fruit attraction

PONENTE

JORGE LOZANO JUSTE

IBMCP (UPV-CSIC)

INVESTIGADOR RYC

P 967010089698

FEPEX · IFEMA MADRID

fruit attraction

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Gracias por ayudarnos a crear en Fruit Attraction un espacio de debate e intercambio a medida para todos los profesionales de la industria hortofrutícola.

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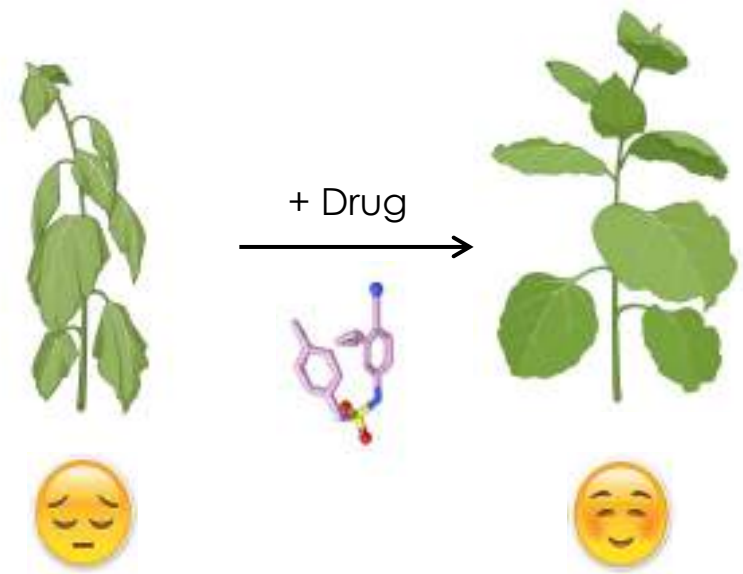

Jorge Lozano-Juste

"BIOTECH ATTRACTION", SEP 2025, IFEMA, Madrid

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UNIVERSITÀ DEGLI STUDI
DELL'INSUBRIA

DIPARTIMENTO DI SCIENZA
E ALTA TECNOLOGIA
Prof.ssa Silvia Gazzola

Medicinal and Crop Protection Chemistry: Breaking Barriers, Building Synergies

Como, October 17th 2025

Certificate of attendance

To whom in my concern,

we confirm that Jorge Lozano Juste attended the international conference titled *"Medicinal and Crop Protection Chemistry: Breaking Barriers, Building Synergies"* held on October 16th–17th, 2025, at the Cloister of Sant'Abbondio, Como, Italy, where he presented a poster communication and he chaired a scientific session.

On Behalf of the Scientific and Organizing Committee

Prof. Silvia Gazzola

Silvia Gazzola

……..

Medicinal and Crop Protection Chemistry: Breaking Barriers, Building Synergies

October, 16th-17th 2025

COMO (Italy)
Sant'Abbondio's cloister
Insubria University

BOOK OF ABSTRACTS

TABLE OF CONTENTS

WELCOME NOTE

Dear Colleagues,

It is our great pleasure to welcome you to the first edition of the conference *"Medicinal and Crop Protection Chemistry: Breaking Barriers, Building Synergies"*, held in the historic Chiostro di Sant'Abbondio in Como (Italy).

This meeting has been conceived to foster dialogue between medicinal chemistry and crop protection chemistry, two areas of research that, despite their many common challenges and opportunities, have rarely been addressed together. Particular attention is devoted to agrodrug discovery, a field often less explored compared to medicinal chemistry, yet of growing importance for global sustainability.

With contributions from distinguished experts in academia and industry, the scientific program highlights emerging strategies, innovative approaches to the discovery of bioactive compounds, and the key challenges shaping the future of both pharmaceutical and agricultural sciences.

The conference is organized within the framework of the STAR project (funded by the Italian Applied Sciences Fund, FISA2022-MUR, in collaboration with Bayer Crop Science), which is dedicated to advancing the sustainability of agrodrugs in Italian agriculture.

We warmly thank all participants for joining us and for contributing to the success of this initiative. We wish you an inspiring and fruitful conference.

Sincerely,

The MCPS Scientific and Organizing Committee

Prof. Silvia Gazzola

Dr. David Barber

Dr. Giulia Cazzaniga

Dr. Roberto Orru

Samuele Bongiolo

SCIENTIFIC AND ORGANIZING COMMITTEE

- **Heads of the scientific and organizing committee**

Prof. Silvia Gazzola

Silvia Gazzola (1988) obtained her Ph.D. in Chemistry from the University of Insubria (Como, Italy) in 2016, working on natural product synthesis. During her doctoral studies, she carried out research stays at the University of Warwick (UK, Prof. Tosin) and at the University of Barcelona (Prof. Mercedes). She then joined Bayer CropScience as a Marie Curie postdoctoral researcher in the Weed Control Department, where she worked on the discovery and development of novel herbicides. This industrial experience strongly shaped her interest in applied research at the interface of chemistry and crop sciences. In 2017, she moved to Wädenswil to join Prof. Riedl's group, focusing on natural product-based antiprotozoal agents. In 2018, she returned to the University of Insubria, starting a research activity in collaboration with Prof. Umberto Piarulli on ligand-targeted systems for cancer therapy.

In 2024, she was awarded a major FIS-A (*Fondo Italiano per le Scienze Applicate*) grant, which enabled her to establish her fully independent research program on innovative delivery systems for agrochemicals in collaboration with Bayer CropScience.
Since February 2025, she has been Associate Professor of Organic Chemistry.

Dr. David Barber

Dave studied chemistry at the University of York and conducted his doctoral studies at the University of Oxford under the supervision of Prof. Darren J. Dixon. In 2013 he joined the group of Prof. Dirk Trauner at LMU Munich as a Marie Skłodowska-Curie postdoctoral fellow working in the field of Photopharmacology. In 2015 he took a position as Lab Leader in Weed Control at Bayer AG, Crop Science Division in Frankfurt am Main. In the subsequent years he worked on the identification and optimization of new herbicide lead compounds to provide farmers with the next generation of sustainable crop protection solutions.

He is currently a member of the "Profile Driven Chemistry" team where his role focuses on leading external collaborations and investigating new early phase research concepts. He is a member of the Society of Chemical Industry Fine Chemicals and Agrisciences groups as well as serving as a scientific representative to CropLife Europe on the topic of PFAS. He was also part of the organizing committee for Theme 1 of the 15th IUPAC International Congress of Crop Protection Chemistry that was held in New Delhi in 2023.

- **Members of the organizing and scientific committee**

Dr. Giulia Cazzaniga

Giulia completed her MSc in Pharmaceutical Chemistry and Technology at the University of Milan in 2020. She then obtained a PhD in Pharmaceutical Sciences from the same university in 2024, focusing on the design of new potential candidates for the treatment of metabolic disorders. As a PhD visiting student at the Institute for Bioengineering of Catalonia, she worked on the development of polymeric nanoparticles for the selective delivery of potential anti-TB drugs.
She is currently a postdoctoral researcher at the University of Insubria (Como, Italy) in the group of Prof. Silvia Gazzola, where she is focused on developing drug conjugates for pharmaceutical and crop protection applications.

Dr. Roberto Orru

Roberto is a biochemist with a strong focus on enzymology and structural biology.
He earned his Ph.D. in biomolecular sciences and biotechnology from the Istituto Universitario di Studi Superiori in Pavia (ITA), where he specialized in the structural and functional characterization of oxidative enzymes in the group of Prof. Mattevi. Roberto's academic journey included significant roles as a postdoctoral fellow at Emory University and as a research associate at the Institute of Molecular Biology and Johannes Gutenberg-Universität Mainz, where he led projects on structural/functional characterization of human proteins and complexes involved neurogenerative disease, circadian rhythm, and genome maintenance.
Currently, Roberto serves as a lead Scientist in Small Molecules Early Discovery Biochemistry at Bayer AG, where he oversees a team dedicated to evaluating and validating new herbicidal modes of action. With a robust background in biochemistry and a commitment to advancing crop protection products, Roberto plays a crucial role in Bayer's target-based early discovery initiatives.

Samuele Bongiolo

Samuele earned both his Bachelor's (2022) and Master's (2024) degrees in Chemistry with honors from the University of Insubria. His Master's thesis, supervised by Prof. Silvia Gazzola, focused on the design of novel linkers for the controlled release of cytotoxic agents in targeted cancer therapies. He also collaborated with Italfarmaco S.p.A. on a related project during his thesis work.

Since November 2024, Samuele has been a research fellow in Prof. Gazzola's group in the frame of STAR project with the aim to develop innovative and sustainable strategies for agrochemical applications.

SPONSORS AND SUPPORTERS

The conference is organized and funded within the framework of the STAR project (**FISA-2022-00922**, Italian Ministry of University and Research).

The event is sponsored by "Società Chimica Italiana – Sezione Lombardia"

The event is supported by Bayer CropScience

The event is supported by Università degli Studi dell'Insubria

Scientific Program

October 16th, Thursday		October 17th, Friday	
8.00 – 9.00	Registration		
9.00 – 9.15	Opening 1st day	8.30 – 8.45	Opening 2nd day
	Chairperson: **Simon Dieterich** *Globachem*		Chairperson: **Dr. Jorge-Lozano Juste** *Universidad Politecnica de Valencia*
9.15 – 10.00	PL01 **Prof. Peter Maienfisch** Title: *Silicon Motifs as Bioisosteres: Expanding the Molecular Design Toolbox for Pharma and Agro*	8.45 – 9.30	PL03 **Dr. Aurelien Bigot** Title: *Bugs, plants and peptides: Unleashing the power of chemical ecology for sustainable crop protection*
10.00 – 10.30	OC01 **Prof. Necla Birgul Iyison** Title: *Unlocking the Future: Harnessing GPCRs for Revolutionary Pesticide Innovations*	9.30 – 10.00	OC08 **Dr. Sebastian Klie** Title: *Target centric crop protection: a digital DMTA framework pairing public plant data with proprietary evidence*
10.30 – 11.00	**Coffee break**	10.00 – 10.30	OC09 **Prof. Marta De Zotti** Title: *Aib-containing peptides as plant protection products*
11.00-11.30	OC02 **Prof. Umberto Piarulli** Title: *RGD and isoDGR integrin ligand-Drug Conjugates for tumor targeting*	10.30 – 11.00	**Coffee break**
11.30 – 12.00	OC03 **Dr. Jokin Carrillo Arregui** Title: *Design and development of Targeted Protein Degraders against epigenetic factors in Multiple Myeloma*		Chairperson: **Prof. Valentina Straniero** *University of Milan*
12.00 – 12.30	OC04 **Prof. Michael Christodoulou** Title: *Targeting ferroptosis in Pyricularia oryzae by natural and nature-inspired siderophores*	11.00 - 11.45	PL04 **Dr. Andreas Blum** Title: *Designing Anticancer Drugs*
12.30 – 14.00	**Lunch - Poster Session**	11.45 - 12.15	OC10 **Dr. Sarah Mazzotta** Title: *Enhancing Bacterial Lectin Affinity with Reversible Covalent Ligands*
	Chairperson: **Dr. Barbara Vergani** *Italfarmaco srl*	12.15 - 12.45	OC11 **Prof. Dan Bebber** Title: *Climate change impacts on crop pests and pathogens*
14.00 – 14.45	PL02 **Prof. Tracey Pirali** Title: *Deuterium in Drug Design: Why Crop Science Should Take Note*	12.45 - 13.00	**Closing Remarks**
14.45 -15.15	OC05 **Dr. Jean-Philippe Combier** Title: *Peptides as a credible alternative for crop protection?*		
15.15 - 15.45	**Coffee Break – Poster Session**		
15.45 – 16.15	OC06 **Prof. Elena Baraldi** Title: *RNAi vs. crop protection chaos: the molecular twist to address* sticky *cases*		
16.15 – 16.45	OC07 **Prof. Francesco Pennacchio** Title: *Plant molecular bioprotection*		
16.45 - 17.00	**Closing Remarks**		
19.00	**Social Dinner**		

Biographies & Abstracts of the Speakers

Keynote Speakers

Prof. Dr. Peter Maienfisch

CreInSol and Honorary Professor of the East China University of Science and Technology

Peter Maienfisch is the founder and owner of CreInSol MCB, a company formed in April 2020. Previously he was Research Portfolio Manager Insect Control & Seedcare at Syngenta Crop Protection AG in Switzerland (until April 2020). In this role he was responsible for defining the research strategies and to govern all insecticide, nematicide and seedcare research projects across technologies from their initiation to the delivery to development. Furthermore, he works as Honorary Professor at the East China University of Science and Technology (ECUST), Shanghai, China, as Part-time Professor at Central China Normal University (CCNU), Wuhan, China and as lecturer at the University of Basel, Switzerland. Peter Maienfisch studied chemistry at the Swiss Federal Institute of Technology (ETH) in Zürich, Switzerland, where he received his PhD in 1983. Afterwards he spent 2 years at the California Institute of Technology (Caltech; Pasadena, CA, USA) to perform post-doctoral research in the group of Prof. Robert E. Ireland. During his career he held several different leadership positions in Crop Protection R&D including Group Leader Insecticide Chemistry, Analytics & Automation at Syngenta, Head of Chemistry in Crop Protection Research at Novartis and Group Leader in Insecticide Research at Ciba.

His track record of innovation and successful introduction of new technologies includes authorship of more than 250 scientific papers and patents. He is the inventor of thiamethoxam (Actara®, Cruiser®, one of the leading insecticides world-wide with annual sales of more than 1 billion $) and championed the development of this innovative insecticide. Furthermore, he initiated research on many new chemical classes at Syngenta and made essential contributions to the discovery and optimization of several new active ingredients, such as Spiropidion, Isocycloseram, Cyclobutrifluram and a malaria vector control compound, which are expected to reach the market in the next couple of years. His scientific contributions also led to many invitations as a speaker and co-organizer of many international congresses, including IUPAC Crop Protection congresses. Furthermore, he is Editor of two books on the “Discovery and optimization of modern Crop Protection Products”

PL01

Silicon Motifs as Bioisosteres: Expanding the Molecular Design Toolbox for Pharma and Agro

Prof. Dr. Peter Maienfisch

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peter.maienfisch@hotmail.com

The discovery and development of new agrochemicals and pharmaceuticals have become increasingly complex, costly, and time-consuming. Among modern design strategies, bioisosteric replacement and scaffold hopping have emerged as powerful tools for creating innovative, biologically active molecules. Within this context, silicon-containing motifs have gained significant attention as versatile bioisosteric substitutes for a range of atoms and functional groups in life science research.

Organosilanes are easily synthetically accessible, inexpensive, and generally non-toxic. Their physicochemical properties often resemble those of their carbon and other analogs, while subtle differences can lead to favorable changes in biological activity, molecular stability, and safety profiles. Moreover, the introduction of silicon frequently enables structural novelty that supports new intellectual property - an increasingly important aspect in competitive research environments.

This presentation will highlight the fundamentals of silicon-based bioisosterism, showcase successful applications in agrochemical and pharmaceutical discovery, and discuss recent examples demonstrating how the strategic incorporation of silicon can expand accessible chemical space and unlock new biological potential. Despite its promise, this approach remains underutilized, offering exciting opportunities for future innovation in molecular design.

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Prof. Dr. Tracey Pirali

University of Piemonte Orientale, Italy

Tracey Pirali is a full professor of Medicinal Chemistry at the University of Piemonte Orientale. She earned her degree in Pharmacy in 2004 and completed her PhD in the laboratory of Prof. Tron in 2008. As a visiting scientist, she worked with Prof. Zhu (Paris, CNRS) and Prof. Greaney (Edinburgh, School of Chemistry).

In 2013, she established her own research group in Novara, Italy at the University of Piemonte Orientale. Prof. Pirali's work focuses on innovative strategies in drug discovery and development to create therapeutic solutions for complex diseases. Her research includes exploring the soft drug concept in topical delivery, utilizing deuterium to enhance the pharmacokinetic profiles of bioactive molecules, employing PROTAC technology for protein degradation modulation, and advancing multicomponent reactions to accelerate synthesis. These approaches target various therapeutic areas, notably cancer immunotherapy via IDO1 enzyme inhibitors and neuropathic pain through voltage-gated sodium channel blockers. These projects have been supported by the European Union, Italian Government, AIRC Foundation, and other sources.

