BOOKLET


Bi&Chem
2024
3rd edition
April 18-19, 2024
ESBS - Parc d'innovation
Strasbourg, Illkirch
ACADEMIA-INDUSTRY
DRUG RESEARCH
SYNTHETIC BIOLOGY
GREEN CHEMISTRY
ARTIFICIAL INTELLIGENCE

PROGRAM

Day 1: Thursday, April 18, 2024

08:30 – 09:00 **Registration**
Breakfast

09:00 – 09:30 **Welcome & Foreword – Christophe ROMIER & Rémi BARILLON**

09:30 – 12:00 **1st Plenary Session**

GREEN CHEMISTRY

Chair: Stefan CHASSAING, Société Chimique de France

Patrick PALE - University of Strasbourg, Strasbourg, France
Green chemistry - from where to where?

Michael LUESCHER - Novartis, Basel, Switzerland
Data-driven decision making to facilitate sustainable process development!

Francesca PARADISI - University of Bern, Bern, Switzerland
Towards integration of biocatalysis in chemical processes

Deniz KARABIYKLI – University of Strasbourg, Strasbourg, France
Green and/or solvent-free Buchwald-Hartwig amination: towards sustainable catalysis

Timothé MAUJEAN – University of Strasbourg, Strasbourg, France
A Thia-Diels-Alder click reaction for the straightforward labelling of peptides under green conditions

12:00 – 13:30 **Lunch & Poster session**

13:30 – 15:00 **1st round tables**

NeuroStra | Le système nerveux de l'adaptation aux pathologie

Open Science

Chair: Katia BEFORT, Société de Biologie de Strasbourg

Stéphanie CHEVIRON, University of Strasbourg, France
Héloïse GAZEAU, University of Strasbourg, France
Jan LEENDERTSE, University of Freiburg, Germany
Raphaël LEVY, University Sorbonne Paris Nord, France
Eric QUEMENEUR, Transgene, Strasbourg, France
Stephanie RENNES, Ministère de l'économie, des finances et de la souveraineté industrielle et numérique, Paris, France
Andrea THORN, University of Hamburg, Germany

Equity and Inclusion in Science

Chairs: Sylvie FOURNEL, Société de Biologie de Strasbourg
Arwen PEARSON, University of Hamburg, Germany

Serena BERNACCHI, Women in Science, Strasbourg, France
Romain BOURDY, University of Strasbourg, France
Emilie DENAT-TURGIS, Rectorat de Strasbourg, France
Marine DESAGE-EL MURR, Women in Science, Strasbourg, France
Isabelle KRAUS, University of Strasbourg, France
Eloi VERRIER, University of Strasbourg, France

15:00 – 16:00 **Coffee Break & Poster Session**

MP Biomedicals

16:00 – 18:30 **2nd Plenary Session**

VectorBuilder

SYNTHETIC BIOLOGY

Chair: Dr. Coraline RIGOUIN, ESBS

Barbara DI VENTURA - University of Freiburg, Freiburg, Germany
Inteins as molecular tools for synthetic biology

Vincent LEBRUN - University of Strasbourg, Strasbourg, France
Design of amyloid-like artificial metalloenzymes

Florence BORDES - Toulouse Biotechnology Institute, Toulouse, France
Combining enzymatic and metabolic engineering in the yeast Y. lipolytica to produce original lipids and polymers

Michael MULOT - Hybrigenics Services, Evry, France
Unraveling the proteome and ubiquitin pathways by chemically induced proximity

Diana SCHWARZ – Karlsruhe Institute of Technology, Karlsruhe, Germany
Influencing tomato root development by genetic modification of MIG transcription factors

20:00 – 22:00 **Gala Dinner at Maison Kammerzell**

Day 2: Friday, April 19, 2024

09:00 – 10:30 **2nd round tables**

Science with and for the Society

Chair: Marcel HIBERT, University of Strasbourg

Marlin DÜRRSCHNABEL, Karlsruhe Institute of Technology, Karlsruhe, Germany
Mélodie FAURY, Muséum national d'Histoire naturelle, Paris, France
Pierre FECHTER, Maison pour la Science, Strasbourg, France
Meriem FOURNIER, INRAe Grand Est, Nancy, France
Bénédicte LEBEAU, University of Haute Alsace, Mulhouse, France
Céline TARNUS, University of Haute Alsace, Mulhouse, France
Agnès VERNET, Science journalist, AJSPI, Lyon, France

Evolution of Science Jobs

Chair: Giovanna LATERZA, Pépite Etena, University of Strasbourg

Farah BOUHEDDA, Merck, Molsheim, France
David BRUCHLEN, ScienceMeUp, Strasbourg, France
Philippe CHAVOT, University of Strasbourg, France
Xavier ESPANEL, Novalix, Strasbourg, France
Amandine PERRET, University of Strasbourg, France
Guillaume VETTER-GENOUD, Quest for Health, Strasbourg, France

10:30 – 11:30 **Coffee Break & Poster Session**

11:30 – 12:30 **Keynote - Raphaël RODRIGUEZ,**

Curie Institute, Paris, France

Chemical control of cell plasticity

12:30 – 13:30 **Lunch & Poster session**

13:30 – 16:00 **3rd Plenary Session**

NEW STRATEGIES IN DRUG RESEARCH

Chair: Christophe DECROOS, University of Strasbourg

Luisa DE COLA - University of Milan, Milan, Italy
Small breakable nanocapsules for crossing body barriers

Julie KARPENKO – University of Strasbourg, Strasbourg, France
Alared: a solvatochromic red amino acid for labeling of bioactive peptides

Vianney POIGNAVENT - Serendip innovations, Strasbourg, France
A modular plant virus-derived nanoparticle for drug vectorization

Laetitia PREAU - Karlsruhe Institute of Technology, Karlsruhe, Germany
Systems approaches identify new drug targets for vascular therapies

Aurora SILVESTRI – IGBMC, Illkirch, France
Structural studies of CBP/p300 complexes and characterization of peptide based CBP inhibitors

16:00 – 17:30 **Round table**

Artificial Intelligence at the Biology / Chemistry Interface

Chair: Christophe ROMIER, Société de Biologie de Strasbourg

Jean-Luc DIMARCQ, IHU, University of Strasbourg, France
Jean-Marc DELTORN, CEIPI, University of Strasbourg, France
Anne JEANNIN-GIRARDON, CRBS, University of Strasbourg, France
Gilles MARCOU, Chemistry faculty, University of Strasbourg, France
Andrea THORN, University of Hamburg, Germany
Nihal Engin VRANA, Spartha Medical, Strasbourg, France

17:30 – 18:30 **Poster/Talks Awards & Drinks**

KEYNOTE

Chair
Christophe ROMIER, Société de Biologie de Strasbourg

Chemical control of cell-state transitions

Raphaël RODRIGUEZ

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Institut Curie, CNRS UMR 3666, INSERM U1143, PSL Research University, Paris, France.

Cells can adopt distinct states independently of genetic alterations, a biological process commonly referred to as 'cell plasticity'. Acquisition of distinct cell states is characterized by the upregulation of the plasma membrane glycoprotein CD44 in development, immunity and cancer. Although often described as a cell-surface marker, the biological function of CD44 has remained elusive for half-a-century. We discovered that CD44 mediates the uptake of specific metals, including copper and iron in various tissue types using hyaluronans as carriers. This glycan-mediated metal endocytosis mechanism enables immune cell activation and acquisition of a therapy-resistant state of cancer cells. Increase of copper(II) in mitochondria sustains NAD(H) redox cycling, enabling the production of metabolites that co-regulate the epigenetic programming of cell identity. In contrast, increase of iron in the nucleus promotes the activity of specific iron- and ketoglutarate-dependent demethylases, activating specific transcriptional programs. We developed new classes of small molecules that selectively interfere with these metal-catalyzed chemical processes in cells. Inactivating mitochondrial copper(II) prevents acute inflammation in vivo demonstrating that control of cell plasticity confers therapeutic benefits. Activation of lysosomal iron induces ferroptosis in therapy-resistant cancer cells, reducing cancer metastasis. These findings illuminate a universal metal uptake mechanism and the critical role of metals as master regulators of cell plasticity, paving the way towards the development of next generation therapeutics.

