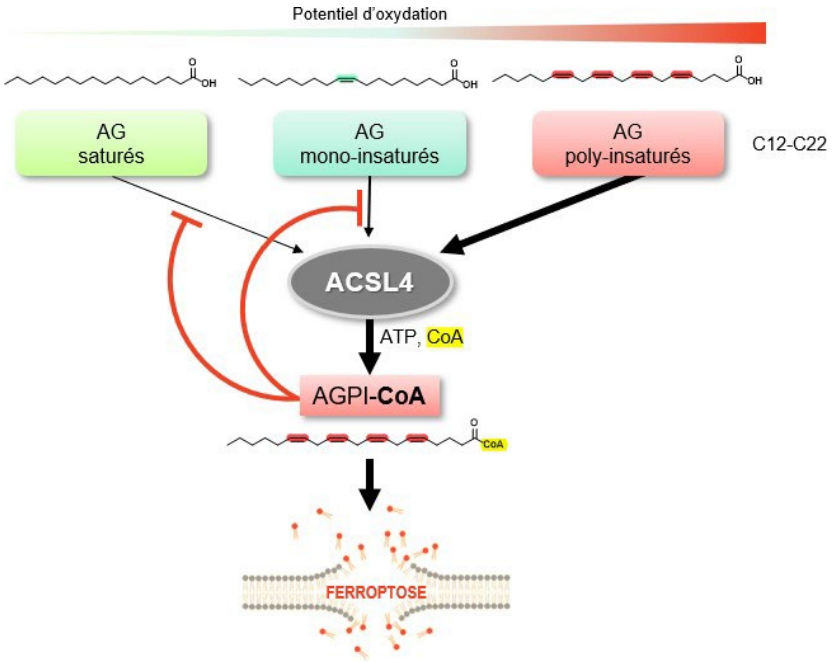

Figure : mécanisme d'inhibition d'ACSL4 par l'arachidonyl-CoA

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Ligation of oligonucleotides induced by Charge-Transfer interactions

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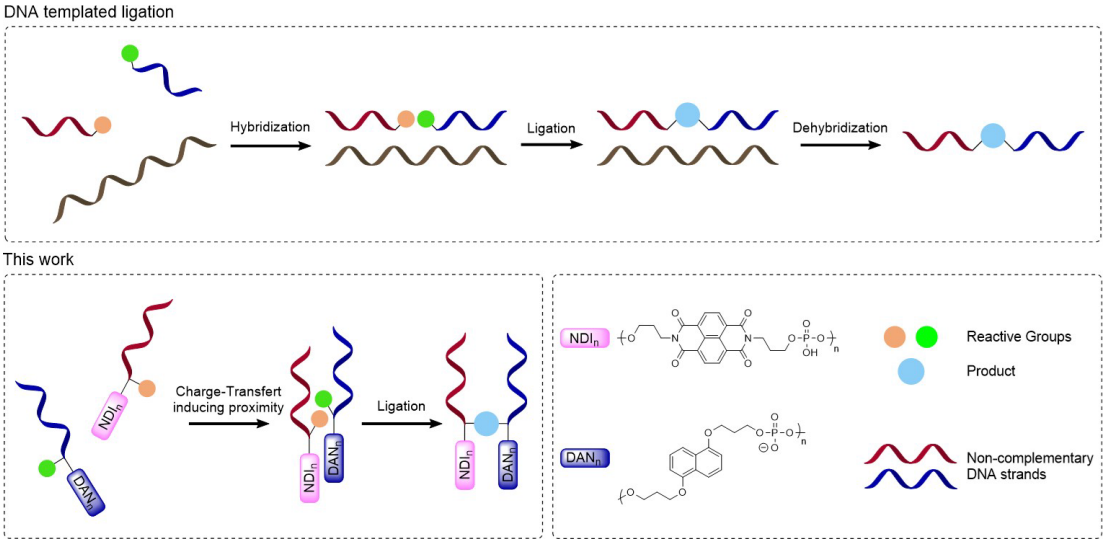
Intermolecular interactions, like hydrogen bonding or Van-Der-Waals forces, are ubiquitous in chemistry guiding both natural (DNA, proteins) and synthetic supramolecular assemblies. Among these interactions, charge transfer (CT) interactions received a particular attention due to the wide range of potential applications. Charge transfer can be defined as the electrostatic attraction between an electron-rich entity, the donor (D), and an electron-poor unit, the acceptor (A). This attraction allowed an alternative stacking between these two species that can lead to strong supramolecular assemblies called CT complexes. Among the various D and A pairs that have been identified, the most popular pair for forming CT complexes is naphthalene diimide (NDI) and dialkoxynaphtalene (DAN). In this context, DAN/NDI interactions can be used to induce proximity effect between two biomolecules, such as oligonucleotides strands. Usually, the ligation of two oligonucleotides carrying reactive functions proceeds through the use of a third strand, acting as a template to bring the reactive groups in close proximity. In this project, we propose to use the charge transfer interaction to enhance the effective molarity of two non-complementary DNA strands in diluted media. We achieved this by synthesizing DAN and NDI phosphoramidite building blocks, which were introduced into DNA sequences. With this method, we developed an innovative and universal ligation approach that proceeds at submicromolar concentrations and in mild aqueous conditions.



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P32

Luminescent Lanthanide Bioprobes as tools for biology

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Lanthanide(III) complexes offer an attractive alternative to the classical organic dyes for fluorescence sensing and imaging because of their fantastic luminescent properties, which comprise (i) line-like emission bands ranging from the visible to the near infrared (NIR), (ii) large stokes shift, (iii) long luminescence lifetimes and (iv) excellent photostability.
In this communication, we will present several examples of luminescent lanthanide(III) bioprobes that we are developing at the LCBM in Grenoble for biological applications:

- probes for copper(II) determination in biological fluids,
- probes for oxygen and reactive oxygen species sensing,
- probes for cell microscopy imaging,
- probes for dual luminescence / magnetic resonance imaging.
-

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Mannose-specific boronolectins: design and synthesis of bis-boronic acids

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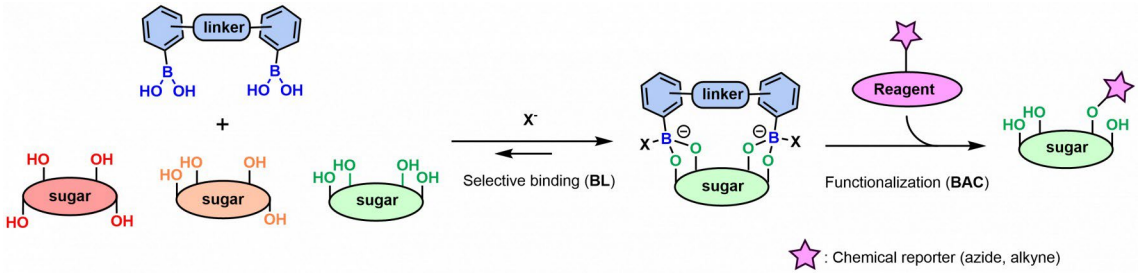
Glycoproteins practically cover all eukaryotic cells and are responsible for numerous cellular communication and recognition events. Glycobiology underwent significant development at the end of the last century but remains hampered by the high structural complexity of glycans.[1] The need for new tools to study the structure and function of glycoproteins is therefore crucial, given that certain diseases result from glycosylation defects or are marked by specific surface oligosaccharides.[2] The recent development of Metabolic Oligosaccharide Engineering (MOE) by Carolyn Bertozzi and coworkers represents a significant breakthrough allowing the study of native glycans in living cells.[3] Our goal is to develop an alternative chemical-based bioconjugation method. To specifically functionalize saccharides of interest, we aim to use boronolectins (BL) for their selectivity coupled with Boronic Acid Catalytic methods (BAC) to ensure reactivity.[4,5] In this communication, we will disclose our latest results regarding the design, the synthesis and the reactivity of mannose-specific boronolectins.