In 2012, Prof. Pirali was awarded the prestigious Farmindustria Prize by the Italian Chemical Society. In 2019 she co-founded ChemICare, a spin-off company dedicated to developing calcium channel modulators for treating Duchenne muscular dystrophy. The company's lead candidate has received orphan drug designations from both the EMA and FDA. Since 2019, she has served as the Director of the Erasmus Mundus Joint Master EMOTION funded by the European Union.

PL02

Deuterium in Drug Design: Why Crop Science Should Take Note

Prof. Dr. Tracey Pirali

Department of Pharmaceutical Sciences, Università degli Studi del Piemonte Orientale, Largo Donegani, 2 28100 Novara, Italy
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Deuterium (D), the heavy isotope of hydrogen (H), differs from hydrogen by the presence of one neutron. It is a rare, stable, non-radioactive, and non-toxic isotope with applications in various fields.

Although replacing hydrogen with deuterium represents the smallest structural modification, it can slow down chemical and metabolic pathways, leading to more stable and effective therapeutics. Many deuterium-labeled drugs arise from the "deuterium switch" approach, in which marketed drugs are modified with deuterium atoms. A notable example is deutetrabenazine, approved in 2017 for Huntington's chorea. To date, nearly 20 deuterated candidates have entered clinical trials.

While the popularity of the deuterium switch has declined due to intellectual property concerns, deuterium is increasingly integrated at the early stages of drug discovery, enabling the design of entirely new compounds. A striking case is deucravacitinib, an allosteric TYK2 inhibitor approved in 2022 for psoriasis.

This lecture highlights significant examples of deuterated active molecules to demonstrate the benefits of deuteration in drug discovery and development. It also points to future opportunities in crop science: deuteration could enhance the stability and persistence of agrochemicals, reduce application frequency and environmental impact, and potentially modulate plant metabolic pathways. By leveraging advances from drug design, crop science may offer innovative and more sustainable solutions through the strategic use of deuterium.

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Dr. Aurelien Bigot

Syngenta

Dr Aurélien Bigot (pronounce BIGO) graduated in chemistry in Strasbourg before moving to Germany in Freiburg to complete his PhD in 2008 with Prof. Breit in the fields of organic synthesis and asymmetric catalysis. Then he joined Syngenta as a postdoctoral fellow followed by a second postdoc with Prof Gaunt in Cambridge before returning to Syngenta in Switzerland as a lab head in 2011. Aurélien has contributed to a number of small molecule projects, most recently as Head of Lead Generation fungicide before transitioning to Biologicals research in 2021, concomitantly to his nomination as a Science and Technology Fellow. He is currently dedicated to biomolecules as potential biocontrol or biostimulant solutions, with a particular focus on peptides and proteins.

PL03

Bugs, plants and peptides – Unleashing the power of chemical ecology for sustainable crop protection

Dr. Aurélien Bigot

Syngenta Crop Protection AG, Schaffhauserstrasse 4332 Stein, Switzerland
aurelien.bigot@syngenta.com

Farmers face globally a shrinking toolkit for crop protection amid tighter regulations, increased public demand for residue-free food, challenges from resistance, and the negative impacts of climate change. At Syngenta Biologicals we are committed to enhancing agricultural productivity in concert with sustainable practices. We pledge to bring to market cutting-edge biocontrol solutions, and one such pioneering approach in our arsenal is the development of peptide-based insecticides. These novel bioinsecticides are designed to provide growers with a targeted and environmentally benign approach to insect pest management, ensuring no residual presence as they degrade into harmless natural amino acids.

Peptide toxins from natural insect predators, such as spiders and scorpions, represent attractive candidates for this purpose as they have been long known for their specificity, potency and rapid onset of toxic effects when injected into insect herbivores (1). However, their effectiveness is markedly diminished when administered orally, a route for which they have not naturally adapted through evolution, particularly in combating the highly damaging pests of the Lepidoptera order (2). We have uncovered that peptides of plant origin from the cyclotide family, kalata B1 and B2, when combined with various animal-derived neurotoxins significantly enhance their potency in controlling highly destructive caterpillars through oral ingestion (3). We report herein our efficacy findings on this concept and our mechanistic investigations, proposing a mode of action wherein cyclotides disrupt the structural integrity of the lepidopteran midgut barrier. This disruption facilitates the translocation of neurotoxins across the gut epithelium into the hemocoel, where they can manifest their lethal effects on the nervous system of insects.

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Dr. Andreas Blum

Merck KGaA

Andreas Blum is Director in Medicinal Chemistry at Merck KgaA in Damstadt (Germany). He graduated from the Philipps-University Marburg (Germany) and obtained his Ph.D. in Medicinal Chemistry in 2007 followed by a postdoc at the Imperial College in London with Prof. Barrett. In 2009, he joined Boehringer Ingelheim Pharma in Biberach (Germany) as lab leader in Medicinal Chemistry where he worked as team member and project leader for several research projects in the area of cardio-metabolics. End of 2016, he moved to Merck KgaA in Darmstadt (Germany) changing the focus of research to oncology and is currently focusing with his group on oncogene chemistry and automation.

PL04

Designing Anticancer Drugs

Dr. Andreas Blum

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Small molecule therapeutics have significantly transformed cancer treatment, greatly improving patients' lives. However, despite the successes of targeted therapies and precision medicine, substantial medical needs remain. The ongoing challenge of resistance to approved therapies necessitates more sophisticated drug-target profiles. The increasing demand for finely-tuned and selective pharmacological effects, along with acceptable ADME (Absorption, Distribution, Metabolism, and Excretion) and toxicological profiles, drives the development of more complex candidate molecules. The effective synthesis of these intricate structures poses significant challenges for medicinal chemists.

In addition to classical small molecule drugs, new modalities have achieved clinical proof of concept and approval. A prominent advancement is the utilization of proteolysis-targeting chimeras (PROTACs), which facilitate the formation of a ternary complex with an E3 ligase and the target, resulting in its ubiquitination and subsequent degradation by the proteasome. This catalytic mechanism allows for deeper therapeutic responses and addresses scaffolding functions, significantly extending the addressable target space in oncology. However, the bifunctional nature of PROTACs often results in large molecules that exceed the rule of five, presenting considerable challenges in their optimization and formulation.

Another modality that has seen significant progress is antibody-drug conjugates (ADCs). These bifunctional molecules leverage the molecular recognition of an antigen by an antibody to deliver a cytotoxic payload to target cells. Beyond established tubulin and topoisomerase I inhibitors, novel payload classes are now being explored. The primary challenges for medicinal chemists lie in optimizing payload activity, linker attachment, stability, and cleavage, often resulting in complex molecular entities for conjugation to antibodies.

This presentation will showcase recent examples of the discovery of small molecules, PROTACs, and ADCs in the field of oncology.

Biographies & Abstracts of the Speakers

Invited speakers

Prof. Dr. Necla Birgül Iyison

Boğaziçi University, Istanbul, Turkey

Prof. Dr. Necla Birgül-Iyison completed her B.Sc. in Biology at the University of Trakya. She earned her M.Sc. in Molecular Biology from the University of Hamburg and successfully defended her Ph.D. at the University of Hamburg's Institut für Zellbiochemie und klinische Neurobiologie. Prof. Dr. Necla Birgül-Iyison holds an Associated Professor position at Boğaziçi University's Dept. of Molecular Biology and Genetics, starting in 2024. Previously, she served as an Assistant Professor in the same department. From 2001 to 2004, she worked as an Instructor at Boğaziçi University's Dept. of Molecular Biology and Genetics. In 2001, she was a Postdoctoral Fellow at the University of Cape Town's Dept. of Genetics in South Africa.

Prof. Dr. Necla Birgül-Iyison was awarded an EMBO Short-Term Fellowship in 2003.

She received a Scholarship from the National Research Foundation in Cape Town (NRF) in 2001. She held a Ph.D. Fellowship from the European Union from 2000 to 2001.

From 1997 to 2000, she was a recipient of a Ph.D. Fellowship from the German Research Foundation in Hamburg. Additionally, she received an M.Sc. Scholarship from the University of Hamburg (Auslands-Stipendium) from 1995 to 1996.

OC01

Unlocking the Future: Harnessing GPCRs for Revolutionary Pesticide Innovations

Prof. Dr. Necla Birgül Ilyson

Boğaziçi University, Department of Molecular Biology and Genetics, Istanbul, Turkey
birgul@bogazici.edu.tr

G-protein coupled receptors (GPCRs) are extraordinary integral membrane proteins that play a vital role in various signaling pathways, making them ideal candidates for therapeutic targets. A notable member of this receptor family is the Allatostatin receptor type-C (AstR-C), classified under class A GPCRs, which is essential for regulating Juvenile Hormone (JH) levels in insects. JH is a key factor in influencing insect growth, development, metamorphosis, and reproduction. So far, only the AST-C peptide has been identified as a natural ligand for AstR-C, emphasizing its uniqueness. This specific interaction positions AstR-C as a groundbreaking candidate for the development of new pesticides, particularly against the invasive Pine processionary moth that is causing significant damage to Mediterranean pine forests. Our research aims to initiate a new era in pest control by discovering novel, highly effective agonists for AstR-C, potentially transforming the future of pesticide innovation. Get ready to change pest management strategies with these groundbreaking, effective, and eco-friendly solutions!

Prof. Dr. Umberto Piarulli

University of Insubria, Como, Italy

Umberto Piarulli is Vice-Rector and Full Professor of Organic Chemistry at the University of Insubria, where he has been a faculty member since 1996. He obtained his degree in Chemistry from the University of Milan and earned his PhD in Chemical Sciences from the University of Lausanne in 1996. He also carried out research as a Visiting Scientist at Cold Spring Harbor Laboratory (NY, USA).

His research has long centered on organic synthesis, asymmetric catalysis, and chiral ligand development. His current scientific activity is primarily focused on the development of drug conjugates for tumor therapy, aiming to advance targeted cancer treatments through innovative molecular strategies.

Prof. Dr. Piarulli has coordinated several international research projects, including a Marie Curie Early Stage Research Training program on foldamers. He is the co-author of over 100 publications in high-impact international journals.

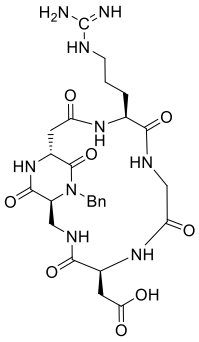
OC02

RGD and *iso*DGR integrin ligands for tumor targeting

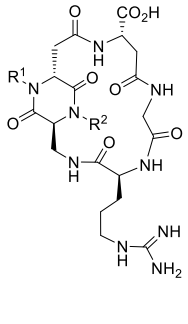
Prof. Dr. Umberto Piarulli[a], and Prof. Dr. Silvia Gazzola[a]

[a] *Università degli Studi dell'Insubria, Dipartimento di Scienza e Alta Tecnologia, Como, Italy*
umberto.piarulli@uninsubria.it

The importance and specificity of protein associations in cellular events and in the etiology of many pathologic processes, raised interest in protein-protein interactions as attractive targets for therapeutic intervention. In cancer, several cell surface protein receptors, such as $\alpha_v\beta_3$, $\alpha_v\beta_5$ and $\alpha_5\beta_1$ integrins, are considered specific molecular indicators of tumor angiogenesis, progression and metastasis. We have recently investigated the synthesis and biological properties of a new class of cyclic peptidomimetics containing a bifunctional diketopiperazine (DKP) scaffold and the tripeptide sequence Arg-Gly-Asp (RGD) or *iso*Asp-Gly-Arg (*iso*DGR), as low nanomolar integrin ligands. Spectroscopic and computational studies of the interaction of *cyclo*[DKP-RGD] ligands with intact cancer cells allowed the determination of the binding epitope and the bioactive conformation of these ligands, whereas cellular activity investigation of *Cyclo*[DKP-RGD] and *Cyclo*[DKP-*iso*DGR] ligands showed effective inhibition of angiogenesis and integrin antagonist activity.



***cyclo*[DKP-RGD]**



***cyclo*[DKP-*iso*DGR]**

These ligands were conveniently conjugated to different cytotoxic payloads: Paclitaxel, α-Amanitin, Daunorubicin and Monomethylauristatin E and F and more recently to MDM2 inhibitors for the reactivation of p53 protein. Different linkers were inserted in the conjugates, including lysosomally-cleavable peptide sequences, for the selective release of the drug as well as cell-penetrating peptides to help the internalization of the constructs. Selective *in-vitro* targeting could be demonstrated comparing the activity of the conjugates in cell lines displaying different expression of integrin receptors.

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Dr. Jokin Carrillo Arregui

CIMA Universidad de Navarra, Spain

Dr. Jokin Carrillo is Director of Drug Discovery and Medicinal Chemist at CIMA Universidad de Navarra, with a strong focus on translational drug discovery. His work spans neuroscience, immune-oncology, and solid tumors, advancing both small molecules and biologics from early discovery to clinical stages. His scientific interests include small-molecule therapeutics, new discovery modalities such as PROTACs and molecular glues, as well as biologic approaches including ADCs.

OC03

Design and development of Targeted Protein Degraders against epigenetic factors in Multiple Myeloma

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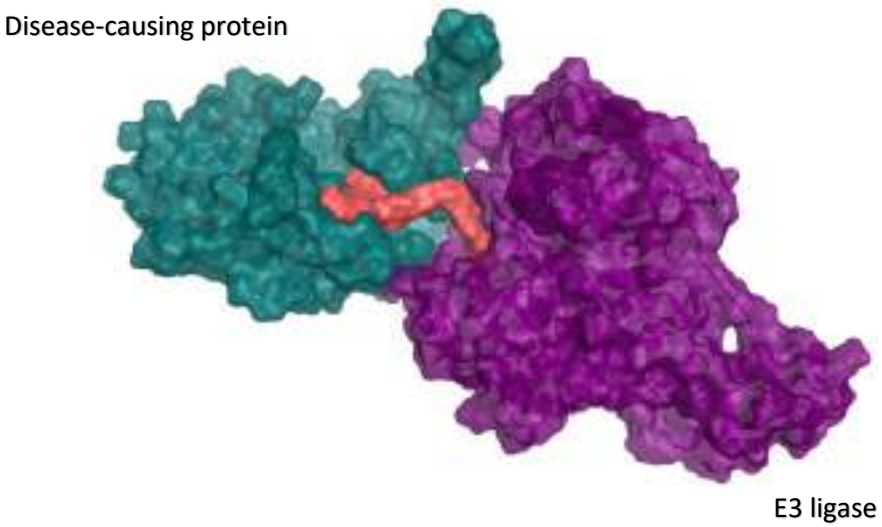
Targeted protein degradation (TPD) is emerging as a transformative approach in oncology, offering the ability to completely remove disease-driving proteins rather than partially block their activity. This is particularly relevant in multiple myeloma, where epigenetic regulators play central roles but remain difficult to modulate with classical inhibitors.

We initiated our work with the discovery of a dual inhibitor showing moderate activity in cellular models. While this compound validated the protein of interest as druggable, its limited efficacy led us to convert it into a proteolysis-targeting chimera (PROTAC). By shifting from inhibition to degradation, we aimed to leverage the ubiquitin–proteasome system to eliminate the protein and abolish all its functions.

To guide this process, we established a TPD workflow platform combining computational and experimental steps. Molecular docking of the inhibitor with the protein of interest identified suitable exit vectors for linker design. Virtual libraries of degraders were then generated with varying linkers and E3 ligase binders, followed by ternary complex simulations to predict affinity and stability. This computational prioritization allowed us to focus synthesis on the most promising candidates, increasing efficiency and reducing cost.

Synthesized compounds were evaluated in biochemical and cellular assays, with selected degraders showing effective protein depletion and improved activity in MM1.S multiple myeloma cells compared to the parent inhibitor. Beyond this case study, the platform has been applied to additional targets, underscoring its value for accelerating the discovery of next-generation therapeutics.



