IUPAC

14th International Symposium on BioOrganic Chemistry

21-24 June 2026 | Milan, Italy

Università degli Studi di Milano

ABSTRACT E-BOOK

ORGANIZERS

UNIVERSITÀ DEGLI STUDI DI MILANO

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

Consiglio Nazionale delle Ricerche

Società Chimica Italiana

POLITECNICO MILANO 1863

RONZONI · INSTITUTE CHEMICAL AND BIOCHEMICAL RESEARCH NONPROFIT RESEARCH FOUNDATION

EuChemS European Chemical Society

ORGANISING COMMITTEE

Barbara La Ferla, *University of Milano-Bicocca*
Cristina Airoldi, *University of Milano-Bicocca*
Daniele Passarella, *University of Milano*
Federica Compostella, *University of Milano*
Francesca Baldelli Bombelli, *Politecnico di Milano*
Francesco Peri, *University of Milano-Bicocca*
Giovanna Speranza, *University of Milano*
Laura Polito, *CNR Milano*
Laura Russo, *University of Milano-Bicocca*
Sara Sattin, *University of Milano*
Sabrina Bertini, *Istituto G. Ronzoni*

International Advisory Board

Amelia Rauter, *University of Lisbon, Portugal*
Ana Marta Matos, *University of Lisbon, Portugal*
Andreas Marx, *University of Jena, Germany*
Angela Agostiano, *University of Bari, EUCHEMS*
Angelo Fontana, *CNR, Italy*
Boris Vauzeilles, *CNRS, France*
Chuan He, *University of Chicago, USA*
Claudia Bonfio, *University of Cambridge, UK*
Cristina Nativi, *University of Firenze, Italy*
Gianluca Farinola, *University of Bari, Italian Chemical Society*
Gianluigi Albano, *University of Pisa, Italy*
Jay Siegel, *University of Hong Kong, China*
Jon Clardy, *Harvard University, USA*
Laura Kiessling, *Massachusetts Institute of Technology, USA*
Margaret Brimble, *University of Auckland, New Zealand*
Mary Garson, *University of Queensland, Australia*
Maurizio Prato, *CIC BiomaGUNE, Spain*
Michal Hocek, *Czech Academy of Sciences, Czech Republic*
Michele Vittadello, *City University of New York, USA*
Motonari Uesugi, *Kyoto University, Japan*
Nikolay Nifantiev, *Russian Academy of Sciences, Russia*
Priyani Paranagama, *University of Kelaniya, Sri Lanka*
Rino Rappuoli, *Biotecnopolo di Siena, Italy*
Valeria D'Auria, *University of Napoli, Italy*
Virinder Parmar, *City University of New York, USA*
Zhen Xi, *Nankai University, China*

Organizing Secretariat

YES Meet Agency *www.yesmeet.com*

ORGANIZERS

UNIVERSITÀ DEGLI STUDI DI MILANO

UNIVERSITA' DEGLI STUDI DI MILANO BICOCCA

Consiglio Nazionale delle Ricerche

Società Chimica Italiana

POLITECNICO MILANO 1863

RONZONI · INSTITUTE
CHEMICAL AND BIOCHEMICAL RESEARCH NONPROFIT RESEARCH FOUNDATION

EuChemS
European Chemical Society

SPONSORS

Platinum Sponsors

ITALFARMACO

Gold Sponsors

Chiesi

Silver Sponsors

GlycanAge

Springer

cytiva

indena 100+ YEARS
SCIENCE IS OUR NATURE. SINCE 1921

Sponsors

RDA APPARECCHI SCIENTIFICI PASSONI

Dipharma Since 1949

CellPress

ACS OMEGA

IS analytica

Other Sponsors

BRUKER

Chem Bio Chem | Chemistry Europe

PLENARY LECTURES

Innovation by evolution (and AI): bringing new chemistry to life

Frances H. Arnold[1]

[1]*California Institute of Technology, Pasadena CA USA*

The most powerful design process ever invented is evolution: it generates incomparable functionality and works at all scales, from molecules to ecosystems. There is nothing like it in the world of human engineering. Humans have used evolution for biological design for thousands of years, choosing who mates with whom and who goes on to parent the next generation. We can now use evolution to explore the future of chemistry by engineering the catalysts of life, enzymes. I will describe how we can direct enzyme evolution to solve challenging chemical problems once thought to be out of reach of biology, and even of chemistry[1,2,3]. Artificial intelligence (AI) methods are revolutionizing how we understand and compose the language of life. I will discuss AI-driven how enzyme discovery combined with evolution can unveil a world of enzymes that transcends biological evolution and perhaps offers a route to genetically encoding almost any chemistry[4].

References:

[1] Chen K, Arnold FH, "Engineering New Catalytic Activities in Enzymes." Nature Catalysis 3, 203-213 (2020). doi: 10.1038/s41929-019-0385-5
[2] Kennemur JL, Long Y, Ko CJ, Das A, Arnold FH, "Enzymatic Stereodivergent Synthesis of Azaspiro[2.y]alkanes." Journal of the American Chemical Society 147, 27165-27171 (2025). doi: 10.1021/jacs.5c07015
[3] Gao S, Das A, Alfonzo E, Sicinski KM, Rieger D, Arnold FH, "Enzymatic Nitrogen Incorporation Using Hydroxylamine." Journal of the American Chemical Society 145, 20196-20201 (2023). doi: 10.1021/jacs.3c08053
[4] Yang J, Li, FZ, Long, Y, Arnold FH, "Illuminating the Universe of Enzyme Catalysis in the Era of Artificial Intelligence." Cell Systems 16, 101372 (2025). doi: 10.1016/j.cels.2025.101372

Supramolecular and hybrid responsive nanomaterials in/for living organism

Luisa De Cola

University of Milano, Department DISFARM, Milan Italy
email: luisa.decola@unimi.it

The use of responsive nanomaterials is gaining importance for medical applications such as imaging agents, drug delivery, tissue regeneration.
We have recently reported disulfide-bridged organosilica nanoparticles to be able to break on demand such materials to release drugs and avoid their accumulation in vital organs[1-4]. Exploring further the use of responsive organic groups we report on organosilica nanoparticles containing single-stranded nucleic acids. The oligonucleotides, can be covalently embedded in the silica network, and their behavior has been investigated[5], but the system can be also programmed to be more dynamic and responsive by designing supramolecular organo-silica systems. We created nanoparticles based on PNA- derivatives that can self-assemble through direct base paring or can be joined through a bridging functional nucleic acid, such as the ATP-binding aptamer[6]. These systems can be followed by confocal microscopy in different cell lines and their biological effect was measured in cells to assess the biological effect of the aptamer.
Discussing dynamic behavior I will show how self-assembly of small molecules, platinum metal complexes can occur in solution, and followed in real time, but also in living organisms. The supramolecular process in transparent animals can be visualized by the bright emission of the assembly and we have studied the process in the small freshwater polyp Hydra. We found that using water soluble luminescent platinum complexes we can follow the assembly in the body of the animal and that the self-assembly trigger unexpected biological event such self-regeneration of tissues.
Finally, moving from in vivo to for generating life the use of silica capsules and hydrogels has recently proved to be an exceptional interesting way to enhance coral settlement through the development of biomimetic microhabitats that replicate the chemical landscape of healthy reefs. The responsive capsules able to entrap large biomolecules, algal exo-metabolites, are embedded in a hydrogel to slow down the release of the actives. The constructs enable to enrich reef microhabitats with bioactive molecules from crustose coralline algae enhancing coral settlement over 20-fold compared to controls[7].

Acknowledgements:

We wish to thank the Project Next Gen EU and MUR as PNRR M4C2, "Mano-HCC", PE_00000019, HEAL ITALIA, CUP E93C22001860006 for financial support.

References:

[1] P. Picchetti et al. ACS Nano 2021, 15, 9701–9716.
[2] P. Picchetti, et al. J. Am. Chem. Soc. 2021, 143, 7681-7687.
[3] M. Sancho Albero, et al. Adv. Healthcare Mater., 2023, 12, 2202932.
[4] M. Sancho Albero, et al. Materials Today Bio, 2025, 30, 101433.
[5] P. Picchetti et al J. Am. Chem. Soc. 2023, 145, 22896-22902.
[6] P. Picchetti et al J. Am. Chem. Soc. 2023, 145, 22903-22912.
[7] D. Wangpraseurt et al. Trends in Biotechnology, 2025, 43, 2232-2250.

Molecular Glycobiology Enabled by Automated Glycan Assembly as Basis for Vaccines, Diagnostics and Therapeutics

Peter H. Seeberger[1,2]

[1]Max-Planck Institute for Colloids and Interfaces, Am Muehlenberg 1, 14476 Potsdam, Germany
[2]Center for the Transformation of Chemistry (CTC), Richard-Wagner-Straße 7a, 04509 Delitzsch, Germany

Following its discovery over two decades ago, automated glycan assembly (AGA)[1] has been developed into a robust and reliable technology that allows for preparation of diverse oligo- and polysaccharides on a solid support employing a synthesizer. Access to ever more complex glycans including complex N-glycans are enabling fundamental investigations into the structure and function of polysaccharide materials, vaccines and diagnostics.
Vaccine programs aimed at protection from most bacteria and fungi found on the WHO list of the most critical microbial threats are underway[2].A vaccine candidate against C. difficile has passed Phase 1 human clinical trials. Vaccine candidates against a host of other pathogens including S. pneumoniae, S. suis and A. baumannii are under development.
Synthetic oligosaccharides have given rise to monoclonal antibodies and nanobodies to kill cancer cells. These antibodies are currently in preclinical developed[3].

References:

[1] Plante OJ., Palmacci ER. Seeberger PH Automated Solid-Phase Synthesis of Oligosaccharides; Science 2001, 291, 1523.
[2] Seeberger, P.H.; Discovery of Semi- and Fully-Synthetic Carbohydrate Vaccines Against Bacterial Infections Using a Medicinal Chemistry Approach; Chem. Rev. 2021, 121, 3598.
[3] Goerdeler F., Reuber E., Lühle J., Leichnitz S., Freitag A., Nedielkov R., Möller H., Seeberger P.H., Moscovitz O. Thiol-mediated Uptake of a Novel Cysteine-containing Nanobody for Anti-Cancer Drug Delivery ACS Cent. Sci. 2023, 9, 1111.

Reactive Oxygen Species: Detection, Imaging, and Translational Roles in Disease Mechanisms and Therapy

Dan Yang

School of Life Sciences and School of Science, Westlake University, Hangzhou, Zhejiang 310030, China

Reactive oxygen species (ROS) are central regulators of cellular signaling, oxidative stress, and pathological progression, yet their dynamic, context-dependent functions remain incompletely understood due to challenges in selective detection and real-time visualization. This lecture presents integrated advances in the development of chemical tools and mechanistic insights toward understanding ROS-mediated biological processes and their therapeutic implications.
We highlight our progress in the design, synthesis, and biological applications of selective fluorescent and chemosensory platforms for five distinct reactive oxygen species, enabling spatiotemporal imaging of ROS fluxes in living systems. Complementary to ROS imaging, we describe novel analytical strategies for the detection and proteomic profiling of tyrosine-nitrated proteins, with a focus on peroxynitrite-mediated post-translational modifications and their functional consequences in redox-dependent disease pathways.
Furthermore, we explore mechanistic connections between mitochondrial dysfunction, oxidative stress, and ferroptosis initiation, and discuss how these insights guide the rational development of ferroptosis-inducing agents for cancer therapy. Together, this work illustrates how bioorganic chemistry bridges molecular sensing, mechanistic biology, and translational medicine, opening new avenues to decode redox biology and treat ROS-associated diseases.

Engineering Natural Origin Regenerative Medicine Platforms and 3D Disease Models Based on Those

Rui Reis

Research Institute on Biomaterials, Biodegradables and Biomimetics, University of Minho, Portugal

Asymmetric Catalysis with Peptides From Simple to Complex Environments

Helma Wennemers

Laboratory of Organic Chemistry, D-CHAB, ETH Zürich, Vladimir-Prelog-Weg 3, 8093 Zürich, Switzerland

In nature, proteins fulfill manifold different functions and are crucial, for example, as enzymes or templates for the controlled formation of structural components such as bones. The Wennemers group is intrigued by the question of whether peptides with significantly lower molecular weights than proteins can fulfill functions for which nature evolved large macromolecules. Specifically, we ask whether peptides can serve as effective asymmetric catalysts, synthetic collagen-based materials, or imaging and targeting agents for fibrotic tissue.

The lecture will focus on stereoselective peptide catalysts of the general type H-Pro-Pro-Xaa. These peptides allow for catalysis via an enamine intermediate, with catalyst loadings of as little as 0.05 mol%, and provide synthetically versatile products from aldol and conjugate addition reactions with high stereoselectivities. The lecture will discuss the scope of the peptide-catalyzed reactions and insights into the mechanism. We will show which structural and functional features distinguish the peptides from other chiral amine catalysts and highlight how changes in the conformational properties enable tuning of the catalytic activity, stereoselectivity, and chemoselectivity. In addition, the lecture will present peptide catalysis in complex environments (e.g. cell lysates) and cascade reactions with enzymes.

Sequence-Based Design of Small Molecules that Target RNA Structure

Matthew David Disney,

UF Scripps, 130 Scripps Way, Jupiter, USA

Understanding the molecular pathways that drive disease and identifying targets that can be modulated with medicines remain central challenges in biology and chemistry. Both coding and non-coding RNAs can directly cause disease through mutation or abnormal expression. Similar to proteins, RNA structure often determines function in both healthy and diseased states. Despite this, RNA is still rarely considered a target for small-molecule therapeutics.

Our research aims to define general principles that govern how small molecules recognize RNA structure. Using evolutionary conservation and experimental binding data, we identify structured RNA motifs that are suitable for small-molecule targeting. By profiling interactions between libraries of RNA folds and small molecules, we uncover recurring and privileged recognition patterns. These interactions are then mapped across the human transcriptome to identify RNAs with targetable structures in cells.

Using this strategy, we have discovered small molecules that bind functional RNA structures and reveal new biology. More recently, we developed approaches that convert otherwise inactive RNA binders into bioactive compounds by recruiting cellular ribonucleases. These chimeric molecules selectively degrade disease-causing RNAs in cells and in mouse models, demonstrating a general strategy to control RNA function and expand the scope of small-molecule therapeutics.

Sugars & proteins: post-translational editing

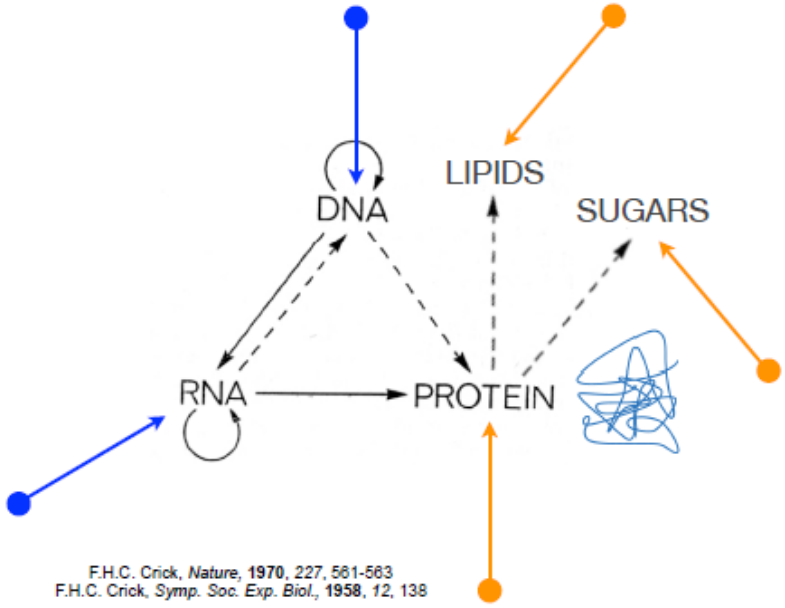
Benjamin G. Davis[1],

[1]*Departments of Chemistry and Pharmacology, University of Oxford;*
[2]*The Rosalind Franklin Institute, Harwell, Oxfordshire;*

Our work studies the interplay of biomolecules – proteins, sugars and their modifications.
Synthetic Biology's development at the start of this century may be compared with Synthetic Organic Chemistry's expansion at the start of the last; after decades of isolation, identification, analysis and functional confirmation, the future logical and free-ranging redesign of biomacromolecules offers tantalizing opportunities.
This lecture will cover past and emerging areas in our group in the chemical manipulation of biomolecules with an emphasis on new bond-forming and bond-breaking processes compatible with biology.

(i)New methods: the development of precise methods that may be applied to biology at a posttranslational level, generating minimal 'scars' or 'traces' (ideally 'trace'-less), could allow broad control of function. The development of chemo- and regio-selective methods with potential to post-translationally 'edit' biology in this way, applied under benign conditions to redesign and reprogramme the structure and function of biomolecules, will be presented.

(ii)'Synthetic Biologics' and their applications: biomimicry; functional recapitulation; effector [drug/agrochemical/gene/radio-dose] delivery; selective protein degradation; inhibitors of pathogen interactions; non-invasive presymptopmatic disease diagnosis; probes and modulators of in vitro and in vivo function illustrate possible resulting technologies.



F.H.C. Crick, *Nature*, **1970**, 227, 561-563
F.H.C. Crick, *Symp. Soc. Exp. Biol.*, **1958**, *12*, 138

KEYNOTE

Probing Function with Designing Structure: Instructive Scaffolds for Tissue Regeneration

Lorenzo Moroni,

Maastricht University, MERLN Institute for Technology-Inspired Regenerative Medicine, Universiteitssingel 40, Maastricht, The Netherlands;

Organs are complex systems, comprised of different tissues, proteins, and cells, which communicate to orchestrate a myriad of functions in our bodies. Technologies are needed to replicate these structures towards the development of new therapies for tissue and organ repair, as well as for 3D in vitro models to better understand the morphogenetic biological processes that drive organogenesis. To regenerate tissues and organs, biofabrication strategies are being developed to impart spatiotemporal control over cell-cell and cell-extracellular matrix communication, often through control over cell and material deposition and placement. This passes often through the fabrication of a scaffold, whether a cell-laden hydrogel construct or an acellular 3D porous network.
Scaffolds for regenerative medicine applications have been historically produced by the adoption of industrial manufacturing technologies, such as textile, moulding, and foaming. With the advent of additive manufacturing (AM), it has been possible to design scaffolds geometry and structure. AM not only enabled the design of architected porous biomaterials with anatomical customization, but also of smart cell-material interfaces able to instruct cell activity and steer tissue regeneration.
Here, we introduce several examples of instructive scaffolds aimed at steering funcional tissue regeneration.
To achieve these targets, the spatiotemporal control over biological signals at the interface between cells and materials is often aimed for. Alternatively, biological activity can be triggered through the control of mechanical cues, harnessing more fundamental know-how in mechanobiology that could be combined with biofabrication strategies. Some of the most recent advancements in merging surface funcationalization and mechanobiology with biofabrication that enabled the control of cell activity are presented, moving towards enhanced tissue regeneration.

Small Molecule Stabilization of Proteins and Nanoparticles: Rethinking Colloidal Stabilization

Francesco Stellacci

Insitute of Materials, Ecole Polytechniquen Fédérale de Lausanne (EPFL), Lausanne, Switzerland

Amino acids have been used for decades in biological and pharmaceutical formulations, yet their stabilizing role is still debated and is often described in non-quantitative or protein-specific terms. In this talk, I will argue that we have been overlooking a general property: amino acids act as modulators of colloidal interactions—not just for proteins, but also for DNA and even synthetic nanoparticles.

I will begin by showing how we systematically measured the interactions between suspended particles using osmotic virial coefficients and potential of mean force[1,2]. We find that the stabilizing effects of amino acids are remarkably consistent across very different systems, suggesting a broad, non-specific mechanism.

To explain this, we developed a theoretical model treating amino acids as weakly interacting small molecules binding to patchy colloidal surfaces. We put this model to the test, comparing predictions against experimental dissociation constants, and the numbers line up: for instance, with proline and lysozyme, theory and experiment agree within a factor of two[3].

The model leads to some clear, testable predictions—like the idea that short peptides should be more effective than the same number of free amino acids, or that charged amino acids only stabilize oppositely charged proteins. We verified each of these in the lab.

Finally, I will show that these weak interactions can have strong consequences: they can suppress liquid-liquid phase separation, block stress granule formation in cells[4], and even double insulin's bioavailability in mice when co-formulated with proline.

Overall, our results suggest we should think of small molecules like amino acids not just as passive ingredients but as active modulators of colloidal behavior—just as we already account for salt when studying electrostatics, we should be paying similar attention to these small molecular players.

References:

[1] Ong et al., Materials Horizons (2022).
[2] Poliukhina et al. ACS Nano (2026).
[3] Mao, et al , Nature (2025).
[2] Xu et al. PNAS (2024).

Chemistry-based design of mRNA to explore new functions

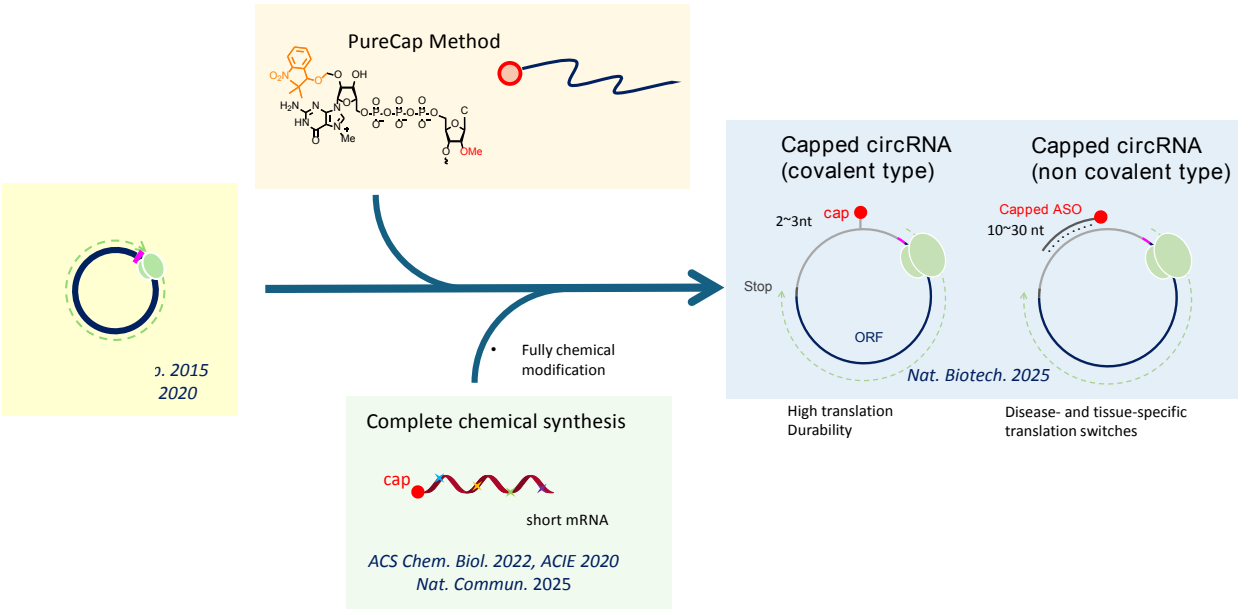
Hiroshi Abe,

Department of Chemistry, Graduate School of Science, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Japan

Messenger RNA (mRNA) therapeutics have emerged as a powerful platform for vaccines and protein replacement therapies. Conventional mRNA production relies on enzymatic transcription; however, chemical approaches provide new opportunities to precisely control RNA structure and function. Chemical modifications such as N1-methylpseudouridine reduce innate immune activation, while optimization of the poly(A) tail and cap structure can improve mRNA stability and translation efficiency.

In our previous work, we developed the PureCap method, which employs a hydrophobic tag attached to a cap analog to enable purification of capped mRNA by reversed-phase HPLC. This approach allows efficient preparation of highly pure capped mRNA and improves translation efficiency by removing uncapped transcripts. Nevertheless, site-specific chemical modification remains challenging in enzymatically synthesized RNA. To address this limitation, we developed strategies for complete chemical synthesis of mRNA using nucleic acid synthesizers. Efficient 5′-phosphorylation and high-yield capping reactions with newly designed reagents enabled the total chemical synthesis of mRNA molecules.

More recently, we introduced an internal cap-initiated translation (ICIT) strategy for circular mRNA. In this system, an m^{7}G cap is positioned internally within the RNA molecule either through covalent attachment to a branched RNA scaffold (cap-circ mRNA) or through non-covalent tethering using an m^{7}G-modified complementary oligonucleotide (cORN). These approaches dramatically enhance translation efficiency, and cap-circ mRNA can produce up to 10^3-fold higher protein expression compared with uncapped circular RNA. Furthermore, when combined with N1-methylpseudouridine modification, these constructs support robust and sustained protein expression in cells and in vivo while minimizing innate immune activation.



These chemistry-driven strategies provide a versatile platform for next-generation mRNA therapeutics.

References:

[1] Iwai, H.; Kimura, Y.;Honma, M.; Nakamoto, K.; Hashimoto, A.; Motosawa, K.; Atago, T.; Asano, K.; Hashiya, F.; Abe, N.; Kobayashi, K.; Ogisu, R.; Yamada, H.; Hiraishi, K.; Saito, S.; Yamamoto, J.; Abe, H. **Nat. Commun.** 2025, *16*, 9995.
[2] Fukuchi, K.; Nakashima, Y.; Abe, N.; Kimura, S.; Hashiya, F.; Shichino, Y.; Liu, Y.; Ogisu, R.; Sugiyama, S.; Kawaguchi, D.; Inagaki, M.; Meng, Z.; Kajihara, S.; Tada, M.; Uchida, S.; Li, T.-T.; Maity, R.; Kawasaki, T.; Kimura, Y.; Iwasaki, S.; Abe, H. *Nat. Biotechnol.* **2025**, *43*, 1543–1552.

Live Cell Imaging Using Small Raman Tags

Mikiko Sodeoka,

RIKEN Center for Sustainable Resource Science,
2-1 Hirosawa, Wako, Saitama, Japan

At present, fluorescence imaging is widely considered to be the gold standard in biological research. Nevertheless, there are problems associated with the use of fluorescence imaging in the study of small bioactive molecules. A common problem is that introducing a large fluorophore to a small bioactive molecule often results in a significant decrease in the molecule's biological activity due to reduced affinity for the target protein and/or reduced cell permeability. To address these issues, we came up with the idea of using small alkynyl group as a vibrational tag. We have successfully demonstrated that Raman spectroscopy combined with small bioorthogonal alkyne tags is an excellent method for imaging of small molecules in live cells[1,2]. And recently, Raman spectroscopy has attracted considerable attention as a new method for live cell imaging[3,4].
In this presentation, I will introduce Raman imaging of small molecules and its potential application in chemical biology research.

References:

[1] Yamakoshi, H, Dodo, K, Okada, M, Ando, J, Palonpon, A, Fujita, K, Kawata, S, Sodeoka, M. Imaging of EdU, an Alkyne-tagged Cell Proliferation Probe, by Raman Microscopy. J. Am. Chem. Soc. 2011; 133: 6102-6105.
[2] Yamakoshi, H, Dodo, K, Palonpon, A, Ando, J, Fujita, K, Kawata, S, Sodeoka, M. Alkyne-tag Raman Imaging for Visualization of Mobile Small Molecules in Live Cells. J. Am. Chem. Soc. 2012, 134, 20681-20689.
[3] Dodo, K, Fujita, K, Sodeoka, M. Raman Spectroscopy for Chemical Biology Research. J. Am. Chem. Soc. 2022, 144, 19651-19667.
[4] Dodo K, Tipping, W, Yamakoshi, H, Egoshi, S, Kubo, T, Kumamoto, Y, Faulds, K, Graham, D, Fujita, K, Sodeoka, M. Alkyne-tag Raman Imaging and Sensing of Bioactive Compounds. Nature Rev. Methods Primer 2025, 5, 20.

Programmable and responsive DNA-based synthetic cells, reactions and structures

Francesco Ricci,

University of Rome Tor Vergata, Via della Ricerca Scientifica, 1, 00133, Rome, Italy.

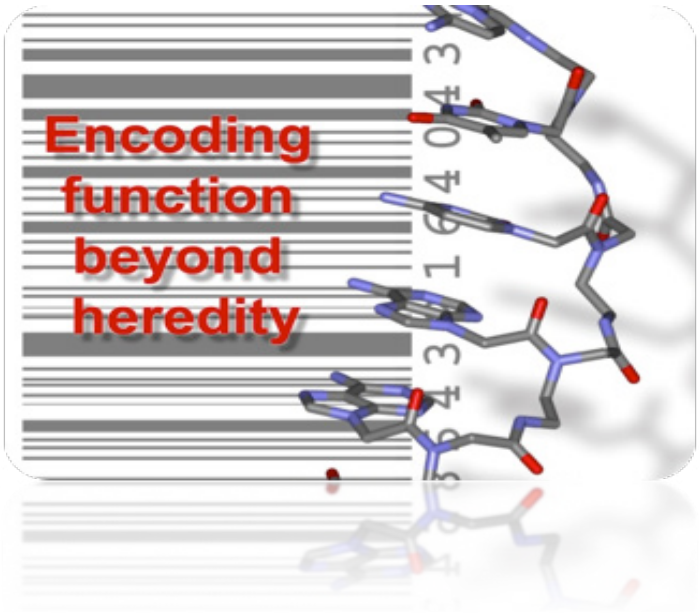
DNA nanotechnology uses synthetic DNA (or nucleic acids) as a versatile material to rationally engineer devices, switches and structures with different applications (e.g., in-vivo and in-vitro diagnostics, drug delivery, genetic circuits etc.). During this presentation I will introduce the field of DNA nanotechnology and I will show how to exploit the “designability” of DNA to fabricate DNA-based structures and synthetic cells that display programmable features and how to control DNA-based reactions with different chemical and environmental stimuli.

Programing responsive assemblies from PNA-encoded and folded peptides

Nicolas Winssinger,

University of Geneva, 30 quai Ansermet, Geneva Switzerland

Life is orchestrated by biomolecules interacting in complex networks of biological circuitry with emerging function. Progress in different areas of chemistry has made the design of systems that can recapitulate elements of such circuitry possible. At the circuitry level, the programmable nature of nucleic acid hybridization provides a powerful platform to design dynamic systems that can respond and integrate diverse logic gates. In order to interface with diverse biomolecular inputs (e.g. cell surface receptors or therapeutic target) and yield outputs other than oligonucleotide sequences (e.g. drugs or fluorophores for sensing) it is desirable to engineer nucleic acid conjugate that can translate assemblies into output through proximity enhanced reactions. Peptide Nucleic Acids (PNA) are endowed with attractive properties for this endeavor as they are more robust and form more stable duplex than their natural counter parts. Several applications from our laboratory to encode and program self-assemblies of small molecules, template chemical reactions and respond to biomarkers will be presented.



References:

[1] Luciferase-induced photoreductive uncaging of small-molecule effectors,Nat. Commun. 2018, 9, 3539.
[2] Coupling of DNA circuit and templated reaction for quadratic amplification and release of functional molecules, J. Am. Chem. Soc. 2019, 141, 16288-16295.
[3] Sense-and-release Logic-gated Molecular Network Responding to Dimeric Cell Surface Proteins, J. Am. Chem. Soc. 2020, 142, 12333-40.
[5] Biosupramolecular systems: integrating cues into responses, J. Am. Chem. *Soc.* 2021, *143*, 4467-4482.
[6] A mating mechanism to generate diversity for the Darwinian selection of DNA-encoded synthetic molecules, N. *Nat. Chem.* **2022**, 2420.
[7] Development of supramolecular anticoagulants with on-demand reversibility, *Nat. Biotechnol.* **2025**, *186*.
[8] Self-assembled proteomimetic (SAP) with antibody-like binding from short PNA–peptide conjugates, *Proc. Natl. Acad. Sci USA. e2412850122.*

Bioorganic Chemistry in Peptide Science: From Proof-of-Concept to Applications in Diagnostics, Therapeutics, and Cosmeceuticals

Anna Maria Papini,

Interdepartmental Research Unit of Peptide and Protein Chemistry and Biology, Departments of Chemistry "Ugo Schiff" and NeuroFarBa, University of Florence, Via della Lastruccia 13, Sesto Fiorentino, Italy.

Bioorganic chemistry is a major driver of innovation in peptides for life sciences, enabling sustainable and highly selective solutions for diagnostics, therapeutics, and cosmeceuticals. Owing to their structural versatility, high affinity, and favorable safety profiles, peptides are increasingly recognized as powerful alternatives to small molecules and biologics. Advances in bioorganic methodologies, including chemoselective ligation and side chain-to-side chain stapling, have enabled the rational design of conformationally constrained peptide analogues with enhanced stability and bioactivity[1]. At PeptLab@UNIFI, research integrates peptide design, synthesis, and functional evaluation within a translational bioorganic framework. Triazolyl bridged and functionalized peptides including peptide-peptide nucleic acid chimeras have been developed as a sophisticated class of multifunctional molecules as antiviral and antibacterial agents, showing promising activity against emerging pathogens and drug-resistant strains[2,3]. In parallel, sustainable and scalable synthetic strategies have been optimized to support GMP-compliant production and efficient technology transfer to industry, addressing the growing challenge of limited CDMO manufacturing capacity driven by the expanding demand for GLP-1 agonists. In diagnostics, peptide-based probes allow precise epitope mapping and the detection of disease-specific antibodies, with applications in autoimmune disorders, infectious diseases, and immunogenicity monitoring of biologic therapies[4]. Beyond healthcare, peptides also drive innovation in cosmeceuticals, exemplified by collagen-modulating peptides such as Definisse KP1, recently translated to the market[5].
Overall, the integration of green chemistry, advanced molecular design, and interdisciplinary collaboration positions bioorganic chemistry as a cornerstone for impactful scientific and industrial advancements.

References:

[1] Cantel S, Le Chevalier Isaad A, Scrima M, Levy JJ, DiMarchi RD, Rovero P, Halperin JA, D'Ursi AM, Papini AM, Chorev M. Synthesis and Conformational Analysis of a Cyclic Peptide Obtained via i to i+4 Intramolecular Side-Chain to Side-Chain Azide−Alkyne 1,3-Dipolar Cycloaddition. J Org Chem 2008, 73: 15, 5663–5674 .
[2] Quagliata M, Stincarelli MA, Papini AM, Giannecchini S, Rovero P. Antiviral Activity against SARS-CoV-2 of Conformationally Constrained Helical Peptides Derived from Angiotensin-Converting Enzyme 2. ACS Omega 2023, 8: 25, 22665–22672.
[3] Tino AS, Quagliata M, Schiavina M, Pacini L, Papini AM, Felli IC, Pierattell R. iRevealing the Potential of a Chimaera: a Peptide-Peptide Nucleic Acid Molecule Designed To Interact with the SARS-CoV-2 Nucleocapsid Protein. 2025, 64: 11, e202420134.
[4] Bracci S, Real-Fernandez F, Pratesi F, Nuti F, Rovero P, Papini AM. Detection of Diagnostic Antibodies in Immune-Mediated Diseases: A Focus on Antigens and Technologies. ChemBioChem 2026, 27: 9, e70354.
[5] Errante F, Pallecchi M, Bartolucci G, Frediani E, Margheri F, Giovannelli L, Papini AM, Rovero P. Retro-Inverso Collagen Modulator Peptide Derived from Serpin A1 with Enhanced Stability and Activity In Vitro. J Med Chem 2024, 67: 6, 5053–5063.

Supramolecular Quantasomes for Artificial Photosynthesis

Marcella Bonchio,

Department of Chemical Science, University of Padova, INSTM unit, via Marzolo 1, Padova-35131, Italy

In oxygenic photosynthesis, the "quantasome hypothesis" led to seminal discoveries correlating the hierarchical structure of natural thylakoid membranes with their complementary photo-redox functions[1]. Indeed, and despite the vast bio-diversity footprint, a unique protein complex, photosystem II (PSII), is used by Nature as the H2O-photolyzer. Man-made systems are still far from replicating the complexity of PSII, showing the ideal co-localization of Light Harvesting antennas with the functional Reaction Center (LH-RC) and embedding a tetra-manganate cluster as the Oxygen Evolving Complex (OEC)[1].
A recent breakthrough in the field of artificial photosynthesis is the discovery of totally inorganic multi-redox metal clusters, as analogs of the PSII-OEC, boosting H2O oxidation to O2 with unprecedented efficiency[2]. We report herein a synthetic, spectroscopic and mechanistic study on the use of multi-metal catalysts for water oxidation and their combined use with visible light sensitizers evolving to supramolecular semiconductors in water[3].
In particular we will report on the design of perylenebisimide (PBI) networks shaped to function by interaction with a polyoxometalate water oxidation catalyst (Ru4POM). Supramolecular "quantasomes" form both in aqueous solution and on photoelectrode surface, showing a: (i) red-shifted, light harvesting efficiency (LHE > 40%), (ii) favorable exciton accumulation and negligible excimeric loss; (iii) a robust amphiphilic structure; (iv) dynamic aggregation into large 2D-paracrystalline domains[3-4]. The outcome is a hybrid organic-inorganic nanomaterial, evolving into a hierarchical super-structure with a striking resemblance to the natural membranes, and enabling water splitting using low energy green photons at overpotentials as low as those of the natural enzyme. Water harvesting at the quantasome core turns out to be regulated by its functionalization with polyethylene glycol (PEG) chains, mimicking the role of water channels within the PSII protein environmen [1].

References:

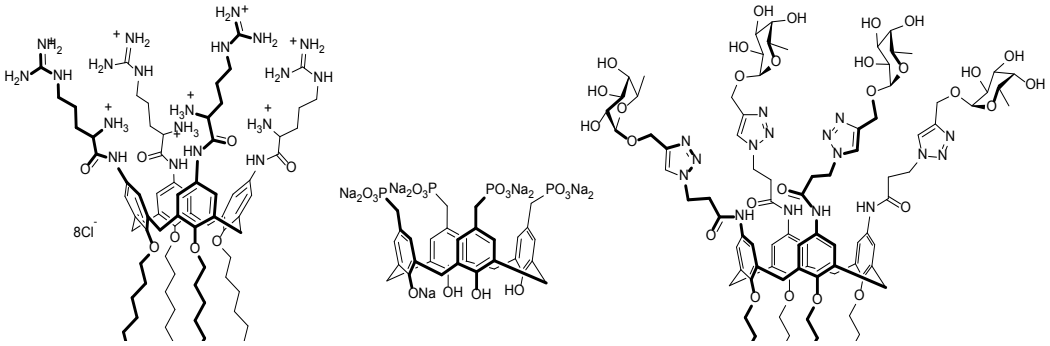
[1] Gobbato T, Volpato G., Sartorel A., Bonchio M. A Breath of Sunshine: Oxygenic Photosynthesis by Functional Molecular Architectures. Chem. Sci. 2023, 14, 12402
[2] Guazzi S., Dürr R.N.; Prato M., Bonchio M. et al. Direct Conversion of Ethanol to Ethyl Acetate by Dynamic Polyoxometalate/Carbon Nanohorn Electrocatalytic Interfaces. J. Am. Chem. Soc., 2025, 147, 34840
[3] Gobbato T., Rigodanza F., Benazzi E., Prato M., Bonchio M. Enhancing Oxygenic Photosynthesis by Cross-Linked Perylenebisimide "Quantasomes". J. Am. Chem. Soc. 2022, 144, 14021
[4] Bonchio M., Rigodanza F., Sartorel A., Prato M. et al. Hierarchical Organization of Perylene Bisimides and Polyoxometalates for Photo-Assisted Water Oxidation. Nature Chemistry 2019, 11, 146.
[5] Cognigni L., Liu, J., Gobbato, T., Rosa-Gastaldo D., Bonchio M. et al. Organic Semiconductor Frameworks Integrating Bay-Substituted Perylene Bisimides as Screw Dislocation Units in Onion-Like π–π Stacked Architectures. J. Mater. Chem. A 2025, 13, 40874.

Calixarenes, versatile and inspiring tools at the service of and protagonist in bioorganic chemistry

Francesco Sansone,

Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parco Area delle Scienze 17/A, 43124 Parma, Italy

Calixarenes are synthetic macrocycles that can be prepared cheaply, in large amounts and selectively defining their size determined by the number of phenolic units constituting the cycle[1]. They possess peculiar features that make them highly versatile scaffolds, with the possibility of applications in many fields. In particular, calixarenes are characterized by an aromatic region, which can be arranged in a defined hydrophobic cavity able to include lipophilic or cationic portions of guests; their geometry and conformations can be modulated; they have two rims, identified by phenolic hydroxy groups (upper) and aromatic para positions (lower), with specific and distinguished reactivities. These rims are rather easily functionalized through regioselective reactions that can generate calixarenes endowed, for instance, with a multiple exposition of ligand units (multivalency), proper solubility including in water and biological environment, amphiphilicity conferring tendency to self-assemble in nanometric objects. Exploiting all these features, during the years, in our group we designed a large variety of calixarene derivatives aimed at the interaction with biologically relevant molecules, such as proteins and nucleic acids[2]. Functionalization with cationic heads like arginine units and lipophilic chains produced very active non-viral vectors able to deliver nucleic acids (plasmids, miRNA, mRNA, mimics) into cells[3]. Calixarenes with anionic groups and a well-preorganized cavity showed activity against synuclein toxic oligomerization[4]. Introduction of proper saccharides produced efficient multivalent inhibitors of medically interesting lectins[5]. In general, in the investigated cases, we could observe the higher efficiency of the multivalent calixarene-based ligands with respect to non-macrocyclic and/or monovalent analogues.



References:

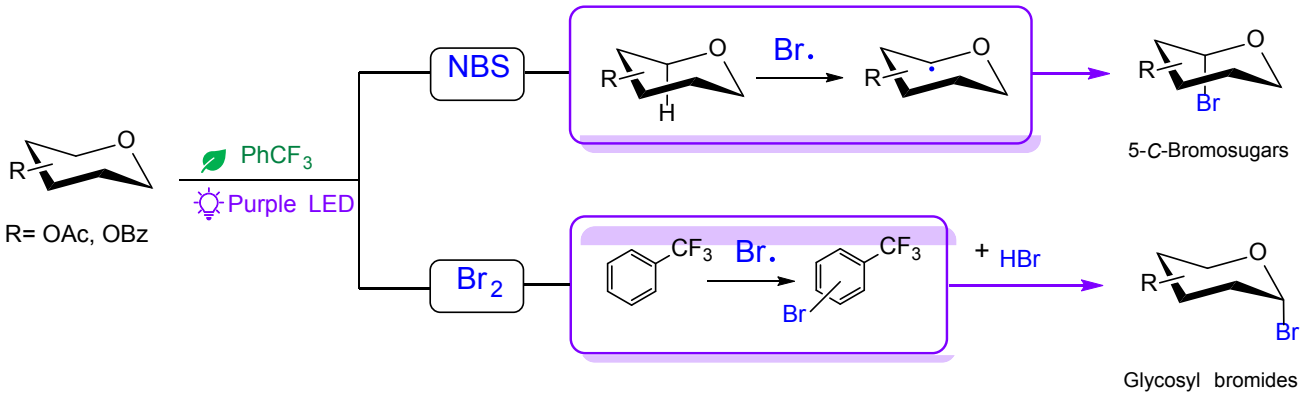
[1] Bohmer V. Calixarenes, macrocycles with (almost) unlimited possibilities. Angew Chem, Int Ed Engl 1995; 34: 713-745.
[2] Baldini L, Casnati A, Sansone F. Multivalent and multifunctional calixarenes in bionanotechnology. Eur J Org Chem 2020; 5056-5069
[3] Gasparello J, Papi C, Zurlo M, Volpi S, Gambari R, Corradini R, Casnati A, Sansone F, Finotti A. Cationic Calix[4]arene Vectors to Efficiently Deliver AntimiRNA Peptide Nucleic Acids (PNAs) and miRNA Mimics. Pharmaceutics 2023; 15(8): 2121.
[4] Dell'Accantera D, Piccinini G, Ciabini C, Felli IC, Volpi S, Marmiroli N, Sansone F, Ruotolo R. A rigid supramolecular solution to a flexible problem: a multifunctional calix[4]arene-based strategy to prevent α-synuclein toxicity. Submitted.
[5] Palmioli A, Moretti L, Vezzoni CA, Legnani L, Sperandeo P, Baldini L, Sansone F, Airoldi C, Casnati A. Multivalent calix[4]arene-based mannosylated dendrons as new FimH ligands and inhibitors. Bioorg Chem 2023; 138: 106613.

Site-selective photobromination of carbohydrates

Vito Ferro,

School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane QLD 4072, Australia

The Ferrier photobromination provides direct synthetic access to valuable 5-C-bromosugars[1]. However, its broader application has been constrained by the use of broad spectrum, energy-inefficient heat lamps for irradiation and a reliance on highly toxic (and banned) CCl4 under reflux. Herein we demonstrate that the reaction proceeds rapidly and efficiently under mild conditions (≤40 °C) using benzotrifluoride (PhCF3) as a safe and environmentally benign alternative to CCl4, with irradiation by a compact photoreactor fitted with purple LEDs (405 nm), and NBS serving as the bromine source[2,3].



Furthermore, we have now developed a simple, rapid and scalable photocatalytic method to prepare glycosyl bromides under mild conditions by substituting Br2 for NBS as the brominating agent. This reaction proceeds via generation of HBr in situ from radical bromination of PhCF3 under purple light irradiation. This method is environmentally friendly, limiting the amount of HBr and waste generated, and we demonstrate its use to prepare glycosyl bromides in flow on a multigram scale. Recent results on new photochemical methods to convert these glycosyl bromides into anhydroalditols, 2-deoxysugars and C-glycosides will also be discussed.

References:

[1] Somsák L, Ferrier RJ. Radical-mediated brominations at ring positions of carbohydrates. Adv Carbohydr Chem Biochem 1991; 49: 37–92.
[2] Zhang G, See NW, Wimmer N, Godinez MJ, Cameron SA, Furneaux RH, Ferro V. Site-selective photobromination of O-acetylated carbohydrates in benzotrifluroride. Org Lett 2024; 26: 5956–5960.
[3] Zhang G, See NW, Sharma S A, Wimmer N, Godinez MJ, Cameron SA, Furneaux RH, Ferro V. Purple light-promoted Ferrier photobromination of O-benzoylated carbohydrates in benzotrifluroride. J Org Chem 2025; 90: 16885–16890.

Sensors for biologically important phosphates: from pyrophosphate to phospholipids

Katrina A. Jolliffe[1,2],

[1]*Australian Research Council Centre of Excellence for Innovations in Peptide and Protein Science, School of Chemistry The University of Sydney, 2006, NSW, Australia;*
[2]*The University of Sydney Nano Institute (Sydney Nano), The University of Sydney, NSW 2006, Australia*

Phosphate oxoanions and phosphorylated biomolecules (such as nucleotides, lipids, and proteins) play key roles in a wide range of biological processes. Therefore, the development of receptors that can distinguish between the large number of biologically occurring phosphate anions [(poly)phosphates and phosphorylated biomolecules] to bind selectively to a target ion (e.g., pyrophosphate) in physiological conditions has numerous potential bioanalytical applications. One of the most successful approaches to date for the recognition of phosphate oxoanions in water is the use of Zn(II)-dipicolylamine binding motifs, which have been found to be particularly selective toward phosphate derivatives over other anions[1,2]. By positioning these recognition motifs on specific scaffolds it is possible to design receptors that can discriminate between phosphate derivatives.
We have exploited this and similar binding motifs using peptidic scaffolds to prepare selective colourimetric and fluorescent sensors for a variety of biologically relevant phosphorylated species and report here on their ability to selectively discriminate their targets for a variety of applications.

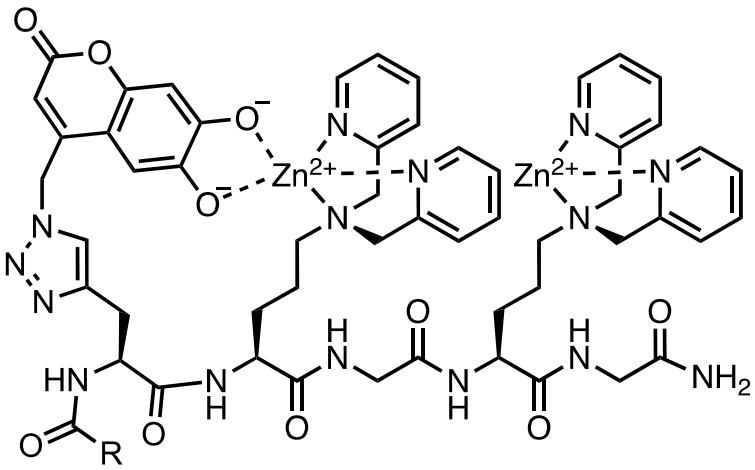


Figure 1. A fluorogenic sensor for cell-surface exposed phosphatidylserine

References:

[1] Ngo, H. T.; Liu, X.; Jolliffe, K. A. Anion recognition and sensing with Zn(II)-dipicolylamine complexes. Chem. Soc. Rev. 2012, 41, 4928–4965.
[2] Nag, A.; Das, S. Fluorescent Sensors of Phosphate Containing Biomolecules. Isr. J. Chem., 2021, 61, 169-184.

Best of Both Worlds or Double-Edged Sword? Antibody-Mediated Delivery of Oligonucleotides

Jan H. Meffert[1], Tina Thien-Ho[2], Alexandros Kostakis[3,4], Enrico Cadoni[1], Martin Bollmark[5], Ulf Tedebark[6], Eugen Stulz[2], Sara Mangsbo[4], Annemieke Madder[1]

[1] Organic and Biomimetic Chemistry Research Group, Department of Organic and Macromolecular Chemistry, Ghent University, Krijgslaan 281, 9000 Ghent, Belgium;
[2] School of Chemistry & Chemical Engineering and Institute for Life Sciences, University of Southampton, Highfield, Southampton SO17 1BJ, United Kingdom;
[3] Strike Pharma AB, Lund, Sweden;
[4] Department of Pharmacy and Science for Life Laboratory, Uppsala University, Uppsala, Sweden;
[5] RISE, Department Chemical Process and Pharmaceutical Development, Forskargatan 18, SE-15136 Södertälje, Sweden;
[6] SynMer AB, SE-17568 Järfälla, Sweden.

The optimisation and further expansion of methods for the synthesis of oligonucleotide conjugates is receiving increased attention due to their importance for further advancement of therapeutic and diagnostic nucleic acid-based applications [1,2]. While the first approved oligonucleotide therapeutics were unconjugated strands delivered via formulations like lipid nanoparticles (LNPs), and small molecule-ON conjugates (e.g., GalNAc-siRNAs) have since reached the clinic, conjugation to larger targeting moieties offers a distinct strategy to overcome persistent challenges. Specifically, linking ONs - such as antisense oligonucleotides (ASOs) or short-interfering RNAs (siRNAs)—to proteins or peptides can enhance properties like cell specificity and cellular uptake, which remain significant hurdles for many ON therapeutics. However, the synthesis of such hybrid molecules typically requires the combination of two orthogonal chemical strategies (peptide/protein versus oligonucleotide chemistry) through one linking chemistry.
In the current talk, our recent advances in the development synthetic approaches towards AOCs (Antibody-oligonucleotide conjugates) using covalent and non-covalent chemistries will be highlighted [3,4,5].

References:

[1] A; Mullard, Antibody-oligonucleotide conjugates enter the clinic. Nat. Rev. Drug Discov. 2022; 21: 6–8. [2] I. Dovgan, O. Koniev, S. Kolodych & A. Wagner. Antibodyoligonucleotide conjugates as therapeutic, imaging, and detection agents. Bioconjugate Chem. 2019; 30: 2483–2501. [3] a) E. de Geyter, E. Antonatou, D. Kalaitzakis, S. Smolen, A. Iyer, L. Tack, E. Ongenae, G. Vassilikogiannakis, A. Madder, Chem. Sci. 2021; 12: 5246; b) A. Madder, E. de Geyter, E. Antonatou, S. Smolen, D. Kalaitzakis, G. Vassilikogiannakis, WO2020174086A2. [4] J.H. Meffert, M. Lopes, E. Cadoni, M. Bollmark, U. Tedebark & A. Madder. Versatile introduction of multifunctional Michael-acceptor moieties on amino-oligonucleotides for bioconjugation purposes. Communications Chemistry 2026; 9:80 [5] T.-T. Ho, J.H. Meffert, A. Kostakis, M. Lopes, M. Pijnappel, L. Buermann, E. Cadoni, M. Bollmark, U. Tedebark, S. Mangsbo, A. Madder, E. Stulz. Versatile antibody-oligonucleotide conjugate based on affinity drug loading enables targeted oligonucleotide delivery to B cells. *under review.*

Can Allostery Turn a Self-Protein into a Pathogenic Antigen?

Giuseppe Melacini,

Department of Chemistry and Chemical Biology, McMaster University, Hamilton ON L8S 4M1, Canada

We propose an allosteric mechanism through which a self-protein converts into an immunogenic antigen capable of driving autoimmune pathology. The mechanism illustrates how a conformational switch exposes otherwise hidden epitopes, enabling antibody binding. Our findings support a general strategy for dampening autoimmune responses by selectively stabilizing non-immunogenic conformational states of self-proteins instead of globally suppressing immunity.

Smart Cancer Nanomedicine

Twan Lammers,

Department of Nanomedicine and Theranostics, Institute for Experimental Molecular Imaging, Center for Biohybrid Medical Systems, RWTH Aachen University Clinic, Forckenbeckstrasse 55, 52074 Aachen, Germany

Nanomedicines are extensively explored for cancer therapy[1]. By delivering drug molecules more effectively and more selectively to pathological sites, nanomedicines assist in improving the balance between drug efficacy and toxicity. The tumor accumulation of nanomedicines is ascribed to EPR and ATR mechanisms[2], which are highly variable, both in animal models and in patients. To address tumor targeting heterogeneity, and to promote cancer nanomedicine clinical translation, we are working on smart tools and technologies to modulate, monitor and predict tumor-targeted drug delivery. In the present lecture, several of these strategies will be highlighted, including physical and pharmacological interventions to prime the tumor microenvironment, and the use of imaging and tissue biomarkers for patient stratification[3-5].

Altogether, our work aims to establish rational and realistic ways forward to improve the performance and clinical impact of cancer nanomedicines.

References:

[1] Lammers T. Nanomedicine tumor targeting. Adv Mater 2024, 36, e2312169.
[2] Dasgupta A, Sofias A, Kiessling F, Lammers T. Nanoparticle delivery to tumors: From EPR and ATR mechanisms to clinical impact. Nat Rev Bioeng 2024, 2, 714-716.
[3] Dasgupta A, Sun T, Palomba R, Rama E, Zhang Y, Power C, Liu M, Sarode A, Weiler M, Motta A, Porte C, Magnuska Z, Elshafei A, Barmin R, Graham A, McClelland A, Rommel D, Stickeler E, Kiessling F, Pallares R, De Laporte L, Decuzzi P, McDannold N, Mitragotri S, Lammers T. Non-spherical ultrasound microbubbles. PNAS 2023, 120, e2218847120.
[4] May J, Moss J, Muller F, Golombek S, Biancacci I, Rizzo L, Gremse F, Pola R, Etrych T, Becker S, Trautwein C, Bulow R, Boor P, Knuchel R, von Stillfried S, Storm G, Puri S, Barry S, Schulz V, Kiessling F, Ashford M, Lammers T. Histopathological biomarkers for predicting the tumour accumulation of nanomedicines. Nat Biomed Eng 2024, 8, 1366-1378.
[5] Rizzo L, De Lorenzi F, Stillfried S, Dadfar S, Hu Q, Tiwari S, Gluer C, Thewissen M, Gremse F, Rutten S, Boor P, Jahnen W, Knuchel R, Kiessling F, Rijcken C, Sofias A, Lammers T. Analysis of nanomedicine primary tumor vs. metastasis targeting using clinical-stage core-crosslinked polymeric micelles. Cell Rep 2025, 44, 116086.

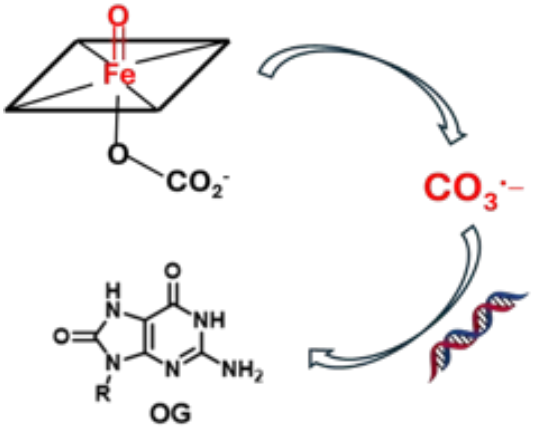
Ribosomal responses to cellular stressors analyzed by nanopore sequencing

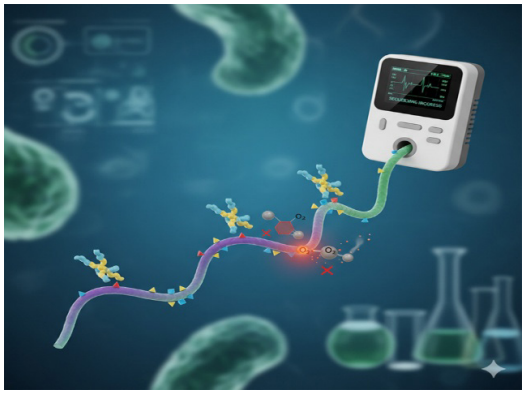
Cynthia J. Burrows, Aaron M. Fleming,

University of Utah, Department of Chemistry, 315 S. 1400 East, Salt Lake City, UT 84112, USA

Oxidative and nitrosative stress in cells are known to lead to DNA damage. RNA is similarly impacted by these stressors, and additionally the epitranscriptomic RNA modifications are remodeled in response to stress. Here, we analyze ribosomal RNA modifications—both enzymatically written modifications and those considered 'damage'—using nanopore direct RNA sequencing. We will discuss (a) the reprogramming of the 230 modifications in rRNA in human cells under oxidative (Fenton) and nitrosative (iNOS) stress in HEK293T cells[1], (b) the introduction of 8-oxoG, inosine, and C-to-U mutations in response to TNFα stress and the implications of rRNA 'tentacles' as reporters of damage[2],and (c) changes in the S. aureas rRNA in response to antibiotic stress[3]. We conclude that rRNA, the most long-lived RNA in the cell, responds to cellular chemistry and adapts to oxidative, nitrosative and antibiotic stress in innovative ways.

In the course of these studies we gained insight to the cellular Fenton reaction of Fe(II) + H2O2 which does not generate hydroxyl radicals or ferryl species but rather is redirected by the presence of physiological bicarbonate (>20 mM) to form carbonate radical instead [4]. This outcome is significant because hydroxyl radical damages all biomolecules, whereas carbonate radical principally reacts with guanine in DNA and RNA, establishing a signaling mechanism whereby oxidative stress initiates a cellular response. Surprisingly, the key player in the cellular labile iron pool appears to be free heme[5].





References:

[1] Fleming AM, Burrows CJ. Nanopore sequencing reveals ribosomal RNA modification changes in human cells experiencing oxidative or inflammatory stress. ACS Chem Biol 2026; revision submitted
[2] Fleming AM, Dingman JC, Burrows CJ. Ribosomal RNA tentacles are targets for free radical damage in mammalian cells during oxidative and inflammatory stress. BioRxiv 2025; https://doi.org/10.1101/2025.09.11.675630.
[3] Copoulos DW, Chevance F, Hughes KT, Burrows CJ, Fleming AM, Looper RE. Nanopore sequencing reveals operon-specific ribosome remodeling accompanying naphthyridone resistance in Staphylococcus aureus. BioRxiv 2025; https://doi.org/10.64898/2025.12.11.693786.
[4] Fleming AM, Dingman JC, Burrows CJ. CO2 protects cells from iron-Fenton oxidative DNA damage in E. coli and humans. PNAS 2024; 121: e2419175121
[5] Fleming AM, Burrows CJ. Hemin recapitulates the labile iron pool in the cellular Fenton reaction with DNA. Submitted.

Chemical Based Aging Research through Fluorescent Live Cell Probes

Young-Tae Chang,

Department of Chemistry, POSTECH, Pohang, Korea

Deciphering the complexity of multicellular organisms requires precise tools to discriminate specific cell types within their native environments. While antibody-based biomarkers are the current gold standard, they often face limitations in live-cell permeability and real-time kinetic monitoring. Here, we present a comprehensive chemical biology platform for live-cell distinction using small-molecule fluorescent probes. We have established an orthogonal strategy encompassing Protein-Oriented (POLD), Carbohydrate-Oriented (COLD), Gating-Oriented (GOLD), and Lipid-Oriented (LOLD) Live-cell Distinction. To further enrich this toolbox, we recently introduced Metabolism-Oriented Live-cell Distinction (MOLD), enabling higher-dimensional discrimination based on cellular metabolic profiles. This multi-dimensional approach has been successfully applied to identify various immune cells and is now being extended to the selective detection of senescent cells. By integrating these cell-selective probes with Photodynamic Therapy (PDT), we demonstrate a practical solution for the targeted elimination of aged cells. This strategy provides a foundational framework for understanding complex cell communities and offers a transformative path toward reverse-aging treatments and regenerative medicine.

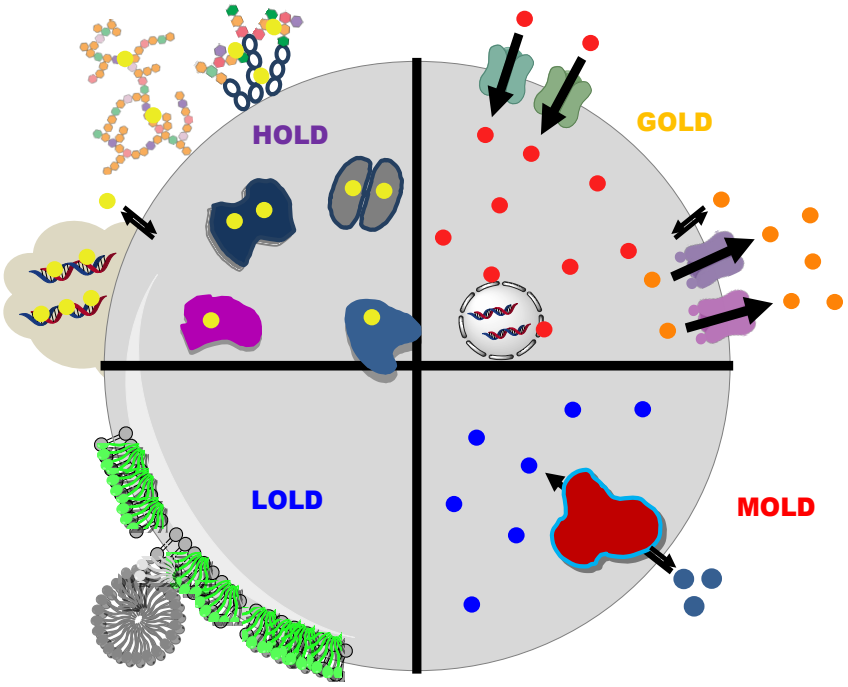


Figure 1. Mechanisms of the live cell distinction: XOLD (X-Oirented Live-cell Distinction).

References:

[1] Sensors and Probes for Bioimaging, Wiley-VCH, Chang, Y. T. & Kang, N. Y., Weinheim, Germany (2023).

C-type Lectin receptors at the heart of sugar-mediated immune recognition of pathogens or altered self: developments and potential applications at the chemistry/biology interface.

Franck Fieschi[1,2],

[1]*Institut de Biologie Structurale, University Grenoble Alpes, Grenoble, France*
[2]*Institut Universitaire de France, Paris, France*

C-type lectin receptors (CLRs) are pathogen-recognition receptors in our immune system and are found predominantly in antigen-presenting cells. They are capable of recognizing carbohydrate structures present on viruses, Gram-positive, Gram-negative bacteria, and even tumour cells, where glycosylations are altered. In all these cases, very different carbohydrate structures must be recognized. These can range from host-derived N/O-glycans in viruses; to lipopolysaccharides in Gram-negative bacteria; to teichoic acid in Gram-positive bacteria; or to altered glycosylation on cancer cells. Through these interactions, CLRs can alternately activate the immune system, internalize pathogens for antigen processing, induce a tolerogenic response, or even be hijacked by pathogens during their infectious cycle. The diversity of carbohydrate structures, their valence, and the molecular context of their coupling (glycans, proteins, lipids) lead to an infinite number of interaction modes and properties. Reflecting this complexity, the family of CLR receptors is vast and, despite the efforts made over the last decade, we are far from having a complete picture of all the recognition motifs and of these glycan/CLR pairs. Over the years, we have developed a library of recombinant CLRs as well as approaches to characterize their recognition properties, with the aim of informing the chemical development of new inhibitors, delivery systems and/or diagnostic tools. I will present several examples, notably relating to SARS-CoV-2, S. aureus and human tumors, in which, by combining chemistry, biophysics and structural biology, we have characterized binding epitopes, identified new targets and contributed to the development of new glycomimetics and macromolecular assemblies for biomedical applications.

Disease Biology-driven Molecular Labeling Toolkits for Precision Theranostics

Sonhan Liu[1], Yuexin Song[2], Bengng Xing[*1,2]

[1]*Department of Applied Biology & Chemical Technology, The Hong Kong Polytechnic University, Hong Kong SAR*
[2]*School of Chemistry, Chemical Engineering, and Biotechnology (CCEB)*
Nanyang Technological University (NTU), Singapore 637371
Email: Bengang@ntu.edu.sg; Bengang.xing@polyu.edu.hk

Bioorthogonal chemical biology has emerged as a powerful transformative strategy for the development of localized molecular probes and clickable handles, enabling multi-specific bio-labeling and dynamic profiling of pathological processes. This methodology utilizes bioorthogonal click conjugations that selectively occur within biological systems without interfering native pathways in living systems. By harnessing unique molecular probes capable of specifically targeting disease-associated markers and facilitating their specific interactions within complex living environments, we can monitor molecular events and biological pathways in real-time, thus gaining valuable insights into cellular dynamics for disease progression and therapeutic response. Such innovative methodology enables the detailed examination of molecular interactions and alterations in cellular behavior, offering deeper understanding of the mechanisms underlying various pathological progression towards future therapeutic development. Moreover, based on the enzyme responsive bioorthogonal conjugation, we have also developed a first-in-class self-programmable enzyme-derived clicking PROTACs (ENCTACs) design strategy that can specifically respond to tumour enzyme stimulation and selectively decompose epigenetic BRD4 protein activities for micro-environment responsive angiogenesis immuno-modulation in vitro and in vivo. In this conference, we will introduce all these latest discoveries.
In this event, we will introduce our latest studies regarding the chemical biology strategies for the specific labeling of various bacteria pathogens and their unique functions for disease manipulation in complex living settings. Our unique orthogonal chemical reporters hold great potential for advancing diagnostic and therapeutic development in precision medicine.

References:

[1] Liu S, Hua C, Li X, Yuan P, Xing BG, A powerful bioorthogonal toolbox boosting the development of immune theranostics, Chem. Sci., 2025, 16, 22870-22899
[2] Sun C, Liu S, Lau JW, Yang H, Chen Y, Xing BG, Enzyme-Activated Orthogonal Proteolysis Chimeras for Tumor Microenvironment-Responsive Immunomodulation, Angew. Chem. Intl. Ed, 2025, 65, e202423057, "Inside Cover".
[3] Xin Y, Kwek G, An X, Sun C, Liu S, Ng S, Lingesh S, Jiang L, Liu G, Xing BG, Enzymes in synergy: Bacteria specific molecular probe for locoregional imaging of urinary tract infection in vivo, Angew. Chem. Intl. Ed, 2024, 64, e202406843, VIP.
[4] Do TC, Lau JW, Sun C, Liu S, Kha KT, Lim ST, Oon YY, Kwan YP, Ma JJ, Mu Y, Liu Y, Carney TJ, Wang X, Xing BG, Hypoxia deactivates epigenetic feedbacks via enzyme-derived clicking proteolysis-targeting chimeras,Science Advances, (2022), 8, eabq2216.

Glycomimetics: From Chemical Mimics to Probes and Therapeutics

Carmen Ortiz Mellet[1],

[1]*Department of Organic Chemistry, Faculty of Chemistry, University of Seville, Seville, Spain*

Carbohydrates and glycoconjugates govern many essential biological processes, particularly those involved in cellular recognition and communication. Glycomimetics, synthetic molecules designed to emulate carbohydrate function, offer powerful tools to probe and manipulate these interactions. However, most reported glycomimetics primarily reproduce the structural features of sugars while failing to capture their intrinsic chemical reactivity, which limits the development of functional analogues of glycans and complex glycoconjugates.
To overcome this limitation, we have developed a class of compounds termed sp2-iminosugars. These molecules combine structural similarity to natural monosaccharides with chemical properties that closely resemble those of carbohydrates, enabling them to mimic not only simple sugars but also the functional behavior of glycopeptides, glycolipids, and oligosaccharides. As a result, sp2-iminosugars interact with carbohydrate-binding biomolecules with high selectivity and can modulate the activity of glycan-processing enzymes as well as receptors and antibodies involved in glycan recognition.
Beyond their molecular versatility, sp2-iminosugars can be incorporated into stimuli-responsive systems, for example, platforms responsive to pH, light, or temperature, allowing controlled engagement with biological targets. When displayed in multivalent architectures, such as on cyclodextrin-based scaffolds, these compounds can reproduce the multivalency that characterizes carbohydrate–protein recognition.
Recent studies highlight their potential in diverse biomedical contexts, including lysosomal storage disorders and Alzheimer's disease, tumor-associated carbohydrate antigen recognition, selective targeting of C-type lectins in antigen-presenting cells, and modulation of innate immune responses (Figure 1). Together, these examples illustrate the promise of sp2-iminosugars as adaptable glycomimetics for applications in chemical biology and medicine[1-4].

The author anckowledges funding from MICIU / AEI / EDRF (PID2022-141034OB-C21) and the EU HE program (MSCA-SE 101130235 – Bicyclos).

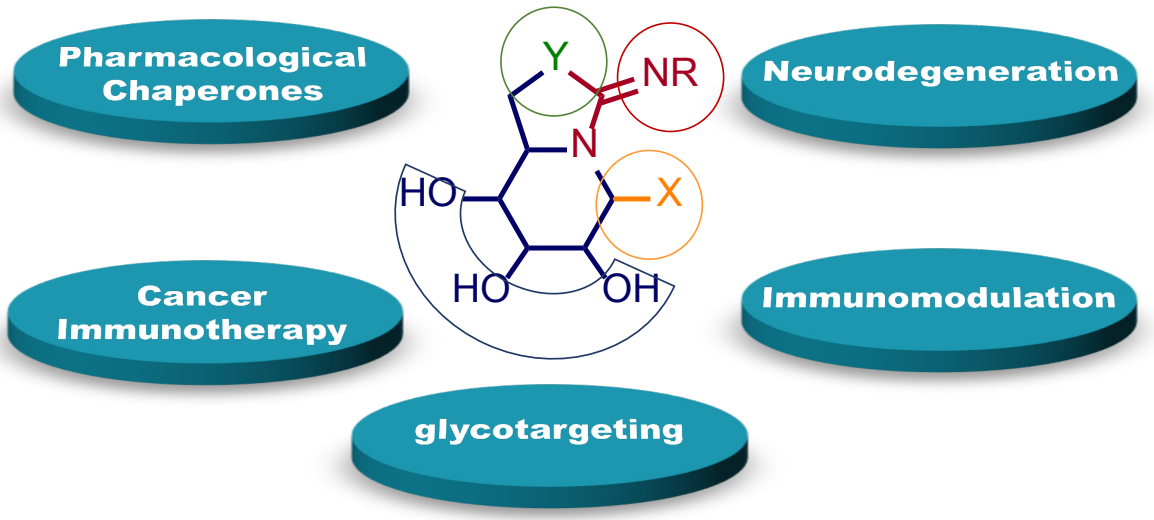


Figure 1. Schematic representation of a typical sp2-iminosugar scaffold highlighting positions amenable to chemical diversification and selected application areas explored to date.

References:

[1] Padilla-Pérez MC, Rodríguez-Marín R, González-Bakker A, N. Khan A, Bastardo-Torío M., Padrón JM, Martín-Loro F, Arroba AI, García-Hernández R., Pérez-Victoria JM, García Fernández J.M, Sánchez-Fernández EM, Ortiz Mellet C. Exploring the influence of the glycone space on the therapeutic potential of sp2-iminoglycolipids. Eur. J. Med. Chem. 2026, 302: 118337.
[3] García-Moreno MI, Kawakami K, Nanba E, García Fernández J.M, Higaki K, Ortiz Mellet C. Neutral sp2-iminosugars exploiting non-glycone interactions for selective acid α- and β-glucosidase activity modulation: Pharmacological chaperones for Gaucher and Pompe diseases. Eur. J. Med. Chem. 2026, 304: 118500.
[4] Lai AC-Y, González-Cuesta, Ho CH, Chi P-Y, Wu K-C, Rocha G, Muñoz-García JC, Angulo J., García Fernández J.M, Chang Y-J, Ortiz Mellet C. α-GalCer sp2-iminoglycolipid analogs as CD1d-dependent iNKT modulators: Evaluation of their immunotherapeutic potential in murine models of asthma and autoimmune hepatitis. Eur. J. Med. Chem. 2025, 282: 117060.
[5] Herrera-Gonzalez I, Gonzalez-Cuesta M, M, Eugenie Laigre E, Goyard D, Rojo J, Garcia Fernandez JM, Fieschi F, Renaudet O, Nieto PM, Ortiz Mellet C. High-Mannose Oligosaccharide Hemimimetics that Recapitulate the Conformation and Binding Mode to Concanavalin A, DC-SIGN and Langerin. Chem. Eur. J. 2023, e2023030417.

Decoding the Glycan Landscape: How Sugar Structure Shapes Function and Recognition

Alba Silipo[a],[b],

[a]Department of Chemical Sciences, University of Naples Federico II, Via Cintia 4, 80126, Naples (Italy)
[b]Department of Chemistry, School of Science, Osaka University, 1-1 Osaka University, Machikaneyama, Toyonaka, Osaka, 560-0043, JAPAN
silipo@unina.it

Deciphering the structural complexity of carbohydrate-based biomolecules remains a difficult challenge due to the intrinsic diversity of sugar world, which still limits automated analyses. Yet, this task is essential for understanding molecular interactions at the atomic level, particularly, but not only, in host–microbe communication. By integrating complementary biophysical approaches, including NMR spectroscopy, computational modeling, native MS, and immunological assays, we can unravel the structures, properties, and functions of glycans and their roles in recognition mechanisms that define the sugar code.
This lecture will explore the dual nature of the glycocode: its beneficial role as a mediator of cross-talk, homeostasis, and immune system development, and its harmful role when exploited by pathogens and cancer cells. I will place a special emphasis on the glyco-features of bacterial cell surfaces that fine-tune eukaryotic immune responses.

References:

Chem Sci. 2025 Nov 27;17(4):2281-2294. doi: 10.1039/d5sc08335d.
Proc Natl Acad Sci U S A. 2025 Jul 29;122(30):e2426211122.
JACS Au. 2025 Sep 25;5(11):5367-5380. doi: 10.1021/jacsau.5c00810.
Adv Sci (Weinh). 2025 Jun;12(21):e2415782. doi: 10.1002/advs.202415782.
JACS Au. 2025 Apr 30;5(5):2257-2269. doi: 10.1021/jacsau.5c00214.
Carbohydr Polym. 2025 Jan 15;348(Pt A):122833. doi: 10.1016/j.carbpol.2024.122833.
JACS Au. 2025 Jun 24;5(7):3311-3327. doi: 10.1021/jacsau.5c00441.
ACS Cent Sci. 2024; 10(2):447-459.
JACS Au. 2024; 4(2):697-712.
Angew Chem Int Ed Engl. 2023;62(43):e202307851.
JACS Au. 2023;3(3):929-942.
ACS Cent Sci. 2022; 8(10):1383-1392.
Angew Chem Int Ed Engl. 2022; 61(14):e202200818.
Carbohydr Polym. 2022; 277:118839.
ACS Cent Sci. 2020; 6(9):1602-1616.
Nat Commun. 2020; 11(1):4142.
Nat Rev Microbiol. 2018; 16(5):304-315.
Nat Commun. 2017; 8(1):115.
Nat Commun. 2014; 5:5106.

Glycans as biomarkers and functional effectors of cardiometabolic diseases - insights from the first 200,000 analysed Human Glycomes

Gordan Lauc[1,2],

[1]*University of Zagreb, Zagreb, Croatia;*
[2]*Genos Glycoscience Research Laboratory, Zagreb, Croatia*

The ultimate layer of molecular complexity is generated by modifying proteins with complex oligosaccharides – glycans. Glycosylation integrates genetic, epigenetic, and environmental information into chemical structures that can be reliably quantified. Hundreds of genes are involved in the complex pathway of glycan biosynthesis and glycome composition is significantly heritable as a complex trait. Alternative glycosylation (attaching different glycans to the same glycosylation site on a protein) modulates protein function and in this way actively participates in the transition from health to disease. By analysing over 200,000 individuals we demonstrated that glycans have significant biomarker potential in predicting different age-related diseases, but also in monitoring pharmacological and lifestyle interventions aimed at decreasing the disease risk. However, glycans are not only biomarkers, but functional effectors on the path from health to disease. For example, glycosylation of IgG is an essential effector of the immune system, but our understanding regulation of glycosylation is still limited. Significant efforts have been invested in studying the role of glycosyltransferases in IgG glycosylation, but today it is clear that enzyme expression is not the key regulatory mechanism. By performing large genome-wide association studies we mapped a network of over 40 genes that associate with IgG glycome composition and are in pleiotropy with different inflammatory diseases. These includes many transcriptional factors, immune specific signalling proteins, chromatin regulators, solute carriers, cytoskeleton and Golgi and ER associated proteins. This complex network works together to maintain homeostasis and preserve normal physiological functions through aging. Through time, the capacity to compensate is decreasing, which leads to loss of some functions and eventually the loss of healt.

Tumor targeting

Dario Neri[1,2]

[1]*Philogen SpA, La Lizza 7, 53100 Siena (Italy)*
[2]*ETH Zürich, Wolfgang-Pauli-Strasse, CH-8093 Zurich (Switzerland)*

In 1900, Paul Ehrlich had postulated the opportunity to use chemical means to tackle disease and generate "Zauberkugeln" (magic bullets): molecules that would preferentially localize and act at the site of disease, helping spare normal tissues.
A modern implementation of the original vision of Paul Ehrlich consists in the ligand-based pharmacodelivery of bioactive payloads to the site of disease. In this lecture, I will show how encoded combinatorial libraries (e.g., phage display antibody libraries and DNA-encoded chemical libraries) have facilitated the discovery of specific protein ligands and the clinical implementation of targeted delivery strategies, for the imaging and therapy of several cancer indications.

References:

D. Neri, R.A. Lerner (2018) "DNA-encoded chemical libraries: a selection system based on endowing chemical compounds with amplifiable information". Annu. Rev. Biochem., 87, 479-502.

S. Cazzamalli, E. Puca, D. Neri (2025). "Past, present, and future of drug conjugates for cancer therapy". Nat. Cancer, 6, 1494-1504.

INVITED LECTURES

Illuminating and controlling cell function with chemogenetics

ArnaudGautier,

SorbonneUniversité,ÉcoleNormaleSupérieure,UniversitéPSL,CNRS, ChimiePhysiqueetChimieduVivant (CPCV), 75005 Paris, France

Cells and organisms are complex machines driven by a set of dynamic biological events tightly orchestrated in space and time. The comprehensive molecular understanding of their inner workings requires acute molecular tools to observe and modulate the key triggers and cell signaling events. To study the molecular mechanisms that govern cells and organisms over differentscalesintimeandspace,wecombinemolecularchemistrywithproteinengineeringand genetic tools to develop novel approaches for the quantitative imaging and acute modulation of individual small molecules, proteins, organelles or cells. Made of organic synthetic molecules coupled to genetic tags, these systems combine the advantage of synthetic molecules with the targeting selectivity of genetically encoded tags, challenging the paradigm of fully genetically encoded systems. During this talk, I will present how these systems can be used for imaging, sensing and controlling cell biochemistry with high spatial and temporal resolution.

Bioorthogonal reactions with mesoionics, new tools for chemical biology

FrédéricTaran

Service de Chimie Bioorganique et de Marquage –
Paris-Saclay University - CEA Saclay 91190 Gif sur Yvette
frederic.taran@cea.fr

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

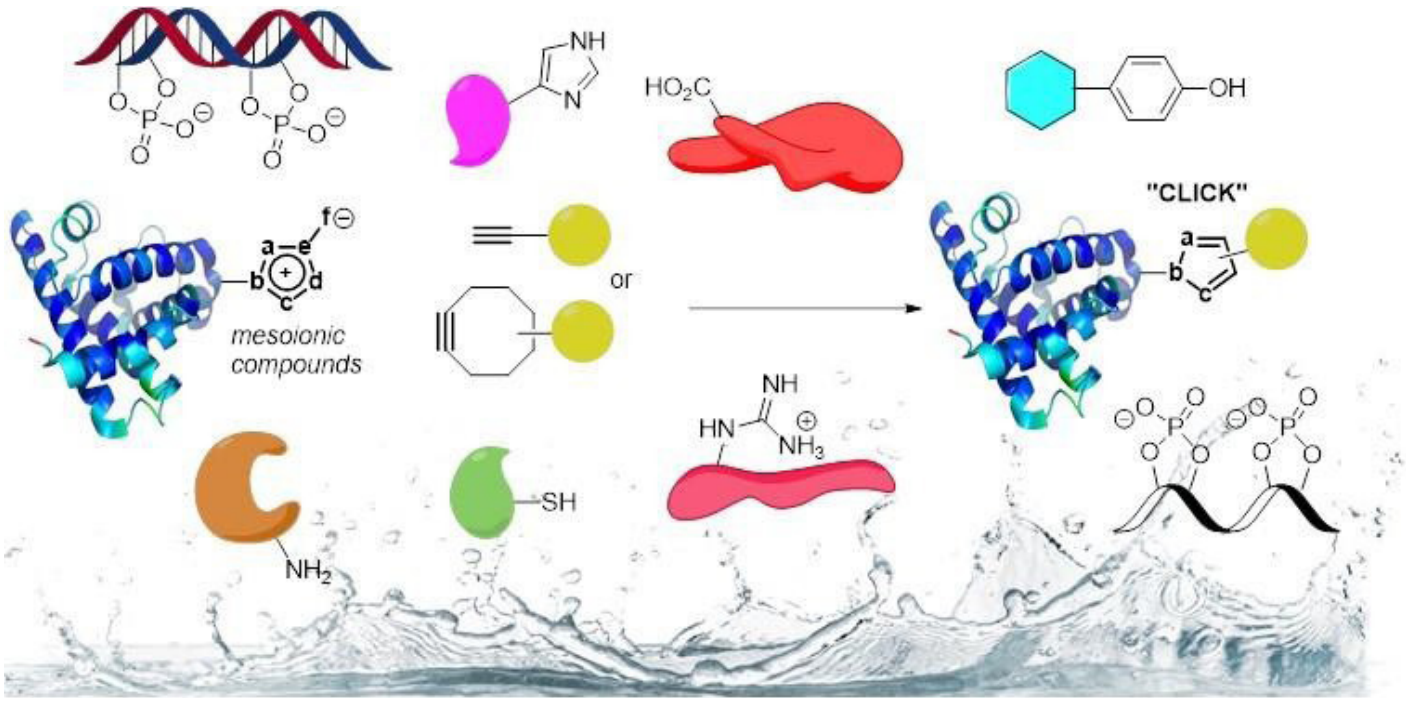


Figure. Chemoselective cycloaddition reactions of mesionics with alkynes.