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A druggable copper-signalling pathway that drives inflammation. S. Solier, S. Müller, T. Cañeque, A. Versini, A. Mansart, F. Sindikubwabo, L. Baron, L. Emam, P. Gestraud, G. D. Pantoș, V. Gandon, C. Gaillet, T.-D. Wu, F. Dingli, D. Loew, S. Baulande, S. Durand, V. Sencio, C. Robil, F. Trottein, D. Péricat, E. Näser, C. Cougoule, E. Meunier, A.-L. Bègue, H. Salmon, N. Manel, A. Puisieux, S. Watson, M. A. Dawson, N. Servant, G. Kroemer, D. Annane, R. Rodriguez*. *Nature* 617, 386-394 (2023).

Persister cancer cells: iron addiction and vulnerability to ferroptosis. R. Rodriguez*, S. L. Schreiber*, M. Conrad* *Mol. Cell* 82, 728-740 (2022)

CD44 regulates cellular plasticity by mediating iron endocytosis. S. Müller, F. Sindikubwabo, T. Cañeque, A. Lafon, A. Versini, C. Ginestier, E. Charafe-Jauffret, B. Lombard, D. Loew, T.-D. Wu, A. Durand, C. Vallot, S. Baulande, N. Servant, R. Rodriguez*. *Nature Chem.* 12, 929-938 (2020)

Visualizing biologically active small molecules in cells using click chemistry. T. Cañeque, S. Müller, R. Rodriguez* *Nature Rev. Chem.* 2, 202-215 (2018)

Salinomycin kills cancer stem cells by sequestering iron in lysosomes. T. T. Mai, A. Hamaï, A. Hienzsch, T. Cañeque, S. Müller, J. Wicinski, O. Cabaud, C. Leroy, A. David, V. Acevedo, A. Ryo, C. Ginestier, D. Birnbaum, E. Charafe-Jauffret, P. Codogno, M. Mehrpour, R. Rodriguez* *Nature Chem.* 9, 1025-1033 (2017)

SESSION 1- GREEN CHEMISTRY

Chair
Stefan CHASSAING, Société Chimique de France ALSACE

Speakers
Patrick PALE, University of Strasbourg, France
Michael LUESCHER, NOVARTIS, Basel, Switzerland
Francesca PARADISI, University of Bern, Bern, Switzerland
Timothé MAUJEAN, University of Strasbourg, France
Deniz KARABIYIKILI, University of Strasbourg, France

Green chemistry creates a new reality for chemistry and engineering by asking chemists and engineers to design chemicals, chemical processes and commercial products in a way that, at the very least, avoids the creation of toxics and waste. Thus, **Green Chemistry** attempts to reduce the environmental impact of the chemical enterprise by developing a technology base that is inherently non-toxic to living things and the environment.
This session will provide insights on the advancements made in this multidisciplinary field, starting with the points of view of an academic researcher and an industrial researcher. Biocatalysis, metal catalysis, flow chemistry, and “click” chemistry will then be presented as creative and innovative tools exploited for greening chemistry.

From where to where ?

Patrick PALE

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Since several decades, chemistry is often associated with various terms, more or less used by industries, politics, media, etc...

In this lecture, the origin of the so-called Green Chemistry will be uncovered. The issues and challenges Green Chemistry is facing will then be reviewed with an emphasis on the most typical and promising aspects.

Data driven decision making to facilitate sustainable process development!

Michael U LUESCHER - michael-1.luescher@novartis.com

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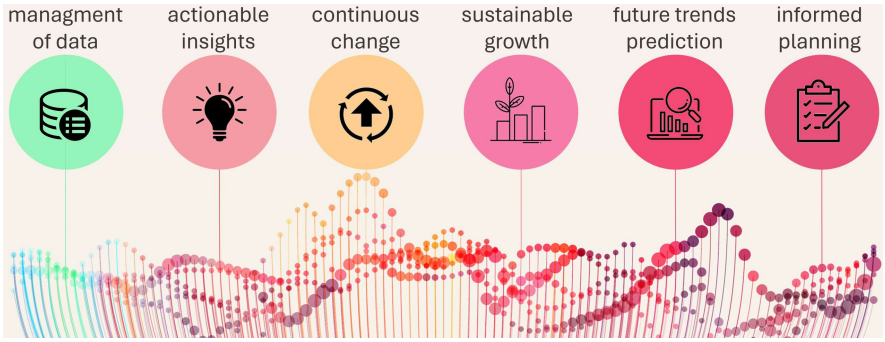

Phasing out actual emissions is the goal but, in the meantime, targets and metrics to guide, define, and measure progress are needed. Transparent metrics and procedures ensure that efforts are based on consensus of the best available evidence – and that carbon-accounting methodologies and accepted data sources are included to publish, communicate, or present data.

Steps into this direction were made with the introduction of the environmental factor (E-Factor) in 1992, bringing attention to the problem of waste generation.[i] Linking waste to the amount of material produced gave rise to a paradigm shift in the concept of efficient chemical processes. However, such assessment often fail to shed light on whether routes are sustainable in absolute terms, falling short in differentiating environmental hazards, footprints, or the depletion of resources for in- and output materials.

The integration of more detailed, unified metrics, and indicators into process development is key to a sustainable chemical industry and to best and sustainably address environmental hotspots, assessments should be possible at earlier stages during process development. However, the development and manufacture of a new medicine is in itself a complex endeavor and sophisticated multistep manufacturing processes consume sources of materials across the globe. This consumption leads to emissions into the environment that have consequences in the different environmental compartments that are exposed to those emissions. The questions then become how a quantification of environmental impacts can be obtained and how to best detect and display environmental hotspots.

Facing the challenge of data availability, data acquisition, or data accuracy, we propose a simple and standardized procedure based on selected metrics and footprint indicators to assess and report the environmental footprints of linear and convergent chemical processes.[ii] The output then focuses on data representation and decision taking, making it easier to communicate in cross-functional environments. All the more so as such analyses are meant to guide the research and should not be mere reporting tools. The proposed metrics and procedures must also be easily understood at the laboratory and pilot plant level and accepted by key stakeholders. To achieve this, an approach consistent of a simple-to-use LCA based metrics toolkit in combination with metrics such as PMI or Environment Health & Safety (EHS) attributes should allow us, in the industry in particular, to guide our research towards ever more sustainable practices.

[i] R. A. Sheldon, *Green Chem.*, 2007, **9**, 1273−1283; (b) R. A. Sheldon, *Green Chem.*, 2017, **19**, 18–43; (c) R. A. Sheldon, *ACS Sustainable Chem. Eng.*, 2018, **6**, 32–48.

[ii] M. U. Luescher, F. Gallou, *Green Chem.*, 2024, doi: 10.1039/D4GC00302K.

Towards integration of biocatalysis in chemical processes

Francesca PARADISI

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The move towards sustainable syntheses is a widespread effort which sees academia and industry developing new strategies and solutions.[1] But why is it that biocatalysis, in general, is still not part of the standard toolbox of a chemist? Enzymes are felt to be challenging to work with, they would require a major revolution of the set-up of an existing process, it appears easier to just replace the catalyst with a more efficient newer one which can be just slotted in, in a well-established multi-step chemical cascade. We are trying to change this by making enzymatic steps just another possibility to be at least considered as an option when designing a multi-step synthesis. Flow chemistry for example, and in general the flow set up, with the compartmentalization of different steps in dedicated reactors, offers new possibility to integrate biocatalytic steps within a chemical cascade,[2] often without the need to redesign the whole pathway. The ability to immobilize enzymes through versatile chemistries and supports, is a pillar of our group.[3–5] Here I will present our latest efforts in the field.[6-8]

References

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[8] Unpublished results.