Prof. Dr. Michail Christodoulou

University of Milan, Italy

Michail Christodoulou was from 2021 an Assistant Professor and from 2024 an Associate Professor of Organic Chemistry in the Department of Food, Environmental and Nutritional Sciences of the University of Milan working on the synthesis of natural and synthetic compounds with antitumor, antifungal or antibacterial activity and in the development of novel green and sustainable enzymatic reactions.

Prof. Christodoulou received his BSc and MS from the Chemistry Department of the University of Patras, Greece, followed by a PhD in Medicinal Chemistry from the General Department of the Agricultural University of Athens, Greece, in 2010 with a thesis on the synthesis of novel bioactive molecules and evaluation of their biological activity. From 2011 till 2015 he worked as a postdoctoral researcher at the University of Milan, Italy, on the design and synthesis of natural and synthetic compounds focusing on different biological targets such as Cancer Stem Cells, the Glycocorticoid Receptor, Topoisomerase I and II, Sirtuins and Microtubules. From 2015 till 2017 he continued his research as a Post-Doctoral researcher at the University of Modena and Reggio Emilia, Italy, where he worked on the AIRC IG15993 project entitled: “Design and development of CDK2 and EGFR type III allosteric inhibitors as anticancer drugs”. From 2017 till 2020 he was an Assistant Professor at the Department of Pharmaceutical Sciences of the University of Milan working on the development of metal-catalysed and metal-free domino reactions and for the synthesis of novel compounds with anticancer activity.

Prof. Christodoulou is author of 75 publications on international peer-reviewed journals and has presented his work at various international conferences in the field of cancer research. He is an active participant in the COST Actions: CA21145 “European Network for diagnosis and treatment of antibiotic-resistant bacterial infections (EURESTOP)”, CA21130 “P2X receptors as a therapeutic opportunity (PRESTO)” and CA22103 “A COMPREHENSIVE NETWORK AGAINST BRAIN CANCER (Net4Brain)”.

OC04

Targeting ferroptosis in *Pyricularia oryzae* by natural and nature-inspired siderophores

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Rice *(Oryza sativa L.)* is the major staple food for more than 50% of world's population. The rice-blast fungus, *Pyricularia oryzae*, represents a major threat to global rice production, between 20% and 40% yield annual losses, causing a significant economic damage. The management of the rice blast disease requires a massive application of fungicides, which accounts for more than 8% of total fungicide market.[1]

Diverse classes of fungicides, during the years, have been used against *P. oryzae*,[2,3] including strobilurins and demethylation inhibitors (DMI).[4] Both classes of antifungal compounds have a single-site mode of action and the fungal pathogen populations developed resistance to them. For this reason, the identification of new targets and the discovery of new scaffolds to combat the pathogen is urgently needed. Ferroptosis was recently described as a new form of a regulated, iron-dependent cell death, which plays a key role also during *P. oryzae* infection.[5] Ferroptosis, in *P. oryzae*, starts from the terminal conidial cell, and then progresses to the other two cells during the appressorium formation and maturation, and this ferroptotic cell death is required for the infection. Herein, we present the synthesis and biological evaluation of natural (Figure 1) and nature-inspired iron chelators (siderophores), containing the catecholamide moiety, as potential inhibitors of ferroptosis in *P. oryzae*.

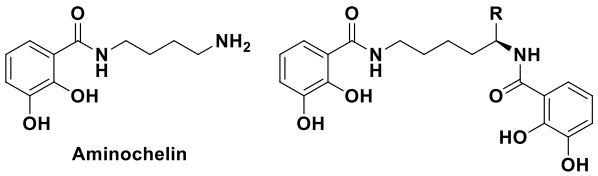

Figure 1. Natural siderophores.

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Dr. Jean-Philippe Combier

CNRS - Le Centre national de la recherche scientifique, France

Jean-Philippe Combier is a molecular biologist specialist of microRNAs and peptides. He has identified different classes of new peptides, including miPEPs: they are peptides encoded by primary transcirpts of microRNAs and they regulate their expression. This led to the creation of the company Micropep Technologies, which has raised around 60M€ and which aims to identify peptides for agronomy.

OC05

Peptides as a credible alternative for crop protection?

Dr. Jean-Philippe Combier

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Use of chemicals in agronomy encounter more and more issues, due to their toxicity against human health and environment. Solving these toxicity problems by keeping sufficient productivity is a huge challenge for the next years. Among the different potential solutions, peptides might be an interesting and promising alternative. Peptides are short polymers of natural aminoacids, present in all living organisms. Whereas several peptides have already been identified for a while, like insulin, the quantity of peptides per organism is largely underestimated, and may comprise several thousand s of peptides per organisms. Among them we identified miPEPs as peptides encoded by primary transcripts of microRNAs, in plants and animals. We spent the last years to evaluate the potential of peptides in agronomy, to increase resistance of plants to different stresses. In parallel, we identified different new classes of peptides, like complementary peptides or anti-fungal peptides.

Prof. Dr. Elena Baraldi

University of Bologna, Italy

Elena Baraldi holds a degree in Agricultural Sciences from the University of Bologna and a PhD in Molecular Biology from EMBL in Heidelberg, Germany. She is currently an Associate Professor in the Department of Agricultural and Food Sciences (DISTAL) at the University of Bologna, specializing in Plant Pathology. She teaches several courses in both undergraduate and graduate programs and is responsible for the Biotechnology and Plant Pathology Laboratory.

Her research focuses on the discovery of new molecules and the development of innovative strategies for plant disease control. One of the main goals of her laboratory is the development of RNAi-based strategies, including the design, production, and testing of double-stranded RNA (dsRNA) for controlling major plant pathogens. The mechanism of action and effectiveness of these molecules are also studied using molecular and cellular biology techniques.

The laboratory is also involved in developing endogenous RNAi strategies, aiming to create plants capable of producing dsRNA against fungal pathogens and insect vectors of phytoplasmas. She is the author of 85 indexed publications and has an H-index of 26.

OC06

RNAi vs. crop protection chaos: the molecular twist to address sticky cases

Prof. Dr. Elena Baraldi

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The management of crop diseases is a challenging task today, since along with the recent Eu legislative restrictions for pesticide usage, new and unexpected diseases are emerging due to climate change and trade globalization causing dramatic production losses. Therefore, much research nowadays is dedicated to find solutions to control pests and pathogens, decrease the pesticides usage and guarantee provision of safe and sufficient crop products.

RNA interference-based strategy is a promising alternative to toxic agrochemicals. This strategy has been applied efficiently to control different diseases, particularly those caused by fungal pathogens. This strategy exploits a natural molecular process necessary to regulate gene expression in eukaryotic cells, called RNA interference, (RNAi) and is based on the application of double strand RNA (dsRNA) molecules targeting important genes of pathogens, thus limiting their growth.

dsRNAs are not toxic, are very specific and easily degradable to simple natural components, but, besides some important gaps that need to be fulfilled to apply RNAi in field, not all pathogens seem sensitive to this approach. In my talk I will briefly explain the mechanism of RNAi, and report on ‘smooth’ and ‘sticky cases’ making life difficult for labs committed to RNAi research for crop protection.

Prof. Dr. Francesco Pennacchio

University of Naples, Italy

Francesco Pennacchio is Full Professor of Entomology at the University of Napoli Federico II (Italy) and Visiting Professor at Newcastle University (UK). In 1989 he received a PhD in Entomology at the University of Napoli Federico II, and, from 1989 to 1991, he was research associate at the Department of Entomology, Texas A&M University, College Station, TX, USA. The study of the molecular physiology of insect multitrophic interactions is at the core of his research interests, along with biotechnologies for insect control that can be developed based on this knowledge.

His work particularly focuses on insect immunity and immunosuppression strategies by parasites and pathogens, and on how environmental stress can alter insect immunocompetence. In 2014 he was awarded the Cozzarelli Prize, by the National Academy of Sciences of USA.

He currently serves as President of the Italian National Academy of Entomology, from 2012 to 2021 was President of the Italian Entomological Society, in 2024 was nominated member of the Accademia dei Georgofili.

He is member of the Council for International Congresses of Entomology and of the Praesidium of the European Congresses of Entomology. In 2022, he was elected EMBO member in recognition of outstanding contributions to life science research. He currently serves as scientific coordinator of Spoke 2 (Reduction of Pesticide Use in Agriculture), AGRITECH - National Center for Technology in Agriculture.

OC07

Plant Molecular Bioprotection

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Recent research aims to develop new, highly specific biopesticides and control strategies to reduce synthetic pesticide use in agriculture. This can be achieved by studying the molecular mechanisms of multitrophic interactions among plants, insects, and their natural enemies, including the role of associated microbiota.
The balance of energy flow in food webs is regulated by interkingdom competitions that span across different trophic levels, from the soil to aboveground communities. These interactions drive co-evolutionary arms races, continuously shaping the virulence factors of pests and the defense barriers of their hosts.
A detailed functional analysis of the factors that modulate these interactions allows for the development of bioinspired control tools that mimic natural pest suppression mechanisms. This research also provides insights for defining protection strategies for beneficial insect species and the ecosystem services they provide.
This presentation highlights recent advances in this field, focusing on new mechanisms that regulate trophic interactions in food webs and how to use this information to develop bioinspired plant protection tools.

Dr. Sebastian Klie

Targenomix GmBH

OC08

Target-centric crop protection: a digital DMTA framework pairing public plant data with proprietary evidence

Dr. Sebastian Klie

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This talk presents a target-centric discovery strategy for crop protection built on a digital DMTA operating model for early discovery. We show how Machine Learning & AI fuse public plant knowledge (structures, omics, annotations) with proprietary screening and assay evidence to accelerate early cycles, improve translation to plant efficacy, and deliver multiple starting chemotypes with plant-relevant signals. The framework is modular and collaborative, aiming to bridge medicinal and crop protection chemistry with reproducible, data-to-decision workflows.

Prof. Dr. Marta De Zotti

University of Padua, Italy

Marta De Zotti is an associate professor in Organic Chemistry at the Department of Chemistry of the University of Padova (Italy). She coauthored more than 100 publications in peer-review journals, and four EU patents on biorationally-designed peptides as ecofriendly plant-protection products, a technology that won the first prize at the Intellectual Property Award 2021 - Agrotech sector (Expo2021 Dubai).

Aib-containing peptides as plant protection products

Prof. Dr. Marta De Zotti[a], Luca Sella[b], Chiara Dalla Torre[a], Francesco Favaron[b], Silvia Tundo[b], Rita Musetti[b], Laura Morbiato[a]

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Plant diseases are essentially controlled in the field with the use of copper-based products and antibiotics, raising environmental and safety concerns. Trichogin GA IV, a non-ribosomal, 11-residue long peptide naturally produced by the fungus *Trichoderma longibrachiatum* has the ability to perturb membrane integrity and permeability, thanks to its well-defined helical conformation stabilized by the presence of three Aib (α-aminoisobutyric acid) residues in its sequence. Recently, trichogin analogs modified at the level of specific residues were designed to be water-soluble and active against plant pathogens[1]. Here, we report on the role of glycine-to-lysine substitutions and of the presence of a C-terminal leucine amide on bioactivity against a variety of fungal and bacterial phytopathogens, affecting a wide range of crops worldwide, including tomato and kiwifruit. Our results show that trichogin GA IV analogs containing two or three Gly-to-Lys substitutions are highly effective *in vitro*, displaying minimal inhibitory and minimal bactericidal concentrations in the low micromolar range. Some lysine-containing analogs were able to significantly reduce bacterial titers and symptom development in infected plants. Our results point to a positive correlation between the number of lysine substitutions and the antimicrobial activity. This correlation was supported by microscopy analyses performed with mono-, di- and tri-Lys containing analogs that showed a different degree of interaction with microbial cells and ultrastructural changes that culminated in cell lysis (Figure 1).[2]

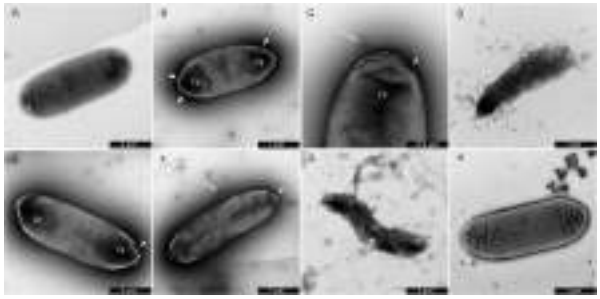

Figure 1. Representative transmission electron microscopy micrographs of *Pseudomonas syringae* pv. *tomato* (Pst) co-incubated with trichogin GA IV analogs. Untreated Pst cell (A), Pst cell co-incubated 2 h with the analogs K2,5,9 (B, C and D), K5,6 (E, F and G) or K6 (H) at the concentration of 10 μM.

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Dr. Sarah Mazzotta

University of Milan, Italy

Sarah Mazzotta received her Master's degree from the University of Calabria in 2016 and she obtained her PhD at University of Seville (2020). Her PhD research activity was focused on the design and synthesis of novel antimicrobial small molecules, especially against adenovirus infections. She was also involved in the preparation of new bioactive compounds from natural sources. In 2020, she started her postdoctoral fellowship at the University of Milan working on the generation of novel glycomimetics as bacterial lectin ligands useful in antimicrobial anti-adhesion therapy. Since 2023 she is an organic chemistry researcher at the same university.

Enhancing Bacterial Lectin Affinity with Reversible Covalent Ligands

Dr. Sarah Mazzotta

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The opportunistic Gram-negative pathogen *Burkholderia cenocepacia* is a globally spread multidrug-resistant bacterium that causes deadly lung infections in immunocompromised or cystic fibrosis patients.[1] It employs lectins, i.e. carbohydrate-binding proteins, as virulence factors to target host tissues through recognition of and adhesion to the glycoconjugates on the host cells' surface. The inhibition of these glycoconjugates-lectin interactions is being explored as an efficient approach to anti-adhesion therapy (AAT), which could be an alternative strategy to prevent and treat bacterial infections.[2] Among the *B. cenocepacia's* lectins, the superlectin BC2L-C has been proposed as a major player in the adhesion process; in particular, its N-terminal fucose-binding domain (BC2L-C-Nt) represents an interesting target to design new antimicrobials for AAT. In this context, our aim consists of developing a new generation of glycomimetics targeting BC2L-C-Nt, to improve the sub-millimolar affinity with the target lectin displayed by the first-generation synthetic ligands.[3,4] The analysis of the fucose binding region in the BC2L-C-Nt domain identified the nucleophilic amino acid residues Cys72 and Lys108 as potential targets to develop covalent ligands. Hence, new glycomimetics were designed through *in silico* studies, connecting a L-fucose scaffold through a linker to a spacer bearing an electrophilic warhead able to react with one of these residues (Figure 1). The most interesting candidates were synthetized through a convergent strategy and subjected to biophysical techniques, such as thermal shift assays (TSA), surface plasmon resonance (SPR), mass spectrometry and X-ray crystallography.[5]

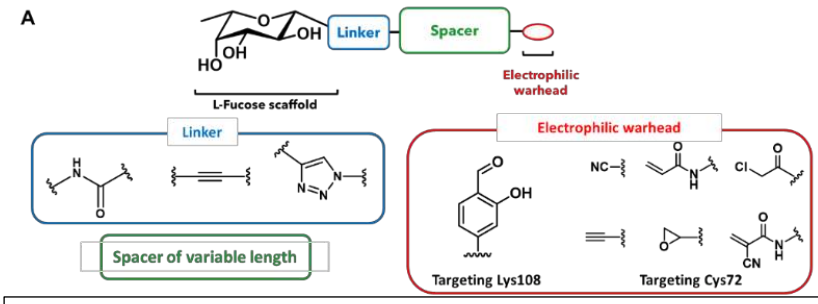

Figure 1. General structure of putative covalent glycomimetics (A) and examples of poses obtained from standard and covalent docking (B).

Reversible covalent ligands targeting Lys108 provided IC_{50} values in the micro-molar range, displaying an improvement in the binding of about two orders of magnitude compared to non-covalent control ligands (millimolar affinity). Cys-targeting irreversible covalent ligands yielded worse affinities in the sub-millimolar range. In summary, the successful development of reversible covalent glycomimetics selectively engaging Lys108 highlights lysine residues as viable and promising targets within BC2L-C-Nt lectin. Future work will aim at exploring novel electrophilic motifs and identify suitable candidates for *in vitro* cellular assays.