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Marquage de la capsule K1 : Optimisation du marquage en MOE et mise au point d'une stratégie marquage utilisant la SEEL

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La majorité des souches d'*Escherichia coli* responsables de méningite néonatale expriment la capsule K1, constituée d'un polysaccharide d'acide polysialique α-2,8. La capsule jouant un rôle central dans l'évasion du système immunitaire de l'hôte du fait de leur similarité structurale glycannique aux Neural Cell Adhesion Molecule (N-CAM)[1]. Malgré cette importance biologique majeure, les stratégies de marquage ciblant spécifiquement la capsule K1 restent peu développées.
Nous souhaitons mettre au points différentes méthodes de marquage de cette capsule (figure 1), incluant l'incorporation métabolique d'oligosaccharides modifiés[2] ainsi que le marquage exo-enzymatique sélectif (SEEL)[3]. Dans ce contexte, la compréhension de la voie de biosynthèse de la capsule K1 constitue un élément clé pour le développement de stratégies de marquage ciblées.(figure 2). La voie de biosynthèse de la capsule se repose, d'une part, sur la synthèse et l'ajout du 3-désoxy-D-manno-oct-2-ulosonate (KDO), qui sert de point d'ancrage au polymère d'acide polysialique[4], et, d'autre part, sur la synthèse de novo de l'acide N-acétylneuraminique (Neu5Ac) avec comme point de départ l' UDP-N-acétylglucosamine (UDP-GlcNAc), converti premierement en N-acétylmannosamine (ManNAc) par l'enzyme NeuC puis en Neu5Ac par l'enzyme NeuB. Le Neu5Ac est ensuite activé par l'enzyme NeuA sous forme de CMP-Neu5Ac et est incorporé lors de l'élongation de la capsule K1 par l'enzyme NeuS[5]. Cette organisation métabolique justifie l'utilisation de rapporteurs dérivés du N-acétylmannosamine et du Neu5Ac, tels que le ManNAz et le SiaNAz disposant d'une modification chimique afin d'effectuer ensuite une conjugaison bioorthogonale, par cycloaddition azide–alcyne catalysée par le cuivre (CuAAC) ou par cycloaddition activée par contrainte (SPAAC), avec une sonde fluorescente
Comme mentionné précédement, l'élongation du polysaccharide capsulaire est catalysée par NeuS, une sialyltransférase spécifique des bactéries, qui ajoute séquentiellement des résidus de Neu5Ac à l'extrémité de la chaîne capsulaire. En exploitant cette enzyme, que nous produisons actuellement de manière recombinante, et des analogues modifiés du CMP-Neu5Ac, il devient possible de mettre en œuvre une stratégie de SEEL, méthode de marquage mise au point par Boons et al qui utilise une sialyltransferase exogène afin d'ajouter une résidue d'acide sialique activé (CMP-Sia) en terminaison de structure glycannique, permettant un marquage spécifique, contrôlé et en terminaison de la capsule K1.

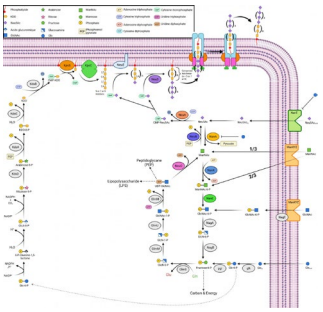

Figure 1 : Différentes stratégies de marquages de la capsule. Selelctive exoenzymatique labeling en mauve. Incorporation métabolique d'oligosaccharide en vert et violet.

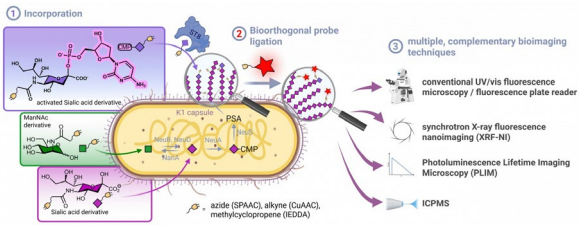

Figure 2 : Voie de biosynthèse de la capsule : A gauche, synthèse et ajout de KDO servant de point d'ancrage à au polymère d'acide polysialique de la capsule. A droite, synthèse de novo et incorporation d'acide sialique pour la synthèse de la capsule

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Modification sélective d'anticorps par une approche de "re-bridging" supporté - vers des conjugués drogue- anticorps originaux et homogènes

Dorian ROUTHIAU (IC2MP)

La forte affinité des anticorps pour leur antigène fait d'eux un outil de choix pour la vectorisation de principes actifs (PA) dans le cadre d'applications diagnostiques et/ou thérapeutiques ciblées. Plusieurs méthodes chimiques de « modification site-sélective » d'anticorps ont été développées au cours des dernières années. Parmi ces méthodes, celle du re-bridging des ponts disulfures s'est avérée particulièrement intéressante. Elle consiste en la réduction des ponts disulfures inter-chaînes de l'anticorps, générant ainsi des fonctions thiol libres (-SH), puis de leur « reconnexion » covalente via une double réaction d'alkylation sur une plateforme chimique (dibromo pyridazinedione, Br2-PD). Cette plateforme chimique comporte généralement une à deux fonctions de chimie click (azoture, tétrazine…) qui sont alors introduite au niveau du pont disulfure lors du re-bridging, et permettent dans un second temps la fonctionnalisation de l'anticorps avec des principes actifs, via réaction de chimie click. Cependant, cette méthode offre tout de même un choix restreint concernant le nombre de PA par anticorps.

Dans ce projet, une nouvelle méthode de fonctionnalisation d'anticorps, sélective et mono-site, est mise au point. Elle se base sur une adaptation sur support solide de la méthode de re-bridging des ponts disulfures. Le contrôle de la densité de greffage des agents de re-bridging à la surface du support permettra de limiter le re-bridging à un seul pont disulfure (effet de pseudo-dilution) et donc d'introduire une seule fonction réactive par anticorps (ex : tétrazine). Le re-bridging permet par la même occasion d'immobiliser de façon covalente l'anticorps sur le support solide, et ainsi d'éliminer les anticorps qui n'auraient pas réagi par un simple lavage. Dans un second temps, une libération contrôlée de l'anticorps par activation enzymatique ou chimique d'une gâchette moléculaire permet l'obtention de l'anticorps « mono-clickable ». Celui-ci peut ensuite être engagé soit : 1. En réaction click avec un principe actif (PA) pour générer un conjugué PA-anticorps avec un seul PA par anticorps, soit 2. Dans 1 à 3 cycles de mono-fonctionnalisation supplémentaires pour re-bridger les 1 à 3 ponts disulfures restants.

L'itération des cycles de mono-fonctionnalisation suivie des réactions de fonctionnalisation permet in fine d'avoir un parfait contrôle sur le nombre de PA greffés (entre 1 et 4), y compris différents entre eux.

Nanoréacteurs activables par chimie bioorthogonale pour la synthèse organique dans les systèmes vivants

Sarah GENTIL (Université de Poitiers)

La chimie bioorthogonale offre la possibilité de réaliser des réactions chimiques non naturelles au sein des systèmes vivants sans interférer avec les processus biologiques. Au cours des dernières années, plusieurs réactions de ligation et de « click-to-release » ont été développées, permettant de comprendre ou de manipuler des processus biologiques par la formation ou la rupture de liaisons chimiques de manière strictement contrôlée. Cependant, l'éventail des réactions pouvant être réalisées dans les systèmes vivants est encore très restreint, surtout si on le compare à la grande diversité des transformations chimiques pouvant être réalisées dans les solvants organiques.
Dans le projet NanoChem, nous proposons d'introduire un nouveau paradigme dans le domaine de la chimie bioorthogonale basé sur des nanoréacteurs pouvant être activés de façon bioorthogonale et conçus pour la synthèse « à la demande » de molécules dans les systèmes vivants. Ces nanoréacteurs seront programmés pour permettre diverses transformations chimiques telles que des réactions de couplage, des cyclisations, des polymérisations, des réarrangements et des processus autocatalytiques. Contrairement aux stratégies développées précédemment, la technologie NanoChem conduira à la formation de liaisons chimiques présentes dans les produits naturels (urée, amide) sans interférer avec les molécules biologiques environnants. Étant donné qu'une telle chimie se déroulera dans un espace confiné, les vitesses de réaction devraient être considérablement accélérées, limitant ainsi les problèmes associés aux conditions de forte dilution rencontrées dans les systèmes vivants. De plus, la technologie NanoChem offrira la possibilité de déclencher des réactions autocatalysées dans les milieux biologiques, conduisant à des processus d'amplification du signal dans lesquels un événement bioorthogonal conduira à l'activation de plusieurs composés bioactifs. Ainsi, ce projet original dans le domaine de la chimie pourrait déboucher sur des applications potentielles dans le domaine de la santé humaine.

Nouveaux PROTACs ciblant PI3Kγ, une vulnérabilité lignée-spécifique dans les leucémies myéloïdes aiguës

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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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Nouvelles amidoximes comme donneurs potentielles de NO

Lilian KARCHER (Université de Lorraine, LRGP) Axelle ARRAULT (Université de Lorraine, LRGP) Raphaël SCHNEIDER (Université de Lorraine, LRGP)

Les maladies cardiovasculaires (MC) sont l'une des premières causes de mortalité au monde. Selon l'Organisation Mondiale de la Santé, 17,9 millions de personnes décèdent chaque année des MCs, représentant ainsi 32 % des décès. La baisse de la biodisponibilité du monoxyde d'azote (NO) est un facteur clé dans certaines pathologies telles que l'angine de poitrine, justifiant le recours à des donneurs de NO. Le NO endogène, présent dans les cellules endothéliales, résulte de l'oxydation de la L-arginine en L-citrulline par l'eNOS. Bien que sa demi-vie soit très courte (30 s environ), NO peut diffuser dans les cellules musculaires lisses, et activer la cascade biochimique responsable de la relaxation des muscles lisses et de la vasodilatation pour réguler la pression artérielle et le flux sanguin dans le système circulatoire.

