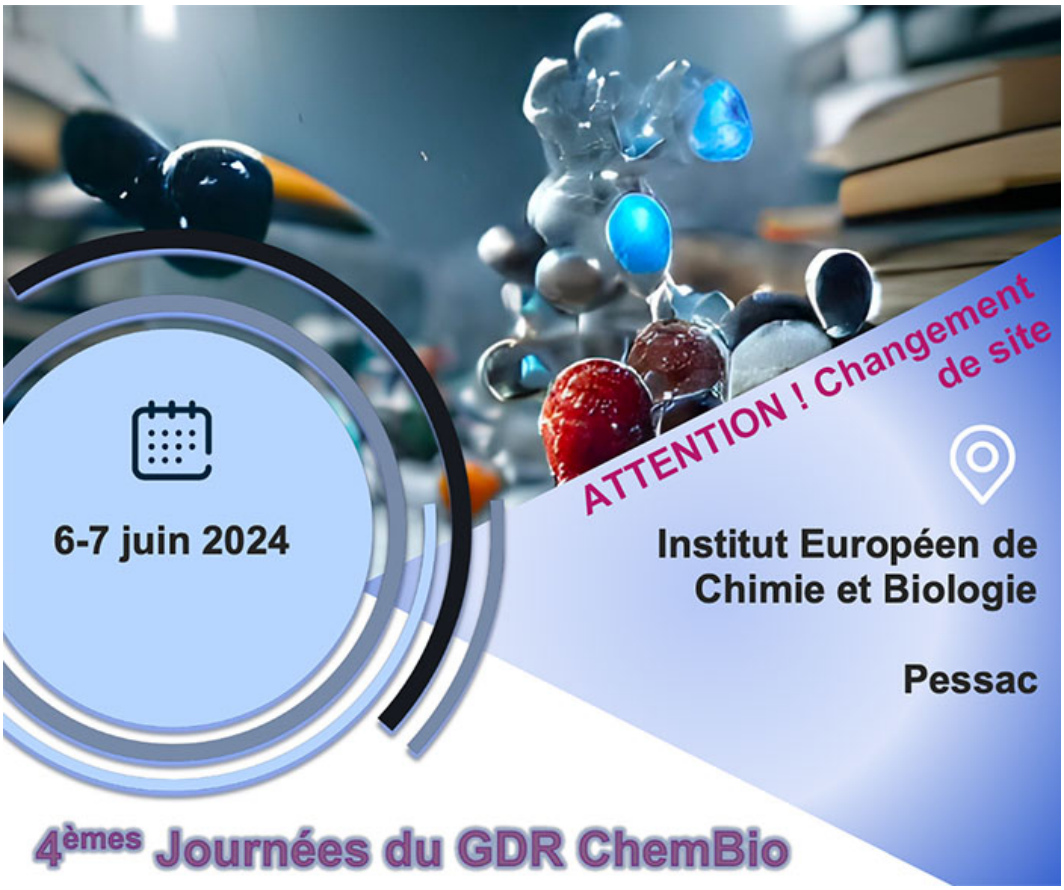
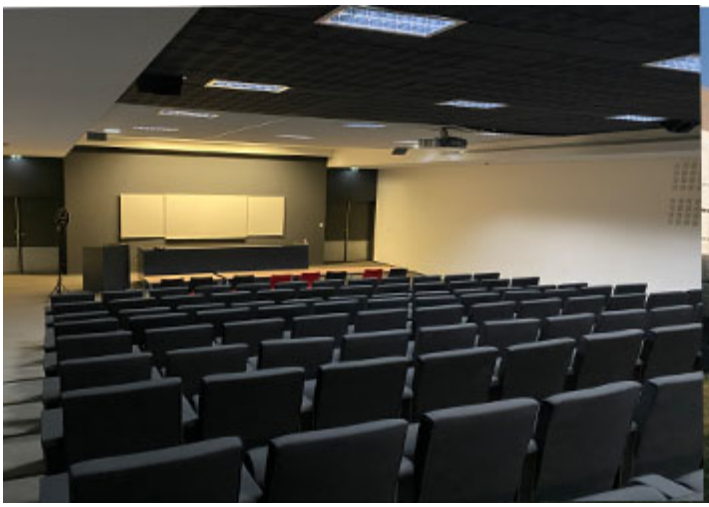
Journées Scientifiques du GDR ChemBio à Bordeaux

Book of Abstracts





Le GDR Chemobiologie remercie chaleureusement la participation et le support de ces sponsors :

Programme

Jeudi 6 Juin 2024

Accueil à partir de 9h00

9h30 - 9h50 : Présentation des journées (CoDir GDR ChemBio et Frédéric Friscourt)

9h50 - 10h30 : Muriel Amblard (IBBM, Montpellier)
Peptides et PROTACs : Outils Moléculaires pour la Modulation de Processus Biologiques Complexes

10h30-11h Pause café

11h00-11h20 : DUO Joseph Boissieras et Jérôme Dejeu (Institut Curie et Université de Franche-Comté)
Non specificity of I-motif ligands and I-Mab antiboby demonstrated by Bio-Layer Interferometry (BLI) and circular dichroïsm (CD)

11h20-11h40 : CO1 Mireille Blanchard-Desce (Université de Bordeaux)
Light on Mater for Life Sciences: Engineering of Molecular Cages for Drug Photorelease

11h40-12h00 : CO2 Agathe Urvoas (I2BC, Paris Saclay)
αRep artificial proteins as modular specific recognition tools

12h00-12H20 : CO3 Guillaume Compain (Université de Bordeaux)
Inhibiteurs peptidiques covalents ciblant des histidines : une nouvelle approche pour bloquer les interactions protéine-protéine

12h20-14h00 Pause déjeuner / Session Posters

14h00-14h40 : Tyler Kaufman (TakT, Paris & Los Angeles)
Science Art: creating an artistic process inspired by science

14h40-15h00 : CO4 Frédéric Taran (CEA Saclay)
Les sydnonimines, de nouveaux composés mésoioniques pour la libération d'isocyanates dans les cellules

15h00-15h20 : CO5 Yann Percherancier (IMS, Université de Bordeaux)
Illuminating Temporal Dynamics: BRET Probes Unveil Chemically-Induced Ion Channel Gating During HTS Campaigns

15h20-16h00 : Flash talks session 1
Flash 1: L. Atlan (Institut Curie), *Design of new biphotonic probes for bio-cell imaging*
Flash 2: A. Dominic (CEA Saclay), *Bioorthogonal reaction for safer and more accurate ImmunoPET imaging*
Flash 3: Z. Renaud (DPM, Univ. Grenoble Alpes), *Click and Cross: Trigger fluorogenic photo-crosslink by click chemistry*
Flash 4: M. Valeo (CBMN, Université de Bordeaux), *Directing cell fate: multifunctional DGL-PEG hydrogels to control hMSCs osteogenic differentiation*

16h00-16h30 Pause café

16h30-16h50 : Elisabetta Mileo
Evolution du site web

16h50-18h30
Table ronde : Perspective de la ChémoBiologie en France
Animée par *Christophe Biot*

Vendredi 7 Juin 2024

9h00-9h40 : Axel Maréchal (ISVV, Bordeaux)
De la terre à la tête : apports récents de la chimie analytique à la compréhension du goût du vin

9h40-10h00 : CO6 Elisabetta Mileo (BIP, Aix Marseille Université)
Structural dynamics insights from in-cell EPR of proteins.

10h00-10h20 : CO7 Hugo Bloux (ICSN)
Synthèse et évaluation de sondes originales ayant un déclencheur ester de borinate pour la détection rapide du peroxyde d'hydrogène

10h20-10h50 Pause café

10h50 - 11h10 : CO8 Daniela Verga (Institut Curie, PSL)
Photoactivatable Warheads for Photoaffinity Labeling of Nucleic Acid Secondary Structures

11h10 - 11h30 : CO9 Enrico Falcone (Institut de Chimie, Université de Strasbourg)
Influence of pH and glutathione on the pro-oxidant activity of copper-based drugs

11h30 - 12h20: Flash talks session 2
Flash 5: J. Couvez (ISM, LCPO, Université de Bordeaux), *Fluorescent organic nanoparticles as nanovectors for drug release activated by temperature/light & MRI monitoring*
Flash 6: E. Brosset-Heckel (LCBPT, Université de Paris Cité), *Solid phase synthesis for protein conjugation*
Flash 7: A. Rodriguez (Institut Curie), *Sondes fluorogéniques excitables à deux photons pour la délivrance de drogue via des réactions bioorthogonales de type « Click-to-Release »*
Flash 8: C. López-Serrano (CBMN, Université de Bordeaux), *Tailoring polymeric hydrogels for stem cell differentiation: impact of mechanical and bioactive properties*
Flash 9: C. Attiach (LCBPT, Université de Paris Cité), *Novel synthetic phospholipids for the development of thiol-responsive liposomes*

12h00-14h Pause déjeuner / Session Posters

14h00-14h20 : CO10 Sébastien Papot (Université de Poitiers)
An enzyme-responsive self-immolative recognition marker for manipulating cell-cell interactions

14h20-14h40 : CO11 Morgane Pasco (CBMN, Université de Bordeaux)
Guanidinium-Stapled Helical Peptides for Targeting Protein-Protein Interactions

14h40-15h00 : CO12 Petra Ivaskovic (Novaptech, Gradignan)
Engineering optical aptasensors for the detection of fungicides

15h00-15h20 : CO13 Jeanne Leblond Chain (ARNA, Université de Bordeaux)
Aptamers for Drug delivery Systems: more than targeting agents

15h20 - Conclusion

Présentations plénières

Peptides et PROTACs : Outils Moléculaires pour la Modulation de Processus Biologiques Complexes

Muriel Amblard

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La recherche de nouveaux médicaments a majoritairement privilégié les petites molécules capables de moduler la fonction des protéines en se liant aux poches enzymatiques ou aux récepteurs. Malgré son succès, cette approche présente des limites pour les mécanismes biologiques régulées par des interactions protéine-protéine (IPP) ou dépourvues d'activité enzymatique. La fin du XXe siècle a vu l'usage de biomolécules plus complexes tels que les anticorps ou les ARN interférents, offrant des avantages indéniables. Cependant, des inconvénients liés à leur taille, leur ciblage intracellulaire, leur stabilité, leur délivrance, leur sélectivité et leur coût élevé subsistent. Au sein de notre équipe, nous explorons d'autres classes de molécules comme des peptides stabilisés, des mimes de structures secondaires de protéines et des PROTACs. Ces approches ont pour objectif la conception d'outils thérapeutiques spécifiques capables d'interférer avec des protéines intracellulaires ciblées, modulant ainsi leur activité ou induisant leur dégradation par détournement du système ubiquitine-protéasome. Les outils moléculaires structurés sont également optimisés pour traverser les membranes cellulaires, facilitant ainsi la délivrance de composés actifs.

SCIENCE ART

TakT Tyler Kaufman

www.taktarts.com

What does it mean to be a Science Artist? It is the ability to take a new approach to the creative process, one that revolves around scientific findings, data, and experimentation. Although Science Art isn't new, the emergence of it today has never had so much importance and influence since Leonardo Da Vinci.

Why? One of the main reasons is the technological revolution of today. With the development of new technologies and tools, artists and scientists can create direct relationships with each other. This bridge renews methods, technics, communication, approaches and creates new ways of expressions which can benefit both worlds in their respective domains.

The importance of the scientific community and the ethical implementation of their findings across the globe is needed for humans and societies to come out of the various crisis we find ourselves today. The spread of the various scientific disciplines need to find new ways to connect to the culture today. Science Art has the potential to help build that bridge so that the public can connect in an emotional, spiritual and philosophical way to knowledge.

To be a science artist, the goals of the art undergo a profound change. As a science artist, your art piece is not strictly based on your personal emotions and ego. It is about creating a poetic interpretation and exploration of different aspects that their scientific partners are working on. Science Art has the ability to create a bridge between people who know nothing about science and sometimes have no interest to begin with and create a context of intrigue, inspiration and comprehension. In some cases, such as extreme Climate Change, this is clearly of the upmost importance.

In music, the main language on a technical composition level is mathematics. There are certain rules (not all) you must follow to be able to compose a classical piece, a successful pop song or an electronic dance song. Frequency manipulation is done heavily on every piece of music we hear on record today.

For this talk, we will explore what Science and Art have in common, The talk will focus on the process of creating science-art as a musician and composer. The talk will also include the new world of AI in music and how the entire lineage of music creation is being dismantled today by the technological innovations currently being released.

To be shown:
Incorporating Binaural Beats and the theoretical science behind the binaural beats in the music and its testing Micro Residence Quarantine: The first Microscopic bacteria show.
Ring of Voices
Scientific Emotions:
Science Art Video Presentation
AI: What AI can do to a composition. Examples showing the before and after AI Mastering. Composition, There will also be a live presentation of a unique hybrid instrument of sitar and an electronic Fender bass.