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Prof. Dr. Dan Bebber

University of Exeter, United Kingdom

Dan Bebber obtained his PhD in Tropical Ecology at the University of Oxford, studying the effect of El Nino-related drought and insect herbivores on tree regeneration in Sabah, Malaysia. He then moved to the Faculty of Forestry, University of Toronto to take up a post-doctoral position in forest regeneration in Ontario, followed by a research into the role of fungi in forest nutrient dynamics at the Department of Plant Sciences, University of Oxford. In 2007 he joined the environmental NGO Earthwatch, based in Oxford, as Head of Climate Change Research, managing an international citizen science research programme into forest carbon dynamics. He joined Exeter in 2013, studying the global distributions of crop pests and pathogens and the impacts of climate change on crop production. He is particularly interested in abiotic and biotic threats to tropical crops like coffee and banana, and works closely with the organization CABI on pest and pathogen impacts. He was Chair of the British Mycological Society's Fungal Biology Research Committee, is co-Technical Director of CABI's Global Burden of Crop Loss initiative, and a member of the BBSRC Sustainable Agriculture and Food Panel.

OC11

Climate change impacts on crop pests and pathogens

Prof. Dr. Dan Bebber

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Climate change is reshaping the ecology of crop pests and pathogens, with major implications for food security worldwide. Rising temperatures, altered precipitation patterns, and elevated atmospheric CO_2 directly influence the abundance, distribution and impacts of insect pests and microbial pathogens, while land use intensification and globalised trade accelerate their spread. Recent research shows that insect pests generally benefit from warming, with expanded ranges into higher latitudes and elevations, earlier seasonal activity, and additional generations per year. For staple crops, warming of 2 °C could increase yield losses from pests by 46% in wheat, 19% in rice, and 31% in maize. Drought and water stress further exacerbate damage, as weakened host plants and reduced natural enemy activity create favourable conditions for pest feeding, though prolonged severe drought or extreme heat can suppress some populations. Conversely, excess rainfall can wash away small insects but often prolongs host plant availability and reduces climatic stress, favouring pest persistence.

Pathogens, particularly fungi and oomycetes, also exhibit climate-driven responses. Observational studies identify temperature as the dominant driver of disease prevalence, with soilborne pathogens increasing in relative abundance under warming. Process-based models project poleward shifts in infection risk, mirroring host crop yield changes, and suggest that disease could negate any potential yield benefits at higher latitudes. Controlled experiments reveal that elevated CO_2 can enhance pathogen impact, potentially by altering host physiology and immunity. Emerging evidence also shows that pathogen assemblages and outbreak risks are strongly influenced by climatic variability, with recent decades marked by rising incidence of severe epidemics across multiple crops.

Beyond climate, agricultural intensification through irrigation, fertilisation and greenhouse cultivation, provides high-quality, buffered host environments that favour pest and pathogen proliferation, while landscape simplification reduces natural biological control. Global trade has amplified biological invasions, with invasive species causing more than US$400 billion in annual losses. Together, these interacting drivers create complex, regionally variable outcomes: temperate and migratory pests are expected to thrive under warming, whereas some tropical species may face thermal limits. Soil pathogens and pests often gain resilience through buffering microclimates.

Overall, climate change is intensifying pressures from both pests and pathogens, threatening to offset advances in crop productivity. Effective responses will require integrated monitoring, predictive modelling, and climate-smart management strategies that harness biodiversity, strengthen biological control, and reduce dependence on pesticides. Addressing these challenges is critical to securing sustainable food production in a rapidly changing world.

Poster Abstracts

P01

Microbial chitinases as biocontrol agents for lepidopteran pests

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The widespread use of synthetic pesticides has raised serious concerns due to their toxic impact on the environment and human health. Consequently, researchers are increasingly exploring sustainable alternatives for crop protection. Among them, the biocontrol, *i.e.,* using natural antagonists or the active molecules they produce to control plant pathogens and insect pests with minimal harm for the environment, shows great promise. In this context, our collaborative research has focussed on chitinases as innovative candidates for the development of integrated pest management (IPM) strategies. Chitinases are enzymes that break down chitin -a polysaccharide that is absent in plants and mammals, but plays essential structural roles in insect pests, phytopathogen fungi, and parasitic nematodes-, thus representing ideal candidates for targeted pest control [1]. Over the past years, we have evaluated the biocontrol potential of both commercial [2] and *in-house* produced bacterial [3] and fungal [4] chitinases, using various *in vitro* and *in vivo* approaches against different lepidopteran species, including the lepidopteran model *Bombyx mori* [2-4] and the insect pest *Spodoptera littoralis* [4]. Our results show the capacity of these hydrolytic enzymes to compromise *in vitro* the structure, permeability, and integrity of the insect peritrophic matrix [2-4] and, when orally administered, to impair larval growth and development, ultimately leading to their death [2-4]. Moreover, larval mortality could be increased when chitinases are co-administered together with *Bacillus thuringiensis* (Bt) toxins [4], thus further highlighting their potential to enhance existing IPM tools.

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P02

What's in Cow Dung Manure? Insights into Its Potential for Supporting Plant Defense System

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Solanum lycopersicum, a prominent vegetable crop, suffers major yield losses from early blight disease driven by *Alternaria solani*. Sustainable alternatives to conventional chemical fungicides are urgently needed to mitigate these losses while minimizing environmental impact. This study investigates the application of the microbial consortium derived from Gir cow dung for enhancing tomato resistance against early blight. Metagenomic analysis of Gir cow dung revealed a rich diversity of beneficial microbes, with Bacillus species being one of the prominent. Three key strains *Bacillus subtilis, Bacillus tequilensis*, and *Bacillus licheniformis* were isolated, characterized, and tested for their antagonistic activity against *A. solani*. The microbial consortium exhibited significant antifungal properties, and the application of the consortium on tomato plants led to a marked reduction in disease progression. Histochemical analyses of treated plants revealed a pronounced increase of hydrogen peroxide, phenolic compounds, and superoxide dismutase, suggesting enhanced activation of plant defense pathways. Comparative gene expression profiling showed the upregulation of key defense-related genes, including PR2b, Chi3, and Pto kinase, in Bo-treated plants, indicating a systemic activation of host defense mechanisms.

P03

Identification of the Allosteric Binding Sites and Ligands of AstR-C of *Thaumetopoea pityocampa*

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Allosteric binding sites on receptors are distinct from orthosteric sites and play a crucial role in modulating the binding and signaling properties of orthosteric sites and their ligands. Allosteric compounds allow for precise regulation of signaling and reduce the risk of overdose; they are generally considered more specific because they bind to sites that are structurally less conserved. Insect G protein-coupled receptors (GPCRs) are promising targets for the development of pest control agents, as many of these receptors control various physiological functions in insects. The C-type Allatostatin Receptor (AstR-C), which belongs to Class A GPCRs, regulates the synthesis of Juvenile Hormone, making it a potential target for pesticides. *Thaumetopoea pityocampa* (T. pit), a well known pest in Mediterranean countries, causes significant damage to pine forests in the region. In our previous study, we identified novel agonists of the AstR-C in T. pit through a comprehensive approach that included homology modeling, virtual screening, molecular dynamics simulations, chemical synthesis, and in vitro/in vivo assays. Building on this established method, the current project aims to develop a safer pesticide with practical functionality by utilizing both in silico and in vitro techniques to identify the allosteric binding pockets and ligands of AstR-C using advanced computational and experimental methods. To locate the allosteric binding sites, we employed several site discovery tools, including AlloSite, PARS, MDpocket, SiteMap, and blind docking methods with Glide and AutoDock Vina. Virtual screening with Glide focused on three potential sites, and the resulting hit molecules underwent molecular dynamics (MD) simulations with Desmond, followed by MM-GBSA analysis using Prime (Schrödinger, Inc.). Ultimately, six compounds—two from each binding site—showed promising results and will be further tested through in vitro and in vivo studies.

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P04

Investigating the Effects of a New Mutation on RyR of *Phthorimaea absoluta* (Lepidoptera: Gelechiidae) on Resistance to Diamide Insecticides

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The tomato leafminer, *Phthorimaea absoluta* Meyrick, 1917 (previously known as *Tuta absoluta*), is a major threat to tomato production worldwide[1]. Diamide insecticides like chlorantraniliprole and flubendiamide target the ryanodine receptor (RyR), keeping it in an open state and disturbing calcium balance[2]. To identify the cause of emerging resistance to current insecticides, we analyze an experimentally identified but uncharacterized I4746K mutation. This study seeks to understand how this mutation affects the RyR structure in response to existing compounds. We created homology models of the *P. absoluta* RyR in open and closed forms using PDB entries 7U9Q, 8DTY, 8DTZ, and 5G09 for the closed state, and 9C1F for the open state[3]. The mutation was introduced in-silico, followed by 100-ns MD simulations for both wild-type and mutant channels. We selected representative conformers from the sampling and clustering process for molecular docking, then conducted an additional 100-ns MD simulations to examine how mutations affect the stability of diamide binding[4,5]. We analyzed important conformational metrics—overall RMSD, per-chain RMSF, and DSSP profiles. Initial results indicate that the I4746K mutation in the open-state model obstructs ligand access to the RyR binding pocket.

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P05

TYMIRIUM® technology: the discovery of Cyclobutrifluram

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Plant-parasitic nematodes pose a significant threat to global agriculture, causing substantial yield losses across major crops. Traditional control methods face increasing restrictions due to environmental and toxicological concerns, creating an urgent need for innovative solutions that combine high efficacy with improved safety profiles. TYMIRIUM® technology, featuring the active ingredient Cyclobutrifluram (a chiral phenyl-cyclobutyl-pyridineamide), was developed as a novel crop protection solution offering dual nematicide and fungicide activity. We outline the discovery journey of its active ingredient, highlighting key decision points in hit identification, lead exploration, and lead optimization phases. The establishment of the nematicide screening platform together with the generation of a focused nematicide screening library was key to identifying high quality hits. Early characterization of the mode of action for the most promising hit series enabled the development of an *in vitro* assay and homology models, establishing a comprehensive toolbox for SAR analysis and structure-based molecular design. These combined efforts led to the discovery of TYMIRIUM® technology at Syngenta which obtained its first registrations in 2022.

P06

Spotlight on New Pesticides: Targeting Allatostatin-A Receptors in *Aedes albopictus*

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Aedes albopictus, also known as the Asian tiger mosquito, is an effective carrier of various arboviruses, including dengue, chikungunya, yellow fever, and Zika, posing major global health risks. Traditional pesticides are increasingly met with resistance and environmental issues, highlighting the need for new vector control methods. G protein-coupled receptors (GPCRs), especially allatostatin-A receptors (AlstR-A), are promising targets for next generation pesticides because of their vital roles in mosquito physiology, including the control of juvenile hormone and feeding behavior. We developed a comprehensive computational pipeline that integrates molecular docking, ADMET prediction, and pesticide-specific optimization. Virtual screening using AutoDock Vina was conducted on targeted peptidomimetic libraries (65,638 compounds) and ChemDiv libraries (68,970 compounds) against the *Aedes albopictus* AlstR-A model derived from AlphaFold3, resulting in a total of 134,608 validated molecular structures. Our approach included pesticide-specific parameters: cuticle penetration properties, species selectivity optimization, environmental safety evaluation, and insecticidal efficacy prediction. Through thorough screening, 500 top candidates were identified using advanced scoring algorithms that combined binding affinity, human safety, and environmental compatibility. Results showed excellent binding affinities (ranging from -12.431 to -5.017 kcal/mol), with 75.3% achieving strong binding (≤-8.0 kcal/mol). The best compound (chemdiv_gpcr_48834) showed an excellent pesticide score (0.9164), strong binding (-11.828 kcal/mol), ideal human safety (1.000), and great environmental compatibility (0.700). The analysis achieved a 96.2% filter efficiency with a mean human safety score of 0.956. This is the most comprehensive systematic analysis of allatostatin-A receptor-targeted pesticides, creating a solid pipeline for species-specific vector control agents ready for testing.

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P07

Target-Based Design and Hit to Lead Optimization of Pyrimidinyl-pyrazole Insecticides

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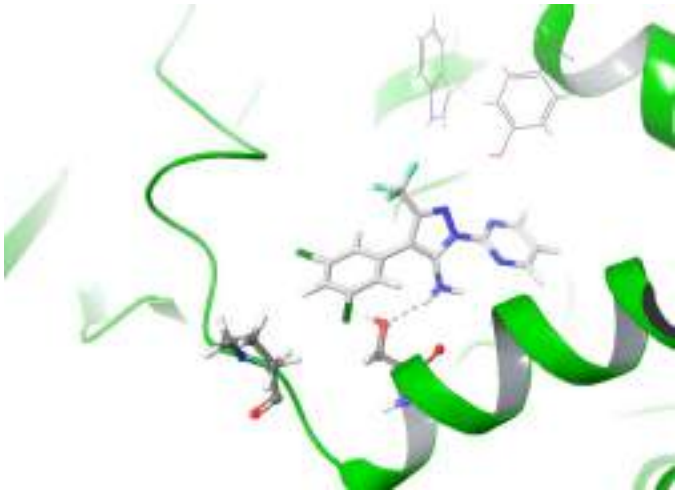
The urgent need for selective, effective, and environmentally sustainable crop protection solutions remains paramount in addressing global pest control challenges. Arthropod pests, particularly insects, cause significant damage to global agriculture, with current worldwide yield losses ranging from 17-30% on major food crops[1]- a figure projected to increase under warming climate conditions[2]. These substantial yield reductions threaten food security, farmer livelihoods, and agricultural sustainability across the globe.

This presentation outlines our exploration of novel insecticides, beginning with pyrimidinyl-pyrazoles identified in patent literature[3] as promising chemical scaffolds. Our research journey will be outlined, from initial hit discovery through lead optimization, encompassing mode of action elucidation, development of specialized tools and capabilities for target-based design, structure-activity relationship studies informing our working hypothesis of ligand-target binding interactions, and strategic alignment of compound optimization with commercial target product profiles - the essential features a product must possess for market viability.



This case study illustrates how modern insecticide discovery integrates multiple scientific disciplines to address the complex challenges of sustainable crop protection.

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P08

Insights into the antibiofilm activity of inorganic nanoparticles functionalized with natural compound derivatives

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Biofilms colonize moisty surfaces, including living tissues, medical devices, water supply systems and food processing equipment, leading to health risks and financial burdens. To address these issues, particularly in light of rising antimicrobial resistance, research is focusing on innovative strategies to either induce biofilm dispersal or prevent its initial formation. In this context, we considered novel antimicrobial-free strategies using compounds acting at sub-lethal concentrations. Based on our previous studies[1], we explored the functionalization of silica nanoparticles with natural compounds, *i.e.*, *p*-amino salicylic acid and *p*-amino cinnamic acid, which had shown anti-biofilm properties. The aim was to develop novel nanoparticles for surface coating, addressing the limitations of current antifouling layers, particularly their short-lived protection and the risk of selecting resistant strains. Following their preparation and analytical characterization, the functionalized nanoparticles were deposited onto glass coverslips as model surfaces via the spin-coating technique. The anti-biofilm properties of the new materials were preliminarily tested toward *Pseudomonas aeruginosa* biofilm. Our results highlighted that some of them prevented biofilm development by modulating bacterial physiology (enhancing bacterial metabolic activity, total protein amount, and oxidative stress) without killing the bacteria[2]. Given their versatility, these functionalized nanoparticles represent promising candidates for the development of novel antibiofilm interfaces.

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P09

Disarming *Mycobacteria*: Salicylate Synthase as an Anti-Virulence Target

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Despite global efforts to advance therapeutic strategies, tuberculosis (TB) remains one of the leading causes of death from a single infectious agent [1]. The emergence of multidrug-resistant *M. tuberculosis* (*Mtb*) strains underscores the pressing need for effective treatment options, with innovative mechanisms of action.

In recent years, our research has focused on developing anti-virulence agents targeting the salicylate synthase (MbtI) from *Mtb*, a key enzyme in the biosynthesis of iron-scavenging mycobactins, crucial virulence factors produced during infection [2]. Notably, MbtI is absent in human cells, making it an attractive and selective therapeutic target [2].