Pour compenser la diminution de la biodisponibilité du NO, des promédicaments donneurs de NO ont été développés. Néanmoins, ces composés présentent souvent des effets indésirables (maux de tête, hypotension et tolérance susceptible d'entraîner la formation d'espèces réactives délétères). La recherche de nouvelles entités capables de libérer NO de manière contrôlée et durable est donc cruciale. Les promédicaments contenant une fonction amidoxime sont des donneurs potentiels de NO particulièrement prometteurs. Les amidoximes interviennent in vivo dans des cascades biologiques impliquées dans la biosynthèse du NO, suggérant ainsi une faible toxicité. De plus, les amidoximes exogènes peuvent être oxydés par les cytochromes P450, enzymes majeures du métabolisme des médicaments, impliquées dans près de 80% des biotransformations médicamenteuses. Ces composés ont démontré une efficacité dans le traitement des pathologies cardiovasculaires, en induisant une diminution de la pression artérielle, une inhibition de l'agrégation plaquettaire et une vasorelaxation in vitro.

Ce travail décrit la synthèse d'amidoximes aromatiques et hétéroaromatiques en vue de leur utilisation comme promédicaments donneurs de NO. Une efficacité accrue, jusqu'à deux fois supérieure, a été observée pour des molécules combinant des fonctions amidoxime aromatiques et aliphatiques. L'hypothèse est que la modulation structurale de noyaux aromatiques et hétéroaromatiques porteurs de fonctions amidoxime pourrait optimiser la libération de NO et améliorer le profil pharmacologique de ces donneurs. Divers motifs structuraux (phénols, pyridines, anilines, …) ont servi de base à la conception de nouvelles amidoximes (voir Figure 1). Des composés portant un à trois motifs amidoxime ont été synthétisés, incluant des analogues aliphatiques, aromatiques et mixtes. L'oxydation des amidoximes, réalisée dans des conditions mimant le milieu biologique, a permis d'évaluer leur aptitude à libérer du NO. Ce travail vise à fournir des nouveaux donneurs de NO potentiellement plus stables et mieux tolérés, contribuant ainsi au développement de traitements innovants des maladies cardiovasculaires.

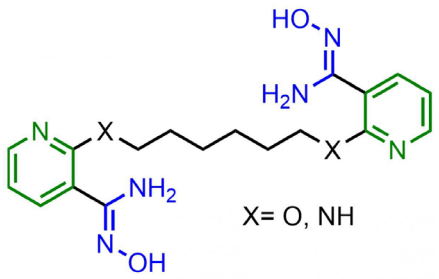

Figure 1 : Exemples d'amidoximes préparés

Nouvelles stratégies anticancéreuses à partir de dérivés indoliques et quinoliniques : de la synthèse au design multi-cibles

Abdallah HAMZE (Univerisité Paris Saclay, Faculté de Pharmacie)

La recherche de nouveaux agents anticancéreux efficaces et sélectifs repose aujourd'hui sur une combinaison étroite entre innovation en chimie de synthèse, design rationnel de petites molécules et évaluation biologique approfondie. Ce séminaire présentera une série de travaux consacrés au développement de dérivés indoliques et quinoliniques comme plateformes privilégiées pour l'élaboration de nouvelles stratégies anticancéreuses, en particulier via l'inhibition de la polymérisation de la tubuline et des histones déacétylases (HDAC).

Une première partie abordera le développement de méthodes de synthèse originales permettant l'accès à des architectures hétérocycliques inédites, notamment par cyclisation catalysée de dérivés d'indole, ouvrant la voie à de nouveaux scaffolds bioactifs. Ces composés ont révélé des activités anticancéreuses significatives in vitro, certaines molécules présentant des puissances nanomolaires associées à un arrêt du cycle cellulaire en phase G2/M.

La suite du séminaire sera consacrée au design d'analogues d'isoCombretastatin A-4, afin d'améliorer leur stabilité et leur efficacité biologique. Plusieurs analogues cycliques ont montré une inhibition marquée de la tubuline, une induction de l'apoptose et une meilleure sélectivité vis-à-vis des cellules tumorales. Enfin, le concept de molécules multi-cibles sera illustré par la conception d'inhibiteurs hybrides tubuline/HDAC à base de quinoline, combinant une forte activité antiprolifératives et un mécanisme d'action dual.

Dans leur ensemble, ces travaux soulignent le potentiel des approches intégrées en chimie médicinale pour générer de nouvelles entités anticancéreuses à fort potentiel thérapeutique.

P40

Novel Fluorogenic Photoactivatable Tags for Interactomic and Biomaging Applications

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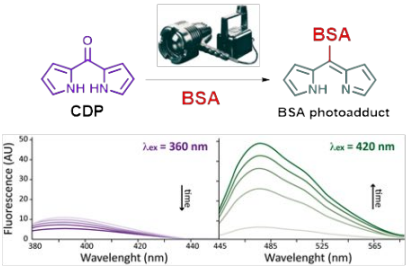
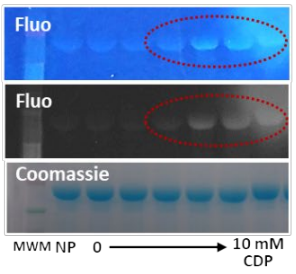
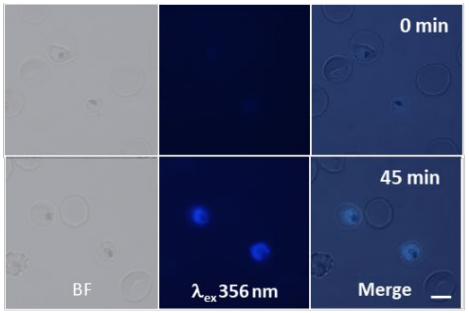
Fluorescent tags are major tools in biological and biomedical research. We propose a unique structural modification applicable to the most important organic fluorophores, to yield analogues endowed with novel properties of photoactivatability, covalent capture and fluorogenesis (PCCF). These tags conjugated to small molecules or macromolecules of interest (e. g., drug, RNA) would permit to identify their biological targets or partners. This approach would be based on interactomic and imaging studies, with a focus on super-resolution microscopy awaited from these PCCF tags. The figure below illustrates an exemple of a fluorescent tag (CarbonylDi**P**yrol, **CDP**) that can be used as a PCCF probe. In A, the fluorometry tracking of the disappearance of CDP fluorescence correlated with the appearance of a more fluorescent bathochromic species over the time of irradiation by UV-A. In B, the tracking by SDS-PAGE of the dose-dependent increase of fluorescence after a fixed time of irradiation and in C, the formation of fluorescent photo-adducts within P. falciparum-infected human erythrocytes. The project objectives will be firstly the synthesis of a small portfolio of tags then its functional screening on simple biological models. Further, a selection of optimal tags will be validated in reference paradigms implicating known ligand-partner couples, then used to explore the interactome of new relevant ligands.



A. Fluorimetric detection of putative BSA photoadducts by irradiation in presence of **CDP** (UVA 100 W lamp, PBS, 4 °C, every 10 min)



B. SDS-PAGE detection of BSA photoadducts by irradiation in presence of **CDP** (UVA 100 W lamp, 45 min, PBS, 4 °C); MWM: molecular weight marker; NP: non-photoactivated



C. Live-cell fluorogenesis of **CDP** (20 µM) upon irradiation (UVA 100 W lamp, 4 °C) in 3D7 *P. falciparum*-infected human erythrocytes (epifluorescence BX60F-3 Olympus microscope); scale bar represents 4 µm.

Quinoline based luminescent imidazolium salts as vector for gene therapy

Justine KAPP (Université de Strasbourg) Laurent DOUCE (Université de Strasbourg)

Molecular salts, particularly those based on imidazolium units, have attracted the attention of the scientific community due to their unique properties and structural versatility, especially those containing a fluorophore[1,2]. Indeed, light and the phenomena associated with it, such as fluorescence, have proven to be a powerful and highly sensitive tools for exploring the nanoscale world (organization, polarity, interactions, etc.). Furthermore, cationic lipids have, for several years, emerged as the best candidates for the delivery of genetic material and thus for gene therapy[3,4]. In 2009, Dobbs et al [5], had already demonstrated that the delivery of siRNA was possible using imidazolium salts. In this context, we have designed new imidazolium salts incorporating a quinoline unit in order to developed a new theragnostic agent. Thanks to the lone pair available on the nitrogen atom, quinoline is capable of interacting with protons and is therefore an ionizable unit. Our imidazolium salts are composed of three parts: a fluorophore, which is rigid and hydrophobic; the imidazolium cation, which is rigid and hydrophilic; and the alkyl chains which are flexible and hydrophobic. The combination of these three antagonist parts makes these salts a new type of highly bioavailable and luminescent molecular platform. This structural arrangement allows for fine-tuning of both the amphipathic and amphiphilic character of our salts, thereby enabling control over the emergence of their biological properties and mesomorphic properties. The quinoline ring offers seven different substitution positions, allowing the establishment of a structure–activity relationship and the supramolecular level study of the behavior of these molecules. Herein, we will present the synthesis and the study of the biological properties of these salts as a function of their substitution position on the quinoline unit.