"De la terre à la tête : apports récents de la chimie analytique à la compréhension du goût du vin"

Pr Axel Marchal

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Le but de l'œnologie est d'aider les vinificateurs à guider la transformation du raisin, en intervenant le moins possible, mais à bon escient, pour obtenir les vins qui révèlent le génie du terroir. Les molécules constituent les vecteurs de ce message de la terre à la tête. Elles sont d'abord synthétisées par la vigne, à des concentrations dépendant des divers facteurs génétiques et environnementaux caractérisant un terroir viticole. Elles sont ensuite extraites, transformées lors de la vinification, puis éventuellement modifiées au cours du vieillissement du vin. Enfin, elles sont observées, senties, goûtées, et cette stimulation des récepteurs sensoriels permet au vin de naître une seconde fois, dans le cerveau du dégustateur. La connaissance des déterminants moléculaires des odeurs et des saveurs du vin constitue donc un enjeu majeur pour la recherche en œnologie. Elle a fait l'objet de nombreux travaux au cours des dernières décennies, en particulier sur les composés volatils responsables des qualités comme des défauts du vin. Malgré ces acquisitions significatives, de nombreuses perceptions demeurent inexpliquées au niveau moléculaire. Plus particulièrement, l'origine chimique des composés sapides du vin, demeurée longtemps méconnue, a fait l'objet de travaux récents. L'utilisation conjointe des techniques modernes de l'analyse chimique (LC-HRMS, RMN) et d'analyse sensorielle se révèle fructueuse pour identifier de nouveaux marqueurs du goût.

Communications Orales

Type de communication : communication orale ☒ flash ☐ affiche ☐

Non specificity of I-motif ligands and I-Mab antiboby demonstrated by Bio-Layer Interferometry (BLI) and circular dichroïsm (CD)

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Résumé:

i-Motifs of DNA (hereafter, *i*-DNA), known *in vitro* for nearly three decades, are unusual, four-stranded structures, in which cytosines are intercalated *via* a stack of hemi-protonated C–C base pairs (CH^+:C) (Fig. 1A, B). Some of these structures have been well characterized *in vitro* but their biological relevance is still under investigation.

Relatively few molecules were reported to interact with i-DNA. The main issues in this regard are the strong pH-dependency, flexibility, polymorphism and complex folding behavior of i-DNA that introduce potential bias into screening methods. In particular, low-pH conditions used to induce the formation of i-DNA can increase the non-specific interactions and afford false-positive compounds. The interactions of the molecules reported as i-DNA ligands were demonstrated by FRET, pH transition or thermal melting methods but few affinity constants were measured.

In this context, we have developed a circular dichroism method to study the interactions between i-DNA and already reported ligands. Using this method along with bio-layer interferometry (BLI) experiments we were able to re-evaluate numerous reported compounds (TMPyP4, mitoxantrone, IMC-48, berberine, *etc*) at physiologically relevant pH. We demonstrated that none of the reported ligands were shown to discriminate between folded and unfolded *i*-motif structures.[1,2]

In a similar context, we also showed by using BLI, pull-down and biophysical experiments that commercial *i*-motif antibody (*i-Mab*) is not able to recognize selectively the *i*-motif structure. Other experiments also indicate that this antibody could unfold the DNA structure. Thus questioning the ability of these sequences to form an i-motif at physiological conditions. [3]

1. Bonnet, H.; Morel, M.; Devaux, A.; Boissieras, J.; Granzhan, A.; Elias, B.; Lavergne, T.; Dejeu, J.; Defrancq, E. Chem. Com. **2022**, 58, 5116-5119. DOI : 10.1039/d2cc00836j
2. Berthiol, F. ; Boissieras, J. ; Bonnet, H. ; Pierrot, M. ; Philouze, C. ;. Poisson, J.F. ; Granzhan, A. ; Dejeu, J.; Defrancq, E. Molecules **2023**, 28:682. DOI : 10.3390/molecules28020682
3. Boissieras, J.; Bonnet, H.; Fidelia Susanto, M.; Gomez, D.; Granzhan, A.; Defrancq, E.; Dejeu, J. Nucleic Acids Res. **2024**, submitted. Available at: 10.1101/2023.11.21.568054

Keywords: I-motif DNA, Bio-layer interferometry, I-motif ligands, Circular dichroïsm

Type de communication : communication orale ☒ flash ☐ affiche ☐

Light on Mater for Life Sciences: Engineering of Molecular Cages for Drug Photorelease

Klausen Maxime, Dubois Victor, Daniel Jonathan, Verlhac Jean-Baptiste and Blanchard-Desce Mireille*

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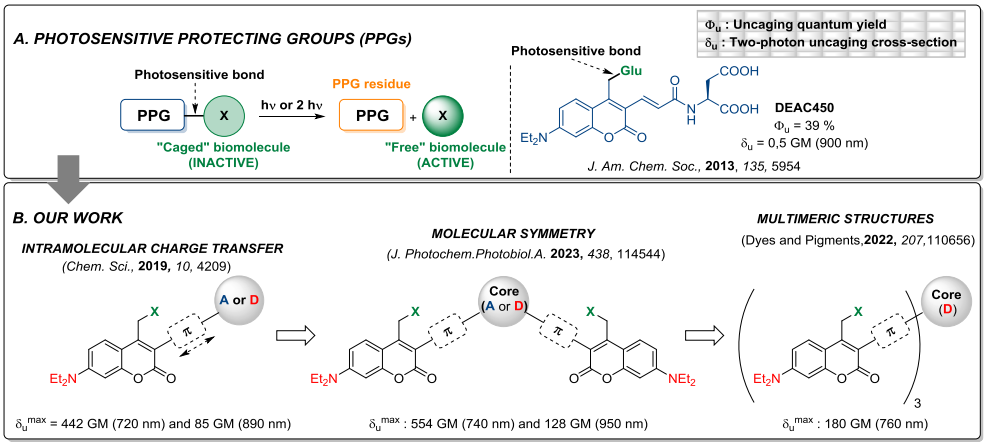
Molecular cages are small organic molecules that are able to link biomolecules of interest and to impede their biological activity. This link can be cleaved by suitable light irradiation, releasing the caged biomolecule and restoring its biological activity.[1] A key issue for biological applications resides in the efficiency (or photosensitivity) of these cages especially their ability to use photons to trigger and spatially control drug delivery to a specific target in living tissues. In that respect, two-photon excitation (2PA) in the biological spectral windows offers many advantages.[2] Yet a major limitation has to be circumvented if real applications in the medical field (oncology, neurology) are sought, i.e., light irradiation conditions compatible with medical uses.

With that aim in view, we have implemented innovative engineering routes towards tailor-made molecular nanotools with suitable photosensitivity for photoactivated drug delivery. In particular two main routes have been investigated: (i) the design of *tandem systems (dyads and triads)* that take advantage of the use of 2PA antennae[3], (ii) the design of polarized *coumarinyl* PPGs derivatives and multimeric derivatives of various symmetry.[4] As a result, new PPGs showing unprecedented 2PU efficiency (δ_u) in the NIR1 region (i.e. 700-1000 nm) were obtained:



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2. M. Klausen, M. Blanchard-Desce, J. *Photochem. Photobiol. C Photochem. Rev.* **2021**, *48*, 100423. DOI: 10.1016/j.jphotochemrev.2021.100423; R. Weinstain, T. Slanina, D. Kand, P. Klan, *Chem. Rev*. **2020**, *120*, 13135. DOI:10.1021/acs.chemrev.0c0066.
3. M. Klausen, V. Dubois, J.-B. Verlhac, M. Blanchard-Desce, *ChemPlusChem.*, **2019**, *84*, 589. DOI: 10.1002/cplu.201900139 and references cited therein.
4. M. Klausen et al, *Chem. Sci.*, **2019**, *10*, 4209-4219. DOI: 10.1039/C9SC00148D; V. Dubois et al, *Dyes and Pigments*, **2022**, *207*, 110656. DOI: 10.1016/j.dyepig.2022.110656; V. Dubois et al, *J. Photochem.Photobiol. A*, **2023**, *438*, 114544. DOI: 10.1016/j.jphotochem.2023.114544.

Keywords: Cages, Photodelivery, Two-photon absorption, Antennae, Coumarins

Type de communication : communication orale ☒ flash ☐ affiche ☐

αRep artificial proteins as modular specific recognition tools

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Résumé :

A family of artificial repeat proteins, named αRep, was designed from the concatenation of a consensus helical motif with 5 hypervariable positions. αRep proteins from the highly diverse library (10^9 variants) present a concave diversified binding surface and a variable number of repeats. αRep proteins are easily produced and highly stable[1]. Using phage display methods, it is possible to select protein binders with high selectivity and affinity for a variety of protein targets (K_D from nM to μM)[2]. These proteins can be easily produced and purified with high yields, genetically engineered in multidomain proteins or functionalized with chemicals or nanoparticles. Applications of these artificial proteins have been explored in various contexts through collaborations with biologists, chemists and physicists. αRep can be used as crystallization helpers for structural biology[3], intracellular tracers in living cells[4], FRET-based biosensors[5] by grafting fluorescent probes or artificial metalloenzymes[6,7] by coupling organometallic complexes into an αRep protein scaffold. As compared with molecular Lego® bricks, αRep proteins can also be engineered into modular functional assemblies[8].

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5. Léger, C. *et al.* Picomolar Biosensing and Conformational Analysis Using Artificial Bidomain Proteins and Terbium-to-Quantum Dot Förster Resonance Energy Transfer. *ACS Nano* **2020**; 14, 5956–5967.
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7. Kariyawasam, K. *et al.* An Artificial Hemoprotein with Inducible Peroxidase- and Monooxygenase-Like Activities. *Chemistry* **2020**; 26, 14929–14937.
8. Moreaud, L. *et al.* Design, synthesis, and characterization of protein origami based on self-assembly of a brick and staple artificial protein pair. *Proc Natl Acad Sci U S A* **2023**; 120, e2218428120.

Keywords: protein engineering; directed evolution; repeat protein, αRep, specific protein binders

Type de communication : communication orale ☒ flash ☐ affiche ☐

Structural dynamics insights from *in-cell* EPR of proteins.

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Résumé :

Understanding how the intracellular medium modulates protein structural dynamics and protein-protein interactions is an intriguing but required topic scientists search to address by studying biomolecules in their native environment. As the cellular environment cannot be reproduced in vitro, investigation of biomolecules directly inside cells has attracted a growing interest in the past 20 years. Indeed, efforts in magnetic resonance spectroscopies have enabled important improvements in the study of structural dynamics directly in the cellular context.

Among magnetic resonances approaches, site-directed spin labeling coupled to electron paramagnetic resonance spectroscopy (SDSL-EPR) has demonstrated to be one of the powerful approaches to study structural properties of biomolecules.[1,2] In particular, nitroxide-based SDSL-EPR couples the benefits of high sensitivity and the lack of size constraints for the biomolecule of interest with the ability to study protein structural transitions and interactions at physiological temperature.[3,4]

In this talk, we will focus on the tools and strategies currently available to investigate cytosolic proteins within cells by SDSL-EPR. We will also discuss the impact of cellular health conditions on the protein folding state (and on the EPR spectra) in bacterial cells.

1. Pierro A., Bonucci A., Magalon A., Belle V., Mileo E. *Impact of cellular crowding on protein structural dynamics investigated by EPR spectroscopy.* Chem. Rev., under review (2024).

2. G. Karthikeyan, A. Bonucci, G. Casano, G. Gerbaud, S. Abel, V. Thomé, L. Kodjabachian, A. Magalon, B. Guigliarelli, V. Belle, O. Ouari, E. Mileo *A Bioresistant Nitroxide Spin Label for In-Cell EPR Spectroscopy: In Vitro and In Oocytes Protein Structural Dynamics Studies.* Angew. Chem. Int. Ed.*, 130,* 1380-1384 (2018).

3. A. Pierro, A. Bonucci, D. Normanno, M. Ansaldi, E. Etienne, G. Gerbaud, E. Pilet, B. Guigliarelli, O. Ouari, A. Magalon, V. Belle, E. Mileo *Probing the Structural Dynamics of a Bacterial Chaperone in Its Native Environment by Nitroxide-Based EPR Spectroscopy.* Chem. – Eur. J.*, 28, e202202249* (2022).

4. A. Pierro, K. C. Tamburrini, H. Leguenno, E. Etienne, G. Gerbaud, B. Guigliarelli, V. Belle, B. Zambelli, E. Mileo *In-cell investigation of the conformational landscape of the GTPase UreG by SDSL-EPR.* iScience, *26 (10),* 107855 (2023).