Through structure-guided design, supported by co-crystal structures of MbtI with lead inhibitors, we identified and optimized small molecules with potent enzymatic inhibition and antimycobacterial activity under iron-restricted conditions [3]. To enhance their intracellular delivery, we employed poly(2-(methacryloyloxy)ethyl phosphorylcholine)–poly(2-(diisopropylamino)ethyl methacrylate) (PMPC–PDPA) polymersomes, which exploit scavenger receptor-mediated uptake to selectively target infected macrophages. These nanocarriers effectively deliver their cargo into the cytosol—the intracellular niche where *Mtb* resides—thus improving therapeutic precision and efficacy [4].

Together, these results support a novel anti-virulence strategy for TB therapy and lay the groundwork for further *in vivo* evaluation of targeted MbtI inhibitors.

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P10

The first study on the chemical-controlled release of agrodrugs by plant glycoside hydrolase for crop protection applications

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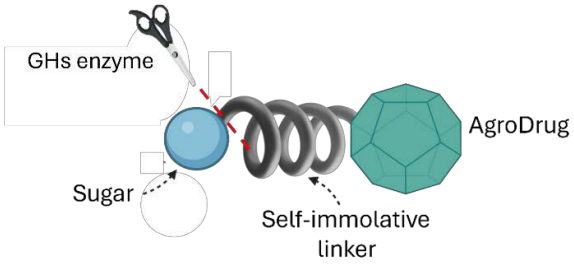
The current demand for safer and more sustainable crop protection tools[1], calls for innovative approaches in agrochemistry. The ligand-targeted drug conjugate approach represents a promising tool to address this challenge by combining principles of agrochemistry and medicinal chemistry; however, it 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 is characterized by a monosaccharide as the cleavable moiety and by the self-immolative spacer, which acts as a bridge between the trigger and the desired molecule, ensuring a controlled and efficient release of the agrodrug. The endogenous activity of glycoside hydrolase (GHs) has been investigated as the triggered stimulus for the cleavage of the linker. After the optimization of the synthesis, the obtained prodrugs were incubated with several plant species, and the plant extracts were analyzed by LC-MS. The results indicated that the agrodrug is efficiently released in the plants by the cleavable prodrugs. Furthermore, to deeply evaluate the release mechanism and its kinetic profile, we also performed *in vitro* assay by incubating the prodrugs with plant extract and then analysing the samples by UHPLC-HRMS. Notably, HRMS analysis of the fragments confirmed the proposed GHs-mediated release of the agrodrug, validating that the degradation is due to a controlled cleavage of the linkers by GHs, and not to an unpredictable metabolic instability.



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Design and synthesis of peptide-based conjugates against *Escherichia coli*: targeting protein-protein interactions as an innovative antimicrobial strategy

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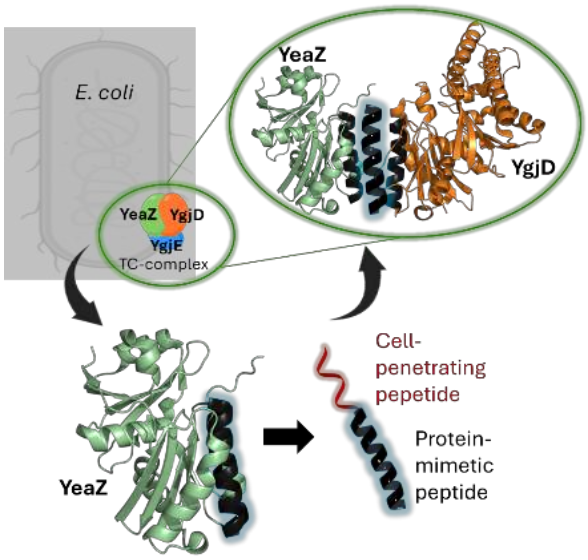
Bacterial Protein-Protein Interactions (PPIs) represent an attractive target to face the urgent challenge of antibiotic resistance. In this context, growing attention has been paid to the threonyl carbamoyl complex YeaZ/YgjD/YjeE, responsible for the t^6A_{37} tRNA universal modification, essential for bacterial survival. Importantly, there are no YeaZ orthologs in eukaryotic cells, suggesting the high selectivity of YeaZ inhibitors. For these reasons YeaZ is a promising target for the development of novel antibacterial agents.[1]

Our research group previously identified and targeted the α2 helical surface domain of *P. aeruginosa*'s YeaZ (*Pa*YeaZ) protein using protein-mimetic peptides (PMPs) conjugated to a Cell-penetrating peptide (CPP) that successfully inhibited the YeaZ dimer formation and bacterial growth.[2] Herein, we present our recent studies on *E. coli*, another of the major human pathogens that can cause a variety of superficial and systematic infections.[3] The functional peptide sequence in *E. coli* YeaZ protein (*Ec*YeaZ) was identified through sequence alignment with the previously identified *Pa*YeaZ sequence, and a small library of *E. coli*-specific CPPs was chosen.[4] The three resulting conjugates were synthesized and fully characterized. The antimicrobial activity was then tested on *E. coli* K12 strain, as well as internalization studies were performed. Our findings indicating that the antimicrobial activity is correlated to the internalization and toxicity of the conjugated CPPs. The *in vitro* evaluation of on EcYeaZ is currently ongoing.



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P12

Medicinal Chemistry and Plant Biology: Optimizing ABA-receptor Agonists for Drought Tolerance in Crops

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Drought is the most destructive force in agriculture, causing annual losses of nearly 40 billion dollars worldwide. The FAO and UN have therefore emphasized the urgent need for innovative strategies to improve crop performance under water-limiting conditions. One effective approach is the activation of abscisic acid (ABA) signaling, which induces stomatal closure and broad physiological adjustments that enhance plant stress tolerance. In this work, we applied a drug discovery approach to identify and optimize small-molecule ABA-receptor agonists for crop protection. A chemical library of 60,000 molecules was screened in vitro, leading to the discovery of novel scaffolds not previously described in scientific or patent literature. Through iterative cycles of structure-guided design, synthesis, and validation, we generated and characterized over 100 new compounds, ultimately defining a chemical series of 10 molecules with enhanced properties. Among them, *Superabactin* emerged as a potent sulfonamide-based agonist with 10-fold higher activity than ABA. *Superabactin* activates ABA signaling in tomato, wheat, and maize, reduces transpiration when applied as a foliar spray, and increases water-use efficiency. Remarkably, a single treatment induces stomatal closure for up to two weeks in maize, conserving soil moisture and improving drought tolerance. These results highlight the potential of medicinal chemistry and chemical biology as powerful tools to develop next-generation biostimulants for sustainable agriculture.

Comparing MDM2 inhibitors in PROTACs: broadening the anchors landscape

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In recent times, proteolysis targeting chimeras (PROTACs) have become a hot topic in medicinal chemistry. Their specific mechanism of action requires the assembly of a ternary complex, mediated by the PROTAC molecule, between the target protein (POI) and a ubiquitin (Ub) E3-ligase. This chemical-induced POI/E3-ligase proximity allows the transfer of Ub units onto the POI surface, labelling it for the proteasomal degradation.[1]
Among the most-established E3 ligases, Mouse Double Minute 2 (MDM2) is of particularly interest. An overexpression of MDM2 in several cancer tissues is documented, resulting in an excessively dysregulated proteasome-dependent degradation of the tumor suppressor protein p53.[2] Considering its central role in tumor development, MDM2 inhibition is a common strategy in cancer treatment research and, despite the lack of FDA-approved drugs, numerous small-molecule inhibitors were designed and developed.[3] Additionally, as demonstrated by Hines *et al.* in the design of a BRD4 bifunctional degrader, MDM2-recruiting PROTACs may display an enhanced biological activity thanks to the synergism of simultaneous POI degradation and reactivation of p53 functions.[4] Despite encouraging results, the applicability of MDM2 inhibitors as E3-ligase recruiters (anchors) in PROTACs has not been extensively explored, with most studies focusing on cis-imidazoline and pyrrolidine-based inhibitors. In this work we explored the applicability of MDM2 inhibitors, which have not been previously exploited as E3 ligase recruiters in PROTACs, to assess their potential as novel anchors.

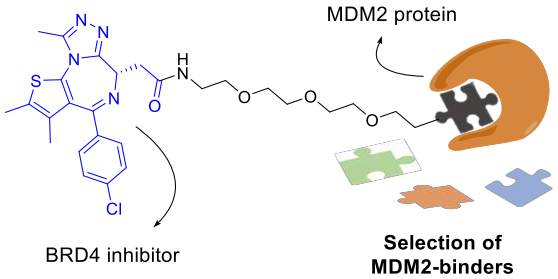

Figure 1. The anchor selection among MDM2 inhibitors is schematically represented

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Design and Synthesis of Carboline-based Small-Molecule Drug Conjugates Targeting $\alpha_5\beta_1$–MDM2 Crosstalk in Glioblastoma

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The p53 protein is a key tumor suppressor involved in genomic stability, cell cycle arrest, and apoptosis. In normal cells it is controlled by its negative regulator mouse double minute 2 (MDM2);[1] however, studies have shown that 94% of glioblastoma (GBM) cell lines exhibit deregulation of the p53-MDM2 pathway that causes suppression of p53 functionalities.[2] Additionally, in GBM the demonstrated overexpression of integrin ligand $\alpha_5\beta_1$ leads to a further suppression of p53 activity through a negative biochemical cross-talk (**Figure 1, a**).[3] Inspired by this discovery, we developed a series of small-molecule drug conjugates[4] (SMDCs) that simultaneously target the overexpressed MDM2 and the integrin receptor $\alpha_5\beta_1$ (**Figure 1, b**). For the conjugation, we selected the first-in-class p53-independent MDM2 inhibitor – SP-141, as payload[5], which showed promising *in vitro* data. After identifying a site for conjugation, we designed a series of derivatives[6] that were subsequently conjugated to an $\alpha_5\beta_1$ integrin receptor ligand, *cyclo*(phg-*iso*DGR-k).[7] We successfully obtained four SMDCs bearing cleavable or non-cleavable linkers in high purity. The preliminary biological activity profile revealed that the synthesized compounds show moderate reduction in potency. Further biological evaluations are currently underway to gain a deeper understanding of their behavior.

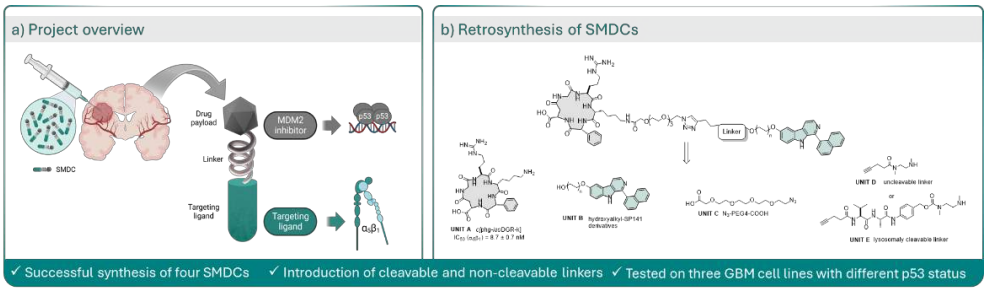

Figure 1. Schematic presentation of the synergistic effect and synthesized SMDC.

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P15

The role of non-conventional peptides extruded by chloroplasts in plant heat stress response

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Non-Conventional Peptides (NCPs) differ from Conventional Peptides (CPs), which are derived from annotated gene regions. NCPs originate from a far wider array of genetic sources, including intergenic/intronic regions, long non-coding RNAs, and pri-miRNAs. Recent discoveries have shown that many NCPs are involved in plant growth and development, however their precise role in mediating plant tolerance to environmental stresses remains poorly explored. The identification of NCPs in crops, including maize and grape, suggests that these molecules may hold significant potential for improving crop agronomic traits. Heat stress (HS) poses a major threat to crop productivity causing widespread cellular damage that results in poor germination, stunted growth, leaf scorching, and critical damage to reproductive processes. The chloroplast, the primary organelle for photosynthesis, acts as a heat sensor detecting thermal damage and initiates a stress response via retrograde signaling pathways, which communicate the organelle's status to the nucleus.
To unravel the potential role of NCPs in this HS-sensing mechanism, we performed peptidomic investigations to identify NCPs generated and extruded by *A. thaliana* chloroplasts when exposed to heat stress. Our analysis revealed specific NCPs, originating from both intergenic and non-coding regions of the chloroplastic genome, whose expression was dependent on heat exposure. The exogenous application of a specific HS-dependent NCP released by the chloroplast during HS enhanced the heat tolerance of Arabidopsis plants.

P16

Harnessing Light to Control Bacterial Adhesion: A New Frontier in the Fight Against AMR

Alessio Colleoni[a,b], Giorgia Tempra[a], Shapla Bhattacharya[c,d], Marco De Amici[a], Rossella Castagna[c,e], Emilio Parisini[c,f], Carlo Matera[a]

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alessio.colleoni@unimi.it

Antimicrobial resistance (AMR) represents a growing global health threat, particularly in the context of healthcare-associated infections. A major factor contributing to the persistence and dissemination of AMR is the formation of microbial biofilms, which provide a protective microenvironment that enhances survival and promotes horizontal gene transfer. Central to biofilm development are bacterial adhesion proteins, which mediate crucial interactions between microbial cells and surfaces, thereby facilitating the establishment of highly resistant microbial communities. Owing to their pivotal role in biofilm formation, adhesion proteins have emerged as promising molecular targets for the development of novel anti-AMR strategies.

Among these, the virulence factor LecB—a lectin located on the outer membrane of Pseudomonas aeruginosa—plays a key role in pathogen persistence and virulence in clinical settings. LecB exhibits strong carbohydrate-binding activity, mediating interactions with both the bacterial outer membrane and exopolysaccharides within the biofilm matrix and has thus attracted considerable attention as a potential antibiofilm drug target.

This study focuses on the identification and development of innovative photoswitchable ligands capable of binding to and modulating LecB activity. Exploiting light-responsive mechanisms, these ligands aim to provide a novel therapeutic modality with high spatiotemporal precision and minimal invasiveness, potentially overcoming the limitations of conventional antimicrobial agents. Starting from the discovery of an initial photoswitchable hit compound targeting LecB, we implemented a computationally guided hit-expansion strategy to identify novel photoswitchable binders with enhanced affinity in their cis-enriched form for subsequent evaluation of their antibiofilm activity. The design strategy, chemical synthesis, photochemical characterization, and preliminary biological evaluation of these compounds will be presented and discussed.

INFORMATION

Conference location

Aula Magna (S.1.8) – 1st floor

Chiostro Sant'Abbondio

Via Sant'Abbondio 12, Como

https://maps.app.goo.gl/fyJJpThpXv3jrZz49

How to reach it

- From Como San Giovanni railway station
  16 minutes walking or bus line N4, N8, C130, C131, C132

- From Como Borghi railway station
  14 minutes walking

Car parking:

- Parking places are available inside Sant'Abbondio Cloister

Social dinner location

Ristorante e Bar Canottieri Lario Como

Viale Giancarlo Puecher, 6, 22100 Como

https://maps.app.goo.gl/mpSTYZKtsEtfeAoC6


SOCIAL DINNER
Life Electric
Il Mannarino Como
Prenota ora da Il Mannarino
Como Lago
Carrefour Market
Scopri Le Offerte Del Momento
Basilica di San Fedele
B&B HOTEL Como City Center
Pizzium
Prenota online in 2 minuti
Pinacoteca Civica
Cesare Ragazzi Laboratories
Coupon Sconto: PREVENZIONE12
Como
Lidl
Il tuo punto vendita Lidl
Como Borghi
CONGRESS
Aula magna del Chiostro di Sant'Abbondio
DentalPro Como
Prenota la tua prima visita
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Google Maps
Via Dante Alighieri
Via Briante
Via Nino Bixio

ACKNOWLEDGEMENTS

The Scientific and Organizing Committee gratefully acknowledges the support of the STAR project (FISA-2022-00922, Italian Ministry of University and Research) and the collaboration with Bayer Crop Science.