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[2] Del Giudice, N. & al. Eur. J. Org. Chem. 2021, 2021, 2091–2098.

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[5] Dobbs, W. & al. J. Am. Chem. Soc. 2009, 131, 13338–13346.

P42

Rational drug design strategy against *Bunyaviricetes* class viruses

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The class of the Bunyaviricetes viruses represent a threat for human health, that could cause fever, abdominal pain, headaches, myalgia… to mortal hemorrhagic fevers. To date, there is no vaccine neither efficient therapeutic molecules against these viruses, that made them essential target for the development of new therapeutic molecules. This class of viruses include notably the Lassa fever virus (LASV), Rift Valley Fever Virus (RVFV) and Crimea Congo Hemorrhagic Fever Virus (CCHFV) present in the priority list of the WHO (World Health Organization).
The Bunyaviricetes possess segmented single strand (-) RNA genome and a cytoplasmic life cycle that starts by synthesizing viral mRNA[1]. The initiation of transcription, which is common to all members, relies on an endonuclease activity that is responsible for cap snatching, providing the primer, starting point of the replication of the virus. It has previously been shown that the cap-snatching endonuclease activity resides in the N-terminal domain of the L protein. Some of these viruses possess also an Exonuclease activity, carried by the C-terminal domain of the NP protein, responsible of the degradation of double strand RNA in the cytoplasm to avoid detection by the innate immune system. These two enzymes, crucial for the life cycle of the virus, possess a catalytic domain with two bivalent ions essential for the nuclease activity (TMIC) and are potent therapeutic targets[2,3].
Thanks to public and private consortium[4], we are designing innovative chelating molecules to prevent catalytic activity of these enzymes. Our rational drug-design approach is done thanks to biochemical characterization to evaluate binding and in vitro inhibition; structural biology analysis to seek specific interactions; and infected cells assays and animal models to evaluate inhibition efficiency *in vivo*.

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3 Hernández S, Feracci M, De Jesus CT, El Kazzi P, Kaci R, Garlatti L, Mondielli C, Bailly F, Cotelle P, Touret F, de Lamballerie X, Coutard B, Decroly E, Canard B, Ferron F, Alvarez K. Identification of potent inhibitors of arenavirus and SARS-CoV-2 exoribonucleases by fluorescence polarization assay. Antiviral Res. 2022 Aug;204:105364. doi: 10.1016/j.antiviral.2022.105364. Epub 2022 Jun 16. PMID: 35716929; PMCID: PMC9212739.

4 Projet Astrid maturation "BUNYANTIVIR" N°ANR-24-ASM1-0002.

P43

Stratégies pour la fonctionnalisation sélective de plateformes moléculaires

Roy LAVENDOMME (Université libre de Bruxelles) **Ivan JABIN** (Université libre de Bruxelles)

Les oligomères macrocycliques tels que les cyclodextrines, les cucurbituriles, les résorcin[ar]ènes, les pillar[ar]ènes et les calix[ar]ènes[1] constituent des plateformes moléculaires de premier plan en chimie supramoléculaire, notamment pour la conception de récepteurs biomimétiques, de capteurs, de transporteurs, de catalyseurs, ou encore de systèmes multivalents.[2] La synthèse de ces architectures fonctionnelles repose généralement sur l'introduction contrôlée de groupes fonctionnels sur une plateforme de départ comportant de nombreux groupes fonctionnels identiques. Toutefois, le développement de méthodes efficaces permettant la modification sélective des oligomères macrocycliques demeure un défi majeur. En effet, au-delà du contrôle des chimio-, régio- et stéréosélectivités, la fonctionnalisation d'un nombre précisément défini de groupes fonctionnels identiques représente une problématique centrale. Cette forme de sélectivité, qualifiée d'« itérosélectivité »,[3] est souvent déterminante pour la fonctionnalisation des oligomères, dans la mesure où l'absence de contrôle conduit à la formation de nombreux itéromères, dont la séparation par des techniques conventionnelles peut s'avérer impraticable.
Le développement de stratégies rationnelles visant à maîtriser l'itérosélectivité constitue l'un des axes de recherche majeurs de notre laboratoire.[4] Nous présenterons plusieurs approches générales mises au point ces dernières années et illustrerons leur potentiel à travers leur application à la synthèse sur mesure de plateformes moléculaires fonctionnalisées.[5]

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P44

Styryl Borondifluoro Indolenines as new photomodulable fluorescent probes based on Directed Photooxidation Induced Conversion

Louis EVRARD (UMR 7199 CNRS Unistra)

Photomodulable fluorescent probes have many applications in advanced bioimaging and microscopy. Upon light irradiation, these molecules can undergo various modifications affecting their photophysical properties and leading to photoconversion or photoactivation. Recently, our group established a new mechanism called "Directed Photooxidation Induced Conversion" (DPIC)[1–3]. When exposed to light, a fluorophore produces singlet oxygen which can then react with the fluorophore, often leading to photobleaching. In the DPIC mechanism, the oxidation is directed towards an Aromatic Singlet Oxygen Reactive Moiety (ASORM) such as furan, which disrupts its conjugation with the fluorophore (cf. figure).
These chemical transformations lead to photophysical variations, namely hypsochromic shifts and fluorescence enhancement. The DPIC concept has already been demonstrated with several fluorophores such as BODIPYs[1,2] and styryl coumarins[3] . In this work, we extend the scope of this mechanism by providing a new class of photoresponsive fluorophores, the Styryl Borondifluoro Indolenines (SBFIs). Based on this new scaffold, we synthesized a total of five fluorescent probes in which the furan was introduced at different positions. Here we show that depending on its location, the conjugation of the furan moiety influences both the photophysical properties of the fluorophore and its photomodulation properties. Overall, this work provides new insights into the DPIC mechanism through a comprehensive structure/properties relationship study on a new class of photomodulable fluorophores.

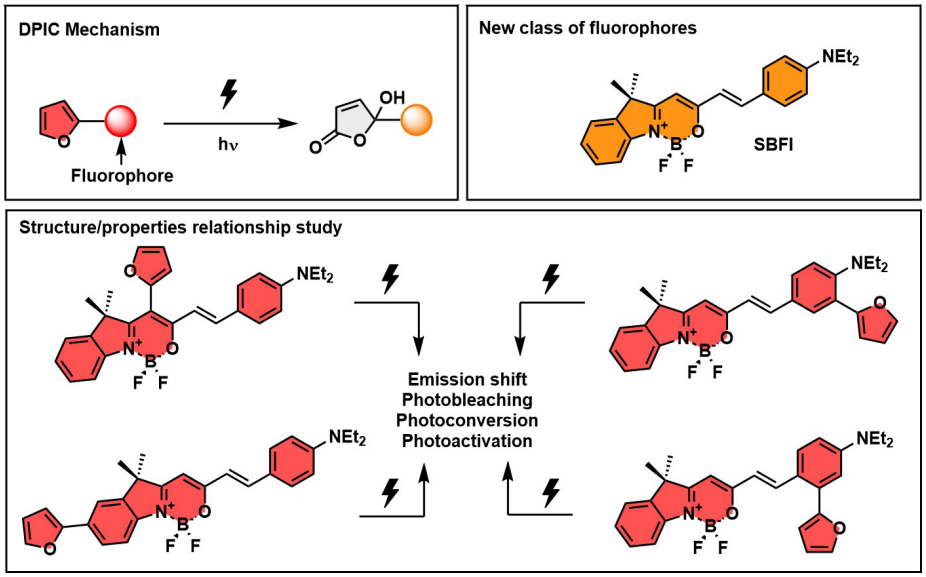

Figure 1: DPIC mechanism applied to Styryl Borondifluoro Indolenines

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P45

Synthèse de prodrogues azobenzènes dérivées d'un produit naturel cytotoxique original

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Les schweinfurthines sont des molécules naturelles cytotoxiques sur différentes lignées cancéreuse et actives in-vivo. Elles inhibent la protéine OSBP impliquée dans l'homéostasie du cholestérol. Toutefois, le caractère ubiquitaire de cette cible limite leur développement thérapeutique en raison de potentiels effets hors cible. L'hypothèse de ce projet est qu'une activation contrôlée spatialement d'analogues de ces composés permettrait d'augmenter leur sélectivité tumorale et de réduire leur toxicité systémique.
Ce projet vise le développement de prodrogues photo-activables des schweinfurthines, dans lesquelles le motif stilbène est remplacé par un azobenzène photoswitchable. Selon leur état d'isomérisation, ces analogues sont conçus pour être actifs ou inactifs vis-à-vis d'OSBP, l'activité pouvant être restaurée à la demande par irradiation lumineuse ou ionisante.
Nous avons réalisé un criblage virtuel de plus de 17 000 dérivés azobenzènes nous permettant de trouver 19 molécules à fort potentiel. Nous avons également développé une voie de synthèse efficace, permettant, via une unique étape de Bayer–Miller, de générer rapidement de nouvelles molécules. Des études photophysiques et biologiques nous permettrons finalement de trouver les sondes dont la différence de sélectivité entre les formes ON et OFF est la plus importante. Ce travail vise à approfondir la compréhension fonctionnelle de l'OSBP et à ouvrir la voie à de nouvelles stratégies thérapeutiques ciblées.