References:

[1] a) Kolodych, S; Rasolofonjatovo, E; Chaumontet, M; Nevers, M-C; Créminon, C; Taran. F. Angew. Chem. Int. Ed., 2013, 52, 12056- 12060; b)Bevilacqua,V; King, M; Chaumontet, M; Nothisen, M; Gabillet, S; Buisson, D; Puente, C; Wagner, A; Taran, F. Angew. Chem. Int. Ed., 2014, 53, 572-5876.

[2] 2.a)Plougastel, L; Koniev, O; Specklin, S; Decuypere, E; Créminon, C; Buisson, D-A; Wagner, A; Kolodych, S; Taran, F. ChemComm, 2014, 50, 9376-9378; b) Liu, H; Audisio, D; Plougastel, L; Decuypere, E; Buisson, D-A; Koniev, O; Kolodych, S; Wagner, A; Elhabiri, M; Krzyczmonik, A; Forsback, S; Solin, O; Gouverneur V; Taran, F. Angew. Chem. Int. Ed. 2016, 55, 12073-12077; c) Bernard, S; Audisio, D; Riomet, M; Bregant, S; Sallustrau, A; Plougastel, L; Decuypere, E; Gabillet, S; Kumar, R.A; Elyian, J; Nguyet Trinh,M; Koniev,O; Wagner, A; Kolodych, S and Frédéric Taran. Angew. Chem. Int. Ed. 2017, 56, 15612-15616; d) M. Ribéraud, E. Porret, A. Pruvost, F. Theodoro, A. L. Nguyen, S. Specklin, D. Kereselidze, C. Denis, B. Jego, P. Barbe, M. Keck, T. D'Anfray, B. Kuhnast, D. Audisio, C. Truillet,* F. Taran.* Chem. Sci., 2024, 15, 18825 – 18831; e) Léa Madegard, Melissa Girard, Estelle Blochouse, Benjamin Riss Yaw, Alberto Palazzolo, Mélanie Laquembe, Davide Audisio, Pauline Poinot, Sébastien Papot and Frédéric Taran. Angew. Chem. Int. Ed. 2025, e202422627; g)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.

Advancement of site selective conjugation for innovative glycoconjugate vaccine design

Roberto Adamo

GSK Vaccines Institute for Global Health, Via Fiorentina 1, 53100 Siena

Glycoconjugate vaccines remain crucial in preventing infectious diseases, with many currently licensed vaccines employing random chemical linkage of carbohydrate antigens to protein carriers. However, this traditional approach can compromise protein epitopes and obscure the precise contribution of the conjugation site to vaccine immunogenicity. Significant advancements in site-selective glycoconjugation techniques are now revolutionizing vaccine design1. These include chemical or enzymatic modification of specific amino acid residues, incorporation of unnatural amino acids, and glycoengineering. These precise methods offer unprecedented advantages by preserving the conformational integrity of protein epitopes, particularly when the protein serves a dual role as both antigen and carrier. Furthermore, they enable a more detailed understanding of how the conjugation site influences the immune response[1].
Our team has actively developed and applied these innovative site-selective methods to generate novel vaccine candidates. We will present recent achievements in the design of glycoconjugate vaccines targeting critical pathogens such as Group Streptococcus, S. pneumoniae , Candida, Neisseria meningitidis, and combined Staphylococcus aureus / Pseudomonas aeruginosa infections[2-4]. The presentation will elaborate on these developments, showcasing new pathways for optimizing the design and improving the immunogenicity of future glycoconjugate vaccines.

References:

(1) Stefanetti, G.; Rondini, S.; Lanzilao, L.; Saul, A.; MacLennan, C. A.; Micoli, F. Impact of conjugation chemistry on the immunogenicity of S. Typhimurium conjugate vaccines. Vaccine 2014; 32 (46): 6122-6129. DOI: 10.1016/j.vaccine.2014.08.056.
(2) R. Adamo, Q. Y. Hu, A. Torosantucci, S. Crotti, G. Brogioni, M. Allan, et al. Deciphering the structure-immunogenicity relationship of anti-Candida glycoconjugate vaccines. Chem. Sci. 2014; 5(11): 4302-431. DOI: 10.1039/c4sc01361a.
(3) Nilo, A.; Morelli, L.; Passalacqua, I.; Brogioni, B.; Allan, M.; Carboni, F.; Pezzicoli, A.; Zerbini, F.; Maione, D.; Fabbrini, M.; et al. Anti-Group B Streptococcus Glycan-Conjugate Vaccines Using Pilus Protein GBS80 As Carrier and Antigen: Comparing Lysine and Tyrosine-directed Conjugation. ACS Chem Biol 2015; 10 (7): 1737-1746. DOI: 10.1021/acschembio.5b00247.
(4) Carboni, F.; Kitowski, A.; Sorieul, C.; Veggi, D.; Marques, M. C.; Oldrini, D.; Balducci, E.; Brogioni, B.; Del Bino, L.; Corrado, A.; et al. Retaining the structural integrity of disulfide bonds in diphtheria toxoid carrier protein is crucial for the effectiveness of glycoconjugate vaccine candidates. Chem. Sci. 2022; 13: 2440-2449, DOI: 10.1039/D1SC01928G.
(5) Sorieul, C.; Mikladal, B.; Wu, D.-Y.; Brogioni, B.; Giovani, C.; Adamo, G.; Romagnoli, G.; Margarit Y Ros, I.; Codée, J.; Romano, M. R.; et al. Multimeric, multivalent fusion carrier proteins for site-selective glycoconjugate vaccines simultaneously targeting Staphylococcus aureus and Pseudomonas aeruginosa. Chem. Sci. 2025; 10.1039/D4SC08622H. DOI: 10.1039/D4SC08622H.

Machine Learning to Boost Detection of Allosteric Fingerprints from Molecular Dynamics

Stefano Artin Serapian[1], Elena Frasnetti[2], Ivan Cucchi[3], Emanuele Casali[1], Alice Triveri[4], Giorgio Colombo[1]

[1]Dept. of Chemistry, University of Pavia, via Taramelli 12, 27100 Pavia, Italy;
[2]Institute for Complex Molecular Systems (ICMS), Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, Netherlands;
[3]Dept. of Mathematics, University of Pavia, via Ferrata 5, Italy; [4]Laboratory of Molecular Modeling and Drug Discovery, Istituto Italiano di Tecnologia, Via Morego 30, 16163, Genoa, Italy

Machine Learning (ML) has tremendously impacted biomolecular modelling and simulations, revolutionizing protein structure prediction, drug design[1], and the study of enzyme reactivity at accuracies comparable to quantum mechanics[2]. Our own research has long focused on deciphering allostery from unbiased atomistic Molecular Dynamics (MD) simulations, and we are increasingly seeking to apply ML models in this context.
We have often employed distance fluctuation (DF) analysis to detect allosteric fingerprints following MD simulations of proteins and protein complexes[3]. Concretely, DF analysis quantifies the degree of concerted movement between residue pairs in a simulated system: the resulting square matrix of DF scores constitutes an ideal source of descriptors for ML models, either as a processable image, or directly as numerical indices.
In this Communication, I will present two projects[4,5] in which DF analysis and other MD-generated descriptors were passed to ML models with promising outcomes. I will first recount our application of a ML model to microsecond-long simulations of different variants of SARS-CoV-2 Spike glycoprotein, helping explain the impact of key mutations on the stability of the protein, and its relevance in terms of sequence evolution. I will then discuss how DF-based active site descriptors, several other MD-derived metrics, and simple molecular fingerprints guided our development of a ML model that could successfully classify small molecules as orthosteric or allosteric inhibitors of cyclin dependent kinases.
Both studies showcase the potential of employing ML to boost the predictive power of MD, with an eye to allostery and beyond.

References:

[1] Catacutan DB, Alexander J, Arnold A, Stokes JM. Machine Learning in Preclinical Drug Discovery. Nat Chem Bio 2024; 20: 960-973.
[2] Sha X, Chen Z, Xie D, Zhou Y. J Chem Theor Comput 2025; 21: 4335–4346.
[3] Castelli M, Marchetti F, Osuna S, Oliveira ASF, Mulholland AJ, Serapian SA, Colombo G. Decrypting Allostery in Membrane-Bound K-Ras4B Using Complementary In Silico Approaches Based on Unbiased Molecular Dynamics Simulations. J Am Chem Soc 2024; 146: 901-919.
[4] Triveri A, Casali E, Frasnetti F, Doria F, Frigerio F, Cinquini F, Pavoni S, Moroni E, Marchetti F, Serapian SA, Colombo G. Conformational Behavior of SARS-Cov-2 Spike Protein Variants: Evolutionary Jumps in Sequence Reverberate in Structural Dynamic Differences. J Chem Theory Comput 2023; 19: 2120-2134.
[5] Frasnetti E, Cucchi I, Pavoni S, Frigerio F, Cinquini F, Serapian SA, Pavarino LF, Colombo G. Integrating Molecular Dynamics and Machine Learning Algorithms to Predict the Functional Profile of Kinase Ligands. J Chem Theory Comput 2024; 20: 9209-9229.

Exploring multivalency effects in G4-forming aptamers for diagnostics and theranostics

Daniela Montesarchio

Department of Chemical Sciences, University of Napoli Federico II, via Cintia 21, I-80126 Napoli, Italy

Among the known aptamers, many are based on guanine-rich oligonucleotides[1]. This is not surprising if we consider that these oligonucleotides share a distinctive ability to fold into stable but also extremely different G-quadruplex (G4) structures. Thus, even very similar guanine-rich DNA sequences can exhibit extraordinarily wide structural variability and provide aptamers with very different recognition abilities.
In this frame, we recently investigated several G4-forming aptamers specifically targeting inflammation-, coagulation-, neurodegeneration- and cancer-related proteins. Here special focus will be devoted to G4-forming aptamers selectively recognizing HMGB1, a chromatin-associated, non-histonic protein which under inflammatory conditions is massively released in the extracellular environment, where it acts as a cytokine contributing to the pathogenesis of cancer[2].
By a SELEX-like procedure, we recently identified the highly effective anti-HMGB1 aptamer L12, a G4-forming 26-mer aptamer which is highly polymorphic[3]. Indeed, its conformational behavior dramatically depends on the sample manipulation and chosen buffer[3,4]. In physiological buffers mimicking extracellular media and without thermal annealing procedure, this aptamer folds into very stable dimeric parallel G-quadruplex structures, which recognize the target protein with much higher affinity than its monomeric counterpart[3]. To obtain L12 analogues more effective for in vivo studies and early detection of this cancer-relevant protein in biological samples, a mini library of covalent dimers of L12 has been investigated[5]. Moreover, to fully exploit multivalency effects, a new approach in which the L12 aptamer was immobilized on silica nanoparticles has been undertaken.

References:

[1] Platella C, Riccardi C, Montesarchio D, Roviello GN, Musumeci D. G-quadruplex-based aptamers against protein targets in therapy and diagnostics Biochim. Biophys. Acta Gen. Subj. 2017; 1861: 1429-1447.
[2] Tang D, Kang R, Zeh HJ, Lotze MT. The multifunctional protein HMGB1: 50 years of discovery Nat. Rev. Immunol. 2023; 23: 824–841.
[3] Napolitano E, Criscuolo A, Riccardi C, Esposito CL, Catuogno S, Coppola G, Roviello GN, Montesarchio D, Musumeci D. Directing in vitro selection towards G-quadruplex-forming aptamers to inhibit HMGB1 pathological activity Angew. Chem. Int. Ed. 2024; 63: e202319828.
[4] Napolitano E, Criscuolo A, Riccardi C, Platella C, Gaglione R, Arciello A, Musumeci D, Montesarchio D. When annealing is detrimental: The case of HMGB1-targeting G-quadruplex aptamers Int. J. Biol. Macromol. 2024; 283(Pt 1): 137148.
[5] Criscuolo A, Napolitano E, Riccardi C, Gaglione R, Piccolo E, Arciello A, Musumeci D, Montesarchio D. Covalently linked dimers of a G-quadruplex-forming aptamer as HMGB1 inhibitors Int J Biol Macromol. 2025; 332(Pt 1): 148479.

Engineering Enzymatic Reactions and Protein Aggregation by Biomolecular Condensates

Paolo Arosio

Department of Chemistry and Applied Sciences, Institute for Chemical and Bioengineering, ETH Zurich, Zurich, Switzerland

It has emerged that membraneless organelles, known as biomolecular condensates, provide cells with an additional layer for organizing and controlling biochemical activity in space and time. This raises fundamental questions about the mechanisms by which condensates modulate biochemical processes, including enzymatic reactions and protein aggregation events. Here, beyond simple concentration effects, we demonstrate roles for interfaces[1][2], condensate size[3], and the dense-phase microenvironment[4]. We discuss how modulation by condensates is not limited to accelerating or inhibiting rates but include enhancement of robustness and precise control of reactions in space and time[4][5]. We highlight implications for engineering synthetic enzymatic condensates and for understanding condensate aging in neurodegeneration.

References:

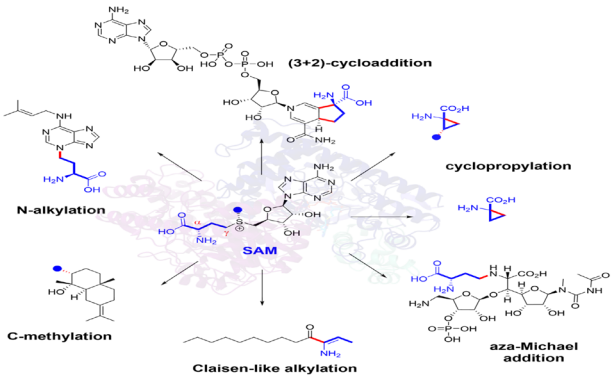
[1] Linsenmeier M. et al., Nat. Chem., 2023, 15, 1340-1349.
[2] Morelli C. et al., Nat. Chem., 2024, 16, 1052-1061.
[3] Gil-Garcia M. et al., Nat. Comm., 2024, 15, 3322.
[4] Stoffel F. et al., Nat. Comm., 2025, 16, 6368.
[5] Papp M. et al., Nat. Chem. Eng., 2025, 2, 394-397.

Enzyme and Natural Product Discovery in Non-Canonical Pathways

Lena Barra

University of Konstanz, Universitätsstraße 10, 78464, Konstanz, Germany

Natural products have been and continue to be of tremendous importance for human health purposes. They have captivated researchers for decades with their remarkable structural complexity, bioactivity, and the intricate enzymatic reactions underlying their biosynthesis. While much attention has been focused on traditional classes such as non-ribosomal peptides, polyketides, and terpenoids, our research program specifically aims to expand upon these systems by uncovering and investigating distinct specialized metabolic pathways to unlock access to novel chemical entities and the associated enzyme-catalyzed chemical transformations.
The talk will focus on our on-going endeavors in the exploration of non-canonical Sadenosylmethionine (SAM)-derived enzyme chemistry by combining genomics-driven computational methods with functional, structural, and mechanistic investigations.
A particular focus will be placed on the exploration of non-classical terpene biosynthetic pathways that generate methyl-modified analogs of central sesquiterpenes. These systems rely on SAM-dependent carbon methylation reactions that give rise to unusual prenyl diphosphate intermediates and thereby provide a unique entry point to terpenes that extend beyond the classical biogenic isoprene rule. In turn, they enable the biocatalytic generation of methyl-modified terpene scaffolds and the systematic investigation of how strategic methyl substitutions influence the biological activity and physicochemical properties of terpenoids, offering an opportunity to explore and exploit a potential "magic-methyl effect" in terpene chemistry [1,2].



References:

[1] Zhou L, Reuter T, Schumann K, Mayer M, Hanauska DM, Barra L. Homoterpene biosynthesis in fungi. Angew Chem Int Ed 2025; 64: e17837.
[2] Reuter T, Dieminger L, Steidle S, Zoller K, Holocher M, Zhou L, Hanauska DM, Racz K, Barra L. Non canonical C16 homoterpene biosynthesis widespread in Actinobacteria. Angew Chem Int Ed 2024; 64: e202418613.

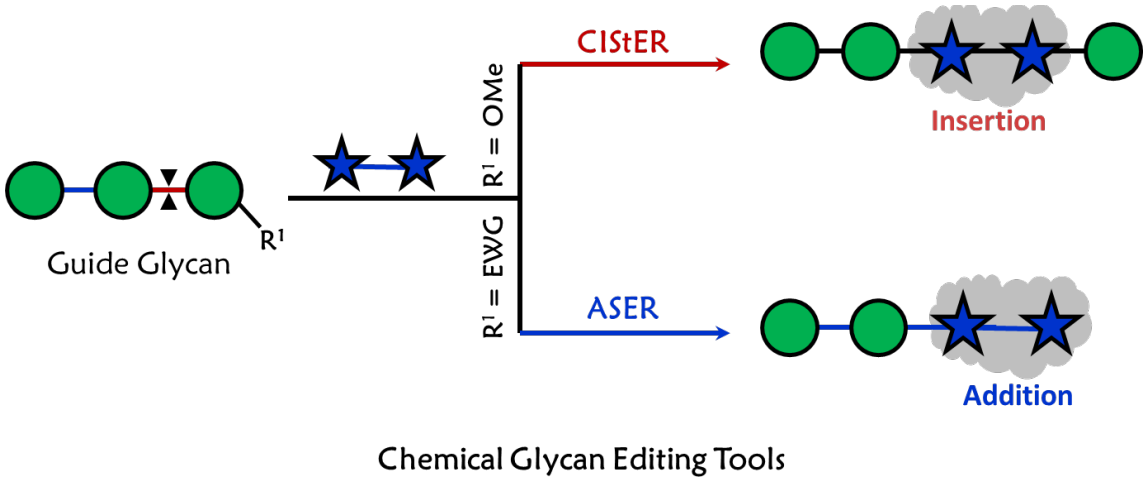
Chemical Glycan Editing Tools

Srinivas Hotha*

Department of Chemistry, Indian Institute of Science Education and Research Pune, Pune – 411 008 (MH)
e-mail: s.hotha@iiserpune.ac.in

Existing strategies for the syntheses of oligosaccharides follow convergent, divergent, chemical or enzymatic routes[1]. Contrary to these, nucleic acids enjoy the unique advantage of PCR, polymerases, and editing methods such as CRISPR2 which have advanced the field to an unprecedented level. Unlike nucleic acids, oligosaccharides are lagging behind due to inherent challenges in their syntheses[3].

In this lecture, a working framework will be presented for the editing of oligosaccharides viz. Cut-Insert-Stitch Editing Reaction (CIStER) technology and Aglycon Swapping Editing Reaction (ASER) that stands on the subtle reactivity patterns[4,5].



Figure

References and Notes:

1) a) S. A. Thadke, B. Mishra, M. Islam, S. Pasari, S. Manmode, B. V. Rao, M. Neralkar, G. P. Shinde, G. Walke, S. Hotha, Nature Commun., 2017, 8, 14019. b) S. Pasari, S. Manmode, G. Walke, S. Hotha, Chem. Eur. J., 2018, 24, 1128. c) G. Walke, N. Kasdekar, Y. Sutar, S. Hotha, Communications Chem., 2021, 4, 15.
2) F. Hille, H. Richter, S. P. Wong, M. Bratovič, S. Ressel, Cell, 2018, 172, 1239.
3) Y. Xue, G. Dong, Acc. Chem. Res., 2022, 55, 2341-2354.
4) S. Sen, S. Kundu, S. Pasari, S. Hotha, Communications Chem. 2024, 7, 73.
5) S. Sen, S. Kundu, S. Hotha, Eur. J. Org. Chem. 2026, e202501206.

From a unique tetrasaccharide scaffold to a broad serotype coverage Shigella flexneri vaccine candidate

Laurence A. Mulard

Institut Pasteur, Université Paris Cité, CNRS UMR3523, Laboratory Chemistry of Biomolecules, 28 rue du Dr Roux, 75724 Paris Cedex 15, France

Shigella flexneri are Gram-negative enterobacteria and the main cause of endemic shigellosis, a major diarrheal disease especially affecting children under five in low- and middle-income countries. Disease burden calls for a Shigella vaccine that would induce broad serotype protection. Shigella flexneri O-antigens, the polysaccharide components of the bacterial lipopolysaccharides, were identified as a prime target for vaccine development. Most S. flexneri serotypes exhibit closely related O-antigens. Structural diversity reflecting serotype specificity derives from site-selective substitutions on a common tetrasaccharide core (Figure 1)[1].

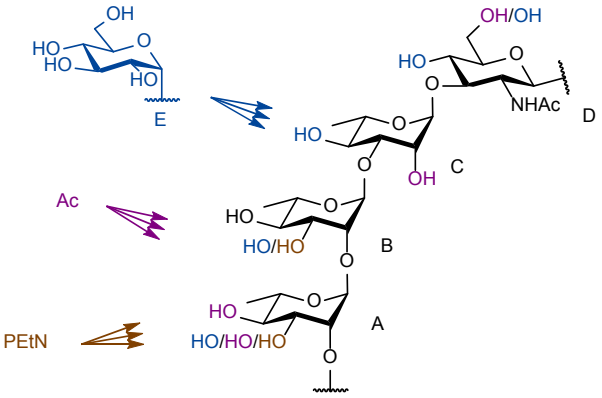


Figure 1. Backbone repeating unit from S. flexneri O-antigens and type-specific substitutions[1].

A semi-synthetic glycoconjugate was designed to help protect against S. flexneri 2a. Promising clinical data[2,3] support further development of this attractive strategy enabling serotype broadening to answer the need in the field. Toward this aim, this presentation exemplifies the concept of multivalent synthetic glycan-based vaccines in the context of S. flexneri. Focus is on the design and chemical synthesis of fine-tuned oligosaccharide surrogates of O-antigens representing the most prevalent serotypes. Key building blocks featuring type-specific substitutions were built from a single orthogonally protected tetrasaccharide scaffold by means of controlled 1,2-cis glucosylation of suitable acceptors. Chain elongation and full deprotection delivered a panel of original linker-equipped type-specific glycan haptens. Conjugation onto a protein carrier provided sets of potential immunogens representative of at least three different S. flexneri serotypes. Immunogenicity data in mice are discussed. The proof-of-concept for a broad coverage synthetic glycan-based S. flexneri glycovaccine is illustrated.

References:

1. Perepelov AV et al, Shigella flexneri O-antigens revisited: final elucidation of the O-acetylation profiles and a survey of the O-antigen structure diversity. FEMS Immunol Med Microbiol 2012; 66: 201-210.
2. Cohen D et al, Safety and immunogenicity of a synthetic carbohydrate conjugate vaccine against Shigella flexneri 2a in healthy adult volunteers: a phase 1, dose-escalating, single-blind, randomised, placebo-controlled study. Lancet Infect Dis 2021; 21: 546-558.
3. Phalipon A and Mulard LA, Toward a multivalent synthetic oligosaccharide-based conjugate vaccine against Shigella: state-of-the-art for a monovalent prototype and challenges. Vaccines 2022; 10: 403.

Design and Development of Immunotherapies for Pancreatic Cancer based on Mucin Glycopeptides

Joseph John Barchi Jr, Achyut Dahal, John Chittum

National Cancer Institute at Frederick, 376 Boyles Street, Frederick MD, 21702 USA

Cellular glycans are critically important for an array of biological functions, in particular, as mediators of the mammalian immune response. During the development of tumors, the structure and presentation of these sugar chains are dramatically altered, leading to modified properties and often enhanced aggression of these neoplastic cells. One of the many varieties of glycans are O-linked chains attached to serine and threonine residues on proteins called mucins (aptly called, "mucin-type glycosylation"). We have been exploring glycopeptides from the tandem repeat (TR) region of MUC4 (a mucin overexpressed on pancreatic ductal adenocarcinomas (PDAC) but absent in normal pancreas tissues) as immunogens for vaccines against PDACs. We have developed nanoparticle platforms that can deliver various TR glycopeptides designed in our lab to antigen presenting cells. This work led us to develop monoclonal antibodies (mAbs) that are specific for PDAC cells and we have shown that these mAbs accumulated selectively in PDAC tumors in vivo. This presentation will outline the foundational studies related to this work and describe our latest vaccine/immunogen designs. Details on some newer mAbs we have developed, along with several therapeutic modalities (Antibody-Drug Conjugates (ADCs) and Chimeric Antigen Receptor-T cells (CAR-T cells)) that we are pursuing against pancreatic cancer will be discussed.

References:

[1] Achyut Dahal, Jerome Schlomer, Laura Bassel, Serguei Kozlov, Joseph J Barchi Jr. Biodistribution of a Mucin 4-Selective Monoclonal Antibody: Defining a Potential Therapeutic Agent Against Pancreatic Cancer. Int J Mol Sci. 2025 26(13), 6042. doi: 10.3390/ijms26136042.

Proof of concept for a single-dose group B Streptococcus vaccine based on capsular polysaccharide conjugated to Qβ virus-like particle

Linda Del Bino, Filippo Carboni, Roberta Cozzi, Giacomo Romagnoli, Giovanna Tuscano, Cristiana Balocchi, Giada Buffi, Margherita Bodini, Cecilia Brettoni, Fabiola Giusti, Sara Marchi, Giulia Brogioni, Barbara Brogioni, Paolo Cinelli, Luigia Cappelli, Chiara Nocciolini, Silvia Senesi, Claudia Facciotti, Elisabetta Frigimelica, Monica Fabbrini, Daniela Stranges, Silvana Savino, Domenico Maione, Roberto Adamo, Benjamin Wizel, Immaculada Margarit, Maria Rosaria Romano

GSK Siena, via Fiorentina 1, 53100, Siena (Italy)

Despite substantial progresses in the prevention of group B Streptococcus (GBS) disease with the introduction of intrapartum antibiotic prophylaxis, this pathogen is a leading cause of neonatal infections. A maternal vaccine to protect neonates against GBS invasive infection is still an unmet medical need[1].
Such a vaccine should ideally be offered during the third trimester of pregnancy and induce strong immune responses after a single dose to maximize the time for placental transfer of protective antibodies. A key target antigen of GBS is the capsular polysaccharide (CPS), an anti-phagocytic virulence factor that elicits protective antibodies when conjugated to carrier proteins. The most prevalent polysaccharide serotypes conjugated to tetanus or diphtheria toxoids have been tested in humans as monovalent and multivalent formulations, showing excellent safety profiles and immunogenicity. However, responses were suboptimal in unprimed individuals after a single shot, the ideal schedule for vaccination during the third trimester of pregnancy. A need for a second dose has also been observed for vaccines targeting GBS proteins both in preclinical and clinical studies.
We investigated the potential of alternative vaccine presentations by conjugating CPS to Protein Nanoparticles (NPs) and Virus-Like Particles (VLPs). NPs and VLPs can be potent delivery systems for protein antigens due to their large size and dense antigen display that enhance immune-cell uptake and activation. Self-assembling virus-like particles conjugated to Group B Streptococcus capsular polysaccharides were obtained, and the resulting glyco-nanoparticles elicited strong immune responses in mice already after one immunization, providing pre-clinical proof of concept for a single-dose vaccine [2].

References:

[1] Madrid, L. et al. Infant group B streptococcal disease incidence and serotypes worldwide: systematic review and meta-analyses. Clin. Infect. Dis. 65, S160–S172 (2017).
[2] Carboni, F., Cozzi, R., Romagnoli, G. et al. Proof of concept for a single-dose Group B Streptococcus vaccine based on capsular polysaccharide conjugated to Qβ virus-like particles. npj Vaccines 8, 152 (2023). https://doi.org/10.1038/s41541-023-00744-5.

Illuminating Drug–Target Interactions in Metabolic Disease through Photo-Crosslinking Chemoproteomics

Jun-Seok Lee

School of Transdisciplinary Innovations & Department of Chemistry, Seoul National University, Gwanak-ro 1, Gwanak-gu, Seoul, Seouth Korea.

Affinity-based chemical probes serve as essential tools for interrogating drug–target interactions and elucidating protein function within complex biological milieux. Photo-crosslinking probes equipped with minimalist alkyl diazirine moieties have garnered particular attention owing to their compact steric footprint and capacity to covalently capture transient or low-affinity interactions under near-native conditions. Nevertheless, the rational design of high-fidelity photo-crosslinkers that accurately recapitulate endogenous drug–target engagement remains a significant challenge. Recent advances in chemoproteomic platforms—integrating optimized photo-crosslinker architectures with bioorthogonal enrichment handles and quantitative mass spectrometry workflows—have substantially expanded our ability to identify previously unrecognized off-targets and delineate novel mechanisms of pharmacological action, as exemplified by systematic profiling studies on BRD4 inhibitors including JQ1 and structurally related analogs.
Extending this chemoproteomic framework, we aim to map the functional target landscape of bioactive small molecules implicated in metabolic regulation, with a particular focus on pathways underlying diabetes and obesity. Through the integration of structure-guided probe design with multiplexed quantitative proteomic profiling, our strategy seeks to comprehensively resolve the cellular interactome of key metabolic modulators, thereby uncovering novel druggable targets and providing mechanistic insight into their modes of action.

References:

[1] A suite of "minimalist" photo-crosslinkers for live-cell imaging and chemical proteomics: Case study with BRD4 inhibitors. Pan, S.; Jang, S. Y.; Wang, D.; Liew S. S.; Li, Z.; Lee, J. S.*; Yao, S. Q.* Angew. Chem. Int. Ed., 2017, 56, 11816-11821.
[2] Chemical proteomics for a comprehensive understanding of functional activity and the interactome Kozoriz, K; Lee, J. S.* Chem. Soc. Rev., 2025, 54, 6186-6207.
[3] Multifunctional Photo-Cross-linking Probes: From Target Protein Searching to Imaging Applications Kozoriz, K; Shkel, O; Hong, K. T.; Kim, D. H.; Kim, Y. K.; Lee, J. S.* Acc. Chem. Res., 2023, 56(1), 25-36.

Opto-bioanalysis: Imaging and controlling GPCR activities in live cells

Takeaki Ozawa,

Department of Chemistry, School of Science, the University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.

Opto-bioanalysis, involving optical methodologies for studying biomolecules, stands as a crucial technology in advancing the sustainable development of our health and welfare, including basic biological and medical research, real-time monitoring for healthcare, noninvasive health management, and disease prevention. To unravel the real physiological functions of biomolecules, we have developed wide spectrum of fluorescence and bioluminescence imaging techniques for spatio-temporal analysis of biomolecules in living cells and organisms[1]. The principle is based on complementation and reconstitution of the split-reporter fragments of luminescent proteins such as green fluorescent proteins (GFPs) and luciferases when they are brought sufficiently close together. The optical imaging techniques engenders a fundamental analytical paradigm, thereby enabling profound insights into intricate living systems. In this talk, I will explain the basic principle underpinning these techniques, and then focus on GPCR functional analysis, particularly a bioluminescence technique of GPCR-b-arrestin interaction analysis[2]. Using the opto-bioanalytical technique, chenodeoxycholic acid (CDCA) was newly identified through chemical library screening as an inhibitor of formyl peptide receptor-1 (FPR1), one of the Gi-coupled class I GPCR[3]. We showed that the CDCA suppress keratinocyte necroptosis in vitro and markedly ameliorated disease-like symptoms in a humanized mouse model, suggesting that FPR1 inhibition may represent a promising therapeutic strategy pending further clinical validation. I will explain the basic principle underpinning these techniques, and conclude the applicability of the analysis of intracellular signals while delineating future prospects.

References:

[1] T. Ozawa*, H. Yoshimura and S.B. Kim, Anal. Chem.(review), 85, 590-609 (2013).
[2] N. Misawa, A. K. M. Kafi, M. Hattori, K. Miura, K. Masuda, T. Ozawa*, Rapid and High-Sensitivity Cell-Based Assays of Protein−Protein Interactions Using Split Click Beetle Luciferase Complementation: An Approach to the Study of G-Protein-Coupled Receptors. Analytical Chemistry. 82, 2552–2560 (2010).
[3] H. Kimura, A. Hasegawa, T. Nishiguchi, H. H. Nguyen, M. Eguchi, T. Ozawa*, R. Abe*, Inhibition of formyl peptide receptor-1-mediated cell death as a therapy for lethal cutaneous drug reactions in preclinical models. Nature Commun., 16, 8708 (2025).

Click-to-Release for on-target activation and off-target deactivation

Marc S. Robillard

Tagworks Pharmaceuticals, Toernooiveld[1], Nijmegen, The Netherlands.

To address the limited therapeutic window of several targeted cancer therapy modalities Tagworks developed a bio-orthogonal cleavage reaction (click-to-release) between a trans-cyclooctene linker and a tetrazine trigger that allows in vivo control over drug activity. It enables controlled on-target cleavage of ADCs in the TME through reaction with a trigger molecule given in a second step, thereby expanding the target scope to non-internalizing receptors. And it enables off-target deactivation of radioimmunotherapy by selective radiolabel cleavage and clearance from circulating radioimmunoconjugates, decreasing bone marrow toxicity. This contribution will cover recent improvements of this click-to-release reaction and its application in ADCs and radioimmunoconjugates.

PD-L1 ligand-Ir(III) complexe conjugates as dual action anticancer agents

Daniela Arosio[1], Giulia Assoni[2], Valentina Pagliara[3], Giovanna Polcaro[3], Pierfausto Seneci[2], Diego Brancaccio[4], Luciana Marinelli[4], Francesco. Sabbatino[3]

[1]Istituto di Scienze e Tecnologie Chimiche "G. Natta" (SCITEC), CNR, Via C. Golgi 19, Milan, Italy
[2]Chemistry Department, Università degli Studi di Milano, Via C. Golgi 19, Milan, Italy
[3]Dipartimento di Medicina e Chirurgia, Università degli Studi di Salerno, Via S. Allende, Baronissi (SA), Italy
[4]Dipartimento di Farmacia, Università degli Studi di Napoli Federico II, Via D. Montesano 49, Napoli, Italy

We have recently reported a novel class of 1,3,5-triazines-based, immune-checkpoint inhibitors targeting the PD-1/PD-L1 axis, among which compound 10 (Tr-10) strongly binds the PD-L1 protein (IC50 = 115 nM), and shows a significant cytotoxic activity in co-cultures of PD-L1-expressing NSCLC cells (PC9 and HCC827) and peripheral blood mononuclear cells (PBMCs)[1].
To further enhance the anticancer activity of Tr-10, we in parallel designed and synthesized a second generation of triazine-based PD-L1 ligands including series of "elongated" and "pseudo-dimeric" ligands" as well as a series of dual-action compounds by conjugating Tr-10 to Ir(III) complex 2. Iridium complexes have garnered considerable attention in biomedical research for their promising anticancer properties, as well as their applications in biosensing and bioimaging, due to their excellent photophysical properties and straightforward synthesis[2].
Accordingly, two positions on Tr-10 have been selected for introducing a spacer ending with a 2-pyridyl-triazole, a suitable ligand for Ir(III) complex formation, and a small set of conjugates between Tr-10 and Ir(III)-complex 2 was synthesized.

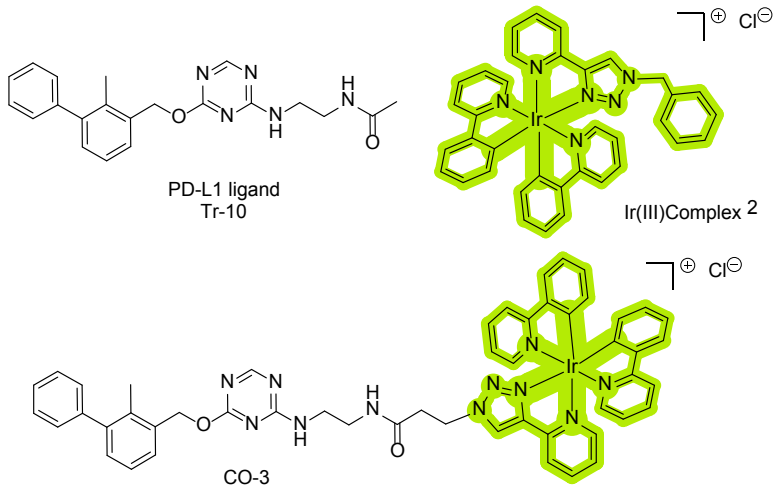


Figure 1: PD-L1 ligand Tr-10 , Ir(III) complex 2 and PD-L1 ligand-Ir(III) complex conjugate Co-3.

The antitumor and immunomodulatory activity of the new conjugates was evaluated in NSCLC cell lines expressing different levels of PD-L1 and in co-culture assays with PBMCs. The results showed that the conjugates, particularly Co-3, promoted PD-L1-dependent tumor recognition and PBMC-mediated tumor cell elimination, and induced damage-associated molecular patterns (DAMPs) leading to immunogenic cell death (ICD), thereby synergistically enhancing tumor immunogenicity and promoting immune-mediated cancer cell killing[3].

References:

[1] Russomanno P, Assoni G, Amato J, D'Amore VM, Scaglia R, Brancaccio D, Pedrini M, Polcaro G, La Pietra V, Orlando P, Falzoni M, Cerofolini L, Giuntini S, Fragai M, Pagano B, Donati G, Novellino E, Quintavalle C, Condorelli G, Sabbatino F, Seneci P, Arosio D, Pepe S, Marinelli L. Interfering with the Tumor-Immune Interface: Making Way for Triazine-Based Small Molecules as Novel PD-L1 Inhibitors. J Med Chem. 2021; 64(21):16020-16045.
[2] Tan CP, Zhong YM, Ji LN, Mao ZW. Phosphorescent metal complexes as theranostic anticancer agents: combining imaging and therapy in a single molecule. Chem Sci. 2021;12(7):2357-2367.
[3] Pagliara V, Assoni G, Polcaro G, Bossi A, Penconi M, Liguori L, Seneci P, Di Leva FS, D'Amore VM, Brancaccio D, Santoro F, Ferrone CR, Ciaglia E, Puca AA, Pepe S, Marinelli L, Arosio D, Sabbatino F. Enhancing non-small cell lung cancer susceptibility to anti-PD-1/PD-L1 therapy through PD-L1 ligand-Ir(III) complex conjugates. Cancer Commun. 2026; under revision.

Biomolecular-engineered Peptide Nucleic Acids (PNAs) as multifaceted health tools

Roberto Corradini,

Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parco Area delle Scienze 17/A, Parma, (IT)
email: roberto.corradini@unipr.it

Peptide Nucleic Acids (PNAs, fig.1) are synthetic mimic of DNA with a pseudopeptide backbone able to tightly bind to complementary oligonucleotides. They have been used in a large variety of biomedical applications, from very sensitive and selective advanced probes for diagnostic genoassays and sensory systems to potential new therapeutic agents targeting RNA/DNA (antisense, anti-miR, anti-gene) and as supramolecular components of 'smart' nanomaterials[1,2]. Recently, the use of PNA as aptamers interacting with high affinity with proteins has also been described[3]. Some of the properties of PNA can be modulated by using chemical modification at the backbone and nucleobase level, thus significantly modifying the PNA properties.

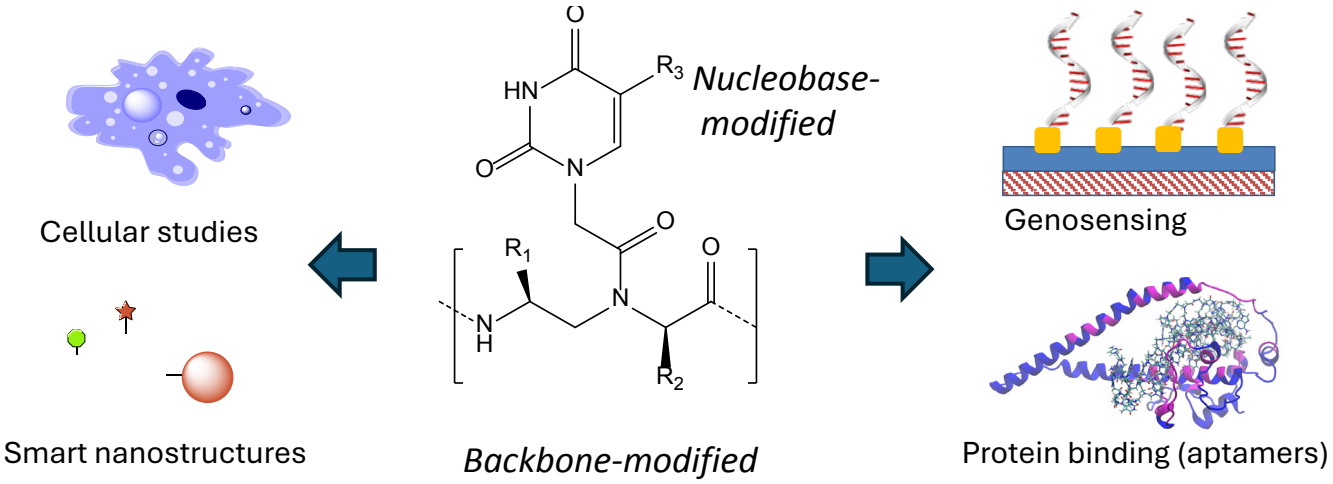


Figure 1. PNAs and modified-PNAs and their uses.

In this talk, examples taken from our group experience on the advantages and drawbacks of PNA in these fields will be discussed, with a special focus on structure-activity of base and backbone in the interactions with nucleic acids and proteins. Our biomolecular engineering approach, based on molecular design supported by computational methods will be described, and latest results on the interactions of PNAs with biological components will be presented.

References:

[1] Picchetti P, Volpi S, Rossetti M, Dore MD, Trinh T, Biedermann F, Neri M, Bertucci A, Porchetta A, Corradini R Sleiman H, De Cola L. Responsive Nucleic Acid-Based Organosilica Nanoparticles. J. Am. Chem. Soc. 2023, 145, 22896 -22902.
[2] Picchetti P, Volpi S, Sancho-Albero M, Rossetti M, Dore MD, Trinh T, Biedermann F, Neri M, Bertucci A, Porchetta A, Corradini R, Sleiman H, De Cola L. Supramolecular Nucleic Acid-Based Organosilica Nanoparticles Responsive to Physical and Biological Inputs. J. Am. Chem. Soc. 2023, 145, 22903−22912.
[3] Basini F, Hambli A, Sahu S, Bagale R, Santhosh Yesupatham M, Ritzenthaler C, Montaigne D, Woitrain E, Happy H, Boukherroub R, Knoll W, Szunerits S, Corradini R. PNA aptamer-based bioreceptors for cardiac biomarker (cTnI) detection: Insight into the structural and stability-related aspects. Nano Today 2026, 67, 102957.

Studying RNA biology and therapeutics using fluorescent base analogues

L. Marcus Wilhelmsson

Department of Chemistry and Chemical Engineering,
Chalmers University of Technology, 41296 Gothenburg, Sweden

We develop and apply a class of minimally perturbing labels for nucleic acids known as fluorescent base analogues (FBAs), which are gaining increasing significance in molecular biology. Recently, we have employed these FBAs to track the cellular uptake of mRNA-based therapeutics[1]. A major challenge for the broader application of such therapeutics is their inefficient productive cellular delivery. The underlying causes of this low delivery efficiency remain unclear, highlighting the need for novel, non-invasive analytical tools. To address this, we have established FBA-based methods that enable live-cell spatiotemporal tracking of mRNA labeled with our FBAs, tCO and 2CNqA, using in vitro transcription[1,2]. We have also developed similar methods to allow for live-cell imaging of short RNAs and antisense oligonucleotides (ASO gapmers)[3]. Comparative analyses of various FBA labels alongside conventional external fluorescent tags in these applications will be presented. Additionally, recent advances from our lab will be discussed, including the spontaneous uptake of fluorescent ATP analogues[4]. One of these ATP analogues facilitates endogenous metabolic labeling of cellular RNAs in non-engineered cell[4], and we are able to monitor this cellular RNA using live-cell confocal microscopy and fluorescence lifetime imaging (FLIM)[5].

References:

[1] T. Baladi, J. R. Nilsson, A. Gallud, E. Celauro, C. Gasse, F. Levi-Acobas, I. Sarac, M. Hollenstein, A. Dahlén, E. Esbjörner, L. M. Wilhelmsson. J. Am. Chem. Soc. 2021; 143: 5413.
[2] P. Pfeiffer, A. F. E. Karlsson, J. R. Nilsson, L. M. Wilhelmsson. J. Biol. Chem. 2025; 301(12): 110825.
[3] J. R. Nilsson, T. Baladi, A. Gallud, D. Bazdarevic, M. Lemurell, E. Esbjörner, L. M. Wilhelmsson, A. Dahlén. Sci. Rep. 2021; 11: 11365.
[4] P. Pfeiffer, J. R. Nilsson, A. Gallud, T. Baladi, H.-N. Le, M. Bood, M. Lemurell, A. Dahlén, M. Grøtli, E. Esbjörner, L. M. Wilhelmsson. Nucleic Acids Res. 2024; 52: 10102.
[5] P. Pfeiffer, N. Bagheri, C. Qian, J. Widengren, L. M. Wilhelmsson. Chem. Comm. 2025: 61; 14971.

Imaging-Guided Design of Targeted Therapuetics

Martin John Schnermann

Chemical Biology Laboratory, Center for Cancer Research,
National Cancer Institute, Maryland, USA

Recentadvancesinantibody-drugconjugates(ADCs)haveconfirmedthepotentialofligand- targeted drug delivery. However, clinical efforts have revealed unexpected toxicity issues.

Importantly, many of these toxicities stem not from target-dependent antibody binding, but from target-independent features. In particular, hydrophobic small molecule/linker combinations have a deleterious effect on the in vivo targeting behavior of the ADC. In vivo optical imaging is ideally suited to assess how payloads and linkers influence ADC properties.

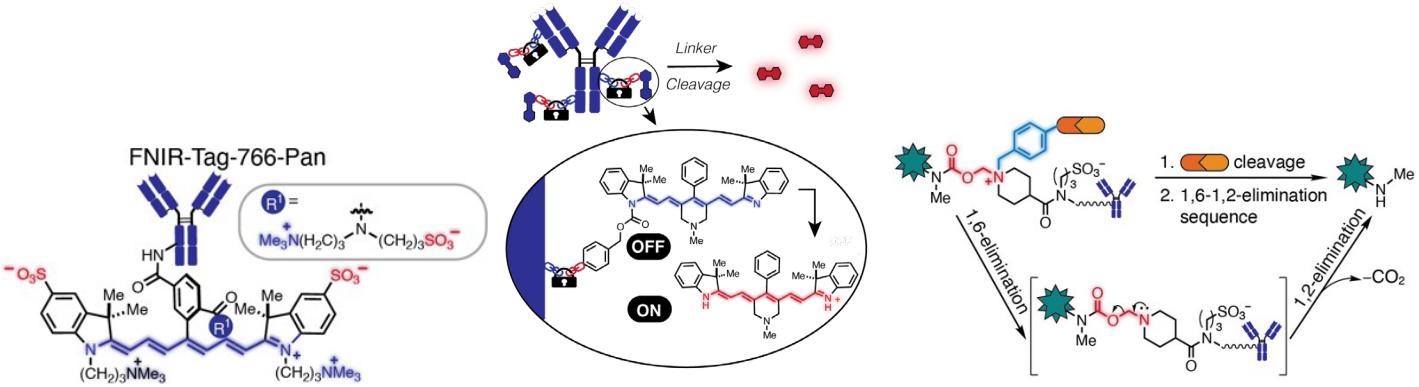
This is because optical probes are small molecules of similar molecular weight and physical properties to drug payloads. To address the role of payload properties, we developed synthetic methods that enable the rapid synthesis of chemically varied heptamethine cyanines.

Using these methods, we assembled and quantitatively compared the in vivo targeting of a substantial series of substituted cyanines. These efforts suggest that highly polar but net neutral (i.e. zwitterionic) substituents dramatically improve the in vivo properties of mAb conjugates.

To examine the role of ADC linkers, we have created a new class of fluorogenic probes in the near-infrared (NIR) range that result from modification of heptamethine norcyanines with stimuli-responsive carbamate linkers. By optimizing the cellular uptake and retention of these probes, we have created mAb-targeted variants that allow us to quantitatively study linker chemistry.

We apply this approach to define both existing and novel cleavablechemistriesinbothcellularandanimalmodels.Finally,wedevelopedzwitterionicbenzyl alpha-ammonium carbamate (BAC) linkers that are being applied to create ADCs with payloads that are incompatible with conventional linker chemistries.

Overall, this talk will describe efforts to develop and apply an "imaging-first" workflow for the design and testing of



References:

[1] Usama, S. M.; Marker, S. C.; Caldwell, D. R.; Patel, N. L.; Feng, Y.; Kalen, J. D.; St Croix, B.; Schnermann, M. J. Targeted Fluorogenic Cyanine Carbamates Enable In Vivo Analysis of Antibody-Drug Conjugate Linker Chemistry. J Am Chem Soc 2021, 143, 21667.
[2] Usama, S.M.; Marker, S.C.; Li, D.H.; Caldwell, D.R.; Stroet, M.; Patel, N.L.; Tebo, A.G.; Hernot, S.; Kalen, J.D.; Schnermann, M. J. Method To Diversify Cyanine Chromophore Functionality Enables Improved Biomolecule Tracking and Intracellular Imaging. J Am Chem Soc 2023, 145, 14647.
[3] Li, X.; Patel, N.L.; Kalen, J.; Schnermann, M.J. Benzyl Ammonium Carbamates UndergoTwo- Step Linker Cleavage and Improve the Properties of Antibody Conjugates. Angew Chem Int Ed Engl 2025, 64, e202417651.
[4] Shrestha, P.; Patel, N.L.; Kalen, J.D.; Usama, S.M.; Schnermann, M.J. Tracking the Fate of Therapeutic Proteins Using Ratiometric Imaging of Responsive Shortwave Infrared Probes. J Am Chem Soc 2025, 147, 8280.
[5] Edupuganti, V.V.S.R.; Escorcia, F.E.*; Schnermann, M.J.* Through every lens: assessing the impact of chemical modifications on antibody-conjugates using in vivo imaging. NPJ Imaging, 2025, 56.

Carbohydrate foldamers and assemblies

Martina Delbianco

Max Planck Institute of Colloids and Interfaces, Potsdam-Golm Science Park, Am Mühlenberg 1 OT Golm, 14476 Potsdam, Germany

Natural biopolymers have inspired the development of synthetic analogues – i.e. foldamers – capable of adopting defined conformations and forming programmable three-dimensional architectures. These compounds are mainly based on peptides and nucleic acids, that are well understood at the molecular level. In contrast, the complexity of carbohydrate synthesis and structural analysis have prevented access to synthetic carbohydrates capable of adopting defined geometries. In the Delbianco group, we synthesize well-defined carbohydrates to understand how the primary sequence affects conformation and aggregation[1].
Building on this fundamental knowledge, we present the rational design and synthesis of glycans adopting stable secondary structures, challenging the common belief that glycans are not capable of folding due to their flexibility. For example, by combining natural glycan motifs, we created a glycan hairpin, a secondary structure not present in nature[2]. Moreover, we designed glycan sequences that assemble into programmable supramolecular architectures, from fibres and particles to hydrogels[3]. Analogous to how the discovery of peptide-based foldamers launched a new field, we anticipate that carbohydrate foldamers and assemblies may find applications in areas across materials science, biology, and catalysis[4-5].

References:

[1] G. Fittolani, D. Vargová, P. H. Seeberger, Y. Ogawa, M. Delbianco, J. Am. Chem. Soc. 2022, 144, 12469-12475.
[2] G. Fittolani, D. Vargová, P. H. Seeberger, Y. Ogawa, M. Delbianco, J. Am. Chem. Soc. 2022, 144, 12469-12475.
[3] N. Hribernik, D. Vargová, M.C.S. Dal Colle, J. Hui Lim, G. Fittolani, Y. Yu, J. Fujihara, K. Ludwig, P.H. Seeberger, Y. Ogawa, M. Delbianco, Angew. Chem. Int. Ed., 2023, e202310357.
[4] S. Djalali, N. Yadav, M. Delbianco, Towards glycan foldamers and programmable assemblies, Nat. Rev. Mater., 2024, 9, 190-201.
[5] K. Liu, M. Delbianco, A glycan foldamer that uses carbohydrate–aromatic interactions to perform catalysis. Nat. Chem., 2025, 17, 883-889.

Cyclodextrin Self-Assembly: From Virus-Like Architectures to Antiviral Systems

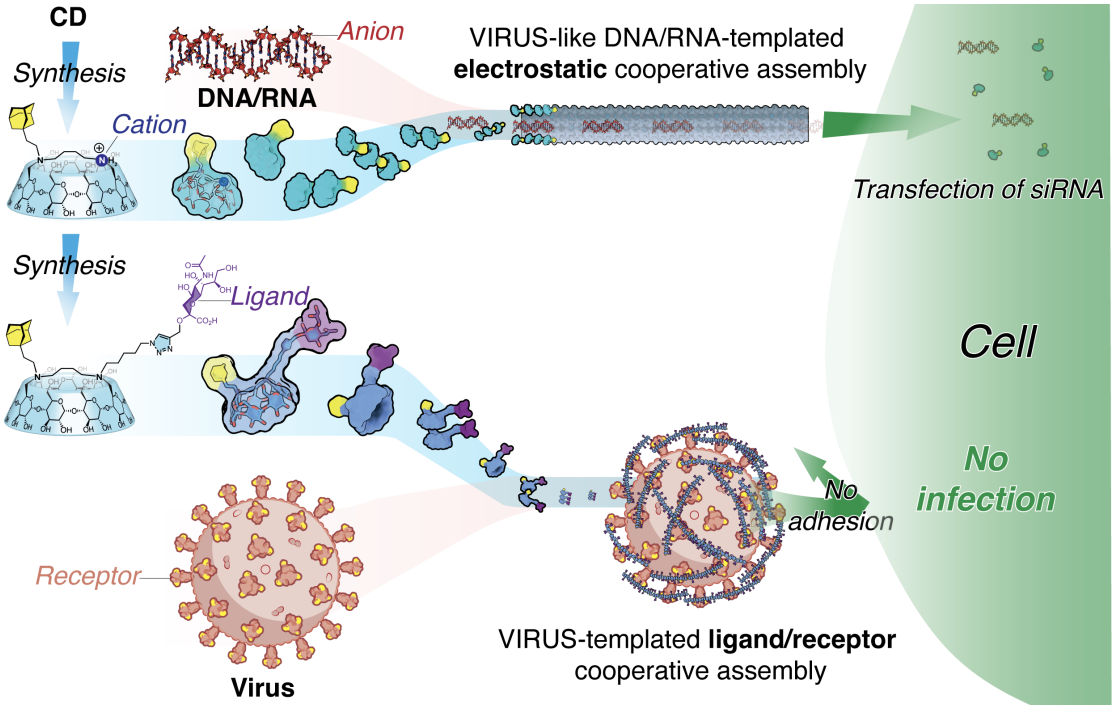
Matthieu Sollogoub[1,2]

[1]Sorbonne Université, CNRS, Institut Parisien de Chimie Moléculaire, IPCM, F-75005 Paris, France
[2]Institut Universitaire de France (IUF), France

Nature uses proteins to build sophisticated architectures such as microtubules, ribosomes, molecular machines, and viral capsids. Reproducing such complex assemblies with artificial small molecules in water remains a major challenge. Our work addresses this issue through a biomimetic strategy based on cyclodextrins as programmable molecular building blocks.

We have developed efficient methods for the regioselective poly-hetero-functionalization of cyclodextrins, allowing multiple functions to be placed with precision on these cyclic oligosaccharides[1,2]. This molecular control endows cyclodextrins with protein-like properties in self-assembly. Suitably designed cyclodextrins undergo DNA-templated, electrostatically driven cooperative assembly to form filamentous virus-like architectures in which a carbohydrate framework replaces the capsid protein[3-5]. Upon further functionalization, the virus itself can template the cooperative assembly of these cyclodextrins through ligand-receptor interactions, generating antiviral systems that block infection.

This work highlights the potential of cyclodextrins as versatile biomimetic platforms at the interface of supramolecular chemistry, nanoscience, and biomedicine.



References:

[1] Sollogoub M, et coll. Site-selective hexa-hetero-functionalization of α-cyclodextrin an archetypical C6-symmetric concave cycle. Nature Commun. 2014; 5: 5354.
[2] Sollogoub M, et coll. Programmed synthesis of Hepta-differentiated β-Cyclodextrin: 1 out of 117655 arrangements. Angew. Chem. Int. Ed. 2021; 60: 12090.
[3] Sollogoub M, et coll. Bridging β-Cyclodextrin Prevents Self-Inclusion, Promotes Supra- molecular Polymerization, and Promotes Cooperative Interaction with Nucleic Acids. Angew. Chem. Int. Ed. 2018; 57: 7753.
[4] Sollogoub M, et coll. Sugars as capsid proteins, formation and cryo-EM structure of a viro-inspired architecture. ChemRxiv 2024, DOI 10.26434/chemrxiv-2024-v90l8.
[5] Sollogoub M, et coll. Transient Supramolecular Polymers by pH-Gated Conformational Control of a Self-Assembling Cyclodextrin. Angew. Chem. Int. Ed. 2025; e202507069.

Carbon Dots-Based Fluorescent Sensing Arrays: Rational Design for Discrimination of Food Colorants and Sulfur species

Xintong Yang, Chuan Dong, Yuexia Zhang, Shaomin Shuang

School of Chemistry and Chemical Engineering, and Institute of Environmental Science, Shanxi University, Taiyuan, 030006, China

Carbon dots (CDs), as novel fluorescent nanomaterials, exhibited great potential in analytical sensing owing to their excellent optical properties, low cost, simple synthetic procedures, and good biocompatibility. However, most reported CDs-based fluorescent sensors rely on single-emission signals, which are susceptible to interference from instruments, background fluorescence, and complex matrices, leading to unsatisfactory accuracy in simultaneous multi-analyte identification and greatly limiting their practical applications[1]. To address these problems, our group rationally designed and constructed CDs-based multi-channel sensing arrays for the discrimination of food synthetic colorants and environmental sulfur species. A series of functionalized CDs with distinct surface functional groups and optical properties was prepared via a one-step hydrothermal method by adjusting precursor types and reaction parameters. Using multiple interaction mechanisms, including inner filter effect, electron transfer, and redox reaction, these CDs exhibited differential fluorescent responses toward different analytes and formed exclusive optical fingerprints[2]. Combined with principal component analysis (PCA) and linear discriminant analysis (LDA), the multidimensional fluorescent response data of the arrays were analyzed for efficient discrimination and quantification. Experimental results demonstrated that the as-prepared sensing arrays exhibited excellent performance for the two types of analytes, with a principal component variance contribution rate of 95%. Successful identification and quantification of the target analytes were realized, and the arrays exhibited satisfactory recovery in complex real samples. This work enriches the rational design strategies of CDs-based sensing arrays and provides a promising tool for screening in food safety and environmental monitoring.

References:

[1] Jing WJ, Yang YJ, Shi QH, Wang Y, Liu FF. Machine learning-based nanozyme sensor array as an electronic tongue for the discrimination of endogenous phenolic compounds in food. Anal. Chem. 2024; 96: 16027-16035.
[2] Yang ZH, Cui XY, Du P, Zhang QX, Zheng XY, Gong XJ, Zhang YX, Dong C. An integrated carbon dots-based sensing platform via alkali-assisted hydrothermal reaction for pH/Fe(II) detection and a sensing array for sulfur species.[J]. J. Hazard. Mater. 2025; 496: 139340.

Protein chemical synthesis and engineering to study protein glycosylation

Xuechen Li

Department of Chemistry, University of Hong Kong, Hong Kong SAR, P. R. China;
xuechenl@hku.hk

Protein chemical synthesis and engineering enable precise access to proteins with defined sequence, modification, and architecture beyond the limits of recombinant expression. By combining solid-phase peptide synthesis with chemoselective ligation methods and related strategies, researchers can assemble full-length proteins, glycoproteins, and backbone-modified analogues bearing site-specific post-translational modifications, noncanonical amino acids, or bioorthogonal handles. These synthetic capabilities allow systematic dissection of structure–function relationships, fine mapping of interaction interfaces, and the creation of proteins with enhanced stability, altered signaling properties, or tailored pharmacokinetics. We have been applying protein chemical synthesis to elucidate the functional effect of protein glycosylation, and explore their therapeutic applications.

References:

[1] Sun Z, Liu H, Li X. Precision in Protein Chemical Modification and Total Synthesis. Chem. 2024; 10: 767-799.
[2] Tan Y, Wei T, Wu H, Li X. Chemical protein synthesis: advances, challenges and outlooks. J. Am. Chem. Soc. 2020; 142: 20288.

Cryo EM of African Horse Sickness Virus VP2 guides vaccine engineering

Nicola GA Abrescia[1,7], Ane Martinez-Castillo[1#], Andrea Aebischer[2#], Philippine Toneatti[3], Lifei Fu[1], Damien Vitour[3], Corinne Sailleau[3], Bernd Hoffmann[2], Kati Franzke[4], Michael Eschbaumer[2], Saskia Weber[2], Eva Calvo[5], Javier Ortego[5], David Gil-Carton[6], Emmanuel Bréard[3], Stéphan Zientara[3], Martin Beer[2].

[1]Structure and Cell Biology of Viruses Lab, Center for Cooperative Research in Biosciences (CIC bioGUNE),Basque Research and Technology Alliance (BRTA); Derio, Spain.
[2]Institute of Diagnostic Virology, Friedrich-Loeffler-Institut, Federal Research Institute for Animal Health, Greifswald, Insel Riems, Germany.
[3]UMR Virology, Laboratory for Animal Health, Department of Animal Health, Paris-Est University, Maisons-Alfort, France.
[4]Institute of Infectology, Friedrich-Loeffler-Institut, Federal Research Institute for Animal Health, Greifswald, Insel Riems, Germany.
[5]Centro de Investigación en Sanidad Animal (CISA), Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria (INIA), Valdeolmos, Madrid, Spain.
[6]Biofisika Institute (CSIC-UPV/EHU), Science Park of the UPV/EHU, Leioa, Spain.
[7]IKERBASQUE, Basque Foundation for Science; Bilbao, Spain.
[#]These authors contributed equally.

African horse sickness virus (AHSV) is a lethal equine pathogen lacking safe licensed vaccines[1].
We determined the 3.1 Å cryo-EM structure of full-length VP2 from AHSV serotype 4, revealing its triskelion architecture and a previously undescribed α-helical domain anchoring the core. Structure-guided mapping identified a VP2 subdomain that, when displayed on nanoparticles using SpyCatcher/SpyTag technology, provided complete protection against viral challenge in mice and induced strong, durable immune responses in horses[2].
These results provide a structural basis for developing safe recombinant vaccines against AHSV and related orbiviruses.

References:

[1] Carpenter S, Mellor PS, Fall AG, Garros C. & Venter GJ. African Horse Sickness Virus: History, Transmission, and Current Status. Annu Rev Entomol 2017; 62, 343-358

[2] Martinez-Castillo A, Aebischer A, Toneatti P, Fu L, Vitour D, et al……, Beer M, Abrescia NG. manuscript under revision 2026.

ORAL

Genome Therapy Meeting Promises for Tumor Growth Inhibition

Zhen Xi

State Key Laboratory of Elemento-Organic Chemistry, and Department of Chemical Biology, National Pesticide Engineering Research Center, Collaborative Innovation Center of Chemical Science and Engineering, College of Chemistry, Nankai University, Tianjin, China

According to the central dogma of molecular biology, chromatin DNA is subject to spatial and temporal regulation at multiple hierarchical levels, including chromatin unfolding, DNA transcription, post-transcriptional processing, mRNA translation, and post-translational modification. Correspondingly, regulatory tools acting at these distinct stages have been identified and artificially harnessed for fundamental biological investigations as well as therapeutic applications. With the increasing understanding of the evolution and progression of complex diseases such as cancer, single-target gene therapy has encountered considerable challenges, particularly with respect to minimizing adverse effects and overcoming drug resistance.

The rapid advancement of gene delivery platforms and regulatory technologies has driven a paradigm shift in gene therapy, expanding its focus from monogenic disorders to multifactorial, polygenic diseases. This transition has enabled therapeutic interventions to become more personalized, precise, safe, and efficient. To achieve optimal outcomes, an emerging strategy is to emulate chromatin-mediated regulation by orchestrating gene expression through the rational combination of diverse regulatory modalities across multiple molecular levels. Such an integrative framework provides a promising avenue to address complex diseases in a manner that more closely resembles natural biological regulation.

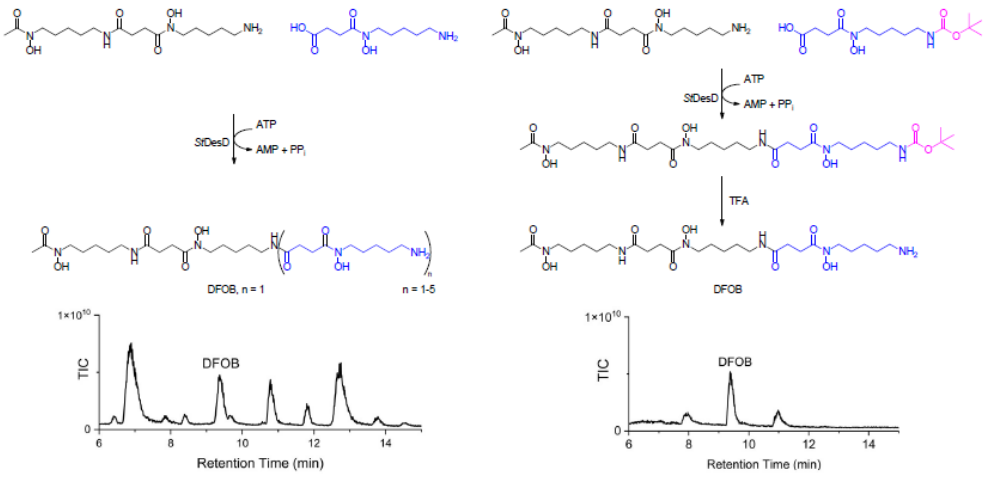
Within this conceptual framework, various gene regulatory tools can be strategically integrated into a unified toolbox and incorporated into chromatin-like delivery vehicles, thereby recapitulating the chromosome-mediated decoding of genetic information for therapeutic purposes. We propose the term genome therapy to describe this artificial, chromosome-inspired regulation of gene networks through the concurrent deployment of multiple regulatory mechanisms. In this work, we present our efforts toward developing multi-gene regulatory strategies for antitumor applications, with particular emphasis on branch-PCR–assembled gene nanovectors designed to mimic chromatin-like activity.

Directing the chemoenzymatic assembly of desferrioxamine B

Todd E. Markham, Athavan Sresutharsan, Callum A. Rosser[1] and Rachel Codd

School of Medical Sciences, Faculty of Medicine and Health,
he University of Sydney, Camperdown, NSW 2006, Australia

Desferrioxamine B is a clinical natural product listed as an essential medicine by the World Health Organisation for its use in treating acute iron toxicity and secondary iron overload as a result of blood transfusion-dependent disorders like β-thalassemia[1].The current commercial production of DFOB relies on whole-cell fermentation of Streptomyces pilosus which results in the co-production of other hydroxamic acid containing analogues and hence, requires rigorous purification to access a clinical grade product. DFOB is seeing broader use in areas beyond its current clinical application including radiopharmaceuticals as a chelator for radiometals, medicinal chemistry as a vector for Trojan horse antibiotic strategies and in chemical biology to probe microbial metabolomes and proteomes. Given this expanded utility and the ongoing need for DFOB as a single isolable product, there is potential to diversify its production methods to overcome the limitations associated with the traditional whole-cell approach.
Our recent work has leveraged the elasticity of a recombinant NRPS-independent siderophore synthetase DesD isolated from Salinispora tropica CNB-440 (StDesD)[2], responsible for the late-stage biosynthesis of DFOB, and N-Boc substrates to drive a chemoenzymatic assembly of DFOB as a single product. This combined chemical and biocatalytic approach afforded N-Boc protected DFOB as a single enzyme-mediated product in high yields, which was readily deprotected in situ to generate the clinical natural product[3]. This approach highlights the merit of using a directed chemoenzymatic approach for DFOB production with aligned benefits in providing new insight into DFOB biosynthetic assembly pathways.



References:

1. Codd, R.; Richardson-Sanchez, T.; Telfer, T. J.; Gotsbacher, M. P. Advances in the Chemical Biology of Desferrioxamine B. ACS Chem. Biol. 2018, 13, 11-25.
2. Nolan, K. P.; Rosser, C. A.; Wood, J. L.; Font, J.; Sresutharsan, A.; Wang, J.; Markham, T. E.; Ryan, R. M.; Codd, R. An elastic siderophore synthetase and rubbery substrates assemble multimeric linear and macrocyclic hydroxamic acid metal chelators. Chem. Sci. 2025, 16, 2180-2190.
3. Markham, T. E.; Sresutharsan, A.; Rosser, C. A.; Codd, R. Directing the chemoenzymatic assembly of desferrioxamine B as a single product using N-tert-butoxycarbonyl-protected substrates. Org. Biomol. Chem. 2025, 23, 7181-7187.

Bioorthogonal reactions based on o-diones and their biological applications

Yan Zhang

School of chemistry, Nanjing University, 163 Xianlin Ave., Nanjing, China

Bioorthogonal reactions allow the in situ labeling of biomolecules in living systems, and the establishment of bioorthogonal reactions was considered as a milestone in chemical biology. With the development of bioorthogonal chemistry, spatial and temporal control on bioorthogonal reactions becomes highly demanded. Photo-trigger provides one way to realize spatial-temporal resolution to bioorthogonal reactions. Based on ortho-diones such as phenanthrenequinone (PQ) that showed unique properties of photo-excited states, we established the first visible light driven bioorthogonal DVPC reaction[1]. The DVPC reaction allowed spatial-temporal labeling of antibodies on live cells and it was able to be used together with the strain-promoted azide alkyne click reaction (SPAAC) withour disturbing each other. Further exploration on the cycloaddition reactions of PQ derivatives with other electron-rich C=C bonds led to the discovery of the bioorthgonal DFC reaction[2], which was the first anionic cycloaddend-promoted bioorthogonal cycloaddition reaction. With the water-mediated formation of the highly electron-rich anionic cycloaddend from furan-2(3H)-one derivatives, which is stabilized in water with high polarity, DFC reaction with ground state o-diones proceeds rapidly in aqueous solution and on live cells. The combined utilization of this reaction together with the two other widely used bioorthogonal reactions SPAAC and IEDDA allows for mutually orthogonal labelling of three types of proteins or three groups of living cells in one batch without cross-talking. Using these bioorthogonal reactions based on o-diones, we were able to label and imaging biomolecules in living systems. The bioorthognal ligation chemistry along with other photo-controllable bond-cleavage process also allowed us to realize spatial temporal control on biological functions of various molecules even in tumor models in vivo[3-5].

References:

[1] Li J, Kong H, Huang L, Cheng B, Qin K, Zheng M, Yan Z, Zhang Y. Visible Light-Initiated Bioorthogonal Photoclick Cycloaddition. J. Am. Chem. Soc. 2018;140;14542-14546.
[2] Xi Z, Kong H, Chen Y, Deng J, Xu W, Liang Y, Zhang Y. Metal- and Strain-Free Bioorthogonal Cycloaddition of o-Diones with Furan-2(3H)-one as Anionic Cycloaddend, Angew. Chem. Int. Ed. 2022, e202200239.
[3] Zhu C, Wang W, Wang Y, Zhang Y, Li J, Dendronized DNA Chimeras Harness Scavenger Receptors To Degrade Cell Membrane Proteins, Angew. Chem. Int. Ed. 2023, 62, e202300694.
[4] Wang W, Zhu C, Zhang B, Feng Y, Zhang Y, Li J. Self-Assembled Nano-PROTAC Enables Near-Infrared Photodynamic Proteolysis for Cancer Therapy, J. Am. Chem. Soc. 2023, 145, 16642-16649.
[5] Lu X, Wang X, Liao H, Sha B, Zhang Y, Li J, Tandem-Activatable PROTAC Prodrug for Tumor Biomarker-Driven Near-Infrared Opto-Proteolysis, Angew. Chem. Int. Ed. 2025, 64, e202510641.

Design of Oseltamivir and Hydroxychloroquine Ionic Salts for Improved Antiviral Performance

Luis C. Branco[a], Diogo A Madeira[a], Vanessa Correia[b]; Luís Santos[b]; Helena R Andrade[b]

[a]LAQV-REQUIMTE, Dept of Chemistry, NOVA School of Science and Technology, NOVA University of Lisbon, Campus de Caparica, 2829-516 Caparica, Portugal.
[b]Antiviral Resistance Lab, Research & Development Unit, Infectious Diseases Department, Instituto Nacional de Saúde Doutor Ricardo Jorge, IP, Av. Padre Cruz, 1649- 016, Lisbon, Portugal

The recent rise in influenza A and B infections has become a pressing concern for the World Health Organization (WHO), with cases estimated to have increased by 20% compared to the previous year. This surge is largely driven by mutations in viral glycoproteins, particularly neuraminidases (NA) and hemagglutinins, which reduce the therapeutic efficiency of commonly used a such as Oseltamivir and Zanamivir[1,2]. These mutations contribute to drug resistance, highlighting the urgent need for novel strategies to improve antiviral efficacy.

In this study, we focus on neuraminidase as a critical biological target. NA catalyzes the hydrolysis of sialic acid residues on host cell membranes, facilitating viral release and propagation. Targeting this enzyme remains a cornerstone of antiviral therapy, yet conventional NA inhibitors face limitations due to solubility, permeability, and pharmacokinetic constraints.

To address these challenges, we have designed and synthesized a series of Hydroxychloroquine and Oseltamivir-based Organic Salts and Ionic Liquids (API-OSILs)[3, 4]. By combining Resimidivir and Oseltamivir with various counter-ions, we aim to enhance its physicochemical properties, including water solubility, membrane permeability, stability, and bioavailability. These modifications are expected to improve therapeutic performance and reduce the impact of resistance-conferring mutations.

Preliminary in vitro studies demonstrate that these Hydroxychloroquine and Oseltamivir-OSILs exhibit enhanced antiviral activity against influenza strains, along with low cytotoxicity, suggesting a favorable therapeutic index. Furthermore, the tunable nature of ionic formulations allows for fine control over drug delivery properties, opening avenues for optimizing pharmacokinetics and formulation versatility.

Overall, this work presents a novel platform for the development of next-generation antiviral drugs, leveraging ionic modifications to enhance drug performance and overcome the challenges associated with viral resistance. These findings highlight the potential of ionic drug design as a generalizable strategy for improving existing APIs and developing innovative therapeutics for emerging infectious diseases.

Acknowledgements:

This work was supported by the InsectERA – Novo sector bioindustrial Project (nºC644917393-00000032), co-financed by PRR - Recovery and Resilience Plan of the European Union (Next Generation EU). The authors also thank the support from FCT/MCTES (UIDB/50006/2020, LA/P/0008/2020 and UIDP/50006/2020 of the Associate Laboratory for Green Chemistry – LAQV). This work also received support from Instituto Nacional de Saúde Doutor Ricardo Jorge (INSA).

References:

[1] Xie, Y; Gong, J; Li, M; Fang, H; Xu, W; Curr. Med. Chem., 2011, 18, 1050–1066.
[2] Handa, M; et al., Drug Discov. Today 2022, 27, 2415–2424.
[3] Shamshina, JL; Rogers, RD; Chem. Rev. 2023, 123, 11894.
[3] Faísca, F; Correia, V; Petrovski, Z.; Branco, LC; Rebelo-de-Andrade, H; Santos, MM; Pharmaceutics 2022, 14, 877.

A Bispecific Small Molecule Mediates Armed Antibodies Targeting of Bone Mineral Matrix

Alberto Dal Corso[1], Cassandra Spinosa[1], Mattia Mason[1], Cristina Visentin[2], Stefano Ricagno[2], Beatrice Rocutto[3], Marco Gobbi[3], Massimo Zucchetti[3], Roberta Frapolli[3], Claudia Nastasi[3]

[1]Università degli Studi di Milano, Chemistry Department, Via C. Golgi 19, 20133 Milan, Italy;
[2]Università degli Studi di Milano, Department of Biosciences, Via G. Celoria 26, 20133 Milan, Italy;
[3]Istituto di Ricerche Farmacologiche Mario Negri, IRCCS, Via Mario Negri, 2, 20156 Milan, Italy

Pre-targeting strategies within antibody research traditionally exploit specific small molecules (SM) as on/off switches of the biologic's pharmacological activity[1-5]. In contrast to these approaches, we propose a new pre-targeting strategy in which a bispecific SM adaptor is used to drive the mAb binding to the bone mineral matrix (hydroxyapatite, HA), i.e., a clinically-relevant receptor so far inaccessible to mAb-based therapeutics.
This SM exploits the exquisite affinity of alendronate (ALN) for HA to selectively bind the bone matrix and install an artificial receptor (R), which can be reversibly targeted by a mAb, loaded with a suitable payload of interest.
The selected ALN-R adaptor showed long-lasting binding to HA both in vitro and in vivo. Competitive SPR experiments and confocal microscopy studies confirmed the R unit recognition by an anti-R mAb fragment. Finally, ALN-R induced the HA accumulation of the mAb armed with a cytotoxic payload, inducing apoptosis of neighbouring cancer cells in vitro.
These findings demonstrate the feasibility of an ALN-based pre-targeting system for recruiting therapeutic antibodies to bone lesions, with potential applications against bone metastases of solid tumours and in other bone-related diseases.

References:

[1] Steiner M, Neri D, Clin. Cancer Res. 2011, 17: 6406-6416.
[2] Campbell DA, Gong B, Kochersperger LM, Yonkovich S, Gallop MA, Schultz PG, J. Am. Chem. Soc. 1994, 116: 2165-2166.
[3] Rossin R, Versteegen RM, Wu J, Khasanov A, Wessels HJ, Steenbergen EJ, ten Hoeve W, Janssen HM, van Onzen AHAM, Hudson PJ, Robillard MS, Nat. Commun. 2018, 9: 1484.
[4] Lee YG, Chu H, Lu Y, Leamon CP, Srinivasarao M, Putt KS, Low PS, Nat. Commun. 2019, 10: 2681.
[5] Zhang AQ, Hostetler A, Chen LE, Mukkamala V, Abraham W, Padilla LT, Wolff AN, Maiorino L, Backlund CM, Aung A, Melo N, Li N, Wu S, Irvine DJ, Nat. Biomed. Eng. 2023, 7: 1113-1128.

3D Bioprinted Glioblastoma Multiforme Model, Impact of Glycosignature on Cell Behaviour and Drug Response

Francesca Cadamuro, Marco Piazzoni, Ilaria Borghi, Francesco Nicotra, Laura Russo

University of Milano-Bicocca, School of Medicine and Surgery, Monza, Italy.

Glioblastoma multiforme (GBM) is an aggressive brain tumor characterized by strong resistance to standard therapies. Predictive experimental models to identify biomarkers and personalised therapies must reproduce the biochemical and structural complexity of the tumor microenvironment.
We developed a multimodal platform (GlycoMatrix_GBM), based on large scale data enabling the rational selection structural requirements and glycosignature associated with tumor progression. A relevant contribution of α-NeuNAc-(2→3)-β-D-Gal- and chondroitin sulfate (CS) was observed. Biomimetic hydrogels were formulated crosslinking hyaluronic acid (HA), CS and gelatin functionalized with α-NeuNAc-(2→3)-β-D-Gal-, to investigate the impact of glycosignature on cell behavior and drug response. HA, CS and gelatin were functionalised with a PEG linker containing an azido group and then crosslinked with a four-arm polyethylene glycol functionalized with dibenzocyclooctyne groups.

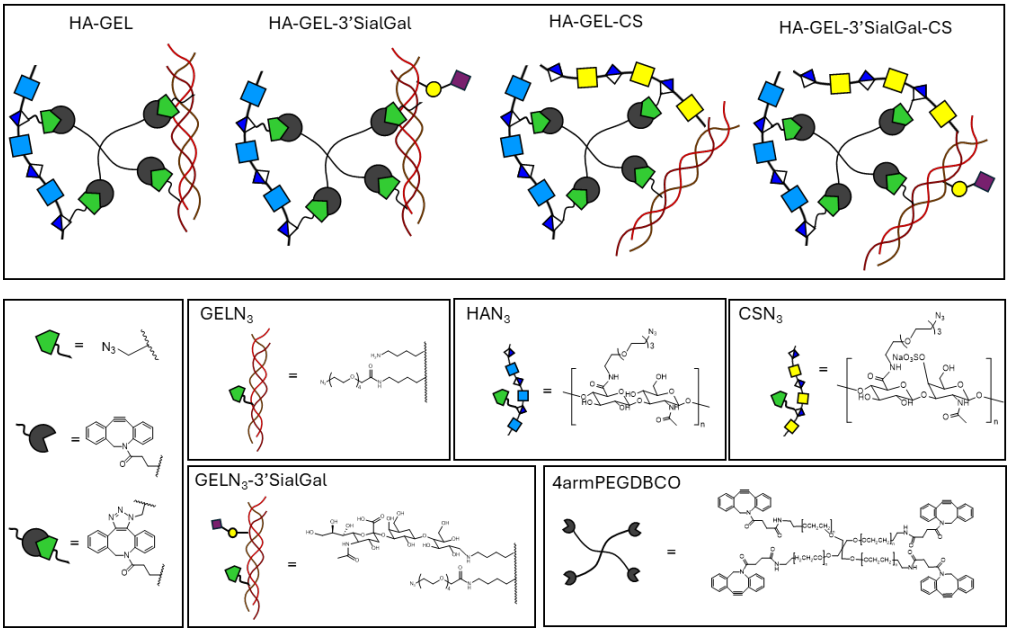


Figure 1: Schematic representation of hydrogels structures

The obtained hydrogel (HA-GEL-3'SialGal-CS) was 3D bioprinted with patient-derived G166 GBM cells and the obtained GBM model was campared with those in which the glycosignature was partial (HA-GEL-3'SialGal, HA-GEL-CS) or absent (HA-GEL), revealing the significant morphological contribution of α-NeuNAc-(2→3)-β-D-Gal- and CS in tumor progression. High-resolution synchrotron nano-computed tomography enabled non-destructive three-dimensional visualization of the constructs, revealing differences in cell aggregation, spatial organization, and ECM deposition across matrices and treatments. The GBM models were treated with antitumor drugs TMZ and MV1035 and multiplex immunofluorescence showed matrix-dependent therapeutic responses. CS promoted a shift from stem-like features toward a proliferative phenotype, whereas α-NeuNAc-(2→3)-β-D-Gal- supported the persistence of stem-like cells under combined therapeutic stress.
Overall, this biomimetic platform highlights the role of glycan-modified ECM in modulating GBM cell behavior and therapy response.

Acknowledgments:

Financial support from: Iniziativa "PNC0000003 - "ANTHEM: AdvaNced Technologies for Human-centrEd Medicine". CUP BICOCCA B53C2200667000; Ministero della Salute, RF-2021–12371959 Tackling immunomodulatory properties of stromal cells to improve therapeutic strategies in lung cancer. MUR PRIN 2022, 2022MY7AZT Dynamic multifunctional hydrogels for glioblastoma therapy (DINGO).