Special thanks are also extended to all speakers, participants, and contributors (special mention to all SynthMedChem member's group) whose efforts and commitment made this conference possible.

We thank you once again for joining the conference *"Medicinal and Crop Protection Chemistry: Breaking Barriers, Building Synergies"* and wish you inspiring discussions and fruitful collaborations.

Silvia Gazzola

David Barber

Giulia Cazzaniga

Roberto Orru

Samuele Bongiolo

SPANISH Drug Discovery Network

Certificate of attendance

This document certifies that:

Jorge Lozano Juste

•

*attended the **XVII Spanish Drug Discovery Network Meeting**,*
held on November 19th – 21st, 2025
in A Coruña, Spain.

A Coruña, November 21st, 2025

Jordi Quintana
President, Spanish Drug Discovery Network

XVII SDDN meeting

A CORUÑA
19th - 21st - November

Identification of new targets for improving abiotic stress tolerance in plants

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[2] Centro Nacional de Biotecnología (CNB-CSIC), Madrid, Spain
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María R. González-Bermúdez mdgonber@ibmcp.upv.es

SUMMARY

Water availability is one of the main limitations for crop productivity.
One strategy to improve plant's drought tolerance is to develop chemical compounds able to manipulate ABA signalling, thus promoting stomata closure and reducing water consumption[1].

Our main goal is to find **new targets** other than ABA receptors that contribute to plant stress tolerance, and which can be regulated by small molecules in order to **activate drought resistance** in crops.

A **chemical screening** will be used to find interesting compounds, followed by a characterization of their *in vitro* and *in vivo* activity. The molecular targets of the selected compounds will then be identified through a genetic screening using a **mapping-by-sequencing** strategy.

1 Identification of small molecules able to trigger stress response

A Pilot chemical screening

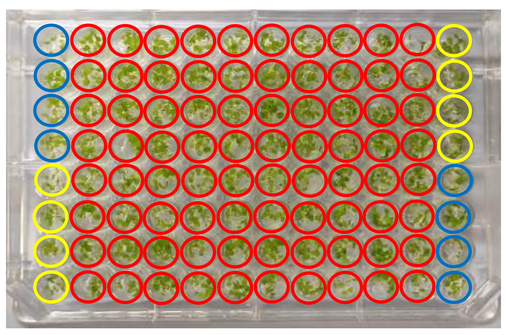
Luciferase reporter assay[2]

pMAPKKK18::LUC$^+$ stress-inducible reporter line

# of compounds

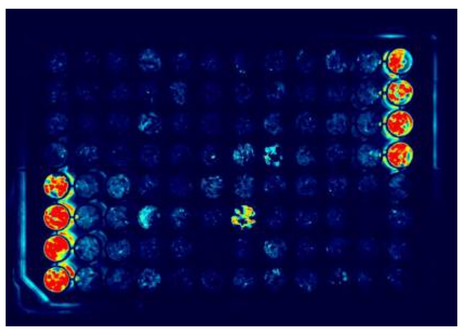
1200 — OTAVA™ natural product-like library

46 — Indole library



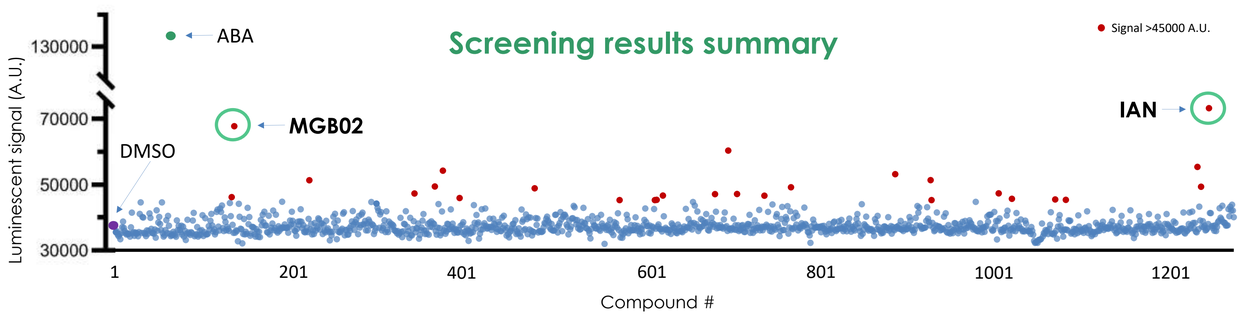
DMSO ABA (25 µM) Test compound (100 µM)

MAPKKK18 is highly induced by **ABA**



LAS-3000 luminescent image analyzer
ImageJ *Rainbow LUC* LUT

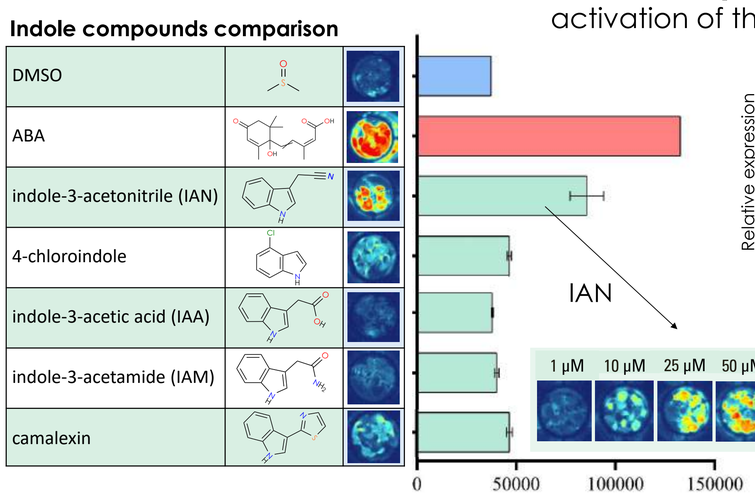
Screening results summary

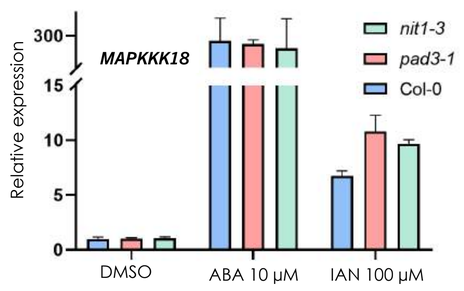


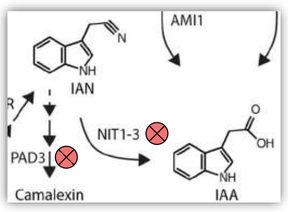
B Discard false positives

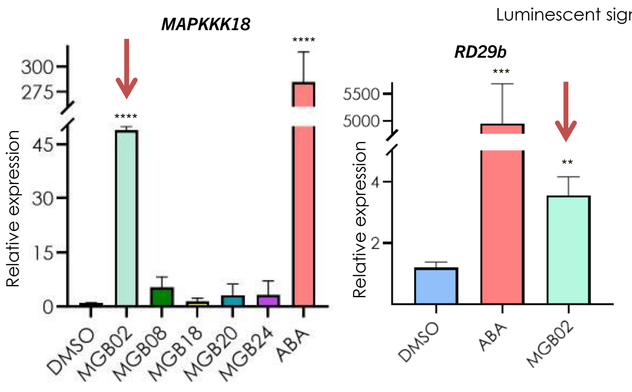
We have found several hits, including **indole-3-acetonitrile (IAN)**, which caused the greatest activation of the reporter.

Indole compounds comparison









Independent t-test compared to DMSO

10 µM ABA
100 µM "MGB" compounds

Upon verification of differential expression of stress genes by qPCR, we chose the novel compound "**MGB02**" to be further investigated.

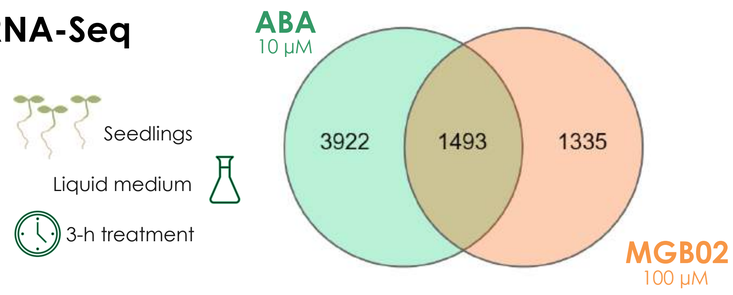
C Hit expansion

Similarity search

Expasy Bioinformatics Resource
SwissSimilarity

2 Characterization of the activity of identified molecules

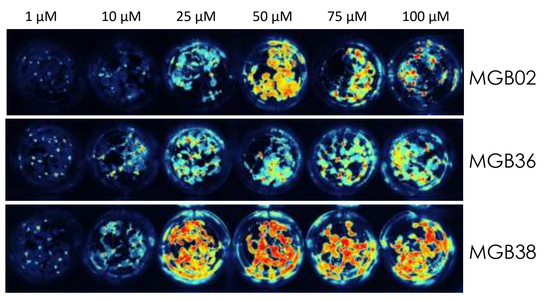
RNA-Seq



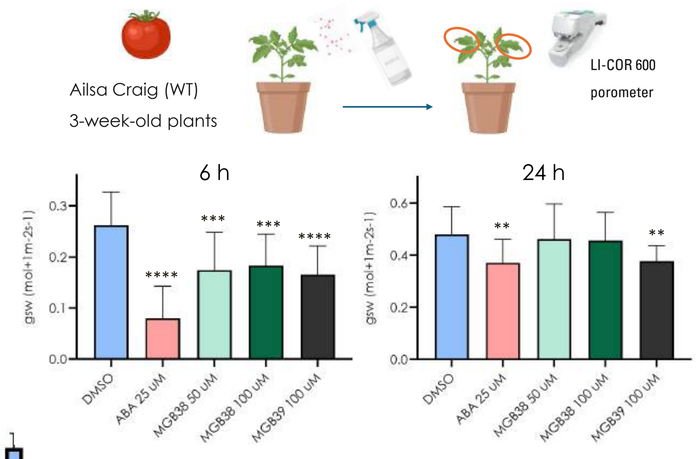
Genes upregulated by **MGB02** and also by **ABA** include genes **involved in ABA synthesis**

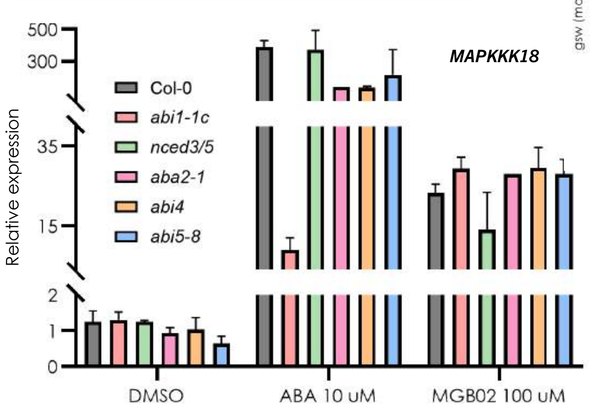
Gene	Fold change
ABA1	2.20
NCED3	7.11
SDR4	2.62

Dose-response luciferase assays



Stomatal conductance





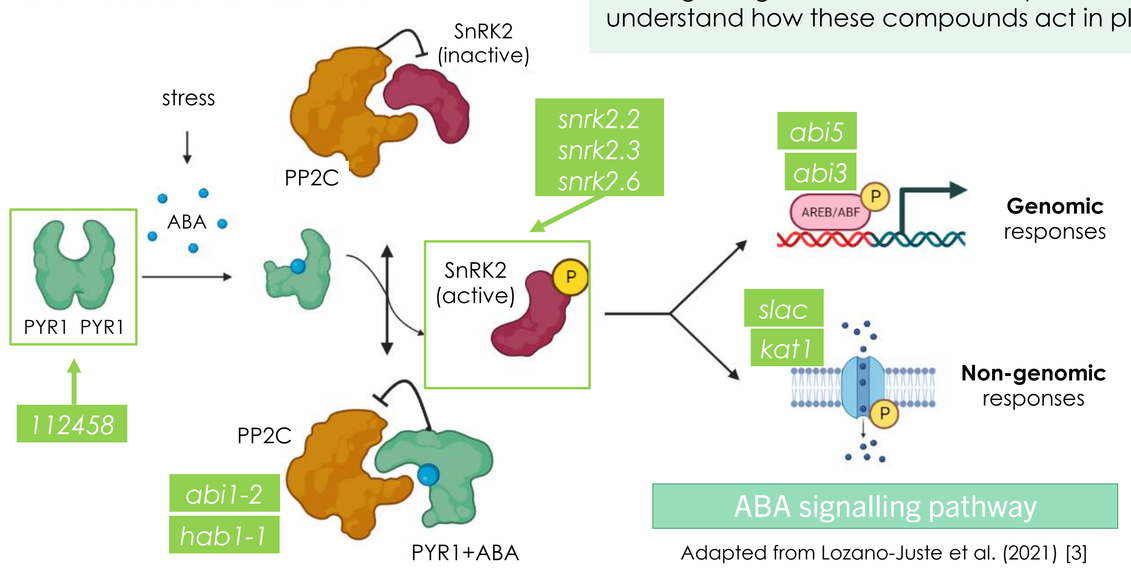
MAPKKK18 expression in Col-0 and ABA mutants after MGB02 and ABA treatments

Ongoing and future experiments

MGB38 has shown greater activity than **MGB02**.

Stomatal conductance measurements in tomato indicate **possible physiological effects**.

Expression analyses, together with **germination** and **root growth** assays, in ABA-synthesis and ABA-signaling mutants, will help to better understand how these compounds act in plants.



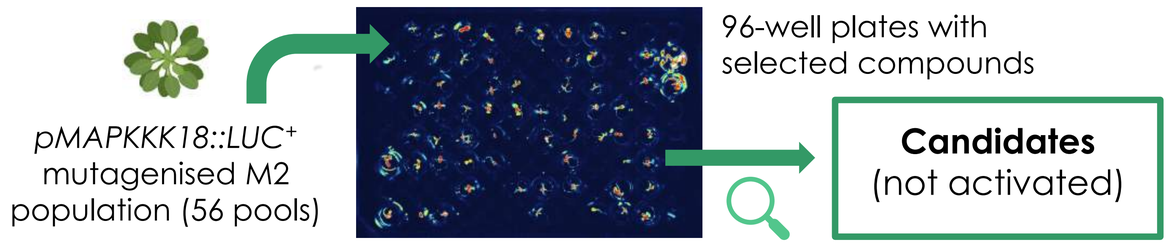
ABA signalling pathway

Adapted from Lozano-Juste et al. (2021) [3]

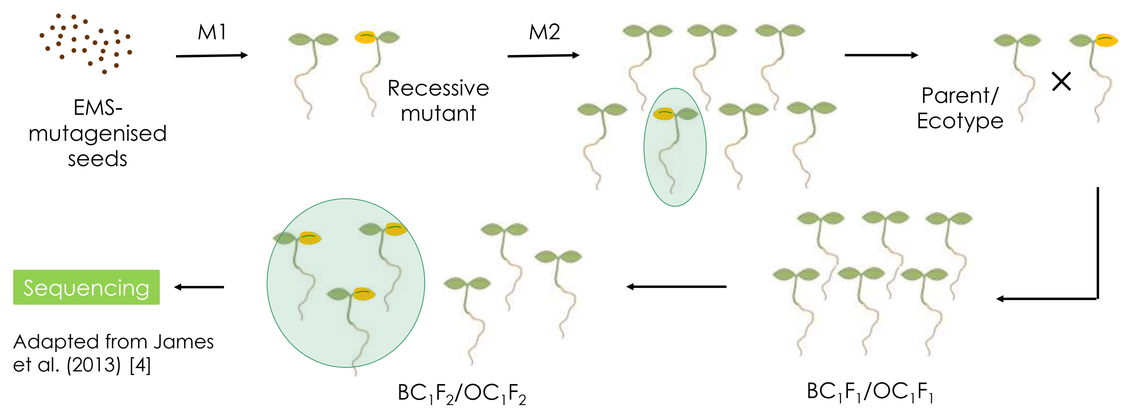
3 Identification of molecular targets of the selected compounds

A genetic screening is being performed to **identify the molecular targets** of the most promising compound by **mapping-by-sequencing**.