Synthesis and characterization of radiation-activated PROTAC for cancer treatment

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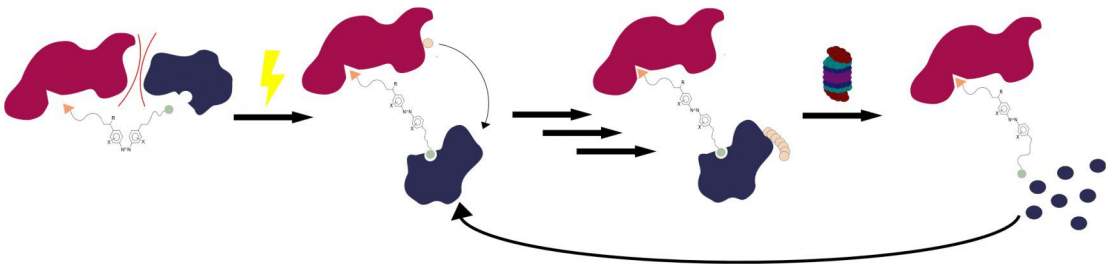
Proteolysis-targeting chimeras (PROTACs) have emerged as a strategy to treat cancer with currently about 30 clinical trials assessing PROTACs including 25 for cancer treatment in 2024. However systemic activity and off-target toxicity remain a major inconvenient of this therapeutic approach and hinder its application. To solve this issue, photoactivable PROTACs have been described but they are limited to shallow activation under the skin. The strategy developed by our team to overcome this difficulty is to develop PROTACs that can be activated by highly penetrating stimuli such as those used in radiotherapy. The compounds designed here can target BET proteins, epigenetic reader proteins involved in regulating gene expression, and induce their degradation after low-dose irradiation. Indeed, activation by radiotherapy was successfully achieved at doses as low as 2 Gy, which is about one order of magnitude more efficient than the best radiation-activated PROTAC described in literature. Moreover, targeted-protein degradation and cytotoxicity have been demonstrated after radiotherapy on human cervix cancer cells. Therefore, we designed PROTACs that allow targeted degradation of proteins and can be activated at high spatiotemporal resolution at any depth in biological tissues, able to reach deep-seated tumors and with limited impact on healthy tissues.



P47

Synthesis and photo-electrochemical characterization of reversible RedOx-responsive metallocene-based fluorescent probes

Lorenzo MENEGHELLI (CPCV, ENS PSL Université – Département de Chimie) Ning JIANG (CPCV, ENS PSL – Département de Chimie), Carolina CHIEFFO (CPCV, Sorbonne Université) Eric LABBÉ (CPCV, ENS PSL – Département de Chimie), Blaise DUMAT (CPCV, ENS PSL – Département de Chimie) Olivier BURIEZ (CPCV, ENS PSL – Département de Chimie), Jean-Maurice MALLET (CPCV, ENS PSL – Département de Chimie)

A very interesting approach for bio-imaging applications which has experienced rapid growth in recent years is the design of stimuli-responsive molecules whose fluorescence can be reversibly switched upon modulation of their redox state.[1] Biocompatible redox reversible fluorescent probes constitute an emerging but under-explored class of molecules especially for the detection of reactive oxygen and nitrogen species (ROS and RNS), which play an important role in signaling processes and in protection against pathogens.[2] A healthy cell naturally undergoes transient increases in ROS and RNS. However, if the balance between oxidants and reductants is chronically disrupted, the excess of oxidizing species can lead to the development of various pathologies including cancer, cardiovascular diseases, neurodegenerative diseases or diabetes. Therefore, the ability to distinguish between transient and chronic changes in real-time oxidative capacity in living organisms is of crucial importance.
Within this context, the project aims at developing original biocompatible, versatile, tunable, and reversible redox-responsive metallocene-based fluorescent probes (referred as dyads) able to target cell membranes and/or subcellular organelles.
Their design features the association of an organic fluorophore of the rhodamine family, chosen for its brightness and biocompatibility, and a ferrocene in order to promote a redox-switchable Photo-induced Electron Transfer (PET) as the key-step of fluorescence control (Figure).
Then, specific modifications of the dyads are done according to the envisaged investigations: simple dyads will be useful to investigate the photo-physico-chemical properties of the probes in solution whereas the grafting of a phospholipid chain or a chloroalkane chain will be used for membrane or for subcellular targeting via the HaloTag strategy, respectively.

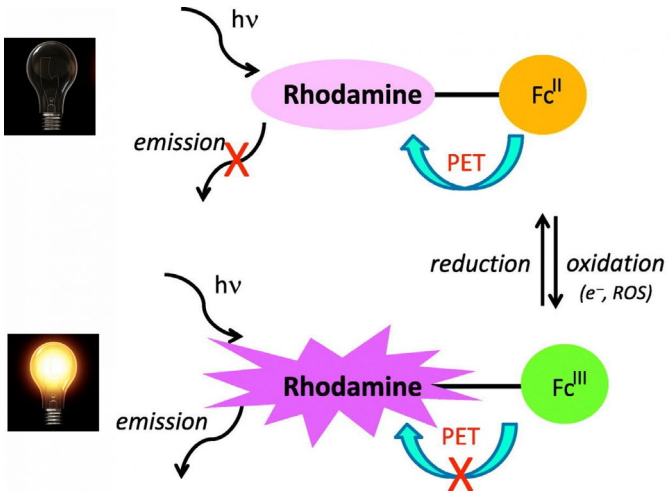


Figure : PET-controlled fluorescence

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2) Kaur A., *et al., Angew. Chem. Int. Ed.* 2016, *55*, 1602-1613.

P48

Synthesis of bioorthogonal trehalose monomycolate analogs for probing the membrane of Mycobacteria

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Corynebacteriales are a family of bacteria including Mycobacterium tuberculosis, the etiologic agent of human tuberculosis. These bacteria exhibit a unique outer membrane, the mycomembrane, which is highly resistant to antibiotics. This mycomembrane is composed of glycolipids named trehalose monomycolate (TMM) (Figure A).
To investigate its biogenesis, several research groups, including ours, have developed TMM analogs bearing a bioorthogonal moiety (Figure B). These analogs were used in metabolic labeling experiments on bacteria (Figure C). Once metabolized, they enable the specific conjugation of a fluorescent or affinity probe via a bioorthogonal reaction allowing the study of the mycomembrane.
Here, we developed the synthesis of three new TMM analogs bearing a bioorthogonal azido group (Figure 1B), expanding the available tools of our laboratory to study the mycomembrane. Those strategies involved several key steps including a Noyori enantioselective reduction of a β-ketoester, a diastereoselctive alkylation and a selective esterification.
Some of these compounds have been tested in metabolic labeling experiments for comparative studies with previous synthetized alkyne-based analogs. Others will also be tested and compared.

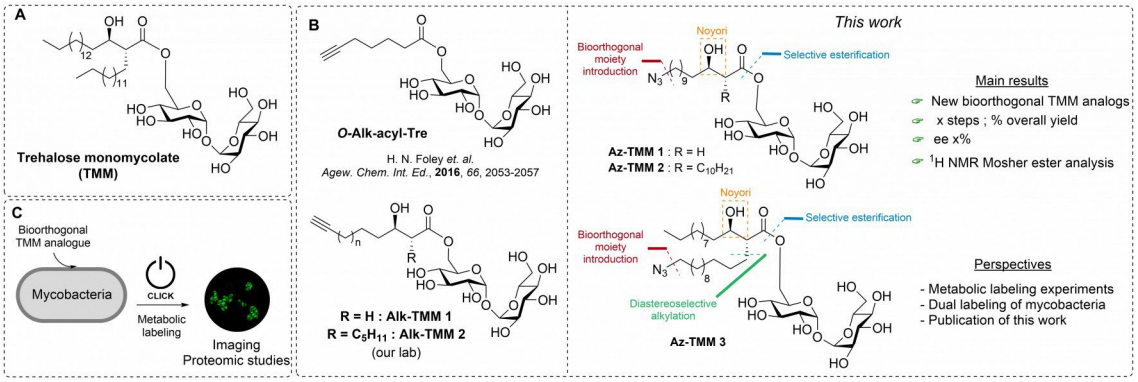


Figure : A) Structure of natural TMM. B) Bioorthogonal TMM analogs previously reported and newly obtained. C) Metabolic labeling approach.