Keywords: in-cell EPR; protein structural dynamics; spin labels

Les sydnonimines, de nouveaux composés mésoioniques pour la libération d'isocyanates dans les cellules

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Résumé: Le développement de réactions chimiques pouvant être réalisées dans des organismes vivants fascine depuis longtemps les chercheurs. Une réaction bio-orthogonale est caractérisée par la réaction de deux fonctionnalités, qui réagissent dans des conditions physiologiques douces et sont inertes vis-à-vis de l'environnement biologique. D'autre part, la découverte de réactions chimiques répondant aux critères du concept de la chimie click continue d'avoir un impact énorme dans de nombreux domaines de recherche. Depuis les travaux pionniers de C. R. Bertozzi, la chimie bioorthogonale s'est développée en particulier dans le domaine de la ligation chimique. Plusieurs réactions permettant de lier des objets moléculaires les plus complexes dans des milieux biologiques tels que le sang, l'intérieur des cellules ou même l'animal ont été développées et exploitées pour diverses applications. En revanche, le nombre de réactions permettant une coupure bioorthogonale est plus restreint. Notre laboratoire est impliqué dans la découverte et l'utilisation de telles réactions.
Des travaux récents de notre équipe ont permis d'identifier de nouveaux composés mésoioniques capables de réagir efficacement avec les alcynes cycliques et de libérer des isocyanates dans les milieux biologiques.[1] Ces propriétés ont notamment été utilisées pour le marquage permanent de cellules.[2]

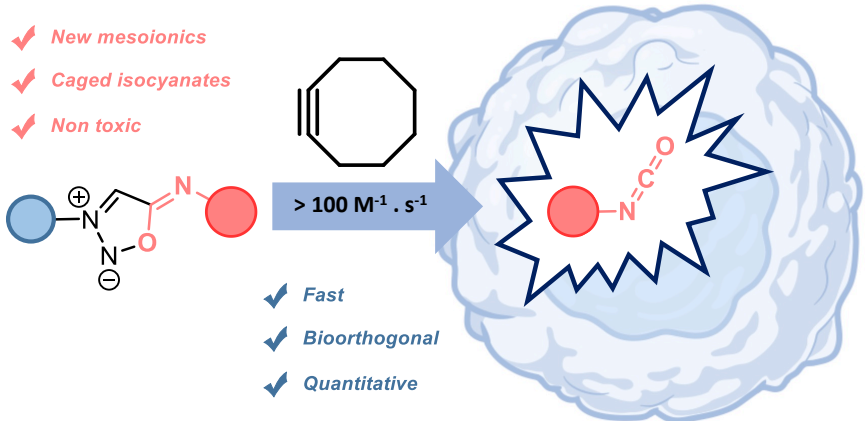

Fig. 1 Générateurs bioorthogonaux d'isocyanates.

[1] **Fast and Bioorthogonal Release of Isocyanates in Living Cells from IminoSydnones and Cycloalkynes.** M. Ribéraud, K. Porte, A. Chevalier, L. Madegard, A. Rachet, A. Delaunay-Moisan, F. Vinchon, P. Thuéry, G. Chiappetta, P. Alexandre Champagne, G. Pieters, D. Audisio, and F. Taran. *J. Am. Chem. Soc.* **2023,** *145*, 4, 2219–2229.

[2] **Synthesis of Sydnonimines from Sydnones and their use for bioorthogonal release of isocyanates in cells.** J. Baudet, E. Lesur, M. Ribéraud, A. Chevalier, T. D'Anfray, P. Thuéry, D. Audisio, F. Taran. *Chem. Commun.* **2024**, *60*, 3657-3660.

Type de communication : communication orale ☒ flash ☐ affiche ☐

Illuminating Temporal Dynamics: BRET Probes Unveil Chemically-Induced Ion Channel Gating During HTS Campaigns

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Résumé :

Ion channels are attractive drug targets for many therapeutic applications. However, highthroughput screening (HTS) of drug candidates is difficult and remains very expensive. We recently have developed various intramolecular and intermolecular assays using the Bioluminescence Resonant Energy Transfert (BRET) technique for monitoring ligand-gated and polymodally-activated ion channels. Thanks to these assays, we can assess in real-time and in live cells the dynamic of ion channel conformational changes, protein-protein interactions, trafficking and cations subnanometric concentration in the vicinity of the gated pore (1–3). Thanks to our BRET probes targeting TRPV1 conformational changes and coupling to the Calmodulin, we successfully screened the small-sized Prestwick library encompassing 1280 FDA- and EMA-approved compounds with high structural diversity (2). Multiparametric analysis of our results indicated that our BRET probes may advantageously be included in ion channel drug screening campaigns. Nonetheless, this former screening was performed using end-point measurement. Recently, using new BRET probes to measure the selective Ca^{2+} and K^{+} concentration in the nanoenvironment of the TRPV1 pore, we have shown that some known inhibitors can trigger a transient and selective gating of TRPV1 (1). This prompted us to explore the potential significance of kinetics/dynamics of cation fluxes in ion channel drug screening using our BRET probes.
We here evaluated the temporal response elicited by the Prestwick compound to either trigger an inward Ca^{2+} flux through TRPV1, P2X4 or P2X7 channels immediately after injection, or to inhibit the chemical activation of these channels. The compounds were successfully categorized based on their capacity to induce one of 8 distinct temporal signatures. It is noteworthy that all identified temporal signatures can be readily subjected to mathematical modeling (4). We will showcase results examining whether the specific shape of the temporal signature, observed post-injection, holds predictive value for potential inhibitory effects on ligand-gated ion channels.

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Keywords: Ion channels, BRET, molecular pharmacology, Drug screening

Type de communication : communication orale ☒ flash ☐ affiche ☐

Inhibiteurs peptidiques covalents ciblant des histidines : une nouvelle approche pour bloquer les interactions protéine-protéine

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Résumé :

Au cours de la dernière décennie, le développement d'inhibiteurs covalents ciblés (TCIs) s'est accéléré avec la mise sur le marché de plusieurs molécules, notamment pour le traitement de cancers et d'infections virales.[1] Ces avantages peuvent inclure, entre autres, une efficacité, une sélectivité et une durée d'action améliorées. De plus, les inhibiteurs peptidiques dotés d'un mode d'action irréversible peuvent représenter des modalités émergentes pour cibler les interfaces d'interaction protéine-protéine étendues pour lesquelles les petites molécules ne sont pas toujours efficaces. Les TCIs ciblent généralement la cystéine, le résidu d'acide aminé le plus réactif, mais la faible abondance des cystéines libres constitue une limitation au développement de TCIs. En revanche, il n'existe qu'une poignée d'études sur l'utilisation de l'histidine comme nucléophile, comme le souligne un article récent,[2] son intérêt potentiel dans la découverte de médicaments est largement négligé. Le fait que l'histidine soit beaucoup moins fréquemment ciblée par les inhibiteurs covalents que la cystéine ou même la lysine peut être attribué à sa plus faible nucléophilie, ce qui la rend plus difficile à cibler. Ces dernières années, notre consortium a développé des inhibiteurs peptidiques de l'anneau β,[3] un composant essentiel du réplisome bactérien qui a été identifié comme une cible pertinente pour le développement de nouveaux agents antimicrobiens. Cette protéine agit via des interactions protéine-protéine avec les polymérases. L'anneau d'*E. coli* contient un résidu histidine qui borde le site de liaison, et ce résidu est largement conservé parmi les pathogènes à Gram-négatif et à Gram-positif. Nous avons exploré la possibilité de cibler ce résidu avec des ogives électrophiles modérées pour former une inhibition covalente. Dans ce travail, nous avons anticipé que la plus faible réactivité de l'histidine pourrait également être contrebalancée par le positionnement précis d'ogives électrophiles à proximité du groupe imidazole de l'histidine en utilisant une approche de conception basée sur la structure.[4] Au cours de cette présentation, je présenterai les derniers résultats obtenus dans notre laboratoire.

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Keywords: inhibiteur covalent ciblé; ; alkylation d'histidine ; peptides ; interaction protéine-protéine ; réplication de l'ADN.

Type de communication : communication orale ☒ flash ☒ affiche ☐

Synthèse et évaluation de sondes originales ayant un déclencheur ester de borinate pour la détection rapide du peroxyde d'hydrogène

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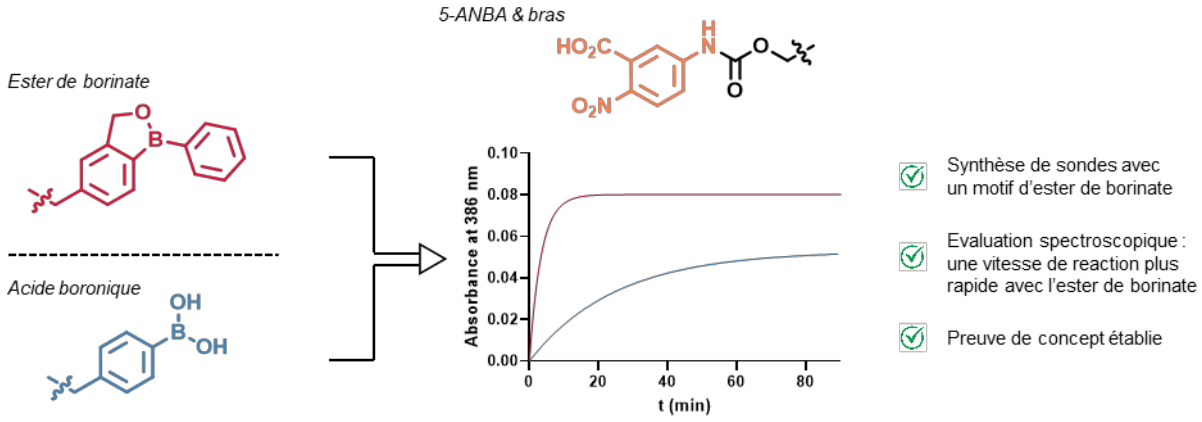
Dans un environnement biologique, le peroxyde d'hydrogène intègre la catégorie des *ROS* (*reactive oxygen species*, espèces réactives de l'oxygène). Naturellement présent dans les cellules à faible concentration, sa sur-production dans les cellules (appelée stress oxydant) peut induire plusieurs pathologies : maladies neurodégénératives et cardio-vasculaires, cancers ou diabètes. [1] De nombreux groupes de recherche se sont intéressés à l'étude de la formation, la propagation et l'impact du peroxyde d'hydrogène dans les cellules en utilisant principalement des sondes fluorescentes. Ces sondes sont composées, en général, de deux parties : la partie comportant le groupe fluorescent et la partie réactive vis-à-vis du peroxyde d'hydrogène. Cette dernière a été très investiguée et le motif basé sur des acides boroniques/esters de boronate est le plus exploré principalement en raison de sa facilité de synthèse. [2] En revanche, les cinétiques de réaction ne sont pas assez rapides pour avoir une estimation en temps réel de la concentration du peroxyde, ainsi qu'une bonne résolution en imagerie. Dans de récentes études, les acides boriniques – atome de bore lié à deux carbones au lieu d'un seul pour les dérivés boroniques – se sont révélés avoir de bien meilleurs résultats cinétiques. [3] Cependant, la synthèse et la purification de ces dérivés sont difficiles. Pour pallier ces inconvénients, nous avons conçu de nouvelles sondes originales contenant un déclencheur ester borinate inclus dans un squelette de type benzoxaborole, supposé être plus facilement accessible et plus stable. La deuxième partie de la sonde est composée d'un groupement chromophore (5-ANBA) connecté *via* un bras auto-immolable de type carbamate. En présence de peroxyde d'hydrogène, cette sonde a montré une vitesse de réaction significativement plus rapide comparée à son homologue acide boronique, validant notre preuve de concept.



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Keywords: sondes, ester de borinate, peroxyde d'hydrogène.

Type de communication : communication orale ☒ flash ☐ affiche ☐

Photoactivatable Warheads for Photoaffinity Labeling of Nucleic Acid Secondary Structures

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Résumé :

Small synthetic molecules have been shown to be able to bind and stabilize the secondary nucleic acid known as G-quadruplex (G4s) *in vitro* and to interfere with biological processes involving genes containing those structures.[1] Together with reversible G4 ligands,[2] reactive compounds capable of forming covalent bonds with G4s upon thermal, photochemical, target proximity and singlet oxygen activation have been conceived. Photochemical activation strategies exploit new class of promising G4 ligands with the potential to be harnessed for identification and isolation of G4s.[3] Differently from thermal activation, photoaffinity labelling of G4 ligands encompasses the potential to obtain spatial and temporal control over the alkylation event, enriching diagnostic and therapeutic strategies. However, to date, only a few examples of alkylating G4 ligands for photolabeling approaches have been described. Herein, the synthesis of new families of photoactivatable G4 ligands is presented together with their biophysical, biochemical, and photochemical characterization (Figure 1).[4]

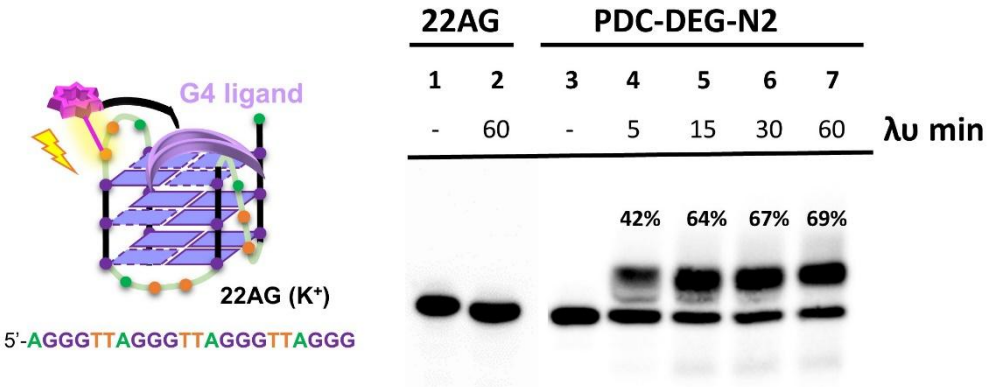

Figure 1. Photoalkylation efficiency of G4 ligands determined by denaturing gel.