Forward chemical genetic screening



Mapping by sequencing



Adapted from James et al. (2013) [4]

References

[1] Vaidya *et al*. 2019. *Nature* 366(6464)
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[3] Lozano-Juste *et al*. 2021. *Methods Mol Biol* 2213, 99-111
[4] James *et al*. 2013. *Genome Biology* 14

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Pioneering Plant PROTACs: Expanding the Agrochemical Toolbox

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Instituto de Biología Molecular y Celular de Plantas, Universitat Politècnica de València, Consejo Superior de Investigaciones Científicas-, ES-46022 Valencia, Spain.

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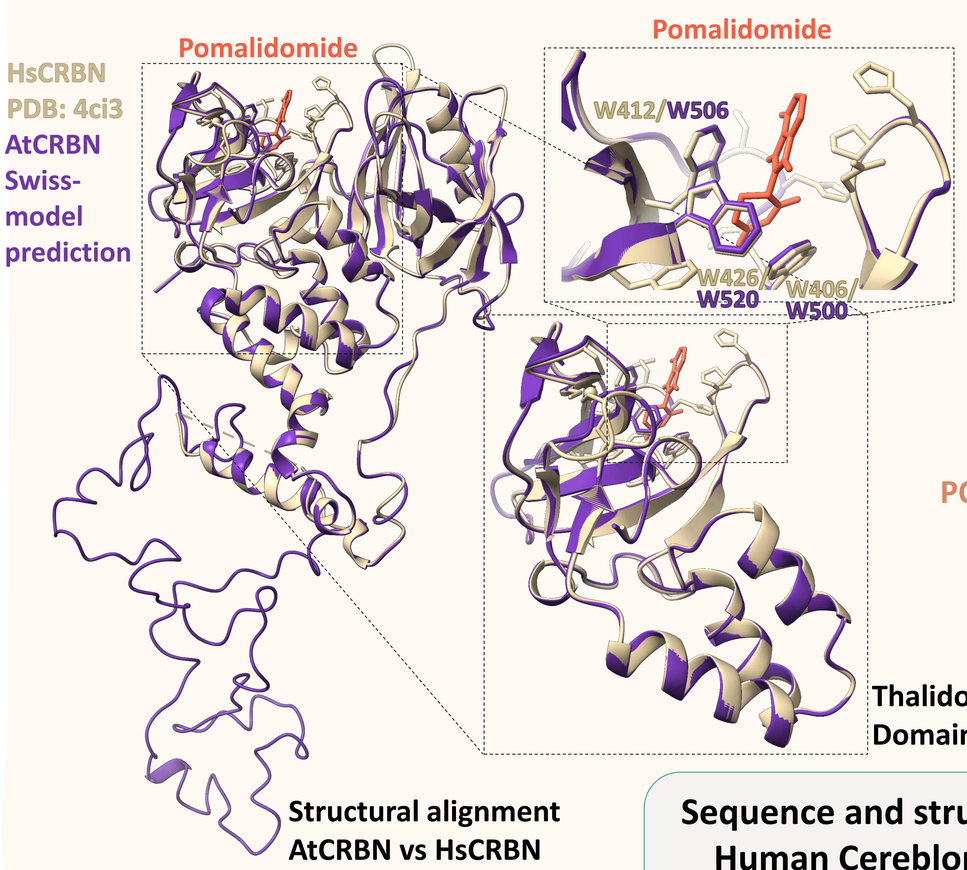
In this pioneering project, we aim to develop a proof-of-concept for the first plant PROTAC (PROteolysis-Targeting Chimeras). We have designed and synthesized a hetero-bifunctional chemical molecule, called PROTAC1, which incorporates an abscisic acid (ABA) moiety linked through a PEG-based linker to the plant E3 ligase binder. This E3 ligase shares a high degree of homology with a human E3 ligase. We followed structure-guided ligand design to develop an ABA analog which specifically binds to ABA-receptor *in vitro* and *in vivo*. Treatment with PROTAC1 shows ABA-receptor degradation activity *in vivo* and reduces the transcriptional activation promoted by ABA. These results open the door to establish PROTACs as an innovative tool for both plant research and the agrochemical market.

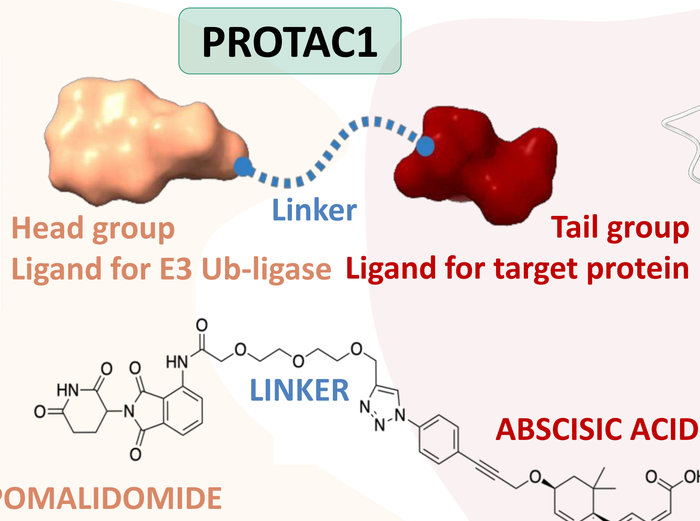
PROTAC1 DESIGN



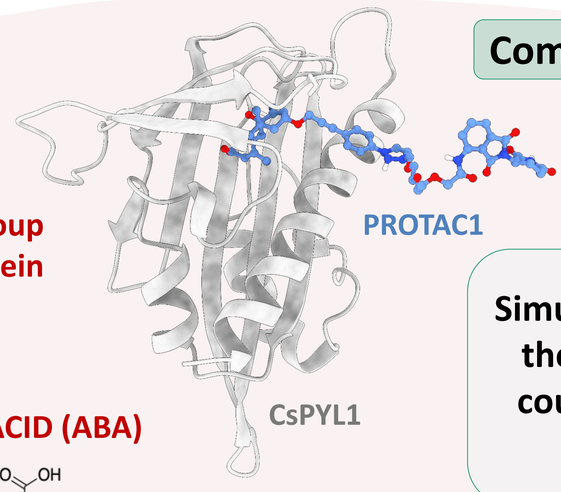
Structural alignment

Sequence and structure are conserved between Human Cereblon (HsCRBN) and *Arabidopsis thaliana* homolog (AtCRBN), especially in the TBD and the Tri-Trp binding pocket

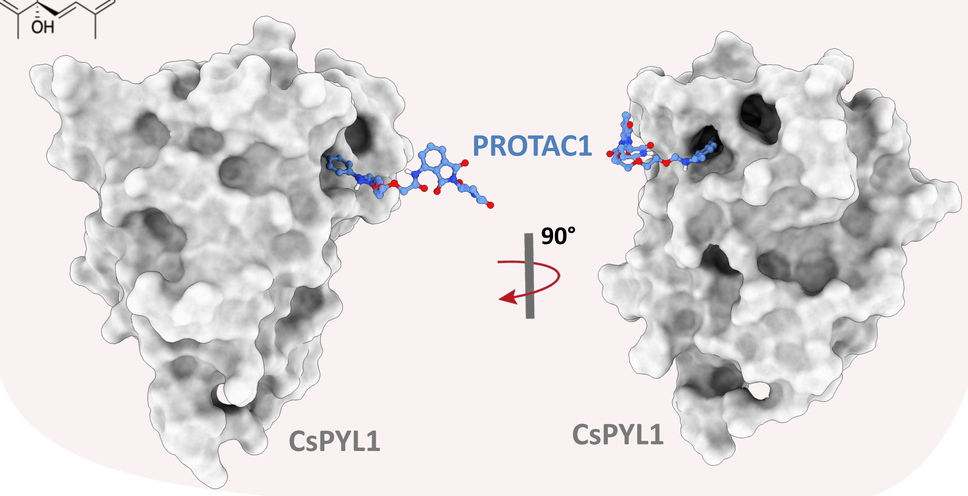
PROTAC1



Computational Docking

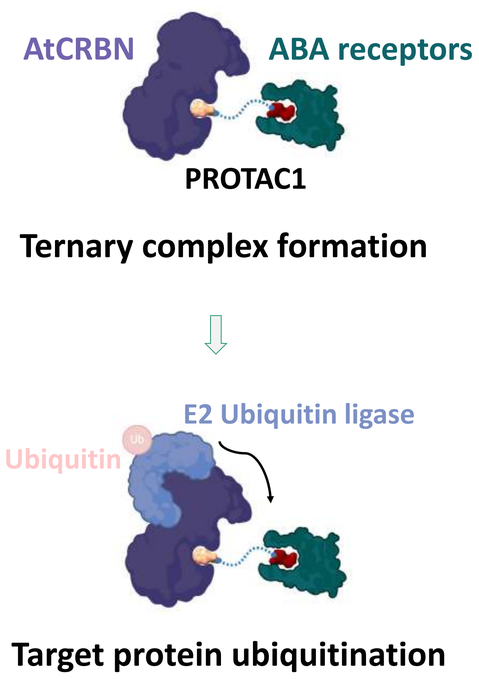


Simulations predicted that the PROTAC1 tail group could efficiently bind to the ABA receptor

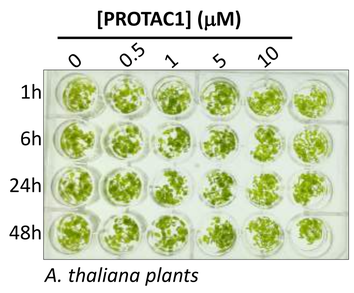


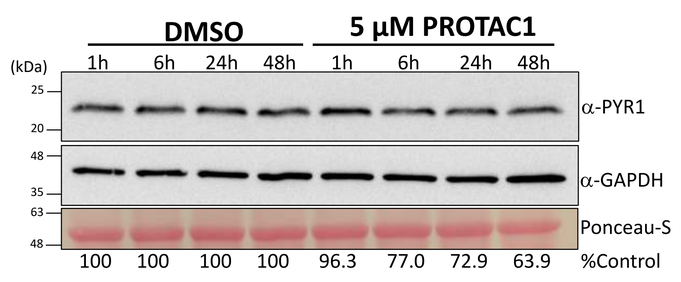
PROTAC1 ASSAYS

PROTAC1 activity

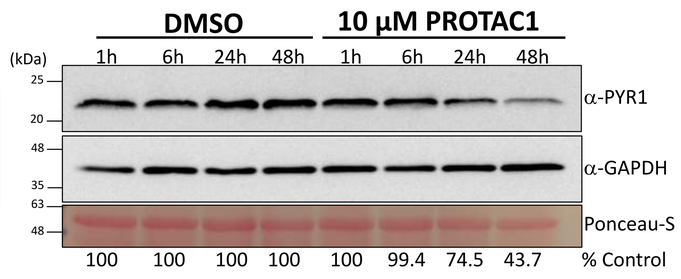


ABA Receptor degradation with PROTAC1

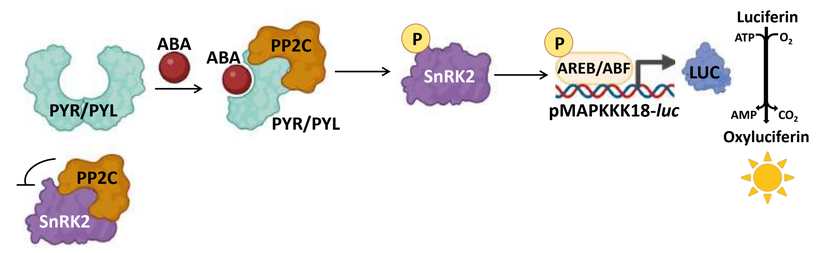


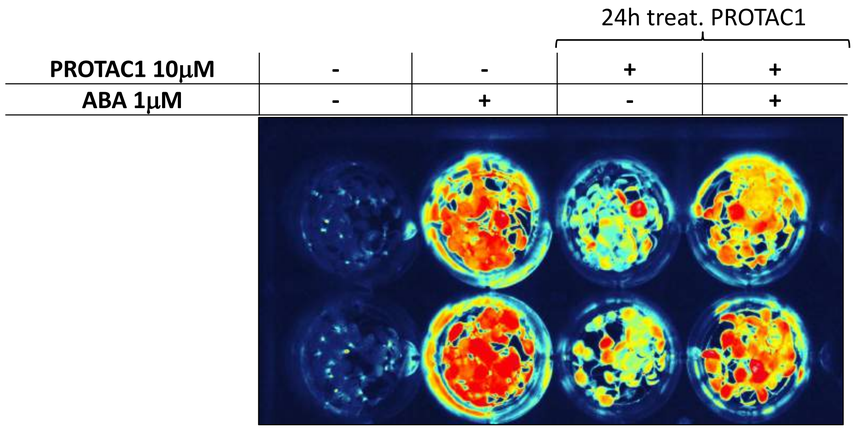


PROTAC1 induces ABA receptor degradation

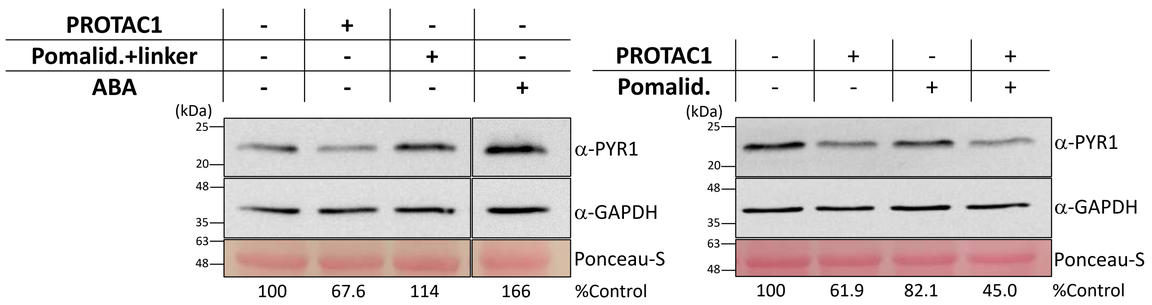


ABA signaling after PROTAC1 and ABA treatment in the pMAPKKK18-LUC+ reporter line

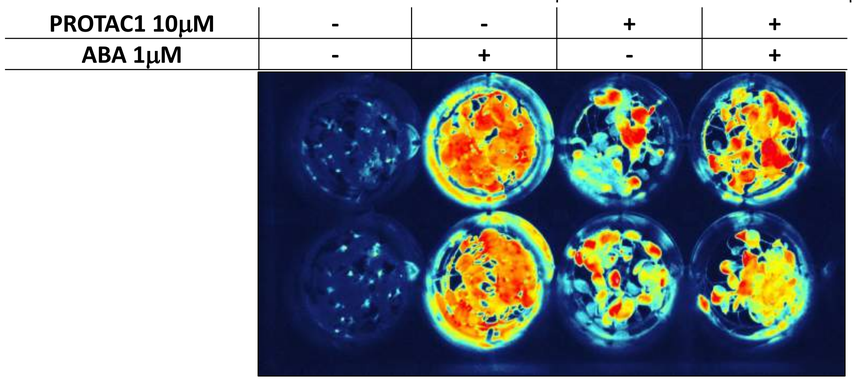




Analysis of ABA Receptor degradation using partial components of PROTAC1



ABA, Pomalidomide and Pomalidomide+linker do not interfere with ABA receptor degradation



PROTAC1 treatments reduce the ABA-induced transcriptional activity

REFERENCES

USING ARTIFICIAL INTELLIGENCE TO IMPROVE DROUGHT RESISTANCE IN CROP PLANTS

Ruiz-Partida Rafa[1], Subramanian Nik[2], Maignan Nicolas[2], Martin Segolene[2] and Lozano-Juste Jorge[1].