P49

Synthesis of Fluorescent Probes Targeting VGLUT3 for in vivo Pharmacological Studies

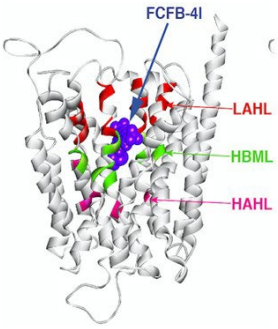
Nicolas PIETRANCOSTA (CNRS)

The discovery that striatal cholinergic interneurons (CINs) rely on both acetylcholine (ACh) and glutamate (Glu) transmission has profoundly changed our understanding of striatal signaling. CINs express the vesicular transporters VAChT and VGLUT3, enabling a cotransmission process in which synaptic vesicles (SVs) can accumulate and release both neurotransmitters. Beyond its classical role as a glutamate transporter, VGLUT3 participates in a broader "vesicular synergy," enhancing the vesicular loading of ACh or monoamines depending on cellular context. This dual functionality contributes to the complex modulation of basal ganglia circuits and has emerging implications for disorders including Parkinson's disease, addiction, anxiety, eating disorders, pain syndromes, and age-related hearing loss.

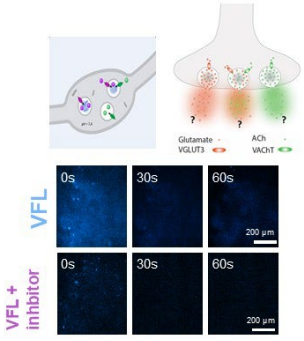
To dissect the molecular mechanisms underlying ACh/Glu cotransmission in CINs, we employed a multidisciplinary strategy combining computational analyses, neuroanatomical mapping, molecular imaging, and chemical probe development. An in silico co-evolution screen of 1,500 synaptic vesicle proteins identified approximately 30 candidate interactors potentially forming functional complexes with VAChT and/or VGLUT3. Many of these candidates belong to the SNARE machinery, a protein assembly that regulates vesicle docking and fusion. Fluorescent in situ hybridization and super-resolution STED microscopy confirmed the presence of these proteins in CINs and demonstrated their colocalization with VAChT- and VGLUT3-positive vesicles. Of particular interest, VAMP2 and VAMP7—two SNARE-associated vesicle proteins—were found on 60% and 24% of VAChT-containing vesicles and 83% and 21% of VGLUT3-containing vesicles, respectively. These distributions suggest distinct molecular architectures enabling either coordinated or independent release of ACh and Glu.

Building on this mechanistic insight, we pursued complementary chemical biology approaches to develop fluorescent probes targeting VGLUT3. Such tools are crucial for quantifying vesicular dynamics and neurotransmitter loading in vivo. Inspired by prior work demonstrating the potential of fluorescent false neurotransmitters for imaging monoaminergic vesicles, we designed glutamate-mimicking fluorescent ligands incorporating coumarin or quinoline scaffolds to replace non-fluorescent bulky moieties such as Trypan Blue. Their synthesis involves classical organocoupling reactions (Sonogashira, Suzuki, Huisgen) and multistep organic transformations, enabling fine-tuning of fluorophore brightness, polarity, and transporter affinity. The ultimate objective is to generate VGLUT3-specific imaging markers suitable for super-resolution microscopy and in vivo delivery, paving the way for theranostic applications that combine functional imaging with pharmacological modulation of vesicular transport.

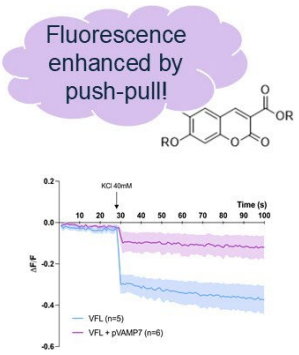
Together, these converging approaches provide an integrated view of the molecular organization and functional regulation of ACh/Glu cotransmission in CINs. Identifying the specific SNARE partners of VAChT and VGLUT3 refines current models of vesicular specialization, while the development of fluorescent VGLUT3 probes provides essential tools to visualize these processes with unprecedented resolution. This combined strategy opens new avenues for targeting vesicle biology in neurological disorders where CIN dysfunction and glutamatergic cotransmission are implicated.



Rational design



Ex vivo evaluation



Glu release quantification by fluorescence

Targeted Release of Drugs using Photolabile Groups and Photoactivatable Nanoparticles : Application to Neovascular Diseases of the Retina

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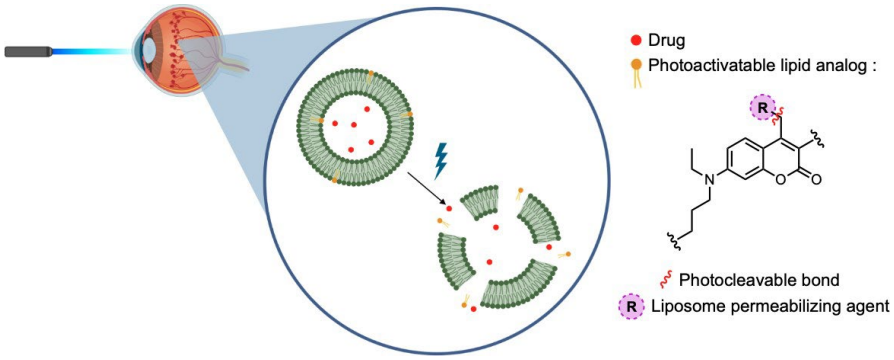
Achieving on-demand, site-specific drug delivery remains a major challenge in modern therapeutics. Here, we propose a novel light-triggered strategy that enables precise spatiotemporal control over therapeutic delivery while minimizing side effects. The approach involves the administration of an inactive but light-activatable nanoparticle [1,2] into the bloodstream, which can be photoactivated to trigger drug release specifically at pathological sites.
Our strategy focuses on the development of light-responsive liposomes based on the concept of light-induced membrane permeabilization [3]. Coumarin-based photolabile protecting groups (PPGs) [4] are chemically modified to mimic lipid structures and incorporated into liposomal membranes. Upon visible light activation, these photoactivatable lipid analogs are expected to release liposome-permeabilizing agents, leading to membrane permeabilization of these lipid nanoparticles and controlled drug release.
This strategy is particularly well suited for neovascular retinal diseases, such as age-related macular degeneration (AMD) and diabetic retinopathy, which remain major causes of vision loss and blindness [5], and where spatial precision is critical to preserve vision.



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P51

Tetracyclic pyrazinotriazapentalene (PyTAP) a new family of red emitting fluorescent scaffold for cellular imaging

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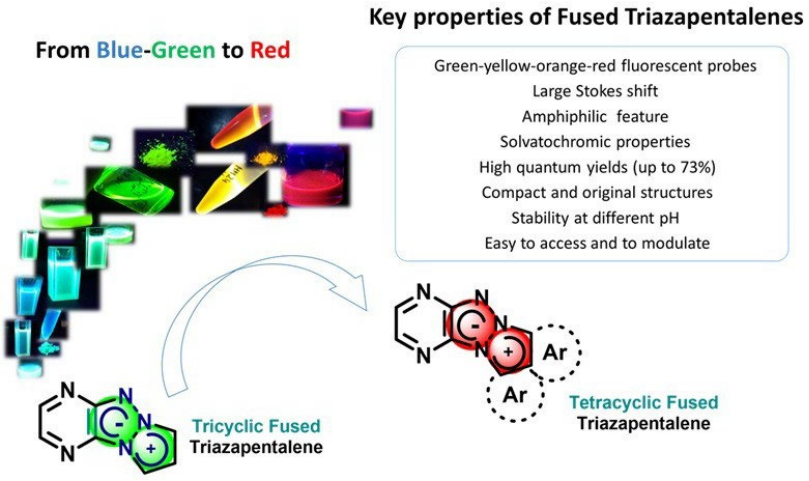
Fluorescent organic molecules are essential compounds for the detection, quantification and understanding of biological processes applied in chemical biology, biochemistry, biomedical research and diagnostic. The main advantages of organic fluorescent molecules include high versatility, moderate molecular size and weight, chemical stability, and ability to exhibit switchable or activatable spectroscopic properties. Although numerous fluorophores have been already described in the literature, the diversity of the molecular frameworks of those commonly used for cell imaging probes is often limited to coumarin, xanthene (fluorescein, rhodamine, Texas), BODIPY and cyanine cores. All these dyes can still not be considered as ideal probes for optical imaging since none of them combines high fluorescence with optimal absorption and emission wavelengths, good chemical and photostability, easy modularity, sufficient water solubility and small molecular weight/size.
In this context, we have designed a new family of organic fluorophores: the tetracyclic pyrazino-1,3a,6a-triazapentalene (PyTAP). This innovative compact scaffold, in its tetracyclic form, shows promising photophysical properties i.e. large Stokes shift, emission wavelength beyond 550nm, quantum yields up to 65% and good photostability. Thanks to the synthetic strategies we have developed, tetracyclic PyTAP can be modulated to optimize and design fluorescent probes for various applications in live cell imaging.