A Thia-Diels-Alder Click Reaction for the Straightforward Labelling of Peptides under Green Conditions

Timothé MAUJEAN,[1] Patrice Marchand,[2] Patrick Wagner,[1] Stéphanie Riché,[1] Julie Karpenko,[1] Frédéric Boisson,[2] Nicolas Girard,[1] Dominique Bonnet,[1]* Mihaela Gulea[1]*

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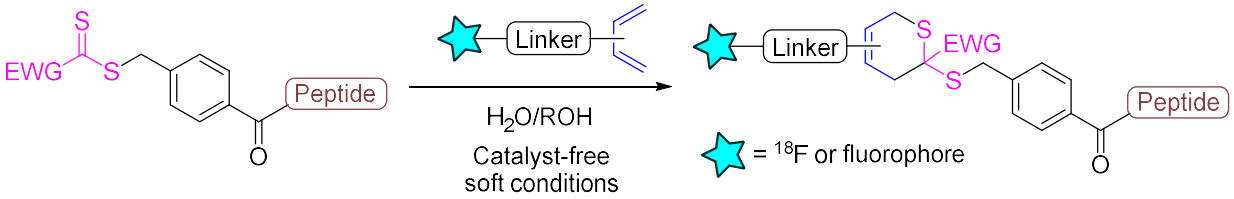
Click reactions represent an efficient method for the chemoselective modifications of peptides of proteins in mild conditions. Amongst these reactions, the Cu-Catalysed Alkyne-Azide cycloaddition (CuAAC) remains the most used system despite the *in vivo* toxicity of the Cu(I) catalyst that may get trapped by the peptide at the end of the reaction [1]. Alternatives such as the Strain-promoted Azide-Alkyne cycloaddition (SPAAC) or the Inverse Electron Demand Diels-Alder reaction (IEDDA) have been developed [2] to overcome this issue but still remain scarcely represented in the literature mostly due to poor accessibility and high cost of the reactive partners.
Herein, we report the use of a thia-Diels-Alder reaction between a dithioester and a diene [3] for the chemoselective labeling of peptides under catalyst-free mild conditions. While this cycloaddition had already been used as a click reaction to functionalise the Bovine Serum Albumin (BSA) with polymers [4], it had never been applied to the chemoselective labeling of peptides for imaging applications. Thus, we developed a practical method to introduce for the first time the phosphonodithioester moiety into a model peptide. Then, the diene was designed to combine good stability and high reactivity towards the dithioester partner while keeping mild reaction conditions. Finally, bioactive peptides were labelled with either fluorine-18 for *in vivo* Positon Emission Tomography (PET) or fluorophores for *in cellulo* optical imaging.



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[1] Kennedy, D. C.; McKay, C. S.; Legault, M. C. B.; Danielson, D. C.; Blake, J. A.; Pegoraro, A. F.; Stolow, A.; Mester, Z.; Pezacki, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 17993-18001.
[2] a) Kim, E.; Koo, H. ***Chem. Sci.*** **2019**, ***10***, 7835-7851. b) Oliveira, B. L.; Guo, Z.; Bernardes, J. L. *Chem. Soc. Rev.* **2017**, *46*, 4895-4950.
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Green and/or Solvent-Free Buchwald-Hartwig Amination: Towards Sustainable Catalysis

Deniz KARABIYIKILI, Philippe Steinsoultz, Martine Schmitt, Laurence Grimaud[1], and Frédéric Bihel[*†2]

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Metal-catalyzed amination reactions are pivotal in synthetic organic chemistry, especially in pharmaceutical and agrochemical industries for diversifying nitrogen-containing compounds. However, conventional protocols rely heavily on solvents, leading to environ- mental concerns and substantial waste generation, with solvents contributing up to 80% of by-products. To address these challenges, we aimed to develop eco-friendly conditions for this vital transformation. We emphasize the importance of transitioning to greener methodologies to reduce the environmental impact of chemical synthesis.(1) We focused on utilizing bio-based alcohol solvents and exploring solvent-free synthesis as alternatives to tra- ditional solvents like THF or toluene. Our efforts led to a novel precatalytic system featuring (Pd(π-allyl)tBuXPhos)Cl, highly effective in green solvents such as ethanol.(1a) Moreover, our catalytic system demonstrates versatility, extending its application to mechanochemical conditions, enabling coupling of aryl halides with various nitrogen-containing substrates.(2) This broadens the reaction scope, highlighting the potential of our approach for sustainable and atom-efficient synthesis. In conclusion, our work represents a significant step towards greener and more sustainable catalytic processes, utilizing bio-sourced solvents and exploring solvent-free methodologies to advance Buchwald-Hartwig amination.

(1) ACS.Catal. 2022, 12, 560; Chem.Eur.J 2017, 23, 13676; ChemSusChem 2016, 9, 3244; Green Chem 2014, 16, 4170; (2) to be submitted (2024)

Keywords: Amination, Green chemistry, Precatalytic system, Biosourced solvents, Mechanochemcal synthesis

SESSION 2- SYNTHETIC BIOLOGY

Chair
Coraline RIGOUIN, ESBS

Speakers
Barbara DI VENTURA, University of Freiburg, Freiburg, Germany
Vincent LEBRUN, University of Strasbourg, France
Florence BORDES, Toulouse Biotechnology Institute, France
Michael MULOT, HYBRIGENICS Services, Évry, France
Diana SCHWARZ, Karlsruhe Institute of Technology, Germany

Synthetic biology is a scientific field that involves redesigning organisms for useful purposes by engineering them to give them new capabilities. This session will explore synthetic biology, ranging from the development of tools for modifying biological systems to protein and metabolic engineering, across a wide range of applications.

Inteins as molecular tools for synthetic biology

Barbara DI VENTURA

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Signalling Research Centres BIOSS and CIBSS
Institute of Biology II
University of Freiburg
Germany

Several molecular biology tools rely on split proteins that are brought back in physical proximity via signal-responsive heterodimerization systems or interacting proteins. This allows for their *functional* reconstitution. Inteins, special proteins that excise themselves out of precursor proteins connecting the flanking polypeptides with a peptide bond, allow for the *physical* reconstitution of full-length proteins out of two split fragments. Once the peptide bond is made, the two protein fragments are irreversibly bound together and the protein regain its function without the need to continuously expose the cells to the external trigger or even after the interacting partners have dissociated.
In this talk, I will discuss what inteins are, and how we have exploited them to create a tool called SiMPI, which can be used to select population of cells carrying two plasmids (in bacteria) or two lentiviral constructs (in mammalian cells) with a single antibiotic. I will also introduce Int&in, a web server that runs a machine learning algorithm to predict active split sites in inteins.

A new scaffold to design artificial metalloenzymes for heterogeneous catalysis

M. Naudé,[1] N. Schulte,[1] L. Pieri,[2] F. Wien,[3] Y. El-Khoury,[4] V. Demais,[5] P. Hellwig,[4] M. Paternostre,[2] S. Bressanelli,[2] P. Faller,[1] and Vincent LEBRUN,[1]

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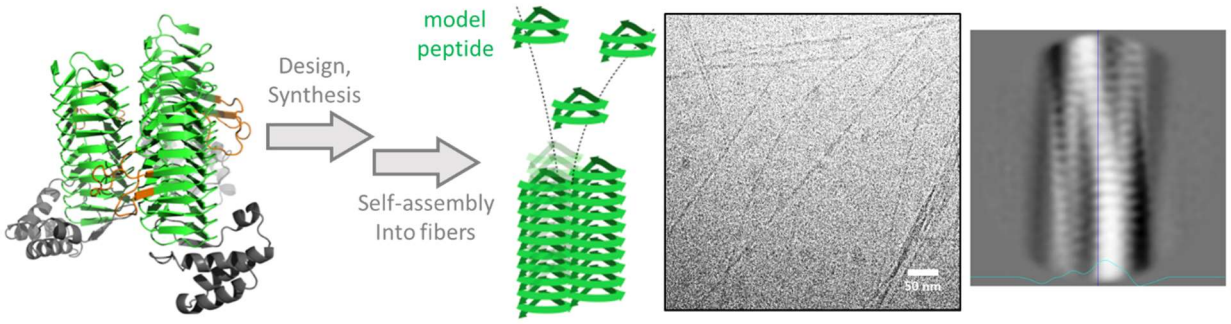
Tandem repeat proteins have been shown to be well-suited for protein design.[1] In that regard, diversifying the elementary units enables more elaborate architectures. The family of β–solenoid proteins has mostly been explored to build protein fibers (eg nanowires).[2–4] Indeed, whether natural or engineered, these proteins show interesting mechanical properties.[5] Here, we explore a fold that have not previously be used is such context: the Type I left-handed β–helix (LβH).[6]