Carborane-Phenyl Bioisosteric Replacement in EGFR Inhibitors: A 3D Approach toward Anti-Glioblastoma Agents

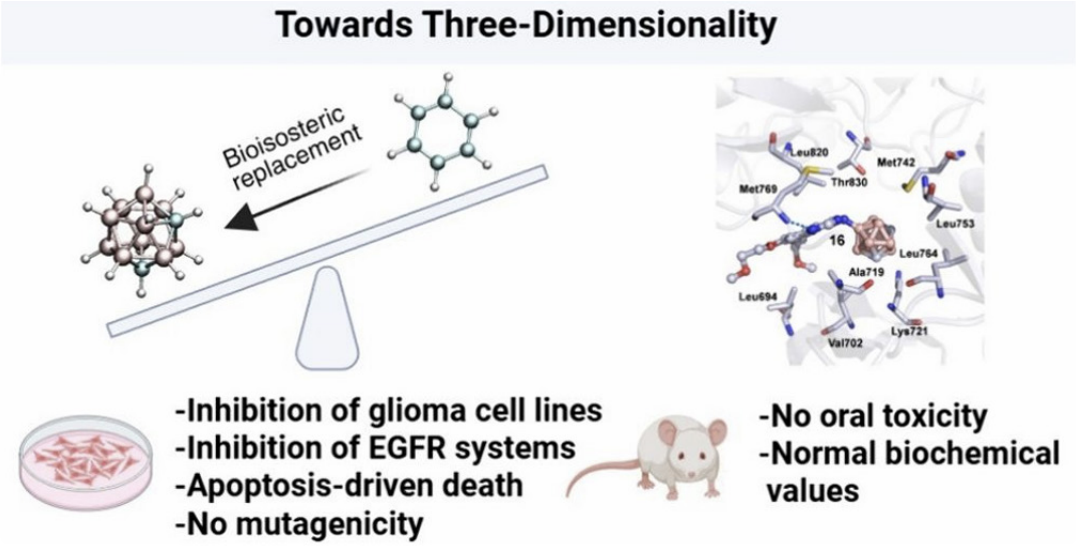
Belén Dávila[1], Pablo Vignolo[1], Ignacio González[1], Jenner N. Bonanata[1], María Fernanda García[1], Hugo Cerecetto[2,3], Marcos Couto[1,3]

[1]Instituto de Química Biológica, Universidad de la República, Igua 4225, Montevideo 11400, Uruguay;
[2]Centro de Investigaciones Nucleares, Universidad de la República, Mataojo 2055, Montevideo 11400, Uruguay;
[3]Instituto de Investigación Una Salud, Universidad de la República, Montevideo 11600, Uruguay.

Phenyl rings are present in nearly half of approved small-molecule drugs; however, their planar aromatic character can contribute to limited solubility, metabolic instability, and suboptimal selectivity[1]. Following the "escape from flatland" paradigm, we explored carboranes as three-dimensional boron-rich bioisosteres to redesign the EGFR inhibitor erlotinib[2]. We report the rational design, synthesis, and biological evaluation of a focused library of 3D carborane-based erlotinib analogues aimed at enhancing anticancer performance, particularly against glioblastoma.

All synthesized analogues displayed improved in vitro activity compared with erlotinib. Para-substituted derivatives emerged as the most promising, showing 2.5- to >12-fold higher cytotoxicity and up to sevenfold selectivity for glioblastoma cells over non-malignant astrocytes. The lead compound moderately inhibited both wild-type EGFR and the drug-resistant EGFRT790M mutant. Molecular docking and dynamics simulations predicted binding within the ATP catalytic site, displaying the characteristic hinge-binding mode of EGFR inhibitors. Notably, cellular potency exceeded biochemical inhibition, suggesting additional mechanisms beyond direct EGFR blockade. Mechanistic studies identified apoptosis as the predominant cell death pathway.

In vivo evaluation revealed favorable acute oral safety (LD50 > 2000 mg/kg), absence of mutagenicity, favorable ADMET predictions, and bloo-brain barrier permeability. Complementary structure,activity relationship analyses highlighted the critical influence of lipophilicity and boron-cluster electronic effects in modulating anti-glioma activity, underscoring the importance of precise physicochemical tuning in boron-rich EGFR-targeted agents[3]. Collectively, these findings validate carboranes as three-dimensional phenyl bioisosteres and support their further development as promising scaffolds for glioblastoma therapy.



References:

[1] Nilova A, Campeau LC, Sherer EC, Stuart DR. Analysis of benzenoid substitution patterns in small molecule active pharmaceutical ingredients: miniperspective. J Med Chem 2020; 63: 13389-13396.
[2] Dávila B, Vignolo P, González I, Lecot N, Bonanata JN, García MF, Echeverría GA, Piro OE, Cerecetto H, Couto M. Escaping from flatland: 3D carborane-based bioisosteres of erlotinib as potential anticancer agents. ACS Omega 2025; 10: 50468-50487.
[3] Dávila B, Vignolo P, Silvarrey M, Benítez A, González Schmidt J, de Arteaga Guidotti C, García MF, Cerecetto H, Couto M. Structure-activity relationships of closo- and nido-carborane erlotinib analogs: lipophilicity as a key modulator of anti-glioma activity. Pharmaceuticals 2025; 18: 1753.

Novel D-Glucuronamide-Based Nucleot(i)de Analogs as Anticancer and Antibacterial Hits

Nuno Manuel Xavier[1,2], Domingos Morais Manuel[1,2],Tânia Moreira[2], Radek Jorda[3], Sérgio Filipe[4]

[1]Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal; E-mail: nmrmxavier@ff.ulisboa.com
[2]Centro de Química Estrutural - Institute of Molecular Sciences, Faculdade de Ciências,Universidade de Lisboa Ed. C8, 5° Piso, Campo Grande, 1749-016 Lisboa, Portugal
[3]Departament of Experimental Biology, Faculty of Sience, Palacký University Olomouc, Šlechtitelů 27, 78371 Olomouc, Czech Republic
[4]UCIBIO-Applied Molecular Biosciences Unit, Department of Life Sciences, NOVA School of Science and Technology, NOVA FCT, Universidade NOVA de Lisboa, 2829-516, Caparica, Portugal

Nucleoside and nucleotide analogs are relevant groups of molecules in medicinal and (bio)organic chemistry, due to their ability to display a variety of biological activities for therapeutic applications. Their anticancer and antiviral potential is well demonstrated by the number of molecules that reached clinical use as chemotherapeutic agents, acting mostly as nucleic acid antimetabolites[1,2]. Their antibacterial potential has also been well reported, although no antibacterial drugs based on nucleos(t)ides were approved so far[3]. Despite their potency, most clinically used nucleos(t)ide analogs suffer from low oral bioavailability, chemotherapy resistance, and systemic toxicity[1,2]. Therefore, the search for novel nucleos(t)ide-like structures that may act by alternative mechanisms of action and overcome these issues is highly relevant in drug discovery.

In this context, in our team we have explored the development of novel bioactive nucleos(t)ide analogs comprising uncommon glycosyl units, such as D-glucuronamide[4,5]. D-Glucuronamide-containing molecules have attracted significant interest in medicinal glycochemistry due to the biological profile reported for both natural and synthetic derivatives[6].

In this communication, we report on the synthesis and anticancer/antibacterial potential of structurally new 6-chloropurine nucleos(t)ide analogs constructed on D-glucuronamide scaffolds, and containing 1,2,3-triazole, phosph(on)ate and/or phosphoramidate moieties.

For their access, D-glucofuranuronolactone was used as a starting material, and key synthetic steps included, among others, amidation, furanose to pyranose isomerization, anomeric azidation, azide-alkyne 1,3-dipolar cycloaddition, Staudinger-phosphite and Arbuzov reaction.

Biological evaluation revealed some molecules with noteworthy antiproliferative activities against cancer cell lines, alongside selective and potent antibacterial effects against a Streptococcus pneumoniae clinical strain, turning them promising "hits" for further investigations.

Acknowledgements:

The authors thank FCT for funding: projects UID/04138/2025 (iMed-ULisboa), UIDB/00100/2020, UIDP/00100/2020 (CQE) and LA/P/0056/2020 (IMS). D. M. Manuel also thank Instituto Nacional de Gestão de Bolsas de Estudos do Governo de Angola and Instituto Superior de Ciências de Educação da Huíla.

References:

[1] Jordheim LP, Durantel D, Zoulim F, Dumontet C. Advances in the development of nucleoside and nucleotide analogues for cancer and viral diseases. Nat. Rev. Drug Discov. 2013; 12: 447–464.
[2] Hruba L, Das V, Hajduch M, Dzubak P. Nucleoside-based anticancer drugs: Mechanism of action and drug resistance. Biochem. Pharmacol. 2023; 215:115741.
[3] Motter, J., Benckendorff, C. M. M., Westarp, S., Brown, P. S., Neubauer, P., Kurreck, A., Miller, G. J. Purine nucleoside antibiotics: recent synthetic advances harnessing chemistry and biology. Nat. Prod. Rep., 2024, 41, 873-884.
[4] Xavier NM, Porcheron A, Batista D, Jorda R, Řezníčková E, Kryštof V, Oliveira MC. Exploitation of New Structurally Diverse D-Glucuronamide-Containing N-Glycosyl Compounds: Synthesis and Anticancer Potential. Org. Biomol. Chem. 2017; 15: 4667–4680.
[5] Xavier NM, Goncalves-Pereira R, Jorda R, Hendrychová D, Oliveira MC. Novel Dodecyl-Containing Azido and Glucuronamide-Based Nucleosides Exhibiting Anticancer Potential. Pure Appl. Chem. 2019, 91: 1085-1105.
[6] Xavier NM, Fortuna A, Ref. Mod. Chem. Mol. Sci. Chem. Eng. (J. Reedijk, ed.), Elsevier, 2019, DOI: 10.1016/B978-0-12-409547-2.11098-4.

Discovery of covalent ligands with AlphaFold3

Yoav Shamir[1], Ronen Gabizon[1], Adi Rogel[1], David Yin-wei Lin[2], Amy H. Andreotti[2], Nir London[1]

[1]Department of Chemical and Structural Biology, The Weizmann Institute of Science, Rehovot 7610001, Israe
[2]Roy J. Carver Department of Biochemistry, Biophysics and Molecular Biology, Iowa State,University, Ames, Iowa 50011, United States of America

Covalent inhibitors have become a prominent modality for research and therapeutic tools, with more than 50 covalent drugs approved by the FDA to date. However, a scarcity of covalency-specific computational methodologies slows further progress. AI models such as AlphaFold3 (AF3) have shown accuracy in ligand pose prediction, but their assessment for virtual screening performance is limited. We show that AF3 co-folding predictions and an associated predicted confidence metric ranks experimental covalent binders with near-optimal classification over property-matched decoys, significantly outperforming physics-based covalent docking tools for a set of kinases. We conducted prospective virtual screening with 900K covalent compounds against BTK, a model kinase. Out of 13 tested predictions, 8 showed covalent binding to BTK, one of which – YS1 – proved to be highly potent – 30nM inhibition in an in vitro kinase assay, and 107nM in a cellular assay. YS1 displays lower thiol reactivity than Ibrutinib, the benchmark BTK inhibitor, exhibits rapid covalent binding kinetics, and leads to significant thermal stabilization upon binding. Alleviating a key concern for covalent binders, YS1 was shown to be selective in chemoproteomic experiments as well as a full kinase panel. Co-crystal structures validated the AF3 prediction of an unusual binding mode to BTK at sub-angstrom accuracy (Fig. 1), underscoring that AF3 can be used to uncover novel binding poses. By design, the main hits bear no similarity to known BTK inhibitors, proving that AF3 can be used practically to discover novel chemical matter for kinases, one of the most prolific families of drug targets.

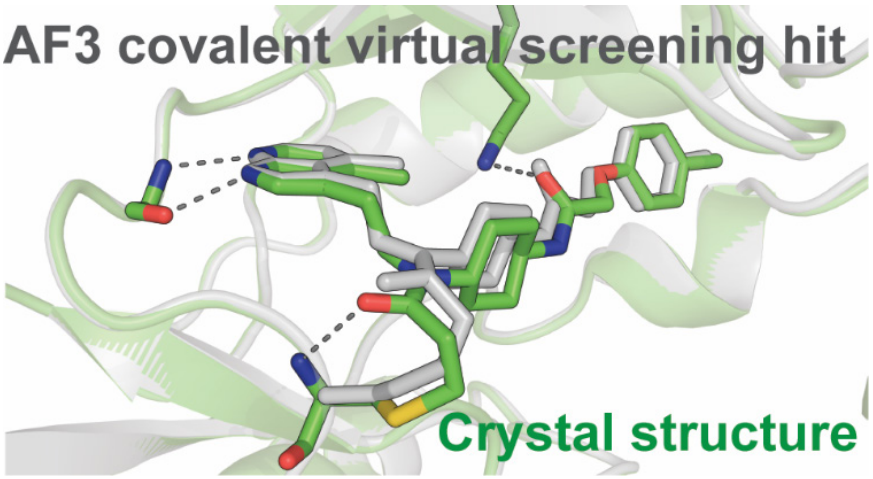


Figure 1. Alignment of the AF3-predicted covalent BTK-YS1 complex and the experimental crystal structure (grey and green, respectively; ligand RMSD 0.5[]). Hydrogen bonds are depicted as dashed lines.

Optimization of a Xanthine-Based Senolytic Lead Compound Targeting HSP90α

Maria Cristina De Rosa[1], Davide Pirolli[1], Benedetta Righino[1], Beatrice Scagnoli[1,3], Alessandro Semeraro[1], Elena Ciampini[2], Emmanuel de Billy[2,3], Francesco Cecconi[2,3], Matteo Benetazzo[4], Alberto Ongaro[4], Michele Maggini[4].

[1]Istituto di Scienze e Tecnologie Chimiche "Giulio Natta" (SCITEC) – CNR, L.go F. Vito 1, Rome, Italy;
[2]Università Cattolica del Sacro Cuore, L.go F. Vito 1 Rome, Italy;
[3]Fondazione Policlinico Universitario A. Gemelli IRCCS, L.go F. Vito 1, Rome, Italy;
[4]Dipartimento di Scienze Chimiche, Università di Padova,Via F. Marzolo 1, Padova, Italy

Cellular senescence is a key driver of aging and age-related diseases, highlighting the urgent need for safe and effective senolytic agents[1]. HSP90 inhibitors have shown promising senolytic potential, although their development is still limited by formulation, toxicity, and cost. In this context, our recent work identified novel HSP90α inhibitors with senolytic activity in vitro and in vivo[2]. Among them, compound K5, a xanthine-based molecule functionalized at positions 1 and 3 of the heterocyclic ring, showed remarkable efficacy and selectivity, supporting HSP90α as a promising target for next-generation senolytic therapies[3]. This study focused on optimizing the K5 structure to generate more potent derivatives by improving interactions within the HSP90 binding pocket, aiming to develop safer, more effective candidates. Compound design was guided by molecular interaction fingerprint (MIF) analysis, leading to the generation of a focused library of K5 derivatives. Binding affinities and binding modes were then assessed through Multi-Site Lambda Dynamics simulations and molecular docking. Thirteen analogues, obtained by systematic substitution on the benzylic aromatic ring at position 1 of K5 with hydroxy, halogen, or trifluoroalkyl groups, were evaluated in a cell-based assay to determine their potency in inhibiting HSP90. Inhibition was assessed by immunofluorescence by quantification of HSF1 relocalization, a marker of HSP90 inhibtiion, in nuclear foci associated with senescence[4]. Compared to K5, four compounds induced HSF1 nuclear foci at lower concentrations, suggesting increased potency. K5-derived compounds emerge as highly promising candidates for senolytic therapy, with ongoing studies assessing their selective activity against senescent cells.

References:

[1] McHugh D, Gil J. Senescence and aging: Causes, consequences, and therapeutic avenues. J Cell Biol 2018; 217:65-77.
[2] Atlante S, Cis L, Pirolli D et al. A Xanthine Derivative With Novel Heat Shock Protein 90-Alpha Inhibitory and Senolytic Properties. Aging Cell 2025; 24:e70047.
[3] Gaetano C, Atlante S, De Rosa MC et al. Compounds useful in the prevention and/or treatment of senescent cell-related pathologies and diseases. Patents WO2023135532A1 and WO2023135533A1.
[4] Sabath N, Levy-Adam F, Younis A et al. Cellular proteostasis decline in human senescence. Proc Natl Acad Sci USA 2020; 117:31902-31913.

Multitarget β-Secretase and Cholinesterase Inhibition by Phenolic Amides from Philippine Single-Origin Artisan Chocolate Revealed by Metabolomics, Enzyme Assays, and Docking

Doralyn S. Dalisay[1,2,3], Chuckcris P. Tenebro[1,2], Diane Monique S. Baladjay[1,2], Neaven Bon Joy M. Marcial[1,2], Josie C. Torrecampo[1,2], Lucille Marie S. Jusa[1,2], Leah Katrine A. Bayog[1,2], Jade Joshua R. Teodosio[2], Derek Gio S. Ong[4], Rex Victor P. Puentespina4, Jonel P. Saludes[1,5,6].

[1]Kasanggang NICER in Functional Food Excellence (KNIF2E) Laboratory, University of San Agustin, Iloilo City, Philippines;
[2]Center for Chemical Biology and Biotechnology (C2B2), University of San Agustin, Iloilo City, Philippines;
[3]Department of Biology, University of San Agustin, Iloilo City, Philippines;
[4]Malagos Agri-Ventures Corporation, Davao City, Philippines;
[5]Center for Natural Drug Discovery and Development (CND3), University of San Agustin, Iloilo City, Philippines;
[6]Department of Chemistry, University of San Agustin, Iloilo City, Philippines.

Alzheimer's disease (AD) is the leading cause of dementia and represents a growing public health burden in Southeast Asia. Multitarget inhibition of β-secretase (BACE1), acetylcholinesterase (AChE), and butyrylcholinesterase (BChE) is a recognized therapeutic strategy to reduce amyloid formation and restore cholinergic signaling during AD progression. Cocoa-derived polyphenols have attracted attention for their potential neuroprotective properties; however, the enzyme-specific roles of cocoa phenolic amides remain insufficiently understood.

The Philippines is an emerging producer of Theobroma cacao L., particularly fine-flavor Trinitario cultivars cultivated under tropical agroecological conditions that influence secondary metabolite composition. In this study, four formulations of Philippine single-origin artisan dark chocolate derived from locally grown T. cacao were evaluated for multitarget anti-AD activity. Functional metabolites were extracted using accelerated solvent extraction with water and characterized by targeted metabolomics. Two phenolic amides, clovamide and N-coumaroyltyrosine, were consistently detected across all chocolate extracts. Their concentrations ranged from 38–97 µg (clovamide) and 57–110 µg (N-coumaroyltyrosine) per 3 g serving of artisan dark chocolate.

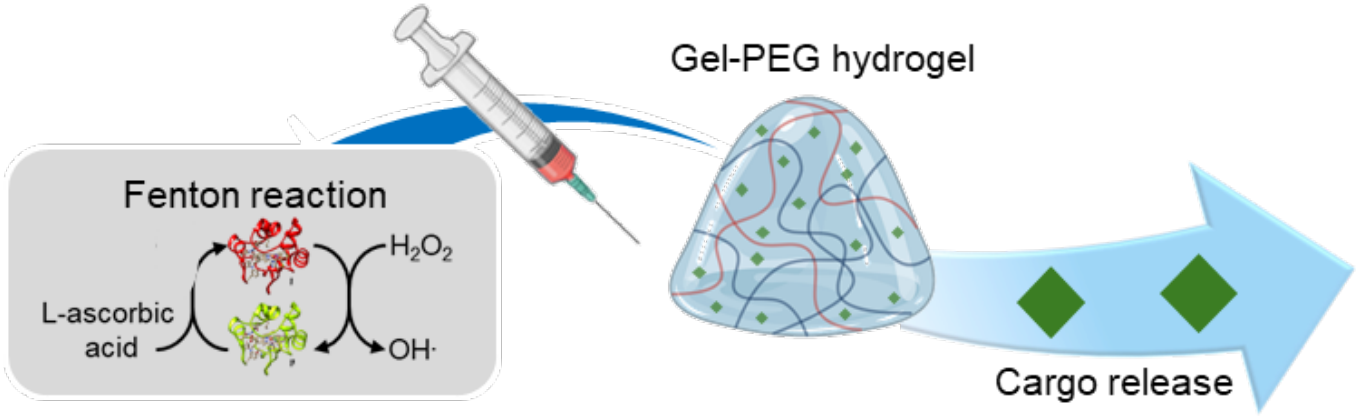
In vitro enzyme assays showed that clovamide and N-coumaroyltyrosine exhibited BACE1 inhibition of 50–54% at 31.25 µg/mL, compared with 99% inhibition by the positive control resveratrol at the same concentration. Extracts from the four chocolate formulations demonstrated 64–82% BACE1 inhibition. Preliminary assays also indicated inhibitory activity against AChE and BChE, supporting a multitarget inhibitory profile. Molecular docking analyses revealed stable binding of both phenolic amides within the catalytic sites of BACE1, AChE, and BChE through hydrogen bonding and π–π interactions with key residues. This study integrates metabolomics, enzymology, and molecular modeling to provide mechanistic insight into cocoa-derived phenolic amides as multitarget modulators of AD-relevant enzymatic pathways.

Very Fast Gelating Injectable Gelatin Hydrogels obtained via Cytochrome C Mediated Radical Polymerization

Andrea Fumaneri[1,2], Edoardo Sisti[1,2], Alessandro Ajo[1,2], Viola Bertolotti[1], Samet Varol[1], Luigi Menduti[1], Luisa De Cola[1].

[1]Dipartimento di Scienze Farmaceutiche, Università degli Studi di Milano, via C. Golgi 19, 20133 - Milano, Italy;
[2]Dipartimento di Biochimica e Farmacologia Molecolare, Istituto di Ricerche Farmacologiche Mario Negri "IRCCS", Via Mario Negri 2, , 20156 - Milano, Italy.

Injectable hydrogels[1] capable of rapid in situ gelation under physiological conditions are highly attractive for minimally invasive surgery and locoregional drug delivery[2]. However, the wide majority of polymeric systems rely on UV photo-crosslinking strategies[3], limiting their in vivo applicability. As a biocompatible alternative, we herein report three novel injectable hydrogels composed of varying amounts of gelatin (Gel) and polyethylene glycol (PEG), crosslinked via a Fenton-like[4] radical polymerization mediated by Cytochrome C (CyC) in the presence of H2O2 and L-ascorbic acid. To the best of our knowledge, this is the first example of hydrogels synthesized through Fenton-like mechanism involving CyC as the iron source.
The Gel-PEG hydrogel formulations prepared with this protocol exhibited very fast sol–gel transition within 1-2 minutes. Rheological analysis showed that mechanical properties and the modulation of the linear viscoelastic region (LVR) can be easily tuned by varying the concentrations of the gelatin and crosslinker. Structural characterization and biodegradation studies revealed as the enzymatic degradation is strongly dependent on the degree of crosslinking. All hydrogels were readily injectable and showed no detectable cytotoxicity in conditioned media assays. The hydrogels showed sustained release of rhodamine 101, reaching ~70% over 7 days. Overall, our combined structural, rheological, biodegradability and release studies showed how our Gel-PEG injectable hydrogels represent a promising platform for the construction of fast-injectable formulations for localized drug-release.
This work was supported by the project "Programmable Bionanomaterials with Protein-Controlled Behavior" (Program-Material), Horizon Europe - Marie Skłodowska-Curie actions, Staff Exchanges - Grant Agreement N. 101182883.



References:

[1] Overstreet D.J., Dutta D., Stabenfeldt S.E., Vernon B.L. Journal of polymer science part B: Polymer physics 2012; 50: 881–903.
[2] Piantanida E., Alonci G., Bertucci A.,De Cola, L. Design of Nanocomposite Injectable Hydrogels for Minimally Invasive Surgery. Accounts of chemical research 2019; 52: 2101–2112.
[3] Chen M., Zhong M., Johnson J. A. Light-Controlled Radical Polymerization: Mechanisms, Methods, and Applications. Chemical reviews 2016; 116: 10167–10211.
[4] Xiao J., Guo S., Wang D., An Q. Fenton-Like Reaction: Recent Advances and New Trends. Chemistry - A European Journal 2024; 30: e202304337.

Mimicking Collagen Fibrils through Hyperstable and Short Collagen-Mimetic Peptide Assemblies

Smriti Mukherjee[a], [b], Ancy Feba[c], Vijayakumar Varshashankari[d], Kanagasabai Balamurugan[c], Niraikulam Ayyadurai[d], Ganesh Shanmugam[a], [b]*.

[a]*Organic & Bioorganic Chemistry Laboratory, Council of Scientific and Industrial Research (CSIR) - Central Leather Research Institute (CLRI), Adyar, Chennai, 600020, India*
[b]*Academy of Scientific and Innovative Research (AcSIR), Ghaziabad-201002, India*
[c]*Advanced Materials Laboratory, Council of Scientific and Industrial Research (CSIR) - Central Leather Research Institute (CLRI), Adyar, Chennai, 600020, India*
[d]*Biochemistry & Biotechnology Laboratory, Council of Scientific and Industrial Research (CSIR) - Central Leather Research Institute (CLRI), Adyar, Chennai, 600020, India*

Collagen, the most abundant fibrous protein in mammals, possesses a characteristic triple-helix structure that governs tissue mechanics and cellular growth, making it indispensable in tissue engineering[1]. However, animal-derived collagen, widely used in biomedical applications, suffers from batch variability, pathogen risk, and immunogenicity. Collagen-mimetic peptides (CMPs), composed of Gly-Pro-Hyp (GPO) repeats, offer a synthetic alternative. Yet, most CMPs require long sequences (≥9 GPO repeats) to form fibrils, making large-scale production and purification difficult[2]. A key challenge is to design short CMPs that not only stabilize the triple helix but also assemble into fibrils capable of effective biological interfacing. Here, we present CMP-based nanofibrils as a new class of biomimetic nanomaterials designed through a supramolecular strategy. Short CMPs with 3–6 GPO repeats were capped with two Fmoc (fluorenylmethoxycarbonyl) moieties at the N-terminus via a lysine linker, while a tyrosine residue was introduced at the C-terminus to promote strong π-π interactions at both the termini[3]. These diFmoc-capped CMPs formed highly stable triple helices (Tm up to 76 °C) with rapid folding kinetics, offering advantages over both native collagen and conventional CMPs. Notably, this strategy reduced the number of GPO repeats required for triple-helix formation to three, the lowest reported to date. The diFmoc-capped CMPs also exhibited significantly higher stability than single-Fmoc-capped analogues. Experimental and computational studies attributed this increased stability to π-π, hydrogen-bonding and cation-π interactions. Furthermore, the diFmoc-capped CMPs formed nanofibrils which promoted fibroblast adhesion and proliferation, driven by receptor recognition of the triple-helical motifs and fibrillar networks.

References:

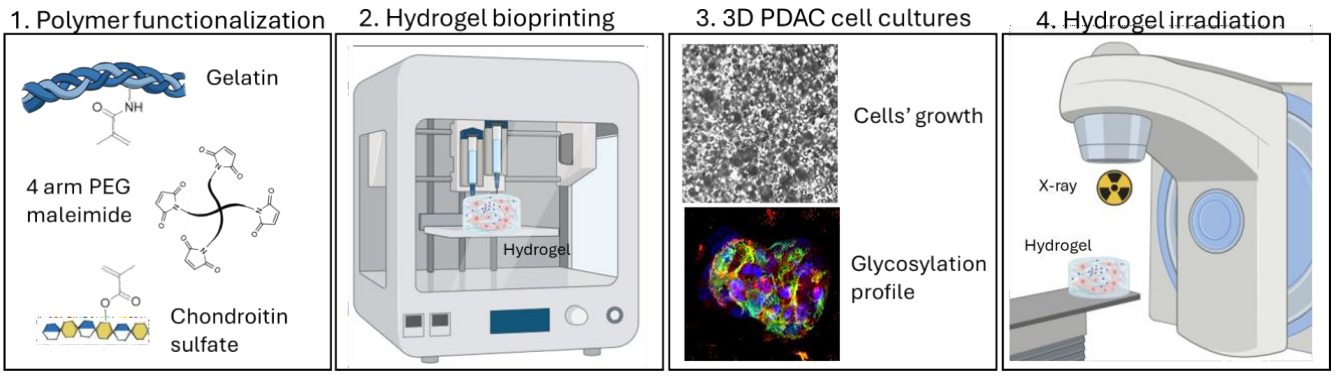
1. Sorushanova, A.; Delgado, L. M.; Wu, Z.; Shologu, N.; Kshirsagar, A.; Raghunath, R.; Mullen, A. M.; Bayon, Y.; Pandit, A.; Raghunath, M.; Zeugolis, D. I., The Collagen Suprafamily: From Biosynthesis to Advanced Biomaterial Development. Adv. Mater. 2019, 31 (1), 1801651.
2. Banerjee, J.; Azevedo, H. S., Crafting of functional biomaterials by directed molecular self-assembly of triple helical peptide building blocks. Interface Focus 2017, 7 (6), 20160138.
3. Mukherjee, S.; Varshashankari, V.; Feba, A.; Ayyadurai, N.; Balamurugan, K.; Shanmugam, G., Hyperstable and Fibril-Forming Collagen-Mimetic Peptides in Shortest Triple Helices: Empowering the Capping by π-systems. Biomacromolecules 2025, 26 (4), 2171-2185.

3D bioprinted hydrogel model to study glycosignature evolution in pancreatic adenocarcinoma (PDAC) after x-ray treatment

MarcoPiazzoni[1],FrancescaCadamuro[1],IlariaBorghi[1],FrancescoNicotra[1],LauraRusso[1,2]

[1]SchoolofMedicineandSurgery,UniversitàdegliStudiMilano-Bicocca,VedanoalLambro(MB),Italy.
[2]Fondazione IRCCS San Gerardo dei Tintori

Pancreatic adenocarcinoma (PDAC) remains one of the deadliest cancers, with a five-year survival rate of only 10%. The lack of early biomarkers often rules out surgery, leaving chemotherapy and radiotherapy as the primary treatments. Aberrant glycosylation of cancer cells has proven to be a hallmark of many cancer types, but their role in PDAC progression is yet to be fully elucidated. We developed a 3D hydrogel in vitro model of human PDAC cell lines designed to mimic the tumor microenvironment to study glycosignature changes following X-ray exposure. The hydrogel consists of gelatin and chondroitin sulfate modified with methacrylate groups, crosslinked with 4-arm maleimide polyethilene gycole using UV light. We calculated polymer functionalization via 1H-NMR and tuned the hydrogel's elastic properties to match native tissue conditions. Pancreatic cancer cells were bioprinted into microsphere hydrogels and growth was monitored for 14 days using AI-driven imaging. Results showed that glyco-related antigen expression in these 3D constructs differed significantly from standard 2D cultures, highlighting the model's superior biological relevance. Finally, these 3D models were exposed to varying X-ray dosages, with their radiobiological response tracked for up to 72 hours. This advanced 3D model provides a reliable platform for investigating the glycosignature evolution of pancreatic cancer cells in relation to the culture environment. By identifying new glycosylation patterns, this research aims to uncover new therapeutic targets and ultimately improving PDAC patients prognosis.



Acknowledgments:

Ministero dell'Università e della Ricerca (MUR) PNC0000003 CUP BICOCCA B53C22006670001. Ministero della Salute RF-2021-12371959. Ministero dell'Università e della Ricerca (MUR) 2022MY7AZT. Fondazione Cariplo 2024-NAZ-0094 CUP BICOCCA H45E24000440007.

Characterization of a Novel Antimicrobial Peptide Discovered through Genome Mining

Jeella Acedo[1,2], James La[1], Caden Albright[1], Micah Ignacio[1], Jenna Buragina[2], Jeroen De Buck[2]

[1]Mount Royal University, Faculty of Science and Technology, Department of Chemistry and Physics, Calgary, Canada;
[2]University of Calgary, Cumming School of Medicine, Department of Microbiology, Immunology and Infectious Diseases, Calgary, Canada.

Antimicrobial resistance (AMR) is considered by the World Health Organization as one of the top 10 global public health threats. Various strategies to address AMR are therefore being pursued including the development of alternative therapies to combat microbial infections. Antimicrobial peptides, including bacteriocins, represent promising alternatives to conventional antibiotics. Bacteriocins are ribosomally synthesized peptides produced by bacteria and are primarily used in food biopreservation and animal industries. In this study, we performed genome mining to identify novel leaderless bacteriocins, a unique class of bacteriocins distinguished by the absence of an N-terminal leader peptide and post-translational modifications. These peptides are attractive candidates for industrial production because of their simple biosynthetic pathway. We subsequently characterized one of the identified novel leaderless bacteriocins we named corynacin. Broth microdilution assays were used to establish its minimum inhibitory concentrations against a suite of bacterial strains, wherein corynacin was found to inhibit the growth of multiple organisms, including three methicillin-resistant Staphylococcus aureus (MRSA) strains. Time-kill assays demonstrated rapid bactericidal activity, with complete elimination of target cells within five minutes of exposure. Membrane disruption was confirmed through fluorescence spectrophotometry, as indicated by increased uptake of propidium iodide. Lastly, safety assessments showed no detectable hemolytic activity against sheep red blood cells and no cytotoxic effects on keratinocyte cell lines. Collectively, these results identify corynacin as a promising antimicrobial candidate with rapid bactericidal activity and a membrane-targeted mode of action. Further studies are required to elucidate its molecular mechanism and explore its potential applications in food safety and/or human and veterinary medicine.

From Extraction to Immunoreactivity: A Chemical-Biology View of C-Phycocyanin from Arthrospira platensis

Kelly Bugatti[1], Laura Esposito[1], Sara Cutroneo[1], Francesca Accardo[1], Luisa Calcinai[1], Barbara Prandi[1], Tullia Tedeschi[1]

[1]*Department of Food and Drug, University of Parma, Parco Area delle Scienze, 27/A, 43124 Parma, Italy*

Arthrospira platensis (spirulina) is gaining attention as a sustainable protein source rich in phycobiliproteins, particularly Cphycocyanin (CPC), a pigment–protein complex with nutritional and functional relevance [1]. Despite its widespread use, the molecular features, digestibility, and potential immunogenicity of CPC remain insufficiently characterized [2]. This work aimed to optimize extraction strategies for CPC, elucidate its molecular architecture, and investigate its digestive fate and immunochemical properties.

Four extraction methods - french press (FP), hydrothermal (HT), ultrasoundassisted (US), and ultraturrax (UT) - were compared in terms of protein yield, purity, and structural integrity. UT and HT provided the highest protein recovery (21.5–24.5%), while SDSPAGE and UHPLCESI/MS analyses revealed intact phycobiliproteins only in FP, US, and UT extracts; HT caused extensive degradation. Purified CPC displayed three distinct chromatographic species corresponding to the αsubunit, βsubunit, and the bilinbound βsubunit. In vitro gastrointestinal digestion showed extensive hydrolysis, with higher DH% in all extracts compared to raw biomass. HRMS peptide profiling demonstrated that FP, US, and UT generated the richest peptide repertoires, predominantly derived from CPC.

Given the reported cross-reactivity between spirulina and crustacean-allergens, purified C-PC was evaluated for IgE binding using sera from crustacean-sensitized patients. Intact CPC exhibited clear IgE reactivity, confirming its relevance as a potential allergen. However, simulated digestion drastically reduced IgE binding, and none of the peptides detected by HRMS corresponded to linear epitopes in allergen databases.

These findings identify UT as the most efficient extraction method and provide an integrated molecular and immunochemical characterization of CPC, supporting its informed and safe use in food and nutraceutical applications.

References:

[1] Musa MN, et al. A review on techno-economic assessment of Spirulina for sustainable nutraceutical, medicinal, environmental, and bioenergy applications. Bioresour. Bioprocess. 2025: 12: 51.

[2] Ferreira de Oliveira AP, Bragotto APA. Microalgae-based products: Food and public health. Future Foods 2022; 6: 100157.

Lipopeptide nanozymes as biocompatible and membrane-safe catalysts for intracellular bioorthogonal reactions

Stefano Fedeli[1,2], Isabel Fraile[2], Michela Pesenti[1], Jonah Voigt[2], Kaliroi Peqini[1], Sara Pellegrino[1], Giorgio Abbiati[1],Anayancy Osorio[2]

[1]Department of Pharmaceutical Sciences, University of Milan, via Golgi 19, 20133, Milan, Italy;
[2]Universtity of Bayreuth, Prof.-Rüdinger-Bormann-Str. 1, 95447, Bayreuth, Germany.

Bioorthogonal chemistry offers the possibility of performing reactions in living systems without interfering with biological processes, enabling diagnostic and therapeutic strategies focused at the disease site. Bioorthogonal catalysis uses transition metal catalysts (TMCs) to generate active molecules through mechanisms inaccessible to natural enzymes. Incorporating hydrophobic TMCs into amphiphilic scaffolds enhances the catalyst's solubility and uptake, thereby amplifying the therapeutic applications of bioorthogonal strategies. This encapsulation results in bioorthogonal 'nanozymes' that operate efficient catalytic processes inside cells and living systems[1].
However, charged amphiphilic scaffolds strongly interact with membrane phospholipids, compromising the cell stability. Cytotoxicity is therefore an inherent limit of these structures, as the surfactant properties that stabilize TMCs also interfere with cell integrity.
Lipopeptides are small biosurfactant molecules featuring a short aminoacidic sequence bonded to an aliphatic hydrocarbon chain. The polarity difference between the hydrophilic amino acids and the hydrophobic chain provides a mild amphiphilic character, resulting in surfactants with excellent biocompatibility. We harnessed lipopeptides to encapsulate TMCs and produce highly biocompatible nanozymes to penetrate the cell without destabilizing the membrane, preserving the cell viability and surface integrity (Figure 1). We prepared iron- and palladium-nanozymes demonstrating the cytosolic activation of fluorescent dyes in macrophages and fibroblasts. Dedicated experiments also confirmed the membrane integrity of the treated cells. Taken together, the developed nanozymes offer a highly biocompatible tool, enabling the design of highly localized treatments based on the intracellular generation of active molecules.

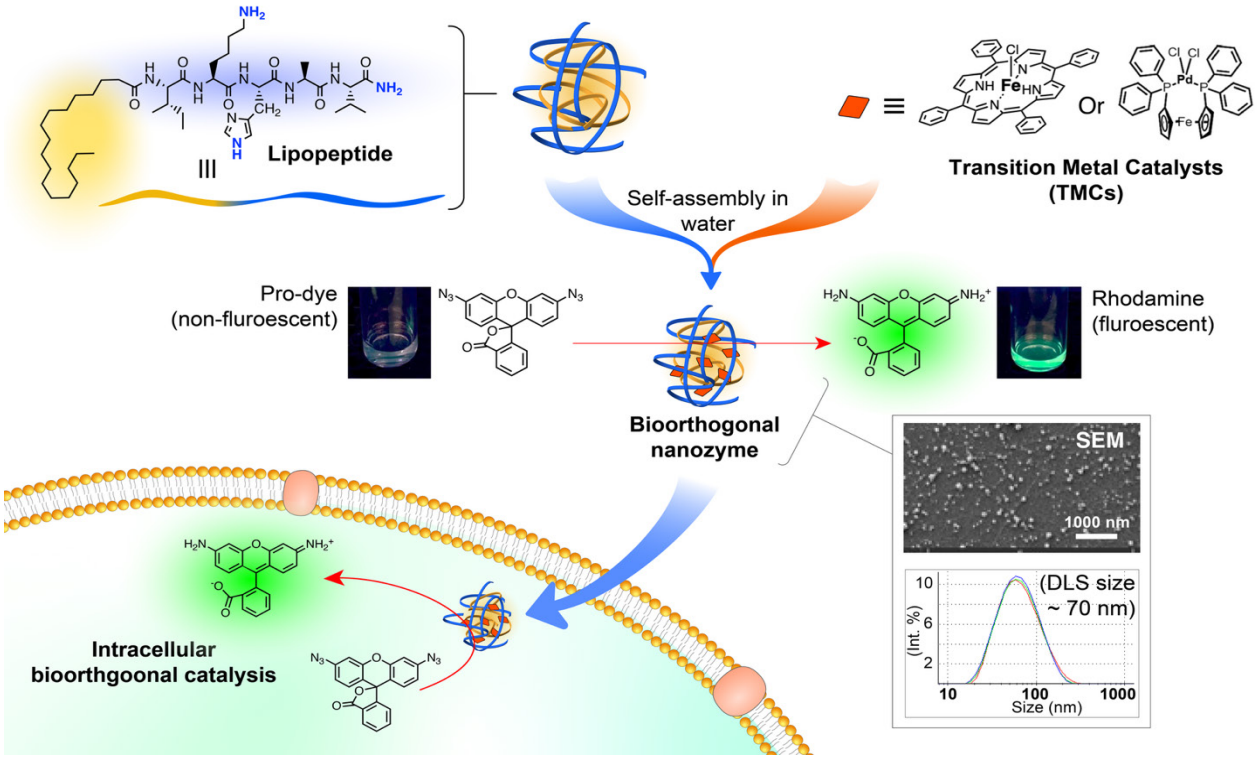


Figure 1. Amphiphilic lipopeptides encapsulate TMCs forming bioorthogonal 'nanozymes': highly biocompatible structures able to operate intracellular catalytis (dye activation)

References:

[1] Fedeli S, Im J, Gopalakrishnan S, Elia JL, Gupta A, Kim D, Rotello VM, Nanomaterial-Based Bioorthogonal Nanozymes for Biological Applications. *Chem. Soc. Rev.* 2021, *50* (24), 13467–13480.

Identification of Novel Sulfonamide-Based Inhibitors of MMP-2 Using Ligand-Based Pharmacophore Approaches

Saad Zekri[1], Nouhaila Ait Lahcen[1], Adnane Ait Lahcen[1], Wissal Liman[2], Ismail Hdoufane[1], Driss Cherqaoui[1,3]

[1]Cadi Ayyad University, UCA, Faculty of Sciences Semlalia, Molecular Chemistry Laboratory, B.P. 2390, 40000 Marrakech, Morocco;
[2]Bioinformatics Laboratory, College of Computing, University Mohammed VI Polytechnic, Morocco;
[3]Sustainable Materials Research Center (SUSMAT-RC), University of Mohammed VI Polytechnic, Benguerir 43150, Morocco.

Matrix metalloproteinase 2 (MMP2) is a zinc dependent endopeptidase involved in extracellular matrix remodeling and plays a pivotal role in tumor invasion and metastasis. Given its association with cancer progression, MMP2 has emerged as a promising therapeutic target. however, the lack of selective inhibitors has hindered clinical success. In this study, we employed an integrated computational strategy to identify potential MMP2 inhibitors. A ligand-based pharmacophore model was developed from a dataset of sulfonamide derivatives with reported inhibitory activity. The model was rigorously validated using a decoy screening approach and statistical metrics, including Receiver Operating Characteristic - Area Under the Curve (ROC-AUC), enrichment factor, and Goodness of Hit score, demonstrating strong predictive power. The validated model was subsequently applied to screen a Food and Drug Administration (FDA) approved drug library to explore repurposing opportunities. Selected hits were further evaluated through molecular docking, which revealed favorable binding affinities and key interactions within the active site of MMP2. To confirm binding stability under physiological conditions, molecular dynamics simulations were performed on both apo and ligand bound systems, followed by trajectory analysis. The combined results highlight several FDA approved candidates with potential inhibitory activity against MMP-2. This work provides valuable insights into the design of selective MMP2 inhibitors and establishes a foundation for further optimization and experimental validation.

Green and sustainable "biocatalytic" synthesis of polymeric electrolytes for Na-ion batteries

Virinder S. Parmar[1,2], Kumar Shivam[2], Monalia Mukherjee[2] and Michele Vittadello[1]

[1]*Department of Chemistry and Environmental Science, Medgar Evers College, City University of New York, Brooklyn, New York 11225, USA*
[2]*Amity Institute of Click Chemistry Research and Studies, Amity University, Noida, UP 201 303,India*
vparmar@mec.cuny.edu

We have fabricated a novel solvent-free polymer electrolyte system for sodium polymer ion batteries, which exhibits commendable ionic conductivity. The TGA and thermal stability data have been used to confirm the structural integrity of the polymer electrolyte. No significant weight loss was observed in the TGA profiles at temperatures corresponding to the boiling points of typical solvents, confirming the absence of residual solvents. The developed polymer electrolyte's utility in the real-world battery setups has been studied. The design, synthesis, and characterization of this novel solvent-free sodium-ion conducting polymer electrolyte system shall be presented at the ISBOC-14 Conference.

References:

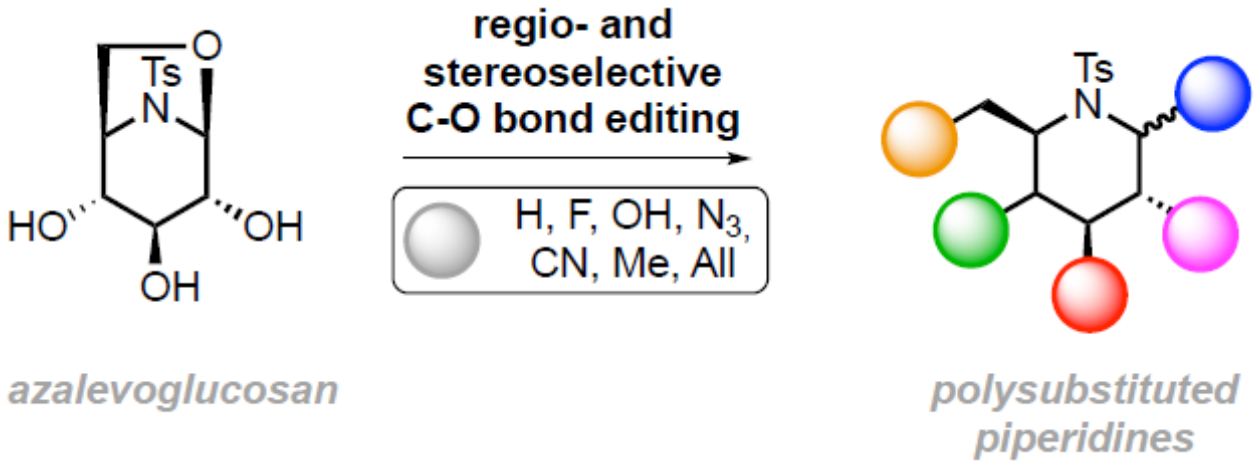
Shivam K, Agrawal ON, Kumar S, Patra R, Mukherjee M, Pandey MK, Parmar VS, Vittadello M. Two-channel sodium-ion conducting polymer electrolytes based on perfluorinated linear hetero-oligomers prepared by enzymatic synthesis and NaTFSI. Journal of Materials Chemistry A, 2025, 13: 33880-33896.

N-sulfonyl azalevoglucosan, a versatile platform for the diversity-oriented synthesis of polysubstituted piperidines

Dylan Yorga, Nicolas Auberger, Yves Blériot, Jérôme Désiré

IC2MP, UMR CNRS 7285 - Université de Poitiers, Poitiers, France,
e-mail : jerome.desire@univ-poitiers.fr

Substituted piperidines and azepanes are key synthetic fragments for designing drugs and play a significant role in the pharmaceutical industry[1]. The reported synthetic methods allow access to mono-, di- and tri-substituted piperidines but tetra- and pentasubstituted piperidines are scarce in the literature. Herein, exploiting the inherent chirality of iminosugars, we present the synthesis of a levoglucosan[2] mimic in which the endocyclic oxygen has been replaced by a *N*-sulfonyl group. The trans diaxial arrangement of its hydroxyl groups allows navigation on the piperidine ring to iteratively install functional groups at C1, C2, C3, C4 and C6 positions using simple experimental protocols with minimal protecting group manipulation and with high regio- and stereoselectivity. The broad functional group scope allows the diversity-oriented synthesis of tetra- and pentasubstituted piperidines including modified iminosugars[3].



References:

[1] J. Shearer, J. L. Castro, A. D. G. Lawson, M. MacCoss, R. D. Taylor, *J. Med. Chem.* **2022**, *65*, 8699–8712.
[2] M. Cerný, *Adv. Carbohydr. Chem. Biochem.* **2003**, *58*, 121-198.
[3] D. Yorga, J. Marrot, A. Poveda, N. Auberger, J. Jiménez-Barbero, J. Désiré, Y. Blériot, manuscript submitted.

Synthesis of Novel 1,2-benziothiazine-fused Galactose Mimetics *via* inverse electon demand Hetero-Diels-Alder Reaction as Selective Galectin-1 ligands

Chiara Mangini[a], Giacomo Biagiotti[a], Ulf Nilsson[b], Barbara Richichi[a]

[a]*Department of Chemistry 'Ugo Schiff', University of Firenze, Via della Lastruccia 3-13, 50019 Sesto Fiorentino, Italy, chiara.mangini@unifi.it*
[b]*Department of Chemistry, Lund University, Box 124, SE-221 00 Lund, Sweden.*

Galectin-1 (Gal-1) has emerged as a pivotal therapeutic target in oncology, owing to its fundamental role in tumor progression, immune evasion, and metastasis[1]. However, despite its clinical promise, the development of Gal-1-selective inhibitors remains challenging. The high structural conservation of the Carbohydrate Recognition Domain (CRD) across galectins family creates a "selectivity barrier," where traditional glycomimetics often fail to discriminate between isoforms[2].
In this communication, we report on a new family of glycomimetics bearing a 1,4-oxathiane ring (see Figure below)[3]. The key step of our synthetic approach is an [4+2] inverse electron demand hetero Diels-Alder (ihDA) route that using D-galactal as dienophile allows accessing to a family of galactose mimetics. Our galactose mimetics showed an unexpected selectivity vs Gal-1 over a wide panel of galectins, thus emerging in the field as as promising lead compounds for the rational design of high affinity and selective inhibitors of this lectin aiming at the disruption of GAL1-glycan axis in cancer.

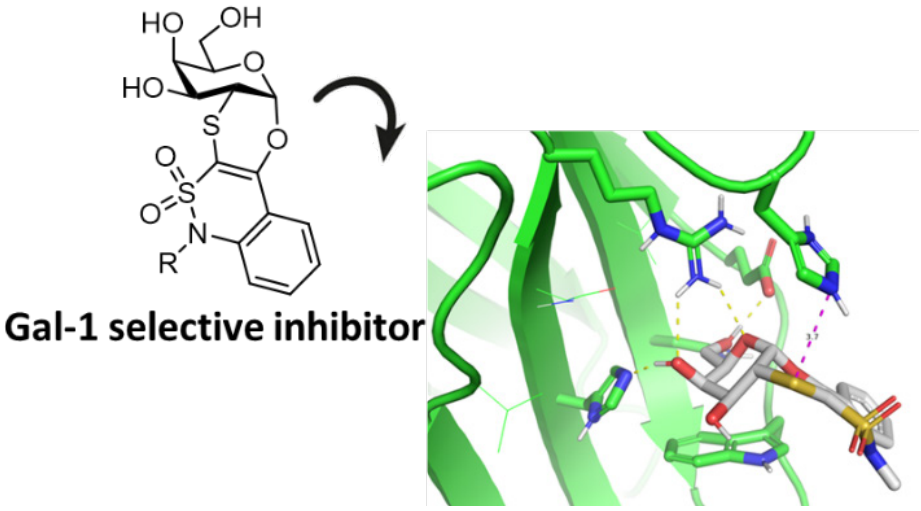


Figure: New galactose glycomimetics and it interaction with Gal-1.

References:

[1] Troncoso MF, […], Rabinovich GA. The universe of galectin-binding partners and their functions in health and disease. *J. Biol. Chem*, **2023,** 299:105400.
[2] Zetterberg FR, […], Nilsson UJ. Discovery of the Selective and Orally Available Galectin-1 Inhibitor GB1908 as a Potential Treatment for Lung Cancer. *J. Med. Chem.,* **2024**, 67, 9374−9388.
[3] Biagiotti G., […], Richichi B. Benzo[c][1,2]thiazine-Based Analogs in the Inverse Electron Demand [4+2] Hetero Diels-Alder Reaction with Glycals: Access to Tetracyclic Fused Galactose and Fucose Derivatives. *Eur. J. Org. Chem.,* **2022,** e202200769.

Funder:

Project funded under the National Recovery and Resilience Plan (NRRP), Mission 4 Component 2 Investment 1.4 - Call for tender No. 3277 of 30 December 2021 of Italian Ministry of University and Research funded by the European Union – NextGenerationEU; Award Number: Project code ECS_00000017, Concession Decree No. 1055 of 23 June 2022 adopted by the Italian Ministry of University and Research, CUP B83C22003930001, project title "Tuscany Health Ecosystem – THE".

Site-Selective Editing of Monosaccharides: Access to New C-5 Modified Chemotypes

Sarah Mazzotta

Dipartimento di Chimica, Università degli Studi di Milano, Milano, Italy

Chemical modification of carbohydrates is significant for several scientific fields such as biotechnology, medicine, and materials science, and plays a crucial role in drug design and development[1].
The modification of carbohydrate backbones through C–H activation represents an emerging strategy for the synthesis of rare sugars and functionalized carbohydrate derivatives. This approach preserves the hydroxy group pattern of the monosaccharide, which is crucial for molecular recognition, while enabling the introduction of new functional groups to modulate interactions with proteins[2].
While several methods for carbohydrate C–H functionalization have recently been reported[3], selective activation at specific positions (C1 and C5) remains a significant challenge. In this work, we report the development of a photo-mediated radical strategy enabling the regio- and stereoselective C–H functionalization of monosaccharides.
This methodology was initially investigated on a panel of fucoside substrates[4] and subsequently applied to other monosaccharides, enabling access to a range of modified sugar scaffolds. The resulting compounds represent valuable building blocks for the development of glycomimetic ligands and for probing molecular recognition processes in lectins.

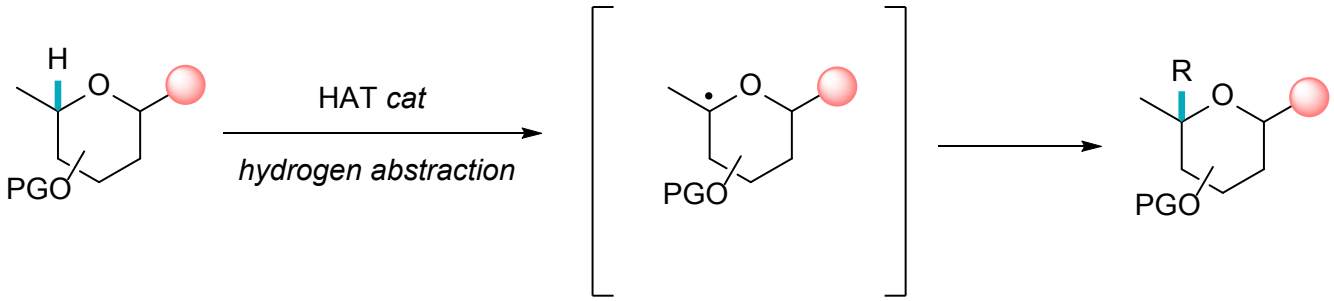


Figure 1: Site-selective functionalization of sugars by C-H activation.

References:

[1] Bernardi A., Sattin S., C-Glycosylcrotylboronates for the Synthesis of Glycomimetics,.Eur. J. Org. Chem. 2020, 30: 4652–466.
[2] Exploiting photoredox catalysis for carbohydrate modification through C-H and C-C bond activation, Shatskiy A., Stepanova E.V., Kärkäs M.D, Nat. Rev. Chem. 2022, 6: 782.
[3] C–H Functionalization on Carbohydrates, Frihed T.G., Bols M., Pedersen C.M., Eur. J. Org. Chem. 2016, 2740–2756.
[4] Editing sugars: decatungstate photocatalyzed site- and stereoselective C–H functionalization in β-fucosides, Mazzotta S., Piro M., Cassera E., Gerola M., Fagnoni M., Ravelli D., Bernardi A., Green Chem. 2026, 28: 2319–2327.

Harnessing Commensal Lipid Architecture: Toward Immunomodulatory glycolipids inspired by *Bacteroides fragilis* Lipid A

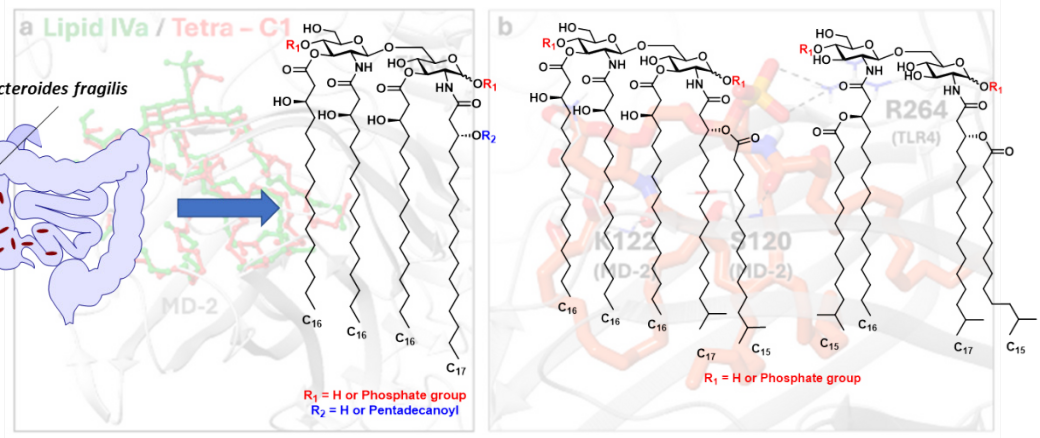
Giuseppe D'Orazio[1], Davie Kenneth[1], Francesca Tanda[1], Giuseppe Stefanetti[2], Ilaria Conti[2], Cristina Manuela Santi[1,3], Alessia Izzo[1], Monica Civera[1], Luigi Lay[1]

[1] *University of Milan, Department of Chemistry, Via C. Golgi 19, Milan, Italy;*
[2] *University of Urbino Carlo Bo, Department of Biomolecular Sciences, Via Ca' Le Suore, 2-4, Urbino, Italy;*
[3] *Laboratory for Polymers and Biomaterials, Fondazione Istituto Italiano di Tecnologia, Genova, Italy.*

Lipid A, the endotoxic component of Gram-negative bacterial lipopolysaccharides (LPS), is a potent immunomodulator through its interaction with the TLR4/MD-2 receptor complex. Despite its relevance as a vaccine adjuvant, native lipid A induces excessive inflammation and toxicity, limiting its biomedical application. Structural modifications have enabled the development of safer derivatives, such as monophosphoryl lipid A (MPL) [1] and 3-O-deacylated monophosphoryl lipid A (3D-MPL) [2], used in licensed human vaccines. Conversely, the pro-inflammatory properties of LPS and lipid A have stimulated interest in antagonists capable of mitigating excessive TLR4-mediated responses associated with sepsis.

In this context, *Bacteroides fragilis* capsular polysaccharide A (PSA) has attracted attention due to its immunoregulatory activity and protective effects against intestinal inflammation. Recent studies have shown that the anti-inflammatory properties of PSA depend on a lipid A–like glycolipid covalently attached to the polysaccharide, although its exact structure remains undefined [3].

To investigate structural features and structure–activity relationships, we synthesized a focused library of lipid A analogs inspired by the glycolipid moiety attached to *Bacteroides fragilis* PSA. Initial derivatives—tetra-acylated and penta-acylated monophosphoryl variants [4]—were complemented with three additional analogs, including branched tri- and penta-acylated forms and a tetra-acylated diphosphorylated derivative. Docking studies highlighted the tetra-acylated C-1 analog as a potential TLR4/MD-2 antagonist. This communication outlines the synthetic strategy and presents computational data and preliminary immunological studies supporting their potential as immunomodulatory agents.



References:

[1] Brade, L.; Kuhn, H.; Kusumoto, S.; et al., The immunogenicity and antigenicity of lipid A are influenced by its physicochemical state and environment, Infec. Immun, 1987, 55, 2636.
[2] Mata-Haro, V.; Cekic, C.; Martin, M.; et al., The Vaccine Adjuvant Monophosphoryl Lipid A as a TRIF-Biased Agonist of TLR4, Science, 2007, 316, 1628.
[3] Erturk-Hasdemir, D.; Seeberger, P.; Kasper, D.; et al., Symbionts exploit complex signaling to educate the immune system, PNAS, 2019, 116, 26157.
[4] Kenneth, D., Santi, C. M., Tanda, F., Izzo, A., Civera, M., D'Orazio, G., Lay, L., Synthesis and Docking Studies of Glycolipids Inspired by Bacteroides fragilis Lipid A. Molecules, 2025, 30(19), 3927.

Engineering glyconanomaterials for the fine regulation of the immune response

Jacopo Tricomi[1], Mike Aoun[2], Anna Bernardi[3], Marco Marradi[1], Rikard Holmdahl[4], Barbara Richichi[1]

[1]Department of Chemistry "Ugo Schiff", University of Florence, via della lastruccia 3-13, 50019, Sesto Fiorentino, Italy.
[2]Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden.
[3]Department of Chemistry, University of Milan, via Golgi 19, 20133, Milan, Italy.
[4]Division of Immunology, Department of Medical Biochemistry and Biophysics, Karolinska Institute, Stockholm, Sweden.

The precise steering of the immune response has emerged as a crucial strategy for the treatment of diverse life-threatening diseases including cancer, autoimmune diseases, and chronic inflammatory disorders[1]. However, to make immunotherapy effective, a precise balance of immune activation *vs* suppression is critical[2]. Glyconanomaterials (GNPs) are versatile platforms for immune modulation, their physicochemical properties, size, surface charge, morphology, and sugar-coating critically affect cell uptake, biodistribution, and interaction with immune components[2]. GNPs surface engineering has been widely investigated using different approaches, and it resulted in the preparation of a wide range of multifunctional GNPs that have been proposed as vaccine prototypes[3]. In this context, the sugar-coating may enable a controlled modulation of the immune response by means of the targeting of specific receptors on immune cells[4]. Notably, the architecture and composition of GNPs must be carefully considered, as these properties ultimately dictate the resulting immunological outcome, enabling the rational design of nanoplatforms capable of directing immune responses toward either activation or suppression[2].
In this communication, by taking advantage of a cellulose nanocrystals/gold nanoparticle hybrid (see Figure below), recently developed by our group[5], we describe our efforts on the understanding of the effect of GNPs coating in the interaction with selected cells of the innate immune system. Particular emphasis is placed on selected saccharides that have been identified as specific ligands for lectin receptors[6,7]. Altogether our data, provide key preliminary insights into how GNPs shape, composition, and lectin-targeting capability collectively influence GNPs interactions with immune cells.

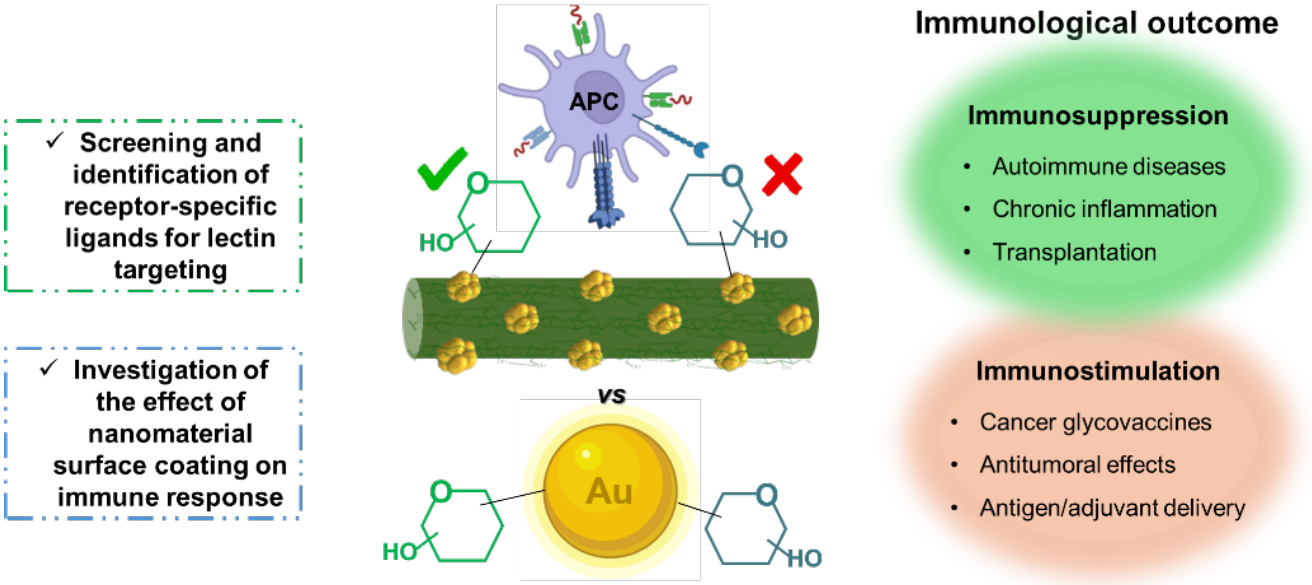


Figure 1

References:

[1] Strzelec M, […] Majka M, Immunomodulation - a general review of the current state-of-the-art and new therapeutic strategies for targeting the immune system. Front. Immunol. 2023; 14: 1127704.
[2] Ragini S, […] Daima HK, Engineered Nanomaterials for Immunomodulation: A Review, ACS Appl. Bio Mater. 2024; 7: 727–751.
[3] Anderluh M, […] Richichi B, Emerging glyco-based strategies to steer immune responses, FEBS J, 2021; 288: 4746-4772.
[4] Johannssen T, Lepenies B, Glycan-Based cell targeting to modulate immune responses, Trends Biotechn., 2017; 35: 334-346.
[5] Minucci, S., […] Richichi B, Multifunctional Hybrid Cellulose Nanocrystals-Gold Nanoplatform and Use Thereof in Medicine. WO/2023/233281, 2023.
[6] Pollastri S, […] Bernardi A, Glycomimetic ligands block the interaction of SARS-CoV-2 spike protein with C-type lectin co-receptors, Chem. Commun., 2022; 58: 5136-5139.
[7] Tricomi J, […] Richichi B, Stereoselective Synthesis of the Gal-α-(1→3)-Gal-β-(1→3)-GlcNAc Trisaccharide: a new Ligand for DCAR and Mincle C-Type Lectin Receptors, ChemBioChem, 2024; 25: e202400026.

Acknowledgment:

Project funded under the National Recovery and Resilience Plan (NRRP), funded by the European Union – NextGenerationEU – Project Title 20224LLK82 - **Glyconanomaterials as vaccine platforms for precision delivery of antigens to dendritic cells (Glyconanovacs)** – CUP B53D23015080006. Project funded under the Novo Nordisk Foundation, **A new type of vaccine for autoimmune disease**, Grant Agreement n°: NNF24OC0090036.

DNA as Drug Carrier: a Hydrophobic β-Cyclodextrin Channel in a Supramolecular Structure by Molecular Dynamics study

Giuseppina Raffaini

Department of Chemistry, Materials, and Chemical Engineering "Giulio Natta", Politecnico di Milano, Piazza L. Da Vin-ci 32, Milano, 20131, Italy

In recent years, DNA has garnered considerable attention as a promising biocompatible drug carrier, capable of enhancing bioavailability and minimizing adverse effects during the drug release process[1]. The solubilization of hydrophobic drugs with anti-inflammatory or cancer therapy properties by forming host–guest inclusion complexes with cyclodextrins (CDs) or CD-based polymers, is of great interest in pharmaceutical applications[2]. The adsorption of drugs and their carriers onto double-stranded DNA is potentially significant for their transport and release within cells, and β-cyclodextrins (βCDs) complexed with therapeutic compounds represent promising drug delivery sys-tems. However, the molecular mechanisms governing the formation and behavior of these supramolecular complexes on DNA structures remain poorly understood. Therefore, we employed molecular mechanics and molecular dynamics simulations at an atomistic level to examine the formation of inclusion complexes between βCDs and quercetin (an antioxidant fla-vonoid with anticancer properties), and their subsequent adsorption and self-aggregation on DNA structure. The adhesion process results from intermolecular interactions between the hydrophobic drugs included in βCD cavities, which create a uniquely ordered hydrophobic channel that wraps along the DNA grooves (Figure 1)[3]. This structure is further stabilized by hydrogen bonds between βCDs, forming a long-range ordered supramolecular structure over time, akin to a thread enveloping the DNA. This study provides insights into understanding supramolecular complexes involving DNA for potential drug delivery applications.

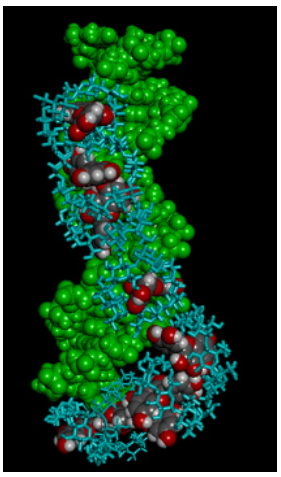


Figure 1. Twelve βCD/Quercetin inclusion complexes adsorbed on DNA structure.

References:

[1] Han, G.M.; Liu, B.; Kong, D.M.; Zhu, L.N. DNA as highly biocompatible carriers for drug delivery. Mater. Chem. Front. 2023, 7, 6345-6365.
[2] Tian, B.; Liu, Y.; Liu, J. Smart stimuli-responsive drug de-livery systems based on cyclodextrin: A review. Carbo-hydr. Polym. 2021, 251, 116871.
[3] G. Raffaini, Chem. Eur. J. 2026, https://doi.org/10.1002/chem.202502895.

Impact of phosphate position in the biocatalytic self-assembly of short carbohydrate amphiphiles

Iva Pashkuleva[1,2], Alexandra Brito[1,2], Ramon Novoa-Carballal[1-4], Manuel Martin-Pastor[5], Rui L. Reis1,2, Rein V. Ulijn[6-7], Ricardo A. Pires[1,2] and

13B's Research Group, I3Bs Research Institute on Biomaterials, Biodegradables and Biomimetics, University of Minho, Headquarters of the European Institute of Excellence on Tissue Engineering and Regenerative Medicine, AvePark, Parque de Ciência e Tecnologia, Zona Industrial da Gandra, 4805-017 Barco, Guimarães, Portugal; 2ICVS/3B's PT Government Associate Laboratory, Braga/ Guimarães, Portugal; 3CINBIO, Universidade de Vigo, Departamento de Química Orgánica, 36310, Vigo, Pontevedra, Spain; 4Instituto de Investigación Sanitaria Galicia Sur (IIS Galicia Sur), 36312, Vigo, Pontevedra, Spain; 5Unidad de Resonancia Magnética, RIAIDT, Universidad de Santiago de Compostela, Campus Sur, Santiago de Compostela, Spain;6, 7, 8 Advanced Science Research Center (ASRC) at the Graduate Center, City University of New York (CUNY), New York, New York 10031, United States; Department of Chemistry, Hunter College, City University of New York, New York, New York 10065, United States; Ph.D. Program in Chemistry and Ph.D. program in Biochemistry, The Graduate Center of the City University of New York, New York, New York 10016, United States.

Stereochemistry is used by living systems to code and transfer information indirectly beyond the simple sequence code[1, 2]. As an example, the pattern of chiral centers in monosaccharides dictates the macromolecular conformation and biological activity of glycopolymers[3-4] but the complex streoselective processes used to orchestrate these patterns and bioactivites are far from being understood. To probe this complexity, a reductionist strategy was used to study the enzymatically triggered self-assembly of amphiphiles derived from glucose-1-phosphate (Cori ester) and glucose-6-phosphate—two key regioisomers in glucose metabolism that follow distinct biochemical pathways.The precursors N-fluorenylmethyloxycarbonyl-glucosamine-1-phosphate (Fmoc-GlcN1P) and N-fluorenylmethyloxycarbonyl-glucosamine-6-phosphate (Fmoc-GlcN6P) were synthesized in a simple one-step reaction[5]. Fmoc-GlcN1P exhibited a stable anomeric equilibrium in either water or phosphate-buffered saline (PBS), with an α:β ratio of 60:40. By contrast, the anomeric ratio of Fmoc-GlcN6P was media dependent: α:β = 27:73 in water and 6:94 in PBS. Alkaline phosphatase (ALP, 50 U) catalyzed the dephosphorylation of both precursors, triggering their self-assembly. The process showed clear regioisomer-, concentration-, and media-dependent differences. At 5 mM in PBS, Fmoc-GlcN6P was dephosphorylated faster than Fmoc-GlcN1P, whereas both transformations proceeded more slowly in water. In PBS, Fmoc-GlcN6P assembled into well-defined right-handed helical fibers via a nucleation–elongation mechanism. In water, assembly followed a micelle-to-fiber transition, producing a mixture of helical and non-helical fibers. By contrast, Fmoc-GlcN1P consistently formed organized right-handed helical fibers under all conditions studied. The anomeric ratio remained unchanged in assemblies derived from Fmoc-GlcN1P but shifted toward ~50:50 for Fmoc-GlcN6P. At higher concentration (20 mM), both regioisomers formed long helical fibers radiating from nucleation centers. These findings highlight how subtle stereochemical differences, combined with enzymatic selectivity and environmental conditions, influence the encoding and transfer of stereochemical information in biocatalytic self-assembling systems.

References:

[1] Castro V.I.B., et al., Bioinspired helical systems with defined chirality assembled from discrete peptide and glycan amphiphiles, Chem Soc Rev, 2025. 54, 8325-8344.
[2] Brito, A., et al., Carbohydrate amphiphiles for supramolecular biomaterials: Design, self-assembly, and applications. Chem, 2021. 7(11):2943-2964.
[3] Ishaq, M.W., et al. Stereochemistry Drives the Macromolecular Conformation and Biological Activity of Glycopolymers. ACS Cent Sci, 2025. 11(9): 1573-1580.
[4] Castro, V.I.B., et al., Cooling rate uncovers epimer-dependent supramolecular organization of carbohydrate amphiphiles. J Mater Chem B, 2024. 12(29): 6996-7000.
[5] Pires, R.A., Controlling cancer cell fate using localized biocatalytic self-assembly of an aromatic carbohydrate amphiphile. JACS, 2015. 137(2): 576-579.

Imaging Intracellular Membrane Dynamics with Conjugated Oligoelectrolytes

Ji-Yu Zhu[1], Samuel J. W. Chan[1,2], Qijian Liang[1], Weiping Li[1], Claudio Bussi[1], Guillermo C. Bazan[1,2,3]

[1]Institute for Digital Molecular Analytics and Science, 59 Nanyang Drive, Singapore 636921, Singapore;
[2]Institute for Functional Intelligent Materials, National University of Singapore, 4 Science Drive 2, 117544, Singapore.

Optical imaging technologies have enabled the study of living systems by revealing otherwise invisible structures and molecular interactions. Cellular membranes are particularly informative targets because their composition and mechanical properties are regulated through homeostatic mechanisms and can reflect the physiological state of a cell and influence processes such as signaling, transport, and stress responses[1,2]. Conjugated oligoelectrolytes (COEs) are a molecular platform for developing lipid-bilayer-specific fluorogenic probes[3]. The hydrophobic chromophore promotes self-assembly within lipid bilayers in an ordered orientation, distinct from conventional membrane probes that rely on hydrophobic anchoring groups. Environmentally-sensitive COE molecules are capable of reporting changes in cellular membrane properties, including rapid variations in membrane tension and water permeability, as well as longer-term alterations in lipid composition[4,5]. Here, we demonstrate that COE probes enable the detection of changes in cellular states and the tracking of dynamic biological processes. Specifically, environmentally sensitive COEs allow imaging of dynamic changes in lysosomal membrane properties at the single-cell and single-vesicle levels. Variations in intracellular vesicle membrane properties can be leveraged to discriminate between cellular states and to visualize cellular responses to pharmacological treatment. More broadly, COEs offer opportunities for developing diagnostic tools and assays aimed at disease recognition and monitoring.

References:

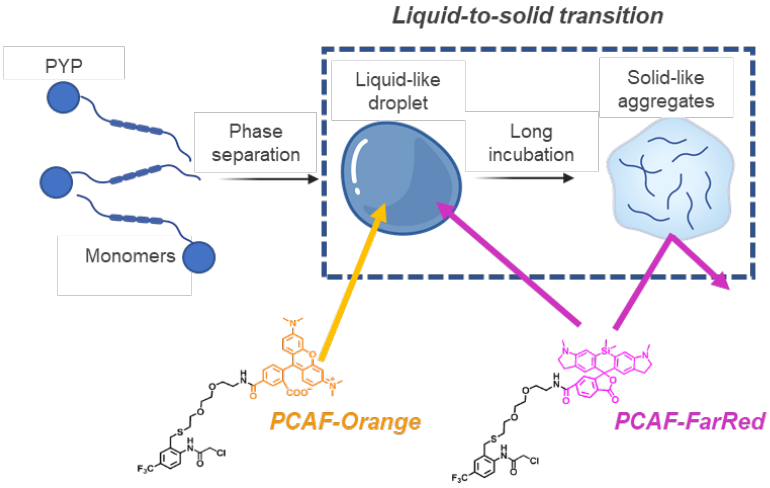
[1] Harayama, T., Riezman, H. *Nat. Rev. Mol. Cell Biol.*, 2018, 19, 281–296.
[2] Bussi, C.; Mangiarotti, A.; Vanhille-Campos, C.; Aylan, B.; Pellegrino, E.; Athanasiadi, N.; Fearns, A.; Rodgers, A.; Franzmann, T. M.; Šarić, A.; Dimova, R.; Gutierrez, M. G., *Nature* 2023**,** *623,* 7989, 1062-1069.
[3] C. Zhou, S. J. Cox-Vázquez, G. W. N. Chia, R. J. Vázquez, H. Y. Lai, S. J. W. Chan, J. Limwongyut, G. C. Bazan, *Sci. Adv.* 2023, 9, eade2996
[4] J.-Y. Zhu, S. J. W. Chan, H. Cui, A. A. Mikhalovsky, F. L. Garcia, B. Y. W. Goh, W. W. M. Soh, A. S. Moreland, J. Limwongyut, S. Shyamasundar, Y. J. Wu, F. Liang, R. Li, G. C. Bazan, *Angew. Chem. Int. Ed.* 2025, 64, e202506396
[5] S. J. W. Chan ,J.-Y. Zhu, B. R. P. Yip, S. Shyamasundar, G. C. Bazan. *Adv. Mater.*, 2024, 37, 2411329.

Live-Cell Monitoring of Liquid–Solid Transitions of Biomolecular Condensates

Motonari Uesugi

Institute for Chemical Research (ICR) and Institute for Integrated Cell-Material Sciences (WPI-iCeMS), Kyoto University, Japan

Biomolecular condensates, or so-called membraneless organelles, transition from liquid into more solid-like states over time, contributing to the development of pathological conditions. This presentation proposes a simple method using photoactive yellow protein (PYP) and its specific fluorescent covalent ligands to distinguish between the liquid and solid states of protein condensates in live cells. The method, compatible with fluorescence-activated cell sorting (FACS), correlates the stiffness of specific protein condensates with their accessibility to PYP ligands, enabling quantitative multicolor monitoring of condensate solidification. We applied this technique to 12 phase-separating proteins and their mutants, finding that TDP-43, particularly its A315T mutant linked to familial amyotrophic lateral sclerosis, most readily forms solid aggregates. Furthermore, this FACS-compatible strategy enabled the isolation of distinct cell populations based on condensate states, allowing for subsequent proteomic and transcriptomic analyses. Our findings demonstrate that condensate solidification is accompanied by the upregulated expression of extracellular matrix proteins, suggesting a previously unrecognized link between solid aggregate formation and extracellular matrix hardening.



References:

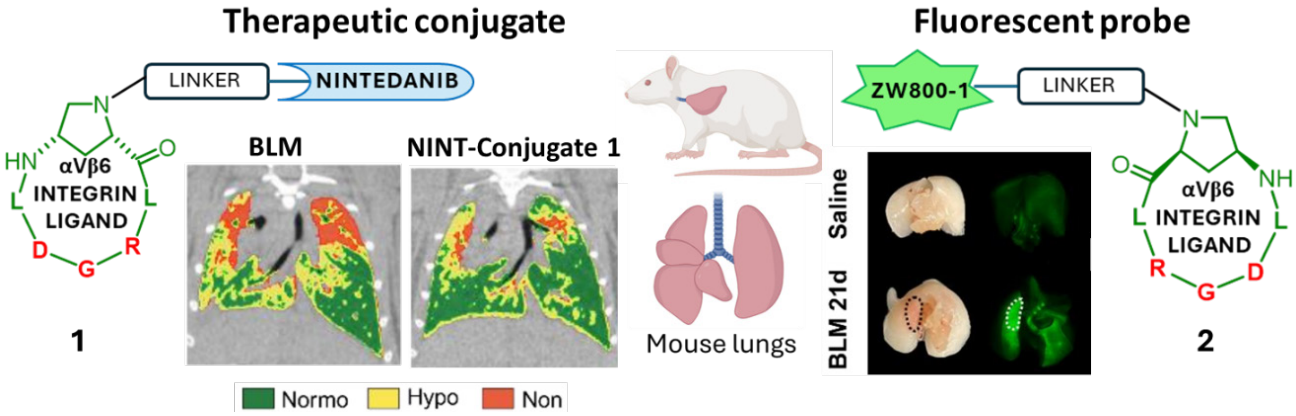
[1] Live-Cell Monitoring and Omics Analysis of Liquid-Solid Transitions of Biomolecular Condensates. Farrag, A., Ota, K., Yoshimura, H., Takemoto, M., Mitarai, T., Kamikawa, T., Abo, M., Singh, V., Cui, C., Zhou, L., Ishidate, F., Fujiwara, T., Sato, S., Hori, Y., Ozawa, T., Kikuchi, K., Uesugi, M. *J. Am. Chem. Soc.* **147**(41), 37056–37064 (2025).

Antifibrotic Efficacy of a Nintedanib–Peptide Conjugate Targeting αVβ6 Integrin in IPF

Andrea Sartori[1], Kelly Bugatti1, Erica Ferrini[2], Margherita Restori[1], Francesca Bianchini[3], Lucia Battistini[1], Monica Baiula[4], Francesca Civera[5], Laura Belvisi[5], Fabio Stellari[2], Franca Zanardi[1].

[1]Department of Food and Drug, University of Parma, P.co Area delle Scienze 27A, 43124 Parma, Italy;
[2]Experimental Pharmacology & Translational Science Department, Chiesi Farmaceutici S.p.A., Parma, Italy;
[3]Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy;
[4]Department of Pharmacy and Biotechnology, University of Bologna, 40126 Bologna, Italy;
[5]Department of Chemistry, University of Milan, 20133 Milan, Italy

Idiopathic Pulmonary Fibrosis (IPF) is a fibrotic lung disease in which the deposition of collagen within the pulmonary interstitium causes stiffness in the lungs and compromises the respiratory function. The decline is progressive and irreversible. Nintedanib, a tyrosine kinase inhibitor able to block the signaling of several growth factors receptors (GFRs), is one of three drugs nowadays approved as pharmacological treatment of IPF. The **α**V**β**6 integrin is overexpressed in fibrotic tissue and is the major activator of transforming growth factor-β (TGFβ), the principal pro-fibrotic mediator. This integrin is a clinically validated fibrosis biomarker, and several *αvβ*6-targeted small molecules and positron emission tomography (PET) tracers have recently proven their therapeutic and diagnostic potential in IPF[1].
Two molecular conjugates, a therapeutic conjugate **1** and a fluorescent probe **2** were developed, where a *αvβ*6-targeted cyclopeptide is covalently linked to either nintedanib or the near-infrared ZW800-1 fluorescent tag via robust linkers[2].