P52

Thiazolium-Based-Aminoacids as Precursors of NHC- Supported gamma-Peptide Foldamers

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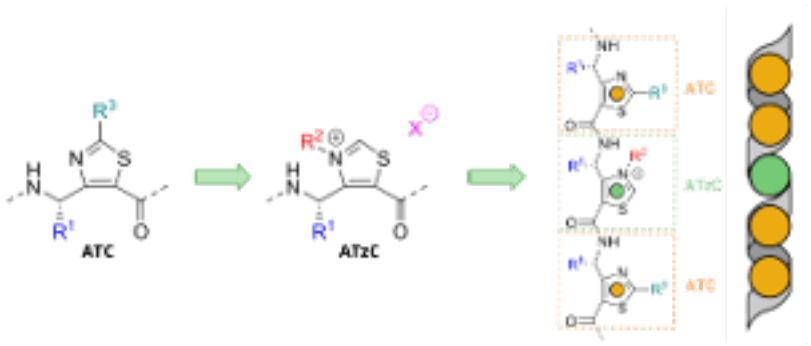
Foldamers represent ideal minimal enzyme mimics, as their predictable and stable secondary structures enable the precise spatial organization of functional groups within confined three-dimensional environments, thereby promoting cooperative and tunable catalytic behavior.[1] In contrast to peptides, foldamer sequences can be extensively modified without disrupting their overall folding. Moreover, whereas proteins rely on a limited monomer alphabet shaped by evolution, foldamer chemistry offers virtually unrestricted chemical diversity, making it uniquely suited for the integration of abiotic catalytic functionalities. Within this framework, thiazole-containing γ-amino acids (ATC) have emerged as powerful building blocks for catalytic foldamers, as ATC oligomers adopt highly regular 9-helical conformations stabilized by a robust network of intramolecular hydrogen bonds.[2] Importantly, the presence of a thiazole ring at the core of ATC residues renders this scaffold inherently compatible with N-heterocyclic carbene (NHC) chemistry.[3] Thiazolium salts, as classical NHC precursors, therefore provide a direct and conceptually elegant entry point for embedding latent carbene functionality within a preorganized foldamer backbone.
Here, we report the development of thiazolium-based γ-amino acids, termed ATzC, designed as close structural analogues of ATC and as precursors of NHC-functionalized foldamers. ATzC building blocks were efficiently synthesized and incorporated into ATC-based γ-peptide sequences using standard solid-phase peptide synthesis protocols. Structural investigations combining X-ray diffraction, NMR spectroscopy, and computational analyses demonstrate that ATzC residues are well tolerated within the foldamer architecture and preserve the intrinsic 9-helical folding propensity of the ATC scaffold. Overall, ATC/ATzC oligomers constitute a modular and tunable platform for the development of structurally defined NHC-supported foldamers. This proof-of-concept study lays the groundwork for exploiting foldamer frameworks in asymmetric NHC catalysis, with initial efforts directed toward benchmark transformations such as intramolecular Stetter reactions.



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Total Synthesis and Biological Evaluation of Cannalactone, a Noncanonical Strigolactone from Hemp

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Strigolactones (SLs) are apocarotenoid phytohormones secreted by plants into the rhizosphere. They act as signaling molecules for the development of arbuscular mycorrhizal (AM) fungi. SLs also play a crucial role in stimulating the seed germination of root parasitic plants such as *Orobanche*, *Phelipanche,* and *Striga*, which are among the most threatening weeds to major crops worldwide. *Phelipanche ramosa* primarily infests rapeseed, hemp, and tobacco, with *P. ramosa* 2a preferentially attacking hemp and *P. ramosa* 1 targeting rapeseed. Due to their significant role in plant development, SLs have been the focus of extensive research. By isolating and characterizing SLs, researchers aim to develop methods to control parasitic plants. Recently, a novel noncanonical SL, named cannalactone, has been discovered in the root exudates of hemp. Cannalactone selectively stimulates the germination of P*. ramosa* 2a seeds compared to *P. ramosa* 1. This work describes a racemic total synthesis of cannalactone. It evaluates its biological activity in the
P. ramosa populations, *Striga hermonthica* and *Orobanche cumana* compared with the natural product. Additionally, synthetic access to a deuterium-labeled standard of this natural product has been developed.

Towards new inhibitors of the IspD enzyme of Bacillus anthracis

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The current geopolitical context requires consideration of bioterrorist threats. *Bacillus anthracis* (responsible for anthrax) is classified among the bacteria that could be used as biological weapons. Possession of a treatment of countering biochemical attack would contribute to decrease the terror that motivates terrorist groups and reassure populations.
The isoprenoid family constitutes one of the largest natural products, and some of which are essential to numerous metabolic processes. The synthesis of the two precursors of isoprenoids occurs via two distinct biochemical pathways: the mevalonate pathway, notably present in mammals, archaea, fungi and the cytoplasm of plants, and the methylerythritol phosphate pathway, present among others in apicomplexa (*P. falciparum*), chloroplasts of plants and in the majority of bacteria, including some pathogens such as *B. anthracis*.[1-3] This unique distribution makes the enzymes of the MEP pathway highly attractive targets for the development of novel antimicrobial and antimalarial drugs.[4] The absence of homologous proteins in humans ensures more selectivity and less undesired side effects in patients. The project consists in developing new antibiotics against *B. anthracis* by targeting the third enzyme in the MEP pathway, IspD, which catalyzes the formation of 4-diphosphocytidyl-2*C*-methyl-*D*-erythritol from MEP and cytidine triphosphate (CTP) with the release of diphosphate (*PPi*).
Several results were recently obtained by the CBAT team. The enzyme Ba-IspD was produced by our team and its structure was solved with a 1.71 Å resolution in collaboration with Dr. F. Borel. Using a fragment-based approach, our team selected twenty fragments from a library of 500 fragments, by applying Surface Plasmon Resonance. The binding of several fragments to Ba-IspD was further confirmed by RMN STD and the inhibition potential of these fragments on Ba-IspD was also evaluated. Several molecules derived from the fragments show IC_{50} values in the micromolar range.

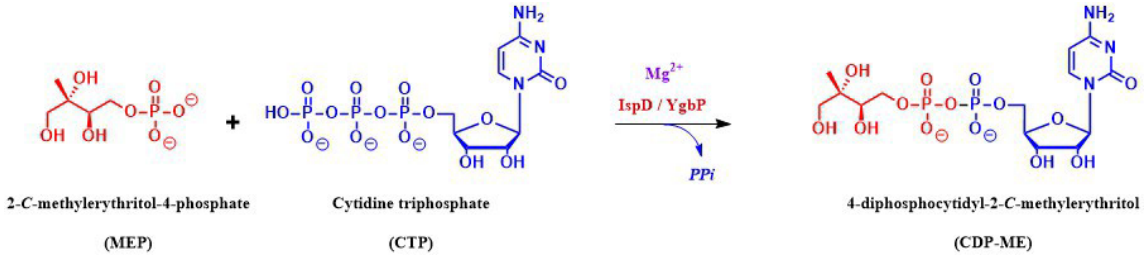

Figure : Reaction catalyzed by IspD.

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P55

Tuning Photophysical Properties of Cyanine-7 Dyes through Dimerization: Toward Theranostic Applications

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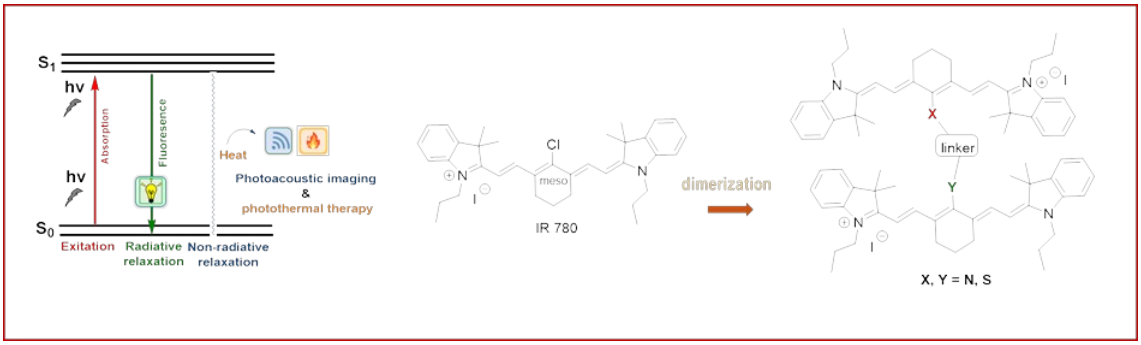
Cyanine -7 dyes exhibit attractive photophysical properties for in vivo applications.[1] These dyes absorb light in the near-infrared (NIR) region and can re-emit it either as fluorescence or as a photoacoustic signal. Owing to their efficient light-to-heat conversion, they also show strong potential for photothermal therapy. Together, these complementary properties enable enhanced diagnostic accuracy as well as improved therapeutic monitoring.
In this work, we report the synthesis and functionalization of cyanine-7 dyes starting from the commercially available IR-780 (X = Cl), selected for its stability and specific reactivity at the meso position of the cyclohexene ring. Structural modulation at this position, achieved through the introduction of various heteroatoms (N, S), allows fine-tuning of the photophysical properties.[2] Moreover, cyanine-7 dimers incorporating different linkers and heteroatoms were obtained by exploiting the reactivity of the meso position. This dimerization strategy is particularly effective in reducing photobleaching, modulating the balance between photoacoustic and fluorescence signals, and enhancing photothermal performance,[3] thereby representing an innovative design strategy for cyanine-7-based theranostic agents.