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Keywords: G-quadruplexes; G4 ligands; Photoaffinity labelling; Biophysics; Biochemistry.

Type de communication : communication orale ☒ flash ☐ affiche ☐

Influence of pH and glutathione on the pro-oxidant activity of copper-based drugs

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Résumé :

In Nature, the redox cycling of copper (Cu) ions is tamed to catalyse dioxygen activation within enzymatic active sites. On the other hand, the aerobic redox chemistry of some Cu-complexes can also lead to the formation of harmful reactive oxygen species (ROS, e.g. $O_2^{\bullet-}$, H_2O_2 and $HO^{\bullet}$) and oxidative stress.[1] Hence, a number of Cu-complexes have been developed for anticancer purposes based on a potential pro-oxidant capacity.[2] However, it has recently been shown that in most cell compartments, including cytosol and nucleus, the ability of such Cu-complexes to catalyse ROS generation is challenged, by the presence of glutathione (GSH) and metallothioneins, which undermine the stability of Cu-based drugs by reducing and dissociating Cu(II) from the ligand and forming redox-inert Cu(I)-thiolate clusters.[3-5] For instance, we and others proved that the stability of Cu-thiosemicarbazones against GSH correlates with their ability to produce ROS and their cytotoxicity.[6,7] These findings suggested that some Cu-complexes may have higher stability and hence activity in organelles devoid of metallothioneins, such lysosomes. We therefore investigated the ROS production catalysed by the anticancer Cu-Dp44mT complex, known to accumulate in lysosomes,[8] in the presence of GSH, and showed that it catalyses ROS production more rapidly at lysosomal pH 5 than at cytosolic pH 7.4, and that lysosomal acidification is critical for its cytotoxic activity.[9] Furthermore, we observed a similar catalytic and cytotoxic behaviour for the Cu-phenanthroline (Cu-Phen) complex.[10] Our spectroscopic investigations showed that the higher pro-oxidant activity results from the higher stability of Cu-Phen against GSH at lysosomal pH. Overall, these studies point to lysosomal targeting as an innovative and effective strategy to improve the stability and the cytotoxic activity of Cu-based drugs.

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Keywords: reactive oxygen species; anticancer drugs; lysosomes.

AN ENZYME-RESPONSIVE SELF-IMMOLATIVE RECOGNITION MARKER FOR MANIPULATING CELL-CELL INTERACTIONS

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The development of innovative strategies for cell membrane engineering is of prime interest to explore and manipulate cell-cell interactions. Herein, we designed an enzyme-sensitive recognition marker that can be introduced on the cell surface via bioorthogonal chemistry. Once functionalized in this fashion, the cells gained the ability to assemble with cell partners coated with the complementary marker through non-covalent click chemistry. The artificial cell adhesion induced natural biological processes associated with cell proximity such as the slowdown of cancer cell proliferation. On the other hand, the enzymatic activation of the stimuli-responsive marker triggered the disassembly of cells, thereby restoring the tumor cell proliferation rate. Thus, our study showed that the ready-to-use complementary markers were valuable tools for controlling the formation and the breaking of bonds between cells, offering an easy way to investigate biological processes associated with cell proximity.

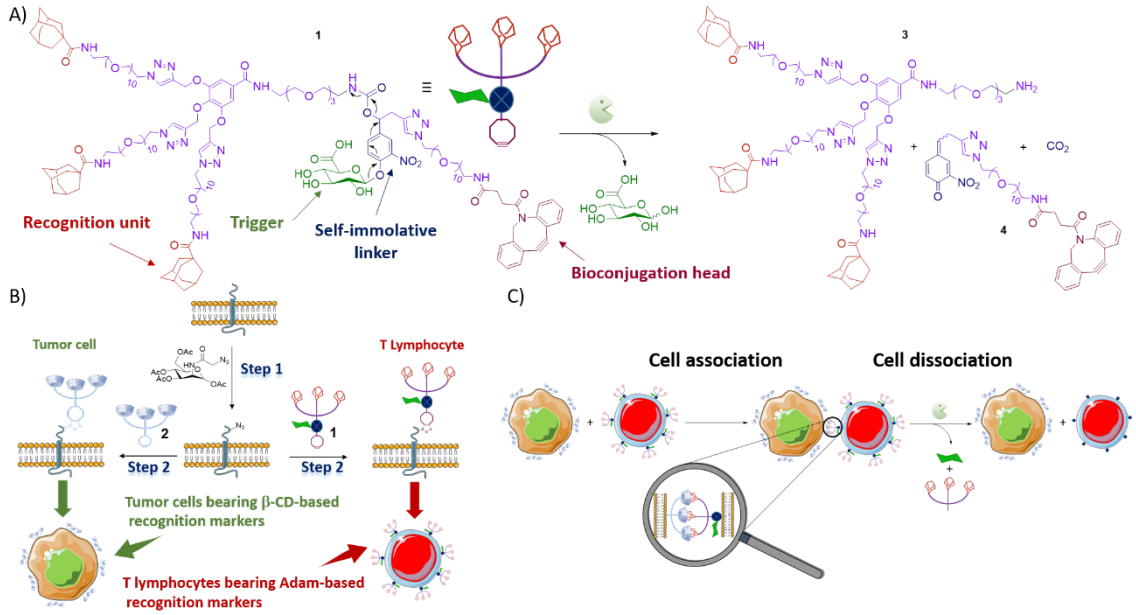

Figure 1. A) Structure and self-immolation mechanism of the artificial recognition marker **1** in the presence of β-glucuronidase; B) Principle of cell surface marker engineering with the complementary artificial markers **1** and **2**; C) Chemistry with cells: formation and breaking of bonds between cells

Type de communication : communication orale ☒ flash ☐ affiche ☐

Guanidinium-Stapled Helical Peptides for Targeting Protein-Protein Interactions

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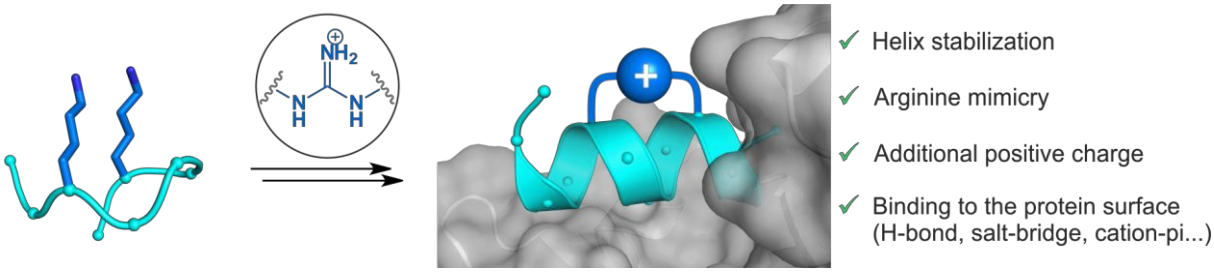
Résumé :

α-Helices are frequent at protein binding interfaces and helical peptides are an excellent starting point to develop inhibitors of protein-protein interactions (PPI). However, α-peptides may have certain pharmacological drawbacks, including conformational flexibility, sensitivity to proteolysis and limited cell permeability. To address these issues, side chain to side chain macrocyclization is a widely used approach to stabilize peptides in their bioactive conformation and prevent proteolysis.[1] A large variety of staples (e.g. lactams, thioethers, hydrocarbons…) has been described and employed successfully, yet efficient trafficking to the cytosol or the nucleus remains a challenge in achieving cellular activity. Therefore, the stapling approach is often combined with point mutations within the sequence to enhance the overall positive charge of the peptide,[2-3] or with bioconjugation to a cell-penetrating peptide. Despite the existing toolbox, there is still the need to diversify macrocyclization techniques to endow peptides with suitable properties.

In this work, we thought to develop a macrocyclization strategy that would simultaneously contribute to structure stabilization and increase positive charge, by forming a guanidinium bridge between side chains. We report an efficient solid-phase synthesis approach for introducing such guanidinium staples from naturally occurring amino acid side chains, and applied it to various biologically active peptide sequences. Positive impacts in terms of helical conformation stabilization and affinity to the protein targets, as well as structural details will be discussed.



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Keywords: Stapled peptide, helix, guanidinium, protein-protein interaction.

Type de communication : communication orale ☒ flash ☐ affiche ☐

Engineering optical aptasensors for the detection of fungicides

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Fungicides are commonly used in agriculture for the control of various plant diseases. Their presence in the environment and food chain has to be actively monitored as they can be carcinogenic and endocrine-disrupting at high doses. Standard detection methods based on mass spectrometry are time-consuming, expensive and use large equipment, which makes them unsuitable for on-site measurements and untrained users. The development of simple, portable devices for the rapid and selective detection of fungicide residues is an imperative and our efforts are devoted to the engineering of such biosensors.[1,2]

Aptamers, single-stranded oligonucleotides which fold into 3D structures, bind to a wide range of targets with high affinity and specificity. As an alternative to monoclonal antibodies, they provide several advantages, including simple, fast and cheap production, easy modification, excellent stability and reproducibility, in particular for the detection of small organic molecules.[3]

Novaptech's innovative technology, **NOVAswitch,** allows the selection of sensing aptamers, which undergo a target-induced conformational change, and their integration in real-time, user-friendly, multiplexed biosensors. In that view, aptamers against three different but chemically related fungicides were selected and sequenced. Their affinity and specificity were assessed by various binding assays (i.e., molecular beacon, SPR, BLI). Following optimization, truncated aptamers were associated to lanthanides nanoparticles, generating optical biosensors. Quantitative detection of fungicides in the ppb range was achieved. Measurements can be carried out using Indigo, a simple, portable spectrophotometer, allowing the detection of fungicides in the field with transmission of the results to a cell-phone.

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Keywords: fungicides, aptamers, aptasensors, fluorimetry, colorimetry

Type de communication : communication orale ☒ flash ☐ affiche ☐

Aptamers for Drug delivery Systems: more than targeting agents

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Résumé :

Aptamers are synthetic single strand DNA, RNA or modified oligonucleotides that adopt a three-dimensional structure leading to the interaction with their given target. They are discovered by Systematic Evolution of Ligands by Exponential enrichment (Selex) from a large library of sequences through iterative cycles of binding with their target and amplification. Their high affinity and specificity make aptamers valuable alternatives to antibodies, and have been explored as therapeutic agents, imaging agents, or targeting moieties. Interestingly, the DNA nature of aptamers offers the possibility to program and control their structure and supramolecular assembly, opening applications in biomaterials and drug delivery.

In our team, we are developing aptamers as multifunctional nanocarriers for targeted drug delivery. In a first project, we have developed aptamers as drug carriers to program the sustained release of anticancer drugs, such as doxorubicin, in vitro and in vivo. Precise design of aptamers enable in vivo reservoirs to maintain a therapeutic drug concentration without concomitant toxicity.

In a second project, we have assembled drug-binding aptamers with targeting aptamers to carry a model drug to a specific protein. The stepwise assembly, loading capacity and targeting ability will be explained. Ongoing projects exploit this strategy to develop targeted nanocarriers for gastric and liver cancer.

Keywords: aptamers; drug delivery; targeted delivery, non-covalent binding…

Communications Flashs

Type de communication : communication orale ☐ flash ☒ affiche ☐

DESIGN OF NEW BIPHOTONIC PROBES FOR BIO-CELL IMAGING

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Since the beginning of the 2000, fluorescent probes have become an important aspect of *Chemical Biology*. These fluorophores are used as visualization tools *in cellulo* in many applications, such as diagnosis and imaging tools.

NIR I to NIR II (700-1700 nm) absorption and emission wavelengths are requirements for bioimaging. NIR fluorescent probes show high spatiotemporal resolution, while preserving their unique advantages such as high sensitivity, low light scattering, reduced autofluorescence and photodamages.[1] One of the way to reach such excitations wavelengths is to use two photon excitation[2]. Molecular engineering of two photon chromophores led to the identification of π-conjugated quadrupolar systems (D-π-A-π-D or A-π-D-πA) or octupolar systems as excellent two-photon absorbers[3]. Unfortunately, there is still a lack of two photon excitable fluorophores that are both efficient and biocompatible.

Our team has synthetized new biphotonic probes, water soluble with biphotonic cross section up to 3630 GM, called Acri-Py[3]. The main goal is to modify the Acri-Py structure (Fig. 1) to improve photophysical properties and red-shift the emission to the NIR. Our strategy consists of changing chemically the acceptors, while keeping the already optimized Acridane core.