In vivo and *ex vivo* assessments of the antifibrotic efficacy of **1** and the diagnostic potential of **2** were carried out in a bleomycin (BLM)-induced lung fibrosis mouse model. Conjugate **1** demonstrated superior antifibrotic efficacy as compared to the separated peptide and drug components, and probe **2** specifically accumulated in the fibrotic lesions of mice lungs. The molecular conjugates **1** and **2** represent a promising theranostic couple for lung fibrosis and *αvβ*6-related pathologies.

References:

[1] Sofia C, Comes A, Sgalla G, Richeldi L. An update on emerging drugs for the treatment of idiopathic pulmonary fibrosis: a look towards 2023 and beyond. Expert Opin. Emerg. Drugs 2023; 28: 283-296.
[2] Bugatti K, Ferrini E, Restori M, Bonfini C, Marchese M et al. Antifibrotic Efficacy of a Nintedanib–Peptide Conjugate and Diagnostic Potential of a Fluorescent Companion Probe Targeting αVβ6 Integrin in Idiopathic Pulmonary Fibrosis. ACS Pharmacol.Transl.Sci. 2025; 8: 3613–3630.

Translating drug conjugate strategies to crop protection: glycoside hydrolase-cleavable linkers for controlled agrodrug release

Giulia Cazzaniga[1], Giusy L. Fratello[1], Samuele Bongiolo[1], Wolfgang Schulte[2], Josephine Mittendorf[2], Marc Linka[3], Francesco Talarico[1], Ralf Braun[2], Roberto Orru[2], Umberto Piarulli[1], David M. Barber[2], Silvia Gazzola[1].

[1]Department of Science and High Technology, University of Insubria, via Valleggio 9, 22100, Como, Italy;
[2]Research and Development, Weed Control, Crop Science Division, Bayer AG, Industriepark Höchst, Frankfurt am Main, Germany;
[3]Research and Development, Entomology, Bayer AG, Crop Science Division, Alfred-Nobel-Straße, Monheim, Germany.
Giulia.cazzaniga@uninsubria.it

The current demand for safer and more sustainable crop protection tools[1], calls for innovative approaches in agrochemistry. The conjugate-based pro-drug strategy represents a promising approach to address this challenge by combining principles of agrochemistry and medicinal chemistry; however, it has been only marginally explored[2]. A key component of these constructs is the chemical linker that covalently connects the bioactive agrochemical to a modulating moiety. Here we report the first study related to the application in crop protection of the concept of chemical cleavable linkers, designed to allow a chemical-controlled release of the free agrodrug under specific external *stimuli*. This first class of cleavable linkers features a monosaccharide as the cleavable moiety and a self-immolative spacer that bridges the trigger and the desired molecule, ensuring controlled and efficient release of the agrodrug. The endogenous activity of glycoside hydrolases (GHs) has been investigated as the triggered *stimulus* for the cleavage of the linker.
Following synthetic optimization, the resulting pro-agrodrugs were evaluated *in vivo* in plant systems and through *in vitro* assays using plant extracts, with advanced LC-MS analyses to monitor release processes and assess the mechanism. Biological assays were also conducted to verify the preservation of insecticidal activity upon release.
Overall, this study introduces a new chemical strategy for controlled agrodrug delivery, opening perspectives for more selective and sustainable crop protection technologies.

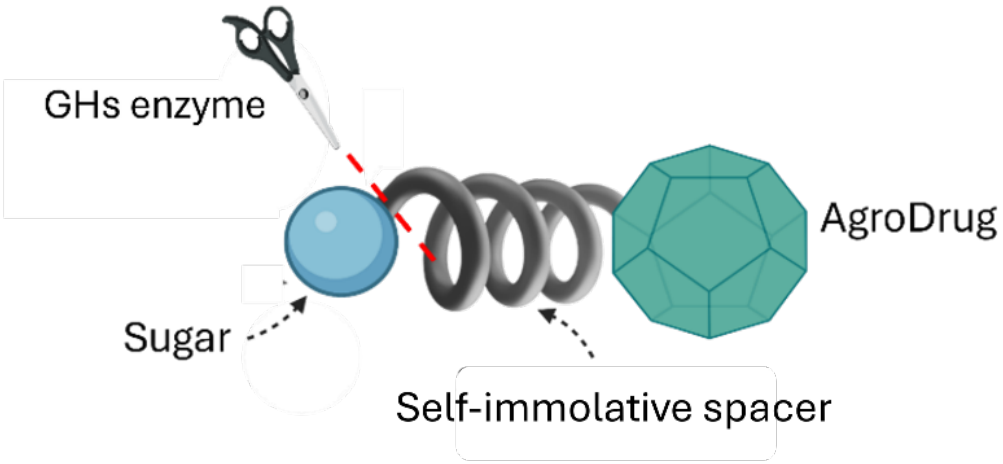


Figure 1. Schematic representation of a sugar-based cleavable pro-agrodrug.

References:

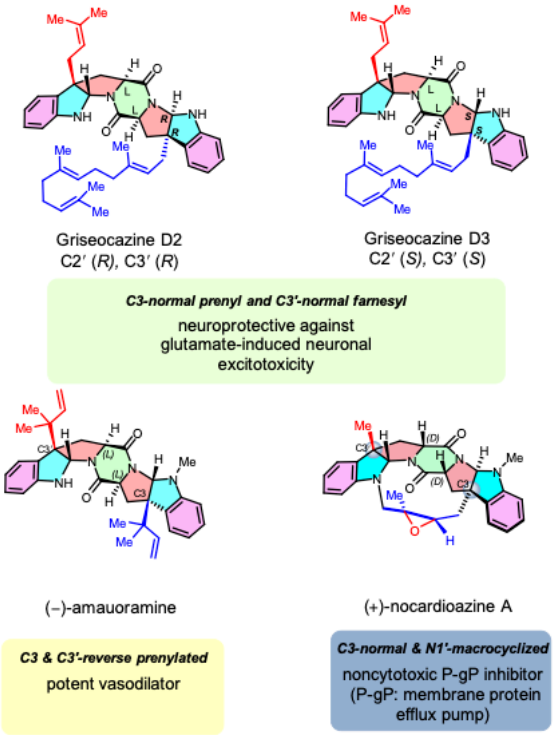
[1] European Commission: Directorate-General for Health and Food Safety, Reducing the risk and use of pesticides, Publications Office of the European Union, 2022.
[2] Cazzaniga, G.; Orru, R.; Barber, D. M.; Gazzola, S. *Top. Curr. Chem* **2025**, 384 (1).

Biomimetic Synthesis of Pyrroloindoline-DKPs Unveil Pro-Apoptotic P-gP Inhibitors with Minimal Cytoxicity

Rajesh Viswanathan, Sharada Sivaraman, Subhasish Pradhan, Kummari Nagaraju and Aharna Guin

Department of Chemistry, Indian Institute of Science Education Tirupati, Andhra Pradesh India

Development of non-cytotoxic inhibitors of the mammalian efflux pump (ABC transporters / P-gP) have been a long standing problem due to the innate flexibility of the Drug binding site evolved in these P-gPs. In human cancers however, three oncogenic marker pumps have been significantly upregulated depending on tissue subtype and aggression level of the cancers. ABCB1, ABCC2 and ABCG2 therefore presents themselves as targets for our mission on selective inhibition of these target pumps without causing cytotoxicity to normal cells. We have demonstrated through biosynthetic and biomimetic studies that one can cleverly place bioactive substituents on Pyrroloindoline-DKPs that cause them to be pro-apoptotic and thereby cause significantly enhanced chemosensitization of paclitaxel in HCT115 cells. Natural products shown below have inspired out synthesis and we developed exquisitely stereochemically complex DKPs in recent work.



References:

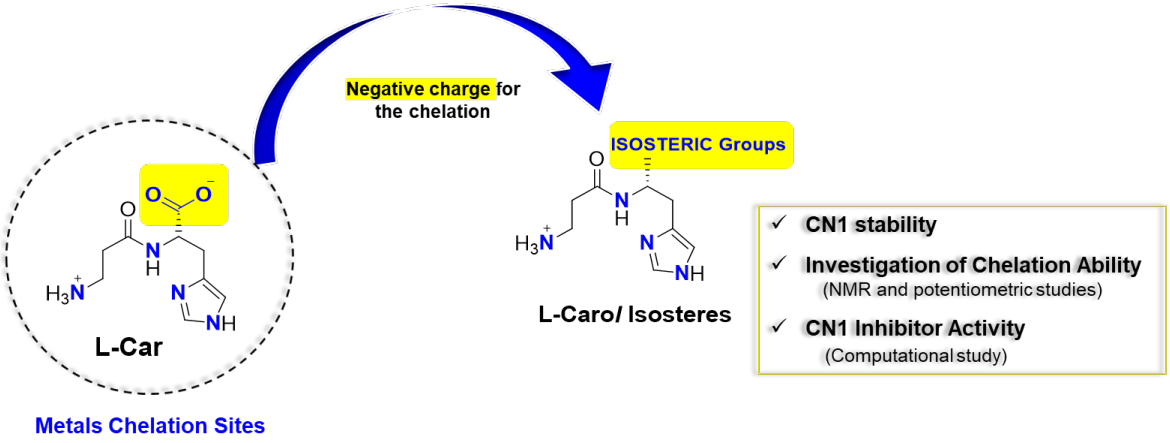
[1] Subhasish Pradhan and Rajesh Viswanathan*; Total synthesis of (−)-griseocazine D2 and D3 *Organic and Biomolecular Chem.* **2025**, *23, 5086-5090.*
[2] Dona Mariya Vincent, Habib Mostafa, Anza Suneer, Sabhashina Radha Krishnan, Mingmin Ong, Yoko Itahana, Koji Itahana, and **Rajesh Viswanathan*** Development of Natural Product-Inspired ABCB1 Inhibitors Through Regioselective Tryptophan C3-Benzylation, *Chem. Eur. J.* **2024**, *30, e202401782*.
[3] Koh, J.; Itahana, Y.; Krah, A.; Mostafa, H.; Ong, M. M.1, Iwamura, S.; Vincent, D. M.; Krishnan, S. R.; Ye, W.; Yim, P. W. C.; Khopade, T. K.; Chen, K.; Kong, P.S.; Wang, L-F.; Bates, R. W.; Kimura, Y.; **Viswanathan, Rajesh.***; Bond, P. J.*; Itahana, K.* Exploring bat-inspired cyclic tryptophan diketopiperazines as ABCB1 Inhibitors. *Commun Chem* ***7****, 158 (****2024****). https://doi.org/10.1038/s42004-024-01225-z.*
[4] Deletti, Swapnil Joshi, Tushar M. Khopade, Amy L. Lane* and **Rajesh Viswanathan*** *et al*. "Unveiling an indole alkaloid diketopiperazine biosynthetic pathway that features a unique stereoisomerase and multifunctional methyltransferase" *Nature Communications*, **2023**, *14*, 2558.
[5] Tushar M. Khopade, Kalyani Ajayan, Dona M. Vincent, Amy L. Lane and **Rajesh Viswanathan*** "Biomimetic Total Synthesis of (+)-Nocardioazine B and Analogs" *J. Org. Chem.*, **2022,** *87,* 11519-11533.

Targeting neurodegeneration with novel L-Carnosine mimics: insights into metal chelation and CN1 interaction[1]

Valeria Romanucci[1], Maria Petrone[1], Rita Pagano[1], Armando Zarrelli[1], Danilo Milardi[2], Francesco Bellia[3], Greta Petrella[4], Simona Cesaroni[4], Daniel Oscar Cicero[4], Sílvia Chaves[5], Giuseppe Giangreco[6], Amedeo Caflisch[6] and Giovanni Di Fabio[1]

[1]Department of Chemical Sciences, University of Naples Federico II, 80126 Napoli, Italy;
[2]Institute of Crystallography, CNR, 95126 Catania, Italy;
[3]Department of Biomedical and Biotechnological Sciences, University of Catania, 95123 Catania, Italy;
[4]Dipartimento di Scienze e Tecnologie Chimiche, Università di Roma "Tor Vergata", 00133 Rome, Italy;
[5]Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal;
[6]Department of Biochemistry, University of Zurich, Zurich CH-8057, Switzerland.

Alzheimer's Disease (AD) is a neurodegenerative syndrome that slowly destroys memory and thinking skills, resulting from the loss of brain cells and their connections[2]. The disorder is driven by multiple factors, including the buildup and aggregation of misfolded proteins and an imbalance of metal ions that may enhance oxidative stress, neuropeptide/protein aggregation and trigger neurotoxic and neuroinflammatory processes.
L-Car is a dipeptide widely distributed in mammalian tissues and serves as a potential drug candidate[3] for neurodegenerative diseases due to its radical scavenger, anti-inflammatory, and well-known zinc-chelating activities[4].



Unfortunately, the therapeutic potential of L-Car is limited by its low bioavailability, as it is rapidly degraded by serum carnosinase (CN1). This specific zinc dipeptidase hydrolyses L-Car into β-alanine and L-histidine by recognizing the carboxyl group[5]. To improve serum stability and metal chelation ability, we report the design and synthesis of new L-Car mimics characterised by different carboxylic isosteres (Figure). The synthetic approach is facilitated by the development of the L-Carnosinol (L-Caro*l*) synthon that can be readily synthesized from L-Car in a few steps. Strategic synthesis of a new L-Carnosinol-based scaffold significantly broadens the synthetic toolbox for the rational design of L-Car derivatives. Contrary to L-Car ($t_{1/2}$ = 5 min), all mimics are very stable at CN1. These data have been further explored by a computational approach aiming to characterize the binding between L-Car mimics and CN1. A further investigation of the biometal chelation capability of the novel mimics has been performed by combining different techniques, including NMR, potentiometric and UV-Vis titrations.

References:

[1] These studies were supported by AIPRAS ETS (http://www.aipras.org/).
[2] Knopman D. S., Amieva H., Petersen R. C., Chételat G., Holtzman D. M., Hyman B. T., Nixon R A., Jones D. T. Emerging Novel Therapeutic Approaches for the Treatment of Alzheimer's Disease. Nat. Rev. Dis. Primers 2021, 7: 33.
[3] Caruso G., Di Pietro G., Cardaci V., Maugeri S., Caraci F. The therapeutic potential of carnosine: Focus on cellular and molecular mechanisms. Curr Res Pharmacol Drug Discov. 2023, 4:100153–100163.
[4] Abate C., Aiello D., Giuffrè O., Foti C. Binding ability of L-carnosine towards Cu2+, Mn2+ and Zn2+ in aqueous solution. J. Mol Liq 2022, 368: 120772.
[5] Chmielewska K., Vittorio S., Gervasoni S., Dzierzbicka K., Inkielewicz-Stepniak I., Vistoli G. Human carnosinases: A brief history, medicinal relevance, and in silico analyses. Drug Discovery Today 2024, 29, 103860.

TMS-substituted Schiff base with four-ring heterocyclic scaffolds and its metal complexes: synthesis, characterization, and anticancer activity

Mihaela Dascalu[1], Alexandru Stoica[1], Maria Cazacu[1], Vladimir B. Arion[1,2]

[1]*"Petru Poni" Institute of Macromolecular Chemistry, Aleea Gr. Ghica Voda 41 A, Iasi 700487, Romania*
[2]*University of Vienna, Institute of Inorganic Chemistry, Währinger Strasse 42, 1090 Vienna, Austria*

Introduction of a trimethylsilyl (TMS) group into physiologically active scaffolds, as well as the isosteric replacement of carbon with silicon (*„carbon–silicon switch*") in pharmacologically relevant structures, including well-known drugs, may represent a promising strategy for the development of novel drug candidates.The 9-trimethylsilylindolo[2,3-c] quinoline-derived Schiff base (HLTMS) and its Cu(II) and Zn(II) complexes, Cu(HLTMS)Cl2 (**1**) and Zn(HLTMS)Cl2 (**2**), were synthesized and thoroughly characterized using elemental analysis, ESI mass spectrometry, single-crystal X-ray diffraction (SC-XRD) for **1**, spectroscopic techniques (UV-Vis, 1H and 13C NMR for HLTMS) for **2**, and electron diffraction (ED) for **2**.
The assembly of the Cu(II) complex significantly improved the antiproliferative activity, whereas the TMS group attachment made HLTMS more lipophilic. Both HLTMS and the Zn(II) complex **2** generated reactive oxygen species under cell-free conditions, consistent with their redox activity as determined by cyclic voltammetry. The cytotoxicity of HLTMS and its metal complexes may have been enhanced by mitochondrial dysfunction. With IC50 values primarily in the low micromolar range, these compounds demonstrated good antiproliferative activity in a spectrum of human cancer cells and disrupted the potential of the mitochondrial membrane.
Coupling the silylation with the addition of functional groups that increase the solubility of the proligand and its metal complexes, the potential of these compounds as photosensitizers in photodynamic therapy may be thoroughly investigated. These results demonstrate the potential of TMS-substituted Schiff bases as practical choices for the creation of anticancer medications.

Acknowledgements:

This work was financially supported by a grant from the Romanian National Authority for Research, project no. PNRR-III-C9-2023-I8-99 within the National Recovery and Resilience Plan.

References:

[1] Wittmann C, Besleaga I, Mahmoudi S, Palamarciuc O, Balan-Porcarasu M, Dascalu M, Shova S, Cazacu M, Kiricsi M, Igaz N, Dömötör O, Enyedy EA, Dvoranová D, Rapta P, Arion VB. Physical properties and cytotoxicity of Cu(II) and Zn(II) complexes with a TMS-substituted indolo[2,3-c]quinoline-derived Schiff base. Dalton Trans; 2025; 54: 7882-7898

Turning Biowaste to Resin: Lignin Recovery from Dried Fruit Shells and Synthesis of phenol- and formaldehyde-free bio-materials

Nunzio Cardullo[1], Claudia Sciacca[1], Beata Strzemiecka[2], Letizia Fusto[1], Miłosław Kozak[3], Vera Muccilli[1]

[1]Department of Chemical Sciences, University of Catania, V.le A. Doria 6, 95125, Catania, Italy.
[2]Institute of Chemical Technology and Engineering, Faculty of Chemical Technology, Poznań University of Technology Berdychowo 4 street, 61-131 Poznan, Poland.
[3]Institute of Powertrains and Aviation, Faculty of Civil and Transport Engineering, Poznań University of Technology, 60-965 Poznań, Poland

The development of novel eco-friendly materials, such as resins partially or fully based on biomass has become one of the main challenge in the sustainable development. Lignin, long dismissed as a low-value by-product, has attracted renewed scientific interest, with research into its valorization revealing significant potential for high-value applications in sustainable polymer synthesis[1]. Some examples of bioresins, where phenol was partially substituted by lignin[2] or tannins[3], have been developed. These biomaterials showed comparable or even better mechanical and thermal properties of phenol-based resins. This work aims at the total replacement of phenol with lignin recovered from agrifood biowaste, for the synthesis of more sustainable resol and novolac resins. Lignin was recovered with a green methodology based on the use of NADES combined with ultrasound extraction from dried fruits hard-shells waste. After the characterization, lignin was employed for resin synthesis in both acid and basic catalyzed processes with safer aldehydes than the cancerous formaldehyde. The analysis of ATR FT-IR highligheted the presence of bands for new brigdes among the phenolic structure of lignin and the aldehyde portion, suggesting the bio-based polimer was formed. The new materials obtained were also subjected to 2D-NMR, real time FT-IR with heating option, and TG analyses. In this work for the first time new bioresins were obtained by total substitution of phenol and formaldehyde hazard reagents with more sustainable ones. This work contributes to the development of new material as green alternative to the current resin globally employed.

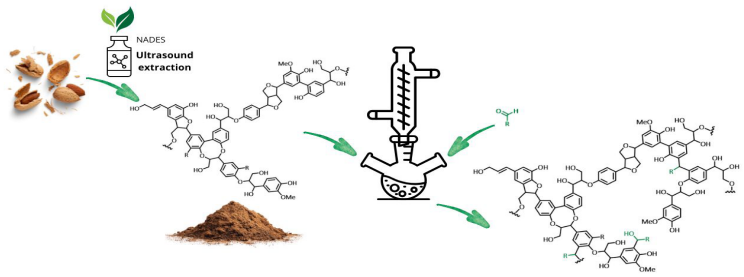


Figure: Schematization of the approach developed for the extraction and synthesis of new bio-based resins.

References:

[1] Bajwa DS, PourhashemG, Ullah AH, Bajwa SG. A concise review of current lignin production, applications, products and their environmental impact. Ind Crop Prod 2019; 139: 111526.
[2] Hu S, Chen X, Ni S, Wang Z, Fu Y, Qin M, Zhang Y. Formaldehyde-Free, High-Bonding Performance, Fully Lignin-Based Adhesive Cross-Linked by Glutaraldehyde. ACS Appl Pol ym Mater 2025; 7: 859-867.
[3] Garcia DE, Glasser WG, Pizzi A, Lacoste C, Laborie MP. Polyphenolic resins prepared with maritime pine bark tannin and bulky-aldehydes Ind Crop Prod 2014; 62: 84–93.

Design, synthesis, and biological evaluation of 1,2,4-oxadiazole salts and their derived functional materials

Sara Amata[1], Virginia Talarico[2], Cinzia Calà[2], Gaspare Crisà[1], Carla Rizzo[1], Silvestre Buscemi[1], Antonio Palumbo Piccionello[1].

[1]STEBICEF Department, University of Palermo, Viale delle Scienze Bld.17, I-90128 Palermo (Italy);
[2]Microbiology and Virology Unit, AOU Policlinico "P. Giaccone", 90127 Palermo, (Italy) .

The worldwide rise in antibacterial resistance is making commonly used antibiotics and traditional treatments increasingly ineffective, presenting a significant danger to contemporary healthcare[1]. This issue transcends particular clinical environments and signifies a systemic problem impacting domains such as surgery, oncology, and medical device implantation[2].
To this end,inspired by a prior study, a range of novel 1,2,4-oxadiazole pyridinium salts have been synthesized and characterized[3].
Initially, 37 substances were evaluated in vitro against the standard strains of Gram-positive *S. aureus* and Gram-negative *E. coli* using dilution and minimum inhibitory concentration (MIC) assays. Subsequently, the five most active salts were evaluated against multidrug-resistant bacteria (*K. pneumoniae, E. coli, S. aureus, S. haemolyticus,* and *E. faecium*). Furthermore, their cytotoxicity, haemolytic activity, and selectivity index have been assessed. Following the integration into PVC films and glycerol gels, disk diffusion assays and diffusion in aqueous solutions were conducted, revealing relevant antibacterial efficacy. This study constitutes a preliminary phase in the creation of potential antibacterial coatings for medical implants.

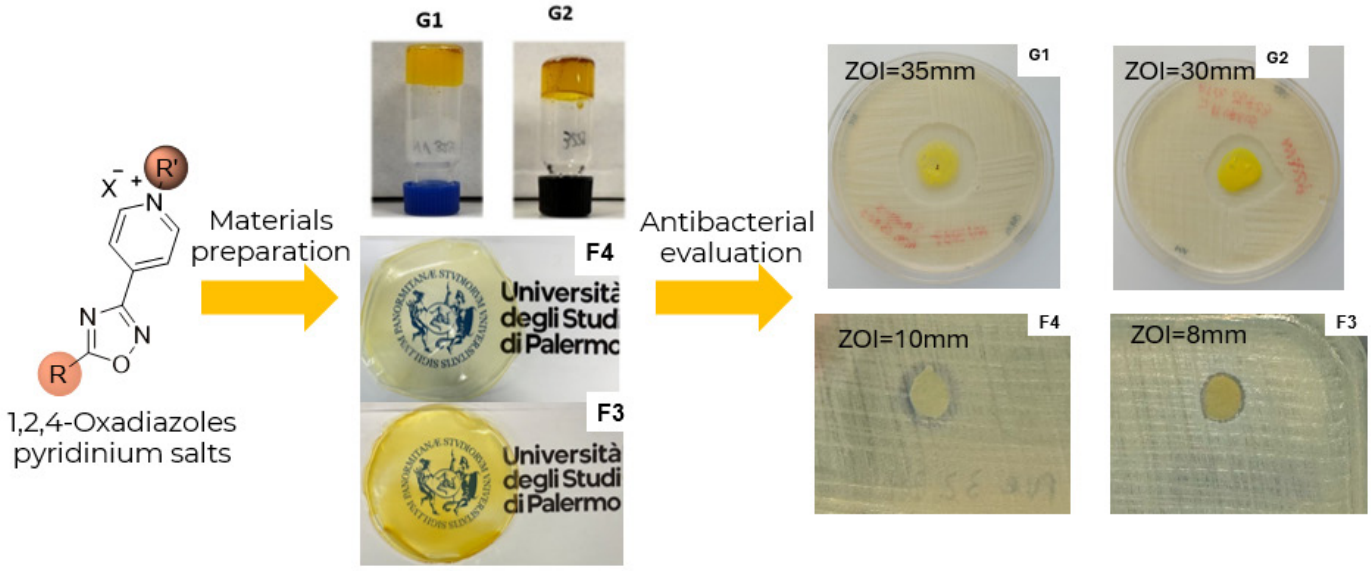


Figure 1. Antibacterial compounds general structure, derived gels and PVC films and disk diffusion test results.

References:

[1] U. Theuretzbacher, Global antibacterial resistance: The never-ending story, Journal of Global Antimicrobial Resistance, 2013, 1, 63-69.
[2] E. Avershina, V. Shapovalova, G. Shipulin,Fighting Antibiotic Resistance in Hospital-Acquired Infections: Current State and Emerging Technologies in Disease Prevention, Diagnostics and Therapy, Frontiers in Microbiology, 2021, 12.
[3] Amata S, Calà C, Rizzo C, Pibiri I, Pizzo M, Buscemi S, Palumbo Piccionello A. Synthesis and Antibacterial Activity of Mono- and Bi-Cationic Pyridinium 1,2,4-Oxadiazoles and Triazoles. International Journal of Molecular Sciences. 2023 Dec 27;25(1):377.

Light-Controlled Nucleic Acid Delivery with Azobenzene Janus Glycosides

José M. García Fernández[1], Zhaoxin Wang[2], Gonzalo Rivero-Barbarroja[3], Juan M. Benito[1], Stephanne Maisonneuve[2], Itziar Vélaz[4], Conchita Tros de Ilarduya[5], Juan Xie[2], Carmen Ortiz Mellet[3]

[1]Institute for Chemical Research, CSIC-University of Seville, Seville, Spain;
[2]Université Paris-Saclay, PPSM, CNRS, Gif-Sur-Yvette; France;
[3]Department of Organic Chemistry, Faculty of Chemistry, University of Seville, Seville, Spain;
[4]Department of Chemistry, School of Sciences, University of Navarra, Pamplona, Spain;
[5]Department of Pharmaceutical Sciences, School of Pharmacy and Nutrition, University of Navarra, Pamplona, Spain.

Therapeutic nucleic acids (NAs) are transforming modern medicine, but their clinical potential is still limited by the challenge of delivering them safely and selectively to target tissues. Addressing this barrier requires delivery systems that combine molecular precision with external control, enabling regulation of the timing and location of cargo release. While viral vectors offer high efficiency, concerns related to immunogenicity, possible genomic integration, and manufacturing complexity remain. Molecularly defined non-viral carriers that assemble dynamically with NAs to form nanoscale complexes represent a promising alternative, offering improved safety and greater design flexibility[1,2].
Here we report azobenzene-bridged ionizable amphiphilic Janus glycosides (IAJGs) as single-component, light-responsive carriers for NA delivery[3]. These glucopyranose-based dimers incorporate a photoswitchable azobenzene linker capable of reversible *E/Z* isomerization, while their amphiphilic ionizable structure enables stable nanocomplex formation with plasmid DNA (pDNA; Figure 1). Photoisomerization modulates key nanocomplex properties, including particle size, surface charge, and internal organization, which in turn influence transfection efficiency. In vitro studies revealed isomer-dependent transfection activity in COS-7, HepG2, and RAW264.7 cells, with particularly pronounced switching effects in macrophages. Importantly, all formulations exhibited high cell viability. In vivo experiments after systemic administration showed organ-selective (linver, lung or spleen) responses depending on the carrier photoisomer. These findings identify photoswitchable IAJGs as structurally defined vectors enabling light-regulated NA delivery and tunable tissue targeting. The authors ackowledge funding from MICIU / AEI / EDRF (PID2022-141034OB-C21, PID2024-157753OB-C21 and PID2024-157753OB-C22) and the EU HE program (MSCA-SE 101130235 – Bicyclos).

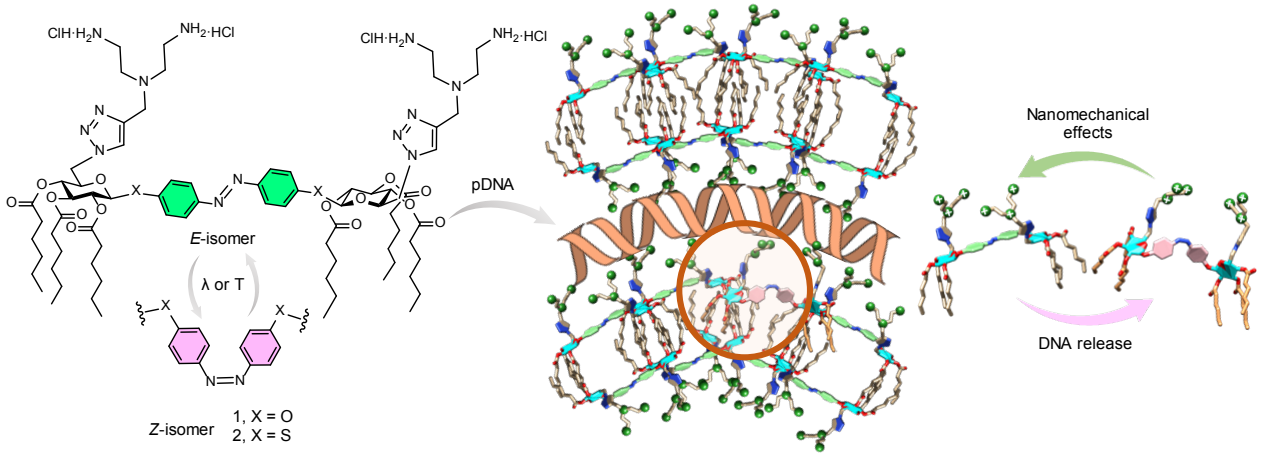


Figure 1. Representative photoswitchable ionizable amphiphilic Janus glycosides (IAJGs) and their mode of action.

References:

[1] Zhang D., Atochina-Vasserman EN, Maurya DS, Huang N, Qi Xiao Q, Ona N, Liu M, Shahnawaz H, Ni H, Kim K, Billingsley BM, Pochan DJ, Mitchell MJ, Weissman D, Percec V. One-component multifunctional sequence-defined ionizable amphiphilic Janus dendrimer delivery systems for mRNA. J. Am. Chem. Soc. 2021; 143: 12315-12327.
[2] Rivero-Barbarroja G **López-Fernández J,** Juárez-Gonzálvez I, Fernández-Clavero C, Di Giorgio C., Vélaz I, Garrido MJ, Ortiz Mellet C, Mendicuti F, Tros de Ilarduya C, García Fernández JM. **β**-Cyclodextrin-based geometrically frustrated amphiphiles as one-component, cell-specific and organ-specific nucleic acid delivery systems. Carbohydr. Polym. 2025; 347: 122776.
[3] Wang Z, Rivero-Barbarroja G,.Benito JM, Maisonneuve S, Vélaz I, Juárez-Gonzálvez I, Garrido MJ, Tros de Ilarduya C, Ortiz Mellet C, Xie J, García Fernández JM. Azobenzene-bridged ionizable amphiphilic Janus glycosides for lightcontrolled, single-component and organ-modulable pDNA delivery. Commun Chem. 2026; 9: 118.

Hybrid Nanoparticle–Ionic Drug Systems as a Platform for Enhanced Therapeutics

Luis C. Branco[a], L. Filipe[a], F. Faisca[a], D. Silva[a], S. Gago[a], S. Costa-Lima[b], D. Mavridou[c], R. Donnelly[d]

[a]*LAQV-REQUIMTE, Dept of Chemistry, NOVA School of Science and Technology, NOVA University of Lisbon, Campus de Caparica, 2829-516 Caparica, Portugal;*
[b]*LAQV-REQUIMTE, ICBAS - School of Medicine and Biomedical Sciences, University of Porto, 4050-313 Porto, Portugal;*
[c]*Dept. of Molecular Biosciences, College of Natural Sciences University of Texas at Austin, USA;*
[d]*School of Pharmacy, Queen's University Belfast, Medical Biology Centre, Belfast, UK.*

Over the past decade, ionic drug formulations have emerged as a powerful strategy to improve the physicochemical and therapeutic properties of active pharmaceutical ingredients (APIs)[1]. By combining ionizable drugs with biocompatible organic counter-ions, these systems can significantly enhance solubility, permeability, and stability, while simultaneously reducing polymorphism-related limitations that often compromise drug performance. Such approaches offer new opportunities to optimize existing drugs and expand their pharmaceutical potential.
Our research group has developed a series of pharmaceutical ionic systems based on antibiotic, antitumoral, and antituberculostatic drugs, demonstrating clear improvements in key pharmacological and physicochemical properties when compared with their parent APIs[2–5]. These results highlight the versatility of ionic drug formulations as a platform for the development of improved therapeutic agents.
In this work, we report recent advances in the design of nanostructured ionic drug formulations, focusing on the development of silica and lipid nanoparticle-based delivery systems incorporating ionic drug salts[4,5]. These hybrid nanomaterials combine the tunable properties of ionic drug formulations with the delivery capabilities of nanoparticle carriers, enabling improved stability, controlled release, and enhanced biological performance.
Biological evaluation revealed promising antibacterial and antitumoral activities, highlighting the potential of this strategy to extend the applicability of a wide range of drugs and to develop innovative therapeutic platforms. Overall, this approach provides a versatile route for designing next-generation nanoparticle-based pharmaceutical systems, with particular relevance for addressing the growing challenge of drug resistance.

Acknowledgements:

This work was supported by the InsectERA – Novo sector bioindustrial Project (nºC644917393-00000032), co-financed by PRR - Recovery and Resilience Plan of the European Union (Next Generation EU). The authors also thank the support from FCT/MCTES (UIDB/50006/2020, LA/P/0008/2020 and UIDP/50006/2020 of the Associate Laboratory for Green Chemistry – LAQV).

References:

[1] Shamshina, JL; Rogers, RD Chem. Rev. 2023, 123, 11894.
[2] Teixeira, S; Santos, MM; Branco, LC; Costa-Rodrigues, J; Int. J. Pharm. 2021, 610, 121262.
[3] Martins, ICB; Forte, A; Diogo, HP; Raposo, LR; Baptista, PV; Fernandes, AR; Branco, LC; Duarte, MT Chemistry Methods 2022, 2, e202100104.
[4] Silva, D; Cordeiro, S; Baptista, PV; Fernandes, AR; Branco, LC; RSC Med. Chem., 2025, 16, 3593.
[5] Faísca, F; Santos, AFM; Ferreira, M; Gameiro, P; Lima, SAC; Branco, LC; Mol. Pharmaceutics 2025, 22, 5361.

Kuquinones derivatives as new potent mTorc1 inhibitors

Silvia Pezzola[1], Alessio Bocedi[1], Enrico Desideri[2], Federica Sabuzi[1], Mariano Venanzi[1], Pierluca Galloni[1]

[1]University of Rome "Tor Vergata", via della Ricerca Scientifica snc 00133, Roma;
[2]University of Rome "Link Campus", via del Casale di Pio V, 00165 Roma.

Kuquinone[1] derivatives (KuQs), such as 1-ethyl-KuQ[1] and 1-methyl-KuQ[2], are well-known for their photocatalytic properties[3]. Cell viability assays demonstrated that KuQs can reduce the 50% of cancer cells growth (IC50) at a concentration in the mM range, that is considerably high[1-2], despite their negligible toxicity against fibroblast[1-2]. In addition, their ability to inhibit Topoisomerase I *in vitro* is also in the mM range[4]. However, major limitations of KuQs are: *i)* the very scarce solubility, and *ii)* the biological activity in the mM range. To overcome these issues, tailored compounds were designed, ameliorating KuQ core with polar groups inspired by Nature, such as the polyphenols family. *In silico* techniques, ranging from quantum-mechanics (QM) to molecular dynamics (MD), were exploited to predict the key properties of these compounds, such as partition coefficient (LogP), absorption distribution metabolism and excretion (ADME), and Lipinsky rules of five. Among the possible biological targets that can be addressed, mTorc1 was selected as the most eligible one, because it is involved in a wide range of cellular regulations, ranging from healthy to pathological condition[5]. Hence, docking studies were performed on mTorc1 comparing the activity of KuQs derivatives to rifampicin – the well-established mTorc1 inhibitor[5]. Results demonstrated that KuQs have a higher docking score and stability within the active site (DGKuQ=-10.8 vs DGrifampicin=-9.2 kcal/mol) with respect to rifampicin. Finally, cellular toxicity and mTorc1 effectors pathway were assessed on hepato-cancer cells, (Hep3B and HuH7), trough cell-viability and western-blot experiments.

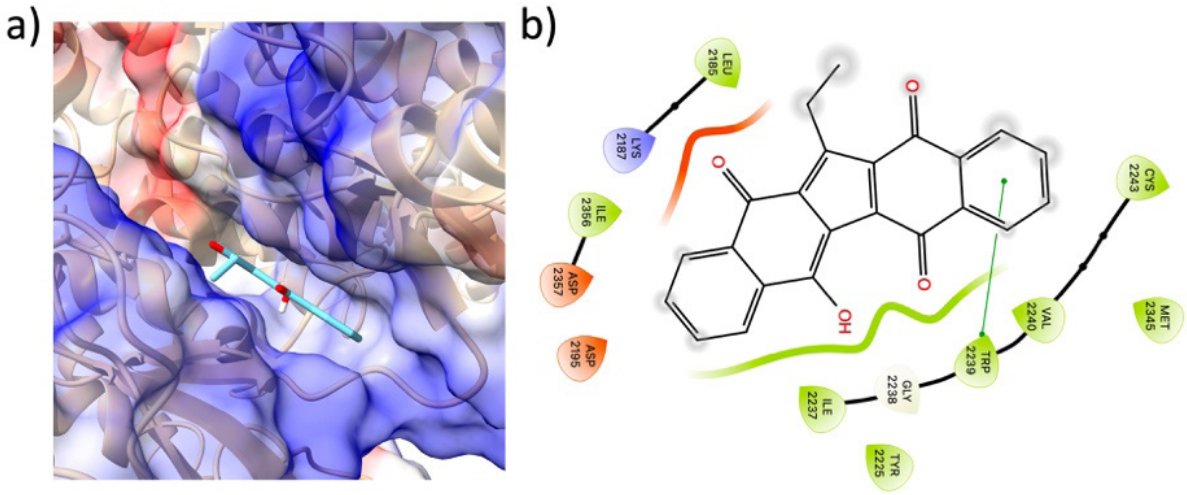


Figure 1. Panel a: docked image of KuQ in the mTorc1 hydrophobic pocket. Panel b: two-dimensional diagram of the interactions between the ligand and the amino acid residues within the active site.

References:

[1] Coletti A, Lentini S, Conte V, Floris B, Bortolini O, Sforza F, Grepioni F, Galloni P. Unexpected one-pot synthesis of highly conjugated pentacyclic diquinoid compounds. J. Org. Chem. 2012; 77: 6873-6879.
[2] Sabuzi F, Lentini S, Sforza F, Pezzola S, Fratelli S, Bortolini O, Floris B, Conte V, Galloni P. KuQuinones Equilibria Assessment for Biomedical Applications. J. Org. Chem. 2012; 82: 10129−10138.
[3] Forchetta M, Sabuzi F, Stella L, Conte V, Galloni P. KuQuinone as a Highly Stable and Reusable Organic Photocatalyst in Selective Oxidation of Thioethers to Sulfoxides. J. Org. Chem. 2022; 87: 14016-14025.
[4] Arno B, Coletta A, Tesauro C, Zuccaro L, Fiorani P, Lentini S, Galloni P, Conte V, Floris B, Desideri A. A small organic compound enhances the religation reaction of human topoisomerase I and identifies crucial elements for the religation mechanism. Biosci. Rep. 2013; 33: e00025.
[5] Xu W, Lin Z, Cortez-Jugo C, Qiao G G, Caruso F. Antimicrobial Phenolic Materials: From Assembly to Function. Angew. Chem. Int. Ed. 2025; 64: e202423654.

Topology-gated CRISPR–Cas12a platform for real-time monitoring of topoisomerase activity and drug evaluation

Neda Bagheri[1], Rosanna Mattossovich[2], Rosa Merlo[2], Anna Valenti[2], Alessandro Porchetta[1]

[1]Department of Chemical Science and Technologies, University of Rome, Tor Vergata, Via della Ricerca Scientifica 1, 00133 Rome, Italy;
[2]Institute of Biosciences and BioResources, National Research Council of Italy, Via Pietro Castellino 111, 80131 Naples, Italy

DNA topology is dynamically altered during essential cellular processes, leading to the accumulation of torsional stress that can compromise genome stability if not properly resolved. Topoisomerases counteract this stress by transiently cleaving and rejoining DNA strands, thereby maintaining proper DNA function. Dysregulation of these enzymes is frequently associated with human cancers, highlighting their importance as therapeutic targets[1]. However, real-time monitoring of topoisomerase activity remains a significant challenge.
We present a CRISPR–Cas12a-based platform[2,3] in which DNA supercoiling functions as a molecular switch to convert topoisomerase activity into a CRISPR-based signal transduction (Figure 1). Positive supercoiled DNA constructs are designed so that topoisomerase-mediated relaxation triggers CRISRP-Cas12a activation, producing an amplified fluorescent readout via collateral cleavage of the reporter molecules. This mechanism converts subtle changes in DNA topology into a direct, real-time signal. By testing inhibitors of both human and bacterial topoisomerases, we demonstrate that the platform reliably detects drug-induced modulation of enzyme activity, validating its potential for evaluating diverse classes of therapeutics.
Overall, this system establishes DNA topology as a readable molecular signal and provides a versatile tool for studying topoisomerase function, real-time enzymatic monitoring, and anticancer and antibacterial drug discovery.

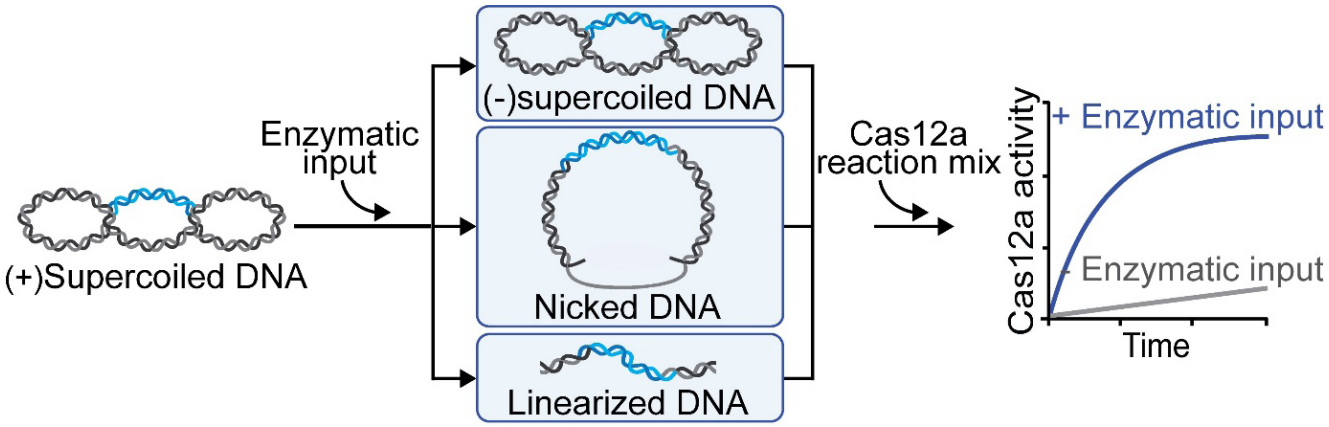


Figure 1. Enzyme-driven reconfiguration of DNA topology. Positively supercoiled plasmid DNA is converted to relaxed or linearized forms by topoisomerases resulting in restoration of Cas12a activity and signal generation.

References:

[1] Yakkala P A, Penumallu N A, Shafi S, Kamal A. Prospects of topoisomerase inhibitors as promising anti-cancer agents. Pharmaceuticals 2013; 16: 1456.
[2] Del Giovane S, Bagheri N, Di Pede A C, Chamorro A, Ranallo S, Migliorelli D, Burr L, Paoletti S, Altug H, Porchetta A. TrAC, Trends Anal. Chem. 2024; 172: 117594.
[3] Bagheri N; Bertucci A; Merlo R; Porchetta A. Synthetic DNA Transducers Integrate DNA Repair to CRISPR Signal Transduction. ACS Sens. 2026;11: 1634–1644.

Exploring the transition from physicochemical characteristics to the application of fluorinated *Janus*-type dendrimers in gene delivery

Marta Rosati[1], Lorenzo Fumagalli[1], Beatrice Lucia Bona[1], Nina Bono[2], Stefania Marcuzzo[3], Gabriele Candiani[2], Giuseppe Lauria Pinter[3], Gabriella Cavallo[1], Pierangelo Metrangolo[1], Francesca Baldelli Bombelli[1].

[1]*Department of Chemistry, Materials, and Chemical Engineering "Giulio Natta", Politecnico di Milano, Via Bassini 6, 20131 Milan, Italy;*
[2]*Department of Chemistry, Materials, and Chemical Engineering "Giulio Natta", Politecnico di Milano, Via Bassini 6 20131 Milan, Italy;*
[3]*Neuroimmunolgy and Neuromuscular Diseases Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, 20133 Milan, Italy*
e-mail: marta.rosati@polimi.it
website: www.suprabionano.eu

Janus-type dendrimers (JDs) are dendritic macromolecules bearing two domains of different polarity. A tailored balance between the two portions allows to control their physico-chemical properties, and therefore their function[1]. The use of fluorinated chains is a powerful tool to increase JDs colloidal stability and influence their self-assembling properties[2]. Moreover, the use of branched fluorinated moieties can be exploited for non-invasive in vivo monitoring by 19F-MRI to develop new theragnostic systems[3, 4].
Here, we show how the balance between a perfluoro-tert-butyl moiety and polyester dendrons of generations 1-3 can strongly affect self-assembling behavior of a family of Fluorinated JDs (FJDs)[3], see Figure 1, and how the final physico-chemical properties can be exploited to synthesize an ionizable fluorinated JD for gene delivery applications[4].

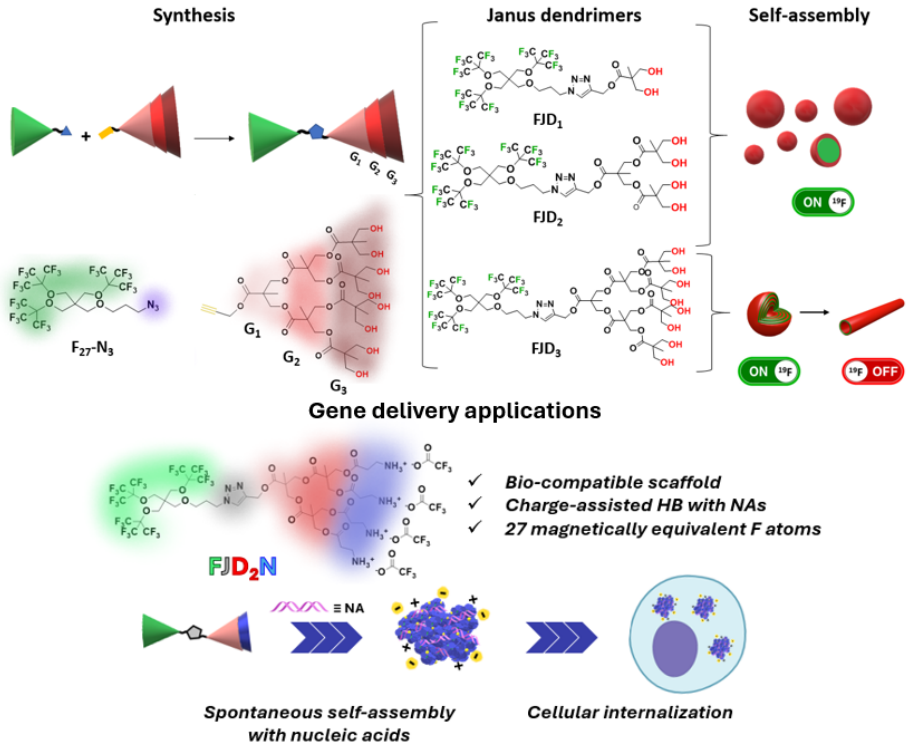


Figure 1. Self-assembling tendency of the three fluorinated JDs (Gen. 1 to 3) and their application as gene delivery vector.

References:

[1] Astruc D, Boisselier E, Ornelas C. Dendrimers Designed for Functions: From Physical, Photophysical, and Supramolecular Properties to Applications in Sensing, Catalysis, Molecular Electronics, Photonics, and Nanomedicine. Chem. Rev. 2010; 110: 1857-1959
[2] Wang M, Liu H, Li V, Cheng Y. A fluorinated dendrimer achieves excellent gene transfection efficacy at extremely low nitrogen to phosphorus ratios. Nat. Commun. 2014; 5: 1–8
[3] Rosati M, Acocella A., Pizzi A, Turtù G, Neri G, Demitri N, Nonappa, Raffaini G, Donnio B, Zerbetto F, Baldelli Bombelli F, Cavallo G, Metrangolo P. Janus-Type Dendrimers Based on Highly Branched Fluorinated Chains with Tunable Self-Assembly and 19F Nuclear Magnetic Resonance Properties. Macromolecules 2022; 55: 2486–2496
[4] Rosati M, Bono N, Fumagalli L. Sebastiani F, Bona BL, Chaves A, Mahmoudi N, Raffaini G, Cavallo G, Iacomino N, Malacarne C, Chirizzi C, Marcuzzo S, Lauria Pinter G, Candiani G, Metrangolo P, Baldelli Bombelli F. A fluorinated Janus-type dendrimer as ionizable one-component nanocarrier for nucleic acids. Nanoscale 2025; 17: 25266-25280.

Beyond Sucrose: Expanding the Chemical Space of Sugarcane-Derived Natural Products through Metabolomic Profiling of Muscovado Sugar

Jonel P. Saludes[1,2,3], Nicole M. Garcia[1,2], Karl Angelo G. Capungan[1,2], Shaira Mae D. Valero[2], Roxzien Shaye G. Sesbreño[4], Mark V. Rosales[4], Hazel Lynn C. Maganto[4], Jhoanna P. Bolencis[4], Naomi Cossette R. Luis[4], Doralyn S. Dalisay[1,5,6].

[1]Kasanggang NICER in Functional Food Excellence (KNIF2E) Laboratory, University of San Agustin, Iloilo City, Philippines;
[2]Center for Natural Drug Discovery and Development (CND3), University of San Agustin, Iloilo City, Philippines;
[3]Department of Chemistry, University of San Agustin, Iloilo City, Philippines;
[4]Department of Science and Technology (DOST) Region VI, La Paz, Iloilo City, Philippines;
[5]Center for Chemical Biology and Biotechnology (C2B2), University of San Agustin, Iloilo City, Philippines;
[6]Department of Biology, University of San Agustin, Iloilo City, Philippines.

Minimally processed cane sugars such as muscovado retain molasses-derived secondary metabolites that are largely removed during conventional white sugar refining. Despite growing interest in muscovado as a functional sweetener, the small-molecule composition of this traditional cane product remains insufficiently characterized from a bioorganic perspective. In this study, a metabolomics-guided analytical workflow was employed to investigate the chemical diversity of Philippine artisanal muscovado sugar.

Untargeted metabolite profiling using liquid chromatography–high-resolution mass spectrometry (LC–HRMS) revealed a structurally diverse set of plant-derived metabolites. Molecular annotation indicated the presence of multiple phenolic acids and flavonoid derivatives, representing key classes of redox-active natural products. Among the metabolites consistently detected across samples were chlorogenic acid, syringic acid, ferulic acid, caffeic acid, and vanillic acid. These phenolic scaffolds are widely reported to exhibit antioxidant, anti-inflammatory, antibacterial, and antihyperglycemic activities, underscoring their potential contribution to the biological properties of muscovado. In addition, several flavonoid-derived metabolites, including schaftoside, swertisin, tricin-7-glucoside, orientin, and kaempferol-related derivatives, were putatively identified, representing structurally diverse flavonoid frameworks known for their redox-modulating and anti-inflammatory bioactivities.

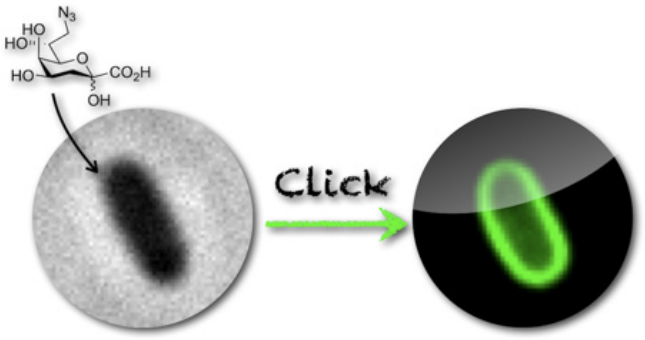
Complementary gas chromatography–mass spectrometry (GC–MS) analysis identified 18 volatile metabolites, including furans, pyranones, pyrazines, and pyrroles, which are heterocyclic compounds generated through Maillard reactions during thermal concentration of sugarcane juice. These findings reveal that artisanal muscovado sugar contains a chemically diverse repertoire of phenolic and heterocyclic small molecules, highlighting minimally processed cane sugar as an underexplored reservoir of structurally diverse bioactive metabolites within the broader chemical space of natural products.

Chemical biology for the detection of pathogens and reactive oxygen species

Boris Vauzeilles

Chemical Biology Department, ICSN, CNRS UPR 2301, Université Paris-Saclay, 91198 Gif-sur-Yvette, France.

The development and application of synthetic tools to explore biological processes, as well as the use of biological systems as a source of inspiration for the design of molecular devices, are the main focus of our research.
This lecture will present a selection of some of our work in this area, which involve the development of new labeling strategies for the detection and identification of live bacteria[1], including *Legionella pneumophila*, a serious pathogen responsible for Legionnaires' disease, as well as the design and evaluation of new, fast-reactive hydrogen peroxide-sensitive borinate triggers for the elaboration of probes for the detection of reactive oxygen species[2].



References:

[1] Dumont, A.; Malleron, A.; Awwad, M.; Dukan, S.; Vauzeille B. *Angew. Chem. Int. Ed.* **2012**, *51*, 3143-3146; Mas Pons, J.; Dumont, A.; Sautejeau, G.; Fugier, E.; Baron, A.; Dukan, S.; Vauzeilles, B.*Angew. Chem. Int. Ed.* **2014**, *53*, 1275-1278; Fugier, E.; Dumont, A.; Malleron, A.; Poquet, E.; Mas Pons, J.; Baron, A.; Vauzeilles, B.; Dukan, S. *PLoS ONE* **2015**, 10(6): e0127700; Cabriel, C.; Bourg, N.; Jouchet, P.; Dupuis, G.; Leterrier, C.; Baron, A.; Badet-Denisot, M.-A.; Vauzeilles, B.; Fort, E.; Lévêque-Fort, S. *Nature Commun.* **2019**, 10:1980 | https://doi.org/10.1038/s41467-019-09901-8 ; Lesur, E.; Baron, A.; Dietrich, C.; Buchotte, M.; Doisneau, G.; Urban, D.; Beau, J.-M.; Bayan, N.; Vauzeilles, B.; Guianvarc'h, D.; Bourdreux, Y. *Chem Commun.* **2019**, DOI: 10.1039/C9CC05754D; Carlier, M.; Lesur, E.; Baron, A.; Lemétais, A.; Guitot, K.; Roupnel, L.; Dietrich, C.; Doisneau, G.; Urban, D.; Bayan, N.; Beau, J.-M.; Guianvarc'h, D., Vauzeilles, B., Bourdreux, Y. *Org. Biomol. Chem.* **2022**, *20*, 1974–1981.
[2] Gatin-Fraudet, B.; Ottenwelter, R.; Le Saux, T.; Norsikian, S.; Pucher, M.; Lombès, T.; Baron, A.; Durand, P.; Doisneau, G.; Bourdreux, Y.; Iorga, B. I.; Erard, M., Jullien, L.; Guianvarc'h, D.; Urban, D.; Vauzeilles, B. *Proc. Natl. Acad. Sci.* **2021**, *118*, e2107503118; Gatin-Fraudet, B.; Pucher, M.; Le Saux, T.; Doisneau, G., Bourdreux, Y.; Jullien, L.; Vauzeilles, B.; Guianvarc'h, D.; Urban, D. *Chemistry – A European Journal* **2022**, *28,* e202201543; Pucher, M. ; Makenthirathasan, K.; Jalaber, H.; Le Saux, T.; Nüsse, O.; Doisneau, G.; Bourdreux, Y.; Gatin-Fraudet, B.; Jullien, L.; Vauzeilles, B.; Guianvarc'h, D.; Erard, M.; Urban, D. *ACS Chem. Biol.* **2025**, *20*, 7, 1574–1583.

Spatially resolved mapping of subcellular proteome with immuno proximity labeling

Peng Zou

College of Chemistry and Molecular Engineering, Peking University, Beijing, China.

Defining the molecular composition of specialized subcellular domains remains challenging, particularly when genetic manipulation or protein overexpression perturbs native organization. We present an immuno-proximity labeling strategy that uses antibody targeting to localize peroxidase catalysis to endogenous proteins, enabling proximity-dependent biotinylation in fixed and permeabilized cells without genetic fusion. By combining antibody-guided horseradish peroxidase with optimized phenol-based radical precursors, this approach affords a labeling radius on the hundreds-of-nanometers scale, allowing capture of membrane-associated, extracellular, and cytoskeletal proteins beyond the reach of short-range ligase-based methods. Using the neuronal axon initial segment as an example, immuno-proximity labeling enables proteomic mapping of a highly specialized subcellular domain defined solely by endogenous markers[1]. Because spatial targeting is encoded chemically by antibody selection, this platform is broadly adaptable to diverse cellular structures and experimental contexts, expanding the scope of in situ spatial proteomics.

References:

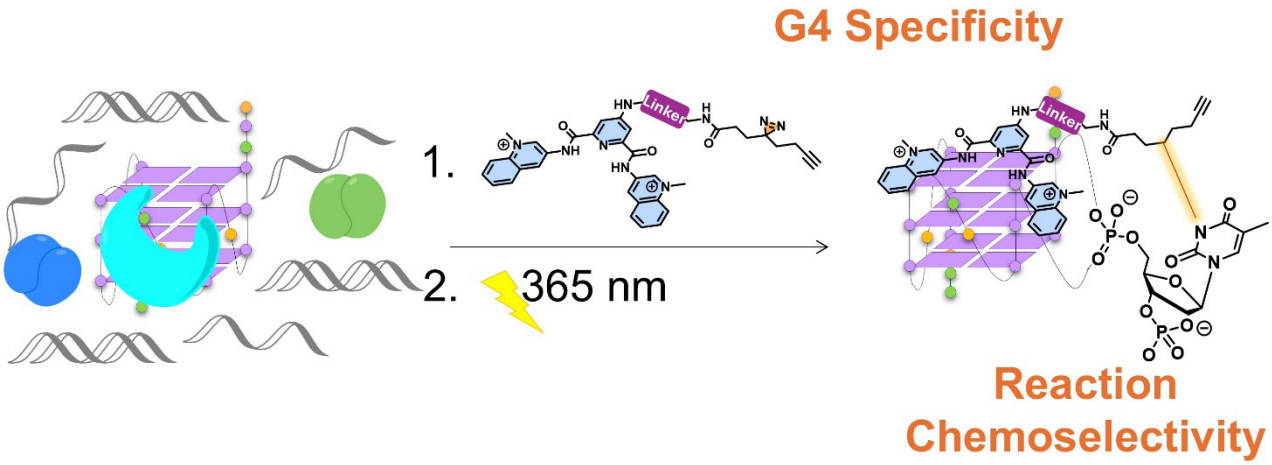
[1] Zhang, W., Fu, Y., Peng, L., Ogawa, Y., Ding, X., Rasband, A., Zhou, X., Shelly, M., Rasband M. N.* and **Zou, P.*** (2023). Immunoproximity biotinylation reveals the axon initial segment proteome. *Nat. Commun.* **14**, 8201.

Photoactivatable warheads for G-quadruplex photoaffinity labelling

Thibaut Masson[1,2], Corinne Landras Guetta[1,2], Charles-Henri Buffet[1,2,3], Tommaso Boselli[3], Valentina Pirota[3], Laurent Cattiaux[1,2], Rahima Chennoufi[1,2], Christine Saint-Pierre[4], Sophie Bombard[1,2], Mariella Mella[3], Didier Gasparutto[4], Filippo Doria[3], Mauro Freccero[3], Daniela Verga[1,2].

[1]CNRS UMR9187, Institut Curie, PSL Research University, F-91405 Orsay, France;
2 CNRS UMR9187, Université Paris-Saclay, F-91405 Orsay, France;
[3]Department of Chemistry, University of Pavia, Viale Taramelli 10, 27100 Pavia, Italy;
[4]University Grenoble Alpes, CEA, CNRS, IRIG, SyMMES-UMR5819, F-38054 Grenoble, France.

G-rich repetitive nucleic acid sequences can fold into G-quadruplexes (G4s) upon coordination with monovalent cations (K+, Na+)[1]. Small natural and synthetic molecules (G4 ligands) can bind to and stabilize G4 structures in vitro, thereby interfering with biological processes involving G4-containing genes[2]. Therefore, G4 ligands represent highly valuable tools for unveiling G4 biological functions. Together with non-covalent reversible G4 ligands, reactive compounds capable of forming covalent bonds with G4s upon thermal and photochemical activation represent a new class of promising G4 ligands with the potential to be harnessed for the identification and isolation of G4s from a biological environment[3]. In particular, photoaffinity labelling (PAL) encompasses the potential to obtain spatial and temporal control over the alkylation event[4]. However, to date, only a few examples of covalent G4 ligands for PAL approaches have been described, and very low alkylation yields plague all of them. Herein, the synthesis of new families of photoactivatable G4 ligands functionalized with different warheads (e.g., benzophenones and diazirines) is described, as well as their photoreactivity in the presence of different different G4s (e.g., 22AG, cMyc, and 25CEBwt). Among the different compounds, diazirine derivatives displayed unprecedented high alkylation yields (up to 70%) together with high G4 selectivity. In addition a remarkable selective *N*- and *O*-alkylation reaction on thymine and guanine was identified using a prototype ligand. These new compounds pave the way for the development of new methodologies, allowing for functional investigation and druggability of G4 in cells[5].



References:

[1] Spiegel J, Adhikari S, Balasubramanian S. The Structure and Function of DNA G-Quadruplexes. Trends Chem. 2020, 2, 123-136.
[2] Varshney D, Spiegel J, Zyner K, Tannahill D, Balasubramanian S. The regulation and functions of DNA and RNA G-quadruplexes. Nat. Rev. Mol. Cell Biol. 2020, 21, 459-474.
[3] Verga D, Hamon F, Poyer F, Bombard S, Teulade-Fichou M.-P. Photo-Cross-Linking Probes for Trapping G-Quadruplex DNA. Angew. Chem. Int. Ed. 2014, 53, 994-998.
[4] Lena, A, Benassi, A, Stasi, M, Saint-Pierre, C, Freccero, M, Gasparutto, D, Bombard, S, Doria, F, Verga, D. Photoactivatable V-Shaped Bifunctional Quinone Methide Precursors as a New Class of Selective G-quadruplex Alkylating Agents. Chem. – Eur. J. 2022, 28, e202200734.
[5] Masson T, Landras Guetta C, Buffet C-H, Boselli T, Pirota V, Cattiaux L, Chennoufi R, Saint-Pierre C, Bombard S, Mella M, Gasparutto D, Doria F, Freccero M, Verga D. Alkyldiazirine warheads for G-quadruplex photoaffinity labelling by N,O-alkylation on Thymine and Guanine Nucleobases. Submitted 2026.

Glyco-Gold nanoparticles: a microfluidic approach to deploy multi-functionality

Marcello Marelli[1], Jennifer Fernandez Alarcon[2], Katiuscia Pagano[3], Luigi Lay[4], Paolo Bigini[5], Laura Polito[1]

[1]Istituto di Scienze e Tecnologie Chimiche "Giulio Natta" SCITEC-CNR, Via G. Fantoli 16/15, Milano 20138, Italy;
[2]Institut Químic de Sarrià (IQS) Universitat Ramon Llull (URL) Via Augusta 390, Barcelona 08017, Spain;
[3]Istituto di Scienze e Tecnologie Chimiche "Giulio Natta" SCITEC-CNR, Via C.Corti 12, Milano 20133, Italy;
[4]University degli Studi di Milano Via Golgi 19, Milano 20133, Italy;
[5]Istituto di Ricerche Farmacologiche Mario Negri IRCCS Via Mario Negri 2, Milano 20156, Italy.

Nanotechnologies become pivotal when a specific strategy is required to carry and guide biomolecules to target biomarkers for both diagnostics and therapeutics.
Among them, glyco-gold nanoparticles (GNPs) are highly promising, with applications in several biological and medical fields[1], but require a refined, precise design in terms of size, shape, and functionalization. These nanosystems successfully coupled the natural multivalent presentation of saccharide moieties, carbohydrate-mediated molecular recognition, and the nanometal core's optical, electronic, and chemical properties. A robust and distinctive nanostructure design calls for a clean, customizable, and highly reproducible synthetic path. We propose implementing microfluidic protocols to directly synthesize Au glyconanoparticles, thereby enabling access to tailored nanosystems in a straightforward manner. Hereby, we present two microfluidic platforms capable of synthesizing Au nanoparticles functionalized with one or more carbohydrate linkers (i.e., glycans based on mannose, glucose, and lactose), tuning their ratios and avoiding post-reaction steps[2]. This approach is UV-light-assisted, proceeds without the use of harsh reducing agents or surfactants, and yields natively sterile ultrasmall GNPs. A second microfluidic strategy has been designed to synthesize colloidal solutions of anisotropic star-shaped and spherical nanoparticles[3,4] at room temperature under mild conditions, and to easily functionalize them via simple ligand exchange. By exploiting this approach, we afforded GNPs with mannose and sialic monosaccharide linkers, which have been successfully employed in the functional polarization of liver macrophages[5].

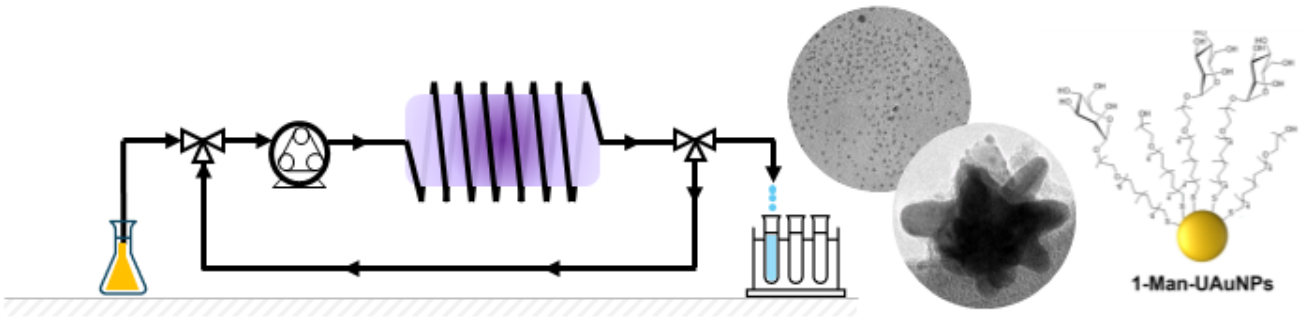


Figure: general microfluidics scheme, gold nanoparticles, and a picture sketch of them

References:

[1] Compostella F, Pitirollo O., Silvestri A., Polito L. *Glyco-gold nanoparticles: synthesis and applications* Beilstein J. Org. Chem. 2017, 13, 1008–1021.
[2] Perez Schmidt P., Pagano K., Lenardi C., Penconi M., Mateu Ferrando R., Evangelisti C., Lay L, Ragona L, Marelli M., Polito L. *Photo-Induced Microfluidic Production of Ultrasmall Glyco Gold Nanoparticles* Angew. Chem. Int. Ed. 2023, 62, e202210140.
[3] Silvestri A., Lay L., Psaro R., Polito L., Evangelisti C. *Fluidic Manufacture of Star-Shaped Gold Nanoparticles* Chem. Eur. J.2017, 23, 9732.
[4] Marelli M., Bossola F., Spinetti G., Sangalli E., Dal Santo V., Psaro R., Polito L. *Microfluidic Synthesis of Hybrid TiO2-Anisotropic Gold Nanoparticles with Visible and Near-Infrared Activity* ACS Appl. Mater. Interfaces 2020, 12, 34, 38522–38529.
[5] Fernandez Alarcon J., Perez Schmidt P., Panini N., Caruso F., Violatto M. B., Sukubo N. G., Martinez-Serra A.,Blanche Ekalle-Soppo C., Morelli A., Moscatiello G. Y.,Grasselli C., Corbelli A., Fiordaliso F., Kelk J., Petrosilli L., d'Orazio G., Mateu Ferrando R., Verdaguer Ferrer A., Fornaguera C., Lay L, Fumagalli S, Recchia S., Monopoli M. P., Polito L, Bigini P., and Sitia G. *Functional Polarization of Liver Macrophages by Glyco Gold Nanoparticles Adv. Sci.* 2025, *12*, 2407458.

Targeted Nrf2 Activation through Controlled Release of Endogenous Lipid-Derived Electrophiles from Reversible Michael Adducts

Rebecca Ferrisi, Giovanna Baron, Alessio Macorano, Francesca Gado, Larissa Della Vedova, Clara Mocchetti, Sofia Messinese, Claudio Papotto, Alessandra Altomare, Giulio Vistoli, Clelia Dallanoce, Giancarlo Aldini.

Department of Pharmaceutical Sciences, University of Milan, Via Mangiagalli 25, 20133 Milan, Italy.

Nuclear factor erythroid 2–related factor 2 (Nrf2) is a transcription factor vital for maintaining cellular redox balance. Therefore, Nrf2 has emerged as a therapeutic target in human diseases, particularly those with oxidative and inflammatory stress components. Reactive carbonyl species (RCS), particularly α,β-unsaturated aldehydes generated during lipid peroxidation, are endogenous electrophiles that activate the Nrf2 pathway[1]. However, these molecules exhibit hormetic behavior: while low concentrations promote protective signaling, excessive levels react with cellular macromolecules, leading to cytotoxic effects and cellular damage during oxidative stress[2].
In this study, we explored a strategy to mitigate electrophile toxicity by forming stable, non-toxic complexes capable of reversibly releasing RCS (Figure 1). This approach enables controlled electrophile delivery, promoting Nrf2 pathway activation at non-toxic concentrations and inducing sustained antioxidant and anti-inflammatory responses while minimizing cellular damage. A series of nucleophile–electrophile (Nu–E) Michael adducts was synthesized by coupling lipid-derived α,β-unsaturated aldehydes—4-hydroxy-2-nonenal (HNE), 4-oxo-2-nonenal (ONE), and crotonaldehyde (CRO)—with endogenous nucleophiles including carnosine (CAR), N-acetylcysteine (NAC), cysteine (Cys), and cysteamine (CST). Kinetic parameters were correlated with computational electrophilicity and nucleophilicity indices, while biological assays evaluated Nrf2 activation and cell viability. ONE-derived adducts were highly stable with negligible electrophile release, whereas HNE- and CRO-based conjugates enabled controlled RCS release. Thiol-containing nucleophiles promoted faster adduct formation and modulated release depending on nucleophilicity and redox conditions.
Overall, reversible Nu–E conjugates function as tunable electrophile reservoirs mimicking endogenous lipid signaling, enabling predictable, redox-dependent control of RCS release and Nrf2 activation with reduced nonspecific reactivity.

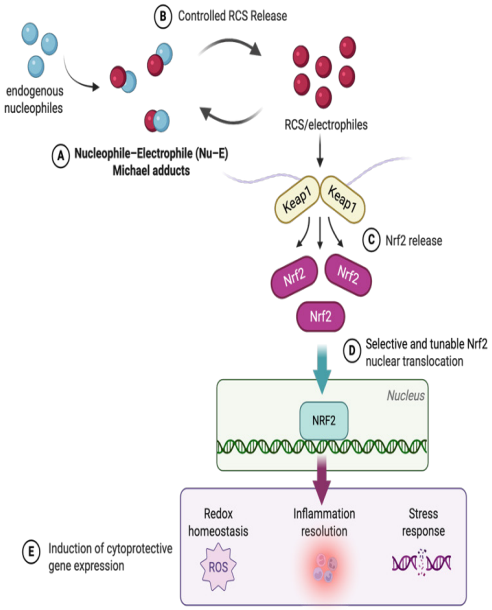


Figure 1. Conceptual framework of reversible Nu–E adducts as controlled RCS releasers for Nrf2 activation.

References:

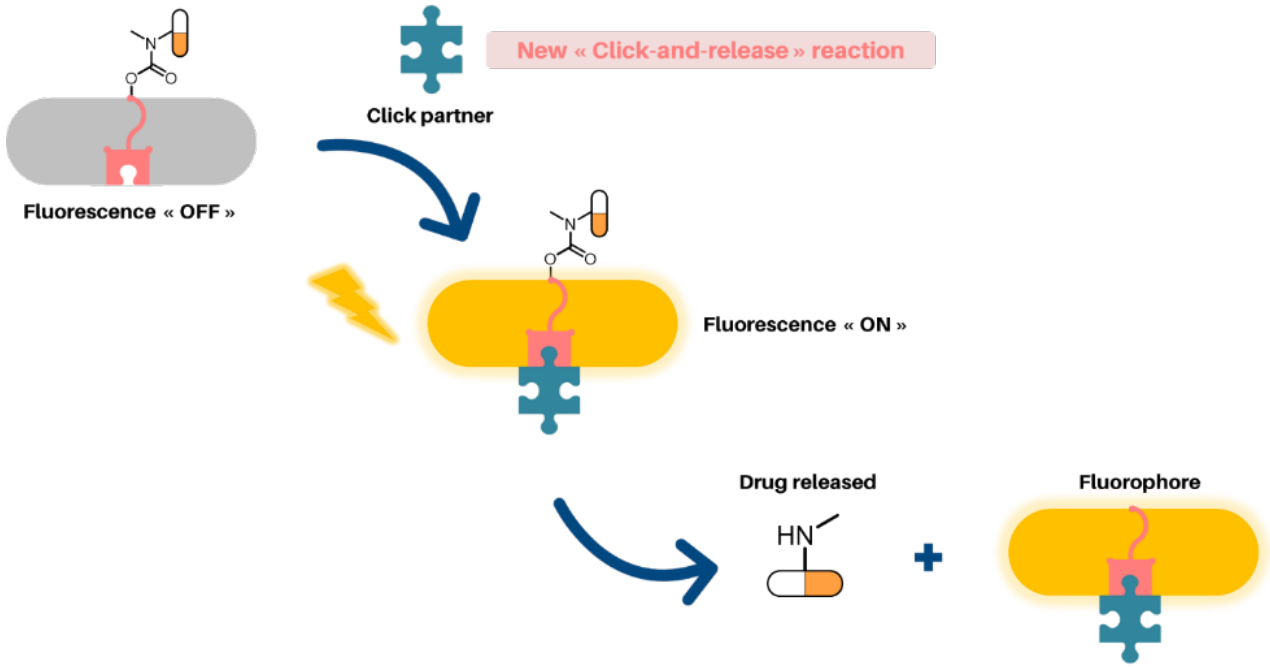
[1] Zhang Y, Sano M, Shinmura K, et al. 4-Hydroxy-2-nonenal protects against cardiac ischemia–reperfusion injury via the Nrf2-dependent pathway. J Mol Cell Cardiol. 2010;49(4):576-586.
[2] Bilska-Wilkosz A, Iciek M, Górny M. Chemistry and Biochemistry Aspects of the 4-Hydroxy-2,3-trans-nonenal. Biomolecules. 2022, 12(1), 145.

A Novel Bioorthogonal Fluorogenic Click-and-Release Reaction or Imaging and Controlled Drug Delivery

Malo Gourvest[1], Kévin Renault[1], Gilles Clavier[2], Florence Mahuteau-Betzer[1]

[1]Institut Curie, Chemistry & Modeling for the Biology of Cancer, UMR 9787/U1196, CS90030, rue Becquerel, 91405 ORSAY Cedex;
[2]Université Paris-Saclay, ENS Paris-Saclay, CNRS, PPSM,Gif-sur-Yvette F-91190, France.

Fluorescent probes are indispensable tools in bioimaging and diagnostics, enabling the visualization of biological molecules and environmental changes with high sensitivity and resolution. However, conventional fluorescence techniques are constrained by limited tissue penetration and photodamage. Two-photon excitation (2PE) addresses these challenges by allowing deep tissue imaging with reduced phototoxicity, yet most dyes are not optimized for 2PE, requiring high laser power due to low absorption cross-sections[1],[2].
To overcome these limitations, this project aims to develop a novel bioorthogonal fluorogenic click reaction that combines high fluorescence turn-on[3] with a click-and-release mechanism for controlled payload delivery[4],[5]. For the first time, both fluorogenic activation and drug release are integrated into a single molecular scaffold, directly linking imaging and therapeutic functions. Preliminary results on our current model already demonstrate rapid click kinetics and promising performance, highlighting the potential of this dual-functional approach.



References:

[1] Pascal S., David S., Andraud C., Maury O.. Near-infrared dyes for two-photon absorption in the short-wavelength infrared: strategies towards optical power limiting Chem. Soc. Rev. 2021, 50, 6613.
[2] Auvray M., Bolze F., Naud-Martin D.,Poulain M., Bossuat M., Clavier G., Mahuteau-Betzer F. On the road toward more efficient biocompatible two-photon excitable fluorophores Chem. Eur. J. 2022, e202104378.
[3] Auvray M., Naud-Martin D., Fontaine G., Bolze F., Clavier G., Mahuteau-Betzer F. Ultrabright two-photon excitable red-emissive fluorogenic probes for fast and wash-free bioorthogonal labelling in live cells Chemical Science 2023, 14, 8119-8128.
[4] van Onzen A. H. A. M.,Versteegen R. M., Hoeben F. J. M., Filot I. A. W., Rossin R., Zhu T., Wu J., Hudson P. J., Janssen H. M., ten Hoeve W., Robillard M. S. Bioorthogonal Tetrazine Carbamate Cleavage by Highly Reactive *trans*-Cyclooctene. J. Am. Chem. Soc. 2020, 142, 10935–10941.
[5] Keppel P., Hecko S., Mikula H. Top Current Chem. 2025, 383, 25.

Protease-resistant peptide vesicles as nanoscale carriers

ElisaMarelli[1], Alessandro Marchetti[1], Greta Bergamaschi[2], Francesca Baldelli Bombelli[1], Pierangelo Metrangolo[1], Claudia Pigliacelli[1]

[1]Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Milan, 20133, Italy
[2]Istituto di Scienze e Tecnologie Chimiche, National Research Council of Italy, Via M. Bianco 9, 20131 Milano, Italy

Peptide self-assembly provides a powerful and modular route to nanoscale materials with programmable structure and function. However, the broader use of peptides in bio-nanomaterials design is often constrained by the high cost of long sequences and their intrinsic susceptibility to proteolytic degradation [1,2].

Here,weaddresstheselimitationsthroughtherationaldesignofultrashortself-assemblingpeptides that form functional nano-systems with tunable physicochemical and biological properties. Specifically, we developed peptide nanovesicles (NVs) arising from the spontaneous self-assembly of a pentapeptide.

The NVs formed in aqueous media efficiently encapsulate fluorescent cargoes and enable sustained, diffusion-controlled release under physiological conditions. Remarkably, the designed NVs exhibit pronounced proteolytic resistance: high-performance liquid chromatography and mass spectrometry analyses show that the peptide remains intact after 24 h exposure to chymotrypsin. Further, cargo release kinetics are preserved under proteolytic conditions, highlightingthebiologicalresilienceofthisminimalpeptidenanocarrier.WefurtherinvestigatedNVs colloidal stability in biologically relevant fluids and revealed a stabilisation effect associated with protein corona formation.

Overall, these findings help to establish chemically tuned ultra short peptides as robust and versatile building blocks for the design of nanoscale carriers.

References:

[1] Sinha N.J., Langenstein M.G., Pochan D.J., Kloxin C.J., Saven J.G., Peptide Design and Self-assembly into Targeted Nano structure and Functional Materials Chem. Rev. 2021, 121, 22, 13915–13935.
[2] iY. Lu H., Lu H.,Wang H. Engineering Peptide Self-Assembly: Modulating Non covalent Interactions for Biomedical Applications, *Acc. Mater. Res.* 2025, 6, 4, 447–461.

Molecular Insights into Sialoglycan Recognition by Siglecs

Cristina Di Carluccio[1,2,3], Roberta Marchetti[1], Antonio Molinaro[1,2], Alba Silipo[1,2]

[1]University of Naples Federico II, Via Cintia 4I, 80126, Napoli, Italy;
[2]CEINGE-Biotecnologie Avanzate Franco Salvatore, Via Gaetano Salvatore, 486, 80145, Napoli, Italy;
[3]Istituto Nazionale Biostrutture e Biosistemi – I.N.B.B, Via dei Carpegna 19, 00165, Roma, Italy.

All cells are coated with a dense layer of glycans at the interface between the cell membrane and the extracellular environment. These complex carbohydrates regulate a wide range of biological processes, including immune recognition, infection, and inflammation, primarily through interactions with glycan-binding proteins[1]. Among these, sialylated glycans, commonly present as terminal residues on glycoproteins and glycolipids, play a central role in immune modulation[2]. Sialic acids display remarkable structural diversity, which is further expanded by modifications such as sulfation, acetylation, and methylation. Alterations in glycan composition, including hypersialylation and aberrant sulfation[3], are frequently associated with pathological conditions such as cancer and immune dysregulation. Siglecs (sialic acid binding immunoglobulin type lectins), specifically recognize sialylated glycans and contribute to the discrimination between self and non-self, thereby regulating immune cell activity[4].
This work aims to investigate the molecular basis of glycan–protein recognition involving sialylated and sulfated glycans and their interaction with inhibitory Siglec-7 and Siglec-9.
Using a multidisciplinary strategy combining advanced NMR spectroscopy, complementary biophysical techniques, and computational approaches, including docking and molecular dynamics simulations, we characterized the interaction patterns of sialylated glycans with Siglec receptors. The analyses reveal how specific structural features, including sulfation patterns and glycan arrangement, influence binding modes.
These findings provide molecular-level insight into the recognition of endogenous sialoglycans by Siglec receptors and highlight how glycan modifications modulate immune signaling[5]. Understanding these interactions contributes to elucidating mechanisms of immune regulation and may help the development of glycan-targeted therapeutic strategies in cancer, infectious diseases, and immune-mediated disorders.