We will first briefly present a sequence analysis of natural LβH-containing proteins.[7] Building on this, we designed a 35-aa de novo peptide that self-assemble into well-defined and robust fibers. We will present their spectroscopic characterization as well as TEM and CryoTEM images (see Figure below). Finally, we will present the use of this peptide as a scaffold for the design of artificial metalloenzymes.



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Combining enzymatic and metabolic engineering in the yeast *Yarrowia lipolytica* to produce original lipids and polymers

Vinciane Borsenberger[1], Zhongpeng Guo[1], Christian Croux[1], Julien Robin[1], Sophie Lajus[1], Marc Guéroult[2], Jean-Marc Nicaud[3], Cécile Neuvéglise[3], Sophie Duquesne[1], Alain, Marty[4], Isabelle André[1], Fayza Daboussi[1], Florence BORDES[1]

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3 -INRAE, AgroParisTech, Université Paris-Saclay, Micalis Institute, Jouy-en-Josas, France

4 -Carbios, Biopôle Clermont Limagne, Saint-Beauzire, France

As an oleaginous yeast, *Yarrowia lipolytica* is an attractive host for the production of lipid and lipid derived products. The efficient use of this yeast as cell factory requires powerful genetic tools dedicated both to the deletion and to the expression of multiple genes.
In a first part, the development of efficient tools for synthetic biology in *Yarrowia lipolytica* will be described

(1) a simple and robust CRISPR/Cas9 multiplexing approach to knock-out multiple gene in one transformation.

(2) an artificial chromosome (yIAC) that enables the efficient construction of metabolic pathways (up to 6 genes) in one step in *Y. lipolytica*.

In a second part, we will describe our efforts in enzymatic and metabolic engineering to modulate the lipid-derived products that could be produced by this yeast. Different case studies will be presented:

(3) the production of a hydroxylated fatty acid of industrial interest, through the expression of a bi-functional fungal hydroxylase/desaturase in an optimized strain for the production of unusual fatty acids. The molecular determinants of the specificity of this enzyme were investigated through mutagenesis and molecular modelling approaches

(4) the rational engineering of the lipid profile of *Yarrowia lipolytica* towards shorter fatty acids for biokerosene application. Thanks to an elegant genome editing technology combined to molecular modeling of the Ketoacyl Synthase domain of Fatty Acid Synthase, we demonstrate the possibility to produce original shortened fatty acids in this yeast.

(5) the tailored production of different high molecular weight polymers with valuable properties. This work allows a 5% (g/g) accumulation of polylactic acid in this yeast and 25% (g/g) accumulation of two medium chain length with different physicochemical properties.

Unraveling the proteome and ubiquitin pathways by chemically induced proximity

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The proteome quality control is critical for the maintenance of cellular functions, and it is assured by the proteostasis network. This complex protein machinery that identifies, rescues or degrade polypeptides is important for biological pathways such as autophagy, protein quality control and proteostasis during stress, aging and diseases. Protein-protein interactions (PPIs) stabilization by small molecules (Glues, PROTACs, ...) has become an attractive approach to target disease-causing proteins for destruction and expand the druggable proteome.

A comprehensive Yeast Two-Hybrid screening platform, which allows to perform unbiased and exhaustive protein interaction screens of highly complex cDNA libraries (135+ libraries), has been adapted to support Targeted Protein Degradation (TPD) projects, and now allows to supports all aspects of this important research field: (1) Protein Interaction discovery to identify pathways for proteins, RNA and DNA; (2) E3 ligases-POI specific chemical inducers discovery or validation; (3) Molecular Glues, PROTACs interactions profiling, deconvolution including off-targets and validation.
The readout and the absence of any washing steps contributes to its high sensitivity. In addition, each putative interaction partner is tested individually, eliminating the competition by abundant or strong binders. Intergraded bioinformatics allow to delineate interacting domains and to attribute confidence scores. Few examples will be exposed.

Keywords: Chemically induced proximity, Drug target deconvolution, Targeted Protein Degradation, molecular glues, PROTACs, proteostasis, protein interactions, E3 ligases

Influencing tomato root development by genetic modification of MIG (mycorrhiza induced GRAS) transcription factors

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The arbuscular mycorrhiza symbiosis (AMS) can be established by over 80% of all land plants. To accommodate the fungal structures inside the root cortex cells the plant undergoes major transcriptional reprogramming to ensure the maintenance of the AMS. Many of the genes involved belong to the family of GRAS transcription factors. Members of the MIG1 (mycorrhiza-induced gene 1) clade are induced upon mycorrhization and play an important role in mycorrhizal root development by adjusting the cortical cell size. This is necessary to adequately harbor the fungus in the cortical root cells during colonization. MIG1 hereby acts as a positive regulator by increasing the size of cortex cells whereas MIG3 shows an antagonistic function. In the agronomic important model organism tomato four putative homologues have been identified. We are using these homologues as targets for genetic engineering of tomato root development to gain enhanced access to limited nutrients in the soil. To achieve this, we try to either overexpress the MedicagoMIG1 homolog in tomato as a positive regulator of radial cell expansion to enhance the cell size or downregulate negative regulators like MIG3 and SCL3 (scarecrow-like 3) by using the CRISPR/Cas12a technology to abolish their negative effects on cortex cells.

Keywords: AM symbiosis, GRAS transcription factors, root development, genetic engineering, CRISPR/Cas

SESSION 3- NEW STRATEGIES IN DRUG RESEARCH

Chair
Christophe DECROOS

Speakers
Luisa DE COLA, University of Milan, Italy
Julie KARPENKO, University of Strasbourg, France
Vianney POIGNAVENT, Serendip Innovations, Strasbourg, France
Laetitia PRÉAU, Karlsruhe Institute of Technology, Germany
Aurora SILVESTRI, IGBMC, Illkirch, France

Drug research is at the crossroads of several disciplines such as biology, chemistry, medicine and pharmacology. The process of drug development to the clinics is complex and faces challenges at every step including but not limited to target identification and validation, hit identification, lead optimization, drug delivery… This session will provide a highlight of current research in the field with examples spanning from systems biology for drug target identification, drug development assisted by biophysical and structural biology techniques, chemical probes for diagnostic to drug vectorization by nanomaterials or biological nanoparticles.