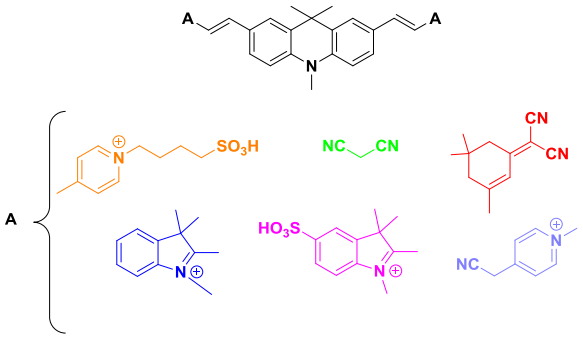

Fig 1 : structure of the synthetized probes

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Type de communication : communication orale ☐ flash ☒ affiche ☐

Bioorthogonal reaction for safer and more accurate ImmunoPET imaging

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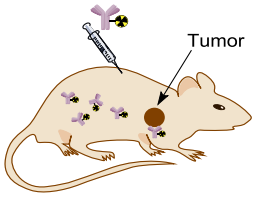
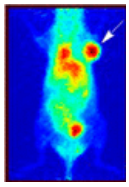
Résumé :

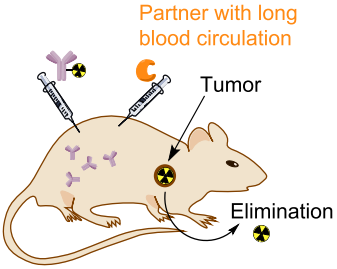
In the classical approach, ImmunoTEP's potential for precision cancer diagnosis has not be fully realized due to imperfect targeting and sub-optimal antibody pharmacokinetics. Indeed, only a limited percentage of the injected dose (generally <10%) reaches its target after several days, due to the intrinsically long biological half-life of antibodies in the body. This results in a persistent background in PET imaging. Furthermore, antibodies are generally labelled with zirconium-89, which has a half-life of 3.2 days. The use of zirconium generates dosimetry problems for the patient and makes the clinical organization of examinations complicated.

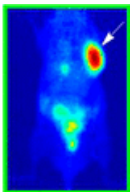




Our approach:

The aim of our work is to improve PET imaging by enabling "chemically controlled" removal of the radioelement using in vivo click reactions. We are planning a bioorthogonal reaction to detach the radioelement from the antibody between a iminosydnone and cycloalkyne. Once released from its antibody, the radioelement should be rapidly eliminated, thus improving the signal-to-noise ratio in ImmunoPET imaging and reducing the dose to the patient. The antibody would remain attached to the click partner, bearing groups such as a PEG arm that allow long blood circulation, so as to maintain its therapeutic activity.





Keywords: Medical imaging, ImmunoPET, bioorthogonal chemistry, clearing agent, masking agent, pre-targeting

Type de communication : communication orale ☐ flash ☒ affiche ☐

Click and Cross: Trigger fluorogenic photo-crosslink by click chemistry

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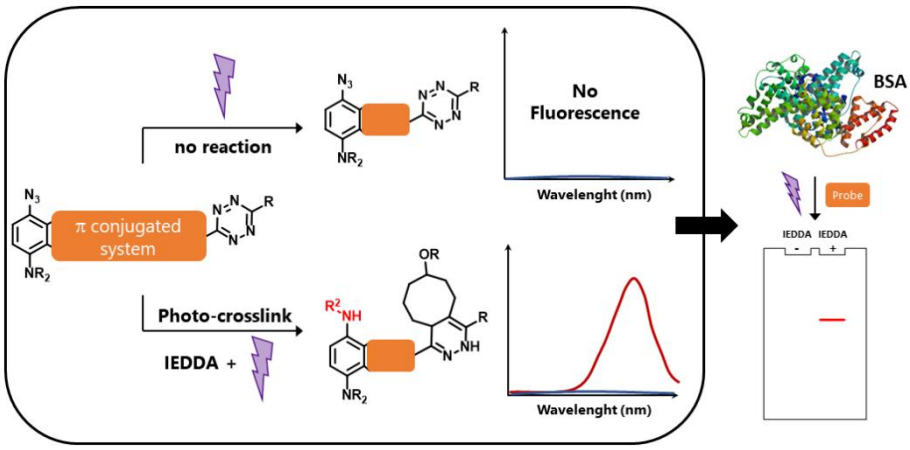
Résumé :

Spatio-temporal chemical modifications to track the transient interactions of proteins or biomacromolecules in living cells are a powerful tool for studying their interactome.[1,2] Photo-cross-linking induced turn-on fluorescence allow both target binding and labelling to be achieved in one step. However, these fluorogenic photo-crosslinker groups are often cumbersome[2] and their presence on biomacromolecules can interfere with their interaction with other partners. Given that technologies now exist to position clickable groups in a site-specific manner on biomacromolecules,[3,4] we describe herein the development of a new fluorogenic photochemical tool that enables photocross-link using visible light triggered by a click chemistry reaction (Click to Cross concept). The advantage is that stappling can be carried out after complexation of the biomacromolecules. The fact that the photo-crosslink reaction can only take place after the click reaction should restrict strongly the fishing of off-targets and the fluorescence background signal.

To this aim, a novel photochemical probe was designed as follows: an aryl azide moiety was connected to an extended π conjugation system that ends with a tetrazine used as a trigger by reacting through an inverse electron-demand Diels-Alder reaction (IEDDA). As proof-of-concept, preliminary *in vitro* studies using BSA as a protein model showed that, under visible light, a fluorogenic probe-protein bond is created only in the presence of a *trans*-cyclooctene (TCO) moiety.



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Keywords: Click and Cross; Fluorogenic Photocross-Linking; Click Chemistry, Proteomic.

Type de communication : communication orale ☐ flash ☒ affiche ☐

Directing cell fate : multifunctional DGL-PEG hydrogels to control hMSCs osteogenic differentiation

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Résumé :

The local properties of the extracellular matrix (ECM) play a central role in the regulation of cell behaviour and fate. Hence, the design of biomimetic materials to guide stem cell differentiation requires the combination of the biochemical and physical features of the niche microenvironment.

Here, for the first time, Generation Five (G5) dendrigrafts of poly-L-lysine (DGL-G5) were used as multifunctional crosslinkers to control the stiffness and surface functionalisation of poly(ethylene) glycol (PEG) hydrogels for the differentiation of human mesenchymal stromal cells (hMSCs) to the bone lineage.

DGL-G5 are multivalent, dendrimer-like nanoparticles presenting one of the highest densities of terminal amine functions, thus enabling broad-range control of hydrogel stiffness and surface conjugation with bioactive peptides. Stiff hydrogels were formed via amide bonds crosslinking between DGL-G5 and carboxyl-terminated PEG chains, modulating the dendrimer crosslinking degree to vary network stiffness within the cell-relevant range (1-100 kPa). A comprehensive characterisation encompassing bulk and surface mechanical properties was conducted using shear oscillatory rheometry, compression, and atomic force microscopy (AFM). The hydrogels exhibited linear, frequency-independent storage moduli (G') and negligible loss moduli (G''), indicating a purely elastic behaviour typical of covalent networks. Bulk Young modulus (E) calculated in rheometry and compression were consistent and agreed with AFM-measured surface modulus, revealing homogeneous stiffness at various length scales.

Hydrogel surfaces were functionalised with an equimolar combination of an RGD-containing peptide and a mimetic of the bone morphogenetic protein 2 (BMP-2), a well-known osteogenic growth factor. The peptides were selectively coupled by the terminal cysteine to the free amines on DGL-G5 using a maleimide-PEG-NHS linker. Surface grafting was estimated via confocal fluorescence microscopy. Subsequently, the osteoinductive potential of DGL-PEG hydrogels on hMSC differentiation was preliminarily assessed through immunofluorescence staining and quantification of early (Runx2) and late (OPN) osteogenic markers.

Keywords: hydrogel, stiffness, mesenchymal stem cells, osteogenic, differentiation

Type de communication : communication orale ☐ flash ☒ affiche ☒

Fluorescent organic nanoparticles as nanovectors for drug release activated by temperature/light & MRI monitoring

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Abstract :

Since the 1980's, nanoscience has opened promising prospects in nanomedecine with the design of more specific and efficient therapeutic agents. Applications include the design of nanocarriers, such as organic polymeric nanovesicles or liposomes, capable of transporting drugs directly to unhealthy cells. This enables more targeted delivery, reducing side effects and improving the effectiveness of treatments by a better bioavailability and the possibility to control spatially and temporally their release by an external stimulus. The control of drug delivery triggered by endogenous acidification of the tumor microenvironment but also by a localized temperature jump would make it possible to deliver anti-cancer drugs to the tumor site and increase their clearance and efficacy. This PhD work, aims to encapsulate, then release under light irradiation, sufficiently concentrated anti-cancer drugs in the target area from vesicles called thermosensitive polymersomes obtained by auto-assembly [1]. The goal is to convert the energy provided by light irradiation in the first spectral biological window (600-1000 nm) into thermal energy by using small organic nanoparticles [2,3] which are functionalized by strongly absorbing dyes (deep red – NIR1 region) that will generate localized heating via thermal relaxation. Thermal elevation will be monitored and controlled by a high-performance MRI temperature imaging technique recently developed by one of the "*IMPACT*" Network team. This is a complex and highly innovative approach that uses different nanoobjects which involve collaboration between synergistic disciplines to fight against cancer.

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Keywords: Nanoparticles; Polymersomes; photothermal therapy; Drug delivery; MRI.

Acknowledgments: *This study received financial support from the French government in the framework of the University of Bordeaux's France 2030 program / RRI "IMPACT "; Impulsion Research Network on biomedical imaging.*

Type de communication : communication orale ☐ flash ☒ affiche ☐

Solid phase synthesis for protein conjugation

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Résumé:

Immunotherapies are often used as treatments for autoimmune and inflammatory diseases, viral infections and are widely used in cancer therapies. The use of antibodies is considered as very promising treatments compared to traditional chemotherapy, radiotherapy or surgery.[1] Since the first use of monoclonal antibodies (mAbs) in cancer therapies, scientists have developed biological approaches to develop bispecific and trispecific antibodies (bsAbs and tsAbs respectively), using recombination and cloning methods.[2,3] These entities can target different biological receptors and are a way to tackle the complexity of such disease. However, biological methods to produce multispecific entities suffer from inherent limitations that are linked to protein folding, cells culture and risks aggregation. More importantly, those strategies often lack modularity and versatility, and do not allow for a rapid screening of combinations.

To address these limitations, we have developed an approach that relies on bioortogonal click chemistry to synthesise multispecific antibodies (msAbs). For this, we are currently focusing on dibromopyridazinediones as a scaffold that can react with mAbs or related fragments (*e.g.*, Fab) and can be functionalised by various chemical functions (*e.g.,* tetrazines or strained alkynes). Inspired by solid-phase peptide synthesis, we want to use fragments of mAbs (Fab and Fab_2) as bricks to synthesise msAbs. To elongate the protein-protein chain on a solid phase synthesis, click pairs for coupling must be chosen wisely and novel click pairs shall be developed to adres the fine tuning of reactivity and stability.

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Keywords: bioconjugation, click chemistry, solid phase synhesis

Type de communication : communication orale ☐ flash ☒ affiche ☐

Sondes fluorogéniques excitables à deux photons pour la délivrance de drogue via des réactions bioorthogonales de type « Click-to-Release »

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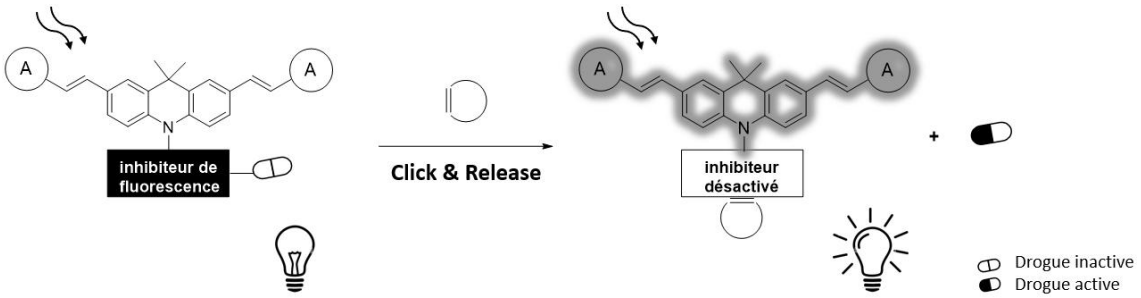
Résumé :

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



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

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Keywords: biphoton, sondes fluorogéniques, réactions bioorthogonales, Click-to-release

Type de communication : communication orale ☐ flash ☒ affiche ☐

Tailoring polymeric hydrogels for stem cell differentiation: impact of mechanical and bioactive properties

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Abstract :

Mesenchymal Stem Cells (MSCs) are adult multipotent stem cells, widely used in tissue engineering since they can differentiate towards various lineages, and thus are suitable in many applications. However, it is challenging to tightly control this differentiation process to obtain a single cell type, bone cells for instance. Achieving improved bone regeneration will likely involve mimicking the cell's native microenvironment, the stem cell niche. To this end, it is important to develop advanced biomaterial scaffolds with properties that can be tuned to replicate inside a cell culture plate the in vivo cellular environment.