References:

[1] S. Wisnovsky, C.R. Bertozzi. Reading the glyco-code: New approaches to studying protein-carbohydrate interactions. Current Opinion in Structural Biology 2022, 75. 102395.
[2] Zhou, J. Y.; Oswald, D. M.; Oliva, K. D.; Kreisman, L. S. C.; Cobb, B. A. The Glycoscience of Immunity. Trends in Immunology 2018, 39, 7. 523–535.
[3] Ma, S.; Zhang, P.; Ye, J.; Tian, Y.; Tian, X.; Jung, J.; Macauley, M. S.; Zhang, J.; Wu, P.; Wen, L. Enzyme-Sialylation-Controlled Chemical Sulfation of Glycan Epitopes for Decoding the Binding of Siglec Ligands. J. Am. Chem. Soc. 2024, 146, 43. 29469–29480.
[4] Smith, B. A. H.; Bertozzi, C. R. The Clinical Impact of Glycobiology: Targeting Selectins, Siglecs and Mammalian Glycans. Nat Rev Drug Discov 2021, 20, 3. 217–243.
[5] Di Carluccio C.; Padilla-Cortés L.; Tiemblo-Martìn M.; Roxana Gheorghita G.; Oliva R.; Cerofolini L.; Masi A.A.; Abreu C.; Tseng H.K.; Molinaro A.; Del Vecchio P.; Vaněk O.; Lin C.C.; Marchetti R.; Fragai M.; Silipo A. Insights into Siglec-7 binding to gangliosides: NMR protein assignment and the impact of ligand flexibility. Advanced Science 2025, 12. 2415782.

Mechanistic insights into protein misfolding and aggregation processes by real-time solution NMR studies

Katiuscia Pagano[1], Federica Malinverno[1], Michela Bollati[2], Simona Tomaselli[1], Henriette Molinari[1], Lucia De Rosa[3], Luca D'Andrea[1], Kaliroi Peqini[4], Sara Pellegrino[4], Luisa Diomede[5], Matteo De Rosa[2], Laura Ragona[1]

[1]*Institute of Science and Chemical Technologies "Giulio Natta" (SCITEC-CNR), Via Corti 12, 20133, Milano, Italy;*
[2]*Institute of Biophysics, National Research Council (IBF-CNR), Via Celoria 26, 20133 Milano, Italy;*
[3]*Istituto di Bistrutture e Bioimmagini (IBB-CNR), Via Pietro Castellino 111, Napoli, Italy;*
[4]*Department of Pharmaceutical Science, "A. Marchesini" General and Organic Chemistry Section, University of Milano, Via Venezian 21, 20133 Milano, Italy;*
[5]*Department of Molecular Biochemistry and Pharmacology, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Via Mario Negri 2, 20156 Milano, Italy.*

Protein misfolding and aggregation is the process by which proteins self-associate to form insoluble fibrillar aggregates. Changes in environmental conditions (pH, temperature) or mutations in the protein sequence trigger fibril formation, which is at the basis of a wide variety of neurodegenerative and systemic disease, such as Alzheimer's disease and hereditary Gelsolin amyloidosis.
Solution NMR spectroscopy offers the unique capability to characterize transient and heterogeneous systems, in atom detail, along the self-assembly process. Real-time residue-level data can effectively depict the protein regions involved in the conformational changes leading to the exposure of hydrophobic residues, causing proteins to misfold and aggregate[1].
We have recently developed a DOSY-ILT NMR approach in which NMR diffusion measurements are coupled with the Inverse Laplace Transform reconstruction method to detect the rapidly interconverting visible species and effectively characterize the early steps of the aggregation process. The method has been successfully applied to elucidate the time-dependent oligomer distribution of the Aβ1-40 amyloid peptide and assess the effect of Epigallocathechin gallate, a known remodeling agent of amyloid fibrils, on Aβ1-40 species distributions[2]. New mechanistic insights on the aggregation process of the amyloidogenic G2-gelsolin domain, carrying D187N pathological mutation, are discussed[3]. DOSY-ILT NMR approach is further presented as a strategy for rapidly elucidating the mechanism of action of aggregation inhibitors, thereby supporting the systematic optimization of compounds potency during the early stages of drug discovery.

References:

[1] Pagano, D. Galante, C. D'Arrigo, A. Corsaro, M. Nizzari, T. Florio, H. Molinari, S. Tomaselli, L. Ragona, Mol. Neurobiol. 2019, 56, 1957--1971.
[2] Pagano, K., De Rosa, L., Tomaselli, S., Molinari, H., D'Andrea, L.D. Ragona, L. Characterizing the oligomers distribution along the aggregation pathway of amyloid Aß1-40 by NMR, 2024 Chem. Eur. J., e202400594 .
[3] Malinverno, F., Bollati, M., Molinari, H., Peqini, K., Pellegrino, S., De Rosa, M., Ragona, L., Pagano, K. Amyloidogenic aggregation of G2-D187N gelsolin domain: mechanistic insights and inhibition by peptidomimetics, *manuscript in preparation* .

Elucidating a dual TREM2-ligand pathway by a cellular three components FRET/FLIM system

Carmela Gallo[1], Dalila Carbone[1,2], Emiliano Manzo[1], Rossella Venditti[3], Annapina Russo[4], Daniela Castiglia[1], Mario Dell'isola[1], Camilla Danisi[4], Laura Fioretto[1],Giuliana d'Ippolito[1], Genoveffa Nuzzo[1], Angelo Fontana[1,2]

[1]CNR, Institute of Biomolecular Chemistry, Via Campi Flegrei, 34 Pozzuoli, Italy;
[2]Department of Biology, University of Naples Federico II, Napoli, Italy;
[3]TIGEM, Telethon Institute of Genetics And Medicine, Via Campi Flegrei,Pozzuoli,Italy;
[4]Department of Pharmacy, University of Naples Federico II, Napoli, Italy.

Triggering receptors expressed on myeloid cells 2 (TREM2), is a transmembrane receptor acting as a key immune regulator mainly expressed on brain microglia, with critical roles in neurological diseases. Recently, we reported Sulfavant A (SULFA), a synthetic sulfolipid binding to TREM2, as a promising therapeutic small molecule that restores microglial homeostasis via an inflammation-sparing mechanism[1,2]. SULFA pointed out a novel disease-modifying approach that extends beyond conventional plaque-targeting strategies in Alzheimer's disease and underlined a different functionality linked to TREM2 binding. Actually, the broad array of TREM2 ligands makes it difficult to predict the outcomes of their binding and the mechanisms underlying the interplay between ligand interaction and cellular pathway is still unknown. Starting from these evidences, we developed a comprehensive methodology to distinguish non-interacting, dimeric and trimeric interacting TREM2-related proteins in living cells, using three components Förster resonance energy transfer (FRET) systems combined with Fluorescence Lifetime Imaging Microscopy (FLIM), and applied Phosphatidylserine (PS) and SULFA as two small anionic ligands triggering different signalling.
This strategy allowed to elucidate the interaction of TREM2 with the adaptor DAP12 and then with SYK or SHP1, two of the suggested interacting proteins that could provide the first step of activating or inhibitory downstream signals. Results showed that effectively PS and SULFA differed for the interaction with the third component, opening for the first time a research window to explain the different outcome of ligand binding to TREM2, and contribute to the systematic understanding of microglial function in the context of neurodegenerative diseases.

References:

[1] Gallo C, Verrillo L, Manzo E, Caiuzzi E et al. Microglial clearance, neuroprotection and cognitive recovery via a novel synthetic sulfolipid in Alzheimer's disease. J Neuroinflammation 2025; 23: 20-38.
[2] Gallo C, Manzo E, Barra G, Fioretto L, et al. *Sulfavant A as the first synthetic TREM2 ligand discloses a homeostatic response of dendritic cells after receptor engagement.* Cell Mol Life Sci 2022; 79: 369-384.

MetabolEx: An Integrated Tool for Small-Molecule Metabolite Generation and Metabolic Pathway Analysis

Serena Vittorio[1], Filippo Lunghini[2], Giada Agazzi2, Valerio Tazzari[2], Anna Fava[2], Alessio Macorano[1], Giulio Vistoli[1], Andrea Rosario Beccari[2].

[1]*Dipartimento di Scienze Farmaceutiche, Università degli Studi di Milano, Via Luigi Mangiagalli 25, I-20133 Milano, Italy;*
[2]*EXSCALATE, Dompé Farmaceutici SpA, Via Tommaso de Amicis 95, 80123 Naples, Italy.*

Accurately predicting metabolite formation is critical for assessing safety risks and optimizing pharmacokinetic properties early in drug discovery. However, the metabolic fate of new drugs candidates remains difficult to anticipate due to the potential for unexpected toxicity and drug–drug interactions[1]. We present MetabolEx, a hybrid platform that combines rule-based metabolite generation with machine-learning prioritization to model Phase I and Phase II metabolism. The system incorporates 194 manually curated SMIRKS-encoded reactions and leverages classifiers trained on 41,041 substrate–metabolite pairs compiled from multiple sources. This approach enables broad enumeration of chemically plausible metabolites while applying probabilistic filtering to limit the combinatorial growth inherent in recursive prediction.
Evaluation on 219 external substrates showed strong performance across three recursive levels. At level 1, MetabolEx reached a recall of 0.84 for primary metabolites. At level 2, it achieved double the precision of leading methods and substantially reduced false positives while maintaining a recall of 0.57. At level 3, the platform yielded a fivefold precision improvement and a 25-fold reduction in false positives relative to exhaustive enumeration, with a recall of 0.35. These results demonstrate that probabilistic filtering effectively narrows high-volume predictions into focused and relevant number of metabolites.
Covering eight major metabolic reaction classes, MetabolEx provides a comprehensive resource for metabolic and toxicological profiling. The platform includes interactive metabolic network visualization, automated toxicity annotation, and is freely available at https://metabolex.exscalate.eu.

References:

[1] Zhang Z., Tang W., Drug metabolism in drug discovery and development. Acta Pharm. Sin. B 2018; 8:721-732.

Decoding myrtle activity against Alzheimer's disease: characterization of metabolic composition and anti-amyloidogenic activity of myrtle leaves extracts

Linda Molteni[1], Luca Moretti[1], Maura Brioschi[1], Diletta Ami[1,2], Antonino Natalello[1,2], Valeria Cassina[3], Alessandro Palmioli[1,2], Cristina Airoldi[1,2].

[1]Department of Biotechnology and Biosciences, University of Milano-Bicocca, P.zza della Scienza 2, 20126 Milan, Italy;
[2]NeuroMI, Milan Center for Neuroscience, University of Milano-Bicocca, 20126 Milano, Italy ;
[3]School of Medicine and Surgery, University of Milano-Bicocca, 20854 Vedano al Lambro (MB), Italy.

The primary challenge in addressing Alzheimer's disease (AD) is the significant lag between the molecular onset and the appearance of clinical symptoms. Consequently, prioritizing primary prevention strategies is imperative[1]. In this context, diet is a promising preventive tool in addressing AD pathogenesis[2]. Myrtle (*Myrtus communis*) is an evergreen aromatic plant historically employed in cooking and liqueur production; while the leaves are often considered a waste product, they could represent a rich source of bioactive compounds[3].

Here we investigated the anti-amyloidogenic activity of the hydro-alcoholic extracts of myrtle leaves against Aβ1-42 aggregation, one of the main hallmarks of AD [4]. By combining advanced analytical techniques (including STD NMR to probe molecular interactions and FT-IR/AFM to assess structural and morphological changes) we demonstrated that myrtle extracts significantly modulate Aβ1-42 aggregation. Moreover, we employed a combined NMR and LC-MS metabolomic approach to identify the compounds responsible for the biological activity of myrtle extracts, revealing the presence of glycosylated flavonoids, hydrolysable tannins and myrtucommulones. These compounds were isolated and further tested for their anti-amyloidogenic properties.

Overall, our findings suggest that myrtle bioactive compounds are promising nutraceutical candidates for the safe and sustainable prevention of neurodegeneration. Their synergistic antioxidant, anti-inflammatory, and anti-amyloidogenic properties allow for the effective modulation of early-stage molecular events.

Acknowldegments:

Project funded by Next Generation EU - "Age-It - Ageing well in an ageing society" project (PE000015), National Recovery and Resilience Plan (NRRP) - PE8 Mission 4, C2, Intervention 1.3". The views and opinions expressed are only those of the authors and do not necessarily reflect those of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them.

References:

[1] Guo J, Huang X, Dou L, Yan M, Shen T, Tang W, et al. Aging and aging-related diseases: from molecular mechanisms to interventions and treatments. Sig Transduct Target Ther 2022; 7(1): 391.
[2] Pandey SN, Singh G, Semwal BC, Gupta G, Alharbi KS, Almalki WH, et al. Therapeutic approaches of nutraceuticals in the prevention of Alzheimer's disease. Journal of Food Biochemistry 2022; 46(12).
[3] Tumen I, Senol FS, Orhan IE. Inhibitory potential of the leaves and berries of Myrtus communis L. (myrtle) against enzymes linked to neurodegenerative diseases and their antioxidant actions. International Journal of Food Sciences and Nutrition 2012; 63(4): 387–92.
[4] Morante-Carriel J, Nájera H, Samper-Herrero A, Živković S, Martínez-Esteso MJ, Martínez-Márquez A, et al. Therapeutic Potential of Prenylated Flavonoids of the Fabaceae Family in Medicinal Chemistry: An Updated Review. IJMS 2024; 25(23): 13036.

WORKSHOP

Do Neural Networks Dream of Drug-Like Molecules? An Introduction and Critical Perspective to Generative AI for Chemical Space Exploration

Giorgio Carbone[1,2], Jacopo Gomena[1], Marco Zambra[1,3]

[1] *Italfarmaco S.p.A., Via dei Lavoratori 54, I-20092 Cinisello Balsamo (MI), Italy;*
[2] *University of Milano-Bicocca, Piazza dell'Ateneo Nuovo 1, 20126 Milano (MI), Italy;*
[3] *University of Insubria, Via Ravasi 2, 21100 Varese (VA), Italy*

The drug-like chemical space is vast and largely unexplored. Generative AI offers a structured framework for navigating it efficiently. This talk introduces key generative approaches and their integration into practical integrated in-silico pipelines. Moving beyond the technical narrative, we critically address the hype surrounding AI in pharma, focusing on generalizability, data scarcity, still-limited clinical evidence, and the challenge of reliably scoring and ranking candidate molecules: a discussion extended to the audience through a live interactive experiment.

POSTER

A calixarene-based fluorescence indicator displacement assay for the selective detection of bacteria

Linda Molteni[1], Stefano Volpi[2], Maria Cremonini[2], Francesco Sansone[2], Alessandro Palmioli[1], Alessandro Casnati[2], Cristina Airoldi[1]

[1] *Department of Biotechnology and Biosciences, University of Milano-Bicocca;*
[2] *Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma*

Antimicrobial resistance (AMR) represents a critical global threat in the 21st century [1]. Traditional antibiotics exert significant selective pressure, driving the emergence of resistance even against last-resort treatments. This crisis underscores the urgent need for rapid diagnostic tools capable of discriminating between bacterial classes (Gram-positive, Gram-negative, and Mycobacteria) to ensure timely and targeted therapy [2]. Zwitterionic calixarenes already showed surprising selectivity for Gram-negative bacteria [3]. In this study, we present a novel fluorescence indicator displacement assay (IDA) based on cationic calixarenes for the selective detection of bacterial classes. We synthesized and characterized a series of calix[n]arene derivatives (n = 4, 6, 8) functionalized with pyridinium groups at the upper rim. These derivatives effectively quench the fluorescence of a polyanionic polymer, PPP (poly(2,5-bis(3-sulfonatopropoxy)-1,4-phenylene)), through direct molecular interaction. The binding mechanisms were elucidated using STD (Saturation Transfer Difference) NMR spectroscopy.
The sensing potential was evaluated by monitoring the restoration of PPP fluorescence upon the addition of bacteria, which competitively displace the calixarene ligands from the polymer. On-cell STD NMR analysis of representative bacterial strains provided mechanistic insights into the binding modes. Notably, the calix[4]arene derivative exhibited superior selectivity for Gram-negative bacteria detection [4].
This cost-effective and rapid chemical system represents a significant addition to the diagnostic toolkit in the ongoing fight against AMR.

Acknowledgments:

This work was funded under the National Recovery and Resilience Plan (NRRP), Mission 4 Component 2 Investment 1.1, by Italian Ministry of University and Research funded by the European Union_NextGenerationEU, Award Number: Project Code 2022285HC5, Concession Decree No. 1064 of 18.07.2023, adopted by the Italian Ministry of the University and Research, CUP D53D23010030006, SAMBA: Self-Assembly of Bacteria-Targeting Materials Across the Mesoscale.

References:

[1] https://www.nihr.ac.uk/blog/a-cornerstone-of-modern-medicine-is-crumbling-tackling-the-threat-of-antimicrobial-resistance-depends-on-research/10992;
[2] Rajapaksha P, Elbourne A, Gangadoo S, Brown R, Cozzolino D, Chapman J. A review of methods for the detection of pathogenic microorganisms. Analyst 2019; 144(2): 396–411
[3] Rispoli F, Moretti L, Vezzoni CA, Tosi E, Molteni L, Ciaramelli C, et al. Clustering Zwitterionic Amino Acids at the Upper Rim of Cone Calix[4]arene Triggers the Selective Recognition of Gram-Negative Bacterial Envelope. Small Structures. 2025 Jun;6(6):2400547. doi:10.1002/sstr.202400547
[4] Manuscript in preparation.

Self-Fluorescent Carvone-Based Polyesters Enable Integrated Delivery and Tracking of PROTAC Nanodegraders

Cristina Blasco-Navarro, María del Mar Noblejas-López, Iván Bravo and Carlos Alonso-Moreno

Universidad de Castilla-La Mancha. Facultad de Farmacia Av. Dr. Jose Maria Sánchez Ibáñez, s/n, Albacete-02071, Spain

Targeted nanotherapies offer an effective strategy to enhance the therapeutic index of anticancer agents by improving efficacy while reducing systemic toxicity. Here, we introduce a novel carvone-derived polyester synthesized via ring-opening copolymerization of cyclic anhydrides and epoxides as a sustainable nanoplatform for the controlled delivery of PROTAC degraders. This biomass-derived copolymer exhibits nonconventional fluorescence arising from cluster-triggered emission (CTE) [1], allowing intrinsic optical monitoring of nanoparticle (NP) behavior without external labels. Given these advantages, we aimed to assess the biomedical relevance of these fluorescent NPs using a therapeutically challenging molecule. THAL-SNS-032, a PROTAC (Proteolysis-Targeting Chimera) degrader of Cyclin-Dependent Kinase 9 (CDK9), was selected as a stringent case study because PROTACs, despite representing a paradigm shift in drug discovery by promoting targeted protein degradation rather than inhibition, often suffer from high molecular weight, poor solubility, and limited cell permeability [2]. Encapsulation of THAL-SNS-032 within the carvone-based NPs preserved its cytotoxic potency while improving biocompatibility and colloidal stability. Fluorescence Lifetime Imaging Microscopy confirmed efficient cellular uptake and time-dependent NP disassembly. Biological evaluation in breast cancer models showed comparable efficacy to the free PROTAC but markedly reduced on-target/off-tumor toxicity in non-transformed epithelial cells. Overall, this work introduces a new class of renewable, self-fluorescent polyesters as multifunctional nanocarriers capable of integrating drug delivery and real-time imaging, establishing their potential for next-generation PROTAC nanotheranostics (Figure 1).

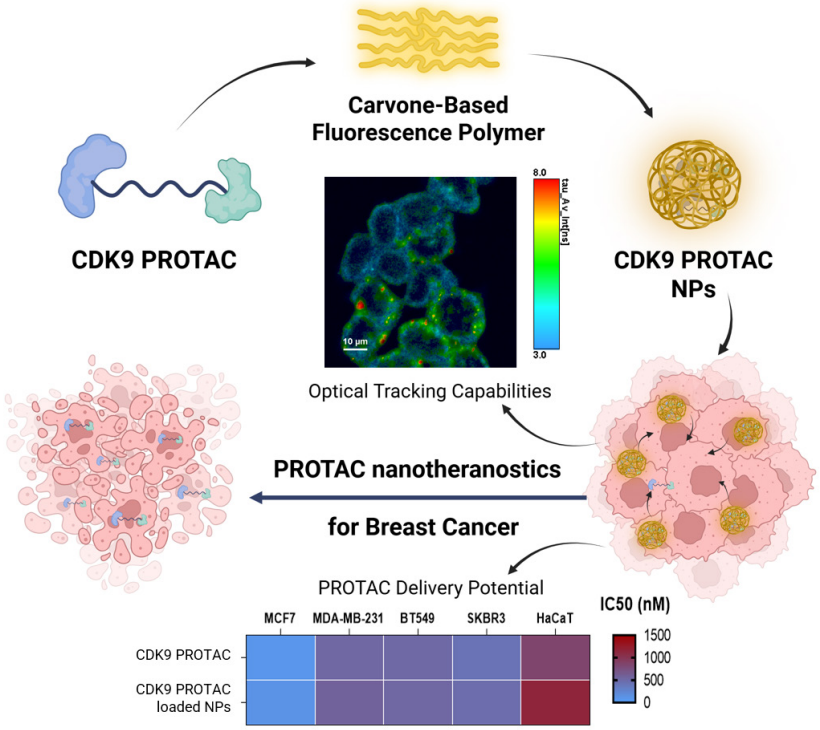


Figure 1. Graphical Abstract illustrating the intrinsic optical capabilities of self-fluorescent carvone-derived polyester nanoparticles for real-time tracking, alongside an in vitro IC^{50} heatmap comparing THAL-SNS-032-loaded NPs with free PROTAC across breast cancer and non-tumoral cell models.

References:

[1] de la Cruz-Martínez, F.; Bresolí-Obach, R.; Bravo, I.; Alonso-Moreno, C.; Hermida-Merino, D.; Hofkens, J.; Lara-Sánchez, A.; Castro-Osma, J. A.; Martín, C. J. Mater. Chem. B 2023, 11, 316-324.
[2] Noblejas-López, M. D. M.; Gandullo-Sánchez, L.; Galán-Moya, E. M.; López-Rosa, R.; Tébar-García, D.; Nieto-Jiménez, C.; Gómez-Juárez, M.; Burgos, M.; Pandiella, A.; Ocaña, A. Antitumoral Activity of a CDK9 PROTAC Compound in HER2-Positive Breast Cancer. Int. J. Mol. Sci. 2022, 23 (10), 5476. https://doi.org/10.3390/ijms23105476

Comparative DNA Interaction of Naphthalimide Derivatives Using Docking and UV–Vis titration

Huda Sunaydih Alsaeedi, Ali Mohammad Alsalme

King Saud University, Riyadh, Saudi Arabia

Naphthalimide-based hydrazide–hydrazone derivatives are promising DNA-interacting scaffolds due to their planar aromatic systems and tunable substituents. This study focuses on synthesizing four representative derivatives, **2a**, **2b** and their morpholine-substituted analogues **3a** and **3b** and evaluate how structural and steric modifications influence DNA binding. [1-3]
All compounds were synthesized through a multistep route and fully characterized via FT-IR and (1H and 13C) NMR. Molecular docking using AutoDock Vina against $d(ATCGAGACGTCTCGAT)_2$ revealed that **2a** and **2b** strongly favor intercalation, driven by extended aromaticity and stabilizing π–π stacking and Van der Waals interactions. However, morpholine substitution altered the binding orientation where **3a** showed mixed intercalative and groove-binding tendencies, while **3b** retained intercalation but exhibited reduced planarity and increased steric influence.

The UV-vis titration data indicated that naphthalimide derivative **2b** demonstrates promising binding affinities. The high binding affinity of 2c could be due to the increased aromatic surface of the naphthol group and the presence of the hydroxyl (OH) group in its structure, which enhances
stacking interactions with DNA. In contrast, the morpholine-naphthalimide derivatives **3a** and **3b** did not show significant improvements in binding affinity. Binding constants followed the trend **2b** > **2a** > **3b** ≈ **3a**, highlighting the influence of aromatic extension and steric bulk on DNA affinity.

Overall, these results demonstrate that subtle structural modifications significantly modulate DNA-binding mode and strength, offering valuable insights for designing next-generation naphthalimide-based DNA-targeting agents.

References:

(1) Kagatikar, S.; Sunil, D. A systematic review on 1,8-naphthalimide derivatives as emissive materials in organic light-emitting diodes. Journal of Materials Science 2022, 57 (1), 105-139. DOI: 10.1007/s10853-021-06602-w.
(2) Kumpulainen, T.; Bakker, B. H.; Hilbers, M.; Brouwer, A. M. Synthesis and Spectroscopic Characterization of 1,8-Naphthalimide Derived "Super" Photoacids. The Journal of Physical Chemistry B 2015, 119 (6), 2515-2524. DOI: 10.1021/jp508334s.
(3) Kucheryavy, P.; Li, G.; Vyas, S.; Hadad, C.; Glusac, K. D. Electronic Properties of 4-Substituted Naphthalimides. The Journal of Physical Chemistry A 2009, 113 (23), 6453-6461. DOI: 10.1021/jp901982r.

DNA Interaction of Thiadiazole-Based Schiff Bases and Their Reduced Analogues

Ali Mohammad Alsalme, Huda Sunaydih Alsaeedi

King Saud University, Riyadh, Saudi Arabia

Schiff base derivatives containing heteroaromatic rings have attracted considerable attention due to their structural tunability and their potential to interact with DNA. The aim of this study is to synthesize selected Schiff bases and their reduced analogues and to evaluate how aromatic size and imine reduction influence their DNAbinding behavior.
Two Schiff bases (2a, 2b) were synthesized through the condensation of thiadiazole derivatives (1a, 1b) with 2hydroxy1naphthaldehyde and anthracene9carbaldehyde. This reaction followed by $NaBH_4$ reduction to yield the corresponding amines (3a, 3b). Structural characterization was confirmed by FTIR and $^{1}H/^{13}C$ NMR spectroscopy.
Molecular docking against $d(ATCGAGACGTCTCGAT)_2$ revealed that 2a and 2b favorably adopt an intercalative binding mode, stabilized by π–π stacking and Van der Waals interactions. The anthracenebased compound 2b exhibited the highest predicted affinity, attributed to its extended aromatic surface. Reduction of the imine bond to a CH_2–NH group increased molecular flexibility in 3a and 3b, shifting their preferred interaction toward groove binding and resulting in slightly lower docking scores.
UV–vis titration supported these trends, showing the strongest binding affinity toward ctDNA for the anthracenecontaining analogue 3b, while the lowest affinity was observed for the naphthylbased Schiff base 2a. These results highlight the significant influence of aromatic ring size and imine reduction on DNAbinding mode and strength, offering useful guidance for the design of future DNAactive Schiff base derivatives.

Utilization of agro-wastes as a substrate for Polyhydroxybutyrate (PHB) production using Pseudomonas stutzeri PSB1

Mohammed B Alshammari

Department of Chemistry, College of Science and Humanities, Prince Sattam Bin Abdulaziz University, Alkharj, Saudi Arabia

Waste from a variety of sources is massive and poses a major risk to the environment. Research interest in the valorization of waste streams has increased due to the disposal issues. Valorization of trash not only lowers waste volume but also lowers environmental contamination. In order to reduce environmental pollution by replacing traditional non-biodegradable polymers, microbial assisted fabrication of polydroxybutyrate (PHB) which is considered as an environmentally friendly biopolymers. Due to their biodegradability, biocompatibility, bio-functionality, bio stability and bio-based origin; biopolymers among different products made from agro-waste, are gaining more attention nowadays that can be applied in a variety of ways. The aim of this work is to optimize the production media utilizing agro-waste as the least expensive carbon source in order to economical production of biopolymer. The chloroform extraction process was applied to determine the dry weight of PHB produced under optimal conditions. Furthermore, the various characteristics of the PHB biopolymer were characterized and identified using Fourier-transform infrared spectroscopy (FTIR), thin-layer chromatography (TLC), and gas chromatography-mass spectrometry (GC-MS) study. Thus, this study concluded that using of agro-waste like potato peel to synthesize value-added product like PHB could help to control the issue related to solid waste disposal and lower the cost of PHB production process.
Keywords: Biopolymers; agro-waste, fermentation, valorization; polydroxybutyrate (PHB).

Polyelectrolyte-Brush-Grafted Cellulose Membranes Decorated with Gold Nanostructures for Uric Acid Detection

Shrooq Khibari [a], Shatha Lahmadi [a], Abeer Beagan [a], Fahad Alharthi [a], Ali Alsalme [a], Khalid Alzahrani [b], Mohammed Almeataq [c], Khalid Alotaibi [a], Abdullah Alswieleh [a]*

[a]*Department of Chemistry, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia*
[b]*Department of Physics and Astronomy, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia*
[c]*King Abdulaziz City for Science and Technology, Riyadh P.O. Box 11442, Saudi*
**E-mail: aswieleh@ksu.edu.sa*

This research introduces a facile method for quantifying uric acid in aqueous solutions using a cellulose membrane decorated with gold nanostructures. The substrate was engineered by functionalizing cellulose with poly[2-(methacryloyloxy)ethyl]trimethylammonium chloride (PMETAC) and cross-linking with ethylene glycol dimethacrylate (EGDMA). Successful modification was verified via FT-IR and XPS analyses. Gold nanostructures were subsequently grown on the functionalized membrane through the reduction of tetrachloroaurate by NaBH4. The peroxidase-mimic catalytic activity of the composite was evaluated using the oxidation of 3,3′,5,5′-tetramethylbenzidine (TMB) by hydrogen peroxide (H2O2) under varying pH conditions. UV–Vis spectroscopy indicated distinct absorbance shifts at 660 nm that correlated with uric acid concentrations. Notably, the sensor exhibited pH-dependent colorimetric transitions, shifting from green to light yellow in neutral-to-basic environments and from yellow to dark green in acidic conditions. Stability and reusability assessments confirmed the material's robustness, highlighting opportunities for long-term application. These results demonstrate the platform's versatility for uric acid detection and underscore the critical role of pH in optimizing assay sensitivity and specificity.
Keywords: Uric acid detection; Gold nanostructures, Cellulose membrane, Polyelectrolyte brush; Colorimetric sensor

References:

1- Khibari, Shrooq, et al. "Gold nanostructures on polyelectrolyte-brush-modified cellulose membranes as a synergistic platform for uric acid detection." Talanta 279 (2024): 126586.
2- Paripovic, Dusko, and Harm-Anton Klok. "Polymer brush guided formation of thin gold and palladium/gold bimetallic films." ACS applied materials & interfaces 3.3 (2011): 910-917.
3- Wu, Dong, et al. "Uricase-stimulated etching of silver nanoprisms for highly selective and sensitive colorimetric detection of uric acid in human serum." Sensors and Actuators B: Chemical 221 (2015): 1433-1440.
4- Kumar, Anand, et al. "A paper based microfluidic device for easy detection of uric acid using positively charged gold nanoparticles." Analyst 140.6 (2015): 1817-1821.
5- Wang, Xue, et al. "A highly selective and sensitive colorimetric detection of uric acid in human serum based on MoS2-catalyzed oxidation TMB." Analytical and bioanalytical chemistry 411.4 (2019): 943-952.

A DOP-based bioorthogonal templated ligation: from reaction scope expansion to a robust DNA detection platforms

Mattia Amariglio, Simone Fortunati, Shaista Nazir, Roberto Corradini, Maria Careri, Marco Giannetto, Alex Manicardi

Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parco Area delle Scienze 17/A, Parma, Italy

The study of biomolecules in their native environments has driven the development of chemical transformations that can proceed in complex biological systems without perturbing endogenous processes [1]. These transformations, referred to as bio-orthogonal, must combine rapid and selective reactivity in aqueous media under physiological conditions, within highly crowded molecular environments.
Despite significant progress in the field, only a limited number of ligation reactions are effective at the cellular level, due to interference from the wide range of functional groups present in vivo and the requirement to remain non-toxic to the biological system [2].
In this context, our group reported a bioorthogonal templated ligation between a 1,4-diketone (DOP) moiety and an α-nucleophile, which proceeds only in the presence of proximity, yielding a stable and robust ligation product (Figure 1A) [3,4]. This transformation proceeds with high specificity and without detectable off-target reactivity, and it has previously demonstrated excellent performance in complex biological media such as cell lysates.
Here, we report the synthesis of a library of α-nucleophile building blocks and their evaluation in PNA:PNA ligation and DNA-templated ligation experiments, with the aim of broadening the reaction scope, enhancing its versatility. As a demonstration, this chemistry was integrated into a sandwich electrochemical magneto-genoassay for the parallel detection of food allergen contaminants [5]. In this context, the use of PNA probes capable of undergoing bioorthogonal ligation, triggered by target DNA recognition, preserves the presence of a reporter moiety required for the subsequent signal generation steps, even after stringent washing conditions that may promote sandwich dissociation, thereby improving assay robustness (Figure 1B).

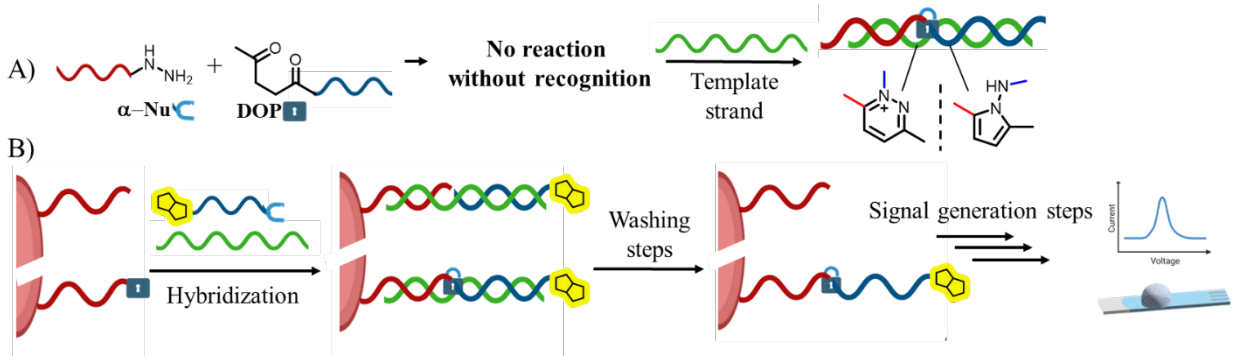


Figure 1: A) Bio-orthogonal ligation. B) Schematic representation of the advantages of the ligation in the genoassay.

References:

[1] Bird RE, Lemmel SA, Yu X, Zhou QA. Bioorthogonal Chemistry and Its Applications. Bioconjug. Chem. American Chemical Society 2021; 32(12): 2457–2479
[2] Schauenburg D, Weil T. Not So Bioorthogonal Chemistry. J. Am. Chem. Soc. American Chemical Society 2025; 147(10): 8049-8062
[3] Manicardi A, Cadoni E, Madder A. Hydrolysis of 5-methylfuran-2-yl to 2,5-dioxopentanyl allows for stable bio-orthogonal proximity-induced ligation. Commun. Chem. Nature Research 2021; 4(1): 146
[4] Manicardi A, Theppawong A, Van Troys M, Madder A. Proximity-Induced Ligation and One-Pot Macrocyclization of 1,4-Diketone-Tagged Peptides Derived from 2,5-Disubstituted Furans upon Release from the Solid Support. Org. Lett. American Chemical Society 2023; 25(36): 6618–6622
[5] Mattarozzi M, Careri M. The role of incurred materials in method development and validation to account for food processing effects in food allergen analysis. Anal. Bioanal. Chem. 2019; 411(19): 4465–4480

Cleavable AgroDrug Conjugates for the Increased Effectiveness of Non-Systemic Agrochemicals

Alexander Apostle[1], Giulia Cazzaniga[1], Giusy L. Fratello[1], Samuele Bongiolo[1], Francesco Talarico[1], Josephine Mittendorf[2], Roberto Orru[2], Wolfgang Schulte[2], Ralf Braun[2], Marc Linka[3], Umberto Piarulli[1], David M. Barber[2], Silvia Gazzola[1]

[1]*Department of Science and High Technology, University of Insubria, Como, Italy;*
[2]*Research and Development, Weed Control, Bayer AG, Crop Science Division, Industriepark* Höchst, Frankfurt am Main, Germany*;*
[3]*Research and Development, Entomology, Bayer AG, Crop Science Division, Alfred-Nobel-Straß*e*, Monheim, Germany*

The EU proposal for the "Sustainable Use Regulations" specified the need for new technologies in agriculture. [1] These new technologies should aim to be more targeted and, thus, use less agrochemicals overall so as to decrease their effect on the surrounding environment. Such a targeted approach to the delivery of agrochemicals can learn from the application of conjugated vectors in the delivery of anticancer payloads to cancer cells, which increase the effectiveness of the drug. [2] Similairly, agrochemicals could be conjugated to a vector, via a cleavable linker, that aids in leaf uptake and translocation, forming an AgroDrug Conjugate (AgDC). We aim to develop AgDCs using glycoside vectors that utilize sugar uptake receptors for the leaf uptake and translocation of agrochemicals to the plant phloem, whereupon the linker can be cleaved, and the agrochemical released. In our initial investigation, we conjugated various glycosides to Fipronil and found that glycoside-Fipronil AgDCs do allow for leaf uptake. It is in this light that, working with Bayer AG Crop Science Division, we have synthesized various AgDCs containing different agrochemicals. These AgDCs will help illucidate the influence of the conjugated agrochemical on translocation within the plant. Understanding the influence of the agrochemical moiety on AgDC translocation can hold the key to developing more effective applications of agrochemicals, and the development of new – more effective – technologies in agriculture.

References:

[1] European Commission: Directorate-General for Health and Food Safety, Reducing the risk and use of pesticides, Publications Office of the European Union, 2022. doi.org/10.2875/609656.
[2] Zambra M, Randelović I, Talarico F, Borbély A, Svajda L, Tóvári J, Mezó G, Bodero L, Colombo S, Arrigoni F, Fasola E, Gazzola S, Piarulli U. Optimizing the enzymatic release of MMAE from *iso*DGR-based small molecule drug conjugate by incorporation of a GPLG-PABC enzymatically cleavable linker. Front Pharmacol 2023; 14: 1215694.

Design and synthesis of streptococcus pneumoniae serotype 6a/6c oligosaccharides as vaccine antigens

Giusi Aresta, Giuseppe D'Orazio, Luigi Lay

DipartimentodiChimica, Università degli Studi di Milano
e-mail:giusi.aresta@unimi.it

Streptococcus pneumoniae (SPn) is a Gram-positive pathogen responsible for severe and potentially life-threatening infections, including pneumonia, sepsis, and meningitis [1]. A major virulencefactorofSPnisitscapsularpolysaccharide(CPS),whichenablesthebacteriumtoevade phagocytosis by the host immune system. According to the World Health Organization (WHO), vaccination remains the most cost-effective strategy for preventing pneumococcal infections. Polysaccharide conjugate vaccines (PCVs) have significantly reduced the incidence of invasive pneumococcal diseases caused by vaccine-included serotypes. However, their long-term effectiveness has been challenged by the emergence of non-vaccine serotypes (NVTs), a phenomenon known asserotype replacement [2]. A notableexample is observed within serogroup 6: following the widespread use of vaccines targeting serotypes 6A and 6B, infections caused by the non-vaccine serotype 6C have increased. In glycoconjugate vaccine design, covalent conjugation of saccharide antigens to immunogenic carrier proteins is required to induce a T cell– dependent immune response. However, multivalent formulations often require large amounts of carrier protein, which may undermine the immunogenicity of the saccharide portion due to pre- existing anti-carrier immunity. Consequently, the identification of novel carbohydrate antigens capable of eliciting cross-protective immunity against multiple serotypes represents an important goal for next-generation pneumococcal vaccines.

The CPS repeating units of SPn serogroup 6 exhibit only subtle structural variations. Serotypes 6A and 6B share a common saccharide backbone composed of galactose–glucose–rhamnose–ribitol phosphate, differing only in the glycosidic linkage between ribitol and rhamnose. In contrast, serotypes 6A and 6C possess the same glycosidic linkage but differ in the identity of one monosaccharide residue [3]. Based on these structural similarities, the development of a vaccine capable of eliciting cross-protective immunity within serogroup 6 is an attractive strategy. In this regard, the primary objective of this study is the chemical synthesis of hybrid oligosaccharide structures that combine key structural elements of the 6A and 6C CPS (compounds 1–4, Fig. 1), as potential antigens for broad-spectrum immunological evaluation.

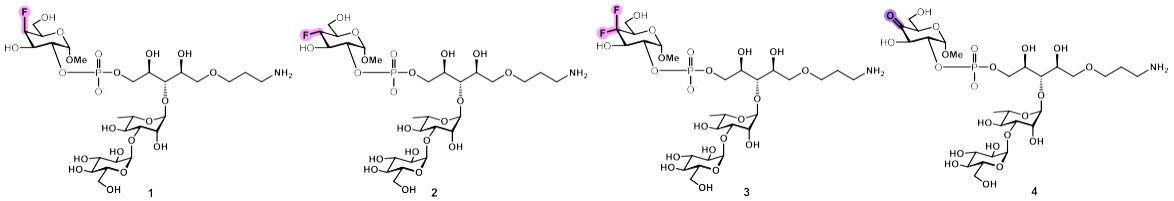


Figure1: Tetrasaccharides synthetic targets.

The synthesized oligosaccharides will be conjugated to a carrier protein to afford neoglycoconjugates, which will be immunologically evaluated in parallel with the corresponding natural6Aand6Cfragmentstoassessandcomparetheirimmunogenicity.Thelatestachievements of this endeavour will be illustrated in this communication.

References:

[1] Brilesetal.,MicrobiolSpectr.2019;7(6).
[2] Løchen,A.,Croucher,N.J.,&Anderson,R.M.2020.ScientificReports,10.
[3] Parameswar,A.R.etal.,ChemBioChem,2009,10(18),2893–2899.

BOIMPY: New Multiphoton-active Dyes for Imaging of Sub-cellular Structures

Connor Brian Armstrong, Patrycja Stachelek

Department of Chemistry, Durham University, Lower Mount Joy, South Road, DH1 3LE, UK

BODIPY dyes have attracted much attention due to their rich photophysical and chemical properties, such as high quantum yields, brightness, stability and modifiable core structure [1]. The desire to shift the photophysical qualities to longer wavelengths while retaining the *facile* synthetic pathway for building the core has driven studies towards the development of new structures, with the goal of extending the conjugated system. An emerging class of small organic molecules, bis(**BO**rondifluoride)-8-**IM**idazodi**PY**rromethene (**BOIMPY**) dyes demonstrate promising applications in the field of bio-imaging and sensing. Birthed from the **BODIPY** scaffold, the utilisation of the *meso* position by introduction of a bridging benzimidazole moiety between pyrroles allows for the binding of twin BF2 units, resulting in a bathochromic shift in dye emission [2,3].

Synthesis and characterisation of a range of **BOIMPY** dyes was achieved, in which full characterisation and spectroscopic analysis was completed. The dyes demonstrate near-IR two-photon excitation, which is beneficial for bio-imaging applications, as lower energy longer wavelengths are less cytotoxic and offer deeper tissue penetration. Current **BOIMPY** dyes exhibit localisation within lipid droplets, remaining non-toxic.

Through modification of the core, intracellular localisation of the dye within the cell can be altered, allowing for production of a range of multiphoton active, red emitting bio-probes. Through attachment of a cationic triphenylphosphine group the core can localise within the mitochondrial network, allowing for imaging with longer wavelengths, bypassing autofluorescence. Beyond this, further modification for attachment of therapeutic agents or biosensors can allow for further utilisation of the multiphoton ability of the dye.

References:

[1] Ulrich G, Ziessel R, Harriman A. The Chemistry of Fluorescent BODIPY Dyes: Versatility Unsurpassed. Angewandte Chemie 2008; 47: 1184–1201
[2] Patalag LJ, Jones PG, Werz DB. BOIMPYs: Rapid Access to a Family of Red-Emissive Fluorophores and NIR Dyes. Angewandte Chemie International Edition 2016; 55: 13340–13344
[3] Patalag LJ, Loch M, Jones PG, Werz DB. Exploring the π system of the (Aza-)BOIMPY Scaffold: Electron Rich Pyrrole Moieties Working in Concert with Electron-Depleted *Meso*-Positions. The Journal of Organic Chemistry 2019; 84: 7804-7814

Ionic Liquids as Molecular Stabilizers for Nucleic Acids: Achieving Long-Term Stabilization and Functional Stability at Room Temperature

Ananya Asmita, Sanjib Senapati

Department of Biotechnology, Indian Institute of Technology Madras, Chennai, India

Current nucleic acid storage relies on resource-intensive cold chains, which are neither sustainable nor practical for DNA-based diagnostics and RNA-based therapeutics. Ionic liquids (ILs) are increasingly used in biomolecular applications, but many are cytotoxic, posing a biocompatibility bottleneck for their use [1]. Inspired by the tunability of ILs, we ask whether biocompatible IL-water mixtures can preserve DNA and RNA at room temperature without compromising biological function. We analyse a 20-member in-house IL library to define microbial and mammalian compatibility. Spectroscopic and electrophoretic analyses show that select ILs maintain DNA structural integrity for over one year and RNA stability for three months. A reporter plasmid DNA encoding a green fluorescent protein remains intact under thermal, shear, and enzymatic stress in IL media and retains functionality for bacterial transformation and mammalian transfection. Similarly, total RNA from HEK293T cells stored in aqueous IL systems survives various stress conditions and is amplifiable through RT-PCR. All-atomistic molecular dynamics simulations reveal that IL cations form hydrogen bonds and electrostatic networks with the phosphate backbone and groove regions, thereby stabilizing the functional B-form DNA [2]. Competitive dye-displacement assays identify IL binding at multiple DNA sites, while isothermal calorimetry quantifies the binding energetics of DNA-IL interactions [3]. Collectively, these results position IL-water systems as a mechanistically grounded, cold-chain-free platform for long-term stabilization of functional nucleic acids, providing a pathway toward ambient-stable genetic materials and mRNA therapeutics.

References:

[1] Ksenia S Egorova, Evgeniy G Gordeev, and Valentine P Ananikov. Biological Activity of Ionic Liquids and Their Application in Pharmaceutics and Medicine. Chemical Reviews 2017; *117* (10): 7132-7189
[2] Ghoshdastidar D and Senapati S. Dehydrated DNA in B-form: ionic liquids in rescue. Nucleic Acids Research 2018; 46(9): 4344–4353
[3] Chandran A, Ghoshdastidar D, and Senapati S. Groove Binding Mechanism of Ionic Liquids: A Key Factor in Long-Term Stability of DNA in Hydrated Ionic Liquids? Journal of the American Chemical Society 2012; *134* (50): 20330-20339

Development of DES-Modified Lignin Nanoparticle and Nanodiamond-Based Smart Nano- Drug Delivery Platforms for the Treatment of Glioblastoma

CerenAytar[1],ÖzgeAkyazı[2]

[1]TÜBİTAKScienceHighSchool,Istanbul,Türkiye;
[2]TÜBİTAKScienceHighSchool,Istanbul,Türkiye

Glioblastomaisanaggressivebraintumorthatishighlychallengingtotreatduetoitsinvasive nature and the blood–brain barrier (BBB) (Seker-Polat *et al*., 2022). Limited BBB permeability of currentchemotherapeuticsnecessitatestargeted-next-generationnanocarriersystems(Rončević*et al*., 2025). In this study, smart nano-drug carriers based on recycled lignin nanoparticles and surface-modified nanodiamonds were developed using deep eutectic solvents (DES) in line with green chemistry principles. DES enable nanomaterial surface functionalization in a controlled, biocompatible, and environmentally friendly way; thus, preparing nanodiamond and lignin nanoparticles in DES provides a key advantage for both sustainability and drug delivery efficiency (Swebocki *et al*., 2023). In this regard Temozolomide was loaded as a model drug via physical adsorption onto the DES-functionalized nanoparticles. Physicochemical analyses (Zeta potential, DLS, FT-IR, XRD, SEM) showed that DES improved colloidal stability, added functional groups enhancing biological interaction, and maintained structural integrity. Particle size optimization to 130–180 nm promoted cellular uptake and BBB penetration. UV–Vis analyses confirmed high drug loadingefficiency(88–99%).Releasestudiesover48hoursshowed-stabilityatphysiologicalpHand a pH-responsive release under acidic tumor-like conditions, enabling targeted drug delivery in the tumormicroenvironment.PreliminarybiocompatibilitytestingonHEK-293Tcellsrevealednegligible cytotoxicity, maintaining cell viability above 90%, confirming safety. In conclusion, this multidisciplinary study presents a modular theranostic platform for glioblastoma and other BBB- related diseases, combining DES-enabled green synthesis, high drug loading, and controlled pH- responsive release, offering a sustainable, cost-effective, and environmentally friendly strategy for future nanomedicine applications.

References:

[1] Seker-Polat,F.,PinarbasiDegirmenci,N.,Solaroglu,I.,&Bagci-Onder,T.(2022).Tumorcellinfiltrationinto thebrain in glioblastoma: from mechanisms to clinical perspectives. Cancers, 14(2), 443.
[2] Rončević, A., Koruga, N., Soldo Koruga, A., & Rončević, R. (2025). Why Do Glioblastoma Treatments Fail?. *Future Pharmacology*, *5*(1), 7.
[3] Swebocki,T.,Barras,A.,Abderrahmani,A.,Haddadi,K.,&Boukherroub,R.(2023,May16).PhysicochemistryofDeep Eutectic Solvents. In Encyclopedia.

Development of potent and selective PINK1 inhibitors

Ali Baghirov[1,2], Steven Ma[2], Tara Shomali[3], Jean-François Trempe[1,3], Nicolas Moitessier[1,2]

[1]McGill University Center for Structural Biology, 3649 Promenade Sir William Osler H3G 0B1, Montréal, QC, Canada
[2]McGill University Department of Chemistry, 801 Sherbrooke St. West H3A 0B8, Montréal, QC, Canada
[3]McGill University Department of Pharmacology & Therapautics, 3655 Promenade Sir William Osler H3G 1Y6, Montréal, QC, Canada

PTEN-induced kinase 1 (PINK1) is an important player in the turnover of damaged mitochondria by E3 ubiquitin ligase Parkin [1]. This process prevents neuronal inflammation and cell death that are implicated in Parkinson's disease (PD) [1]. PINK1 phosphorylates ubiquitin (Ub) which in turn recruits Parkin to be phosphorylated by PINK1 at its Ub-like (Ubl) domain [1]. Phosphorylated Ubl domain binds RING0 domain, releasing the catalytic Rcat domain and initiating ubuiqitination and subsequent degradation of damaged mitochondria [1]. Modulating PINK1 activity has crucial pharmacological implications since PINK1 lies at the intersection of PD and cancer biology [1, 3]. Structural understanding of PINK1 interaction with small molecules requires probing of chemical space in PINK1's binding pocket, which we aim to do in this work [1]. PRT062607 was previously identified as a strong PINK1 inhibitor (IC50 ~ 2 μM) both in vivo and in vitro; however, PRT062607 is not selective for PINK1 and inhibits a number of other kinases (Fig. 1a) [2]. We set out to develop more potent and selective PINK1 binders using the scaffold of PRT062607. We developed a synthetic route to PRT062607 analogues using nucleophilic aromatic substitution (SNAr) reactions of 2,4-dichloropyrimidine-5-carboxamide (comp. 1) as our starting material. Comp. 1 first undergoes regioselective SNAr reaction with aniline analogue, followed by another SNAr with a primary amine (Fig. 1b, 1c). We created a library of nearly 30 compounds with PRT062607 scaffold to be tested for potency using kinase assay wherein phosphorylated Ub is detected on a Western Blot (Fig. 1d) [2]. Selected candidate inhibitors will then be subjected to PINK1 selectivity tests.

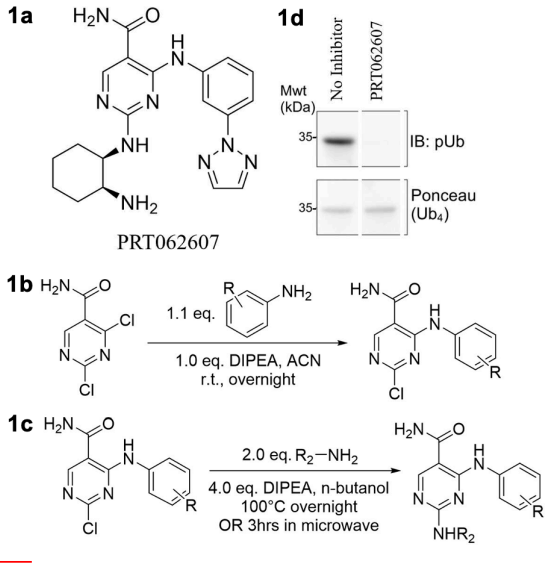


Fig. 1: Development of PINK1 inhibitors. (1a) The structure of PRT062607; (1b) The 1st SNAr reaction of comp. 1 with aniline analogue; (1c) The 2nd SNAr reaction with primary amine leading to PRT062607-type scaffold; (1d) PINK1 kinase assay: PINK1 incubated with Ub and either no inhibitor or PRT062607 are analyzed on a Western blot by detection of phosphoubiquitin (pUb) by immunoblotting (normalized to tetraubiquitin (Ub4) stained with Ponceau)

References:

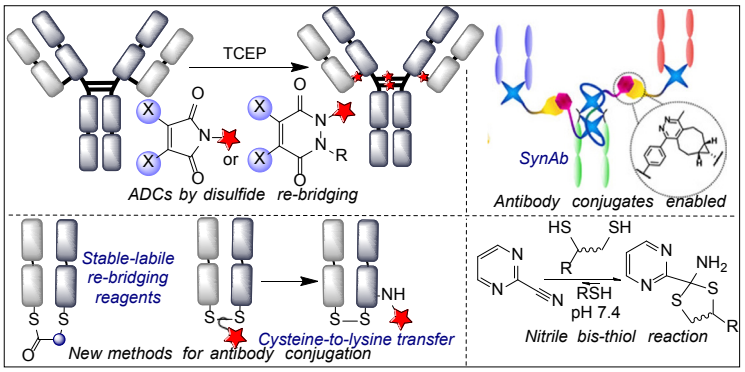
[1] Sauvé, V., Stefan, E., Croteau, N. et al. Activation of parkin by a molecular glue. Nat Commun 2024; 15: 1-12
[2] Rasool, S., Shomali, T., Truong, L. et al. Identification and structural characterization of small molecule inhibitors of PINK1. Sci Rep 2024; 14: 1-14
[3] Wang, M., Luan, S., Fan, X. et al. The emerging role of PINK1 in cancer biology. Cancer Sci 2022; 113: 4037-4047

Bis-thiol Selective Biocompatible Chemistries and Applications to Antibody Conjugates as Targeted Therapeutics

Prof. James Baker, Prof. Vijay Chudasama and coworkers

University College London, Department of Chemistry, 20 Gordon St, London, UK;

Antibody conjugates combine the exquisite targeting ability of antibodies with the diverse functionality of small molecules, and are the foundation of a range of therapeutic and diagnostic modalities. A powerful example is that of antibody drug conjugates (ADCs), which represent exemplar 'magic-bullet' anti-cancer therapeutics. It has been established that highly controlled, site-selective chemical modification strategies result in superior ADCs, including inferring improved in vivo properties. The targeting of disulfide bonds, reduced to form bis-thiols, with re-bridging reagents represents a particularly appealing option to achieve this site-selectivity. Several leading reagent classes developed in our labs to achieve disulfide re-bridging bioconjugation will be described, with a focus on recent innovations enabled (e.g. the modular construction of synthetic antibodies (SynAbs)1) and examples of new strategies explored (e.g. stable-labile designs2 and cysteine-to-lysine (CLT) transfer3 etc.), along with challenges and opportunities. Discussion will then shift to our work investigating new dynamic bis-thiol selective chemistries. This will include the recently described nitrile bis-thiol (NBT) reaction4, and ongoing work on this, and related, bioorthogonal reaction pathways.



References:

[1] Thoreau, F.; Szijj, P. A.; Greene, M. K.; Rochet, L. N. C.; Thanasi, I. A.; Blayney, J. K.; Maruani, A.; Baker, J. R.; Scott, C. J.; Chudasama, V., Modular Chemical Construction of IgG-like Mono- and Bispecific Synthetic Antibodies (SynAbs). ACS Cent. Sci. 2023, 9 (3), 476-487.
[2] Chrzastek, A.; Thanasi, I. A.; Irving, J. A.; Chudasama, V.; Baker, J. R., Dual reactivity disulfide bridging reagents; enabling new approaches to antibody fragment bioconjugation. Chem. Sci. 2022, 13 (39), 11533-11539.
[3] Forte, N.; Benni, I.; Karu, K.; Chudasama, V.; Baker, J. R., Cysteine-to-lysine transfer antibody fragment conjugation. Chem. Sci. 2019, 10 (47), 10919-10924.
[4] Patel, M.; Forte, N.; Bishop, C. R.; Porter, M. J.; Dagwell, M.; Karu, K.; Chudasama, V.; Baker, J. R., The Nitrile Bis-Thiol Bioconjugation Reaction. J. Am. Chem. Soc. 2024, 146 (1), 274-280.

Development of fluorinated lipid nanoparticles as gene delivery carriers

Martina Beccalli[1], Marta Rosati[1], Valentina Dichiarante[1], Federica Sebastiani[2,3], Marco Cavazzini[4], Federico Fenaroli[5], Francesca Baldelli Bombelli[1]

[1]Department of Chemistry, Materials, and Chemical Engineering "Giulio Natta", Politecnico di Milano, Via Bassini 6, 20133 Milan, Italy;
[2]Department of Pharmacy, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen, Denmark;
[3]Division of Physical Chemistry, Department of Chemistry, Lund University, Naturvetarvägen 22, 22100 Lund, Sweden;
[4]Consiglio Nazionale delle Ricerche (CNR) 2, Istituto di Scienze e Tecnologie Chimiche "Giulio Natta" (SCITEC) - Sezione Golgi, Via Golgi 19, 20113 Milan, Italy;
Department of Chemistry, Bioscience and Environmental Engineering, University of Stavanger, Kristine Bonnevies vei 22, 4021 Stavanger, Norway

RNA-based therapies show great promise for treating diverse diseases, but their in vivo use requires delivery systems that protect RNA from degradation, promote cellular uptake, and enable intracellular release. Lipid nanoparticles (LNPs) are already used clinically for RNA delivery, such as vaccines against SARS-CoV-2 and polyneuropathy treatment.[1] However, delivery into the cytosol is very inefficient, being less than 5%.[2] Recently, fluorination of polymers has been proved to enhance both cellular uptake and endosomal escape.[3,4] Hence, we developed a fluorinated cationic ionisable lipid (F-CIL) bearing 9 magnetically equivalent fluorine atoms per chain to be incorporated into LNPs to improve their bio-nano interactions. This lipid should enhance genetic material encapsulation, strengthen interactions with cellular membranes, and promote intracellular NA release. The fluorinated tag may also enable in vivo tracking through 19F-MRI.[5] Here we describe the F-CIL design and the LNP formulation process. Fluorinated LNPs (F-LNPs) have been characterized by dynamic light scattering, ζ-potential and small angle X ray scattering. Moreover, we present preliminary biological studies to determine efficacy and cytotoxicity of fluorinated LNPs. Results show that increasing mol % of F-CIL in LNPs leads to increased dimension, more negative surface charge, and changes in the internal structure. Enhanced cellular internalisation is exhibited by LNP containing 10 mol% F-CIL. Further structural and biological studies are planned to complete the characterisation of F-LNPs and find a relationship between composition, structure and biological function.

References:

[1] Hou X, Zaks T, Langer R, Dong Y. Lipid nanoparticles for mRNA delivery. Nat. Rev. Mater. 2021, 6, 1078-1094
[2] Herrera M, Kim J, Eygeris Y, Jozic A, Sahay G. Illuminating endosomal escape of polymorphic lipid nanoparticles that boost mRNA delivery. Biomater. Sci., 2021, 9, 4289
[3] Sancho-Albero M, Ayaz N, Sebastian V, Chirizzi C, Encinas-Gimenez M, Neri G, Chaabane L, Luján L, Martin-Duque P, Metrangolo P, Santamaría J, Baldelli Bombelli F. Superfluorinated extracellular vesicles for in vivo imaging by 19F-MRI. ACS Appl. Mater. Interfaces 2023, 15, 8974-8985
[4] Lv J, Wang H, Rong G, Cheng Y. Fluorination promotes the cytosolic delivery of genes, proteins, and peptides. Acc. Chem. Res. 2022, 55, 5, 722–733
[5] Bona BL, Koshkina O, Chirizzi C, Dichiarante V, Metrangolo P, Baldelli Bombelli F. Multibranched-based fluorinated materials: tailor-made design of 19F-MRI probes. Acc. Mater. Res. 2023, 4, 1, 71–85

Activity based (bio)sensor for the monitoring of MutyH DNA glicosylase activity

Erica Belforte, Andrea Celeste Di Pede, Alessandro Porchetta

University of Rome "Tor Vergata", via della Ricerca Scientifica 1, Rome, Italy

DNA is continuously exposed to mutagens that can induce structural damage, with significant consequences for human health. The most common oxidative lesions is 8-oxo-7,8-dihydroguanine, often resulting in G:C to T:A transversion mutations [1]. When this oxidized base pairs with cytosine within the DNA double helix, it is recognized and excised by the DNA glycosylase OGG1, initiating the base excision repair (BER) pathway. If OGG1 fails or if the damage occurs during DNA replication, a mispairing of 8-oxo-guanine: A arises. This mispairing is recognized by the glycosylase MUTYH, which removes the adenine to prevent mutagenesis. Germline mutations in MUTYH cause MUTYH- associated polyposis (MAP), a hereditary cancer syndrome that significantly increases the risk of colorectal cancer and other type of cancer (Figure 1).
Different molecular methods for assessing DNA repair activity have been developed so far, primarily centred on the use of indirect techniques[2]. However, they present limitations, including long analysis times and limited applicability in clinical settings. To enable direct monitoring of MUTYH activity, only few examples using chemically modified DNA probes with fluorescence readout have been reported[3]. They exhibit limited sensitivity and involve a high degree of chemical synthesis complexity. Here, we report a DNA-based activity sensor that enables direct and sensitive monitoring of MUTYH glycosylase activity. The probe consists of a double stem–loop DNA architecture incorporating a single 8-oxoG:A mismatch and is designed to undergo a defined conformational rearrangement upon MUTYH-mediated base excision repair. This structural transition results in fluorescence signal activation, allowing real-time kinetic monitoring of MUTYH activity. The platform was validated using purified enzymes and biological samples, demonstrating its potential as a versatile tool for studying MUTYH function in physiologically relevant contexts.

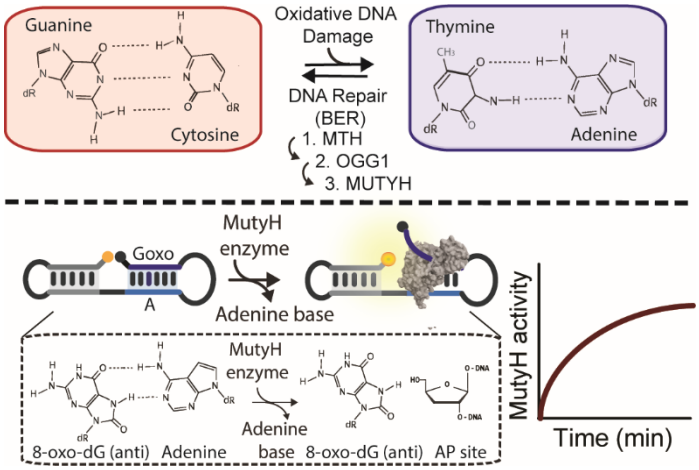


Figure 1 Schematic representation of the BER repair process and the DNA probe for the detection of MUTYH activity

References:

[1] Conlon, S. G., Khuu, C., Trasvina-Arenas, C. H., Xia, T., Hamm, M. L., Raetz, A. G., & David, S. S. Cellular repair of synthetic analogs of oxidative DNA damage reveals a key structure–activity relationship of the cancer-associated MUTYH DNA repair glycosylase. ACS Central Science, 2024,10(2), 291-301.
[2] Zhu, R. Y., Majumdar, C., Khuu, C., De Rosa, M., Opresko, P. L., David, S. S., & Kool, E. T. Designer fluorescent adenines enable real-time monitoring of MUTYH activity. *ACS Central Science*, 2020, *6*(10), 1735-1742.
[3] Nagel, Z. D., Margulies, C. M., Chaim, I. A., McRee, S. K., Mazzucato, P., Ahmad, A., ... & Samson, L. D. Multiplexed DNA repair assays for multiple lesions and multiple doses via transcription inhibition and transcriptional mutagenesis. *Proceedings of the National Academy of Sciences*, 2014, *111*(18), E1823-E1832.

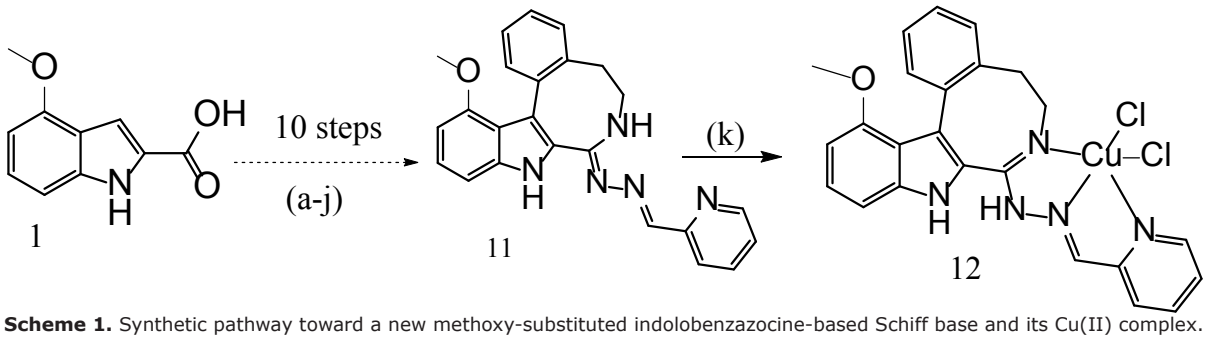
Indolobenzazocine-Derived Schiff Base and Its Copper(II) Complex as Potential Bioactive Agents

Alexandra BÎRZU, Mihaela DASCĂLU, Gheorghe ROMAN, Vladimir ARION, Maria CAZACU

Petru Poni Institute of Macromolecular Chemistry of Iaşi, 41A Grigore Ghica Vodă Alley, 700487, Iaşi, Romania, birzu.alexandra@icmpp.ro

Compounds based on the indole and benzazocine scaffold represent promising building blocks for the development of anticancer agents due to their ability to inhibit cell proliferation, induce apoptosis, and interfere with the cell cycle[1–3]. The biological activity of these structures can be tuned through structural modifications (substitutions) and coordination to transition metals, particularly Cu(II), which has been shown to enhance their anticancer activity compared to the corresponding free ligands[3–5].

In this work, key precursors for the synthesis of a methoxy-substituted indolobenzazocine structural frameworks are presented, on the way to Schiff base formation with 2-formylpyridine and its subsequent coordination with Cu(II) (Scheme 1). Preliminary molecular modeling studies indicated that methoxy substitution on the indolobenzazocine framework could enhance the biological activity of the resulting derivatives. The multistep synthetic sequence involved esterification of 4-methoxy-1*H*-indole-2-carboxylic acid, followed by protection of the indole nitrogen with an ethoxymethyl group, ester hydrolysis, and amide coupling with 2-(2-iodophenyl)ethanamine. Subsequent Boc protection of the amide nitrogen enabled an intramolecular Pd(II)-catalyzed Heck cyclization to form the tetracyclic indolobenzazocine scaffold. After deprotection and thionation to the corresponding thiolactam, hydrazone formation and condensation afforded the target Schiff base (**HL**), which was further coordinated to Cu(II) to give the complex **[Cu(HL)Cl$_2$]**. All intermediates were purified by column chromatography or recrystallization and characterized by NMR and ESI mass spectrometry, and, several intermediates by single crystal X-ray diffraction. Preliminary biological evaluation supports their investigation as potential anticancer agents.



Scheme 1. Synthetic pathway toward a new methoxy-substituted indolobenzazocine-based Schiff base and its Cu(II) complex.

Acknowledgements:

This work was financially supported by a grant from the Romanian National Authority for Research, project no. PNRR-III-C9-2023-I8-99 within the National Recovery and Resilience Plan.

References:

[1] Xu D, Xu Z. Indole Alkaloids with Potential Anticancer Activity. Curr Top Med Chem. 2020;20(21):1938–1949. doi: 10.2174/1568026620666200622150325. PMID: 32568021.
[2] Meng-Lan Luo, Wei Huang, Hong-Ping Zhu, Cheng Peng, Qian Zhao, Bo Han. Advances in indole-containing alkaloids as potential anticancer agents by regulating autophagy. Biomedicine & Pharmacotherapy. 2022;149:112827. doi: 10.1016/j.biopha.2022.112827.
[3] Kuznetcova I, Ostojić M, Gligorijević N, Aranđelović S, Arion VB. Enriching Chemical Space of Bioactive Scaffolds by New Ring Systems: Benzazocines and Their Metal Complexes as Potential Anticancer Drugs. Inorg Chem. 2022 Dec 19;61(50):20445–20460. doi: 10.1021/acs.inorgchem.2c03134. Epub 2022 Dec 6. PMID: 36473464; PMCID: PMC9768754.
[4] Behera N, Behera T, Rout J, Moharana S. Significant Aspects of Heterocyclic Schiff Bases and Their Metal Complexes. IntechOpen. 2024. doi: 10.5772/intechopen.115087.
[5] C. Wittmann, O. Dömötör , I. Kuznetcova , G. Spengler , J. Reynisson , L. Holder , G. J. Miller , E. A. Enyedy , R. Bai, E. Hamel and V. B. Arion , Dalton Trans., 2023, 52, 9964 —9982.

Advanced Shape Memory Polyurethanes for Tendon Tissue Regeneration

Beatrice L. Bona, Federica Compostella, Caterina Ricci, Andrea Spitaleri, Stefano Vaghi and Elena Del Favero.

Department of Medical Biotechnology and Translational Medicine, University of Milan, Milano (Italy)

Tendinopathies are a group of debilitating musculoskeletal conditions that affect hundreds of millions of people globally, causing persistent pain, functional limitations, reduced quality of life, and a significant socioeconomic impact. Their complex aetiology makes the development of universally effective therapeutic solutions particularly challenging. Even when surgical intervention is employed, tendon repair commonly results in fibrovascular scar tissue, displaying inferior mechanical properties, and reduced elasticity relative to native tendon tissue[1]. These limitations increase the risk of re-injury, chronic symptoms, and long-term functional deficits.

To address these challenges, regenerative medicine approaches have gained substantial attention, with scaffold-based strategies emerging as especially promising[2]. Engineered scaffolds can provide mechanical support while simultaneously delivering biological and structural cues that regulate cell behavior, stimulate extracellular matrix production, and promote the formation of more organized, tendon-like tissue. Through careful control of material composition, architecture, and biofunctionalization, scaffolds can actively influence the healing process toward more regenerative outcomes.[1,2]

Within the TEN4CARE Horizon project, this work focuses on the development of a novel class of shape memory polyurethane biomaterials intended as bulk components of advanced scaffolds for tendon repair. These polymers enable precise tuning of mechanical performance and biological interactions. By modifying polymer composition and incorporating targeted chemical functionalization, both shape memory behavior and biointerface properties can be tailored to meet the mechanical and surgical demands of tendon healing.

Herein we will present initial insights into the rational design, synthesis, and characterization of advanced thermoplastic shape-memory polyurethanes, laying the groundwork for innovative medical devices aimed at improving tendon regeneration.

References:

[1] Ratcliffe A, Butler DL, Dyment NA, Cagle PJ, Proctor CS, Ratcliffe SS, Flatow LL. Scaffolds for Tendon and Ligament Repair and Regeneration. *Ann Biomed Eng*. 2015 March ; 43(3): 819–831. doi:10.1007/s10439-015-1263-1.
[2] Wang S, Ou Z, Xiao F, Feng X, Tan L, Cheng S, Wu D, Yang C, Yao H. Advanced bioactive materials and strategies for tendon repair and function restoration. Journal of Orthopaedic Translation 55 (2025) 204–227.

We thank the TEN4CARE project (Grant agreement ID: 101178590) for funding

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

Clara Bonin, Blaise Dumat, Arnaud Gautier

Sorbonne université- ENS PSL, 4 Place Jussieu, Paris, France

Bioluminescence is the production of light by living organisms via a chemical reaction between an enzyme (luciferase) and its substrate (luciferin). This natural phenomenon has been used to probe biological processes in cellular and animal models [1]. However, natural luciferins emit below 600 nm, where light is strongly absorbed by biological tissues. Hence the importance to develop far-red or NIR-emitting bioluminescent reporters which can be obtained by engineering both the luciferin to tune its emission wavelength, and the luciferase to ensure the compatibility between the enzyme and its modified substrate. In this project, we explore a bioluminescent system from the N. nambi fungus, because of the small size (28.5 kDa) of its luciferase nnLuz and the simple structure of its luciferin, 3-hydroxyhispidin, which gives a green luminescence (525 nm) and shows potential for tunability. A library of 3-hydroxy-hispidin analogs was synthesized during the first part of the project. The luciferin's structure resembles a dipolar chromophore, the luminescence can be red-shifted using known strategies: increasing the electron donor's strength and the length of π-conjugation. To obtain bright bioluminescent reporters, we will perform directed evolution on nnLuz to optimize binding and reaction with the most promising substrates. Protein mutant libraries will be generated by random mutagenesis and expressed in bacteria or yeast for high-throughput evaluation and screening of bioluminescence properties using camera-based imager [2]. Camera-assisted colony screening will allow the identification of variants with high bioluminescence efficiency. In addition to enhancing the brightness, we may also discover orthogonal luciferases useful for multiplexing experiments.

References:

[1] Yao Z, Zhang BS, Prescher JA. Advances in bioluminescence imaging: new probes from old recipes. Curr Opin Chem Biol. 2018; 45:148-156
[2] Love AC, Caldwell DR, Kolbaba-Kartchner B, Townsend KM, Halbers LP, Yao Z, Brennan CK, Ivanic J, Hadjian T, Mills JH, Schnermann MJ, Prescher JA. Red-Shifted Coumarin Luciferins for Improved Bioluminescence Imaging. J Am Chem Soc. 2023, 15 ;145(6) : 3335-3345.

Synthesis of piperidine-based profluorescent nitroxides and evaluation of their sensing properties

Sasikan Boonsanong, Supattra Kaewtaro, Chittreeya Tansakul

Division of Physical Science and Center of Excellence for Innovation in Chemistry, Faculty of Science, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand

Profluorescent nitroxides are molecular probes used for the detection of redox-active analytes [1]. In these systems, the nitroxide moiety functions as a fluorescence quencher, suppressing emission from the attached fluorophore. Upon reaction with electron- or hydrogen-donating analytes, the nitroxide is reduced to a diamagnetic hydroxylamine, leading to fluorescence recovery [2]. In this study, three piperidine-based profluorescent nitroxides (probes **1**, **2**, and **3**) were synthesized and evaluated for their ability to detect ascorbic acid. The performance of these probes was compared to evaluate their sensing efficiency, and future studies are planned to include comparisons with pyrrolidine-based profluorescent nitroxide probes [3]. Probe **1** was synthesized via an ester coupling reaction, while probes **2** and **3** were prepared through amide coupling reactions. For probes **1** and **2**, subsequent click coupling reactions were employed to install the fluorophore moiety. The results revealed that probe **3** exhibited the strongest fluorescence quenching efficiency, followed by probes **1** and **2**, respectively. In contrast, fluorescence emission studies demonstrated that probe **2** showed the highest fluorescence recovery, followed by probes **1** and **3**, respectively. These findings highlight the influence of probe structure and linker chemistry on both quenching efficiency and fluorescence response, providing valuable insights for the rational design of profluorescent nitroxide-based sensors.

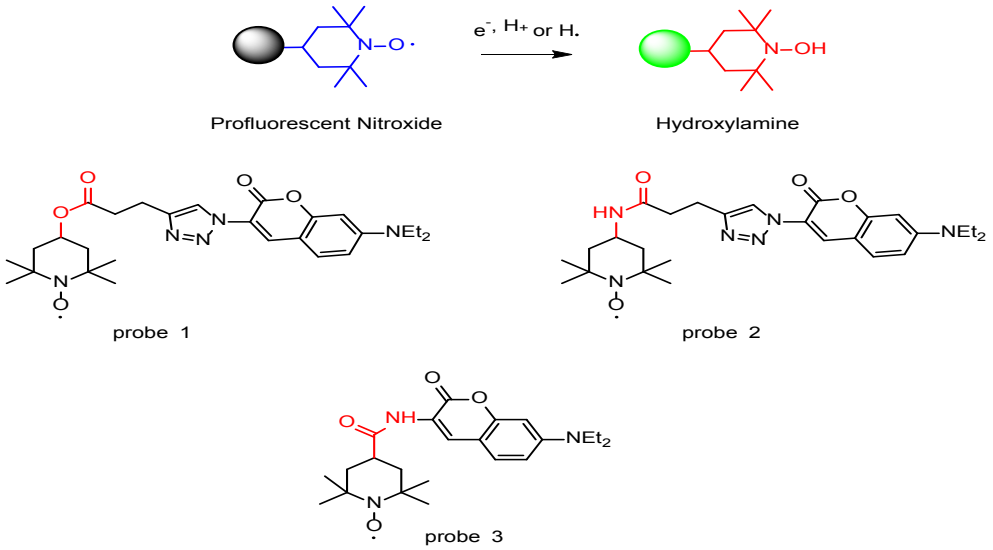


Fig. 1 The chemical structures of probes **1**, **2**, and **3**

References:

[1] Blinco JP, Fairfull-Smith KE, Morrow BJ, Bottle SE. Profluorescent nitroxides as sensitive probes of oxidative change and free radical reactions. Aust J Chem 2011; 64: 373-389
[2] Matsuoka Y, Ohkubo K, Yamasaki T, Yamato M, Ohtabu H, Shirouzu T, Fukuzumi S, Yamada K. A profluorescent nitroxide probe for ascorbic acid detection and its application to quantitative analysis of diabetic rat plasma. RSC Adv 2016; 6: 60907-60915
[3] Cerullo G, Negro M, Parimbelli M, Pecoraro M, Perna S, Liguori G, Rondanelli M, Cena H, D'Antona G. The Long History of Vitamin C: From Prevention of the Common Cold to Potential Aid in the Treatment of COVID-19. Front. Immunol 2020; 11: 574029

Beyond the Cavity: Tuning Substrate and Product Selectivity through Supramolecular Confinement

Francesca Bordignon, Fabrizio Fabris, Alessandrro Angelini, Alessandro Scarso

F. Bordignon, Prof. F. Fabris, Prof. A. Angelini, Prof. A. Scarso, Dipartimento di Scienze Molecolari e Nanosistemi, Università Ca' Foscari Venezia, Via Torino 155, 30172 Mestre Venezia (ITALY)

Supramolecular catalysis within the hexameric resorcin[4]arene capsule (R6) has emerged as a powerful strategy for mimicking enzymatic behavior, offering a unique chemical environment to control reaction pathways. This research explores the versatility of R6 as both a standalone nano-catalyst[1] and a nanoreactor[2] for encapsulated transition metals, with a specific focus on achieving non-conventional selectivities.
In the field of terpene chemistry, the capsule's internal cavity acts as a Brønsted acid catalyst, significantly influencing product selectivity. Specifically, the cyclization of CBD[3] demonstrates how spatial confinement can divert traditional reaction pathways. For sclareol, the R6 environment promotes a shift toward the C8 carbocation pathway, which is typically disfavored in bulk acidic media, highlighting the capsule's in stabilizing specific transition states.
Furthermore, the encapsulation of Au(I) catalysts within R6 enables sophisticated substrate selectivity[4] during the hydration and cyclization of alkynes. While uncofined gold catalysts show negligible discrimination between different alkynes, the R6 cavity imposes strict steric constraints, favoring the transformation of compact substrates over flexible ones with selectivity ratios reaching up to 30:1. Beyond selectivity, the capsule enhances catalyst stability and alters regioselectivity, occasionally promoting the formation of aldehydes over the standard Markovnikov products. Collectively, these studies underscore the potential of supramolecular capsule to provide precise control over complex molecular transformations through confinement and site-isolation effects.

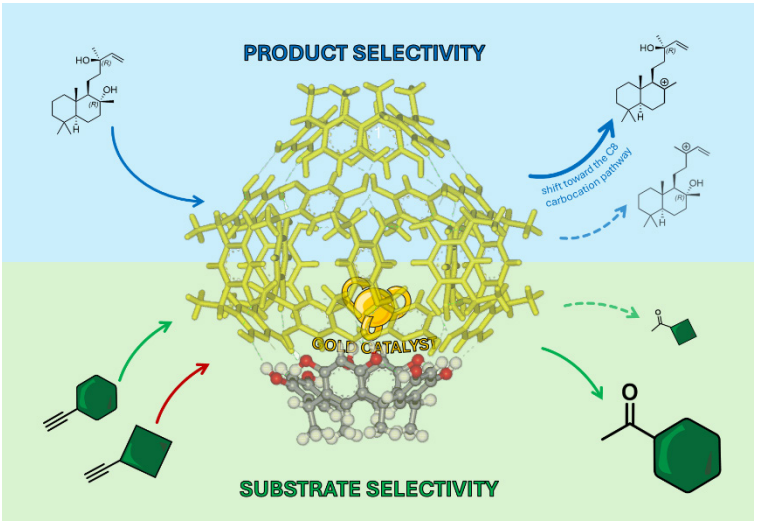


Figure 1. Supramolecular confinement within the R6 capsule provides product and substrate selectivity.

References:

[1] (a) Borsato G, Scarso A, Catalysis Within the Self-Assembled Resorcin[4]arene Hexamer, In: Sadjadi S., editors.: Organic Nanoreactors, Chennai: Academic Press; 2016, 203-234. (b) Zhu Y, Rebek J, Yu Y. Cyclizations catalyzed inside a hexameric resorcinarene capsule. Chem. Commun. 2019; 55: 3573-3577. (c) Catti L, Zhang Q, Tiefenbacher K. Advantages of Catalysis in Self-Assembled Molecular Capsules. Chem. Eur. J. 2016; 22: 9060-9066. (d) Iuliano V, Della Sala P, Talotta C, De Rosa M, Soriente A, Gaeta C, Neri P. Supramolecular control on reactivity and selectivity inside the confined space of H-bonded hexameric capsules. Curr. Opin. Coll. Interf. Sci. 2023; 65: 101692.
[2] Cavarzan A, Scarso A, Sgarbossa P, Strukul G, Reek JNH, Supramolecular Control on Chemo- and Regioselectivity via Encapsulation of (NHC)-Au Catalyst within a Hexameric Self-Assembled Host. J. Am. Chem. Soc. 2011; 133: 2848-2851.
[3] Bordignon F, Calmanti R, Alvise P, Fabris F, Scarso A. Confinement Effects in Catalysis: Steering the Product Selectivity in Cannabidiol Isomerization by the Resorcinarene Supramolecular Capsule. ChemCatChem 2024; e202400278.
[4] Lorenzetto T, Bordignon F, Munarin L, Mancin F, Fabris F, Scarso A. Substrate Selectivity Imparted by Self-Assembled Molecular Containers and Catalysts. Chem. Eur. J. 2024; 30: e202301811.