Small Breakable nanocapsules for crossing body barriers

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Nanoparticles have recently emerged has possible vectors for the protection, transport, and release of biomolecules, as recently also demonstrated in their use for COVID vaccine. Amongst the biggest challenges for the use of nanoparticles for drug delivery are their complete elimination and their capability of crossing barriers [1] within the human body.
Many materials have been tested for biocompatibility and degradability in vivo. Silica and in particular organosilica has emerged as a possible component for the creation of capsules and porous systems able to entrap a large number of active components and even deliver them on demand [2].
In this study we report a carrier based on organosilica nanocapsules, able to entrap both small molecules and chemotherapeutic active compounds to be used for cancer treatment.
We demonstrated that even proteins, and we used Green Fluorescent Protein (GFP) to be visible, can be successfully encapsulated into nanocapsules and release on demand. We have employed a caco2 cell line showing their internalization and localization around the nuclear membrane. Due to the presence of the disulfide groups in the silica framework, constituting the shell of the capsules, a reducing agent, such as Glutathione (GSH), can destroy the capsules [3]. The disulfide bridges are infact reduced into thiols allowing the breakability of nanocapsules and their release of GFP. The size of these nanocarriers is only 40 nm and we showed that they are able to cross the natural EpiIntestinal barrier (provided by MatTek). Such a barrier i sone of the obstacle that we need to overcome to treat gastrointestinal disease. The nanoparticles can be followed by the fluorescence of the GFP and their penetration through the human layer has been demonstrated collecting them at the bottom after their passage. The lack of their degradation upon interacting with cells was checked by their morphology and size before and after the experiment. In order to establish the lack of cell membrane damage during their crossing Trans Epithelial Electrical Resistance (TEER) was measured and the unchanged values confirmed the safety of the capsules.
Finally a study on drug delivery was carried out by encapsulation of doxorubicin into the nanocapsules to check the *in vivo* biodistribution and the pharmacological activity of the drug.

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Alared: a solvatochromic red amino acid for labeling of bioactive peptides

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Fluorescent probes for rapid detection of bacteria are needed for the diagnostics of bacterial infections as a measure to reduce the spread of antibiotic resistance. Here we report the design and synthesis of bacteria-targeting turn-on fluorescent peptides incorporating Alared, an environmentally sensitive fluorescent unnatural amino acid based on the Nile Red fluorophore. The new peptide-based probe named **UNR-1** possessed deep red emission and enabled rapid fluorescence staining of live and dead Gram-positive and Gram-negative bacteria, while also exhibiting selectivity over mammalian cells. The probe was compatible with diffraction-limited and super-resolution fluorescence microscopy and with flow cytometry. At the same time, the solvatochromic properties of Alared were suitable for probing the local microenvironment of the probe. For instance, the defined cellular localization of the probe enabled monitoring of the perturbations in the bacteria cell envelope caused by heat inactivation and exposure to antibiotics.

A modular plant virus-derived nanoparticle for drug vectorization

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Virus-like particles (VLPs) are nanometric structures resulting from the self-assembly of one or more viral capsid proteins. They lack genetic material and, consequently, are non-infectious. The vaccine potential of VLPs is well established, and several prophylactic vaccines now on the market (e.g., hepatitis B vaccines or those against the human papillomavirus) have utilized this technology. Indeed, due to their sizes and their ordered and repetitive structures, VLPs resemble viruses and are thus "naturally" recognized by the immune system. They are therefore an ideal tool for inducing potent immune responses. Furthermore, VLPs can be genetically modified or chemically coupled to carry biomolecules of interest (proteins, peptides, RNA, etc.) for therapeutic applications, diagnostics, or imaging.
Serendip innovations' breakthrough lies in a modular VLP derived from a grapevine virus. This VLP can be tailored to enclose therapeutic compounds of interest within its internal cavity and to display cell-targeting proteins on its surface. The VLP is composed of a single protein, called the capsid protein (CP), which spontaneously self-assembles in plants (60 CPs form a VLP). Modifying this CP allows for the creation of VLPs whose internal and external surfaces are functionalized with proteins or peptides of interest after assembly. Using ovalbumin-derived antigens, we have demonstrated the ability of this platform to trigger CD4+ and CD8+ immune responses *in vitro* and *in vivo*. Furthermore, we have carried out a proof-of-concept vaccination study in a mouse cancer model to validate the therapeutic potential of our platform. These pioneering efforts pave the way for the development and use of new vectorization systems based on plant-derived VLPs.

Systems approaches identify new drug targets for vascular therapies

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Selective targeting of the vascular growth process is crucial to alleviate hypoxia in pa- tients with cardiovascular disease. VEGF-based therapies require strategies for the precise titration of VEGF signaling output. Bulk and single-cell sequencing analysis of WT and zebrafish mutants with a VEGF gain-of-function scenario identified several pathways reg- ulating VEGF signaling output. We found that Vegfa bioavailability is fine-tuned by the opposing actions of Vegfa decoy receptor Flt1 and Esm1 produced by parenchymal cells. Vegf signaling strength controls EC size to determine lumen diameter in developing vessels. Additionally, parenchymal Vegfa and Apelin act in synergy to titrate endothelial VEGF sig- naling strength in venous ECs to induce sprouting. Single-cell sequencing of FACS-sorted ECs identified a subset of venous ECs expressing the Apelin-receptor (Aplnr) and VEGF receptor-2/Kdrl. Upon exposure to both parenchymal Apelin and Vegfa, the activated Aplnr and Kdrl genetically interact to amplify VEGF signaling output, promoting the formation of a specialized venous angiogenic cell. We conclude that precise titration of VEGF sig- naling output is achieved by regulating VEGF ligand level and VEGFR2 signaling strength via genetic interaction with others receptors activated by a combination of tissue-derived cues. This opens novel therapeutic avenues for interfering with vascular remodeling defects in disease conditions.

Keywords: angiogenesis, VEGF

Structural studies of CBP/p300 complexes and characterization of peptide based CBP inhibitors

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Intrinsically disordered proteins are crucial for cellular processes, as they are highly flexible and can bind to multiple targets. ACTR and CBP/p300 are coactivators that regulate gene expression of highly regulated genes by interacting with many transcription factors. However, overexpression of these proteins has been linked to various diseases, including cancer and metabolic disorders. My PhD project aims to study a new therapeutical strategy to target the interacting disordered domains of ACTR and CBP/p300, characterizing them bio- chemically and structurally within a transcription factor complex to gain insights into their function. A library of synthesised peptide AD1 domain of ACTR, containing non-canonical amino acid modifications, such as α-methylated leucine and D-amino acids, is used to specifi- cally interact with the NCBD domain of CBP/p300, stabilising the formation of the complex. The project aims to characterize the biological effects of these modified ACTR peptides on CBP/p300-mediated activities, transcription activation of nuclear receptors and acetylation activity, as well as to study the three-dimensional structure of CBP/P300 functional complexes with the nuclear receptors PPARγ2/RXRα. To this end, we have developed a set of approaches combining expertise in biochemistry, biophysics and Cryo-EM.

Keywords: CBP/p300, nuclear receptor, coregulators, Cryo, EM, gene transcription

ROUND TABLES

OPEN SCIENCE

Chair - Katia BEFORT, Société de Biologie de Strasbourg

Speakers

Stéphanie CHEVIRON, University of Strasbourg, France
Héloïse GAZEAU, University of Strasbourg, France
Jan LEENDERTSE, University of Freiburg, Germany
Raphaël LEVY, University Sorbonne Paris Nord, France
Éric QUEMENEUR, Transgene, Strasbourg, France
Stéphanie RENNES, Ministère de l'économie, des finances et de la souveraineté industrielle numérique, Paris, France
Andrea THORN, University of Hamburg, Germany

Open science is a set of principles and practices that aim to make scientific research from all fields accessible free of charge to everyone for the benefit of scientists and society as a whole. It includes several principles, like open methodology, open source, open data, open access, open peer review, open educational resources. Several current challenges of open science will be discussed at the round table, including democratization of access to the results of high-quality, increase of the effectiveness of research, innovation through the reuse of results, and advance knowledge as a common asset for humanity? Interactions between academic and industry will be addressed.

EQUITY & INCLUSION IN SCIENCE

Chairs - Sylvie FOURNEL, Société de Biologie de Strasbourg
Arwen PEARSON, University of Hamburg, Germany

Speakers
Serena BERNACCHI, Women in Science, Strasbourg, France
Romain BOURDY, University of Strasbourg, France
Émilie DENAT-TURGIS, Rectorat de Strasbourg, France
Marine DESAGE-EL MURR, Women in Science, Strasbourg, France
Isabelle KRAUSS, University of Strasbourg, France
Éloi VERRIER, University of Strasbourg, France

Various people may suffer disadvantages in science (diversity is not just about women):
- neurodivergent
- migration background (linguistic/cultural challenges)
- less privileged backgrounds
- non-male (women, trans, non-binary)
- people with care responsibilities (children, elder care, sick relatives)
- people with disabilities

In this round table, we will focus on Women and People with disabilities.