In this project, we developed PEGDA hydrogels with tunable mechanical properties, including elasticity and viscoelasticity, as well as bioactivity achieved through the immobilization of a mixture of RGD and a mimetic peptide of the BMP-2 protein. By varying both the total polymer concentration and the molecular weight of the polymer chains, we obtained five hydrogels with different elasticity and viscoelasticity, evaluated through both oscillatory rheology and uniaxial compression. Solid-state nuclear magnetic resonance (ssNMR) was used to assess molecular mobility. Using a photoactivated crosslinker, we controlled the functionalization density independently of the mechanical properties. Finally, we investigated the impact of these properties on the osteogenic differentiation of hMSCs, finding that cells cultured on all hydrogels expressed an early osteoblast marker (Runx2) after two weeks, even in the absence of a differentiation-inducing medium.

Keywords : hydrogels, stem cells, bone tissue engineering, mechanical properties

Type de communication : communication orale ☐ flash ☒ affiche ☐

Novel synthetic phospholipids for the development of thiol-responsive liposomes

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Résumé :

Chemotherapy, a cornerstone in cancer treatment, faces hurdles such as non-specific targeting and adverse effects, prompting the exploration of nanoparticle-based delivery systems. These platforms generally exploit enhanced permeability and retention effects for targeting while addressing chemotherapy's limitations.[1,2]

Among these, liposomes, with their unique properties and biocompatibility, have garnered significant attention.[3] However, conventional liposomal formulations suffer from inadequate drug release at target sites, diminishing therapeutic efficacy.[4] To overcome this, stimuli-responsive liposomes, triggered by elevated GSH levels in the tumour microenvironments, have emerged as a frontier in cancer nanomedicine. Yet, existing formulations encounter stability issues and premature drug release, necessitating novel approaches.[5]

This project aims to develop thiol-sensitive liposomes that strike a balance between stability during circulation and reactivity in cancerous environments for controlled drug delivery in cancer therapy. By connecting a lipophilic tail to a hydrophilic head through an environment-sensitive linker, we aim to identify the optimal structure ensuring stability during circulation while maintaining thiol sensitivity for targeted drug release. Comprehensive characterization of the developed liposomes has been performed with a focus on release kinetics. Subsequently, the developed thiol-sensitive liposomes will undergo evaluation for drug release profiles, cytotoxicity against cancer cells in vitro, pharmacokinetic properties, and biodistribution in animal models.

By addressing these objectives, the research aims to advance thiol-sensitive nanoparticles, potentially overcoming challenges associated with premature cargo release. Hence this advancement could lead to improved efficacy and specificity in cancer treatment.

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Keywords: Organic Chemistry; Liposomes; Nanomedecine; Drug release

Communications par Affiches

Type de communication : communication orale ☐ flash ☐ affiche ☒

Systematic investigation of i-motif ligands

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Résumé :

i-Motifs are unusual secondary structures formed by stacking of hemiprotonated cytosine base pairs (CH^+:C) in cytosine-rich DNA strands.[1] Such structures have been well-studied *in vitro* and have also been detected in cells via immunostaining,[2] but their cellular roles remain unclear, mostly due to the lack of validated chemical biology tools to interrogate their biological functions. While numerous i-motif "ligands" have been reported in the literature, their effects on the stability of i-motifs remain strongly contradictory.[3–4] This is largely due to the fact that widely used methods to study DNA–ligand interactions, such as FRET- and CD-melting, are prone to artifacts when applied to i-motifs. Therefore, there is an urgent need to develop robust, unambiguous methods to study the effects of ligands on the stability of i-motifs.

A characteristic feature of i-motifs is their pH dependence. This feature can be exploited to study the stabilization effect of ligands. Here, we used isothermal potentiometric titration (i.e., controlled and stepwise increase of pH from 5.5 to 7.5 and back) to monitor the stability of i-motifs by circular dichroism. This way, we are able to observe the effects of various ligands on the reversible transition between i-motif and single-stranded DNA, quantitatively characterized by the ligand-induced shift of the transition midpoint (ΔpH_T).

Using this method, we tested several compounds that have been previously reported to interact with i-motifs. Surprisingly, most ligands showed none or very little effect on pH_T of various endogenous i-motifs[6]. In fact, stabilization induced by these ligands was only observed with specific sequences containing one or, better, two long loops. This phenomenon was already described for $[Ru(phen)_2dppz]^{2+}$ by Pages et al.,[5] but our results might indicate that most effects previously observed with other compounds might arise from non-specific interactions with i-motifs loops. Although several i-motif "ligands" described in the literature are yet to be tested, the quest for genuine structure-selective, i-motif stabilizing ligands remains open.

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Keywords: i-motif DNA; Circular dichroism; i-motif ligand

Type de communication : communication orale ☐ flash ☐ affiche ☐

From design to cellular activity: constrained peptide-foldamer inhibitors of p53-hDM2 interaction

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Résumé :

The tumor suppressor p53 is a transcription factor that regulates cellular responses by inducing cell death under stress conditions. The basal quantity of p53 in a cell is regulated by hDM2, an E3 ubiquitin ligase. However, overexpression of hDM2 in cancer leads to uncontrolled cell growth and tumor progression. Restoring the levels and activity of wild-type p53 through the use of inhibitors that target the hDM2-p53 interaction presents a promising strategy for cancer treatment.[1,2]

p53 interacts with a short region that adopts an α-helical conformation upon binding to hDM2. This region offers a basis for the design of inhibitors. However, conventional natural linear peptides have some limitations, including conformational flexibility, susceptibility to proteolysis and restricted cell permeability. To enhance and optimize these properties, innovative approaches have been developed, including peptide macrocylization and foldamer chemistry.[3-6]

In this work, we combined foldamer chemistry and macrocyclization strategies to enhance the potency of peptide-foldamer hDM2 ligands previously reported in the group. We generated a collection of stapled peptide-foldamer hybrids that we screened for their ability to inhibit p53-hDM2 interactions in a biochemical assay. This effort led to the identification of several inhibitors with high affinity for the target. From these lead compounds, we conducted molecular optimization to produce cell-active molecules capable of restoring p53 tumor suppressor activity. This research may offer new approaches to facilitate the generation of more effective foldamer-based inhibitors of protein-protein interactions and a more comprehensive understanding of the optimizations necessary to achieve cellular activity in the context of peptide lead optimization.

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Keywords: Peptide; Foldamer; Protein-protein interaction; Inhibitor; Helix; Macrocyclization; Thioether; p53-hDM2 Interaction; Cell viability

Type de communication : communication orale ☐ flash ☐ affiche ☒

DNA nanostructure based on conditional kissing interactions

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Résumé :

Thanks to its programmability, stability and accessible synthesis, DNA has been used as a biomaterial to detect molecules, treat diseases, deliver drugs and produce nano-objects.

Aptamers are single-stranded DNA (or RNA) molecules able to bind specific targets with high affinity and specificity. Among them, aptaswitches are dynamic aptamers which conformation change can enable a second interaction with a partner called aptakiss, through a well described kissing interaction. Moreover, the kissing interaction can be controlled by the presence or the absence of the aptaswitch target. Indeed, “positive” aptaswitch will engage a kissing complex with the aptakiss in the presence of its target; whereas, for “negative” aptaswitch, the kissing complex will be displaced upon target addition. This conditional kissing interaction has been used for small molecule detection or to trigger supramolecular nanostructures assemblies.

In this work, we exploited such kissing interactions to build a DNA nanostructure. Depending on the presence of a trigger, this DNA nanomachine adopt different supramolecular assemblies.

In a first step, we have designed Holliday Junction-Like structures using 4 DNA helixes assembled in a cross. Each cross extremity was flanked with aptaswitches and aptakisses, in order to get conditional assemblies. Two aptaswitches responsive to adenosine were used: the “positive” aptaswitch realizes a kissing interaction in the presence of adenosine and the “negative” realizes kissing only in the absence of adenosine. We demonstrated that the supramolecular assembly is conditioned to the presence of adenosine, through native electrophoresis. A first actuator is proposed and its functionality is monitored through FRET.

As perspectives, this type of structure based on aptaswitches could enable the implementation of logic gates. However, this will require the development of aptaswitchs; a general protocol for aptaswitch selection is proposed.

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Keywords: Aptamer, Nanostructure, Kissing Complex…

Type de communication : communication orale ☐ flash ☒ affiche ☒

Two-Photon Dye-based Fluorogenic Organic Nanoparticles: Surface functionalization for Hyperbright Biosensors or Biomarkers

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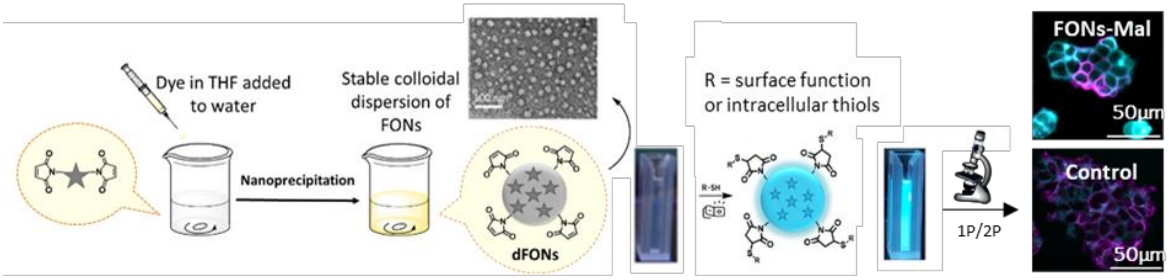
Abstract : Light-emitting nanoparticles are a unique class of optical nanomaterials combining improved brightness and photoresistance compared to standard dyes[1]. Among the numerous existing luminescent nanoparticles (QDs, UCNPs, P-dots…), the dye-based Fluorescent Organic Nanoparticles (dFONs)[2] are less known, while they offer many promises. As they only consist of hydrophobic organic dyes aggregated in water, their optical and physico-chemical properties only depends on the structure of the dye building blocks.[3] dFONS can be designed to be stealthy and used for *in vivo* single particle tracking or bioimaging[4,5]. For these purposes, surface functionalization is essential to target the biomolecules of interest[6].

Today, *there is no option to directly functionalize the surface of such dFONs*.

In this context, we propose an original approach based on the direct dye-functionalization through maleimide-thiol reaction. We synthesized a functional hydrophobic dye with maleimide functions, which upon nanoprecipitation in water, leads to ~15nm nanoparticles bearing maleimide surface groups. Interestingly, the pristine dFONs-maleimide are not fluorescent and turns on upon thiol surface reaction (Michael addition). For the first time, we demonstrated that such dFONs could be used as intracellular thiol sensors, working in the µM range (1 or 2P excitation). In addition, we proved that dFONs can be functionalized with small molecules like biotin. The resulting dFONs-biotin show comparable size and brightness as QDs[7], while being metal-free. The dFONS-biotin sucessfully recognise streptavidin, opening up interesting prospects as ultra-bright biomarkers.



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Keywords: fluorescence, nanoparticles, bioimaging, biosensing, surface functionalization

Type de communication : communication orale ☐ flash ☐ affiche ☒

Fluorescent Organic Nanoparticles for Optogenetic Applications

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Résumé :

Dye-based fluorescent organic nanoparticles are an exotic class of nanoparticles obtained by nanoprecipitation in water of pure dyes only. While the photophysical and colloidal properties of the nanoparticles strongly depend on the nature of the aggregated dyes, their excellent brightness in the visible and in the near infrared make these nanoparticles a unique and versatile platform for in vivo imaging. This work examines the promising utilization of these nanoparticles for in vivo optogenetics applications. Their photophysical properties as well as their biocompatibility and their capacity to activate chrimson opsin in vivo through fluorescence reabsorption process are discussed. Additionally, an illustrative example of employing these nanoparticles in fear reduction in mice through close-loop stimulation is presented.

Through an optogenetic methodology, the nanoparticles demonstrate an ability to selectively shutting-down neurons implicated in the fear response, thereby enabling precise spatiotemporal modulation of neuronal activity. The findings show that dye-based fluorescent organic nanoparticles represent an original and innovative strategy for optogenetic applications, holding substantial potential in the domain of translational neuroscience and pave the way for novel therapeutic modalities for anxiety and stress-related disorders.