3D Bioprinted Tissue Models, Impact of Glycosignature and Morphology in IBD

Ilaria Borghi[1], Francesca Cadamuro[1], Marco Piazzoni[1], Francesco Nicotra[1], Laura Russo[1,2]

[1] *Università degli Studi Milano -Bicocca, Vedano al Lambro (MB), Italy;*
[2] *Fondazione IRCCS San Gerardo dei Tintori*

Inflammatory bowel disease (IBD) comprises a spectrum of chronic, relapsing-remitting inflammatory conditions of the gastrointestinal tract, primarily characterized by mucosal barrier dysfunction and increased intestinal permeability. To overcome the limitations of traditional 2D models, this project utilizes high-resolution Digital Light Processing (DLP) bioprinting to fabricate 3D scaffolds that recapitulate the complex intestinal microenvironment. Hydrogels based on methacrylated gelatin, collagen and hyaluronic acid (GelMA, ColMA, HAMA) are employed to reconstruct the intestinal extracellular matrix (ECM)[1]. The research focuses on the impact of altered glycosignature, specifically fucosylation and sialylation, which are key regulatory glycosignatures known to be dysregulated in IBD pathogenesis. Specifically, fucose (α-Fuc-(1→3)-β-D-Gal) and sialic acid (α-NeuNAc-(2→6)-β-D-Gal) motifs are covalently conjugated onto the 3D-printed scaffolds through a heterogeneous reductive amination reaction targeting the primary amino groups (lysine residues) of collagen and gelatin[2].
Scaffold morphology, specifically projections mimicking intestinal villi, is designed to influence the growth and assembly of a co-culture of Caco-2 enterocyte-like cells and HT29-MTX mucus-producing cells. In the current phase, these DLP-based constructs are assessed for mechanical stability and shape fidelity.
This research seeks to establish a robust 3D platform that can be extended to patient-derived cells for personalized medicine and drug testing, bridging the gap between simplified in vitro cultures and clinical applications.

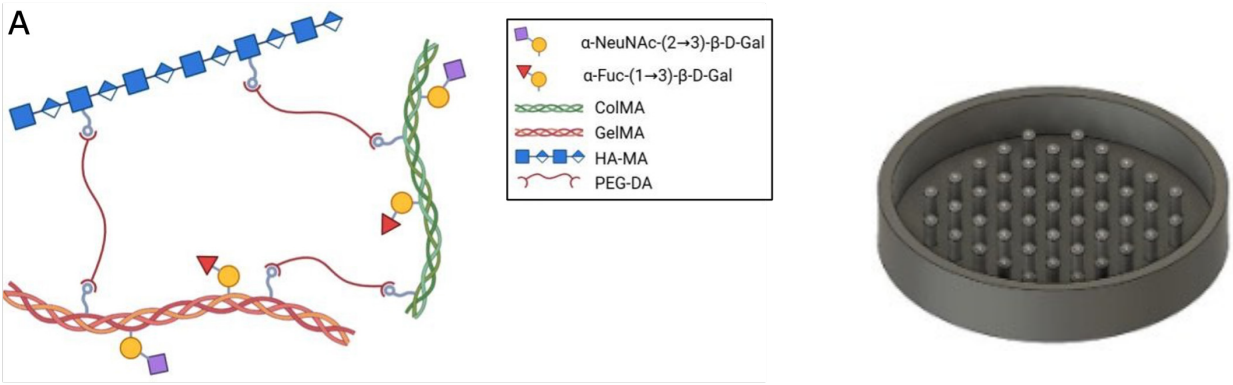


Figure 1: A) Schematic representation of the hydrogel (GelMA, ColMA, HAMA) and pathological sugar motifs (fucose and sialic acid) covalently conjugated to the scaffold, B) CAD model of the hydrogel scaffold mimicking the human intestinal villi.

Acknowledgments:

Iniziativa "PNC0000003 - "ANTHEM: AdvaNced Technologies for Human-centrEd Medicine". CUP BICOCCA B53C22006670001.

References:

[1] Cadamuro F, Nicotra F, Russo L. 3D printed tissue models: From hydrogels to biomedical applications. Journal of Controlled Release 2023, 354: 726–745.
[2] Cadamuro F, Marongiu L, Marino M, Tamini N, Nespoli L, Zucchini N, Terzi A, Altamura D, Gao Z, Giannini C, Bindi G, Smith A, Magni F, Bertini S, Granucci F, Nicotra F, Russo L. 3D bioprinted colorectal cancer models based on hyaluronic acid and signalling glycans. Carbohydrate Polymers 2023, 302: 120395.

Integrating Molecular Dynamics with Self-Assembly Characterization of Peptides for Antimicrobial Applications

Flavia Borrelli[1], Alfonso Gautieri[2], Nina Bono[1], Claudia Pigliacelli[1]

[1] *Department of Chemistry, Materials and Chemical Engineering "G. Natta", Politecnico di Milano, Via Edoardo Bassini 6, 20133, Milan Italy*
[2] *Department of Electronics, Information and Bioengineering, Politecnico di Milano, Piazza Leonardo da Vinci 32, 20133, Milan Italy*

The global threat of antimicrobial resistance requires innovative therapeutic strategies. While antimicrobial peptides (AMPs) are promising alternatives, their clinical translation is often restricted by high production costs, systemic toxicity, and poor metabolic stability. This work aims to overcome these barriers by designing short, self-assembling peptides that exploit supramolecular organization to enhance stability and reduce toxicity compared to their monomeric counterparts.[1]
We integrated coarse-grained molecular dynamics simulations to predict aggregation propensity and guide the development of a peptide library.[2] Experimental validation of initial candidates via circular dichroism (CD) spectroscopy revealed spectral features consistent with intermolecular π-π stacking (**Fig. 1a**) [3]. Dynamic light scattering (DLS) showed the formation of nanoscale aggregates (**Fig. 1b**) and transmission electron microscopy (**Fig. 1c**) confirmed the formation of spherical aggregates.

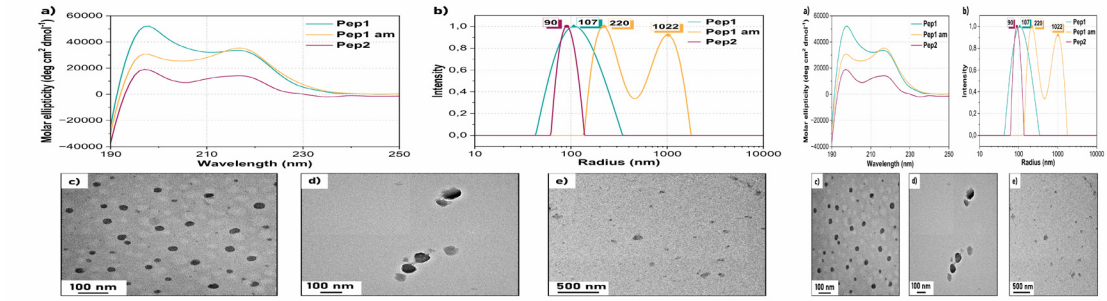


Figure 1: CD (**a**) and DLS (**b**) characterization of self-assembled peptides. TEM analysis of Pep1 (**c**).

Preliminary in vitro antibacterial assays by standard broth microdilution methods showed limited activity under conventional mass-based dosing (μg/mL).[4] Ongoing work is therefore focused on further structural optimization of peptide sequences to enhance antibacterial performance and refine supramolecular structure activity relationships. Parallely, as we expect the bioactive entity tob e the assebled nanoparticle rather than the peptide monomer, we are developing adapted dosimetry protocols to quantify nanoparticle number concentration per mL, enabling more accurate evaluation of antimicrobial efficacy in self-assembled peptide systems.

References:

[1] Chou S, Guo H, Zingl FG, Zhang S, Toska J, Xu B, ... & Mou X. Synthetic peptides that form nanostructured micelles have potent antibiotic and antibiofilm activity against polymicrobial infections. Proc Natl Acad Sci 2023; 120: e2219679120
[2] Frederix PW, Scott GG, Abul-Haija YM, Kalafatovic D, Pappas CG, Javid N, ... & Tuttle T. Exploring the sequence space for (tri-) peptide self-assembly to design and discover new hydrogels. Nat Chem 2015; 7: 30-37
[3] Azoulay Z, Aibinder P, Gancz A, Moran-Gilad J, Navon-Venezia S, Rapaport H. Assembly of cationic and amphiphilic β-sheet FKF tripeptide confers antibacterial activity. Acta Biomater 2021; 125: 231-241
[4] International Organization for Standardization (ISO), ISO 20776-1:2019.

Tackling Pancreatic Ductal Adenocarcinoma with an Innovative Covalent Targeting of Glycolysis

Giulia Antonini[1], Alessio Mainetti[1], Alessandra Fiore[2], Antonio Scarano[3], Lea Sicuro[4], Serena Faggiano[3], Adriana Celesia[2], Chiara Tesoriero[5], Raffaella Pacchiana[2], Andrea Vettori[5], Luca Mollica[4], Lucia Tamborini[1], Massimo Donadelli[2], Paola Conti[1], Stefano Bruno[3], Chiara Borsari[1,*]

[1]Department of Pharmaceutical Sciences, University of Milan, Via Mangiagalli 25, 20133 Milan, Italy
[2]Department of Neurosciences, Biomedicine and Movement Sciences, Section of Biochemistry, University of Verona, 37134 Verona, Italy
[3]Department of Food and Drug, University of Parma, Parco Area delle Scienze 23/a, 43124, Parma, Italy
[4]Department of Medical Biotechnologies and Translational Medicine c/o L.I.T.A / University of Milan, Via F.lli Cervi 93, 20090 Segrate (MI), Italy
[5]Department of Biotechnology, University of Verona, 37134 Verona, Italy

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive cancer with poor prognosis. Metabolic reprogramming drives its malignancy, making cancer metabolism an attractive therapeutic target. However, anti-glycolytic therapies face clinical limitations due to toxicity. Inhibition of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB), particularly the PFKFB3 isoform, may offer a safer therapeutic window.[1] Herein, we report the first covalent PFKFB3 inhibitor featuring moderately reactive, drug-like warheads targeting a previously unexplored cysteine within the active site. Biochemical assays confirmed irreversible enzyme inhibition and covalent binding. Our lead compound selectively reduced viability across multiple PDAC cell lines and, in vivo, effectively suppressed tumor growth in zebrafish xenograft models, highlighting its potent and specific antitumor activity. Moreover, combination of compound **6** with standard chemotherapeutics (Gemcitabine, FOLFIRINOX) enhanced efficacy, revealing synergistic effects. This work introduces a novel covalent PFKFB3 inhibitor and supports anti-glycolytic therapy as a promising strategy for PDAC treatment.

References:

[1] Boyd S, Brookfield JL, Critchlow SE, Cumming IA, Curtis NJ, Debreczeni J, Degorce SL, Donald C, Evans NJ, Groombridge S, Hopcroft P, Jones NP, Kettle JG, Lamont S, Lewis HJ, MacFaull P, McLoughlin SB, Rigoreau LJ, Smith JM, St-Gallay S, Stock JK, Turnbull AP, Wheatley ER, Winter J, Wingfield J. Structure-Based Design of Potent and Selective Inhibitors of the Metabolic Kinase PFKFB3. J Med Chem. 2015; 58 (8): 3611-25.

Acknowledgements:

This work was supported by the Guido Berlucchi Foundation Mini Grant CANCERCOPE, number G43C23002440001, the Umberto Veronesi Foundation, My first SEED Grant DM 737/2021 from MUR, Proof of Concept funding from the Seed4Innovation acceleration program and Fondo Italiano per la Scienza FIS2 (grant number, FIS-2023-02269) from Italian Ministry of University and Research (to C.B.). In addition, this study was supported by funds from University of Milan - Piano di sostegno alla Ricerca 2025 - LINEA 2.

Development of Novel Solid-Phase Synthesis for Nucleoside Mono-, Di- and Triphosphates and their Use to Detect DNA Replication in Malaria Parasites

Anne-Sophie C. Braun, David H. Hilko, Katherine T. Andrews, Sally-Ann Poulsen

Institute for Biomedicine and Glycomics, Griffith University, Nathan, QLD, Australia

Analogues of the endogenous nucleoside thymidine are widely used as metabolic chemical probes to investigate DNA replication and dissect features of the cell cycle or other cellular processes. *Plasmodium*, the parasite that causes malaria, lacks the enzyme thymidine kinase needed for the incorporation of current thymidine-based chemical probes into its DNA. To address these limitations, we designed, synthesised and validated next-generation chemical probes based on the 5-vinyl-2'-deoxyuridine monophosphate (VdU-$P_{1)}$ scaffold in *Plasmodium*. The VdU-based probes enable the detection of labelled parasites via a catalyst-free inverse-electron-demand Diels-Alder (IEDDA) click-reaction with a fluorescent tetrazine dye and was compatible in live-cell DNA labelling and imaging, reported by us recently.1 To provide malaria researchers with new and better tools to study the cell cycle and growth of *Plasmodium*, we designed VdU-based probes that enter the thymidine metabolism pathway further downstream than VdU-P1, skipping other kinases that are potential metabolic roadblocks. The synthesis of nucleoside di- and triphosphate probes using known methods is challenging due to very low product yields, complex mixutres of reaction byproducts, and the highly polar nature of the desired compounds, making purification difficult and laborious.2 To address the limitations of current methods we have developed a novel solid-phase synthesis. Yields are high and the synthetic approach is compatible with sensitive functional groups, leading to clean reactions and uncomplicated purification (Figure 1). I will describe this new synthesis approach and the application of mono-, di- and triphosphates of VdU to study DNA synthesis in wild type P. falciparum parasites.

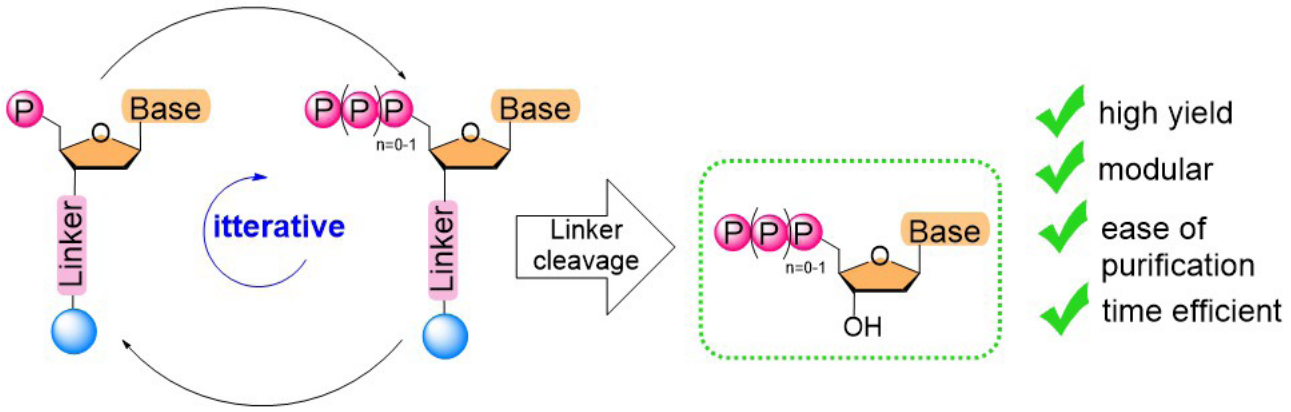


Fig. 1: New solid-phase synthesis method for nucleoside di- and triphosphate chemical probes

References:

[1] Braun, A.-S. C.; Fisher, G. M.; Hilko, D. H.; Macdonald, J. R.; Thomas, S.; Andrews, K. T.; Poulsen, S.-A. Vinyl-DNADetect Probes to Assess DNA Proliferation in Plasmodium Parasites using Inverse-Electron-Demand Diels–Alder Click Reactions. *ACS Chemical Biology* **2025**. DOI: 10.1021/acschembio.5c00429.
[2] Roy, B.; Depaix, A.; Périgaud, C.; Peyrottes, S. Recent Trends in Nucleotide Synthesis. *Chemical Reviews* **2016**, *116* (14), 7854-7897. DOI: 10.1021/acs.chemrev.6b00174.

Modular Quantum Dot Nanoprobes for Targeted pH Sensing at the Plasma Membrane of HER2+ Cancer Cells

Sofía Blas-Gómez[1], Andrés Garzón-Ruiz[1,2], Carlos A. Moreno[3], Agustín Lara[3], Iván Bravo[1,*]

[1] *Departamento de Química Física, Facultad de Farmacia, Universidad de Castilla-La Mancha, 02008, Albacete, Spain;*
[2] *Departamento de Química Física y Analítica, Universidad de Jaén, 23071, Jaén, Spain;*

[3] *Departamento de Química Inorgánica, orgánica y bioquímica, Facultad de Farmacia, Universidad de Castilla-La Mancha, 02008, Albacete, Spain;*

Nanoscale fluorescent biosensors offer unique opportunities to monitor biochemical processes, yet their efficacy is often limited by poor control over cellular and subcellular localization. This work introduces a general strategy to reprogram these sensors using a modular architecture that integrates a fluorescent core, a sensing ligand layer, and a biological targeting vector. As a proof of concept, an intracellular pH-sensitive quantum dot biosensor (QD-DPA) was functionalized with the HER2-targeting antibody trastuzumab (QD-DPA-AB). Physicochemical characterization confirmed successful conjugation and high colloidal stability. Using fluorescence lifetime imaging microscopy (FLIM), we demonstrated that this reprogramming redirected the biosensor from non-specific intracellular uptake to the plasma membrane of HER2+ SKBR3 cancer cells, effectively discriminating them from HER2-negative MCF7 cells (Luminal A subtype). The nanobiosensor preserved its robust, monotonic lifetime-based pH response (range 6.0–8.0), providing a quantitative and concentration-independent readout. This platform enabled real-time monitoring of perimembranous pH dynamics and successfully visualized drug-induced proton fluxes following pharmacological inhibition of H+/K+-ATPases with omeprazole, which caused a localized pH increase of over two units at the cell surface. By decoupling sensing modality from biological addressability, this framework establishes a transferable blueprint for engineering next-generation nanodevices for precision diagnostics and mechanistic studies in defined biological microenvironments.

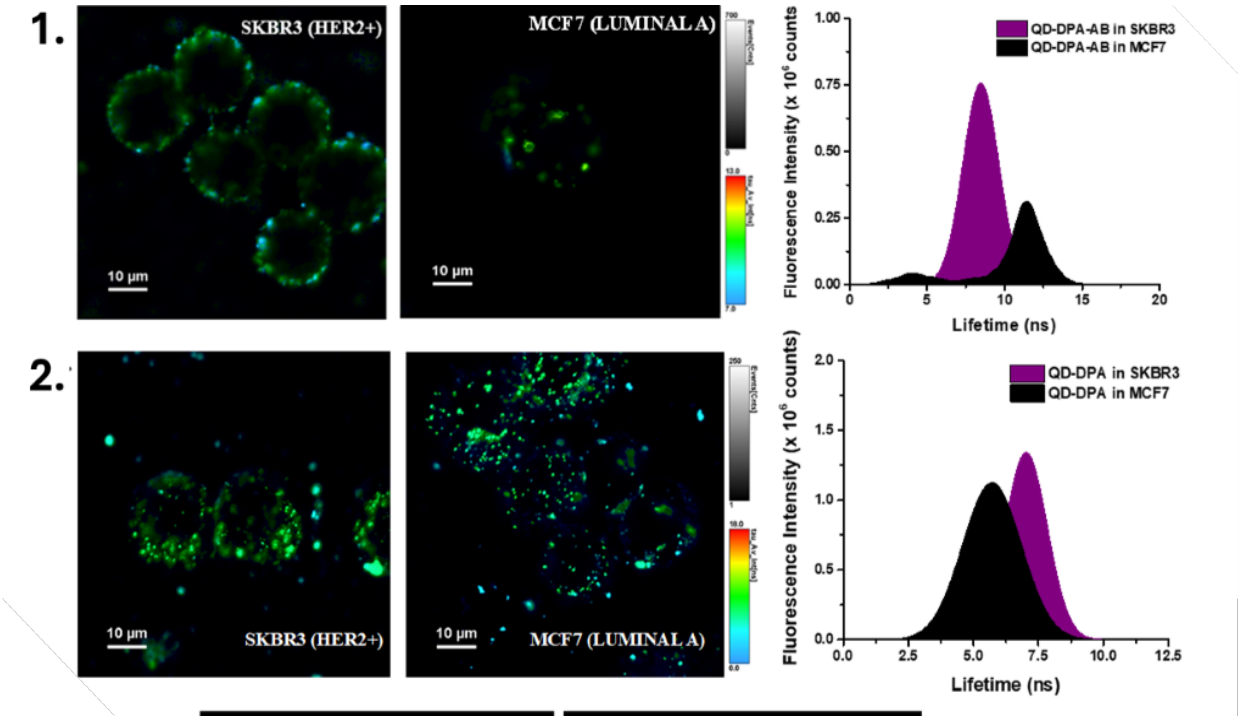


Figure 1. Evaluation of cellular selectivity using FLIM images and fluorescence lifetime histograms after 2 h of incubation: (1) targeted nanobiosensor (QD-DPA-AB) and (2) untargeted control (QD-DPA) in HER2+ (SKBR3) and HER2-, Luminal A, (MCF7) breast cancer cell lines.

References:

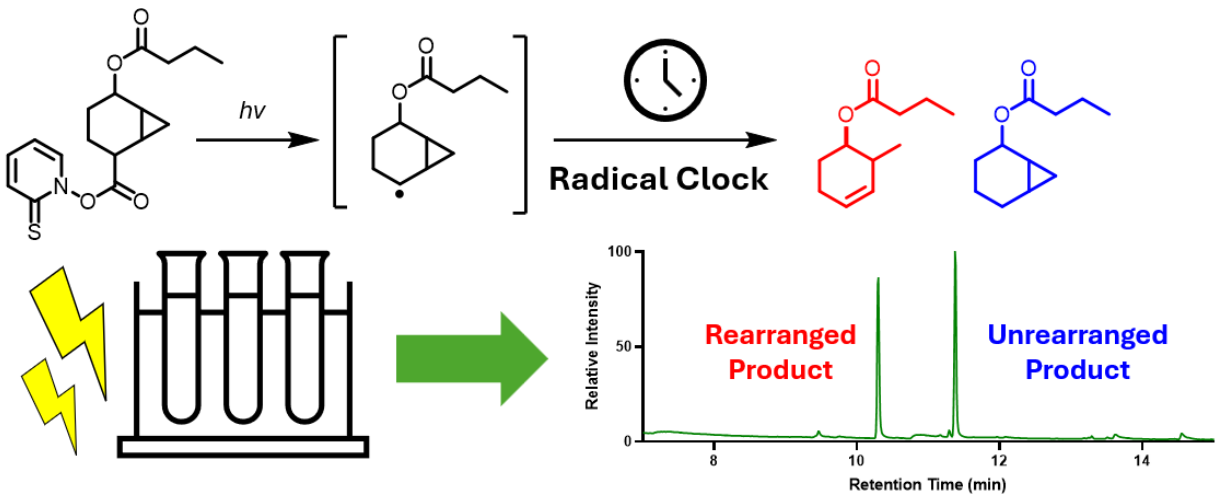
[1] Pacheco-Liñán PJ, Bravo I, Nueda ML, Albaladejo J, Garzón-Ruiz A. Functionalized CdSe/ZnS Quantum Dots for Intracellular pH Measurements by Fluorescence Lifetime Imaging Microscopy. ACS Sens 2020; 5: 2106–2117
[2] Herrera-Ochoa D, Pacheco-Liñán PJ, Bravo I, Garzón-Ruiz A. A novel quantum dot-based pH probe for long-term fluorescence lifetime imaging microscopy experiments in living cells. ACS Appl Mater Interfaces 2022; 14: 2578–2586

Substituted Norcaranes as Mechanistic Radical Clock Probes: Characterization of Radical Rearrangement

Julia B. Buczynski, Luke R. Churchman, Craig M. Williams, James J. De Voss

The University of Queensland, address, Brisbane, Australia

Cytochromes P450 (P450s) are heme-containing monooxygenases capable of catalysing a diverse array of transformations. Norcarane (bicyclo[4.1.0]heptane) has been widely employed as a mechanistic probe to distinguish between concerted enzymatic mechanisms and those proceeding via radical or cationic intermediates, as each pathway yields distinct rearranged products. In most P450 systems, product distributions consistent with radical intermediates are typically observed. However, when norcarane derivatives were used to probe the mechanism of CYP101B1, enzymatic turnover produced no rearranged products, suggesting a mechanistic divergence from canonical P450 reactivity. To determine whether this unexpected outcome arose from the enzyme or the probe itself, the intrinsic rearrangement behaviour of the norcarane derivatives was systematically investigated, confirming their suitability as mechanistic probes. Validation was achieved by generating the putative radical intermediate, elucidating the structures of the resulting rearrangement products, and determining the rate of rearrangement. To generate the radical intermediates, the pyridine-2-thione-*N*-oxycarbonyl (PTOC) esters of both *endo*- and *exo*-bicyclo[4.1.0]hept-2-yl butyrate were synthesized as radical precursors in 6 and 8 steps, respectively [1]. Upon irradiation, the PTOC ester underwent Barton decarboxylation to give the target radical which was subsequently quenched to afford both the corresponding norcarane and a rearranged product, later identified as a methylcyclohexanone derivative through comparison to synthetic standards. The rate of radical rearrangement was determined through pseudo-first order kinetic experiments and was found to be comparable to those reported for the parent norcarane scaffold [2]. Hence, this study demonstrated that ester-substituted norcaranes are suitable and predictable mechanistic probes.



References:

[1] Buczynski J, Churchman L, Bell S, Williams C, De Voss J. Substituted Norcaranes as Mechanistic Radical Clock Probes: Characterization of Radical Rearrangement. J Org Chem 2026; 91: 3659-3668.
[2] Friedrich E, Holmstead R, CyclopropylcarbinylAllylcarbinyl Radical Rearrangements in the Simple Bicyclo[3.1.0]Hexyl and [4.1.0]Heptyl Systems. J Org Chem 1972; 37, 2550-2554

Synthesis of Acinetobacter baumannii LAC-4 Polysaccharide Fragments

Mohini Burnwal, Giuseppe D'Orazio, Luigi Lay

University of Milan, Department of Chemistry, Via Camillo Golgi 19 20133, Milan, Italy

Acinetobacter baumannii (Ab) is an opportunistic pathogen of major clinical concern due to its remarkable adaptability and widespread multidrug resistance. The incidence of both hospital-acquired and community-acquired infections caused by Ab has increased significantly in recent years, particularly in cases of pneumonia and severe urinary tract infections. Its ability to persist on abiotic surfaces for prolonged periods promotes survival in healthcare environments and facilitates transmission, contributing to its emergence as a serious global health threat. Consequently, the identification and characterization of Ab virulence factors are essential for the development of new therapeutic strategies and vaccines.

Among the known Ab strains, LAC-4 has been identified as a hypervirulent isolate in mouse model as compared with other clinical and laboratory strains. This strain displays high resistance to serum-mediated killing and reproduces several key features of human pulmonary Ab infections, including significant extrapulmonary dissemination.

The LAC-4 strain consists of trisaccharide repeating units (1, Figure 1) composed of α-D-glucosamine (a), α-L-fucosamine (b), and α-8-epi-legionaminic acid (c). Synthetic fragments of bacterial polysaccharides provide valuable tools for studying their interactions with immune receptors and for performing antigen-mapping studies aimed at supporting the development of semisynthetic glycoconjugate vaccines.

As part of our efforts to access the fragments, the trisaccharide repeating unit and longer oligomers, we report here the synthesis of disaccharide consisting of fragment a and b, and the design of a novel route towards 8-epi-legionaminic acid building block (c). This would be further incorporated into the complete trisaccharide repeating unit. The resulting synthetic glycans will be conjugated to immunogenic proteins and nanoparticles for subsequent immunological evaluation.

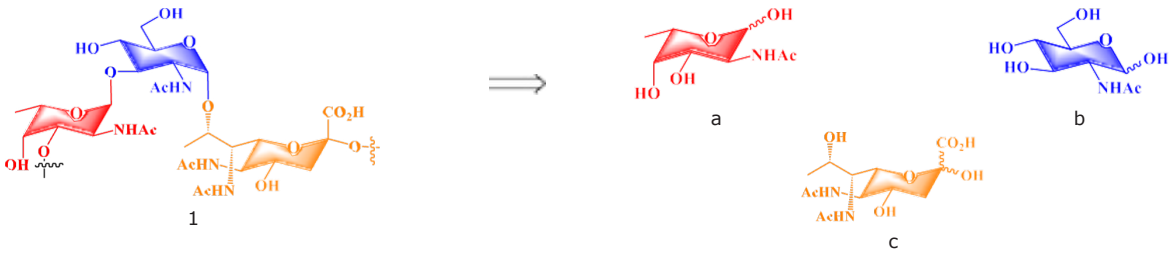


Figure 1: Building blocks of the trisaccharide repeating unit of LAC-4 strain polysaccharide

Acknowledgements:

This project has receiving funding from the European Union's Horizon Europe research and innovation programme under the Marie Skłodowska-Curie Grant Agreement no. 101119575.

References:

1. Evgeny Vinogradov, Leann MacLean, H. Howard Xu, Wangxue Chen, the structure of the polysaccharide isolated from Acinetobacter baumannii strain LAC-4, Elsevier. 2014, 390, 42-45.
2. Silvia Pires, Dane Parker, Innate Immune Responses to Acinetobacter baumannii in the Airway, INTERFERON & CYTOKINE RESEARCH, 2019, Vol. 39, 441-449.
3. Greg Harris, Rhonda Kuo Lee, Christopher K. Lam, Gregory Kanzaki, Girishchandra B. Patel, H. Howard Xu, Wangxue Chena, A Mouse Model of Acinetobacter baumannii-Associated Pneumonia Using a Clinically Isolated Hypervirulent Strain, ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 2013, 57, 3601-3613.

Green Chemistry Metrics of Protein Extraction Protocols from Canola Meal

Kristian Caldo, Ivan Crisostomo, Evelyn Wong

Science Department, Ambrose University, Calgary, Alberta, Canada

Extracting proteins from agricultural by-products adds value to what would otherwise be considered waste. The global shift towards plant-based diets has created a rising demand for plant-based protein sources. One protein source example is canola meal, which is a valuable by-product of the canola industry. Several protocols have been previously developed to extract canola meal proteins for different applications. This study aimed to develop an efficient and sustainable process for extracting proteins from hexane-extracted canola meal. Initially, three methods for extracting proteins from canola meal were evaluated and compared. These methods include the traditional Osborne, alkaline extraction-isoelectric precipitation, and saline extraction-dialysis techniques. The green chemistry metrics of the three techniques were assessed using the life-cycle assessment, green circle and the green matrix methods. Comparison of the three protein isolation techniques showed that salt extraction-dialysis method was the most sustainable and cost-effective. This method was consequently optimized to further increase yield while maintaining good green chemistry metrics.

Target synthesis of *Acinetobacter baumannii* oligosaccharide fragments from ATCC 17961 and ATCC 17978 strains

Rachel Carpaye, Giuseppe D'Orazio, Luigi Lay

Department of Chemistry, University of Milan, Via Camillo Golgi 19, 20133 Milan, Italy

Acinetobacter baumannii (*A. baumannii*), a pathogen listed by the World Health Organisation as a critical priority for new therapeutics, has exhibited increasing resistance to carbapenem antibiotics over the past decade. This growing concern, prevalent in hospitals, threatens today's modern medicine and public health globally[1].
Numerous surface saccharides of *A. baumannii* have been structurally elucidated, including those from the clinical isolates ATCC 17978 and ATCC 17961 strains[2]. As shown below, both strains share the same pentasaccharide repeating unit, with the only difference being an O-acetylation found in ATCC 17978 (**Figure 1**).

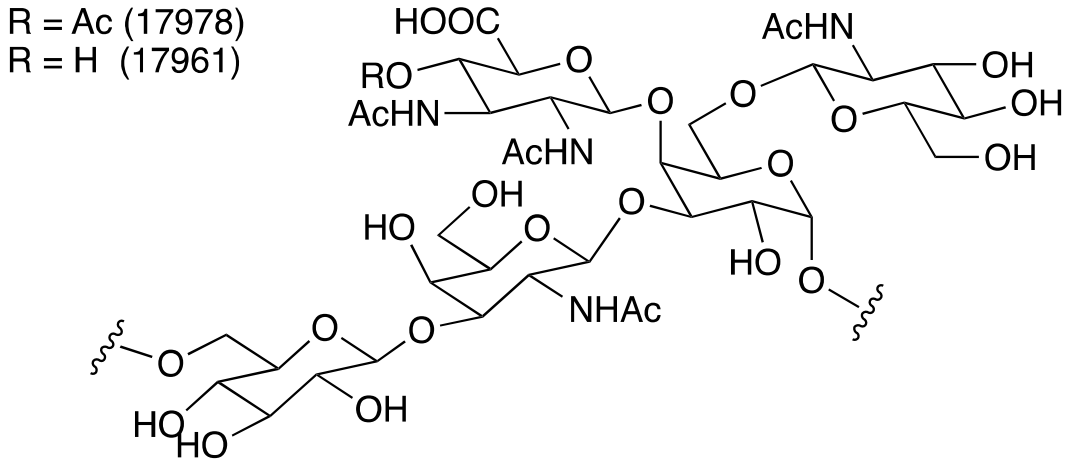


Figure 1. Structure of the pentasaccharide repeating unit of ATCC 17978 and ATCC 17961 strains.

This research, funded by MSCA-DN ACINETWORK [3], focuses on the synthesis of ATCC 17978 and ATCC 17961 *A. baumannii* oligosaccharide fragments for immunoevaluation in hopes of developing a semi-synthetic glycoconjugate vaccine. In this communication, we will illustrate the latest achievements concerning this project.

References:

[1] (a) A. Y. Peleg, H. Seifert and D. L. Paterson, *Clin. Microbiol. Rev*., 2008, **21**, 538-582., (b) M. Nguyen and S. G. Joshi, *J. Appl. Microbiol*., 2021, **131**, 2715-2738., (c) O. Ayobami et al., *Antimicrobiol Resistance and Infection Control*, 2020, **9,** 1-10., (d) European Centre for Disease Prevention and Control, https://www.ecdc.europa.eu/en/news-events/protocol-survey-carbapenem-resistant-acinetobacter-baumannii-Europe,
[2] D. Giguère, *Carbohydr. Res.* **2015**, *418*, 29-43.
[3] ACINETWORK (GA n. 101119795), https://acinetwork.eu/

Bio-derived hybrid functional materials based on pyroglutamic acid and organosilicon moieties

Antonia-Francesca Cojocariu[1], Mihaela Dascalu[1], Alina Ghinet2,3,4, Maria Cazacu[1]

[1]*"Petru Poni" Institute of Macromolecular Chemistry, 41A Gr. Ghica Voda Alley, Iasi 700487, Romania*
[2]*"Alexandru Ioan Cuza" University of Iasi, Faculty of Chemistry, 11 Carol I Blvd., Iasi 700506, Romania*
[3]*Junia, Health and Environment Department, Laboratory of Sustainable Chemistry and Health, Lille F-59000, France*
[4]*University of Lille, Inserm, CHU Lille, Institute Pasteur Lille, U1167 - RIDAGE - Risk factors and molecular determinants of aging-related disease, Lille F-59000, France*

The coupling of exclusively synthetic organosilicon fragments with biosourced organic moieties represents an emerging class of hybrid functional materials that synergistically combine the robustness and physicochemical stability of silicon-based compounds with the sustainability, structural diversity, and biological relevance of natural molecules. While most organosilicon derivatives are characterized by hydrophobicity and physiological inertness, naturally occurring compounds are typically hydrophilic and biologically active. The combination of these contrasting properties is challenging, but offers new opportunities for the design of hybrid systems with tunable interfacial, mechanical, and biological characteristics of interest for coatings, biomedical materials, and environmentally friendly functional systems [1,2].

In this context, pyroglutamic acid was selected as a renewable and structurally versatile building block due to its natural origin, intrinsic chirality, high functional group density, and suitability for chemical modification [3]. As a cyclic derivative of glutamic acid, pyroglutamic acid provides both amide and carboxylic functionalities, enabling selective derivatization and facile incorporation into hybrid architectures while preserving biocompatibility.

Two complementary modification strategies were explored. In the first approach, the organic compound was functionalized with phenyltrimethylsilyl groups via Cu(I)-catalyzed Ullmann-type coupling, providing access to aryl–silicon-substituted derivatives with increased hydrophobicity and enhanced thermal stability. In the second approach, pyroglutamic acid derivatives bearing unsaturated side chains were attached to siloxane substrates through hydrosilylation, leading to silicone-containing hybrid materials.

The obtained compounds were structurally characterized by NMR, FT-IR, and MS, and their thermal behavior was evaluated by TGA/DSC, together with surface and wettability measurements. Biological compatibility assays will be the subject of future studies.

Acknowledgements:

This work was financially supported by a grant from the Romanian National Authority for Research, project no. PNRR-III-C9-2023-I8-99 within the National Recovery and Resilience Plan.

References:

[1] Brook MA, Chen Y. Strategies to improve the sustainability of silicone polymers. Macromolecules 2025; 58: 3742–3763
[2] Cazacu M, Racles C, Zaltariov MF, Dascalu M, Bele A, Tugui C, Bargan A, Stiubianu G. From amorphous silicones to Si-Containing highly ordered polymers: some Romanian contributions in the field. Polymers 2021; 13: 1605
[3] Gang FL, Zhu F, Li XT, Wei JL, Wu WJ, Zhang JW. Synthesis and bioactivities evaluation of *L*-pyroglutamic acid analogues from natural product lead. Bioorg Med Chem 2018; 26: 4644–4649

Rational design, synthesis and evaluation of novel GSA-10 analogues for their remyelination activity

Annalisa De Cicco[1], Antonella Damiana Recchia[2], Tommaso Fabiano[2], Federica Santoro[3], Fancesco Saverio di Leva[3], Diego Brancaccio[3], Davide Guggiari[4], Pierfausto Seneci[4], Luciana Marinelli[3], Antonella Ragnini-Wilson[2], Daniela Arosio[1]

[1]CNR-Istituto di Scienze e Tecnologie Chimiche (SCITEC) "Giulio Natta", via C. Golgi 19, Milan, 20133, Italy
[2]University of Roma "Tor Vergata", Department of Biology, via della Rierca scientifica 1, Rome, 00133, Italy
[4]University of Naples "Federico II", Department of Pharmacy, via D. Montesano 49, Naples, 80131, Italy
[3]University of Milan, Department of Chemistry, via C. Golgi 19, Milan, 20133, Italy

The transmission rate of electrical impulses in nerves is preserved by **myelin**, an essential lipid-rich biomaterial that insulates the axons of vertebrate neurons[1]. Damage to myelin leads to severe neurological disorders, including **multiple sclerosis**. Restoring the myelin sheath could be an important therapeutic strategy for the treatment of these disorders[2].
Recent studies identified the **Hedgehog (Hh) signaling pathway, and** in particular the G-protein-coupled receptor **Smoothened (Smo)**, as a promising molecular target. This pathway transmits important information for cell differentiation in embryonic cells, but is silent in the adult central nervous system (CNS) [3]. However, during remyelination, Hh signaling is reactivated, and Smo drives the transition from neural stem cells to adult oligodendrocytes, responsible for myelin production[3].
GSA-10 (Figure 1), a dihydroquinoline dione derivative, has emerged as a promising Smo modulator[4]. It interacts with Smo, causing glioma-associated oncogene homologue (Gli1) inhibition and adenosine monophosphate–activated protein kinase (AMPK) activation, thereby promoting oligodendrocyte progenitor cell (OPC) differentiation. Unfortunately, the poor solubility of **GSA-10** makes it unsuitable for in vivo testing. Thus, we aim to synthesize **novel GSA-10 analogues** with improved potency and drug-like properties (Figure 1). Molecular docking studies guided the design of a targeted library, identifying the n-hexyl chain and the quinolone scaffold as important moieties for Smo binding and Gli1 inhibition. New synthesized compounds will be evaluated *in vitro* to determine their biological activity and therapeutic remyelination potential.

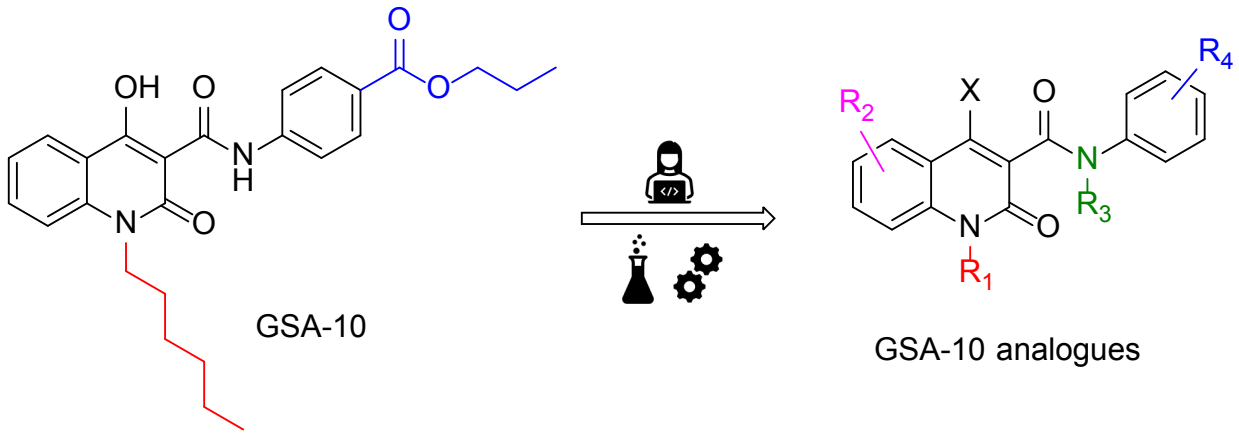


Figure 1. GSA-10 and general structrure of **GSA-10** analogues.

References:

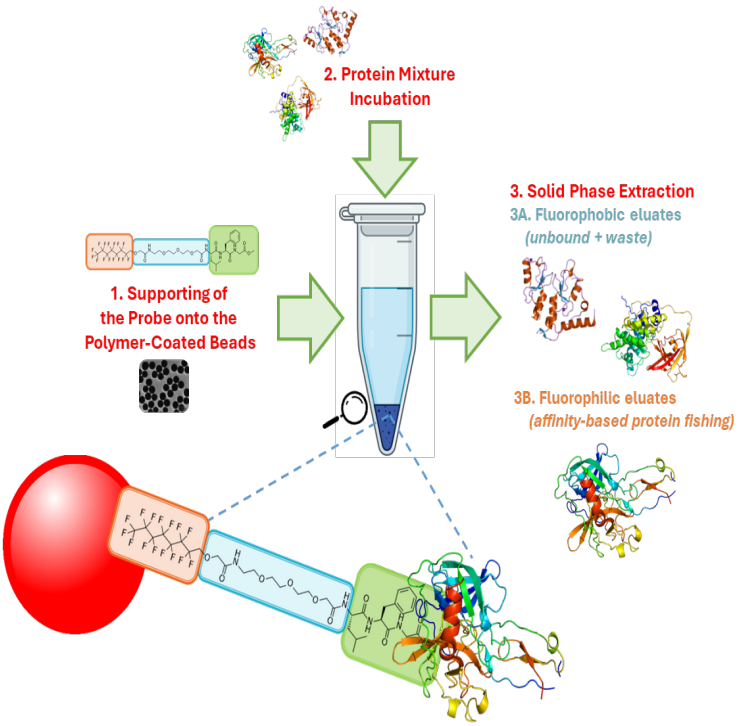
[1] Stassart, R.M., Möbius, W., Nave, K.-A., Edgar, J.M. The Axon-Myelin Unit in Development and Degenerative Disease. Front. Neurosci. 2018; 12: 467.
[2] Lemus, H.N., Warrington, A.E., Rodriguez, M. Multiple sclerosis: mechanisms of disease and strategies for myelin and axonal repair. Neurol. Clin. 2018; 36: 1-11.
[3] Huang, P., Nedelcu, D., Watanabe, M., Jao, C.; Kim, Y.; Liu, J., Salic, A. Cellular Cholesterol Directly Activates Smoothened in Hedgehog Signaling. Cell 2016; 166: 1176-1187.
[4] Del Giovane, A., Russo, M., Tirou, L., Faure, H., Ruat, M., Balestri, S., Sposato, C., Basoli, F., Rainer, A., Kassoussi, A., Traiffort, E., Ragnini-Wilson, A. Smoothened/AMP-Activated Protein Kinase Signaling in Oligodendroglial Cell Maturation. Front. Cell. Neurosci. 2022; 15: 801704.
This project was supported by Fondazione Italiana Sclerosi Multipla (FISM), Grant n.2023/R-Multi/001

Develpoment of a Tailor-Made Fluorophilic Enrichment Platform for Non-Covalent Protein Fishing

Riccardo De Simone,[1] Davide Roncareggi,[2] Giada Cetrola,[1] Erica E. Ferrandi,[1] Laura Sola,[1] Sergio Romeo[1,3] and Ivan Bassanini[1].

[1]Istituto di Scienze e Tecnologie Chimiche "Giulio Natta" - Consiglio Nazionale delle Ricerche, Via Mario Bianco 9, 20131 Milano, Italy;
[2]Dipartimento di Scienze Biomolecolari per la Salute - Università degli Studi di Milano, Via Pascal 36, 20133 Milano, Italy;
[3]Dipartimento di Scienze Farmaceutiche - Università degli Studi di Milano, Via Mangiagalli 25, 20133 Milano, Italy

The identification of molecular targets of bioactive small molecules is crucial for elucidating their mechanisms of action. In this context, compound-centric chemical proteomics (CCCP) combines affinity-based protein fishing with mass spectrometry to selectively isolate and characterize protein interactors from complex proteomes under near-native conditions[1,2]. However, conventional biotin–avidin-based strategies suffer from drawbacks such as irreversible protein tagging, interference from endogenously biotinylated proteins, and nonspecific binding, leading to high background noise and reduced interpretability. To overcome these limitations, we developed a (bio)orthogonal fluorophilic enrichment platform that exploits fluorous solid-phase extraction (F-SPE) for non-covalent protein fishing[3]. The system integrates silica microbeads coated with a perfluorinated, antifouling *N,N*-dimethylacrylamide co-polymer as the adsorbent matrix and tailor-made fishing probes equipped with a perfluorinated tag via a PEG linker. Using papain as a model enzyme, our platform enabled selective and reversible affinity-based isolation of the target from complex protein mixtures through a simple fluorophilic gradient protocol. This approach establishes a versatile, orthogonal alternative to traditional CCCP workflows, paving the way for next-generation interactome mapping under biocompatible conditions.



References:

[1] Kozoriz K., Lee J. S. Chemical proteomics for a comprehensive understanding of functional activity and the interactome. Chem Soc Rev 2025; 54: 6186–6207.
[2] Bennett J.L., Nguyen G. T. H, Donald W. A. Protein-Small Molecule Interactions in Native Mass Spectrometry. Chem Rev 2022; 122: 7327–7385.
[3] Bassanini I., Galli C., Ferrandi E. E., Vallone F., Andolfo A., Romeo S. Perfluorinated Probes for Noncovalent Protein Recognition and Isolation. Bioconjug Chem 2020; 31: 513–519.

Reformulating Propofol for enhanced solubility and lower dose requirements

Evan Debnath, Sanjib Senapati

Department of Biotechnology, Indian Institute of Technology Madras, Chennai, India

Active pharmaceutical ingredients (APIs) are the major components of drug formulations essential for treating diseases. The two important factors of drug bioavailability are aqueous solubility and permeability. Currently, about 60-70% of available drugs are reported to have low aqueous solubility, despite having good permeability. This fraction of insoluble drugs is expected to increase as the pharmaceutical industry shifts its attention towards targeted therapies. Conventional solubilization approaches rely heavily on specialised excipients, which often introduce toxicity, instability, or formulation challenges. To overcome these issues, we propose an Ionic liquid-based reformulation technology (rAPI) in which an API can act as either a cation or an anion, depending on its chemical structure, paired with a suitable biocompatible cation or anion[1,2]. One such molecule is Propofol (PRO), an insoluble but widely used intravenous anaesthetic whose marketed lipid emulsion formulation is associated with injection-site pain and stability issues[3]. We synthesise Propofol–IL (PRO-IL) conjugates using pharmaceutically acceptable organic counterions and thoroughly characterise them via Nuclear magnetic resonance (NMR), Fourier transform infrared (FTIR) spectroscopy, powder X-ray diffraction (PXRD), thermogravimetric analysis (TGA), and differential scanning calorimetry (DSC). PRO-ILs exhibited a hundredfold enhancement in aqueous solubility when compared with that of parent propofol, improved thermal stability, and faster dissolution compared to the commercial formulation. Preliminary pharmacokinetic and pharmacodynamic studies indicate enhanced bioavailability, faster onset, and prolonged anaesthetic duration. These results establish IL-based rAPI technology as a safe, scalable, and versatile reformulation strategy, paving the way for next-generation, excipient-free anaesthetic formulations with superior performance and patient compliance.

References:

[1] Chandran A, Ghoshdastidar D, Senapati S. Groove binding mechanism of Ionic liquids: A key factor in long-term stability of DNA in hydrated Ionic liquids? Journal of the American Chemical Society 2012; 134: 20330-39.
[2] Shamshina, Julia L, and Robin D. Rogers. Ionic liquids: new forms of active pharmaceutical ingredients with unique, tunable properties. *Chemical Reviews* 2023; 123.20: 11894-11953.
[3] Kotani Y, Shimazawa M, Yoshimura S, Iwama T, and Hara, H. The experimental and clinical pharmacology of propofol, an anesthetic agent with neuroprotective properties. CNS neuroscience and therapeutics 2008; 14(2): 95-106.

A chemogenetic strategy for tracing cellular history into protein assemblies

Lina El Hajji, Arnaud Gautier

Sorbonne Université, École Normale Supérieure, Université PSL, CNRS, Chimie Physique et Chimie du Vivant, 4 Place Jussieu, Paris, France (CPCV)

Biological imaging has enabled the visualization of biological events occurring within cells and complex organisms, with continuously improved spatiotemporal resolution. Capturing such events can be achieved through performing time-lapse fluorescence microscopy, where a field of view featuring the fluorescently-labeled biomolecule of interest is imaged at a given rate over a specific duration. Long term time-lapse microscopy can however be time-intensive, and usually captures only a limited number of fields of view. Recently, cellular recorders based on growing protein assemblies have been proposed to overcome these limitations and record cellular events inside cells. When an event of interest occurs, a fluorescent reporter is incorporated within the protein assembly, leaving a fluorescent mark on it. To gain information on the kinetics and timeline of the recorded events, molecular timestamps can be incorporated in the protein assembly at given times [1-5]. While several scaffolds and timestamping methods have been explored, existing timestamping strategies for fiber-based event recording are currently limited by a low temporal resolution. Here, we present a chemogenetic strategy for incorporating tightly-spaced timestamps into intracellular fibers. Our strategy allowed us to record various types of fast-occurring events in mammalian cells with high temporal resolution.

References:

[1] Lin, D.; Li, X.; Moult, E.; Park, P.; Tang, B.; Shen, H.; Grimm, J. B.; Falco, N.; Jia, B. Z.; Baker, D.; Lavis, L. D.;Cohen, A. E. Time-Tagged Ticker Tapes for Intracellular Recordings. *Nature Biotechnology* **2023**, *41* (5), 631–639.
[2] Linghu, C.; An, B.; Shpokayte, M.; Celiker, O. T.; Shmoel, N.; Zhang, R.; Zhang, C.; Park, D.; Park, W. M.; Ramirez, S.; Boyden, E. S. Recording of Cellular Physiological Histories along Optically Readable Self-Assembling Protein Chains. *Nat Biotechnol* **2023**, *41* (5), 640–651.
[3] Wang, R.; Jiang, J.; Li, Z.; Liu, T.; Wang, Y.; Xie, M.; Piatkevich, K. D. Fluorescent Protein-Based Ticker Tapes for Multiplexed Recordings of Transcriptional Histories in Single Cells in Culture and in Vivo. September 12, 2025. https://doi.org/10.1101/2025.09.08.675004.
[4] Yan, Y.; Lu, J.; Li, Z.; Zhao, Z.; Shay, T. F.; Wang, S.; Lei, Y.; Wang, Y.; Chen, W.; Parker, P.; Yang, H.; Qi, A.; Sun, Y.; Bergles, D. E.; Baker, D.; Lin, D. Genetically Encoded Assembly Recorder Temporally Resolves Cellular History. *Nature* **2026**. https://doi.org/10.1038/s41586-026-10323-y.
[5] Zheng, L.; Shi, D.; Yan, Y.; Zhou, B.; Lim, J.; Hou, Y.; An, B.; Adhinarta, J. K.; Lin, M.; Ko, B.; Joesten, W. C.; Gautam, M.; Huez, E. D. M.; Kim, E. C.; Klyder, E. G.; Chang, B.; Pitchiaya, S.; Roberts, M. T.; Cai, D. J.; Boyden, E. S.; Wei, D.; Liò, P.; Linghu, C. Scalable and Multiplexed Recorders of Gene Regulation Dynamics across Weeks. *Nature* **2026**. https://doi.org/10.1038/s41586-026-10156-9.

Investigating the molecular recognition features of carbohydrate and steroid Sulfatase S1 towards sulfamate and sulfate substrates

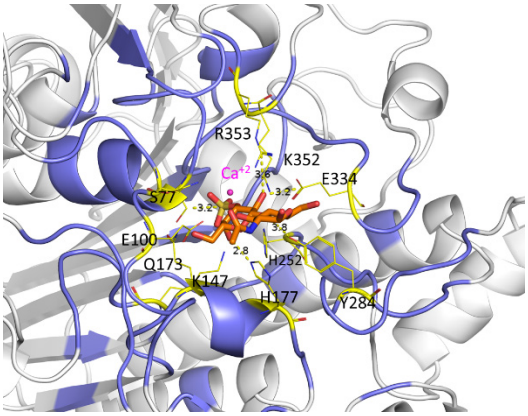
Stefano Elli[1,2], Charles W E Tomlinson[2,3,4], Edwin A Yates[5], Martin Fascione[3,6], Spencer J Williams[7], Conor J Crawford[8] and Alan Cartmell[2,3,4].

[1]Istituto di Ricerche Chimiche e Biochimiche G. Ronzoni, via G. Colombo 81 20133, Milano, Italy;
[2]Department of Biology University of York, YO10 5DD, York, UK;
[3]York Structural Biology Laboratory, Department of Chemistry, University of York, YO10 5DD, York, UK;
[4]York Biomedical Research Institute, University of York, YO10 5DD, York, UK;
[5]Department of Biochemistry, Cell and Systems Biology, Institute of Systems, Molecular and Integrative Biology, University of Liverpool, L69 7ZB, Liverpool, UK;
[6]Department of Chemistry, University of York, YO10 5DD, York, UK;
[7]School of Chemistry and Bio21, Molecular Science and Biotechnology Institute, University of Melbourne, Victoria 3010, Parkville, Australia;
[8]Leibniz-Forschungsinstitut für Molekulare Pharmakologie im Forschungsverbund Berlin e.V. (FMP), Rudower Chaussee 17,12489 Berlin, Germany

Sulfatases are enzymes that remove sulfate groups from biomolecules ranging from hydrophobic steroids to hydrophilic polysaccharides therefore, regulating a wide variety of biological processeses. In nature, more than 90% of sulfatases belong to the S1 family. These enzymes are characterised by a conserved sulfate catalytic system, centered on a post-translationally formed formylglycine (FGly) nucleophile.[1,2,3]. Both steroid and carbohydrate sulfatase are linked to disease states where overactivity leads to cancer and inflammatory bowel disease (IBD). S1 steroid sulfatases are promiscuous, whilst S1 carbohydrate sulfatases display high specificity. Yet, their sulfate catalytic sites are identical. Sulfamate based inhibitors have been developed that target the FGly nucleophile and are covalent inhibitors of S1 steroid sulfatases but, interestingly, they are completely inactive against S1 carbohdyrate sulfatases. The molecular details, including the dynamic and conformational features, underpinning the different responses are currently unclear. In this study, the molecular recognition of the carbohydrate sulfatase BT1636, from the human symbiont *Bacteroides thetaiotaomicron*, and the aryl sulfatase 1HDH, from *Pseudomonas aeruginosa*, was assessed towards sulfated and sulfamated substrates; combining models from X-ray crystal structures with MD simulation, and DFT theory. This study investigates the inhibition mechanism of aryl sulfamates that are promising inhibitors of aryl-sulfatases, and is preparatory for the design inhibitors against carbohydrate sulfatases, potentially opening-up new routes for the treatment of not only IBD but colon cancer where inflammation is a key trigger.

References:

[1] Hanson SR, Best MD, W
ong C-H. Sulfatases: Structure, Mechanism, Biological Activity, Inhibition, and Synthetic Utility. Angew. Chem. Int. Ed. 2004; 43: 5736– 5763
[2] Luis A. S. *et al.* A single sulfatase is required to access colonic mucin by a gut bacterium. Nature 2021; 598: 332-337
[3] von Bülow R *et al*. Crystal Structure of an Enzyme-Substrate Complex Provides Insight into the Interaction between Human Arylsulfatase A and its Substrates During Catalysis J. Mol. Biol. 2001; 305: 269-277



GLYLOID® Functionalization with Boronic Acids: Toward New Functional Polysaccharide Materials

Emiliano Esposito[1], Claudio Lutti[1,2], Giulia Condello[1,3], Irene Tagliaro[3], Marco Guerrini[1], Sabrina Bertini[1]

[1]Institute of Chemical and Biochemical Research G. Ronzoni, Via G. Colombo 81, 20133, Milan, Italy,
[2]Department of Chemistry, Università degli Studi di Milano, Via golgi 19, 20133, Milan, Italy,
[3]Department of Materials Science, University of Milano-Bicocca, 20125, Milan, Italy

GLYLOID®, a galactoxyloglucan polysaccharide isolated from the seed kernel of Tamarindus indica, is widely used in several industrial fields because of its physicochemical and biological properties.[1] It can serve as a highly biocompatible and versatile platform for different kinds of chemical modifications due to the presence of a large number of exposed 1,2- and 1,3-diols. As an antimycotic agent, its natural properties provide a robust foundation for the development of advanced functional materials.
Boronic acids (BAs) and their derivatives are strong Lewis acids characterized by a vacant p orbital that enables them to form coordinate covalent bonds with nucleophiles. These compounds are known for their high biocompatibility and safety; for instance, boric acid has an LD_{50} comparable to that of common table salt.[2] The primary biological relevance of boronic acids arises from their ability to reversibly react with sugar diols in aqueous media, forming stable boronate esters. This interaction allows them to bind effectively to carbohydrates such as ribose and glucose, a mechanism that underlies their use in sensing, bioconjugation, and enzyme inhibition.[3] Exploring the chemical space of GLYLOID® functionalization with boronic acid moieties represents a significant opportunity to create synergistic "smart" biopolymers.[4] Grafting boronic acid derivatives onto a polysaccharide backbone can significantly modulate water solubility at neutral pH and introduce specific target-recognition capabilities.[5] Such functionalized materials hold great potential for the development of antimycotic biofilms designed to inhibit pathogen adhesion and growth. In the ophthalmic field, these materials could be particularly valuable as mucoadhesive antimicrobial barriers or as vehicles for topical delivery, leveraging their biocompatibility to treat ocular infections or protect corneal tissue. This functionalization strategy represents a promising frontier for natural-source-derived materials in advanced biomedical applications.

References:

[1] Shukla, AK., Bishnoi, RS., Kumar, M., Fenin, V. & Jain, CP. Applications of Tamarind seeds Polysaccharide-based copolymers in Controlled Drug Delivery: An overview. Asian J. Pharm. Pharmacol 2018; 4:23-30.
[2] Baker, SJ. et al. Therapeutic potential of boron-containing compounds. Future Med. Chem. 2009; 4: 1275–1288.
[3] Mehta, NV., Abhyankar, A. & Degani, MS. Elemental exchange: Bioisosteric replacement of phosphorus by boron in drug design. Eur. J. Med. Chem. 2023; 260 :115761.
[4] Dembitsky, VM., Terent'ev, AO., Gursky, ME. & Baranin, SV. Fascinating and intriguing biomolecules: The chemistry of boron complexes with carbohydrates, glycolipids, and steroids. Vietnam Journal of Chemistry 2025.
[5] García Cambón, TA. et al. Benzoxaborole-grafted high molecular weight chitosan from prawn: Synthesis, characterization, target recognition and antibacterial properties. Carbohydr. Polym 2023; 316: 120925.

New-Generation Self-immolative Spacers for the Release of Anticancer Drugs from ADCs

Failla Mattia[1], Ubiali Elia[1], Marchini Mattia[2], Steinkühler Christian[2,3], Scheuermann Jörg[4], Dal Corso Alberto[1].

[1]Università degli Studi di Milano, Dipartimento di Chimica, Via C. Golgi 19, 20133 Milano, Italy;
[2]Italfarmaco SpA, Via dei Lavoratori 54, 20092 Cinisello Balsamo (MI), Italy;
[3]Exiris srl, Via di Castel Romano 100, 00128 Castel Romano (RM), Italy;
[4]ETH Zürich, Department of Chemistry and Applied Biosciences Institute of Pharmaceutical Sciences, Vladimir-Prelog-Weg 3, 8093 Zürich, Switzerland.

The targeted delivery of cytotoxic agents via antibody-drug conjugates (ADCs) has become a highly attractive method for treating various types of cancers.[1] From the structural viewpoint, traditional ADCs are composed of a monoclonal antibody (mAb) linked to a cytotoxic agent via a protease-cleavable peptide linker and a self-immolative (SI) spacer. In recent years, the significant success of this emerging technology in different types of cancers has stimulated the global effort on finding different ADC's components and new connections between them, in order to improve the pharmacokinetic properties of the whole ADC construct.[3] For instance, a fast self-immolation mechanism of a proline-based SI spacer for the release of alcohol payloads from carbamate prodrugs[4] has been investigated, through successful new drug-linker syntheses and conjugation on engineered mAb. In this communication, I will describe the structure and activation kinetics of new-generation self-immolative spacers, designed to release hydroxy-bearing drugs. Upon synthesis of the linker-spacer-payload modules and their conjugation to a model antibody, the ADCs were incubated in the presence of a protease and the metabolites were analyzed by LC-MS. In these analyses, the two linker-spacer modules showed markedly different drug release kinetics (Figure 1), providing important structural information for the optimization of new ADC as candidates for follow-up preclinical studies.

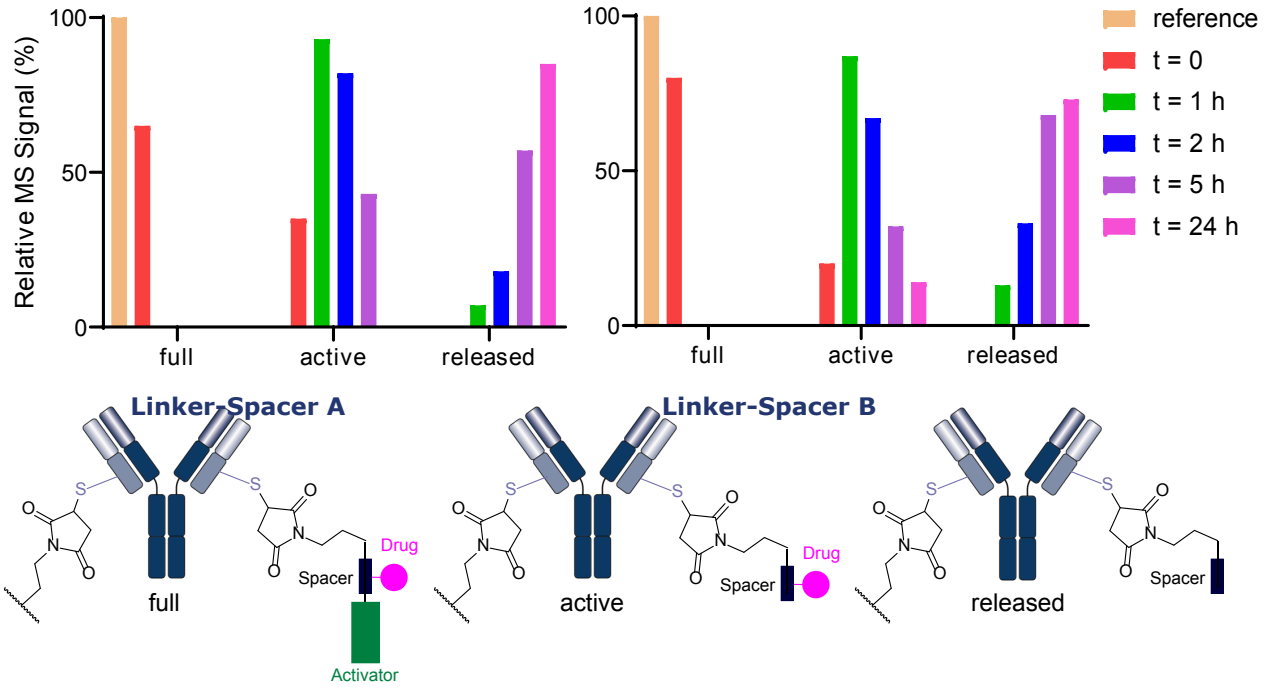


Figure 1. Schematic representation of the different linker metabolites observed by LC-MS spectrometry upon ADC incubation with trypsin, and relative abundance over 24 h (37 °C, pH 7.4). The two new Linker-Spacer modules (A or B) showed efficient activation upon incubation with trypsin, yet different release kinetics of the cytotoxic payload.

References:

[1] T. Journeaux, G. J. L. Bernardes, *Nat. Chem.* **2024**, *16*, 854 – 870.
[2] A. Dal Corso, L. Pignataro, L. Belvisi, C. Gennari, *Chem. Eur. J.* **2019**, *25*, 14740 – 14757.
[3] A. Dal Corso, V. Borlandelli, C. Corno, P. Perego, L. Belvisi, L. Pignataro, C. Gennari, *Angew. Chem. Int. Ed.* **2020**, *59*, 4176 – 4181.
[4] M. Mason, L. Bisbal Lopez, F. Bashiri, A. Herrero, A. Baron, R. Bucci, L. Pignataro, C. Gennari, A. Dal Corso, *ChemBioChem* **2024**, *25*, e202400174.

Determination of the antioxidant capacity of hydrophilic and lipophilic extracts from algae of the southern Peru.

Sheyla J. Figueroa-Valencia[1], Teresa Cano de Terrones[1], Vianca Brillit Vásquez Toledo[1], Mercedes Lucia Villagómez Castillo[1], Olger Nicolas Acosta Angulo[1], Elizabeth Figueroa-Valencia[1,2,3], Carlos Areche Medina[4]

[1]Facultad de Ciencias Naturales y Formales -Universidad Nacional de San Agustín de Arequipa, Avenida Independencia s/n, Arequipa 04001, Peru.
[2]Department of Experimental Plant Biology, Faculty of Science, University of South Bohemia, Branišovská 1760, 370 05 České Budějovice, Czech Republic
[3]Laboratory of Algal Biotechnology, Centre ALGATECH, Institute of Microbiology of the Czech Academy of Sciences, Novohradská 237—Opatovický mlýn, 379 01 Třeboň, Czech Republic
[4]Department of Chemistry, Faculty of Sciences, University of Chile, Santiago 8320000, Chile

Seaweeds are rich in polysaccharides, minerals, vitamins, and other bioactive compounds such as polyphenols, peptides, lipids, and pigments. They represent an important source of bioactive extracts with nutraceutical applications due to their natural compounds, including pigments and lipids, as well as pharmacological potential associated with antioxidant, anti-inflammatory, and anticancer activities[1,2]. In this context, the present study evaluated the bioactive potential of biomass extracts from two marine seaweeds, *Chondracanthus chamissoi* (red alga) and *Macrocystis pyrifera* (brown alga), collected from the southern coast of Peru. For each species, five different extracts were obtained using the following solvents: n-heptane, ethyl acetate, acetone, ethanol, and methanol.The bioactive potential was assessed by determining antioxidant capacity using the ABTS method. The assay was performed according to the procedure described by Arnao, M.B. et al.[3] for each extracts.The results showed that *Macrocystis pyrifera* exhibited higher hydrophilic and lipophilic antioxidant capacity than *Chondracanthus chamissoi* in all extracts evaluated. This suggests that M. pyrifera contains a higher concentration and greater diversity of bioactive compounds capable of neutralizing free radicals, highlighting its potential as a more promising natural source of antioxidants. Consequently, this species may have greater potential for application in the development of nutraceutical or functional products.

References:

[1] Mohamed, S.; Hashim, S.N.; Rahman, H.A. Seaweeds: A Sustainable Functional Food for Complementary and Alternative Therapy. Trends Food Sci. Technol. 2012, 23, 83–96.
[2] Holdt, S.L.; Kraan, S. Bioactive Compounds in Seaweed: Functional Food Applications and Legislation. J. Appl. Phycol. 2011, 23, 543–597
[3] Arnao, M.B., Cano, A. & Acosta, M. (2001). The hydrophilic and lipophilic contribution to total antioxidant capacity. Food Chemistry, 73, 239–244.

Fluorinated Janus-type Dendrimer-Based Nanocarrier for Nucleic Acid Delivery in Amyotrophic Lateral Sclerosis *In Vitro* Models

Lorenzo Fumagalli[1], Marta Rosati[1], Giuseppe Lauria Pinter[2], Francesca Baldelli Bombelli[1], Stefania Marcuzzo[2,3], Pierangelo Metrangolo[1]

[1]Department of Chemistry, Materials, and Chemical Engineering "Giulio Natta", Politecnico di Milano, 20131 Milan, Italy;
[2]Neuroimmunolgy and Neuromuscular Diseases Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, 20133 Milan, Italy;
[3]Brains Lab, Joint Research Platform, Fondazione IRCCS Istituto Neurologico Carlo Besta, 20133 Milan, Italy

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive motor neuron degeneration and severe muscle atrophy[1]. Growing evidence indicates that microRNAs (miRNAs) play a central role in the molecular pathways underlying muscle degeneration and impaired regenerative responses, making them attractive therapeutic candidates[2]. However, the safe and efficient intracellular delivery of nucleic acids (NAs) remains a major obstacle to their clinical translation.
Here, we evaluated FJD2N, a fluorinated Janus-type dendrimer bearing four terminal ammonium groups, as a non-viral platform for NAs delivery. In aqueous environments, FJD2N self-assembles into positively charged micellar structures, capable of forming stable dendriplexes with nucleic acids, enabling their cellular uptake. The biological performance of the carrier was assessed in commercial cell lines and in primary cell cultures derived from G93A-SOD1 mice, a purported model of ALS. Immunofluorescence analyses demonstrated efficient internalization of the carrier, while molecular biology studies revealed modulation of the selected miRNAs and its downstream target genes involved in regenerative pathways. Importantly, no cytotoxic effects were observed, as confirmed by proliferation assays and caspase expression levels[3,4].
Overall, this new vector is a promising candidate for gene delivery applications and further *in* vitro tests on a larger scale are needed to better understand its functioning.

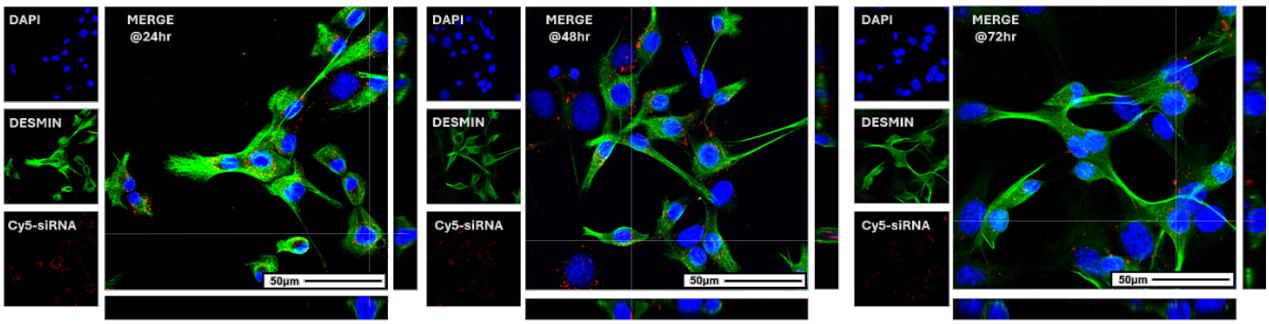


Figure 1: Internalization of the NA observed via confocal microscopy on C2C12 cells treated with Cy5-conjugated Luciferase GL3 siRNA complexed with FJD2N at N/P ratio = 30.

References:

[1] S. Marcuzzo et al., Exp Neurol, 2011, vol. 231, pp. 30-37
[2] E. Giagnorio et al., J Cell Sci, 2021, vol. 134, Issue 12
[3] M. Rosati et al., Nanoscale, 2025, vol 17, pp. 25266-25280
[4] F. Baldelli et al., Non-Viral Vectors for Gene Therapy. WO2023170543A1, September 14, 2023

sp²-Iminosugar Trimannosyl Glycolipid Mimetics as a New Class of TLR4 Antagonists

José M. García Fernández[1], M. Carmen Padilla-Pérez[2], Alan Chuan-Ying Lai[3], Elena M. Sánchez-Fernández[2], Chieh-Hsin Ho[3], Po-Yu Chi2, Ko-Chien Wu[3], Ya-Jen Chang[2], Carmen Ortiz Mellet[2]

[1]*Institute for Chemical Research, CSIC-University of Seville, Seville, Spain;*
[2]*Department of Organic Chemistry, Faculty of Chemistry, University of Seville, Seville, Spain;*
[3]*Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan*

Toll-like receptor 4 (TLR4) is a central mediator of inflammatory signaling and is implicated in a range of pathological conditions, including ischemia, neuropathic pain, neurodegenerative disorders, and cancer. Conventional glycolipid-based TLR4 antagonists typically act by binding to the $(TLR4)_2(MD\text{-}2)_2$ complex, thereby blocking interactions with endogenous ligands. In contrast, trimannosyl glycolipid conjugates (MGCs) operate through a distinct mechanism. These molecules feature a branched scaffold bearing three mannose residues and a hydrophobic lipid tail.1 MGCs selectively inhibit TLR4-mediated immune activation in lipopolysaccharide (LPS)-stimulated human monocytes and dendritic cells by modulating lipid raft organization at the plasma membrane, which disrupts the colocalization of the CD14 co-receptor with TLR4 (Figure 1).
Here, we investigate the replacement of the α-D-mannopyranosyl units with sp2-iminosugar motifs to generate new conjugates with improved chemical and enzymatic stability. sp2-Iminosugars are carbohydrate mimetics particularly well suited for the construction of α-glycan2 and glycoconjugate surrogates3,4, offering a robust alternative to natural glycosidic linkages while preserving key structural features required for molecular recognition. Moreover, the intrinsic structural versatility of sp2-iminosugars enables the rational design of diverse derivatives, allowing systematic variation of the iminosugar core, the glycosidic linkage, spacer architecture, and lipid chain properties. Preliminary immunological studies indicate that these sp2-MGC derivatives retain the TLR4 antagonistic activity observed for the original MGCs.
The authors anckowledge funding from MICIU / AEI / EDRF (PID2022-141034OB-C21 and PID2024-157753OB-C21) and the EU HE program (MSCA-SE 101130235 – Bicyclos).

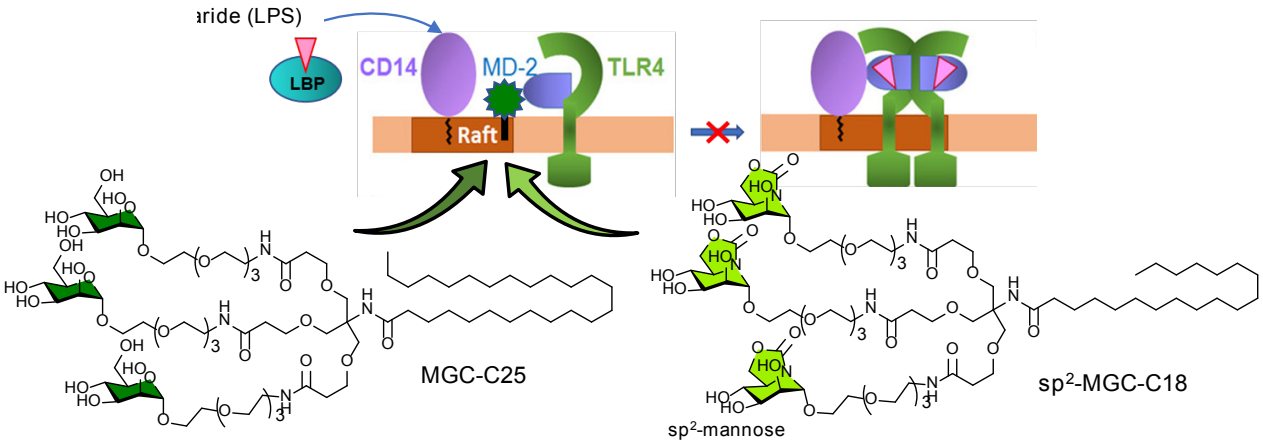


Figure 1. Structures of the trimannosyl glycolipid conjugate MGC-C25 and of the mimic sp2- MGC-C18, and illustration of the postulated membrane-targeted TLR4 antagonism mechanism.

References:

[1] Flacher V, Neuberg P, Point FDaubeuf F, Muller Q, Sigwalt S, Fauny J, Remy JS, Frossard N, Wagner A, Mueller CG, Schaeffer E. Mannoside Glycolipid Conjugates Display Anti-inflammatory Activity by Inhibition of Toll-like Receptor-4 Mediated Cell Activation. ACS Chem. Biol. 2015; 10: 2697-2705.
[2] Herrera-Gonzalez I, Gonzalez-Cuesta M, M, Eugenie Laigre E, Goyard D, Rojo J, Garcia Fernandez JM, Fieschi F, Renaudet O, Nieto PM, Ortiz Mellet C. High-Mannose Oligosaccharide Hemimimetics that Recapitulate the Conformation and Binding Mode to Concanavalin A, DC-SIGN and Langerin. Chem. Eur. J. 2023, e2023030417
[3] García-Moreno MI, Kawakami K, Nanba E, García Fernández J.M, Higaki K, Ortiz Mellet C. Neutral sp2-iminosugars exploiting non-glycone interactions for selective acid α- and β-glucosidase activity modulation: Pharmacological chaperones for Gaucher and Pompe diseases. Eur. J. Med. Chem. 2026, 304: 118500
[4] Lai AC-Y, González-Cuesta, Ho CH, Chi P-Y, Wu K-C, Rocha G, Muñoz-García JC, Angulo J., García Fernández J.M, Chang Y-J, Ortiz Mellet C. α-GalCer sp2-iminoglycolipid analogs as CD1d-dependent iNKT modulators: Evaluation of their immunotherapeutic potential in murine models of asthma and autoimmune hepatitis. Eur. J. Med. Chem. 2025, 282: 117060

Preventing biofilm formation through silica-based nanoparticles functionalized with natural compound derivatives

Giulia Cazzaniga[1,2], Cristina Cattò[1], Matteo Mori[1], Patricia Hayes[4], Dan Yang[4], Nuwan H. Arachchi[4], Federica Villa[3], Francesca Cappitelli[3], Alice Melocchi[1], Lucia Zema[1], Stefania Crespi[5], Paul J. Molino[4], Stefania Villa[1] and Arianna Gelain[1]

[1]University of Milan, Department of Pharmaceutical Sciences, via L. Mangiagalli 25, 20133 Milan, Italy
[2]University of Insubria, Department of Science and High Technology, via Valleggio 9, 22100, Como, Italy
[3]University of Milan, Department of Food, Environmental and Nutritional Sciences, via G.Celoria 2, 20133 Milan, Italy
[4]University of Wollongong, AIIM Faculty, Intelligent Polymer Research Institute, Wollongong, NSW 2522, Australia
[5]University of Milan, Department of Earth Sciences "Ardito Desio", via L. Mangiagalli 34, 20133 Milan, Italy

Biofilm formation is a strategy used by microorganisms to survive in the environment, enabling them to colonize a wide variety of surfaces (living tissues, water supply systems, food processing equipment, *etc.*). Biofilms can provide health benefits (*e.g.*, gut microbiota) but also pose risks, since many human microbial infections can be aggravated by their presence, leading to increased tolerance to antibacterial drugs.
To overcome the spread of multidrug-resistant pathogens, we focused our efforts on the development of new anti-biofilm surfaces capable of preventing biofilm formation without interfering with microbial life, with the aim of reducing the selection of resistant mutants.
Based on our previous works concerning the identification of natural compound derivatives (*p*-aminosalicylic and *p*-aminocinnamic acids) as non-toxic anti-biofilm agents[1,2], we studied their potential application in the functionalization of silica nanoparticles to develop new anti-biofilm coatings[3].
The obtained nanosystem were used to coat glass coverslips as model surfaces (Figure 1). The anti-biofilm activity of the new material was tested against *P. aeruginosa* as a model for Gram negative bacteria, leading to promising results that will be presented.

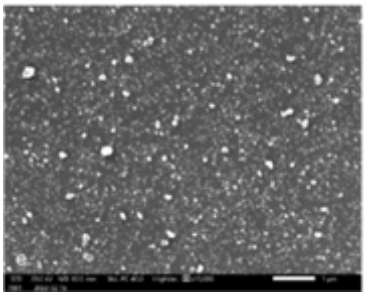


Figure 1: SEM image of an example of coated surface.