To address these issues, several points can be addressed:

1- Diagnosis
- What types of studies can/should be/have already been conducted?
- On what parameters should the questions be asked?
- Who should conduct the studies (researchers, university, association, HR system, etc.)
- What studies already exist? At what level?
Local: universities, institutes etc., national, European
- What are the differences between France and Germany?

2- Proposed solutions
- At what level? During studies? Before recruitment? During recruitment? After recruitment?
- Who? (Institutions, Human resource department, university or institute, associations, ministries, others, etc.)
- What solutions? Local? In France? in Germany?

3- Management and training PIs in benevolent management: the solution?
What already exists? Is this the solution?

SCIENCE WITH & FOR THE SOCIETY

Chair - Marcel HIBERT, University of Strasbourg

Speakers

Marlin DÜRRSCHNABEL, Karlsruhe Institute of Technology, Karlsruhe, Germany
Mélodie FAURY, Muséum national d'Histoire naturelle, Paris, France
Pierre FECHTER, Maison pour la Science, Strasbourg, France
Meriem FOURNIER, INRAe Grand Est, Nancy, France
Bénédicte LEBEAU, University of Haute Alsace, Mulhouse, France
Céline TARNUS, University of Haute Alsace, Mulhouse, France
Agnès VERNET, Science journalist, AJSPI, Lyon, France

Science with and for Society. A mission set out in the 'Loi de Programmation de la Recherche'

The challenge is to strengthen the relationship between researchers and the lay public by building trust, familiarity and reciprocity into the relationship. This strategy requires the link between science and society to be recognized as a dimension of scientific activity.

It aims to

- contribute to democratic and scientific debate
- support public decision-making
- enable everyone to understand and participate in the surrounding environment.

However, there are still many unanswered questions surrounding this mission:

- Is this the role of scientists?
- What are the benefits of getting involved?
- How can we get involved? How can projects be developed?
- What can be achieved?

Through a few examples of projects, interactions and support, we will try to provide some clues to this question.

EVOLUTION OF SCIENCE JOBS

Chair - Giovanna LATERZA, Pépite Etena, University of Strasbourg

Speakers

Farah BOUHEDDA, Merck, Molsheim, France
David BRUCHLEN, ScienceMeUp, Strasbourg, France
Philippe CHAVOT, University of Strasbourg, France
Xavier ESPANEL, NovAliX, Strasbourg, France
Amandine PERRET, University of Strasbourg, France
Guillaume VETTER-GENOUD, Quest for Health, Strasbourg, France

In an era of rapid scientific advancement and shifting career landscapes, the "Evolution of Science Jobs" roundtable aims to explore the dynamic changes in the science employment sector. This engaging session is designed for young researchers eager to understand the evolving opportunities and challenges within their field. The roundtable will bring together a distinguished panel of experts, each offering unique insights into different aspects of the science job market.

Our panel includes Guillaume Vetter Genoud, director of the deeptech startup incubator Quest for Health, who will provide an insider's perspective on the role of innovation and entrepreneurship in shaping science careers. David Bruchlen, CEO of Science Me Up - a recruitment agency specialized in technical profiles - will discuss trends in hiring, skill demands, and how young researchers can enhance their employability in a competitive job market. Adding to this, Xavier Espanel, SVP of Co-located Research at Novalix, will share views on pathways for scientists interested in research and development outside academia. We will also hear Farah Bouhedda who -after pursuing the research valorization path- has joined Merck as R&D Scientist. Additionally, Amandine Perret, specialist in transversal training for PhDs, will address the critical skills that go beyond technical expertise that are essential for career progression in today's interdisciplinary and collaborative scientific landscape. Moderation will be handled by Giovanna Laterza -Program Manager at the University Entrepreneurship Center Pepite Etena- who will guide the discussion to uncover actionable insights and practical advice for young scientists planning their careers.

This roundtable is an unmissable opportunity for young researchers to gain valuable career guidance and envision their future in the ever-evolving world of science jobs.

ARTIFICAL INTELLIGENCE AT THE BIOLOGY / CHEMISTRY INTERFACE

Chair - Christophe ROMIER, Société de Biologie de Strasbourg

Speakers

Jean-Luc DIMARCQ, IHU, University of Strasbourg, France
Jean-Marc DELTORN, CEIPI, University of Strasbourg, France
Anne JEANNIN-GIRARDON, CRBS, University of Strasbourg, France
Gilles MARCOU, Chemistry Faculty, University of Strasbourg, France
Andrea THORN, University of Hamburg, Germany

Artificial Intelligence (AI) is receiving an enormous attention due to the major impact it could have on our lives, including on our scientific jobs. A lot is being written on AI but what is AI, what are its strengths and weaknesses, how it impacts and should impact our daily work in biology, chemistry, medicine and beyond, how it should evolve, and how it could/should be regulated, remain major questions that need to be answered to really apprehend AI and tailor this technology to address our scientific needs. This round-table gathers AI specialists with different backgrounds that will provide specific perspectives on AI to better understand this technology, its implications, and its potential to be used as a tool to develop our future research.

POSTERS

P1

A Composition of clays of western soils of Algeria

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The clay is a sedimentary rock, made up of specific minerals, with puff pastry (phyllo silicates) or fibrous structure (sepiolitis and polygorskite). These geotechnical characteristics are essential to explain their differences in absorption qualities and their plasticity. The uses of clay, particularly those rich in SiO_2 and Al_2O_3, are many and varied. They are used in construction materials, artisanal and industrial ceramics, cement manufacturing, the pharmaceutical industry, water treatment (removal of dyes and pollutants) and pottery.

The main objective of this study is the study of the physicochemical properties of clays from western Algeria, such as the determination of humidity level, pH, swelling index, colloidality loss in fire.

This study aims to understand the relationship between the properties, measured by the swelling potential on the one hand, and the measured rheological properties and the mineralogical structure of these suspensions, determined by XRD and Infrared spectroscopy, on the other hand

Keywords: Clays – Mineralogical composition, Therapeutic effect, Physicochemical properties

P2

A Thia-Diels-Alder Click Reaction for the Straightforward Labelling of Peptides under Green Conditions

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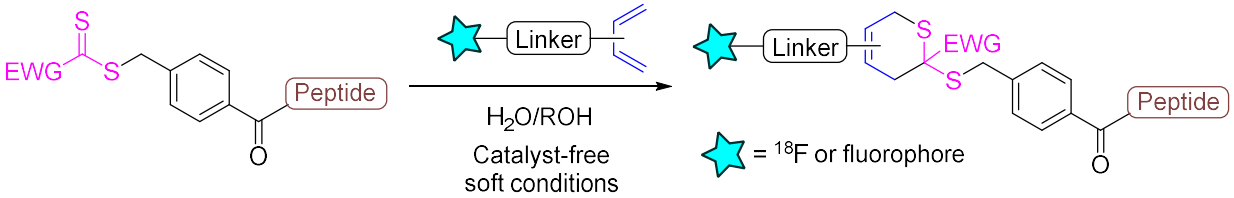
Click reactions represent an efficient method for the chemoselective modifications of peptides of proteins in mild conditions. Amongst these reactions, the Cu-Catalysed Alkyne-Azide cycloaddition (CuAAC) remains the most used system despite the *in vivo* toxicity of the Cu(I) catalyst that may get trapped by the peptide at the end of the reaction [1]. Alternatives such as the Strain-promoted Azide-Alkyne cycloaddition (SPAAC) or the Inverse Electron Demand Diels-Alder reaction (IEDDA) have been developed [2] to overcome this issue but still remain scarcely represented in the literature mostly due to poor accessibility and high cost of the reactive partners.
Herein, we report the use of a thia-Diels-Alder reaction between a dithioester and a diene [3] for the chemoselective labeling of peptides under catalyst-free mild conditions. While this cycloaddition had already been used as a click reaction to functionalise the Bovine Serum Albumin (BSA) with polymers [4], it had never been applied to the chemoselective labeling of peptides for imaging applications. Thus, we developed a practical method to introduce for the first time the phosphonodithioester moiety into a model peptide. Then, the diene was designed to combine good stability and high reactivity towards the dithioester partner while keeping mild reaction conditions. Finally, bioactive peptides were labelled with either fluorine-18 for *in vivo* Positon Emission Tomography (PET) or fluorophores for *in cellulo* optical imaging.