Keywords: optogenetic, fluorescence, organic nanoparticles, close-loop, two-photon absorption

Type de communication : communication orale ☐ flash ☐ affiche ☒

Development of aptasensors for antibiotic monitoring

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Résumé :

Antibiotics are extensively used in agri-food industry and healthcare for their broad-spectrum antibacterial properties. However, their uncontrolled use has led to significant environmental pollution and food safety risks[1]. Among these, the rise of antibiotic resistance and its direct threat to human health has emerged as a pressing concern. Hence, there is a growing need for on-site antibiotic detection in both environmental and food assessments. Aptamer-based biosensors, offering a practical and cost-effective solution, have garnered significant attention in addressing this demand[2].

Aptamers are single-stranded nucleic acid molecules that fold into unique three-dimensional structures capable of specifically binding to target molecules with high affinity. They serve as recognition element in various applications, mimicking the properties of antibodies but with unique advantages such as stability and ease of synthesis and modification. Novaptech's cutting-edge technology capitalizes on the many benefits provided by aptamers in pollutants biosensing.

Novaptech identified aptamers for the specific and quantitative detection of nine aminoglycosides (streptomycin, kanamycin…) and tetracyclines. Exploiting their intrinsic switching and binding properties within fluorescence-based optical biosensors, in-field detection devices are currently in development, while other valuable classes of antibiotics are under investigation.

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Keywords: biosensor, aptamer, antibiotic

Type de communication : communication orale ☐ flash ☐ affiche ☒

Biochemical and functional characterization of SARS-CoV-2 Unique Domain (SUD) in Nsp3 – RNA G4 complexes and therapeutic properties of G4-ligands inhibiting their formation

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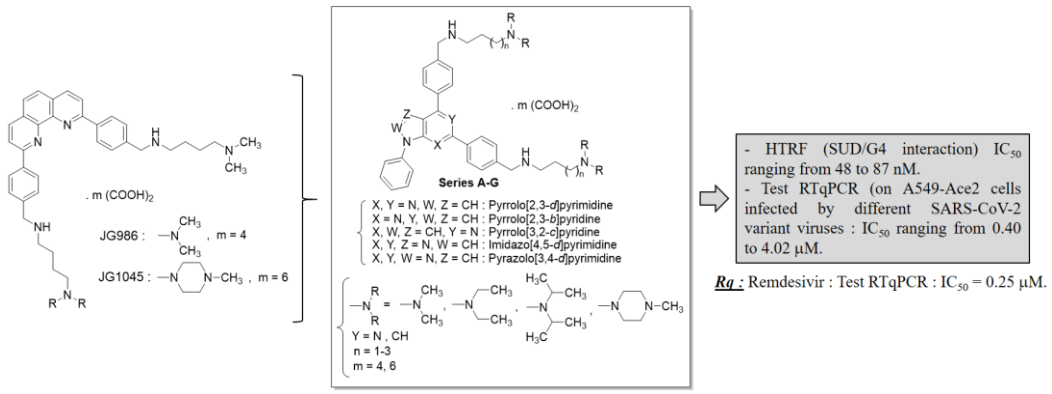
Résumé :

The multi-domain non-structural protein 3 (Nsp3) is an essential component of SARS-CoV viruses replication complex. Many functions of this protein remain unknown and may be targeted by new antiviral drugs. We have recently shown that the SARS-Unique Domain (SUD) present in SARS-CoV-2 Nsp3 can bind to cellular RNA G-quadruplexes (G4s). These interactions can be disrupted by mutations that prevent oligonucleotides from folding into G4 structures and, interestingly, by molecules known as specific ligands of these G4s.[1]



By taking into account the various structural parameters required concerning the previously described G4 ligands, we have developed new pyrrolopyrimidine bioisoster compounds analogs (series A to G) of the first identified bioactive phenanthroline hits.[2] Herein, we report on the synthesis of these new compounds and their efficient in vitro activities targeting the SUD/G4 interaction (by HTRF) and SARS-CoV-2 replication (in A549-Ace2 cells infected by different variant viruses). The pharmacological properties of these molecules have been further characterized. Two compounds combining the highest antiviral potencies and the lowest toxicities are currently tested in animal models of viral infection.

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Type de communication : communication orale ☐ flash ☐ affiche ☒

Ingénierie de nouvelles métalloenzymes

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Résumé :

Les métalloenzymes sont des enzymes dont l'activité catalytique implique des ions métalliques présents dans leur site actif. Les propriétés électroniques des métaux associés à l'environnement chiral des protéines offrent une grande diversité de réactivités chimiques. Dans le but de créer de nouvelles métalloenzymes capables de catalyser diverses réactions, plusieurs stratégies ont été explorées. D'une part, une approche d'évolution dirigée d'une métalloenzyme humaine a été initiée afin de détourner son activité enzymatique vers de nouveaux substrats. D'autre part, des métalloenzymes ont été conçues à partir d'une ossature protéique artificielle conçue au laboratoire [1]. Pour cela, une des protéines issues d'une bibliothèque de protéines artificielles appelées αRep a été utilisée. Sa structure dimérique très stable forme une cavité offrant plusieurs possibilités pour créer de nouvelles métalloenzymes. Par exemple en y greffant par couplage covalent sur une cystéine unique un complexe organométallique [2], [3] ou en utilisant l'ossature protéique αRep comme structure de base pour créer des sites métalliques *de novo* par modélisation.

Pour étudier l'interaction entre les ions métalliques et les métalloenzymes artificielles, diverses méthodes biophysiques ont été utilisées : spectrophotométrie UV-visible, microcalorimétrie, RPE, dichroïsme circulaire, Spectrométrie d'émission atomique par plasma micro-ondes (MP-AES) etc… L'activité catalytique des biohybrides a été étudiée sur un composé organophosphoré dont l'hydrolyse est suivie par spectrophotométrie UV-visible.

[1] A. Urvoas *et al.*, « Design, Production and Molecular Structure of a New Family of Artificial Alpha-helicoidal Repeat Proteins (αRep) Based on Thermostable HEAT-like Repeats », *Journal of Molecular Biology*, vol. 404, n° 2, p. 307‑327, nov. 2010, doi: 10.1016/j.jmb.2010.09.048.

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[3] K. Kariyawasam *et al.*, « An Artificial Hemoprotein with Inducible Peroxidase- and Monooxygenase-Like Activities », *Chemistry – A European Journal*, vol. 26, n° 65, p. 14929‑14937, 2020, doi: 10.1002/chem.202002434.

Type de communication : communication orale ☐ flash ☐ affiche ☒

Synthesis and reactivity of oxaziridines and diaziridines as ReACT bioconjugation reagents

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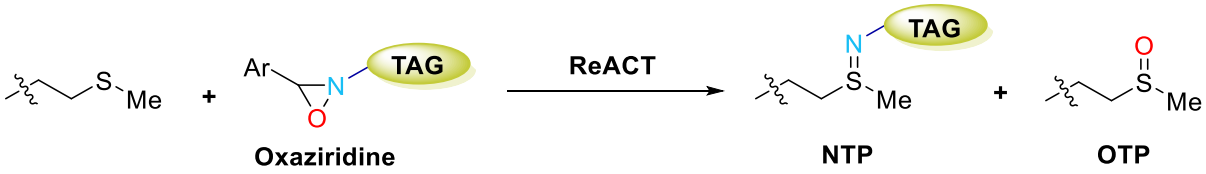
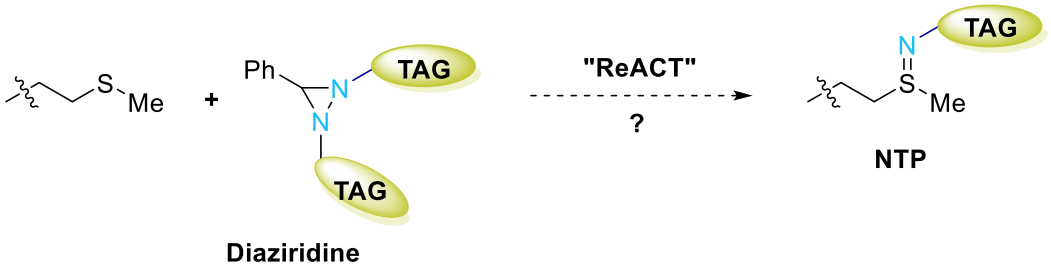
Résumé:
ReACT (Redox Activated Chemical Tagging) chemistry is a recently emerged bioconjugation method allowing selective protein modification at methionine residues[1] and biotin tagging[2]. This ligation method is based on the chemoselective reaction of oxaziridines with sulfides, forming sulfimides as *N*-transfer product (NTP) and resulting in sulfide conjugation with various tags (Scheme 1). However, an unproductive *O*-transfer product (OTP, sulfoxide) can also result from the reaction of oxaziridines with sulfides. The efficiency of each competing pathway and the stability of NTPs are related to the chemical structure of the starting oxaziridine.[3] Various oxaziridines were synthesized and the NTP/OTP ratio obtained from their reaction with a model methionine derivative will be presented. In addition, we considered the development of synthetic routes to diaziridines which could represent alternative ReACT reagents avoiding the formation of undesired OTP byproducts (Scheme 2).



Scheme 1 : ReACT bioconjugation using oxaziridines as bioconjugation reagents



Scheme 2 : ReACT-inspired reaction using diaziridines as bioconjugation reagents

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2. Cotton *et al. ACS Chem. Biol.* **2022**, *17*, 3270–3275.
3. Elledge *et al. PNAS,* **2020**, *117*, 5733–5740.

Keywords: Bioconjugation; Methionine; Oxaziridine; Diaziridine

Abstract poster

Titre : Dual targeting of gastric cancer stem cells using bivalent aptamers

Authors : Mengyuan Cao, Anissa Zaafour, Gorann Lepied, Christine Varon, Jeanne Leblond Chain, Pierre Dubus

In 2020, gastric cancer diagnoses reached a significant 1.1 million count around the world, ranking it simultaneously as the fifth most recurrent cancer worldwide. 90% of these cancers are gastric adenocarcinoma, a specific tumoral subtype affecting the stomach epithelial tissues. Appropriate and eradicative treatments have been explored against this pathology for years and now range from the most conventional chemotherapies to the sharpest targeted therapies. Despite these consistent improvements, multiple treatment resistance patterns have been identified and appear to emerge from gastric cancer stem cells (GCSCs). C. Varon's team has characterized several GCSC's biomarkers such as EpCAM (CD326) or CD44 which showed good targetability. In this project, we aim at developing dual-targeted therapies against these GCSCs biomarkers to improve chemotherapy and reduce tumor resistance.

Aptamers are synthetic DNA or RNA sequences with high affinity and specificity for their target. As compared to antibodies, they display a better thermal stability, are easier and safer to synthesize, especially for bivalent aptamers as compared to fastidious synthesis of bivalent antibodies. In this project, we developed a bi-specific aptamer to improve the selective recognition of GCSCs. CD44v9 binding aptamer (Apt4 or Apt7) was hybridized with EpCAM binding aptamers (SYL3C or Ep1) through hybridization of a 15-nucleotides linker. The assemblies were assessed by native PAGE. The targeting ability of LSYL3C-LApt4 and LEpT1-LApt7 assemblies for GCSCs was compared to conventional antibodies by flow cytometry. The specificity of the assemblies was assessed on gastric cancer cell lines and on mouse embryonic fibroblasts ($MEF^{CD44-/EpCAM-}$) as negative controls, and showed a relevant specificity for EPCAM+CD44v9+ GCSC in GC cell lines. Doxorubicin (DOX) loading by DNA intercalation was performed. The DOX-loaded aptamers anticancer efficacy was evaluated on GCSCs. The next steps of this work will rely on the optimization of linker design between the chosen aptamers and the characterization of aptamer/drug and aptamer/receptor interactions.

Type de communication : communication orale ☐ flash ☐ affiche ☒

Targeting the Bacterial DNA Replication Machinery: From linear peptide ligands to constrained macrocyclic inhibitors of the bacterial sliding clamp

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Résumé :

The bacterial β-clamp or sliding clamp (SC) is a protein involved in the replication of chromosomal DNA during cell division. This highly conserved protein among species is essential for the viability of the bacteria and has emerged as an attractive target for developing new antibacterial compounds to fight resistant bacteria.[1] The SC serves as an anchoring platform for replicative bacterial DNA polymerases through a well-conserved binding site which can accommodate short peptide motifs. Starting from the SC binding sequences of E. coli DNA polymerases IV and III, short linear peptides were synthesized to inhibit the interaction between the SC and DNA polymerases. Some peptides binding with sub-µM affinities to E. coli SC were identified.[2] Further optimization guided by X-ray structures of peptide-SC complexes, led to the design of high-affinity linear peptide inhibitors with KD values in the 30-50 nM range.[3]
This study focuses on exploring the potential advantages of macrocyclization to enhance the properties of these SC binders. Macrocyclized peptides, because of their constrained structure, could substantially enhance properties such as cell membrane permeability, stability to protease degradation, and/or affinity for the target. In this poster, we present the design and the synthesis of macrocyclic peptide-based SC ligands along with their binding affinity to E. coli SC, determined by isothermal titration calorimetry (ITC). Additionally, we obtained single crystals of a protein-cyclic inhibitor complex and now report preliminary structural data, providing a first insight into the molecular interactions and conformation of macrocycle inhibitor.