References:

[1] Cattò C, Dell'Orto S, Villa F, Villa S, Gelain A, Vitali A, Marzano V, Baroni S, Forlani F, Cappitelli F, PLoSONE, 2015,10(7), e0131519.
[2] Cattò C, Grazioso G, Dell'Orto S, Gelain A, Villa S, Marzano V, Vitali A, Villa F, Cappitelli F, Forlani F, Biofouling, 2017, 33, 235-251.
[3] Cazzaniga G, Cattò C, Mori M, Hayes P, Yang D, Arachchi NH, Villa F, Cappitelli F, Melocchi A, Zema L, Crespi S, Molino PJ, Villa, S, Gelain A, Mat.Tod. Chem.,2024, 42, 102375.1-102375.15

Structural insight into C-5 modified β-Fucosides Targeting the BC2L-C Lectin of B. cenocepacia

Arianna Gorgoni, Giulia Antonini, Jacopo Gori, Irene Gado, Andrea Panzeri, Francesca Vasile, Laura Belvisi, Anna Bernardi, Sarah Mazzotta

Università degli Studi di Milano, Dipartimento di Chimica, Via Golgi 19, Milano, Italy

Burkholderia cenocepacia is a multidrug-resistant Gram-negative pathogen associated with severe opportunistic infections, particularly in cystic fibrosis and immunocompromised patients. A critical step in its pathogenesis is bacterial adhesion to host tissues, mediated by lectin–carbohydrate interactions, through the *superlectin* BC2L-C[1]. Targeting BC2L-C represents a promising strategy to interfere with the early stages of infection[2,3]. In this study, we focus on the C-5 functionalization of b-fucoside scaffolds to access derivatives capable of engaging secondary interaction sites within the lectin and suitable for the development of multivalent ligands. To achieve this goal, we employed a stereoselective decatungstate anion (TBADT)-mediated photochemical Giese-type alkylation, recently developed in our group, which enables the late-stage introduction of functionalized side chains at the C-5 position of b-fucosides (Figure 1). This methodology provides an efficient route to broaden the chemical space of the fucose core with high control over the newly formed stereocenter.[4]

Given the impact of the C-5 side-chain conformation on lectin recognition, the conformational preferences of the newly introduced substituents were investigated by combining conformational analysis and molecular dynamic simulations with NMR studies, providing insight into their spatial orientation and flexibility of the new ligands, both in the free state and in interaction with BC2L-C-*Nt*. These studies show that the C-5 substituent conformation is remarkably restricted and preorganized (Figure 1). They provide important information for the use of this novel chemotype in molecular design and will guide the rational design of next-generation glycomimetics.

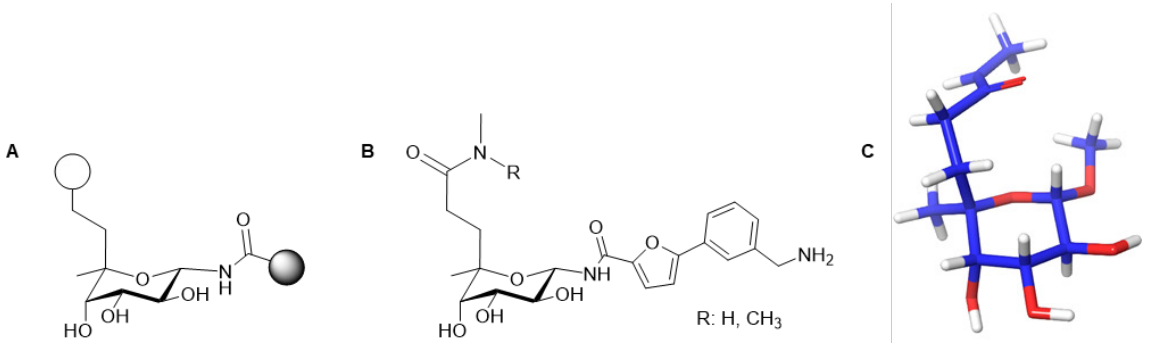


Figure 1. *(A) General molecular scaffold of C-5 modified β-fucoside derivatives; (B) Representative molecular structure of the C-5 modified BC2L-C ligand; (C) 3D structure of the global minimum obtained from conformational analysis of the C-5 substituted fucose ring.*

References:

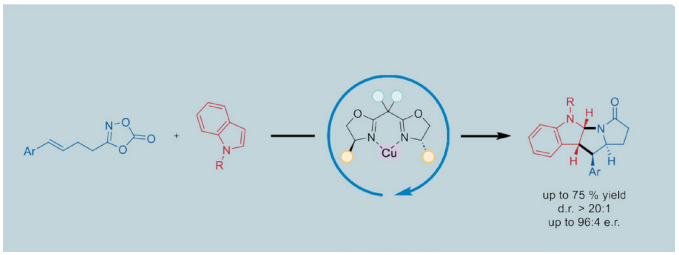
1. Šulák O, Cioci G, Lameignère E, et al. Burkholderia cenocepacia BC2L-C Is a Super Lectin with Dual Specificity and Proinflammatory Activity. Saper MA, ed. *PLoS Pathog*. 2011;7(9):e1002238. doi:10.1371/journal.ppat.1002238
2. Mazzotta S, Antonini G, Vasile F, et al. Identification of New L-Fucosyl and L-Galactosyl Amides as Glycomimetic Ligands of TNF Lectin Domain of BC2L-C from Burkholderia cenocepacia. *Molecules*. 2023;28(3):1494. doi:10.3390/molecules28031494
3. Antonini G, Fares M, Hauck D, et al. Toward Dual-Target Glycomimetics against Two Bacterial Lectins to Fight *Pseudomonas aeruginosa – Burkholderia cenocepacia* Infections: A Biophysical Study. *J Med Chem*. 2025;68(9):9681-9693. doi:10.1021/acs.jmedchem.5c00405
4. Mazzotta S, Piro M, Cassera E, et al. Editing sugars: decatungstate photocatalyzed site- and stereoselective C–H functionalization in β-fucosides. *Green Chem*. 2026;28(5):2319-2327. doi:10.1039/D5GC05775B

Copper-Catalyzed Intermolecular Asymmetric Dearomation of Indoles via Nitrene Transfer

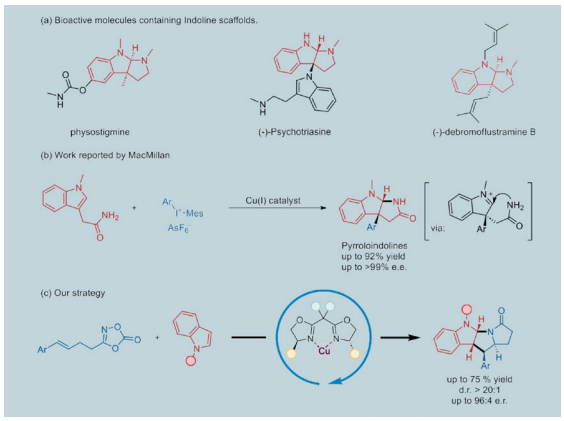
He Chang[1,2]; Prof. Zhong Guofu[2]; Prof. Yu Wing-Yiu, Michael[1*]

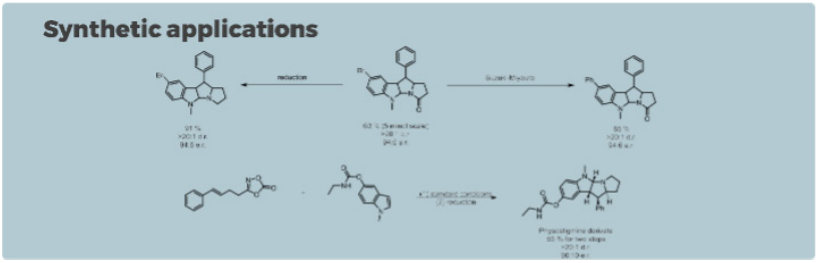
[1]*Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong;*
[2]*Eastern Institute of Technology, Ningbo, Zhejiang, P. R. China*

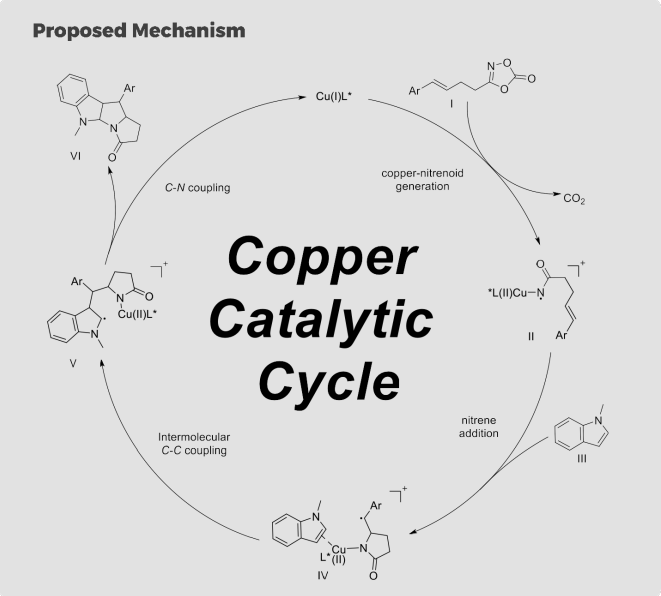
Abstract
The development of efficient strategies to construct enantioenriched 3D molecular architectures from planar aromatic precursors remains a cornerstone of modern synthetic chemistry. This work reports a novel copper-catalyzed intermolecular asymmetric dearomative cyclization of indoles initiated by nitrene transfer. By employing a chiral copper catalyst and nitrene precursors, we have achieved the direct assembly of pyrroloindoline and furoindoline scaffolds—privileged motifs prevalent in numerous bioactive alkaloids like Physostigmine and Gliocladin C. The reaction proceeds under mild conditions, offering a streamlined route to complex polycycles with vicinal quaternary and tertiary stereocenters in high yields and excellent stereoselectivity. Mechanistic investigations indicate a cascade pathway involving a high- valent copper-nitrene intermediate followed by a regioselective C3-attack and stereoselective cyclization. This methodology not only expands the utility of Catalytic Asymmetric Dearomatization (CADA) but also provides a robust platform for the late-stage functionalization of complex heterocycles and the total synthesis of natural products.

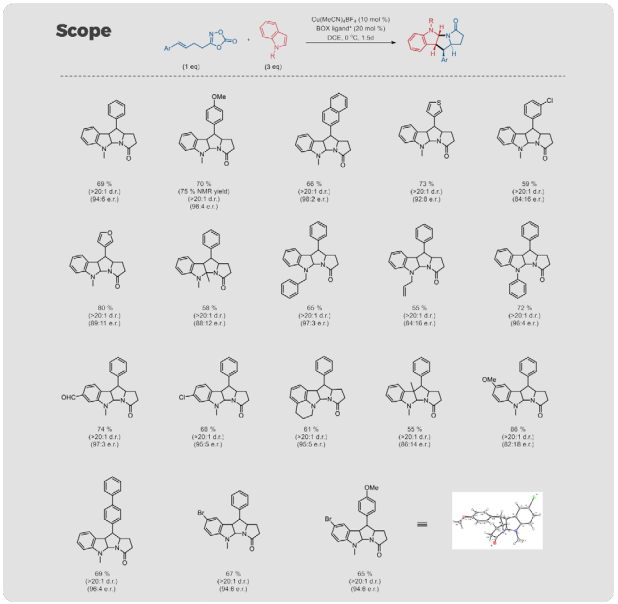


Introduction
Biological Significance: Pyrroloindoline and furoindoline skeletons are "privileged scaffolds" prevalent in bioactive alkaloids (e.g., Physostigmine, Gliocladin C).1
Synthetic Challenge: Direct construction of C3-quaternary chiral centers via dearomatization requires precise control over chemo-, regio-, and enantioselectivity.
State of the Art: Catalytic Asymmetric Dearomatization (CADA) provides an efficient route to 3D molecular complexity from planar indoles.2,3
This Work: We developed a Cu-catalyzed cascade dearomative cyclization that facilitates rapid access to polycyclic indoline derivatives.
This strategy emphasizes: High efficiency and mild reaction conditions; Construction of vicinal quaternary/tertiary stereocenters; Broad substrate scope for complex heterocycle synthesis.









Conclusion

We have developed an efficient copper-catalyzed intermolecular asymmetric dearomative cyclization of indoles initiated by nitrene transfer. The innovation lies in utilizing a chiral copper-nitrene species to achieve precise construction of vicinal quaternary and tertiary stereocenters in pyrroloindoline and furoindoline scaffolds under mild conditions. The reaction demonstrates a broad substrate scope with excellent functional group tolerance and high stereoselectivity. Mechanistic studies suggest the process involves a nucleophilic attack of the indole C3-position on a high-valent copper-nitrene intermediate, followed by a stereoselective cyclization. This methodology provides a robust route for the synthesis of bioactive indole alkaloids, with future prospects focused on extending this nitrene transfer strategy to other heteroaromatic systems and complex natural product total synthesis.

Acknowledgement:

Financial support was provided by the Start-Up Funding for scientific research of EIT and the 2024 Ningbo Yongjiang Talent Program.

References:

(1) Neuropharmacology 2021, 182, 108303.
(2) Nat Synth 2022, 1 (3), 203–216.
(3) J. Am. Chem. Soc. 2012, 134 (26), 10815–10818.

Targeting Human Antigen R (HuR): Advancing from Small Molecule Inhibitors to PROTACs for Therapeutic Intervention

Salma S.Hesse[a], Elisa Facen[b], Dalila Paladino[b], Josef Houser[c], Luciana Marinelli[d], Alessandro Provenzani[b], Daniela. Arosio[e], Pierfausto Seneci[a]

[a]Department of Chemistry, Università degli Studi di Milano, Via C. Golgi 19, 20133 Milan, Italy
[b]CIBIO Department, University of Trento, Via Sommarive 9, 38123 Trento, Italy
[c]Central European Institute of Technology, Masaryk University, Kamenice 753/5, 625 00 Brno, Czech Republic
[d]Department of Pharmacy, University of Naples Federico II, Via D. Montesano 49, 80131 Naples, Italy
[e]Istituto di Scienze e Tecnologie Chimiche "G. Natta" (SCITEC) - CNR, Via C. Golgi 19, 20133 Milan, Italy salma.hesse@unimi.it

Human antigen R (HuR) is a key post-transcriptional regulator primarily involved in messenger RNA (mRNA) translation and degradation.1 Overexpression and cytoplasmic accumulation of HuR are strongly associated with various diseases, including cancer, inflammation, and cardiovascular, muscle, kidney, and liver disorders, positioning HuR as an attractive therapeutic target. Reported strategies to target HuR include the use of small interfering RNAs (siRNAs) and small molecule inhibitors. While several compounds have been proposed, they face significant challenges, such as limited solubility, poor bioavailability, and off-target effects on other RNA-binding proteins (RBPs). Thus, effectively targeting HuR remains a major challenge in biomedical research.2
Through screening a large, small molecule library, we identified a promising hit compound as a potential HuR inhibitor with favorable biochemical properties. Docking studies of this hit provided deeper insights into its interactions with HuR, facilitating structure-activity relationship (SAR) exploration and guiding the structural optimization of analogues with improved affinity and pharmacokinetic profiles.
.

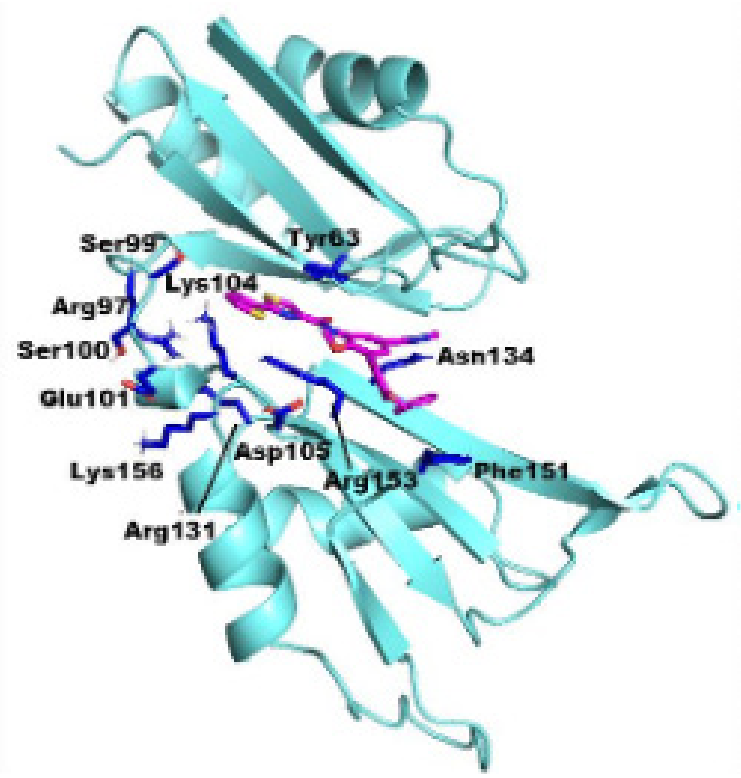


Figure 1: Molecular docking of the Hit compound and HUR

In addition to large compound library newly synthesized hit analogues, bifunctional PROtein-Targeted Chimeras (PROTACs), were synthesized to induce E3 ligase-promoted HUR degradation via the proteasome-ubiquitine machinery and subjected to biochemical and cellular profiling. This led to the identification of several promising leads with enhanced affinity and pharmacokinetic properties, which will be presented along with their biochemical evaluation.

References:

[1] Zucal C, D'Agostino V, Loffredo R, et al. Curr Drug Targets 2015, 16, 499-515.
[2] Assoni G, La Pietra V, Digilio R, et al. Adv Drug Deliv Rev. 2022, 181, 114088.

Enzyme-Activated Orthogonal Proteolysis Chimeras for Tumor Microenvironment-Responsive Immunomodulation

Ming Yao Ho[1] Caixia Sun[1], Songhan Liu[1], Jun Wei Lau[2], Hanyu Yang[1], Yun Chen[1], and Bengang Xing[3]

[1] School of Chemistry, Chemical Engineering and Biotechnology, Nanyang Technological University, 21 Nanyang Link, Singapore S637371, Singapore;
[2] Department of Chemistry, National University of Singapore, Singapore117543, Singapore.
3 Department of Applied Biology & Chemical Technology, The Hong Kong Polytechnic University, 11 Yuk Choi Road, Hung Hom, Kowloon, Hong Kong SAR;
[3] Institution, address, city, country

Precise modulation of dynamic and complex tumor microenvironment (TME) to disrupt tumorigenesis and reshape intratumoral immune infiltration has emerged as promising approaches for enhanced cancer therapy. Among recent innovations, proteolysis-targeting chimeras (PROTACs) represent a burgeoning chemical knockdown technology capable of degrading oncogenic protein homeostasis and inducing dynamic alternations within carcinoma settings, offering potential for antitumor manipulation. However, achieving selectivity in PROTACs that respond to disease environmental stimulation and precisely perturb on-target proteins remains challenging. The multi-step synthesis and limited permeability, attributed to high-molecular-weight and heterobifunctional structures, further hinder their in vivo efficacy. Herein, we present a unique TME-responsive enzyme-activated clickable PROTACs, which features a short peptide-tagged pomalidomide derivative to undergo tumor-specific cleavage by cathepsin protease to induce orthogonal crosslinking of the exposed cysteine with 2-cyanobenzothiazole-labeled epigenetic protein-ligand JQ1, facilitating in situ degrader formation within tumor regions only. Systematic protein profiling and proteomic analysis revealed that such TME-specific clickable-PROTACs not only selectively eliminate epigenetic proteins without tedious pre-synthesis to bridge disparate small-molecule bi-warhead fragments, but also demonstrated superior tumor penetration compared to conventional high-molecular-weight PROTACs. Importantly, these clickable-PROTACs efficiently downregulated immune checkpoint programmed death-ligand 1 (PDL1) both in vitro and in vivo, remodeling TME for enhanced therapeutics, especially in anti-tumoral immunomodulation.

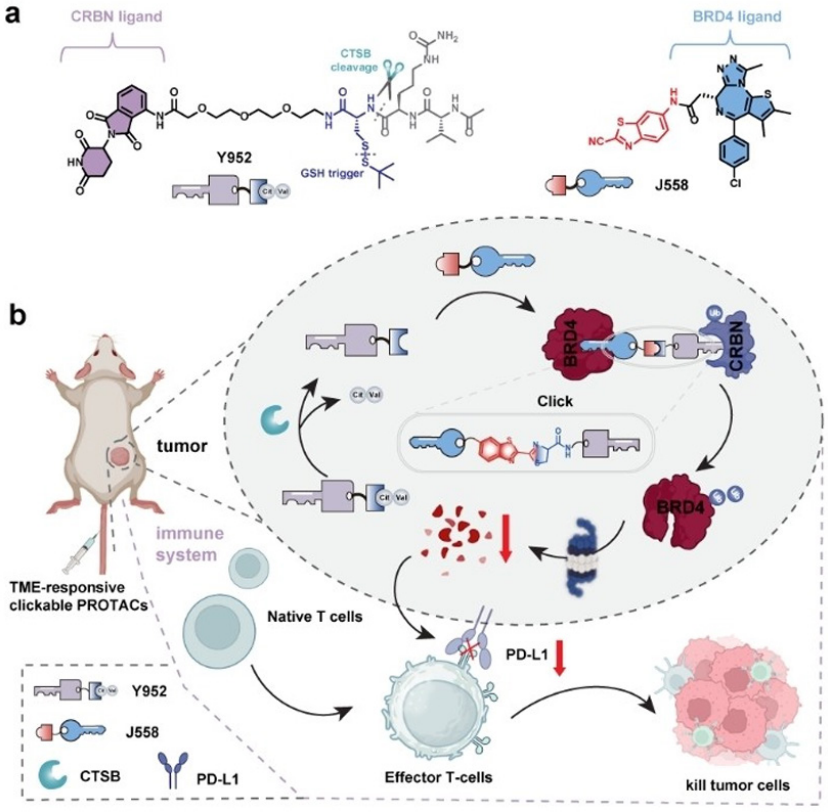


Figure 1. Schematic of Enzyme-Activated Orthogonal Proteolysis Chimeras for Tumor Microenvironment-Responsive Immunomodulation

Analytical Identification and Quantification of Bornyl Acetate in *Amomum villosum* by HPTLC and GC–MS

Jaehee Hyun, Soyoung Shin, Yongmi Kim, Wookyu Lee, Jaeuk Seo, Changsoo Kim, Jinhee Hwang

National Center for Medicinal Resources Management, Herbal Medicine Research Division, National Institute of Food and Drug Safety Evaluation, Cheongju, Republic of Korea

Amomum villosum Lour. (Zingiberaceae) is a medicinal plant widely used as an aromatic stomachic agent in traditional medicine. Bornyl acetate, a major monoterpene ester in *A. villosum*, contributes to its characteristic aroma and has been reported to exhibit various pharmacological activities, including antioxidant and anti-inflammatory effects. Due to these properties, bornyl acetate has been recognized as a key chemical marker for the quality evaluation of *A. villosum*. In the current Korean Pharmacopoeia, bornyl acetate is used as a reference compound in the thin-layer chromatography (TLC) identification test for *A. villosum*. However, quantitative specifications for this compound have not yet been established, highlighting the need for reliable analytical methods for quantitative determination. In this study, a combined analytical approach was developed for the identification and quantitative determination of bornyl acetate in *A. villosum*. Identification was performed using high-performance thin-layer chromatography (HPTLC), while quantitative analysis was conducted using gas chromatography–mass spectrometry (GC–MS). Methanol extracts of *A. villosum* samples were analyzed under optimized GC–MS conditions, and quantification was carried out using an external standard calibration method. The developed method was applied to commercial samples to determine the content of bornyl acetate. This analytical approach provides fundamental data for the quantitative evaluation and quality control of *A. villosum* and may contribute to the future establishment of pharmacopoeial standards.

References:

[1] He ZD, Qiao CF, Han QB, Cheng CL, Xu HX, Jiang RW, But PP, Shaw PC. Authentication and quantitative analysis on the chemical profile of *Amomi Fructus*. J Agric Food Chem 2005; 53: 8785–8790.
[2] Li Y, Kong D, Wu H. Analysis and evaluation of essential oils from *Amomum villosum* and related species. Molecules 2013; 18: 13136–13147.
[3] Ulrich SF, Rothauer A, Hagels H, Kayser O. Influence of light, temperature, and macronutrients on growth and scopolamine biosynthesis in *Duboisia* species. Planta Med 2017; 83: 937–945.

Effect of drying methods on Fludioxonil and Tebufenozide Residues in Welsh Onion

Jaebin Im, Mihyun Cho, Myungheon Kim, Changhyeon Park, Moo-Hyeog Im

Department of Food Engineering, Daegu University, Gyeongbuk 38453, Korea

In this study, we compared changes in fludioxonil and tebufenozide residue levels in Welsh onions using different drying methods: hot-air, infrared, and freeze-drying. Welsh onions were sprayed three times with fludioxonil (20% SC) and tebufenozide (8% WP) at 0.6 kg a.i./ha with 7- and 3-day intervals. After removing the roots and outer layers, the harvested Welsh onions were washed, dried, and cut into 8-mm slices. For hot-air and infrared drying, the slices were placed on trays and dried at 75 ℃ for 80 min, 70 ℃ for 50 min, and 65 ℃ for 90 min. Freeze-drying was performed at −70 ℃ for three days. The limits of quantitation for both pesticides were 0.01 mg/kg. Recovery rates were 75.6–100% and 90.9–103.5% in fresh Welsh onions, and 101.9–113.3% and 107.2–107.7% in dried Welsh onions for fludioxonil and tebufenozide, respectively. The initial residue levels of fludioxonil and tebufenozide in fresh Welsh onions were 1.46 and 1.27 mg/kg, respectively. After hot-air, infrared, and freeze-drying, fludioxonil residue levels ranged from 0.54–5.14, 0.50–6.57, and 4.18–6.71 mg/kg, while tebufenozide residues ranged from 0.43–2.79, 0.46–6.41, and 4.31–5.86 mg/kg, respectively. Residue levels increased after drying, and among the three drying methods, hot-air drying resulted in the lowest pesticide residue levels in Welsh onions.

Monitoring and Risk Assessment of Pesticide Residues in Fish species Using GC and LC-MS/MS

Myungheon Kim[1], Mihyun Cho[1], Jaebin Im[1], Changhyeon Park[1], Yoonmi Lee[2], Moo-Hyeog Im[1]

[1]*Department of Food Engineering, Daegu University, Gyeongbuk 38453, Korea*
[2]*Food Safety and Processing Research Division, National Institute of Fisheries Science, 216, Busan 46083, Korea*

The unintentional contamination of seafood with pesticides necessitates extensive monitoring. This study aimed to evaluate safety and actual human exposure levels by monitoring 68 pesticide residues, including those previously detected in seafood and those with potential contamination risks. A total of 160 samples were collected from eight species, including marine fish (starry flounder) and freshwater fish (eel, catfish, rainbow trout, crucian carp, common carp, leather carp, and mudfish), with 20 samples per species. Monitoring was conducted using GC-MS/MS and LC-MS/MS. The results indicated that no pesticide residues were detected in marine fish, whereas residues were detected in several freshwater fish species. Specifically, one case was found in eel, catfish, crucian carp, and rainbow trout, three cases in mudfish, and five cases in leather carp, while no residues were detected in common carp. The detected pesticides included chlorpyrifos, oxadiazon, and thifluzamide, with residue levels ranging from 0.005 to 0.01 mg/kg. Risk assessment was conducted using six exposure scenarios based on the monitoring results. Dietary risk assessment was performed by comparing the estimated daily intake (EDI) with the acceptable daily intake (ADI), expressed as %ADI. The evaluation revealed that %ADI values ranged from 0.0000% to 0.1110%, indicating a very low risk level. These findings suggest that dietary intake of pesticide residues in seafood poses minimal health risks and confirms the overall safety of consumption.

Light-Controlled of Protein–Ligand Affinity: Photoswitchable Binding of Photochromic Ligands to Hen Egg White Lysozyme

Tetuya Aso, Taéko Inada[1],

1School of Science, Kitasato University, 1-15-1 Kitasato Minami-ku Sagamihara, JAPAN;

Pochromic ligands provide a versatile strategy for the reversible **m**odulation of protein function, and promising components for biomimetic materials. We previously demonstrated reversible modulation of lysozyme activity through the photoisomerization of such ligands. Herein, we investigated the non-covalent interactions between dithienylethene-based ligands and hen egg white lysozyme (HEWL) using fluorescence spectroscopy, circular dichroism, and molecular docking. Two ligands bearing 5,5′-carboxyl groups and either a perfluorocyclopentene (daeF) or perhydrocyclopentene (daeH) core, were prepared. Both ligands exhibited efficient photochromic switching under alternating 313/530 nm irradiation in 1% DMSO buffer (pH 5.2–9.1), even in the presence of HEWL. Fluorescence quenching of tryptophan residues followed linear Stern–Volmer behavior with no significant temperature dependence, suggesting predominantly static quenching. Spectral analysis indicated a more hydrophobic environment around tryptophan residues in the closed forms. Both ligands bound to HEWL in a 1:1 ratio. The daeH/HEWL system exhibited a pronounced photoresponse: the binding constant at 313 nm photostationary state reached 10^5 M^{-1}, approximately one order of magnitude higher than that of the open form, and largely independent of pH. In contrast, the daeF/HEWL system showed a weak response, with the closed form (10^5 M^{-1}) having only twofold higher affinity than the open form. Docking analysis indicated that both ligands bind near substrate subsite B, interacting with Trp62. The closed form of daeH establishes an additional ionic interaction with an arginine residue, likely enhancing affinity. These results indicate the potential of photochromic ligands for the modulation of protein–ligand interactions.

Synthesis, structural studies, and determination of the pharmacokinetic profile of new phosphonate derivatives of fluorinated acetanilide

Klaudia Jaworska, Grzegorz Dutkiewicz, Maciej Kubicki, Donata Pluskota-Karwatka

Faculty of Chemistry, Adam Mickiewicz University in Poznań, Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland

Acetanilide represents an important structural motif in medicinal chemistry and serves as a versatile scaffold for the development of biologically active compounds. Structural modifications of the acetanilide core have produced derivatives exhibiting various biological activities, including antimicrobial, anti-inflammatory, and anticancer effects[1]. Introducing a phosphonate group into the structure of a compound can increase its water solubility, improve its bioavailability, and enable it to act as a prodrug that is enzymatically converted into its active form in the body[2]. Fluorine-containing aromatic moieties may contribute to improved pharmacokinetic parameters and p*K*a values of the compound[3].
In light of the above findings and as part of our ongoing research aimed at developing biologically active phosphonates[4,5], this project focused on the synthesis of a series of novel phosphonate derivatives of fluorinated acetanilide. The first stage of the synthesis involved the Arbuzov reaction, which enabled the introduction of a phosphonate group into the acetanilide molecule. In the next stage, nucleophilic substitution reactions with various bromides led to the formation of the corresponding *N*-substituted derivatives (Figure). Preliminary *in silico* studies of the compounds obtained revealed their favorable physicochemical and pharmacokinetic properties, including good permeability through cell membranes and compliance with drug-likeness criteria.
The synthesized compounds represent a new series of structurally characterized phosphonate derivatives built on a fluorinated acetanilide scaffold. Their predicted physicochemical properties suggest that these molecules may serve as promising candidates for further biological evaluation.

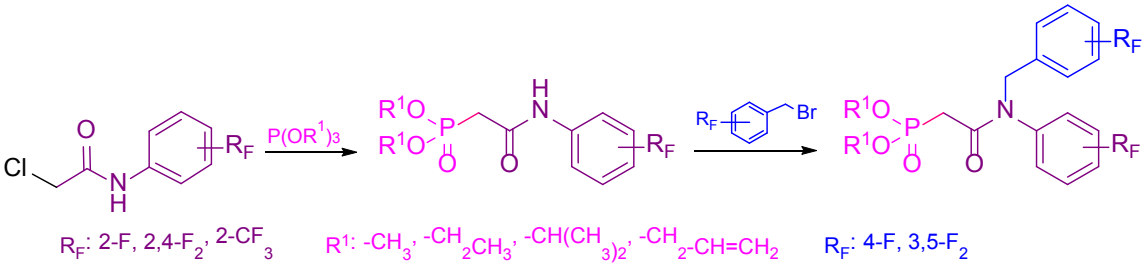


Figure. Synthetic approach to the target compounds.

References:

[1] Singh R K, Kumar A, Mishra A K. Chemistry and pharmacology of acetanilide derivatives: a mini review. Lett. Org. Chem. 2019; 16: 6-15.
[2] Voráčová M, Yli-Kauhaluoma J, Kiuru P. The key phosphorus moieties in drug design: antimicrobials and beyond. Future Med Chem. 2024; 16: 2455-2458.
[3] Gillis E P, Eastman K J, Hill M D, Donnelly D J, Meanwell N A. Applications of fluorine in medical chemistry. J. Med. Chem. 2015; 58: 8315–8359.
[4] Kwiczak-Yiğitbaşı J, Pirat J-L, Virieux D, Volle J-N, Janiak A, Hoffmann M, Mrzygłód J, Wawrzyniak D, Barciszewski J, Pluskota-Karwatka D. Synthesis, structural studies and biological properties of some phosphono-perfluorophenylalanine derivatives formed by SNAr reactions. RSC Adv., 2019; 9, 24117-24133.
[5] Ciesielska K, Wawrzyniak D, Dutkiewicz G, Kubicki M, Jankowski W, Hoffmann M, Kame Kl, Rolle K, Pluskota-Karwatka D. Diastereoselective synthesis and biological evaluation of new fluorine-containing α-aminophosphonates as anticancer agents and scaffold to human urokinase plasminogen activator inhibitors. Europ. J. Med. Chem., 2025; 283, 117116.

Development of efficient purification methods for circular mRNA

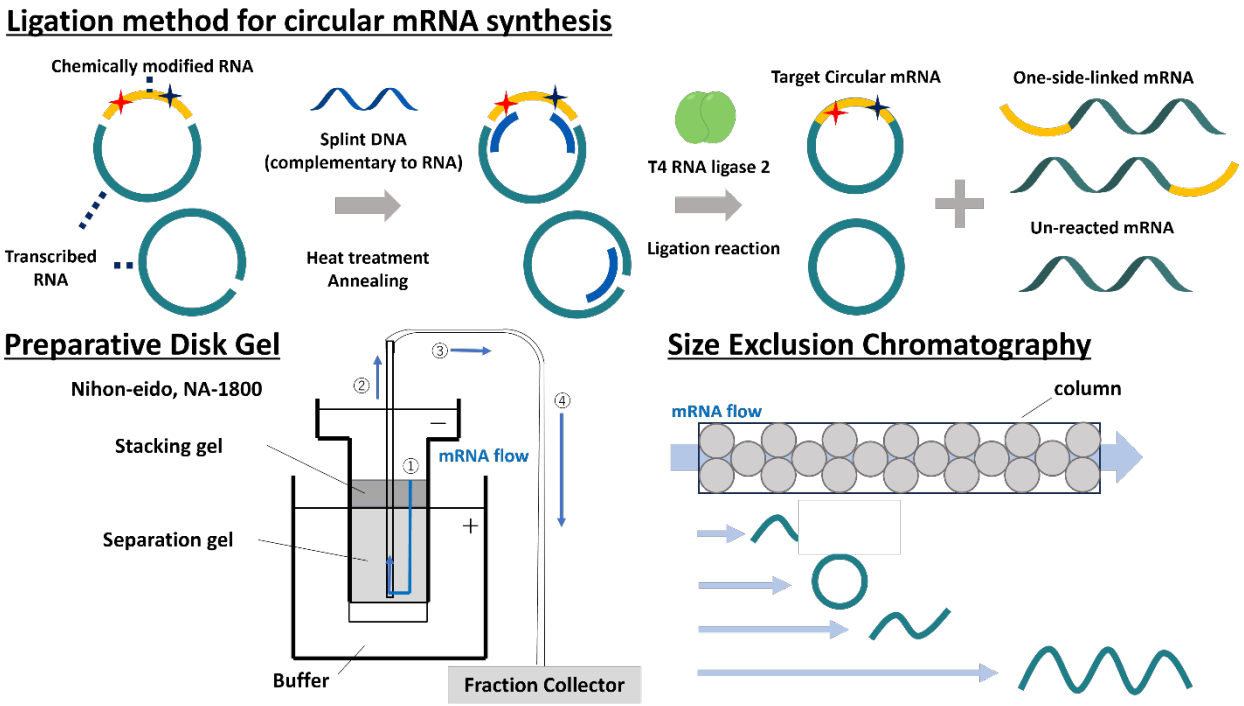
Shiryu Kajihara[1], Kosuke Fukuchi[1], Naoko Abe[1], Yuko Nakashima[1], Fumitaka Hashiya[2], Hiroshi Abe[1,3]

[1]Graduate School of Science, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Japan;
[2]Research Center for Materials Science, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Japan;
[3]Institute for Glyco-core Research (iGCORE), Nagoya, Japan

Circular mRNA has emerged as a promising next-generation therapeutic platform due to its exceptional stability against exonucleases and its ability to provide sustained protein translation[1]. While enzymatic ligation allows for flexible sequence design and site-specific chemical modifications, efficient large-scale purification remains a significant challenge. Specifically, separating the target circular mRNA from its linear precursor—which has the exact same sequence length—is difficult due to their nearly identical physicochemical properties.
In this study, we investigated three purification strategies to achieve high resolution and recovery by exploiting topological differences. First, conventional gel extraction was evaluated but found unsuitable for large-scale preparation due to low recovery rates and complex multi-step operations. Second, we applied preparative disc gel electrophoresis. By optimizing conditions such as gel concentration and electrophoresis time, we demonstrated the potential for high-resolution separation of circular forms from linear precursors[2,3].
Furthermore, we examined size-exclusion chromatography (SEC). Although separation was difficult with a single column, we significantly improved the resolution by connecting multiple SEC columns with different pore sizes in series. This multi-column SEC system successfully enabled the separation and recovery of circular mRNA from the reaction mixture. This presentation will report the detailed results of these purification methods and their potential for advancing the production of high-quality circular mRNA for medical applications.

References:

[1] Wesselhoeft RA, Kowalski PS, Anderson DG. Engineering circular RNA for potent and stable translation in eukaryotic cells. *Nat Commun* 2018; 9: 2629
[2] Cunningham L, Kittikamron K, Lu Y. Preparative-scale purification of RNA using an efficient method which combines gel electrophoresis and column chromatography. *Nucleic Acids Res* 1996; 24: 3647-3648
[3] Okegawa Y, Koshino M, Okushima T, Motohashi K. Application of preparative disk gel electrophoresis for antigen purification from inclusion bodies. Protein Expr Purif 2016; 118: 77-82

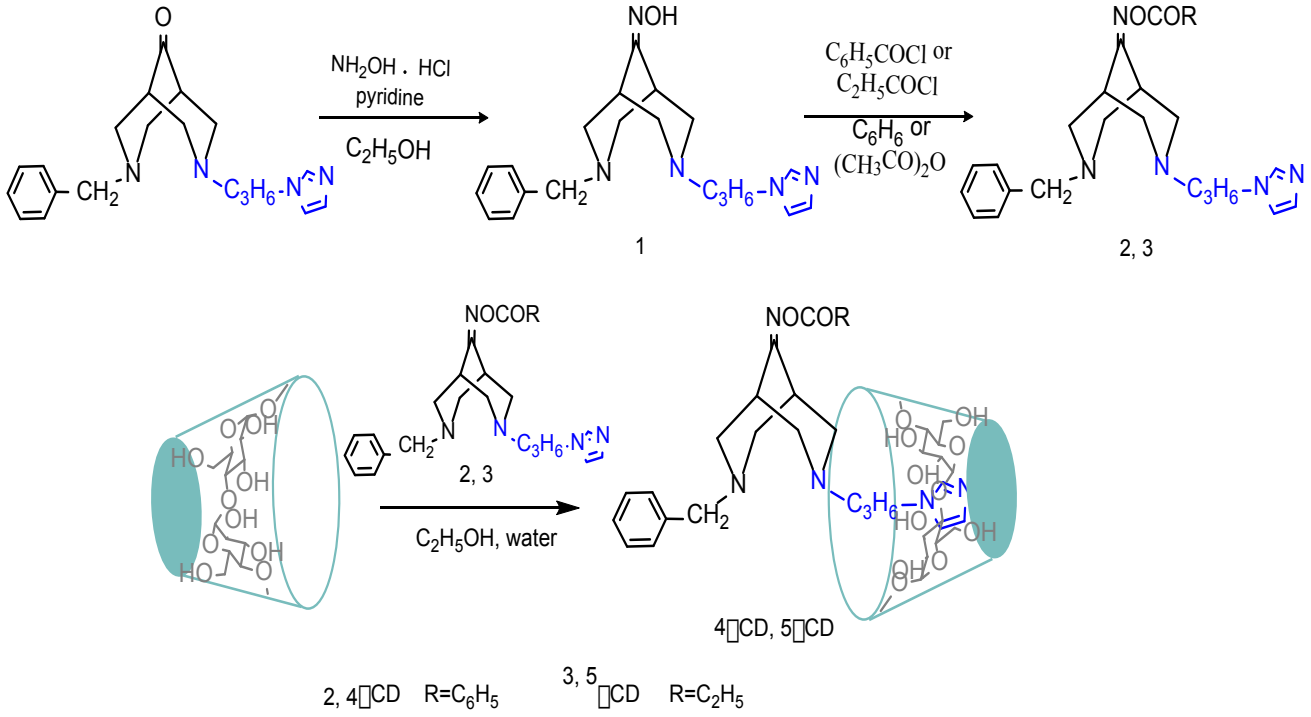


Synthesis of Novel Imidazole Derivatives and Evaluation of the Growth-Stimulating and Myelostimulating Activities of their β-CD Inclusion Complexes

Altynay B. Kaldybayeva[1,2], Valentina K. Yu[2], Tolegen M. Seilkhanov[3], Layilya Baktybayeva[1], Nurzhan S. Mukhamadiyev[4]

[1]Al-Farabi Kazakh National University, 71 Al-Farabi Ave, Almaty, Kazakhstan
[2]A.B. Bekturov Institute of Chemical Sciences, 106 Sh.Ualikhanov St., Almaty, Kazakhstan
[3]Sh. Ualikhanov Kokshetau University, 76 Abay St., Kokshetau, Kazakhstan
[4]Kazakh Research Institute of Plant Protection and Quarantine named after Zh. Zhiyembayev, 1 Kultobe St., Almaty, Kazakhstan

This study describes the synthesis of novel imidazole derivatives incorporating a bispidine moiety and the evaluation of the growth-stimulating and myelostimulating activities of their β-cyclodextrin (β-CD) inclusion complexes. Imidazole-containing 3,7-diazabicyclo[3.3.1]nonan-9-one oxime was synthesized by oximation with hydroxylamine hydrochloride in pyridine, followed by the preparation of the corresponding imidazole-bispidine oxime esters (Scheme 1). The structures of the synthesized compounds were confirmed by IR and NMR spectroscopy. Encapsulation of the obtained imidazole derivatives with β-cyclodextrin was performed to afford biologically acceptable supramolecular systems.



Scheme 1 - Synthesis of novel imidazole derivatives β-CD inclusion complexes

The synthesized compounds were evaluated for their effects on seed germination energy, laboratory germination rate, and germination intensity, as well as for their potential myelostimulating activity. The myelostimulation study showed that complex 5βCD reduced platelet counts, while increasing erythrocyte levels, hemoglobin concentration, and mean platelet volume, indicating moderate activity in leukopoiesis, erythropoiesis, and thrombopoiesis. Biological screening for growth-stimulating activity demonstrated that complex 5βCD promoted growth in wheat and soybean seedlings, whereas complex 4βCD exhibited inhibitory effects across all tested seed varieties.

This Research is funded by the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan (AP22688235, BR27101179).

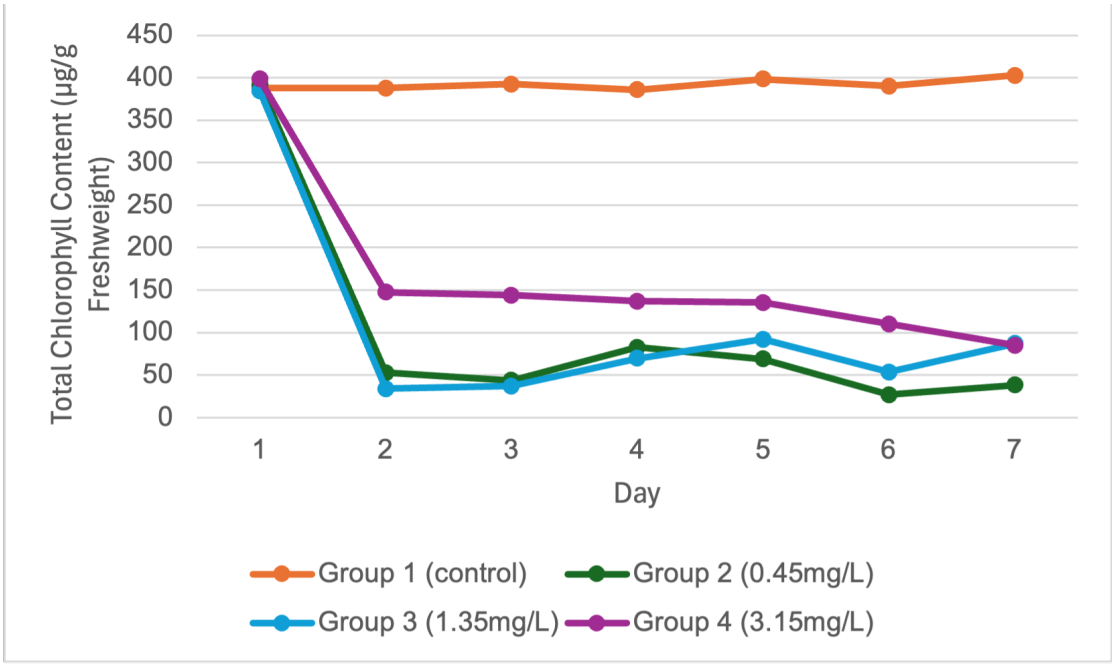
Investigating the Impact of Ibuprofen-Contaminated Water on the Chlorophyll Levels of *Lemna minor*

Beliz Kasacı, Murat Moralı, Zeynep Şeyhoğlu, Ceren Özçelik

Hisar School, Göktürk, Istanbul, Turkey

Pharmaceutical pollution, particularly non-steroidal anti-inflammatory drugs such as ibuprofen, has raised concerns due to their potential ecological impacts, including bioaccumulation, disruption of plant photosynthesis, and contamination of freshwater ecosystems resulting from improper wastewater management and agricultural runoff [1]. This study aims to explore the effect of ibuprofen concentration on the chlorophyll content of *Lemna minor (L.minor)*, an aquatic species that is utilized as a sensitive bioindicator for aquatic health [2]. *L. minor* was exposed to four different concentrations of ibuprofen : 0, 0.450, 1.351, and 3.153 mg/L to assess the effect of ibuprofen concentrations on chlorophyll content of *L. minor* over seven days at 25°C and 5-6 hours photoperiod. The chlorophyll levels were quantified via spectrophotometric analysis at 665.1nm, corresponding to the absorption maxima of chlorophyll-a and 644.8nm for chlorophyll-b[3]. The baseline references of the control group chlorophyll content at t=0 are used for data analysis. The first round of data collection indicates the reduced chlorophyll content with rising ibuprofen levels. Notably, a sharp decline was observed within the first 24 hours. Fluctuations in chlorophyll-a and b content in the diverse groups were found to be consistent with the similar studies that observed ibuprofen can have stimulating effects as well as on growth[4]. Further data collection will be collected to confirm the statistical significance of the findings. These findings provide a basis for further research about the tolerance of *L. minor* and highlight the ecological risks of ibuprofen in aquatic systems.

Table 1. Changes in Chlorophyll Content of Lemna minor Under Ibuprofen Exposure



References:

[1] Hirsch R, Ternes T, Haberer K, Kratz K. Occurrence of antibiotics in the aquatic environment. Sci Total Environ 1999; 225: 109-118
[2] Van Dyck I, Vanhoudt N, Vives i Batlle J, et al. Effects of environmental parameters on Lemna minor growth: An integrated experimental and modelling approach. J Environ Manage 2021; 300: 113705
[3] Lichtenthaler HK, Buschmann C. Chlorophylls and carotenoids: Measurement and characterization by UV–VIS spectroscopy. Curr Protoc Food Anal Chem 2001; F4.3: F4.3.1–F4.3.8
[4] Ikebe Otomo J, Araujo de Jesus T, Gomes Coelho LH, et al. Effect of eight common Brazilian drugs on Lemna minor and Salvinia auriculata growth. Environ Sci Pollut Res 2021; 28: 43747-43762

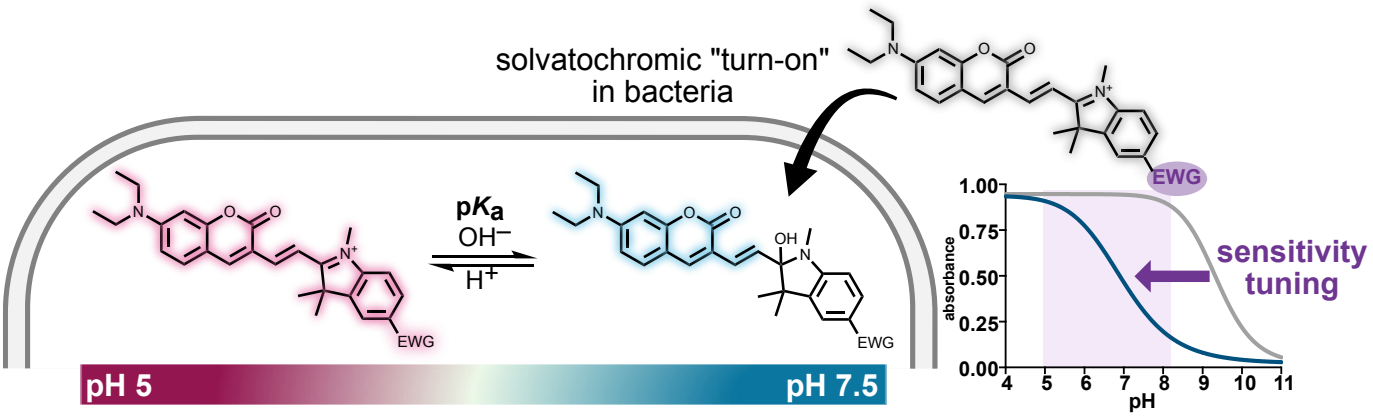
A ratiometric pH sensor for Gram-positive and Gram-negative bacteria.

Dorothea Kossmann[1], Aya Iizuka[2,3], Nina Khanna[2,4], and Pablo Rivera Fuentes[1]

[1]*Department of Chemistry, University of Zurich, 8057, Zurich, Switzerland;*
[2]*Department of Biomedicine, University of Basel, 4031, Basel, Switzerland;*
[3]*Swiss Institute of Bioinformatics, 4051, Basel, Switzerland;*
[4]*Division of Infection Diseases, University Hospital Basel, 4031, Basel, Switzerland*

Persister cells are phenotypically dormant bacteria that survive antibiotic treatment without genetic resistance. Their formation is modulated by environmental fluctuations, especially exposure to low pH. To understand how individual cells adapt to pH stress, methods are required to analyze single-cell physiology. Yet most pH probes are optimized for mammalian cells and poorly suited for bacterial applications, as bacteria preferentially take up positively charged, polar, or zwitterionic molecules.[1-3]

We report a ratiometric fluorescent probe for sensing cytoplasmic pH in bacteria.[4] Our probes are based on hemicyanine dyes that exhibit good cellular uptake in both Gram-positive and Gram-negative bacteria. Additionally, our probes exhibit improved photophysical properties for bacterial imaging, particularly increased brightness due to the apolar nature of the intracellular space. By tuning the electrophilicity of the molecular scaffold, we obtained a pH-sensing CouCy probe that preferentially reacts with OH^- and exhibits a ratiometric emission change. The response is rapid and reversible, enabling real-time tracking of pH fluctuations around neutrality and biologically relevant acidification. We validated the live-cell imaging using *Escherichia coli*, *Staphylococcus epidermidis*, and a clinically isolated methicillin-resistant *Staphylococcus aureus* strain. Furthermore, the probes enabled monitoring of phagocytosis of clinical strains by immune cells and allowed distinction of virulence phenotypes based on intracellular pH. Our probes are promising tools for detecting phenotypic heterogeneity of clinically relevant bacteria.



References:

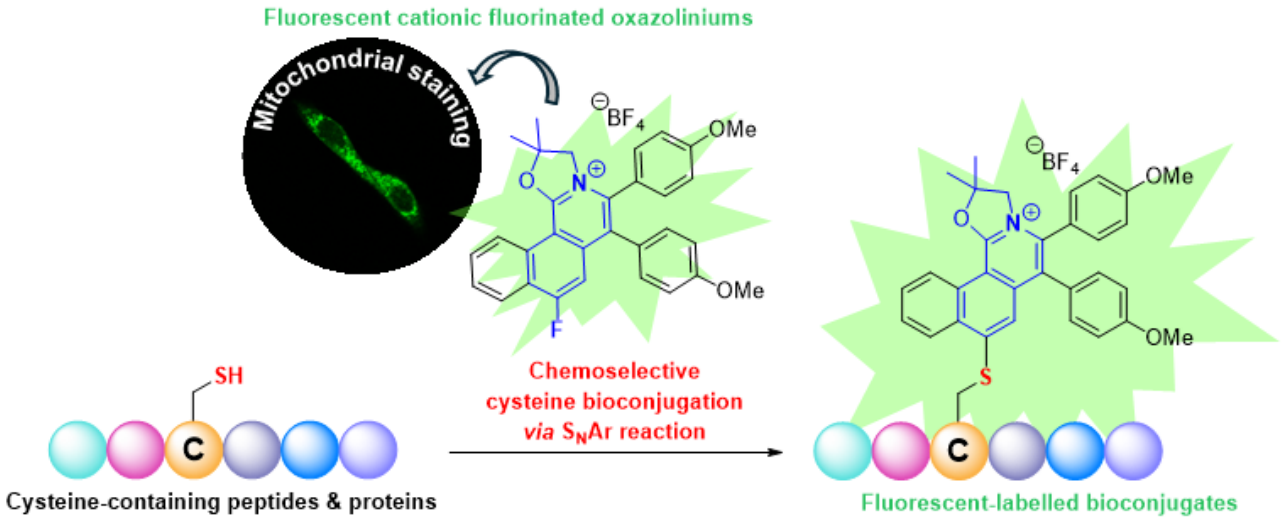
[1] Krulwich, T. A.; Sachs, G.; Padan, E. Molecular Aspects of Bacterial pH Sensing and Homeostasis. Nat Rev Microbiol 2011, 9: 330-343.
[2] Leimer, N.; Rachmühl, C.; Palheiros Marques, M.; Bahlmann, A. S.; Furrer, A.; Eichenseher, F.; Seidl, K.; Matt, U.; Loessner, M. J.; Schuepbach, R. A.; Zinkernagel, A. S. Nonstable *Staphylococcus Aureus* Small-Colony Variants Are Induced by Low pH and Sensitized to Antimicrobial Therapy by Phagolysosomal Alkalinization. J Infect Dis 2016; 213: 305–313.
[3] Ropponen, H.-K.; Richter, R.; Hirsch, A. K. H.; Lehr, C.-M. Mastering the Gram-Negative Bacterial Barrier – Chemical Approaches to Increase Bacterial Bioavailability of Antibiotics. Adv Drug Deliv Rev 2021; 172: 339-360.
[4] Kossmann, D.; Iizuka, A.; Khanna, N.; Rivera-Fuentes, P. A Ratiometric pH Sensor for Gram-Positive and Gram-Negative Bacteria. J. Am. Chem. Soc. 2026, 148: 4754–4765

Fluorescent Cationic Fluorinated Oxazoliniums for Cysteine Bioconjugation via SNAr Reaction

Karen Ka-Yan Kung[‡1], Yosephine Tania Limanto[‡1], Ajcharapan Tantipanjaporn[1], Jie-Ren Deng[3], Lai-Yi Tsang[3] and Man-Kin Wong[1,2]

[1]Research Institute for Future Food, Department of Food Science and Nutrition, The Hong Kong Polytechnic University, Hung Hom, Hong Kong, China.
[2]Centre for Eye and Vision Research (CEVR), 17W Hong Kong Science Park, Hong Kong, China.
[3]Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Hong Kong, China.
[‡]These authors contributed equally to this work.

Fluorescent labeling provides a powerful approach for attaching fluorophores to biomolecules, resulting in fluorescent bioconjugates with high selectivity and diverse functionalities for visualizing and tracking biological processes. Cysteine is frequently used as a bioconjugation site because of its strong nucleophilicity and low natural abundance. Cysteine arylation by fluorinated aromatic compounds via nucleophilic aromatic substitution (SNAr) has demonstrated advantages over metal- or photo-catalyzed arylation. Recent advances have been made in fluorescence analysis using small-molecule fluorescent probes, including the incorporation of fluorine to fluorophores to improve imaging capabilities, targeting functionalities and overall biological activities. To achieve fluorescent cysteine bioconjugation, attachment of a fluorescent dye to the bioconjugation reagents is necessary, requiring additional synthetic effort. Thus, it is interesting to develop a fluorescent bioconjugation reagent without the need for addition of a separate fluorescent dye. Although many cationic polycyclic heteroaromatics, including isoquinoliniums, quinoliziniums, and pyridiniums, are recognized as water-soluble fluorophores, oxazoliniums remain relatively unexplored. In this study, we report the synthesis of fluorescent cationic fluorinated oxazoliniums for cysteine bioconjugation through SNAr.[1] By using rhodium (Rh)-catalyzed reaction, fluorinated oxazolinium compounds were prepared *via* a modular approach. We also studied photophysical properties and applications of fluorescent cationic fluorinated oxazoliniums in labeling peptides and proteins under mild conditions, with conversion up to 99%. Live cell imaging studies reveal good compatibility of these oxazoliniums as fluorescent dyes for mitochondrial targeting.



References:

[1] K. K.-Y. Kung, Y. T. Limanto, A. Tantipanjaporn, J.-R. Deng, L.-Y. Tsang and M.-K. Wong, Fluorescent Cationic Fluorinated Oxazoliniums for Cysteine Bioconjugation via SNAr Reaction, RSC Chem. Biol. 2026, manuscript accepted.

Cluster-triggered emission biopolymers for the development of photonic applications

Agustín Lara-Sánchez,*[1] Felipe de la Cruz-Martínez,[1] Cristina Martín,[2] Jesús Naranjo,[1] Karina Dueñas,[3] Oscar Gulias,[3] Santi Nonell,[3] Roger Bresolí-Obach[3]

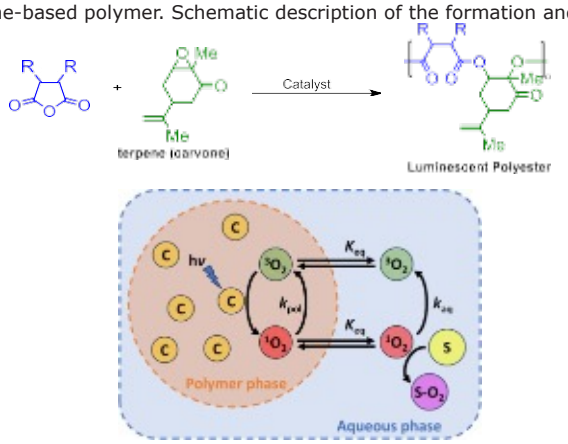
[1]Universidad de Castilla-la Mancha, Departamento de Química Inorgánica, Orgánica y Bioquímica-Centro de Innovación en Química Avanzada (ORFEO-CINQA), Facultad de Ciencias y Tecnologías Químicas, Avda. Camilo José Cela, 10, 13071-Ciudad Real, Spain;
[2]Universidad de Castilla-la Mancha, Departamento de Química Física, Facultad de Ciencias Ambientales y Bioquímica, Avd. Carlos III, S/N, 45004-Toledo, Spain;
[3]AppLightChem, Institut Químic de Sarrià, Universitat Ramon Llull, Via Augusta 390, 08017-Barcelona, Spain. (Agustin.Lara@uclm.es)

The design of new and more environmentally friendly materials with innovative luminescent properties is of great interest. Their unique properties, such as low toxicity, excellent biocompatibility, and tunable cluster-triggered emission luminescence (CLgens) in response to external stimuli, make them ideal probes for biophotonic applications.[1] However, the relationship between the chemical structure of CLgens and their unexpected optical properties is still the missing link to enhance their applications.

This study aimed to relate the chemical structure of the newly synthesised CLgens from biomass-derived monomers such as carvone (Figure 1). The spectroscopic studies at steady-state and time-resolved levels help unravel the structure-properties and how this is affected by an external physical stimulus such as temperature and, later, pH. Based on these promising results, and as a proof of

concept, the thermal sensitivity was successfully tested at the microscale level to visualise how temperature rises in photothermal methods and monitor intracellular state parameters such as pH.[2] So, if the luminescent properties of CLgens do not lack properties previously associated only with traditional chromophores, can they be extrapolated to other types of excited state applications? The real question is: could these excited states transfer energy to oxygen and form reactive oxygen species (ROS)? The preliminary results on the carvone polymers suggest that this is possible and that the long-excited lifetimes could efficiently transfer their excess energy to molecular oxygen to produce ROS such as 1O2. Still, more importantly, they have excellent photoantimicrobial capabilities against Staphylococcus aureus (S. aureus).

Figure 1. Carvone-based polymer. Schematic description of the formation and decay of 1O2.



References:

[1] Bresolí-Obach R, Castro-Osma J A, Nonell S, Lara-Sánchez A, Martín C. Polymers showing cluster triggered emission as potential materials in biophotonic applications. J. Photochem. Photobiol., C. 2024; 58: 100653.
[2] Dueñas-Parro K, Gulias O, Agut M, de la Cruz-Martínez F, Lara-Sánchez A, Castro-Osma J A, García-Reyes J F, Sánchez-Ruiz A, Martín C, Nonell S, Bresolí-Obach R. Cluster and Kill: the Use of Clustering-Triggered Emission Materials for Singlet Oxygen Photosensitization in Antimicrobial Photodynamic Therapy. Adv. Optical Mater. 2025; 13: 2402179.

Pesticide-Induced Acetylcholinesterase Regulation and Human Neuroblastoma Cells Cytotoxicity via a Microfluidic Platform

Ming-En Lee[1], Kuan-Fu Chen[1], Ching-Kuo Lee[2]

[1]Ruah International Academy, *No. 336, Sec. 6, Roosevelt Rd., Taipei, Taiwan* (R.O.C.);
[2]*Taipei Medical University, No. 250, Wuxing St., Taipei* Taiwan (R.O.C.).

Pesticides are widely used to control insects and other arthropods, thereby reducing crop damage and pest infestation. However, their chemical properties, mechanisms of action, and toxicological profiles vary substantially. In this study, we focused on relatively safe and commonly used pesticides, including cypermethrin and azadirachtin, to investigate their effects on acetylcholinesterase regulation and human neuroblastoma cells cytotoxicity.
In addition, microfluidic technology offers several advantages over conventional methods for mixing, reaction, and separation, including faster processing, reduced reagent consumption, smaller working volumes, improved energy efficiency, lower chemical waste generation, and compatibility with high-throughput and automated operations. These features make microfluidic platforms highly suitable for toxicological screening and cellular analysis.
Therefore, this study investigated the effects of various pesticides and their metabolites on acetylcholinesterase (AChE) regulation and cytotoxicity in human neuroblastoma cells. Preliminary results suggest that differences in chemical structure lead to distinct effects on AChE regulation and SH-SY5Y cell toxicity. The half-maximal inhibitory concentration (IC50) values of cypermethrin and its metabolite PBC toward AChE were 250 μM and >450 μM, respectively. Molecular docking analysis was also performed to further explore the factors influencing these interactions (Figure 1).

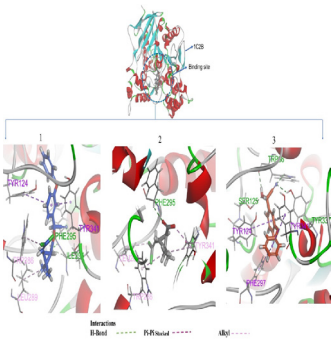


Fig.1 3D structures of binding modes between sites of acetylcholinesterase in (PDB code: 1C2B) and cypermethrin was calculated by molecular docking.

References:

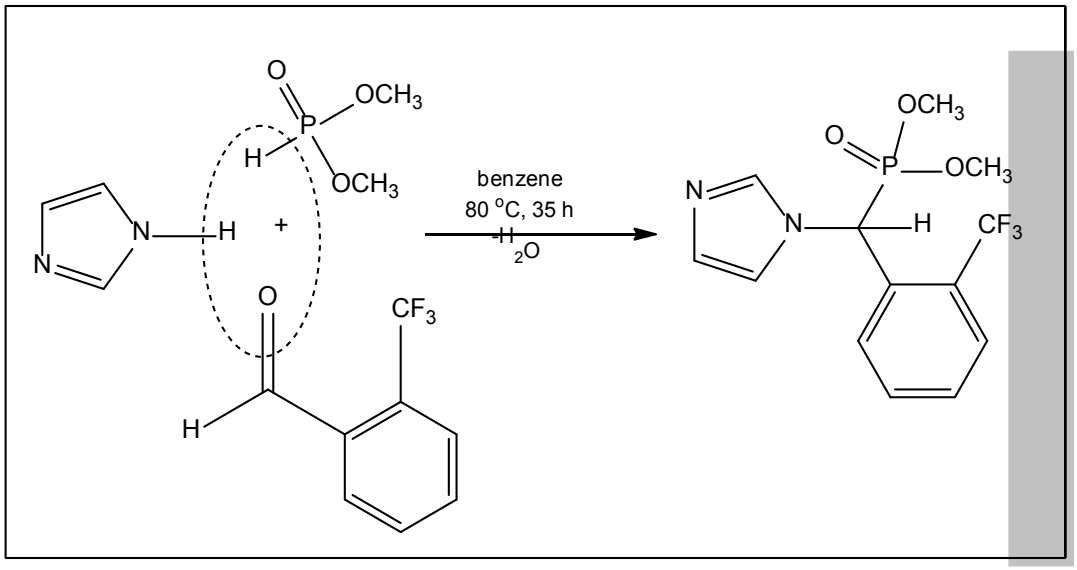
[1] Martínez, MA., Lopez-Torres, B., Rodríguez, JL., Martínez, M., Maximiliano, JE., Martínez-Larrañaga, MR., Anadón, A., Ares, I. Toxicologic evidence of developmental neurotoxicity of Type II pyrethroids cyfluthrin and alpha-cypermethrin in SH-SY5Y cells. Food and Chemical Toxicology 2020; 137:111173.
[2] Li, Y, Li, D, Zhao, P, Nandakumar, K, Wang, L., Song, Y. Microfluidics-Based Systems in diagnosis of Alzheimer's disease and biomimetic modeling. Micromachines 2020;11: 787.

α-Aminophosphonate–β-Cyclodextrin Complex as a Promising Plant Growth Biostimulant

Aigul Erbosynovna Malmakova[1,2], Kamila Babazhankyzy Otegulova[2], Maksat Aiman[3], Anel Tles[4]

[1]Kazakh-British Technical University, Almaty, Kazakhstan;
[2]A.B. Bekturov Institute of Chemical Sciences, Kazakhstan;
[3]Kazakh National Women Teacher Training University,
[4]Abai Kazakh National Pedagogical University,

α-Aminophosphonates are organophosphorus analogues of α-amino acids where the carboxyl group is replaced by a phosphonate moiety. Their chemical stability and balanced electronic properties confer various biological activities, including antibacterial, enzyme-inhibitory, and plant-growth-promoting effects; however, poor solubility and bioavailability often limit their use.
In this study, a new fluorine-containing α-aminophosphonate - dimethyl((1H-imidazol-1-yl)(2-(trifluoromethyl)phenyl) methyl)phosphonate - was synthesised via a one-pot Kabachnik–Fields reaction. The CF_3 group and imidazole fragment were incorporated to improve membrane permeability and biomolecular interactions.



To improve the solubility and bioavailability of the synthesised molecule, it was incorporated into the hydrophobic cavity of **β**-cyclodextrin (**β**-CD), a natural cyclic oligosaccharide possessing strong inclusion capabilities. The structures of both the free compound and its β-CD inclusion complex were confirmed using IR, 1H NMR, and 13C NMR spectroscopy. The IR spectrum exhibited characteristic absorption bands corresponding to NH, PH, PO, and P–O–C functional group vibrations, confirming the presence of the phosphonate moiety. The principal absorption bands were observed at 1589 cm-1 (aromatic C=C), 1313 cm-1 (C–N), 1279 cm-1 (P=O), 1014 cm-1 (C–F), and 767 cm-1 (P–C).
The 1H NMR spectrum of compound (II) shows multiplet signals in the region δ 7.05-7.89 ppm, assigned to the protons of the imidazole ring (H-2ax, 2eq, 4ax, 5ax, 4eq, 5eq). The methoxy protons (H-9,9,9 and H-17,17,17) appear as two singlets at δ 3.60 and δ 3.62 ppm, respectively. The methine proton (H-6) is observed as a multiplet at δ 5.15 ppm, whereas the aromatic protons (H-12-H-15) of the 2-(trifluoromethyl)phenyl fragment resonate as multiplets in the range δ 7.59-8.00 ppm.
The 13C NMR spectrum supports these data and demonstrates the expected carbon framework. Signals in the upfield region δ 119.7-134.9 ppm correspond to the carbon atoms of the imidazole ring (C-2, C-4, C-5). Resonances at δ 53.6 and δ 54.0 ppm are attributed to the carbon atoms of the P(O)(OCH3)2 group. In the downfield region, signals of the aromatic carbons of the benzyl-trifluoromethyl fragment are observed at δ 123.7, 126.8, 130.2, 131.0, and 133.5 ppm.
Biological testing was performed on seeds of spring wheat (variety "Kazakhstan 10"). Treatment with the β-CD-aminophosphonate complex resulted in higher germination energy, increased seedling height, and improved overall plant health compared to the untreated control. Germination energy reached 95.0%, significantly higher than the control (82.0%) and other groups. Treated seeds also demonstrated improved germination and vigour in laboratory conditions. The average seedling height was 11.5 cm, approximately 2 cm taller than the control.
These results show that forming complexe of fluorinated α-aminophosphonate with CD is an effective way to create environmentally friendly plant growth stimulants.

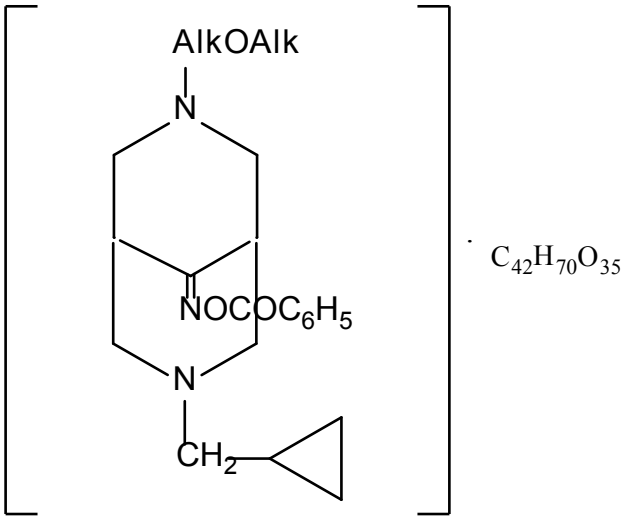
The research was funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. AP22685628).

Local Anesthetic Activity of the β-Cyclodextrin Inclusion Complex

Aigul Erbosynovna Malmakova[1,2], Kamila Babazhankyzy Otegulova[2], Vagiz Alsu[3]

[1]*Kazakh-British Technical University, Almaty, Kazakhstan;*
[2]*A.B. Bekturov Institute of Chemical Sciences, Kazakhstan;*
[3]*Kazakh National Women Teacher Training University*

Introduction.
The development of new biologically active compounds based on the 3,7-diazabicyclo[3.3.1]nonane framework is an important area of medicinal chemistry due to their broad pharmacological activity. Bispidine derivatives exhibit analgesic, neuroleptic, antimicrobial, and antifungal properties. Structural modification of this scaffold, including the introduction of various substituents, can significantly affect their biological activity and expand their practical applications.
The aim of this study was to evaluate the local anesthetic activity of the *β*-cyclodextrin inclusion complex of the O-benzoyl oxime of 3-alkoxyalkyl-7-cyclopropylmethyl-3,7-diazabicyclo[3.3.1]nonane (LA-189) and to compare its efficacy, depth, and duration of anesthesia with reference anesthetics (lidocaine, procaine, and trimecaine) using a standard in vivo method.



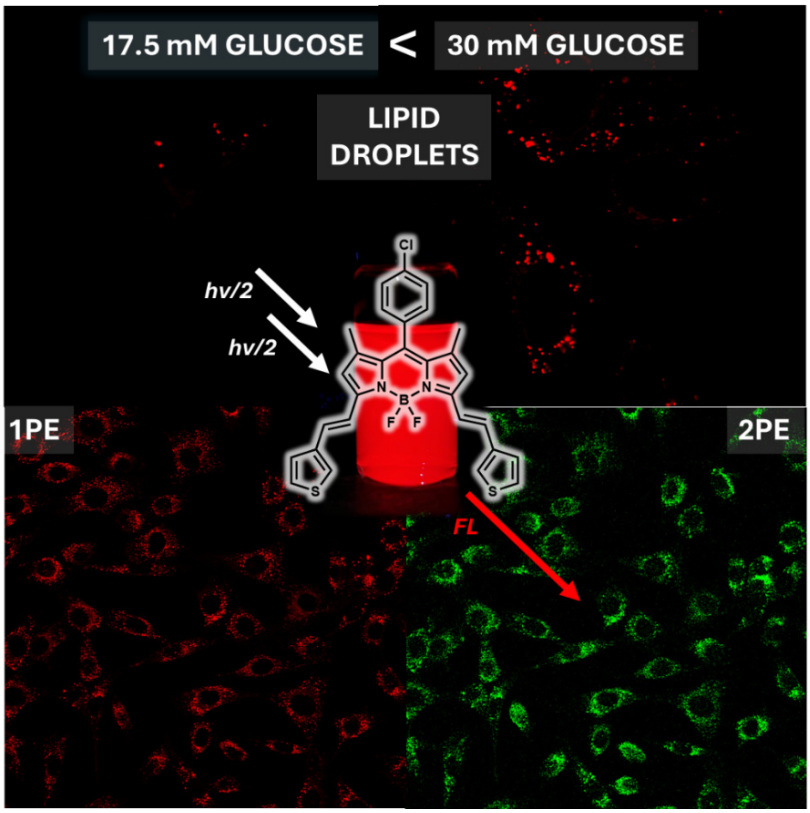
The pharmacological effect of the *β*-cyclodextrin inclusion complex of the O-benzoyl oxime of 3-alkoxyalkyl-7-cyclopropylmethyl-3,7-diazabicyclo[3.3.1]nonane was compared with reference drugs: Lidocaine, Procaine, and Trimecaine. The assessment was performed using a standard in vivo methodology for determining the depth and duration of anesthesia.
LA-189 demonstrated the greatest depth of anesthesia, with an anesthesia index of 36. At a concentration of 0.25%, its anesthetic potency significantly exceeded that of trimecaine, lidocaine, and procaine by 1.1-, 1.55-, and 1.44-fold, respectively ($p < 0.05$).
Regarding duration of action, LA-189 also showed pronounced superiority. The duration of complete anesthesia reached 56.66 min, which was 2.83, 3.9, and 5.66 times longer than that of trimecaine, lidocaine, and procaine, respectively. The total duration of anesthetic effect was 76.66 min, compared to 38.3 min for trimecaine, 30.8 min for lidocaine, and 29.1 min for procaine, corresponding to a 2.0-, 2.4-, and 2.6-fold prolongation.
In conclusion, the β-cyclodextrin inclusion complex LA-189 demonstrated significantly enhanced local anesthetic activity compared with the reference drugs lidocaine, procaine, and trimecaine. The compound showed the greatest depth of anesthesia (anesthesia index 36) and markedly prolonged duration of action, with complete anesthesia lasting up to 56.66 min and a total anesthetic effect of 76.66 min. These values substantially exceed those of the reference anesthetics. The results indicate that LA-189 possesses superior potency and duration of action, highlighting its potential as a promising candidate for further pharmacological and preclinical studies as a novel long-acting local anesthetic.

The research was funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. AP26198287).

Lipid Droplet Response to Glucose in Fibroblast Cells Using Multiphoton-active Red-emitting BODIPYs

Paolo James Mastroeni, Patrycja Stachelek

Department of Chemistry, Durham University, Lower Mountjoy, South Road, Durham, DH1 3LE, United Kingdom



Boron-dipyrromethenes (BODIPYs) are popular dyes in the fields of bioimaging and theranostics due to their rich photophysical characteristics, versatility and biocompatibility [1]. Presented herein are two BODIPYs with 3,5-thienylenevinylene units bathochromically shifting spectral bands. Spectroscopic and *in cellulo* effects of attaching via the thiophene's 2-position compared to the 3-position were studied. Comprehensive characterisation found that the 2-position offered stronger donation into the BODIPY core and red-shifted emission, whereas attachment at the 3-position induced a twist in the core, lowering the molar extinction coefficient with less efficient participation in conjugation.

Single-photon red or two-photon near-infrared excitation showed both dyes are bright and photostable; they possess competitive two-photon absorption cross-sections of 397 GM (1 GM = 10−50 cm4 s photon−1) at 950 nm and 279 GM at 820 nm, respectively. Low energy excitation is important to reduce cytotoxicity and increase tissue penetration [2].

Laser scanning confocal microscopy with single-photon and two-photon excitation showed lipid droplet (LD) accumulation for both dyes. Incubation with oleic acid, known to cause LD proliferation, confirmed the dyes can be used quantitatively [3]. Additionally, both dyes retain within LDs for 24 hours with minimal toxicity. These features were used to study the LD response of cells to extracellular glucose; a notable increase was observed upon a change from 17.5 mM to 30 mM glucose (13.6 to 68.5 mean LDs per cell). Studying LD response to glucose is crucial to understand diseases such as cancer and diabetes, and fluorescent dyes could be diagnostic tools to achieve this [4].

References:

[1] G. Ulrich, R. Ziessel, and A. Harriman, 'The Chemistry of Fluorescent Bodipy Dyes: Versatility Unsurpassed', *Angew. Chem. Int. Ed.*, vol. 47, no. 7, pp. 1184–1201, Feb. 2008, doi: 10.1002/anie.200702070.
[2] P. J. Mastroeni *et al.*, 'Synthesis, characterisation and application of red-emitting BODIPY dyes for multiphoton microscopy of lipid droplets', *Dyes and Pigments*, vol. 243, p. 113045, Dec. 2025, doi: 10.1016/j.dyepig.2025.113045.
[3] S. Nakajima, M. Gotoh, K. Fukasawa, K. Murakami-Murofushi, and H. Kunugi, 'Oleic acid is a potent inducer for lipid droplet accumulation through its esterification to glycerol by diacylglycerol acyltransferase in primary cortical astrocytes', *Brain Res.*, vol. 1725, p. 146484, Dec. 2019, doi: 10.1016/j.brainres.2019.146484.
[4] A. González, C. Calfío, M. Churruca, and R. B. Maccioni, 'Glucose metabolism and AD: evidence for a potential diabetes type 3', *Alzheimers Res. Ther.*, vol. 14, no. 1, p. 56, Dec. 2022, doi: 10.1186/s13195-022-00996-8.

Photoresponsive Azobenzene Ligands for G-Quadruplex DNA: Synthesis and *In Vitro* Studies

A. Matusiak, K. Matczyszyn1, M. Dudek

Institute of Advanced Materials, Faculty of Chemistry, Wroclaw University of Science and Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland

G-quadruplexes (G4s) are secondary DNA structures formed in guanine-rich sequences exposed during transcription, replication, and DNA repair. Their increased prevalence in cancer cells makes them attractive therapeutic targets, as stabilization of G4 structures can block DNA and RNA polymerases, leading to replication stress and genomic instability. However, most G4-targeting ligands operate through static, unidirectional mechanisms, limiting dynamic control over G4 function. To address this limitation, a series of substituted azobenzene derivatives was designed and synthesized as photoresponsive ligands for G4 structures. The compounds were systematically studied in terms of their physicochemical properties and interactions with DNA using complementary biophysical techniques, enabling the identification of key structural features governing G4 binding and stabilization. Based on these findings, a selected derivative was further optimized, leading to the development of a visible-light-responsive ortho-fluoroazobenzene ligand, exAzoPy$_2$. Its interaction with G4 DNA was investigated using circular dichroism and fluorescence spectroscopy. The compound exhibits isomer-dependent modulation of G4 topology: the *cis*-enriched photostationary state promotes folding of antiparallel G4 structures, whereas photoinduced *cis*-to-*trans* isomerization favours their unfolding. In addition, exAzoPy$_2$ generates topology- and isomer-dependent induced circular dichroism (ICD) signals, enabling chiroptical discrimination between different G4 conformations. These results demonstrate that substituted azobenzene derivatives can serve as versatile, light-responsive tools for controlling and probing G4 DNA architecture, providing a platform for precise regulation of G4 structures in biological systems.

References:

[1] Matusiak A, Drąg M, Deiana M, Janicki MJ, Dudek M. Tunable G-Quadruplex Ligands: Azobenzene Derivatives for Light-Controlled DNA Modulation. Chem Eur J 2025; 31
[2] Matusiak A, Trojnar J, Matczyszyn K, Deiana M, Dudek M. Light-Controlled Folding and Chiroptical Sensing of G-Quadruplex DNA. article under review

High-pressure SAXS studies of selected model lipid nanostructures

Jakub Męch[1,2], Agnieszka Klonecka[1,2], Maciej Kozak[1,3]

[1]SOLARIS National Synchrotron Radiation Centre, Jagiellonian University, Krakow, Poland;
[2]Doctoral School of Exact and Natural Sciences, Jagiellonian University, Krakow, Poland;
[3]Department of Biomedical Physics, Adam Mickiewicz University, Poznań, Poland

The effect of extreme conditions, including high pressure (HP), on the structure and function of biological membranes remains largely unexplored. This underlines the importance of investigating of the impact of high pressure on biological membranes. However, a possible solution is the combination of high-pressure chamber with an optimal technique. In this context, using small-angle X-ray scattering (SAXS) with a high-pressure chamber may provide a viable approach. The model membrane chosen for this study was a bicelle system composed of 1,2-ditetradecanoyl-sn-glycero-3-phosphocholine (DMPC) and 1,2-dicaproyl-sn-glycero-3-phosphocholine (DHCP). The specific phase transitions depend on the pressure, the composition, and the molar ratio of DMPC to DHPC. SAXS data were collected at the SMAUG beamline at NSRC SOLARIS facility in Kraków, Poland. Measurements were performed over a wide range of pressure. This project demonstrates the impact of high-pressure on model biological membranes, as well as the potential application of HP-SAXS in such research and illustrates how an experiment of this kind is performed.
The research was supported in part by a research grant (2020/39/B/NZ9/03196) from National Science Centre (Poland).

Glycoglycerolipids as Versatile Anchors for Bioactive Molecules in Quantum Dot–Based Biosensing Platforms

Diego Colombo,[1] Martina Quaglia,[1] Valentina Pelliccioli,1 Giuseppe Junior Mosca,[2] Simone Russo,[2] Pietro Pettinari,[3] Giovanni L. Beretta,[3] Paola Perego,[3] Giuseppe Vitiello,[2,4] Laura Morelli[1]

[1]Department of Medical Biotechnology and Translational Medicine, Università degli Studi di Milano, via Saldini 50, 20133 Milano, Italy;
[2]Department of Chemical Sciences, University of Naples Federico II, 80126 Naples, Italy;
[3]Molecular Pharmacology Unit, Department of Experimental Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, 20133 Milan, Italy;
[4]CSGI, Center for Colloid and Surface Science, 50019 Sesto Fiorentino, Italy.