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P3

Analysis of putative interaction partners of virulence factors from the nematode trapping fungus Arthrobotrys flagrans and its host Caenorhabditis elegans during their interaction

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Nematophagous fungi are a widespread group of predatory fungi that capture nematodes as a food source under nutrient-starvation conditions and in the presence of nematodes. The fungi sense nematodes through nematode-specific ascaroside pheromones. An indicator for the predatory lifestyle is the formation of specialized traps to catch the nematodes, in which the fungus lures them by producing volatiles as attractants (Yu, H. et al., 2021). During the infection process the fungus secretes various virulence factors which enable the colonization of the nematode (Wernet, N. et al., 2021a) (Fischer, R., & Requena, N., 2022). The virulence factors CyrA and NipA from the nematode-trapping fungus Arthrobotrys flagrans are the first ones to be characterized, yet their specific roles and interacting proteins during infection with the host Caenorhabditis elegans remain unclear (Emser, J., et al., 2024, in re- vision). Therefore, mass spectrometric analyses (MS) will be employed to search for putative interacting proteins of CyrA and NipA. Promising candidates will undergo further molecular characterization through interaction studies, reporter fusions, and gene deletions. Identifying interaction partners of the virulence factors within the fungus and its nematode host can provide insights into their functioning as well as increase the knowledge about host-pathogen interactions.

Keywords: nematode trapping fungi, host pathogen interaction, virulence factors

P4

Aptamer-based targeted therapeutic approach in sepsis-induced disseminated intravascular coagulation

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According to the Third International Consensus, sepsis is defined as “a life-threatening organ dysfunction caused by a dysregulated host response to infection”. Septic shock is the most severe form of infection which in 30% of cases can lead to disseminated intravascular coagulation (DIC) with a mortality rate of 60%. DIC is associated with an excess of coagulation and a deficiency of fibrinolysis.

We hypothesise that a treatment against DIC targeting both the procoagulant response and restoring fibrinolytic insufficiency in patients with septic DIC might limit microthrombi formation. Our research project aims to develop an innovative strategy based on bifunctional nucleic acid aptamers. These are short oligonucleotide sequences with high affinity and specificity for their targets and with many advantages over antibodies. The bifunctional aptamer is composed of an anti-phosphatidylserine aptamer to bind fibrinolytic microvesicles and an aptamer directed against thrombin to reduce excessive coagulation activity.

Our current results indicate that aptamers targeting thrombin and phosphatidylserine have a stability in Foetal Serum Bovine which depends on aptamers. We will then assess the stability of bifunctional aptamers and evaluate the in vitro efficiency of our strategy. Afterwards, we will determine it the efficacy and the tolerance on a murine model of DIC.

Keywords: sepsis, disseminated intravascular coagulation, aptamer, microvesicle

P5

Bone marrow-derived cells impact metastases formation in pancreatic cancer

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Pancreatic cancer is characterized by early dissemination and is associated with poor prognosis. To develop into metastases, disseminated cancer cells require appropriate niches at distant organs. Metastatic niches are formed, at least in part, by bone marrow derived cells (BMDCs). Prior the arrival of cancer cells, BMDCs form pre-metastatic niches supporting adhesion, growth and immune evasion of incoming cancer cells.

Our group has shown that inhibition of the cell adhesion molecule CD44, on pancreatic cancer cells and on host cells, in several animal models blocked the metastatic process. Additionally, we have detected clusters of CD44+ BMDCs, in the liver prior metastases formation. We are currently assessing the impact of a Cd44 knockout specifically in BMDCs using the Cd44fl/fl; VavCreERT2 inducible mouse model, before and during metastatic niche formation. The removal of Cd44 from BMDCs leads to a drastic reduction in metastasis in vivo. In vitro, using a triple co-culture system including primed BMDCs, pancreatic cancer cells and cells from the microenvironment, we show that CD44 is involved in CCL2-, CCL5- and CXCL12-mediated migration and VCAM-1- and fibronectin-mediated adhesion. We additionally demonstrate an involvement of CD44 in the immunosuppressive function of BMDCs by influencing their cytokine expression profile.

Keywords: cancer, immunology, mouse model

P6

CD44, a versatile molecule impacting cancer cells and the surrounding stroma in gastrointestinal cancers

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Due to the inherent inefficiency of the metastatic process, cell population bottlenecks that select for cells possessing critical properties must exist. Stemness may be one such property. In colorectal cancer however, it was recently shown that metastatic cells are differentiated. In contrast, the maintenance of distant metastases requires a dedifferentiation step into stem cells in a process called plasticity. This reprogramming of cancer cells is boosted by signals from the microenvironment. Upon inhibition of CD44, a family of transmembrane glycoproteins, we can block cell plasticity by broadly modulating reprogramming signals in state-of-the-art LGR5DTR/eGFP tumoroids ex vivo. In addition, we show that the pleiotropic functions of CD44 as a co-receptor for several signaling pathways
are essential for plasticity.
The inhibition of the co-receptor functions of CD44 on cancer cells was also shown to have a major impact in several pancreatic cancer models. Targeting CD44 in the pancreatic tumor stroma also impacts tumor development. In addition, destabilizing the metastatic ecosystem through inhibition of CD44 in activated niche-forming cells such as bone-marrow derived cells, also could prevent further metastatic development.
Altogether, the combined action of CD44 at different levels of the metastatic process makes it an attractive target for therapy.

Keywords: CD44, plasticity, gastrointestinal cancers, organoids

P7

Chemoenzymatic synthesis of protein pseudo-(2)rotaxane

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Intrinsically disordered proteins (IDPs) display enhanced conformational flexibility and structural heterogeneity. They are able to recognize diverse molecular targets and engage in multivalent interactions. For instance, transcriptional co-activators ACTR (p160) and p300/CBP contain IDP regions which are involved in the formation of multiprotein complexes with nuclear receptors regulating the transcription of many genes.

The interaction domains (the activation domain of ACTR and the nuclear coactivator binding domain (NCBD) of p300/CBP) can be synthesized chemically. The objective of this work is to deepen the study of the ACTR/NCBD complex as well as its influence on bio- logical mechanisms. For this, (2)rotaxane protein complex will be designed and synthesized. Its synthesis will be carried out by cyclization of the ACTR activation domain when it is bound to NCBD. The cyclization will be carried out by enzymatic ligation using the plant asparginyl endopeptidase, OaAEP1b. We will also study the influence of the (2)rotaxane formation on the inhibition of protein-protein interactions in vitro. Ultimately, the objective is to study the formation of a protein complex with the topology of (2)rotaxane in the cells and the subsequent inhibition of native protein-protein interactions.

Keywords: Chemical peptide synthesis, Protein protein interaction, Molecular topology

P8

Context-dependent conformational and dynamic properties of prolines in proline-rich peptide elucidated by 4,4-difluoroproline incorporation

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Protein-protein interactions rely on structural features such as post-translational modifications, ligand binding, and conformational changes. Binding regions, often unstructured, are recognized by specialized peptide binding domains like SH3, SH2, and PDZ. However, the disordered nature of these regions complicates understanding and predicting interactions. Proline, highly represented in such regions, is known to influence conformational dynamics. In our work, we focused on the interaction between the proline-rich region and SH3 domain in the BIN1 protein which plays a critical role in centronuclear myopathies (CNM). To over- come structural challenges, we used Nuclear Magnetic Resonance (NMR) techniques. We synthesized a library of fluorinated peptides of the BIN1 fragment (298-320) by inserting 4,4-difluoroproline (4,4-DFP). Fluorine, selected for its sensitivity and high gyromagnetic ratio, served as the spectral probe, simplifying the NMR spectra of the polyproline peptide segment.