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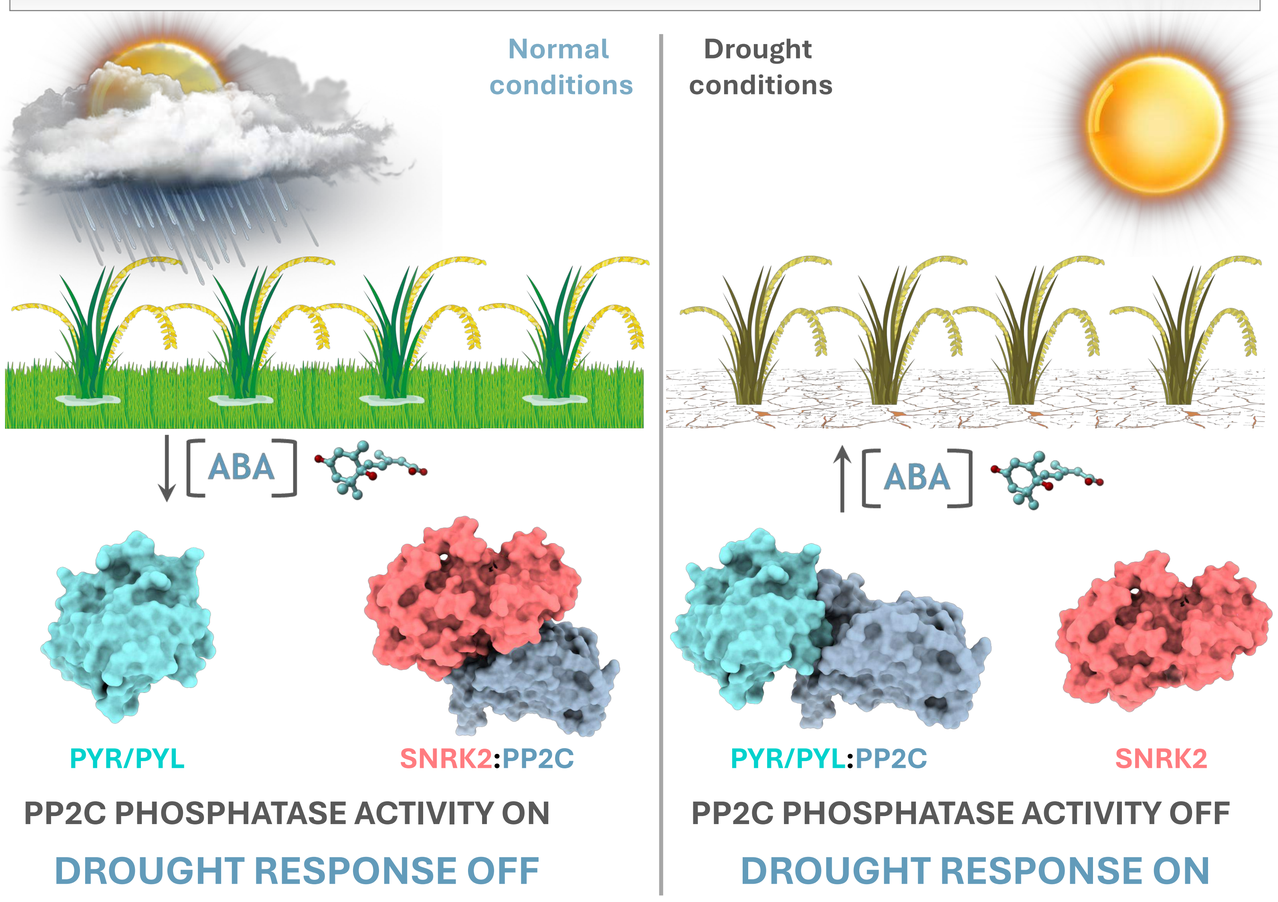
Water is a necessary resource that sustains life on earth. Unfortunately, climate change is severely affecting rainfall, leading to a higher incidence of droughts that have a major impact on rain-fed farming systems, which account for 80 % of the world's cropland and produce about 60 % of global agricultural output. Therefore, solutions to improve water use efficiency in crops are becoming crucial to contribute to food security. Under drought stress, the inhibition of clade A subfamily of protein phosphatases type-2C (PP2Cs) modulates plant transpiration. Indeed, it has been extensively reported that genetic inactivation of PP2Cs generates mutant plants more tolerant to drought and, in consequence, more productive than wild type plants in water limited conditions. However, this genetic approach often leads to plants with a growth penalty, limiting its use. Alternatively, there is an emerging field for the development of chemical compounds designed to increase water use efficiency on demand. However, the high cost of the compounds and/or their lack of activity in the field might have prevented the industry from developing these molecules into commercial products. In the last years, artificial intelligence (AI) has emerged as a powerful tool in drug discovery but it has never been used to improve drought resistance in agriculture so far. Among the multiple advantages of using AI, the reduction in economical cost and the accuracy of the prediction models are the primary drivers for the adoption of this technology. In this project we will develop PP2C inhibitors targeting not only the model plant *Arabidopsis thaliana* but importantly staple crops like maize and wheat. Towards this end we will use AI through machine learning algorithms to screen millions of compounds *in silico* to develop new PP2C inhibitors to improve water use efficiency in plants. Here we present the results a proof-of-concept pilot screening (4M molecules) performed using Arabidopsis PP2Cs as targets. We have obtained an unprecedented success rate of 85 % of bioactive hits among the top 27 compounds tested *in vitro*. We think that the application of AI will contribute towards the development of biotechnological solutions to reduce water consumption and to improve plant productivity with fewer resources to cope with climate change and an increasing population.

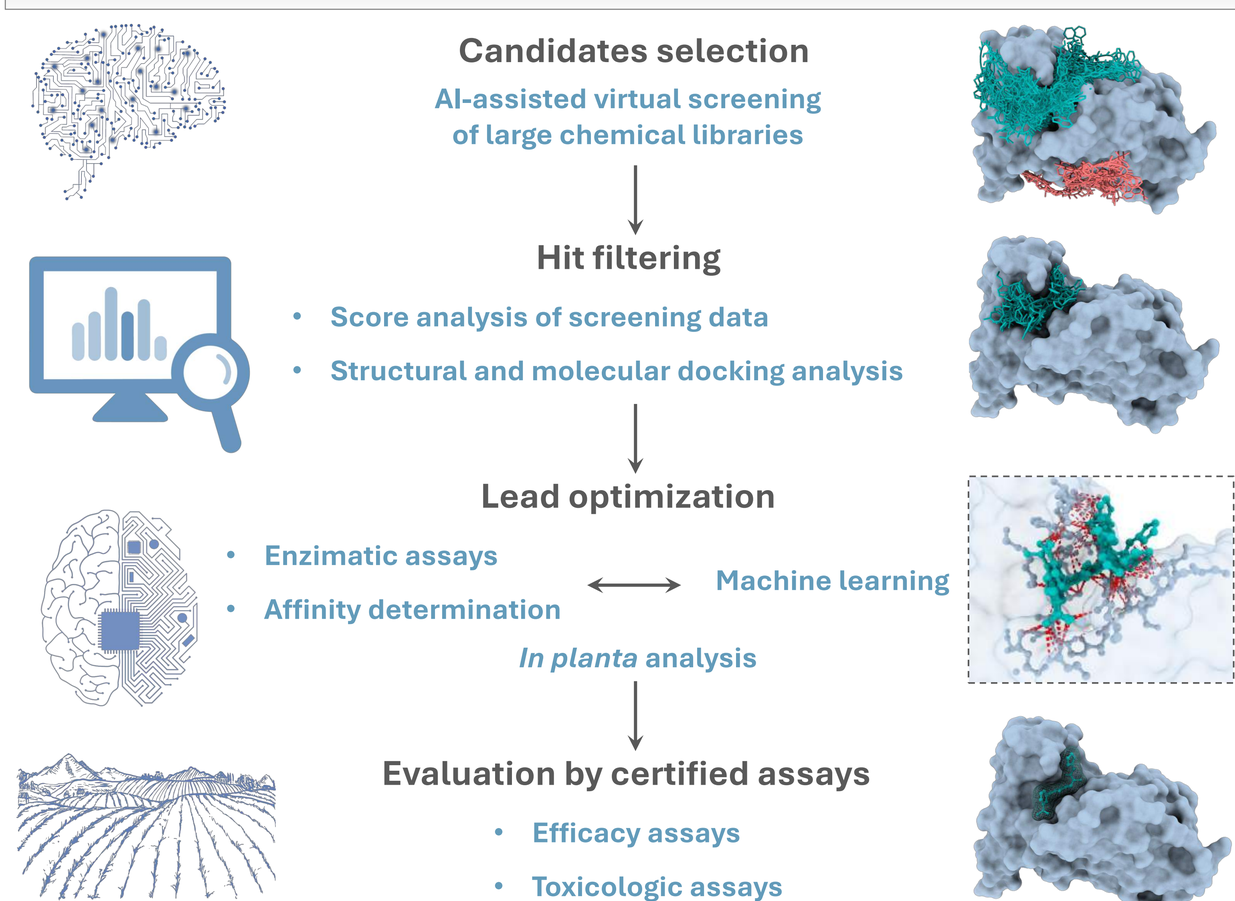
HYPOTHESIS

Artificial intelligence can be harnessed to develop bioactive compounds inhibiting clade A PP2Cs thus activating plant adaptation to drought.

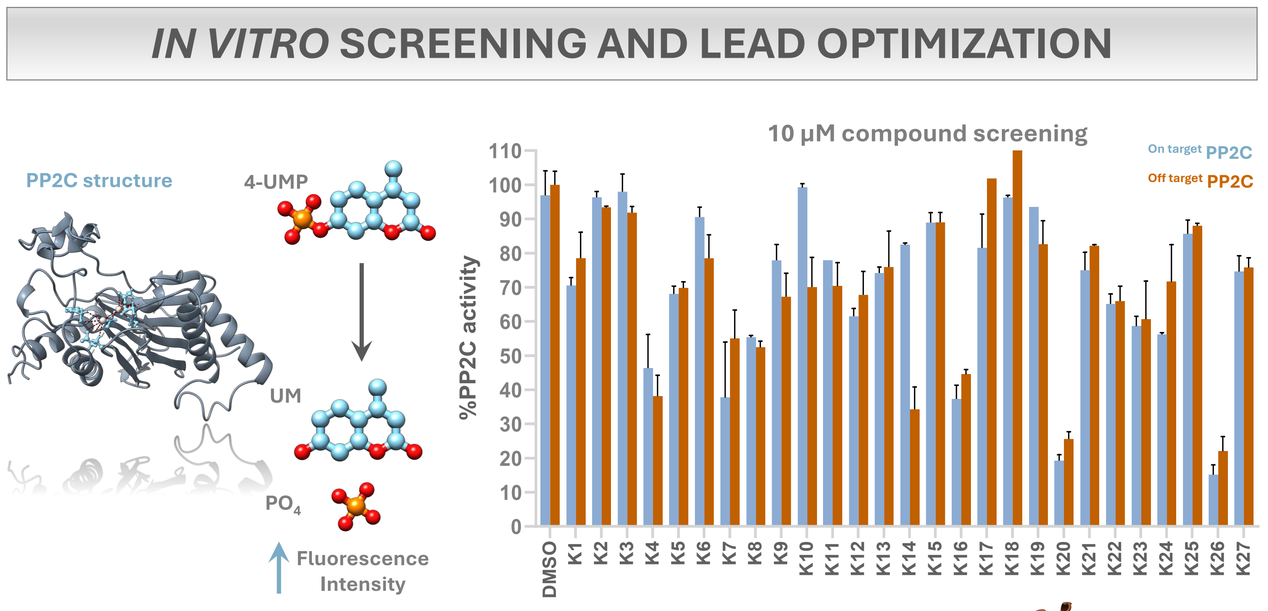
BACKGROUND



IDENTIFICATION OF PP2C INHIBITORS USING AI

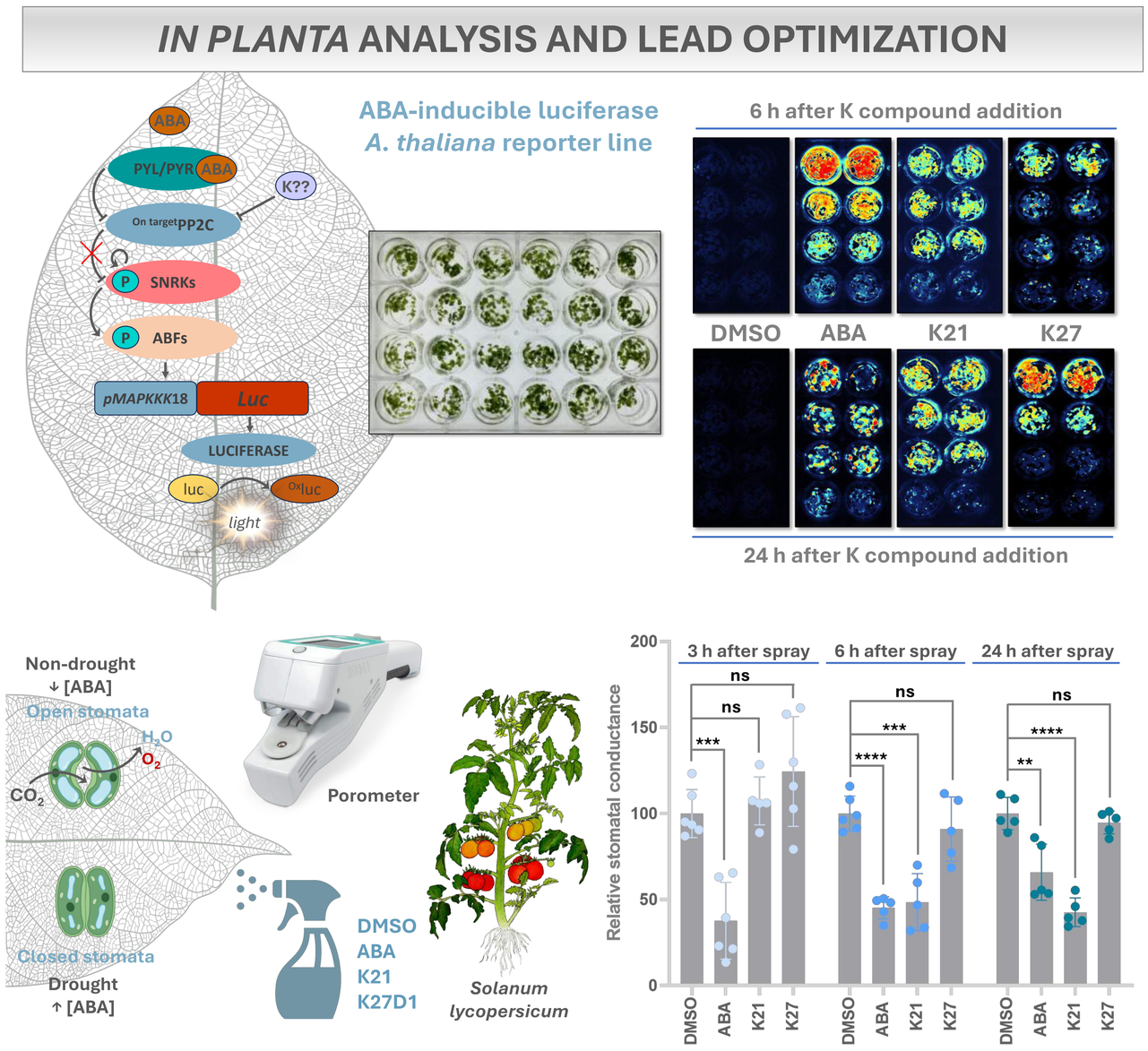


IN VITRO SCREENING AND LEAD OPTIMIZATION



Compound	K4	K8	K14	K16	K20	K21	K24	K26	K27
$IC50_{PP2C}$ (µM)	2.8	7.4	3.6	2.0	3.3	10.6	8.6	1.5	19.6

IN PLANTA ANALYSIS AND LEAD OPTIMIZATION



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20th European Weed Research Society Symposium

EWRS 2025

CERTIFICATE OF ATTENDANCE

JORGE LOZANO-JUSTE

has attended the

20th European Weed Research Society Symposium

Joint approaches for sustainable weed management

held in Lleida (Catalonia, Spain)

from 1 to 4 July 2025.

Prof. Dr. Jordi Recasens
Universitat de Lleida
Head of the local host committee

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