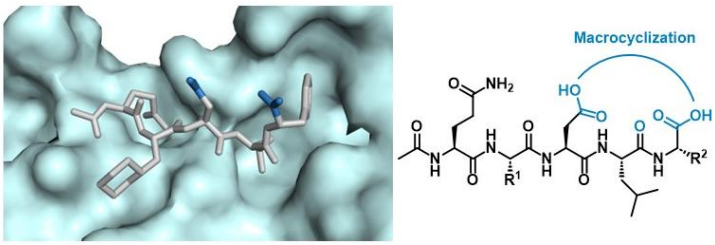

Figure: General macrocyclization approach for the design of constrained SC peptide ligands

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Keywords: antibacterial; peptidomimetics; protein-protein interaction inhibition; macrocycles

Type de communication : communication orale ☐ flash ☐ affiche ☒

Design and synthesis of Estrogen Receptor PROTACs for cosmetic safety

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Cosmetic safety is an important concern for consumers and is highly regulated. The cosmetic industry uses active molecules to improve product efficiency, but these molecules must be first evaluated for their potential effects on the human body. Modern toxicity is based on the Adverse Outcome Pathway paradigm, and deciphering the mechanism of action of these active ingredients is crucial.

PROTACs are heterobifunctional molecules which induce the targeted degradation of a protein of interest (POI) directly inside the cell. They are made up of three distinct parts: (i) a ligand of the POI, (ii) a linker, and (iii) an ubiquitin E3 ligase ligand. When the PROTAC binds to its POI, the corresponding ubiquitin E3 ligase is recruited leading to POI ubiquitination and consequent degradation by the proteasome. PROTAC technology has been applied to various therapeutic areas such as oncology, neurodegenerative or viral diseases.[1] PROTACs are structurally diverse molecules, and the most successful ones involve fine-tuning the linker between the two respective ligands (POI and E3).

The originality of our project lies in the use of PROTACs to detect potential endocrine disruptors in the context of cosmetic ingredients. There is much debate about the definition of an endocrine disruptor; binding to a hormone receptor is not enough to provoke a potentially adverse effect. With our PROTAC approach, our goal is to bring new input to the debate by looking at the effects of a test compound in Estrogen Receptor (ER) chemically Knocked Down (KD) cells, without the biases brought by the classical genetic KD techniques. Our research group is interested in the design and synthesis of PROTACs which target ER in order to evaluate the endocrine disruptor activity of a compound of interest for cosmetic applications. In practice, the compound will be incubated in parallel with both wild-type and ER KD cells (resulting from treatment with the ER PROTAC). Activation of the ER signalling pathway will be compared between the two conditions allowing us to evaluate its potential as an endocrine disruptor. These PROTACs will be developed and used as *in vitro* predictive tools.

Our work started with the synthesis of original PROTACs from estradiol derivatives to identify the importance of the linker's position on the steroid, and to find the most efficient E3 ligase. Biological evaluation was performed to find the best conditions (time and concentration) to evaluate specific ER extinction upon PROTAC treatment.

Several original PROTACs from ethinylestradiol have been synthesized and tested *in vitro*. Preliminary assays are quite promising with significant reduction of ER in two dedicated cell lines.

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Keywords: PROTAC, Estrogen Receptor, Cosmetic predictive tools

Type de communication : communication orale ☐ flash ☐ affiche ☒

The Myrosinase-Glucosinolate System, a valuable tool in bioconjugation

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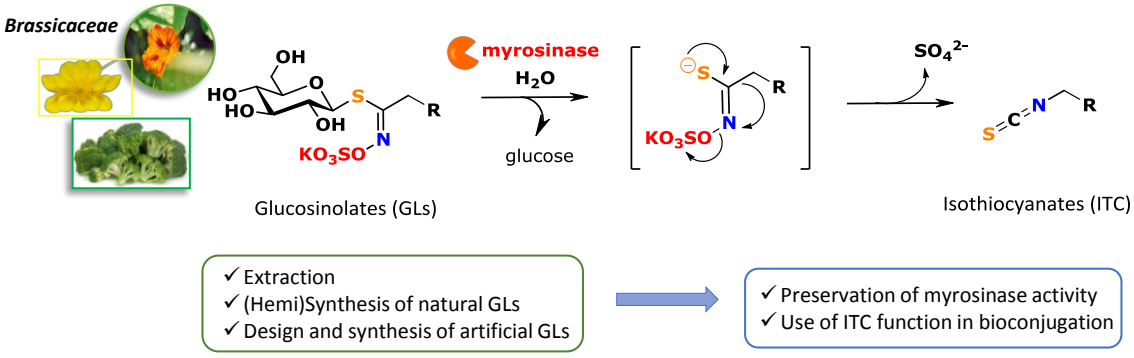
Glucosinolates (GLs) are sulfur-containing secondary metabolites, that are specific biomarkers of the plants of the *Brassicaceae* family, involved in the mechanism of defense of these plants against aggressions.[1] The hydrolysis of the C-S anomeric bond by a specific β-thioglucohydrolase, namely myrosinase, leads to the formation of a transient thiohydroxamic species which in turn undergoes a Lossen rearrangement, thus liberating a sulfate ion and an isothiocyanate (ITC). Thanks to this unique biochemical transformation in Nature, glucosinolates are thus responsible for the multiple biological activities of these plants such as antifungal, antibacterial or insecticidal properties. GLs and ITCs also have some beneficial impact on human health, with direct antitumor activity and chemopreventive effect. All known GLs (*ca* 140 molecules) all display a remarkable structural homogeneity based on a β-D-glucopyranosyl unit, a variable aglycon linked through an *O*-sulfated anomeric (*Z*)-thiohydroximate function. Over the last years, we have shown that using this unique myrosinase-tandem reaction, we were able to prepare *in-situ* ITCs from the corresponding stable, non-toxic and water-soluble GLs precursors.[2] Indeed, as strong electrophiles, the ITCs are well known and useful in bioconjugation,[3] but are toxic and difficult to handle and to store.



Herein, we would like to focus on our recent results about the design and synthesis of artificial synthetic glucosinolates in the light of their use in bioconjugation.

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Keywords: glucosinolates, myrosinase, bioconjugation, isothiocyanates

Type de communication : communication orale ☐ flash ☐ affiche ☒

Co-assembly of amylin and amyloid-β peptide?

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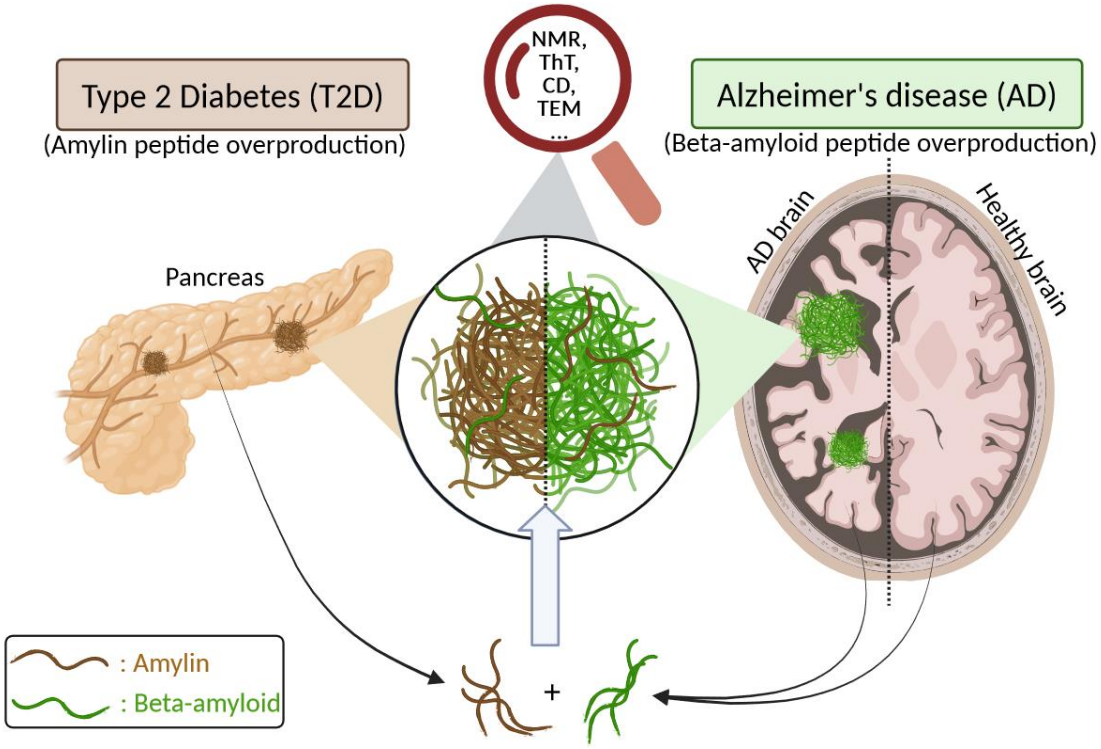
Neurological Alzheimer's disease (AD) and metabolic disordered Type 2 Diabetes (T2D) share a common physiological process: the self-assembly of disease-specific peptide, beta-amyloid (Aβ) for AD and human islet amyloid polypeptide (hIAPP or amylin) for T2D[1]. My project aims to determine whether amylin can trigger the self-assembly of Aβ[2,3]. Indeed, on the first hand, some studies have reported the presence of amylin peptide in Aβ aggregates of AD patients' brains, showing that amylin is capable of crossing the blood-brain barrier and assuming a potential interaction with Aβ[3]. On the other hand, epidemiologic studies showed that the prevalence of AD among T2D patients is doubled[4], making amylin a potential culprit in the accentuated onset of the AD. My main objective is to find physicochemical evidence of Aβ and amylin interaction. Here I will show preliminary data where both peptides self-assembly and co-assembly were monitored using ThT fluorescence, NMR and CD analysis along with microscopy (AFM and TEM) imaging. The experiments were performed under various conditions that include the presence of well-known modulators of peptide self-assembly such as metal ions.



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Keywords : Peptide ; Amyloid ; Alzheimer's Disease ; Type II Diabetes ; Aggregation

Type de communication : communication orale ☐ flash ☐ affiche ☒

Étude de la performance des dérivés du thiophène dans les applications en photovoltaïque.

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Résumé :

La recherche dans le domaine des énergies renouvelables, notamment dans le domaine de l'énergie solaire, retient actuellement toute l'attention de la communauté scientifique. Notre laboratoire s'investit également dans ce domaine en pleine expansion. Ce travail se concentre sur l'utilisation des matériaux organiques dans le domaine photovoltaïque, qui montre récemment des résultats prometteurs. En effet, les cellules solaires à base de molécules organiques ont récemment atteint un rendement de 15,8% en août 2023 [1], se rapprochant ainsi des performances des cellules à base de silicium qui dominent actuellement ce secteur. Atteignant un rendement record de 36,1% en 2023, comme rapporté par l'Institut Fraunhofer pour les Systèmes d'Énergie Solaire (Fraunhofer ISE) et l'institut de recherche néerlandais AMOLF [2].
Parmi les matériaux les plus compétitifs actuellement utilisés dans ce domaine pour leur bon rapport qualité-prix figurent les dérivés de thiophène et les fullerènes [3]. Ce travail est une étude théorique visant à optimiser la conversion photovoltaïque des matériaux organiques à base de thiophène en tant qu'électrodonneurs et du fullerène C61 en tant qu'électroaccepteur.
Les calculs des géométries et des structures électroniques de ces composés sont effectués en utilisant la théorie fonctionnelle de la densité (DFT) au niveau de la théorie 6–31 G (d, p) et la base B3LYP dans le vide et la formulation Perdew-Burke-Eenzerhof (PBE) de l'approximation généralisée du gradient avec des conditions aux limites périodiques (PBC) dans une (1D) et deux (2D) dimensions. De plus, les propriétés électroniques (HOMO, LUMO, HOCO, LUCO, Egap et Voc) sont déterminées dans le vide et dans les conditions périodiques PBC 1D et 2D pour comprendre l'effet du changement structurel notamment le nombre d'unités de thiophène. Les propriétés d'absorption-énergies d'excitation (Eex), la longueur d'onde d'absorption maximale (λmax), les forces d'oscillateur et l'efficacité de récolte de la lumière sont étudiées en utilisant la méthode DFT dépendante du temps. Nous avons effectué tous les calculs en utilisant le programme GAUSSIAN 09-D. La visualisation des molécules après optimisation de la géométrie a été réalisée par le programme GaussView 06.
Les résultats montrent la possibilité de contrôler les propriétés optiques et électroniques du matériau donneur en jouant sur la longueur de la chaîne polythiophène. La modélisation moléculaire par la méthode DFT peut être un outil essentiel pour prédire les principaux paramètres qui contrôlent les performances d'une cellule solaire organique, avant de passer à la synthèse. D'autre part, nos travaux démontrent l'efficacité du calcul théorique dans les PBC.

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Keywords: photovoltaique; matériaux organiques ; thiophène; DFT; GAUSSIAN 09-D.

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