Colloidal quantum dots (QDs) have emerged as promising analytical tools in biomedical and environmental fields thanks to their tunable optical and magnetic features. In particular, metaloxide and carbon-based QDs offer notable advantages, including large specific surface area, reduced cytotoxicity, long emission lifetimes, high photostability, narrow fluorescence bands, and single-wavelength excitation, that make them highly effective alternatives to traditional fluorescent probes [1].
The objective of this study is to develop fluorescent colloidal QDs coated with tailored glycolipids to create an optical biosensing platform with selective molecular recognition capability [2]. Our approach starts from zinc oxide QDs stabilized with oleylamine (OLA), forming an internal lipophilic monolayer suitable for subsequent functionalization with an outer amphiphilic shell enriched with synthetic glycolipids. Glucosylacylglycerols were selected as coating agents due to their versatile architecture: the glycerol unit allows the incorporation of one or two acyl chains, while the primary hydroxyl of glucose can be derivatized with linkers enabling the attachment of bioactive molecules designed for specific sensing applications. The nature of the fatty acid chains plays a crucial role in modulating interactions with the underlying OLA layer.
Here, we present the synthesis of a small library of glucosylacylglycerols, their integration into newly engineered glycolipidcoated fluorescent QDs, and the resulting physicochemical and biological characterization of these nanostructured biosensors.

References:

[1] Van den Kieboom, C.H. et al., Trends in Analytical Chemistry, 2015, 7 , 58.
[2] PIANO NAZIONALE DI RIPRESA E RESILIENZA (PNRR) Missione 4 - Componente 2 - Investimento 1.1 - Finanziato dall'Unione europea - Next Generation EU - Bando PRIN 2022 - D.D. n. 104 del 02.02.2022 - Progetto "GLYBIOSENS" - Codice indentificativo: 2022PJP24F - CUP E53D23009450006

Development of Orthogonal Methods for Comprehensive Characterization of Oligonucleotide Drug Products and Impurities

Giorgio Eisele[1] Annamaria Naggi[1], Cristina Gardini[1], Elena Urso,[2], Roberto Marciano[1], Rosachiara Salvino[2], Marco Guerrini[2]

[1]Centro Alta Tecnologia Institute of Chemical and Biochemical Research G. Ronzoni, S.r.l Milano, Italy;
[2]Institute of Chemical and Biochemical Research G. Ronzoni, Via G. Colombo 81, 20133, Milan, Italy

Defibrotide (DFT) is a complex multi-target drug composed of 90% single-stranded and 10% double-stranded phosphodiester oligonucleotides, produced through the controlled depolymerization of porcine DNA [1].
While DFT was approved in the US in 2016 for treating hepatic veno-occlusive disease (VOD) [2], detailed information regarding its structure-activity relationship (SAR) and potential degradation products remains scarce in existing literature. The objective of this study was to establish a structural "fingerprint" using orthogonal analytical methods to identify chain composition, sequence motifs, and process signatures. The research utilized NMR spectroscopy (1H, 13C, 31P, HSQC), LC-MS, and molecular weight analysis on both the intact drug and homogenous fractions.
Additionally, the activity of single-strand-specific nucleases was investigated to characterize resulting fragments via LC-MS. Preliminary experiments successfully detected irregular species, including base-less fragments, sequences with two terminal phosphate groups, and oxidized species linked to the manufacturing process.
These results demonstrate that modern technology provides a significantly deeper understanding of DFT than the outdated techniques previously utilized. Such comprehensive characterization is vital for correlating structural features with in vitro biological properties and supporting the development of generic versions of this complex oligonucleotide mixture.

References:

[1] Pescador R, Capuzzi L, Mantovani M, Fulgenzi A, Ferrero ME. Defibrotide: properties and clinical use of an old/new drug. Vascul Pharmacol. 2013 Jul-Aug;59(1-2):1-10. doi: 10.1016/j.vph.2013.05.001.
[2] Fedeli G, Diamantini G, Mantovani M, Prino G. 1993, Process for obtaining chemically defined and reproducible polydeoxyribonucleotides, US patent: 5,223,609

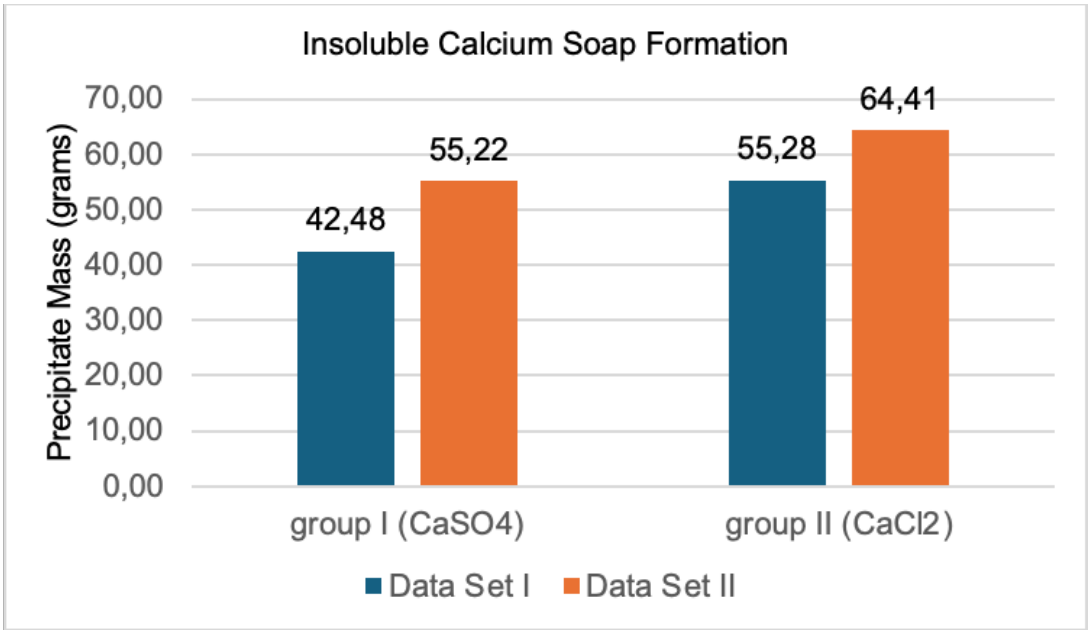
Calcium-Induced Micellar Disruption: Evaluating the Bioaccessibility of Vitamin D in Fortified Oat Milk

Sonat İda Çetin, Berk Kılıç, Eda Yıldırım, Ceren Özçelik

Hisar School, Göktürk, Istanbul, Turkey

*Plant-based beverages are marketed as nutritional substitutes for cow milk, yet their functional equivalence depends significantly on fortification and the bioaccessibility of vitamin D [1]. The aim of this in vitro study was to determine the role of calcium ions in micelle-facilitated vitamin D absorption by the intestinal epithelium. Increased free calcium ion concentrations may disrupt micellar structures and hinder vitamin D bioavailability [2]. In order to test this hypothesis, 1mol/L oleic acid and 1mol/L NaOH were mixed to form sodium oleate to mimic the interaction between free fatty acids and calcium. A 0.1mol/L sodium oleate solution was synthesized and interacted with water to form the micelle structures through its amphipathic nature. Calcium chloride (CaCl*2) and calcium sulfate (CaSO4) were mixed separately into the sodium oleate solutions. The total dry mass of insoluble calcium soaps formed by the addition of CaCl2 were greater than that of CaSO4. Spectrophotometric analysis confirmed the high ionic availability of CaCl2 with an *OD*600 of ≈ 0.005, while CaSO4 remained largely insoluble with ≈ 3.39. The procedure was repeated with commercial oat milk divided into three experimental groups: Group I (control), representing micellization with existing calcium from production: Group II (CaCl2) and Group III (CaSO4). To mimic digestion, these samples were treated with lipase and incubated at 37°C. Gravimetric measurements demonstrated an inverse relationship between calcium salt solubility and vitamin D bioaccessibility. Selecting low-solubility calcium sources, such as CaSO4, is critical for optimizing effective vitamin D delivery in fortified dairy products.

Table 1. Impact of Calcium Fortification Source on Total Precipitate Mass



References:

[1] Drewnowski A, Henry CJ, Dwyer JT. Proposed nutrient standards for plant-based beverages intended as milk alternatives. Front Nutr 2021; 8: 761442
[2] Zhou H, Zheng B, Zhang Z, et al. Fortification of plant-based milk with calcium may reduce vitamin D bioaccessibility: An in vitro digestion study. J Agric Food Chem 2021; 69: 4223-4233

NMR real-time analysis of exo-metabolites decodes the mechanism of action of antibacterial molecules, nanoparticles, and materials

Simona Tomaselli[1], Simona Losio1, Michela Alfè[2], Valentina Gargiulo[2], Roberto K. Salinas[3], Laura Ragona[1]

[1]Institute of Science and Chemical Technologies "Giulio Natta" (SCITEC-CNR), Via Corti 12, 20133, Milano, Italy;
[2]STEMS-CNR, Via G. Marconi 4, Naples, Italy;
[3]Institute of Chemistry, University of São Paulo, São Paulo, Brazil

Understanding the mechanism of action of antimicrobial agents is critical for guiding the development of new drugs to overcome antimicrobial resistance. We present a label-free NMR-based approach to characterize the mechanism of action of antibacterial compounds and materials by the analysis of metabolites secretion kinetics. The method (KINEXO, KINnetics of EXOmetabolites) is set-up using Escherichia coli and Staphylococcus aureus as representative Gram-negative and Gram-positive model organisms. By monitoring the real-time production of key secreted metabolites (acetate, formate, lactate, ethanol, pyruvate, succinate) in response to antimicrobial treatment and analyzing the secretion kinetics, we can classify the agents' mechanisms of action. We validate KINEXO using agents with well-characterized mechanism of action and we further apply it to silver nanoparticles, whose mechanism of action remains under debate. Agents that disrupt the cell wall reduce secretion rates while maintaining end-point metabolite concentrations, with only moderate lag phase extension. In contrast, agents that act on intracellular pathways drastically prolong lag phases and reduce both secretion rates and end-point concentrations. When plotted in 3D parameter space defined by exo-metabolite secretion lag time, secretion rate and end-point concentration, antibacterial agents cluster according to their mode of action, offering a mechanistically informative phenotypic readout [1]. The platform is proposed as a robust analytical framework for rapid antimicrobial profiling and mechanism-based screening of novel bioactive agents.

References:

[1] Tomaselli, S., Salinas, R.K., Alfè, M., Gargiulo, V., Losio, S., Ragona L., Anal. Chem. 2026, 98, 9, 6772–6782

Collectin-11 Antagonists in a Therapeutic Approach to Minimize Complement-Mediated Immune Injury

Fabricio Ramirez-Cortes, Said Rabbani, Martin Smiesko, Deborah Berta, Pierre Bena, Daba-Rokhya NDiaye, Menna Zahran, Daniel Ricklin, Rachel Hevey

University of Basel, Dept. Pharmaceutical Sciences, Klingelbergstrasse 50, Basel, Switzerland

Collectin-11 (CL-11) is an initiator protein of the innate immune pathway and plays an important role in ischemia–reperfusion injuries. It contributes to both acute and chronic kidney injury. In a mouse kidney transplantation model, inhibition or knockdown of CL-11 was shown to reduce immune-mediated kidney damage and improve overall kidney function [1-3].

CL-11 is a member of the lectin family, a class of carbohydrate-binding proteins that recognize glycans on cell surfaces. Glycans decorate the extracellular surface of cells and mediate interactions with other cells and soluble molecules. They participate in numerous biological processes, including inflammation, cell adhesion, and host–pathogen recognition. Consequently, lectins have attracted increasing attention as potential therapeutic targets [4]. However, despite their extensive structural diversity, carbohydrates typically exhibit weak binding affinities and unfavorable pharmacokinetic properties. To overcome these limitations, glycomimetic compounds can be designed to mimic the structure and function of native glycans while providing improved affinity, specificity, and bioavailability [5].

Here, we explored the design of glycomimetic antagonists targeting CL-11. Molecular dynamics simulations and docking studies were performed to characterize the ligand-binding mode of

CL-11 and to identify potential extended binding site motifs. Based on these insights, several glycomimetic libraries were designed and evaluated in vitro using a thermal denaturation–based nano-differential scanning fluorimetry assay and a polymer-based competitive binding assay.

This work supports the development of therapeutic candidates for the treatment of

ischemia–reperfusion injury and provides new tools to further investigate the physiological role of CL-11.

References:

[1] Farrar, C. A. et al. Collectin-11 Detects Stress-Induced L-Fucose Pattern to Trigger Renal Epithelial Injury. J. Clin. Invest. 2016, 126 (5), 1911–1925.
[2] Wu, W. et al. Collectin-11 Promotes the Development of Renal Tubulointerstitial Fibrosis. J. Am. Soc. Nephrol.
2017, 29 (1), 168–181.
[3] Howard, M. C. et al. L -Fucose Prevention of Renal Ischaemia/Reperfusion Injury in Mice. FASEB J. 2020, 34 (1), 822–834.
[4] Hevey, R. et al. Sweet Turning Bitter: Carbohydrate Sensing of Complement in Host Defence and Disease. Br. J. of Pharmacol. 2020, 178 (14), 2802–2822.
[5] Hevey R. Pharmaceuticals 2019, 12, 55.

Natural and engineered methyltransferases for biocatalytic terpene precursor modifications

Dr. Tatjana Reuter, Lars Dieminger, Prof. Dr. Lena Barra

University of Konstanz, Department of Chemistry, Universitätsstraße 10, 78464 Konstanz, Germany

Terpenes constitute the largest class of natural products and are of major pharmaceutical and industrial relevance. Methods that enable programmable structural modification of terpene scaffolds to fine-tune biological or olfactory properties are therefore of considerable interest.[1] In this context, methylation reactions are particularly attractive due to the well-known "magic methyl effect" in drug discovery, where the introduction of a single methyl group can markedly influence potency, selectivity, or pharmacokinetic properties.[2] Despite their importance, strategies for the controlled introduction of methyl substituents into terpene scaffolds remain limited. Most terpenes follow the classical "biogenic isoprene rule", consisting of carbon skeletons assembled from C5 units.[3] In contrast, homoterpenes containing an additional C1 unit represent only a small fraction of the approximately 180,000 known terpenoids.[4] However, their biosynthetic pathways provide unique opportunities to uncover enzymatic strategies for targeted backbone modifications.

We recently discovered a biosynthetic pathway toward a new family of homoterpenes that represent methyl analogs of germacrane and eudesmane sesquiterpenes.[5] This pathway is widespread in actinobacteria and proceeds via the C6-methylated prenyl diphosphate (E)-prekantenol diphosphate generated by a unique family of methyltransferases. Such methylated prenyl diphosphates offer opportunities for combinatorial biosynthesis by exploiting the catalytic plasticity of terpene cyclases.

The poster will focus on our ongoing work to discover and engineer novel methyltransferase chemistry for the biocatalytic generation of backbone-modified terpenes.

References:

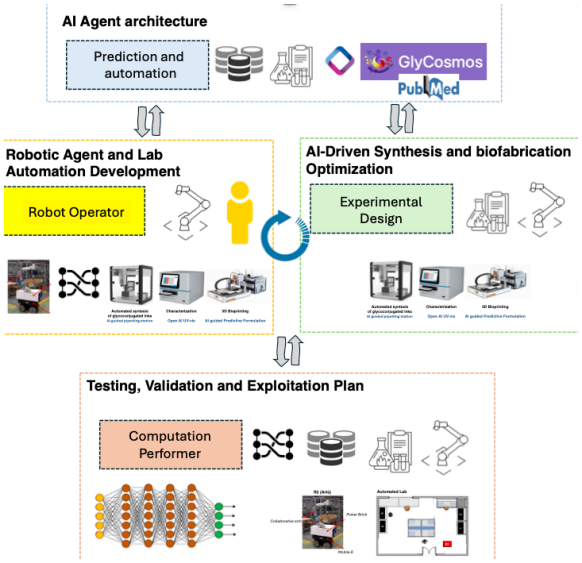
[1] Chen R, Wang M, Keasling J D, Hu T, Yin X, Expanding the structural diversity of terpenes by synthetic biology approaches. Trends Biotechnol 2024; 42 (6): 699-713
[2] Schönherr H, Cernak T, Profound methyl effects in drug discovery and a call for new C-H methylation reationcs. Angew Chem Int Ed 2013; 52: 12256-12267
[3] a) Wallach O, Zur Kenntniss der Terpene und der ätherischen Oele. Justus Liebigs Ann Chem 1885; 239: 1-54. b) Ruzicka L, The isoprene rule and the biogenesis of terpenic compounds. *Experientia* 1953; 9 (10): 357-367
[4] Zeng T, Liu Z, Zhuang J, Jiang Y, He W, Diao H, Lv N, Jian Y, Liang D, Qiu Y, Zhang R, Zhang F, Tang X, Wu R. TeroKit: A Database-Driven Web Server for Terpenome Research. J. Chem. Inf. Model. 2020, 60 (4), 2082–2090.
[5] Reuter T, Dieminger L, Steidle S, Zoller K, Holocher M, Zhou L, Dominik M H, Racz K, Barra L, Angew Chem Int Ed 2025, 64 (5), e202418613

AI Agent and Collaborative Robotic Platform for the synthesis of tissue mimics

Laura Russo[1,2], Ilaria Borghi[1], Francesca Cadamuro[1], Marco Piazzoni[1], Francesco Nicotra[1]

[1]*Università degli Studi Milano - Bicocca, Vedano al Lambro (MB),*
[2]*IRCCS Fondazione San Gerardo dei Tintori, Monza (MB)*

The synthesis of biomaterials is fundamental for applications in biomedicine, tissue engineering, and drug delivery. In particular, the extracellular matrix (ECM) and its glycosignature play crucial roles in cell fate induction, including pathogenesis. The design of biomaterials that replicate the structural and biomolecular complexity of ECM, with particular emphasis of glycosignature, enables the creation of in vitro tissue models that replicate functional and structural features of human tissues [1-3]. The capacity to generate patient specific in vitro tissue models will allow to identify personalized therapeutic treatments. However, the high number of structural and biochemical variables to define and replicate, require the use of AI and the abandonment of artisanal approaches to fasten the research and limit human errors. Automated manufacturing systems and 3D bioprinting, integrated withArtificial Intelligence (AI), Machine Learning (ML), and Deep Learning (DL), can streamline the synthetic process, defining and tuning the structural and biomolecular properties of the construct, including the highly specific glycosignature, to generate the required personalized in vitro 3D tissue model.
The development of AI agent applications and a collaborative automated platform for the automated synthesis of personalized 3D bioprinted tissue models will be presented, highlighting their potential to improve efficiency and predictive capabilities in biopolymer fabrication.



***Acknowledgment*:**

Financial support from: Iniziativa "PNC0000003 - "ANTHEM: AdvaNced Technologies for Human-centrEdMedicine". CUP BICOCCA B53C2200667000; Ministero della Salute, RF-2021-12371959 Tackling immunomodulatory properties of stromal cells to improve therapeutic strategies in lung cancer.

References:

[1] Nicolas J. et al. Biomacromolecules 2020. 21, 1968.
[2] Cadamuro F. et al. Journal of Controlled Release 2023. 354, 726.
[3] Cadamuro F. et al, Carbohydrate Polymers 2023. 302, 120395

Fluorescent Tracers for αVβ6 Integrin-mediated Imaging of Pulmonary Fibrosis

Andrea Sartori[1], Michela Spirelli1, Kelly Bugatti[1], Annalisa Morelli[2], Anita Salmaso[2], Alfredo Cagnotto[2], Paolo Bigini[2], Lucia Battistini[1], Franca Zanardi[1]

[1]Dipartimento di Scienze degli Alimenti e del Farmaco, Università di Parma, Parco Area delle Scienze 27/A, 43124, Parma, Italia;
[2]Dipartimento di Ricerca Biochimica e Farmacologia molecolare, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, via Mario Negri, 2, 20156, Milano, Italia.

The integrin αVβ6 is nearly undetectable in healthy adult tissues but is upregulated in pathological conditions such as tumours [1] and idiopathic pulmonary fibrosis (IPF) [2]. Owing to its disease specific expression, this integrin has emerged as a biomarker for targeted diagnostics and therapeutics [3]. In fact, in addition to targeted drugs the precision medicine needs probes to visualize the diseased regions or the pathological processes with the aim to get an early diagnosis, to stratify the patients for the therapy, and to monitor therapeutic response.
Building on our expertise in the field of RGD-binding integrin cyclopeptides [4], the fluorescent conjugates **1**-**4** were synthesized (Figure 1) to selectively visualize the fibrotic regions of the lungs overexpressing integrin αVβ6. These compounds are formed by αVβ6-targeting cyclopeptides linked to the fluorescent moieties ZW800-1 (compounds **1**-**2**) or sulfo-cyanine5 (compounds **3**-**4**).
These tracers were evaluated *in vivo* in a bleomycin-induced murine model of pulmonary fibrosis, showing a significant increase in fluorescence intensity in fibrotic lungs. The selectivity of compounds **1**-**4** for integrin αVβ6, and their ability to concentrate in diseased tissue overexpressing this integrin highlight their potential to improve both pre- and post-diagnostic workflows.

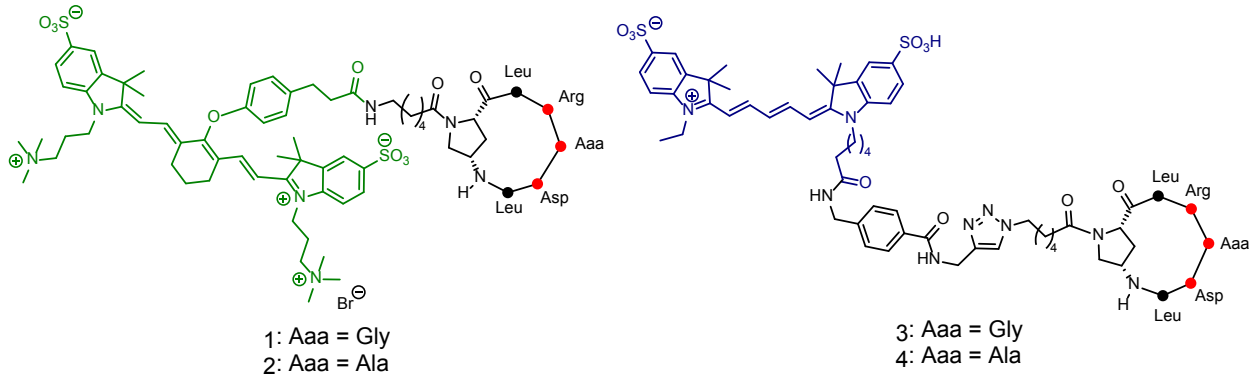


Figure 1. Structures of the synthesized fluorescent probes. Probes **1** and **2** bear fluorophore ZW800-1 (green), probes **3** and **4** sulfo-Cy5 (blue).

References:

[1] Brzozowska E, Deshmukh S. Integrin Alpha v Beta 6 (αvβ6) and Its Implications in Cancer Treatment. Int. J. Mol. Sci. 2022, 23(20), 12346.
[2] Sgalla G, Iovene B, Calvello M, Ori M, Varone F, Richeldi L. Idiopathic Pulmonary Fibrosis: Pathogenesis and Management. Resp. Res. 2018 Feb; 19(1):32.
[3] Koivisto L, Bi J, Häkkinen L, Larjava H. Integrin αVβ6: Structure, Function and Role in Health and Disease. Int. J. Biochem. Cell Biol. 2018; 186–196.
[4] Bugatti K, Bruno A, Arosio D, Sartori A, Curti C, Augustijn L, Zanardi F, Battistini L. Shifting Towards αVβ6 Integrin Ligands Using Novel Aminoproline-Based Cyclic Peptidomimetics. Chem. Eur. J. 2020; 26 (59): 13468–13475.

Identification of Natural Chemotypes as KPC-3 Carbapenemase Inhibitors

Beatrice Sciarra[1], Silvia Cammarone[1], Arianna Speroni[1], Alessandra Carattoli[2], Maria Luisa Mangoni[3], Mattia Mori[4], Francesca Ghirga[1]

[1]Department of Chemistry and Technology of Drugs, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185 Rome, Italy;
[2]Department of Molecular Medicine, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185 Rome, Italy;
[3]Department of Biochemical Sciences "Alessandro Rossi Fanelli", Sapienza University of Rome, Piazzale Aldo Moro 5, 00185 Rome, Italy;
[4]Department of Biotechnology, University of Siena, Piazza S. Francesco, 53100 Siena, Italy

Carbapenems are β-lactam antibiotics that exert bactericidal activity by acylating penicillin-binding proteins (PBPs), key enzymes involved in bacterial cell wall biosynthesis [1]. Compared with other β-lactams, carbapenems display high stability toward hydrolysis by most β-lactamases because of their distinctive chemical structure. Nevertheless, the increasing emergence of carbapenemases—β-lactamases with mutations in the active site capable of hydrolyzing carbapenems—has significantly compromised their clinical efficacy [2]. Among these enzymes, Klebsiella pneumoniae carbapenemase (KPC) is particularly widespread, with KPC-2 and KPC-3 representing the most prevalent allelic variants detected in multidrug-resistant clinical isolates [3]. Class A carbapenemases, including KPC-3, employ a catalytic serine residue (Ser70) in the active site to form a reversible covalent bond with the β-lactam ring of the substrate, followed by hydrolysis mediated by an active-site water molecule [4].

The aim of this study was to identify novel compounds capable of inhibiting the enzymatic activity of KPC-3 and potentially restoring the efficacy of β-lactam antibiotics such as carbapenems and ceftazidime. An in-house natural product library was subjected to in silico screening using the crystallographic structure of KPC-3. Compounds identified as virtual hits were subsequently evaluated through biochemical assays performed on KPC-3 in the presence and absence of imipenem. Enzymatic activity was monitored by a colorimetric assay, in which the shift from red to yellow indicated hydrolysis of the β-lactam ring.

Three natural flavonoids showed a measurable delay in the colorimetric transition, suggesting partial inhibitory activity. However, the inhibition was incomplete, likely due to the inability of these compounds to form covalent interactions with the catalytic serine residue, resulting in non-competitive behavior with imipenem. These preliminary results identify flavonoids as promising natural chemotypes for the development of KPC-3 inhibitors. To improve their inhibitory potential and achieve competitive inhibition, a focused library of derivatives bearing electrophilic functional groups designed to covalently target Ser70 has been planned, and their synthesis is currently in progress.

References:

[1] Gutmann L, Kitzis MD, Yamabe S, Acar JF. Comparative evaluation of a new beta-lactamase inhibitor, YTR 830, combined with different beta-lactam antibiotics against bacteria harboring known beta-lactamases. Antimicrob Agents Chemother 1986; 29: 955-957
[2] Papp-Wallace KM, Endimiani A, Taracila MA, Bonomo RA. Carbapenems: past, present, and future. Antimicrob Agents Chemother 2011; 55: 4943-4960
[3] Wei W-M, Xu Y-L, Zheng R-H, Zhao T, Fang W, Qin Y-D. Theoretical study on the mechanism of the acylate reaction of β-lactamase. ACS Omega 2021; 6: 12598-12604
[4] Villa L, Capone A, Fortini D, Dolejska M, Rodríguez I, Taglietti F, De Paolis P, Petrosillo N, Carattoli A. Reversion to susceptibility of a carbapenem-resistant clinical isolate of Klebsiella pneumoniae producing KPC-3. J Antimicrob Chemother 2013; 68: 2482-2486

Enhancing Glioblastoma Therapy with Multivalent Glycomimetics

Lucy A. R. Spicer,[1] Laura, Diaz Casado[1], Sayyed Ahmadreza Mohammadi,[1] Asma Akbarpour,[1] Marco Piazzoni,[2] Francesco Milanesi,[3] Oscar Francesconi,[3] Laura Russo,[2] and Sara Sattin[1]

[1]University of Milan, Dipartimento di Chimica, via Golgi, 19, 20133, Milano Italia;
[2]University of Milan-Bicocca, Dipartimento di Medicina e Chirurgia, Via Raoul Follereau, 3, 20854 Vedano al Lambro (MB), Italia;
[3]University of Florence, Dipartimento di Chimica 'Ugo Schiff' (DICUS), Via della Lastruccia, 3, 50019 Sesto Fiorentino (FI), Italia

Glioblastoma (GBM) is an aggressive class of malignant brain cancer which remains incurable due to intrinsic therapy resistance and tumour relapse. Newly diagnosed patients are treated by surgically removing the tumour and placing a solid chemotherapy within the resection cavity, followed by adjunctive chemo and radio therapy. While clinical trials have indicated this treatment can prolong survival,[1] the prognosis remains exceptionally poor. To improve outcomes, this work proposes an alternative post-operative implant co-therapy that utilises Mannose Binding Lectin (MBL) inhibitors within a hydrogel formulation. This treatment has the potential to reduce post-surgical inflammation caused by the innate immune system, a known source of secondary brain damage in ischemic brain injury.[2]
The synthesis of the multivalent glycomimetic **2** (Figure 1), a known MBL inhibitor,[3] was optimized to half-gram scale for its formulation and testing in bio responsive hydrogels. While the synthesis of a novel multivalent scaffold **3** (Figure 1) was developed to assess scaffold rigidity towards target affinity. The aim of this work is to reduce treatmentrelated complications following GBM tumour removal and establishing MBL as a therapeutic target to minimise post-surgical brain damage, while also clarifying MBL's uncertain role to GBM development.

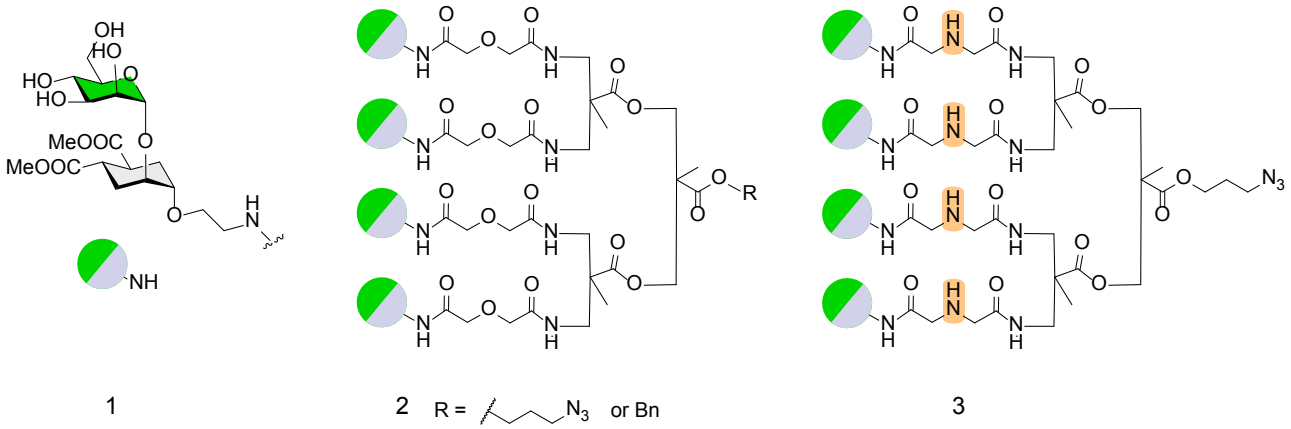


Figure 1: Structures of the multivalent glycomimetics employed in hydrogel formulation. Each compound incorporates four pseudo-1,2-mannobiose moieties (**1**), designed to mimic mannoserich glycans such as Man-9.

References:

[1] Zhang YD, Dai RY, Chen Z, Zhang YH, He XZ, Zhou J. Efficacy and safety of carmustine wafers in the treatment of glioblastoma multiforme: a systematic review. Turk Neurosurg. 2014;24(5):639–45.
[2] Orsini F, Villa P, Parrella S, Zangari R, Zanier ER, Gesuete R, et al. Targeting Mannose-Binding Lectin confers long-lasting protection with a surprisingly wide therapeutic window in cerebral ischemia. Circulation. 2012 Sep 18;126(12):1484–94.
[3] Goti G, Palmioli A, Stravalaci M, Sattin S, De Simoni MG, Gobbi M, et al. Scaffold optimisation of tetravalent antagonists of the Mannose Binding Lectin. Chem - Eur J. 2016;22(11):3686–91.

Inflammation at the Crossroads of Metabolism and Disease: Modulating TLR4/TLR2 to Redefine Diabesity and Systemic Pathology

Lucrezia Spinelli[1], Felicitas Lauber[2], Serena Vittorio[1], Giulio Vistoli[1], Günther Weindl[2], Laura Fumagalli[1]

[1]Università degli Studi di Milano, Department of Pharmaceutical Sciences, Via Mangiagalli 25, 20133, Milan, Italy.
[2]University of Bonn, Pharmaceutical Institute, Pharmacology and Toxicology Section, Gerhard-Domagk-Straße 3-53121 Bonn, Germany.

Inflammation is a fundamental biological response essential for tissue repair and homeostasis; however, when chronic, it contributes to the development of numerous non-communicable diseases (NCDs), including cardiovascular, neurodegenerative, oncological, and metabolic disorders such as obesity and type 2 diabetes mellitus [1–3]. These conditions share a common background of chronic low-grade inflammation that disrupts metabolic homeostasis and promotes insulin resistance, underlying the concept of "diabesity." Adipose tissue plays a central role in this process by acting as an endocrine and immune organ that releases pro-inflammatory mediators, thereby sustaining a vicious cycle between inflammation and metabolic dysfunction.

Given the central role of inflammation across NCDs, targeting key inflammatory pathways represents a promising therapeutic strategy. Toll-Like Receptors (TLRs), particularly TLR2 and TLR4, are critical mediators linking metabolic stress to innate immune activation [4,5]. Modulation of signal transduction following TLR activation offers a valuable opportunity for the development of novel therapies for inflammation-driven diseases.

Based on this rationale, a series of small-molecule modulators targeting TLR2/4 activation were designed, synthesized, and screened to identify dual inhibitors. Screening in HEK293 reporter cells overexpressing TLR2 or TLR4 identified several compounds that significantly inhibited NF-*κB* signaling without affecting cell viability or showing agonistic activity. Lead compounds exhibited concentration-dependent inhibition in the low micromolar range for both receptors. These effects were confirmed in THP-1 macrophages and primary human peripheral blood mononuclear cells, where the compounds reduced TLR2- and TLR4-mediated tumor necrosis factor secretion while preserving cell viability. These findings highlight promising candidates for further therapeutic development.

References:

[1] Huang, N.-Q.; Jin, H.; Zhou, S.; Shi, J.; Jin, F. TLR4 Is a Link between Diabetes and Alzheimer's Disease. *Behavioural Brain Research* **2017**, *316*, 234–244.
[2] Bès-Houtmann, S.; Roche, R.; Hoareau, L.; Gonthier, M.-P.; Festy, F.; Caillens, H.; Gasque, P.; Lefebvre d'Hellencourt, C.; Cesari, M. Presence of Functional TLR2 and TLR4 on Human Adipocytes. *Histochem. Cell Biol.* **2007**, *127*, 131–137.
[3] Campos-Bayardo, T.I.; Román-Rojas, D.; García-Sánchez, A.; Cardona-Muñoz, E.G.; Sánchez-Lozano, D.I.; Totsuka-Sutto, S.; Gómez-Hermosillo, L.F.; Casillas-Moreno, J.; Andrade-Sierra, J.; Pazarín-Villaseñor, L.; et al. The Role of TLRs in Obesity and Its Related Metabolic Disorders. *Int. J. Mol. Sci.* **2025**, *26*, 2229.
[4] Zeng, F.; Zheng, J.; Shen, L.; Herrera-Balandrano, D.D.; Huang, W.; Sui, Z. Physiological Mechanisms of TLR4 in Glucolipid Metabolism Regulation: Potential Use in Metabolic Syndrome Prevention. *Nutrition, Metabolism and Cardiovascular Diseases* **2023**, *33*, 38–46.
[5] Fahed, G.; Aoun, L.; Bou Zerdan, M.; Allam, S.; Bou Zerdan, M.; Bouferraa, Y.; Assi, H.I. Metabolic Syndrome: Updates on Pathophysiology and Management in 2021. *Int. J. Mol. Sci.* **2022**, *23*, 786.

Molecular Modeling of Indolobenzazocine Derivatives as Potential Anticancer Agents Targeting Tubulin

Alexandru-Constantin Stoica, Mihaela Dascălu, Maria Cazacu

1 Department of Inorganic Polymers, "Petru Poni" Institute of Macromolecular Chemistry, Aleea Grigore Ghica Voda 41A, 700487, Iasi, Romania

Cancer is a sneaky illness that is hard to cure. Despite advancements in current anticancer treatment, drug resistance and the low selectivity of anticancer medications that induce severe side effects continue to be major issues. The creation of novel molecular structures is a desirable choice. One of the most appealing molecular targets for antitumor medications is tubulin [1], which is essential for cell division [2] and the preservation of cell form and structure [3-4]. The development of indolobenzazocine derivatives as potential inhibitors of tubulin polymerization, capable of inducing tumor cell death, is proposed in this work. To predict the interactions between the ligands and the amino acid residues forming the protein binding pocket, the proposed compounds were docked into the tubulin active site. The compounds proposed for development are schematically presented in Figure 1a, while an example of a predicted binding mode is illustrated in Figure 1b.

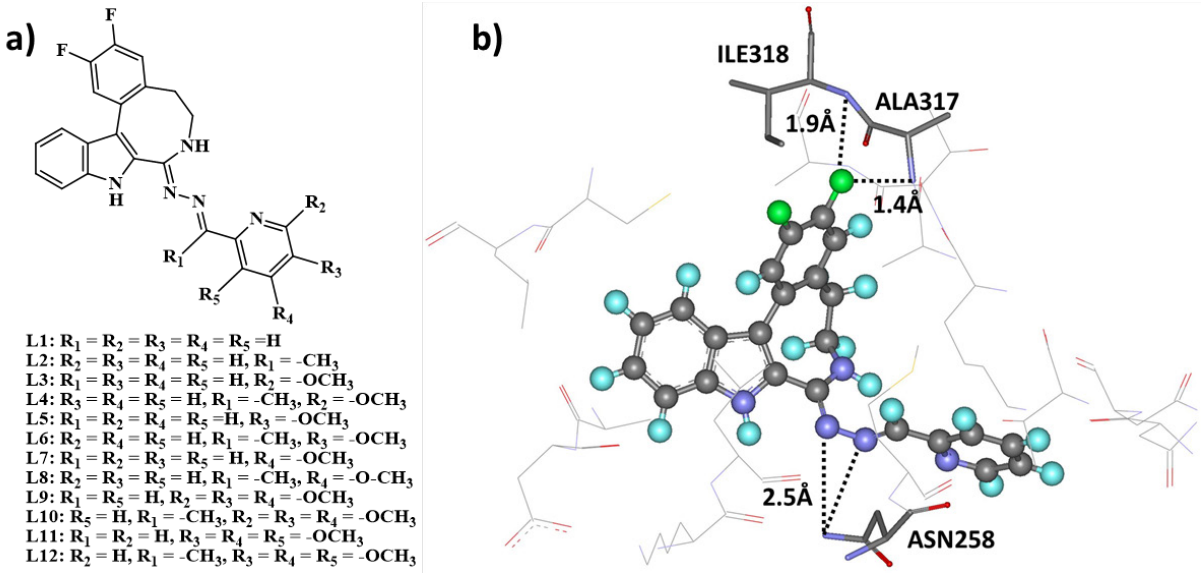


Figure 1. a) Indolobanzazocine derivatives proposed for development; b) binding mode at the active site in tubulin, predicted by molecular docking calculations.

Molecular docking calculations predicted that the selected compounds exhibit a favorable binding mode, establishing strong N–H···F hydrogen bonding interactions. These results suggest that the proposed compounds are promising candidates for synthesis and further evaluation as potential anticancer agents.

References:

[1] Hawash M, Highlights on Specific Biological Targets; Cyclin-Dependent Kinases, Epidermal Growth Factor Receptors, Ras Protein, and Cancer Stem Cells in Anticancer Drug Development. Drug. Res 2019; 69: 471–478
[2] Arnst K E, Wang Y, Hwang D-J, Hue Y, Costello T, Hamilton D, Chen Q, Yang J, Park F, Dalton J T, Miller D D, Li, W A Potent, Metabolically Stable Tubulin Inhibitor Targets the Colchicine Binding Site and Overcomes Taxane Resistance. Cancer Res 2018; 78: 265–277
[3] Brancale A, Silvestri R, Indole, a core nucleus for potent inhibitors of tubulin polymerization. Med. Res. Rev 2007; 27: 209–238
[4] La Regina G, Coluccia A, Naccarato V, Silvestri R, Towards modern anticancer agents that interact with tubulin. Eur. J. Pharm. Sci 2019; 131: 58–68

Acknowledgements:

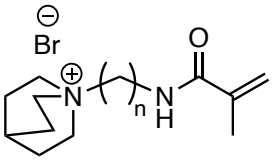
This work was financially supported by a grant from the Romanian National Authority for Research, project no. PNRR-III-C9-2023-I8-99 within the National Recovery and Resilience Plan.

Synthesis and Characterization of Antibacterial and Hydrolytic Resistant Quinuclidine-Containing Methacrylamide Monomers for using in Dental Resin Adhesive

Veerapat Suksai[1], Supitcha Talungchit[2], Somjin Rattanasatien[2], Supakit Paosen[3], Chittreeya Tansakul[1*]

[1]Division of Physical Science and Center of Excellence for Innovation in Chemistry, Faculty of Science, Prince of Songkla University, Songkhla 90110, Thailand;
[2]Department of Conservative Dentistry, Faculty of Dentistry, Prince of Songkla University, Songkhla 90110, Thailand;
[3]Division of Biological Science and Center of Antimicrobial Biomaterial Innovation-Southeast Asia, Faculty of Science, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand

Currently, resin dental materials, which are tooth-colored filling materials, are becoming increasingly popular. These resin materials are used in conjunction with dental adhesive that comprises various types of monomers, predominantly methacrylates, which can be degraded in aqueous and acidic environments generated by cariogenic bacteria (*Streptococcus mutans* and *Enterococccus faecalis*) [1]. This research investigated new antibacterial methacrylamide monomers to extend their lifespan. Moreover, *N*-heterocyclic compounds have been reported to exhibit antibacterial activity and show minimal cytotoxicity, as demonstrated by quinuclidine [2], which is included in the monomer structure for antibacterial effects in the oral cavity. **n-MAQB** monomers (Fig. 1) containing ten- (n=10), eleven- (n=11), twelve- (n=12) and fourteen-carbon (n=14) chain length were synthesized through a five-step reaction process including key substitution and reduction reactions. Antibacterial activity was tested, and the results were shown as the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC). The synthesized monomers showed increased antibacterial potency against both *S. mutans* and *E. faecalis* with increasing chain length, peaking at **14-MAQB**, with MIC/MBC values of 78.125/156.25 µg/mL for *S. mutans* and 78.125/625 µg/mL for *E. faecalis*. Cytotoxicity is currently being evaluated to select the most suitable monomer. The selected monomer will be mixed with commercial dental monomers to form a resin adhesive, which will then be tested for degree of conversion, water sorption, water solubility, and mechanical strength.



n = 10, 11, 12, 14

n-MAQB

Fig. 1 Structure of **n-MAQB**

References:

[1] Gong B, Li Z, Zhou Y, Yuan Y, Luo C, Wang Q, Li Z. The role of oral environmental factors in the degradation of resin-dentin interfaces: A comprehensive review. J Dent 2025; 159: 105839
[2] Herman JL, Wang Y, Lilly EA, Lallier TE, Peters BM, Hamdan S, Xu X, Fidel Jr PL, Noverr MC. Synthesis, Antifungal Activity, and Biocompatibility of Novel 1,4-Diazabicyclo[2.2.2]Octane (DABCO) Compounds and DABCO-Containing Denture Base Resins. Antimicrob Agents Chemother 2017; 61(4): e02575-16

Abstract title: *Artificial nanocarriers inspired by exosome targeting mechanisms*

Giulia Tamboia[1], Bianca Dumontel[3], Marije E. Kuipers[4] , Giada Rosso[3], Esther N. Nolte-'t Hoen[4], Valentina Cauda[3], Luisa De Cola[2]

[1]*Università degli Studi di Roma Tor Vergata, Via Cracovia 50, 00133 Roma, Italy;*
[2]*Dipartimento di Scienze Farmaceutiche, Università degli Studi di Milano, Via Golgi 19, 20133 Milano, Italy;*
[3]*Dipartimento di Scienza applicata e tecnologia, Politecnico di Torino, Corso Duca degli Abruzzi 24, 10129 Torino, Italy;*
[4]*Department Biomolecular Health Sciences, Utrecht University, Yalelaan 1, 3584 CL Utrecht, Netherlands*

Targeting represents a key goal in modern medicine, as delivering therapeutics to specific sites can enhance efficacy even at low doses while reducing off-target effects. Direct delivery of therapeutics and imaging agents is essential for theranostic systems. Targeted approaches improve safety, limit damage to healthy tissues, and enable patient-specific customization, contributing to personalized medicine [1]. Accordingly, drugs and nanomaterials have been functionalized with various moieties to promote accumulation in tumors or specific organs.

Among nanomaterials, porous silica nanoparticles (NPs) are efficient drug delivery platforms thanks to biocompatibility, stability, tunable degradability, high drug loading capacity, and straightforward surface functionalization. Our group developed hollow silica NPs with a hydrophilic cavity and disulfide bonds embedded in the silica framework. In reducing environments, these bonds are converted to thiols, triggering degradation of the nanocapsules (ssNCs) and release of the loaded therapeutics [2].

In this contribution, we investigate how ssNCs can be combined with natural and synthetic targeting strategies. Extracellular vesicles (EVs) play a key role in intercellular communication and retain the homing tropism of their parental cells[3]. While natural EVs membranes can allow organ-specific targeting [4], the low yield from their purification motivated the development of artificial lipid formulations mimicking EVs targeting [5]. Different formulations were produced to replicate the bone-targeting ability of prostate cancer-derived EVs. The most stable formulations were used to coat the silica nanocapsules, developing hybrid nanocarriers. These nanocarriers were then modified by incorporating full-length proteins or protein fragments within the lipid shell and evaluated *in vitro* and *in vivo*.

References:

[1] Percivalle NM, Carofiglio M, Conte M, Rosso G, Bentivogli A, Mesiano G, Vighetto V, Cauda V. Artificial and Naturally Derived Phospholipidic Bilayers as Smart Coatings of Solid-State Nanoparticles: Current Works and Perspectives in Cancer Therapy. Int. J. Mol. Sci. 2022; 23:15815.
[2] Prasetyanto EA, Bertucci A, Septiadi D, Corradini R, Castro-Hartmann P, De Cola L. Breakable Hybrid Organosilica Nanocapsules for Protein Delivery. Angew Chem Int Ed Engl. 2016; 55(10):3323-7.
[3] Dumontel B, Jiménez-Jiménez C, Vallet-Regí M, Manzano M. Bioinspired extracellular vesicle-coated silica nanoparticles as selective delivery systems. Mater Today Bio. 2023; 23:100850.
[4] Sancho-Albero M, Decio A, Akpinar R, De Luigi A, Giavazzi R, Terracciano LM, De Cola L. Melanoma extracellular vesicles membrane coated nanoparticles as targeted delivery carriers for tumor and lungs. Materials Today Bio. 2025; 30:101433.
[5] Rosso G, Van Veen SMA, Sancho-Albero M, Tamboia G, Empereur-Mot C, Perego C, Kuipers ME, Dumontel B, Ajó A, Nolte-'t Hoen EN, Pavan GM, De Cola L, Albertazzi L, Cauda V. Rational Design of EV-Mimicking Nanoparticles with Polarity-Based Recognition Potential for Advanced Nanocarrier Development. ACS Applied Nano Mater. 2025; 8 (26): 13257-13273.

Ethynylbenzaldehydes as novel reaction-based "turn-on" fluorescent probes for sensitive primary amine detection in liquid, vapor, food, proteins, and cellular systems

Ajcharapan Tantipanjaporn[1], Jie-Ren Deng[2], Kwok-Heung Aries Chan[1], Ka-Yan Karen Kung[1], Man-Kin Wong[1]

[1]State Key Laboratory of Chemical Biology and Drug Discovery, Research Institute for Future Food, Department of Food Science and Nutrition, The Hong Kong Polytechnic University, Hung Hom, Hong Kong, China;
[2]Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Hong Kong, China

Monitoring amine levels is critical as both exposure to volatile amines and increased biogenic amines in human body are related to adverse effects to human health. Thus, the development of fluorescent probes for easy and efficient amine detection is of great importance. Here, we are the first to establish ortho-ethynylbenzaldehyde (EBA) as the reaction site for development of sensitive and selective "turn-on" fluorescent probes to detect primary amines. The reaction of EBA with primary amines involves imine formation followed by 6-endo-dig cyclization reaction, yielding isoquinolinium products with a significant red-shifted absorbance and intense 'turn-on' fluorescence.
To establish the structure–photophysical property relationship (SPRR) for selective primary amine detection, we designed and synthesized nine EBA analogs (EBA-1a–1e and EBA-2–5). Our EBA derivatives demonstrated rapid primary amine sensing (30 min) with a limit of detection reaching 0.45 μM. The photophysical properties are highly tunable offering absorption (338-430 nm), emission (410-535 nm), large Stokes shift (up to 115 nm), and high fluorescence quantum yield (up to 0.86). EBA-loaded paper strips provide a portable and cost-effective method for detecting primary amines in solution, vapor, and food samples. Furthermore, EBAs enable efficient fluorogenic protein labeling and in-gel fluorescent imaging with clear signals observed by naked eye under 365 nm UV light. Due to their favorable membrane permeability, low-to-moderate cytotoxicity, and "turn-on" response, EBA-1a–1e and EBA-4–5 were successfully employed for wash-free live-cell imaging. Notably, EBA-1a–1e and EBA-4 showed high mitochondrial selectivity serving as selective fluorescent probes for mitochondria [1].

References:

[1] Tantipanjaporn, A., Deng, J. R., Chan, K. H. A., Kung, K. Y. K., Wong, M. K. Ethynylbenzaldehydes as novel reaction-based "turn-on" fluorescent probes for primary amine detection in solution, vapor, food, proteins, and live cells. Sens. Actuators B Chem. 2025; 422: 136673

Investigation on the multivalent effect on the immune response to glycan antigens: *Shigella flexneri* 2a as a model

Tom Thouvenin[1,2], Marion Bouchet[2], Marielle Tamigney[2], Jean-Maurice Mallet[1*], Laurence Mulard[2*]

[1]*Laboratoire CPCV, Chemistry department, École Normale Supérieure, PSL University, Sorbonne University, 24 rue Lhomond 75005, Paris, France*
[2]*Laboratory for Chemistry of Biomolecules, Institut Pasteur, Université Paris Cité, 24 rue du Docteur Roux 75015, Paris, France*

Shigella flexneri are the main cause of the endemic form of shigellosis, a major diarrheal disease, especially in low-income countries. Numerous vaccine strategies are currently being studied. Among those, glycoconjugates from *S.flexneri* lipopolysaccharides were found particularly attractive. The promising strategy we have developed involves synthetic surrogates of the O-antigen component of the lipopolysaccharides of interest in place of the natural surface antigen. Focusing on *S.flexneri* 2a (SF2a), we have developed SF2a-TT15 [1] a synthetic glycan-protein conjugate, that was found strongly immunogenic in young adults [2]. SF2a-TT15 features a chemically synthesized 15mer glycan hapten that corresponds to three repeating units of the O-antigen.

Furthermore, we aim to investigate the influence of multivalency on antigenicity and immunogenicity. The multivalent effect refers to a phenomenon whereby multiple copies of the same antigen are presented on a core structure. This mode of presentation is expected to promote binding to multiple immune receptors, thereby enhancing immune recognition, resulting in an immune response of enhanced quality [3]. As a multivalent scaffold, we chose dextran, a cheap and flexible polysaccharide that can be modified and grafted with antigenic moieties [4]. Modification can be controlled so that the substitution ratio is optimized toward increased immune recognition. This concept will be exemplified with *S.flexneri* 2a, initially using synthetic 5mer oligosaccharides representing one O-antigen repeating unit and, following parameter optimization, using the known synthetic 15mer hapten component of SF2a-TT15. Aiming at simplification, this strategy may pave the way to the use of shorter glycan components in the final conjugation design.

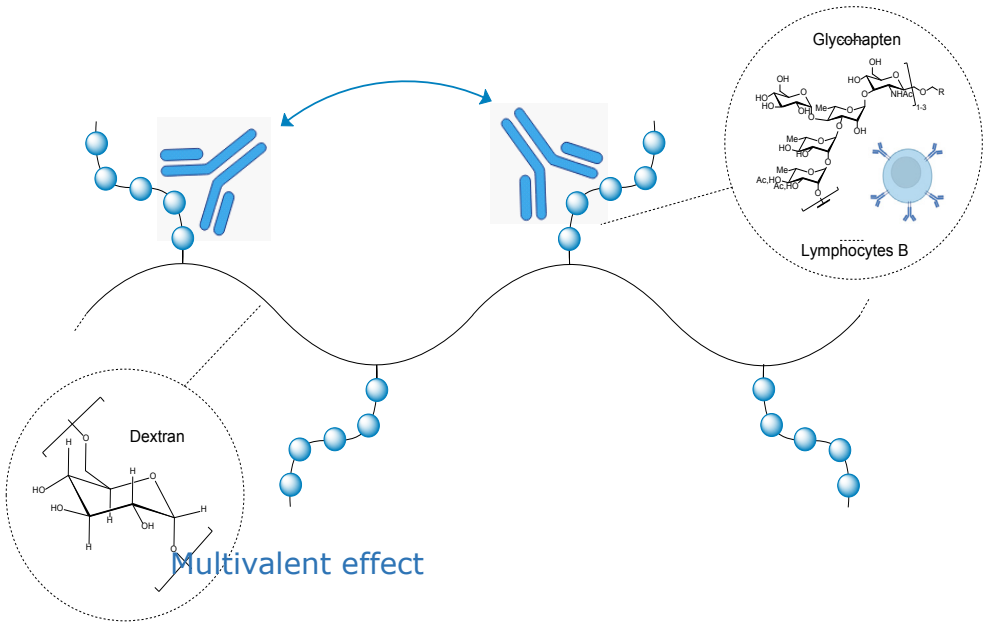


Fig 1 : Design of dextran back-bone grafted with glycans to study the multivalent effect

References:

[1] Van Der Put R, Smitsman C, De Haan A. The First-in-Human Synthetic Glycan-Based Conjugate Vaccine Candidate against Shigella. ACS Central Science, 2022; 8(4): 449-460
[2] Cohen D, Mulard L, Phalipon A. Safety and immunogenicity of a synthetic carbohydrate conjugate vaccine against Shigella flexneri 2a in healthy adult volunteers: a phase 1, dose-escalating, single-blind, randomised, placebo-controlled study. *The Lancet Infectious Diseases, 2021; 21(4) : 546-558*
[3] Kitov P, Bundle D. *On the nature of the multivalency effect: a thermodynamic model*. American Chemical Society 2003, 15(52): 16271-16284
[4] Mallet JM, Papini AM, Mazzoleni A. Selective capture of anti-N-glycosylated NTHi adhesin peptide antibodies by a multivalent dextran conjugate. ChemBioChem 2022; 23(3): e202100515

Stimulus-Responsive Mechanically Fibrillated Silk/Chitosan Gels for Advanced Ibuprofen Delivery Systems

Ngoc Phan Tran[1],Yoko Okahisa[2], Satoko Okubayashi[2]

[1]*International Institute for Sustainability with Knotted Chiral Meta Matter, Hiroshima University, Hiroshima, Japan*
[2]*Faculty of Fiber Science and Engineering, Kyoto Institute of Technology, Kyoto, Japan*

Addressing the growing demand for innovative healthcare biomaterials, this study presents the development of novel 3D nanofibrous hydrogels and aerogels composed of chitosan and mechanically nanofibrillated silk (150–300 nm). Fabricated via a wet-mechanical method and neutralization, these natural bio-organic composites were designed as advanced platforms for therapeutics and wound management. The biocompatible and biodegradable hydrogels demonstrated exceptional drug encapsulation efficiency (>25%) and high loading capacity (>10%), featuring controllable, stimulus-responsive drug release profiles suitable for targeted delivery [1]. Subsequent processing via supercritical CO2 (scCO2) drying yielded highly porous aerogels that maintain structural integrity while optimizing biological interactions. Comprehensive characterizations revealed that silk fibroin incorporation significantly reinforced the matrix, achieving a high mechanical modulus (>2.5 MPa at 80% strain), a remarkable swelling ratio (>400%), and ideal exudate uptake (>100%) [2]. Furthermore, ibuprofen-loaded scCO2 aerogels exhibited ultra-low density (0.085 g/cm³) and exceptional porosity (~98%), enabling sustained and controllable therapeutic delivery [3]. These findings underscore the strong translational potential of chitosan/silk fibroin nanocomposites in developing next-generation transdermal drug delivery systems and advanced wound dressings, aligning with future trends in chemical biology and medicinal development.

References:

[1] N. P. Tran, Y. Okahisa, S. Okubayashi. Chitosan hydrogel containing silk fibroin nanofibrils for controllable properties and its application to drug delivery system. Next Materials 2025; Volume 6,100288, ISSN 2949-8228.
[2] N. P. Tran, Y. Okahisa, S. Okubayashi. Chitosan aerogel containing mechanically fibrillated fibroin and its model test for wound dressing. Polymer Engineering & Science 2025; 65(3), 1340-1349.
[3] N. P. Tran, Y. Okahisa, S. Okubayashi. Ibuprofen-loaded chitosan/silk fibroin nanofibrils aerogel for drug delivery and model test for wound dressing. Next Materials 2025; 6, 100501, ISSN 2949-8228.

Ferritin-polyamine conjugates for targeted delivery of siRNA

Despoina Maria Varouhaki[1] Gabriele Cianfoni[1], Luca Pisano[1], Francesca Ghirga[1], Bruno Botta[1], Constantinos M. Athanassopoulos[2], Quaglio Deborah[1,*]

[1]*Department of Chemistry and Technology of Drugs, University of Sapienza, Piazza Aldo Moro 5, Rome, Italy*
[2]*Department of Chemistry, University of Patras, Panepistimioupoli, Rio, Greece*

Small interfering RNA (siRNA) has emerged as a powerful tool for gene silencing, offering therapeutic potential for treating various diseases. However, the clinical success of nucleic acid-based therapies depends on developing effective delivery systems, which face challenges such as targeted delivery, stability, and efficient cellular uptake. To overcome these limitations, a "humanized" chimeric Archaeal ferritin (*HumAfFt*) was engineered as a nanocarrier to transport negatively charged siRNA duplexes. In a previous work, to enhance siRNA electrostatic loading and subsequent cellular delivery, the internal cavity of *HumAfFt* was functionalized with cyclic polyamines (PAs), which were conjugated to strategically placed cysteine residues inside the *HumAfFt* through chemoselective thiol-coupling. The research activity aimed to develop a more efficient ferritin-based delivery system to improve RNA encapsulation via electrostatic interactions and, thus, RNA release from endosomal compartments[1]. Herein, our strategy envisages the creation of a synthetic library of poly-cationic molecules to establish the best relationship between the structure of positively charged linkers and negatively charged oligonucleotides and the expected interaction (namely, the structure–interaction relationship approach). Accordingly, linear polyamine linkers were designed and synthesized, namely R-PA-3.2. The synthetic approach relies on a straightforward strategy where iterative amidation reactions couple the carboxylic groups of *N*-protected amino acids to the amino group of the main chain. The key building blocks have been identified in methylamine, *β*-alanine, and glycine in different ratios. Based on previous polycationic linkers, these compounds were decorated with a pentafluorobenzenesulfonamide moiety for the selective bioconjugation of cysteine residues inside the protein inner cavity (Figure 1).

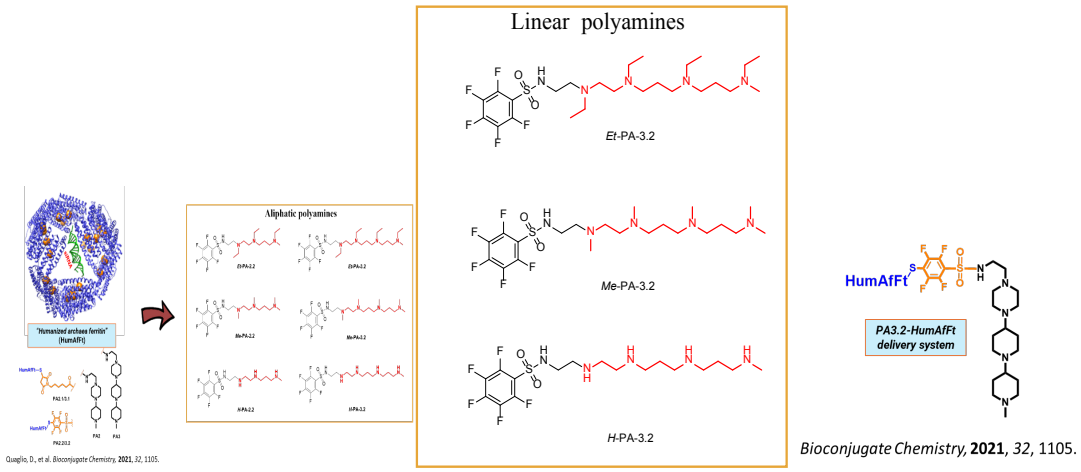


Figure 1. Encapsulation of small oligonucleotides via the functionalization of the internal cavity with polyamines.

References:

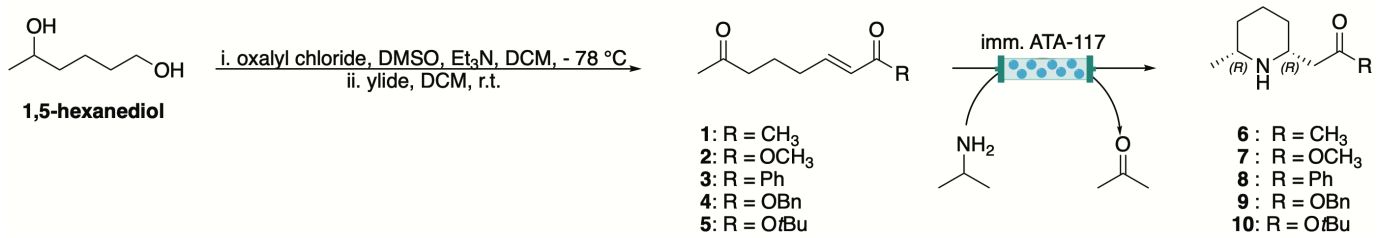
[1] Natalia Pediconi, Francesca Ghirga et al. Design and Synthesis of Piperazine-Based Compounds Conjugated to Humanised Ferritin as Delivery System of siRNA in Cancer Cells. *Bioconjugate Chemistry*, 2021, 32(6), 1105-1116

Chemo-enzymatic flow synthesis of enantiopure piperidines

Sara Vicinanza[1], Stefania Patti[2], Morena Pirotta[2], Ilaria Magrini Alunno[2,4], Francesca Annunziata[3], Raffaella Gandolfi[1], Chiara Borsari[1], Ivan Bassanini[2], Daniela Monti[2], Erica Elisa Ferrandi[2], Lucia Tamborini[1].

[1]Department of Pharmaceutical Sciences, University of Milan, Via Mangiagalli 25, 20133, Milan, Italy;
[2]Istituto di Scienze e Tecnologie Chimiche "G. Natta" (SCITEC), CNR, Via Bianco 9, 20131, Milan, Italy;
[3]Department of Food, Environmental and Nutritional Sciences, University of Milan, Via Celoria 2, 20133, Milan, Italy;
[4]Scuola Universitaria Superiore IUSS Pavia, Palazzo del Broletto, Piazza della Vittoria 14, 27100 Pavia, Italy.

Chiral amines are important building blocks in 40–45 % of small molecule pharmaceuticals, as well as in numerous industrially important fine chemicals and agrochemicals1. Furthermore, environmental regulations and the increasing demand for enantiopure compounds as high-value products for different sectors necessitate the integration of traditional chemical synthetic methods with greener (bio)catalytic approaches2. Since nitrogen-containing heterocycles represent a privileged structure in many APIs3, in this work we focused our attention on the asymmetric synthesis of enantiopure piperidines as high-value scaffolds for the synthesis of different alkaloids4. A pyridoxal 5'-phosphate (PLP)-dependent transaminase (ATA-117) was selected and immobilized to perform a stereoselective transamination, followed by a spontaneous intramolecular aza-Michael reaction (IMAMR, Scheme 1), to synthesize natural (-)-pinidinone (**6**)5. First, two chemical steps were performed in batch to prepare the desired substrate **1**, namely an oxidation reaction followed by a Wittig olefination using commercially available ylides. Then, after expressing and purifying the enzyme, various trials were conducted to immobilize the (*R*)-selective biocatalyst. Eupergit®C was chosen as the carrier for the covalent immobilization of ATA-117 to enhance its operational stability and reusability. The reaction was then optimized in a continuous flow system evaluating substrate concentration, isopropylamine equivalents, reaction temperature, residence time, type and amount of cosolvent. The protocol was extended to different substrates to isolate variuos 2,6-disubstituted chiral piperidines (compounds **7**-**10**).



Scheme 1: Chemo-enzymatic asymmetric flow synthesis of 2,6-disubstituted piperidines.

References:

[1] E.Abahàzi, P. Sàtorhelyi, B. Erdélyi, B.G. Véertessy, H. Land, C. Paizs, P. Berglund, L. Poppe, Biochem. Eng. J. 2018, 123, 270-278.
[2] J. Albarran-Velo, D. Gonzales-Martinez, V. Gotor-Fernandez, Biocatal. Biotransfom. 2018, 36, 102-130.
[3] E. Vitaku, D.T. Smith, J.T. Njardarson, J. Med. Chem. 2014, 57, 10257−10274.
[4] S.P. France, S. Hussain, A.M. Hill, L.J. Hepworth, R.M. Howard, K.R. Mulholland, S.L. Flitsch, N.J. Turner, ACS Catal. 2016, 6, 3753−3759.
[5]J. Ryan, M. Siaciulis, A. Gomm, B. Macià, E. O'Reilly, V. Caprio, J. Am. Chem. Soc. 2016, 138, 15798-15800.

Starving the beast: Exploiting the molybdate transporter ModABC to combat Clostridium perfringens infections

Julia Wieruszewska[1, 2], Joanna Sławek[1], Artur Biela[1]

[1]*SOLARIS National Synchrotron Radiation Centre, Jagiellonian University, Krakow, Poland,*
[2]*Doctoral School of Exact and Natural Sciences, Jagiellonian University, Krakow, Poland*

The antimicrobial resistance crisis necessitates novel „anti-virulence" strategies targeting bacterial physiology, such as the molybdate uptake system (ModABC) in the lethal anaerobe *Clostridium perfringens*. As humans lack homologous high-affinity transporters, the periplasmic receptor ModA represents a selective target to starve the pathogen of energy without inducing broad-spectrum resistance.
Bioinformatics identifies ModA as a membrane-anchored lipoprotein. To enable structural studies, we engineered expression constructs lacking the N-terminal lipobox (SP) for soluble protein production. Our integrative structural pipeline combines X-ray crystallography to resolve the ligand-binding pocket, cryo-EM to visualize the full transporter in lipid nanodiscs, and biophysical assays (ITC, DSF) to quantify ligand binding thermodynamics.
Computational analysis classifies *C. perfringens* ModA as a Cluster II solute-binding protein with a „Venus fly-trap" mechanism. Homology modeling predicts a conserved anion-binding pocket capable of hexacoordinating molybdate via a hydrogen-bonding network. Structural superposition suggests this pocket allows for isostructural mimicry by tungstate, a competitive antagonist. Beyond the isolated receptor, we aim to capture the full transporter in distinct conformational states (e.g., pre-hydrolysis) to elucidate the coupling between ligand binding and membrane translocation.
This proposal outlines a structural framework for targeting the molybdenum uptake pathway. Preliminary analysis supports the feasibility of using tungsten-based inhibitors to lock the transporter in a non-productive „dead-end" state. Elucidating the ModA structure will facilitate the design of innovative therapeutics that disarm *C. perfringens* by disrupting essential anaerobic metabolism. Ultimately, this highlights the potential of precision antimicrobials to exploit unique bacterial vulnerabilities.

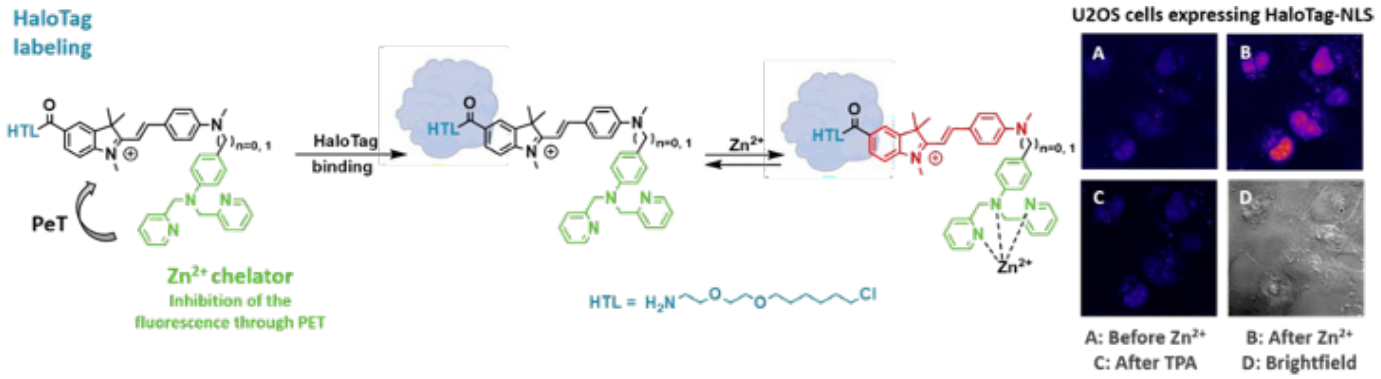
Genetically-targeted and red-emitting fluorescent indicators for subcellular zinc imaging

Manon Wittwer[1], Giorgia Rosati[1], Romain Berraud-Pache[2], Jean-Maurice Mallet[1] and Blaise Dumat[1]

[1]*Laboratoire Chimie Physique Chimie du Vivant (CPCV), Ecole Normale Supérieure, CNRS UMR 8228, Paris, 75005, France*
[2]*Laboratoire d'Archéologie Moléculaire et Structurale (LAMS), Sorbonne Université, CNRS UMR 8220, Paris, 75005, France*

Zinc is a metal ion with several key biological roles, including in brain plasticity and neurodegenerative disorders. [1] Understanding the dynamics of Zn^{2+} release during synaptic activity requires real-time monitoring at the subcellular level. Biologists usually rely on zinc-sensitive fluorescent proteins but they generally display limited dynamic range (1 – 2 fold).[2] Synthetic fluorescent zinc indicators often display improved sensing properties, but lack precise cellular targeting. Semi-synthetic alternatives combining molecular indicators with genetically-encoded proteins have recently emerged to address this limitation, although current systems are exclusively restricted to the blue/green emission regions. [3,4]

We have previously designed red-emitting HaloTag probes based on a hemicyanine core with excellent photophysical properties. [5] Because of the styryl bond, they behave as push-pull viscosity-sensitive molecular rotors, where the formation of a covalent bond between the probe and HaloTag locks the molecule's excited-state conformation, drastically enhancing the fluorescence properties of the probe-protein complex (up to 101-fold). Incorporation of specific sensing groups into this scaffold enables the design of genetically targeted, red-emitting Zn^{2+} probes. To optimize probe sensitivity, the molecular design was guided by DFT calculations to rationalize the photoinduced electron transfer (PeT) process.
Here, we report the first examples of genetically-targeted and red-emitting fluorescent indicators for zinc imaging. Once reacted with HaloTag, these indicators display bright red-shifted emission (> 600 nm) turned on by Zn2+ cations, enabling the successful imaging of zinc in live cells. Ongoing work focuses on developing cell-impermeant analogues and implementing directed evolution to further enhance the overall brightness.



References:

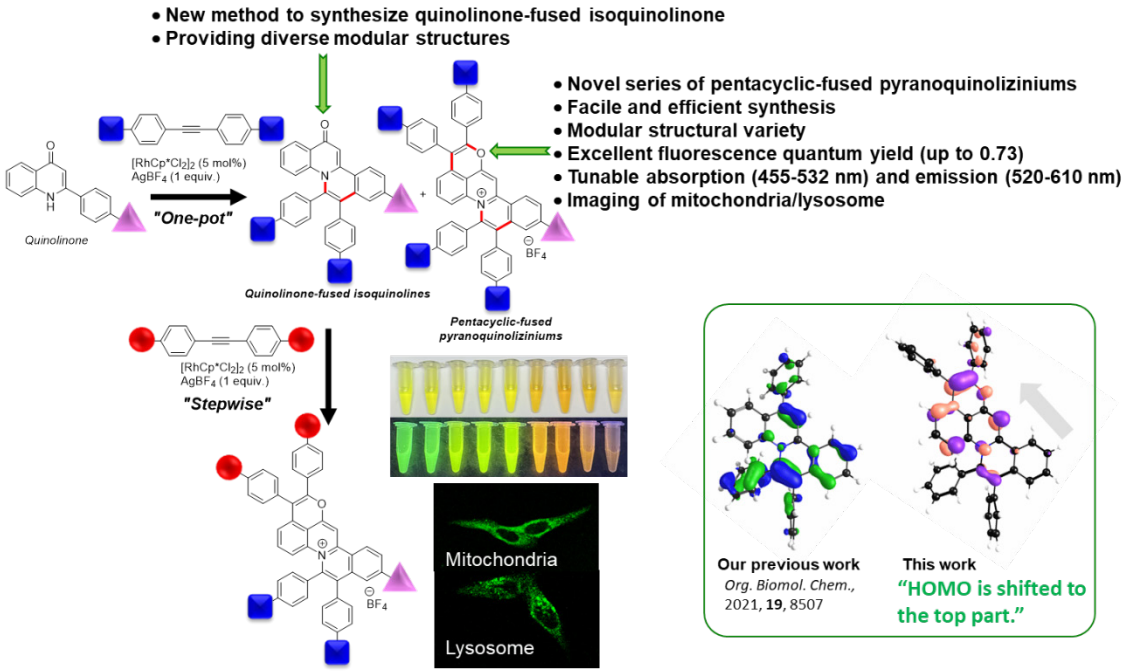
[1] Frederickson, C. J.; Koh, J.-Y.; Bush, A. I. T. Nat. Rev. Neurosci. 2005, 6 (6), 449–462.
[2] Pratt, E. P. S., Damon, L. J., Anson, K. J., & Palmer, A. E. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research, 2021, 1868(1), 118865.
[3] Zastrow, M. L., Huang, Z., & Lippard, S. J. ACS Chemical Biology. 2020, 15(2), 396-406.
[4] Kowada, T., Watanabe, T., Amagai, Y., Liu, R., Yamada, M., Takahashi, H., Matsui, T., Inaba, K., & Mizukami, S. Cell Chemical Biology. 2020, 27(12), 1521-1531.
[5] Dumat, B., & Chieffo, C. Chemistry – A European Journal. 2025, 31(9).

Fluorescent Pentacyclic-fused Pyranoquinoliziniums for Molecular Imaging and Photoredox Catalysis

Man-Kin Wong,[1] Ajcharapan Tantipanjaporn,[1] Ka-Yan Karen Kung,[1] and Jie-Ren Deng[2]

[1]*Research Institute for Future Food, Department of Food Science and Nutrition, The Hong Kong Polytechnic University, Hung Hom, Hong Kong, China.*
[2]*Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Hong Kong, China.*
Email: mankin.wong@polyu.edu.hk

Organic fluorescent compounds are of great importance with diverse applications in chemical biology, molecular imaging, and materials science. Quinolizinium is one type of cationic fluorophores containing a quaternary bridgehead nitrogen atom found in naturally occurring compounds and belongs to the class of nitrogen-doped polycyclic aromatic hydrocarbons. However, the synthesis of quinoliziniums is challenging due to prefunctionalization requirement, harsh reaction conditions, and multistep synthesis. Here, we present modular synthetic strategies for efficient synthesis of novel fluorescent quinoliziniums by using one-pot and stepwise rhodium(III)-catalyzed C–H annulations. In the one-pot synthesis, the reaction between 2-aryl-4-quinolones and 1,2-diarylalkynes proceeded in a chemo- and regioselective manner to give quinolinone-fused isoquinolines and pentacyclic-fused pyranoquinoliziniums[1]. The structural diversity of the pentacyclic-fused pyranoquinoliziniums was expanded by strategic incorporation of electron-donating (OMe and OH) and electron-withdrawing (Cl) substituents on the top and bottom parts of the pyranoquinoliziniums. These fluorescent pyranoquinoliziniums exhibited tunable absorptions (455–532 nm), emissions (520–610 nm), fluorescence lifetime (0.3–5.6 ns), large Stokes shifts (up to 120 nm), and excellent fluorescence quantum yields (up to 0.73). Using the fluorescent pyranoquinoliziniums as subcellular targeting fluorescent probes has been demonstrated. Recently, we have also explored the use of the fluorescent pyranoquinoliziniums as photocatalysts for visible light photoredox catalysis.



References:

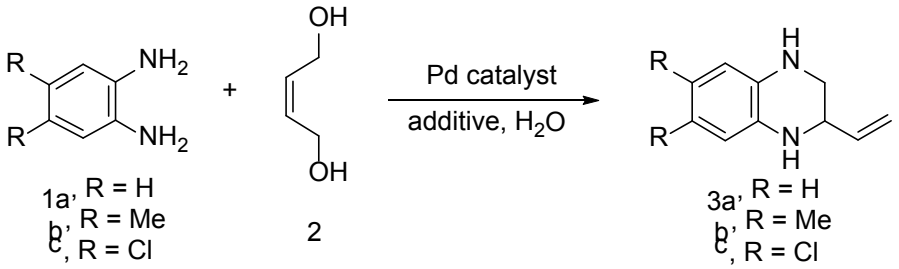
[1] Tantipanjaporn A, Kung KYK, Deng JR, Wong MK. Modular synthesis of pentacyclic-fused pyranoquinoliziniums as organelle-selective fluorescent probes. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* 2024; 319: 124524.

Direct palladium/carboxylic acid-catalyzed tandem allylation of *o*-phenylenediamines with but-2-ene-1,4-diol in water

Kuang-Feng Chu[1], Shyh-Chyun Yang[1-4]

[1]*School of Pharmacy, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan;*
[2]*Department of Fragrance and Cosmetic Science, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan;*
[3]*Department of Medical Research, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan;*
[4]*School of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei, Taiwan*

A palladium-catalyzed protocol for the direct activation of C–O bonds in but-2-ene-1,4-diol has been developed using water as a suspension medium. The presence of a carboxylic acid was found to play a crucial role in promoting allyl–OH bond cleavage, leading to a marked enhancement in both reaction rate and product yield. Under the optimized conditions, *o*-phenylenediamines undergo a palladium-catalyzed tandem allylation and cyclization reaction with but-2-ene-1,4-diol, affording 1,2,3,4-tetrahydro-2-vinylquinoxalines in good yields. Mechanistic considerations suggest that the transformation proceed via π-allylpalladium intermediates, enabling efficient sequential C–N bond formation in an aqueous environment. Notably, the use of but-2-ene-1,4-diol as an allylating agent obviates the need for preactivated allyl substrates, thereby enhancing the operational simplicity and sustainability of the method. This catalytic system provides a straightforward, efficient, and environmentally benign approach for the construction of nitrogen-containing heterocycles and highlights the beneficial effect of carboxylic acid additives in palladium-catalyzed allylic substitution reactions conducted in water.



Targeting EndoG by small molecules to modulate neurodegeneration

Jason L. J. Lin[1], Wei-Zen Yang[1], Yi-Ping Chen[1], Woei-Chyn Chu[2], and Hanna S. Yuan[1]

[1]*Institute of Molecular Biology, Academia Sinica, Taipei, Taiwan;*
[2]*Department of Biomedical Engineering, National Yang Ming Chiao Tung University, Taipei, Taiwan.*

Mitochondrial endonuclease G (EndoG) is a non-specific endonuclease that cleaves DNA to maintain mitochondrial genome integrity and homeostasis. Because EndoG plays multiple essential roles in DNA processing and degradation, dysregulated EndoG expression has been linked to several diseases, including heart and Parkinson's disease. By screening a panel of natural compounds, we identified two polyphenols that modulate the enzymatic activity of human EndoG (hEndoG) in opposite ways: one acts as an activator and the other as an inhibitor. Crystal structures of EndoG in complex with these compounds reveal distinct regulatory mechanisms. The inhibitor binds to the His-Me finger DNA-binding motifs of the EndoG dimer, thereby obstructing access to DNA substrates. In contrast, the activator binds at the dimer interface, stabilizing the EndoG dimer and enhancing its enzymatic activity. Functionally, the inhibitor attenuates α-synuclein-induced dopaminergic neuronal loss, supporting a key role for EndoG in α-synuclein–mediated Parkinsonism. Together, these findings provide a molecular framework for targeting EndoG with polyphenolic modulators to treat diseases associated with either reduced or excessive EndoG activity.

Conjugated Oligoelectrolytes as Optical Probes

Ji-Yu Zhu[1,2], Samuel J.W. Chan[1,2], Guillermo C. Bazan[1,2]

[1]*Institute for Digital Molecular Analytics and Science, 59 Nanyang Drive, Singapore 636921, Singapore;*
[2]*Institute for Functional Intelligent Materials, National University of Singapore, 4 Science Drive 2, 117544, Singapore*

Cell membranes organize biological systems by enabling compartmentalization and the formation of distinct microenvironments, which are essential for supporting complex cellular functions. Fluorescent probes offer a straightforward means of visualizing biological structures.[1] Materials capable of selectively interacting with lipid bilayers while providing measurable optical signals are thus valuable tools for probing cell function. Conjugated oligoelectrolytes (COEs) are a promising class of optical reporters featuring a delocalized π-conjugated backbone with ionic functionalities. This molecular architecture mimics the hydrophobic and hydrophilic distribution of lipid bilayers, enabling spontaneous self-assembly and stable association within cellular membranes.[2] The conjugated backbone of COEs can be easily modified to modulate their electronic and photophysical properties.[3] We outline strategies for chemical modifications, including donor-acceptor engineering, that have been leveraged to create a palette of probes tailored for fundamental research or application-specific bioimaging.[4] In combination with various imaging modalities, including time-resolved and two-photon microscopy, we demonstrate how these probes enable visualization of membrane-associated phenomena across multiple spatial scales, including the detection of lipid-bilayer-bound extracellular vesicles, tracking single vesicles within the cell, as well as *in vivo* imaging. Overall, these capabilities establish COEs as a versatile platform for developing probes capable of tracking the localization and physicochemical properties of intracellular membranes in living cells.

References:

[1] Klymchenko, A. Acc. Chem. Res. 2023, 56, 1, 1–12
[2] J.-Y. Zhu, G. C. Bazan. Cell Rep. Phys. Sci., 2023, 4, 101429.
[3] C. Zhou, Z. Li, Z. Zhu , G. W. N. Chia , A. Mikhailovsky, R. J. Vazquez, S. J. W. Chan, K. Li, B. Liu, G. C. Bazan. Adv. Mater., 2024, 37, 2411329.
[4] Chan S. J. W., Zhu J.-Y., Yip B. R. P., Shyamasundar S., Bazan G. C. Adv. Mater., 2024, 37, 2411329.

SECRETARIAT

Tel.: +39 0818770604
Fax: +39 0818770258
E-mail: info@yesmeet.it
Via San Nicola, 4
80067 Sorrento (NA) - Italia