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P56

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

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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, two photon 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 turn on factor, and an excellent two photon absorption cross section.

In this work we present our ongoing research to develop a new class of theranostic tools: two photon excitable fluorogenic probes for click to release bioorthogonal reactions.[3,4] These click to release 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 proof of concept experiment in living cells validated the approach. This represents a novel theranostic platform that couples precise drug delivery with real time imaging.

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Development of a hyphenated LC-MS method to characterize N- glycan structures of recombinant glycoproteins produced in microalgae

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This project is an interdisciplinary work at the interface between glycobiology and analytical chemistry that aims to develop powerful methodologies for high- resolution mass spectrometry (MS) analysis coupled with liquid chromatography (LC) to perform the most comprehensive and detailed structural characterization of glycoproteins. Various glycomic and glycoproteomic approaches will be used to characterize the microheterogeneity and macroheterogeneity of glycosylation. These methods will be developed on commercial model glycoproteins, then used for the structural analysis of glycoproteins produced in *Chlamydomonas reinhardtii* and *Phaeodactylum tricornutum*.

We are currently developing an LC-MS/MS method (PGC or C18 pepmap column ; Vanquish UHPLC - Orbitrap Exploris 120; Collision Induced Dissociation (CID)) to characterize the structure of N-glycans (glycomers) released from model glycoproteins (bovine fetuin, RNase B, and avidin). Then we will develop an LC-MS/MS method (PGC column; Vanquish UHPLC - FTICR 18T, Electron-induced dissociation (EID)) to generate alternative carbohydrate fragmentation (A and X) that is more informative for the differentiation of N-glycan isomers.

The LC-MS/MS methods developed with the PGC column and the C18 pepmap column enabled to separate all the different N-glycan glycomers harbored by RNase B. Using the C18 pepmap column, glycomers were eluted according to their degree of glycosylation but isomers couldn't be separated. With the PGC column, glycomers were also separated, even if they were not eluted according to their degree of glycosylation. However, N-glycan isomers could be separated. Despite the obtention of diagnostic fragments B and Y using CID-based fragmentation confirming oligomannosidic structures on Rnase B, the different isomers could not be differenciated. Therefore the LC-MS/MS method based on EID allowing to generate fragments A and X of N-glycans is necessary for the further characterization of each isomer and finally their differentiation.

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P58

Developing xenonucleic acid-based ligands for biodetection

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The detection of toxins and pathogens is of the utmost importance for risk management and the protection of population. Notably, Lateral Flow ImmunoAssays (LFIA) are a sensible, specific, rapid, cost-effective and user-friendly diagnostic tool, and forms the basis of many Point-of-Care Tests (POCT), but lacking multiplexing capacity. Here, we propose to evaluate Xeno-Nucleic Acid oligomer (XNAs) barcodes to create a new range of ligands with a similar affinity to that of the classical biotin/avidin system. Our study mainly focuses on the impact of the modified structure of different XNAs: DesoxyriboNucleic Acids (DNA), Peptide Nucleic Acids (PNA) and Locked Nucleic Acids (LNA). Our primary objective is to combine a previously developed highly sensitive method, involving the pre-incubation of the capture antibody, the conjugated antibody and the antigen prior to LFIA migration [1] [2], with XNA labelling of the capture antibodies and the immobilization of complementary XNA sequences onto the strip.

We have thus determined the kinetic constants (K_D, k_a, k_{dis}) using two complementary methods: BioLayer Interferometry (BLI – Octet®) and Surface Plasmon Resonance (SPR – Biacore®). Alongside the differences in affinity between XNA oligomers, we investigated impact of sequence variation on hybridization strength, considering factors such as sequence length, proportion of GC-bases and their distribution.

Our study shows that DNA/LNA hybrids are the strongest hybridizing XNA pair, with a K_D of 3.2 x 10^{-11} M, which is 2 log-lower than that of the other XNA couples studied (Fig. 1). This exceptional value is partly due to the low dissociation strength of the locked LNA structure, which is probably caused by the strand's more rigid structure. The strongest hybridization strengths were achieved with longer sequences, containing a high number of successive GC-bases. This provides information on the hybridization conformation between to XNAs.

We now propose integrating the DNA/LNA hybrids into bioimmunological tests, such as ELISA or LFIA, in order to improve their multiplexing capacity.

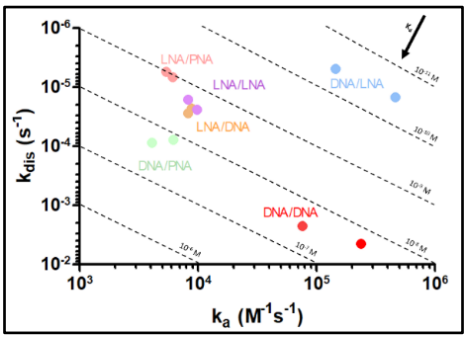

Figure : 2D-isoaffinity kinetic plot obtained by SPR-Biacore® for different XNA couples

[1] A. Nazareth, T. Snowden, Y. Cheng, US. Pat., US8268636B2, 2012.
[2] M. Yang, M. Goolia, W. Xu, H. Bittner, A. Clavijo, *Virol. J.*, 2013, 10:125.

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PROGRAMME

Dimanche 22 mars	Lundi 23 mars	Mardi 24 mars	Mercredi 25 mars	Jeudi 26 mars
	Session 1 *Modération : A. Specht*	***Session 3*** *Modération : S. Desrat*	***Session 5*** *Modération : F. Mahuteau*	***Session 7*** *Modération : V. Hélaine*
	8:30 CP1 : Gilles Guichard	**8:30 CP3 : Arnaud Chevalier**	**8:30 CP5 : Maria Duca**	**8:30 CP7 : Didier Roche**
	9:20 CO1 Charlène David	9:20 CO12 Anthony Augé	9:20 CO23 Camille Richagneux	9:20 CO33 Alexis Mai
	9:40 CO2 Norberta Delporte	9:40 CO13 Manon Wittwer	9:40 CO24 Massimo Trincas	9:40 CO34 Matthieu Simon
	10:00 Pause café	**10:00 Pause café**	**10:00 Pause café**	10:00 CO35 Walid Hajeb
	10:30 CO3 Mathilde Guilleton	10:30 CO14 Malo Gourvest	10:30 CO25 Mélanie Etheve-Quelquejeu	**10:20 Clôture des RECOB20**
	10:50 CO4 Julie Di Adamo	10:50 CO15 Sarah Griesbaum Dubourg	10:50 CO26 Julie Chea Ing	**10:30 Pause Café – panier repas**
	11:10 CO5 Jose Garcia Coll	11:10 CO16 Sophie Walter	11:10 CO27 Médéric Degardin	**11:00 Navette Bus Modane**
	11:30 CO6 Tom Di Santo	11:30 CO17 Mélina Fabe	11:30 CO28 Marine Le Stum	
	11:50 CO7 Florian Vinchon	11:50 CO18 Carlotta Figliola	11:50 CO29 Firas El Kadiry	
	12:30 Déjeuner - temps libre	**12:30 Déjeuner - temps libre**	**12:30 Déjeuner - temps libre**	
	Session 2 *Modération : PY. Renard*	***Session 4*** *Modération : K. Alvarez*	***Session 6*** *Modération : N. Lebègue*	
16h30 et 18h15 Navette Bus Aussois	**16:30 CP2 : Julia Chamot-Rooke**	**16:30 CP4 : Suzanne Peyrottes**	**16:30 CP6 : Sébastien Gouin**	
18:30 Accueil	17:20 CO8 Xavier Franck	17:20 CO19 Isabelle Krimm	17:20 CO30 Marius Bichot	
19:20 Apéritif	17:40 CO9 Meven Jobic	17:40 CO20 Juliette Lafon	17:40 CO31 Fabien Thoreau	
19:45 Dîner	18:00 CO10 Gilles Bruylants	18:00 CO21 Arnaud Tessier	18:00 CO32 Mathieu Scalabrini	
20:45 Introduction	18:20 CO11 Cécile Dupont	18:20 CO22 Isabelle Vieira De Almeida		
	19:30 Dîner	**19:30 Dîner**	**18:45 Assemblée générale**	
	20:45 CO Exposants	20:45 CO Exposants	**19:30 Dîner : Fondue Savoyarde – Soirée dansante**	
	21:15 Session posters pairs	**21:15 Session posters impairs**		

20e RECOB
Aussois 22-26 mars 2026
REncontres de Chimie Organique Biologique