Keywords: Fluoroproline, Intrinsically Disordered Protein (IDP), fluorine NMR, proline rich motifs (PRM), amphiphysin 2 (BIN1)

P9

Contribution of CD44 Expressed on Tumor-Associated Macrophages (TAMs) to the Progression of Pancreatic Cancer

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CD44 isoforms have been shown to promote tumor growth and metastasis in pancreatic ductal adenocarcinoma (PDAC). However, this family of transmembrane glycoproteins is not only expressed on cancer cells but also in the stroma which makes up to 90% of the PDAC tumor volume. Tumor-associated macrophages (TAMs) are the most prominent immune cells in the PDAC microenvironment. Since CD44 isoforms are involved in the progression of PDAC and are expressed on macrophages, the aim of this project is to investigate its potential role in the polarization of macrophages using the Cd44 knockout mouse model: Cd44fl/fl;Csfr1Cre. We also aim at exploring the consequences of a macrophage-specific deletion of Cd44 on tumor invasion, angiogenesis, and immunosuppression. Our results show that M2-polarized bone marrow derived macrophages (BMDMs) express more CD44 as compared to M1-polarized macrophages. Additionally, the Cd44 knockout in BMDMs reduces their polarization to the M2 phenotype. Finally, in-vivo experiments indicate that the Cd44 knockout in macrophages leads to a reduced number of liver metastasis in mice orthotopically injected with pancreatic cancer cells. These preliminary results suggest the potential role of CD44 expressed on TAMs on their polarization and their pro-tumoral effects.

Keywords: CD44, PDAC, pancreatic cancer, Tumor, associated macrophages

P10

Green and/or Solvent-Free Buchwald-Hartwig Amination: Towards Sustainable Catalysis

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Metal-catalyzed amination reactions are pivotal in synthetic organic chemistry, especially in pharmaceutical and agrochemical industries for diversifying nitrogen-containing compounds. However, conventional protocols rely heavily on solvents, leading to environ- mental concerns and substantial waste generation, with solvents contributing up to 80% of by-products. To address these challenges, we aimed to develop eco-friendly conditions for this vital transformation. We emphasize the importance of transitioning to greener methodologies to reduce the environmental impact of chemical synthesis.(1) We focused on utilizing bio-based alcohol solvents and exploring solvent-free synthesis as alternatives to tra- ditional solvents like THF or toluene. Our efforts led to a novel precatalytic system featuring (Pd(π-allyl)tBuXPhos)Cl, highly effective in green solvents such as ethanol.(1a) Moreover, our catalytic system demonstrates versatility, extending its application to mechanochemical conditions, enabling coupling of aryl halides with various nitrogen-containing substrates.(2) This broadens the reaction scope, highlighting the potential of our approach for sustainable and atom-efficient synthesis. In conclusion, our work represents a significant step towards greener and more sustainable catalytic processes, utilizing bio-sourced solvents and exploring solvent-free methodologies to advance Buchwald-Hartwig amination.

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Keywords: Amination, Green chemistry, Precatalytic system, Biosourced solvents, Mechanochemcal synthesis

P11

Editing peptide properties by alpha-methylation

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Intrinsically disordered proteins (IDP) constitute a significant part of a eukaryotic proteome and are involved in numerous signalling pathways1. These proteins have no stable tertiary structure under physiological conditions and therefore might have more than one function. Not all existing protein conformations are functionally relevant, and others are involved in many misregulations leading to diseases progression. Our project focuses on two IDPs Nuclear Coactivator Binding Domain (NCBD) of Creb binding protein (CBP) and Activation Domaine 1 (AD1) of Activator for Thyroid and Retinoid Receptors (ACTR) which form a stable complex and are known to participate in many cellular processes such as cellular growth, migration and apoptosis 23. The goal of our project is to coerce rigidification of the backbone of the AD1-ACTR by alpha methylation, and hence stabilize some biologically relevant conformations. Alpha methylation was also proven to compel NCBD/ACTR complex stabilization. To validate our point, we are using solid phase peptide synthesis to prepare different variants of ACTR and then study them by X-ray crystallography, nuclear magnetic resonance and isothermal titration calorimetry.

Keywords: intrinsically disordered proteins, alpha, methylation, SPPS, ACTR, NCBD, X, ray crystallography, NMR, ITC

P12

EFFECT OF BINGE LIKE SUCROSE INTAKE ON NEUROINFLAMMATORY GENE EXPRESSION IN RATS

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Eating disorders, characterized by inappropriate food consumption, are associated with severe physical, psychosocial, and neurological consequences (obesity, anxiety, memory issues). Among these disorders, binge eating disorder (BED) is the most prevalent. It is characterized by the consumption of a large amount of food in a short period, accompanied by a sense of loss of control. However, despite recent studies suggesting that alterations in structures of the brain's reward circuitry may underlie these disorders, the neurobiological mechanisms involved remain poorly understood. Understanding this psychiatric condition and the underlying brain mechanisms is of major interest in terms of public health and therapeutic approaches. In this context, we have established a model of BED simulating uncontrolled sucrose intake in rats. The objective of our study is to characterize the transcriptional and protein regulations following binge-like sucrose consumption, focusing on neuroinflammatory processes, and to determine the brain structures and cell types where they occur. Our initial results revealed opposite gene regulation of the NF-kB subunit p105 in the medial prefrontal cortex and the ventral hippocampus of binge-eating rats, thus suggesting a role of the NF-kB system in the maladaptive behaviors observed in binge eating.

Keywords: binge eating disorder, neuroinflammation, NFkB, brain, reward circuit

P13

Effect of the loss of the interaction between the Cohesin complex and its NIPBL regulator in vivo

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The DNA is highly compacted and organized within the eukaryotic nucleus, enabling specific regulation of nuclear processes by restricting the access to the genetic information but also by bringing together specific functional elements of the genome. The Cohesin com- plex (SMC1A/SMC3/RAD21) plays a key role in the three-dimensional organization of the eukaryotic genome. Cohesin is involved in a large number of nuclear processes, ranging from the cohesion of sister chromatids to the formation of chromatin loops. Reflecting its large functional implications, Cohesin dysregulation is associated with numerous diseases. Notably, Cohesin is found mutated in many cancers and is responsible of specific neurodevelopmental diseases termed cohesinopathies. The best characterized cohesinopathy is the Cornelia de Lange Syndrome that is characterized by autism spectrum disorders, intellectual disability and physical deformities. Cohesin operates through two mechanisms: stable DNA tethering and dynamic loop extrusion, yet the regulation of these processes remains poorly understood. I am using the zebrafish, a recognized CdLS model, to investigate the functional importance of specific residues and regions of the Cohesin complex. These analyses enable me to characterize the functional importance and role of these residues and regions to better understand the regulation of the complex and how CdLS mutations perturbs it.

Keywords: Cohesin, Cohesinopathies, Zebrafish, Genome organisation, CdLS

P14

Exploring Structure-Activity Relationships of a highly potent inhibitor of the metalloenzyme IspH

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Antibiotic-resistant bacteria emerge and spread worldwide, underlining the importance of finding new solutions to combat them. IspH, also called LytB, is an oxygen-sensitive (4Fe- 4S) enzyme involved in the methylerythritol phosphate (MEP) pathway. It converts €- 4-hydroxy-3-methylbut-2-enyl diphosphate (HMBPP) into isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), the two crucial building blocks needed for the biosynthesis of isoprenoids. The MEP pathway is essential for the survival of most pathogenic bacteria, including those classified by the WHO. As this pathway is absent in humans, it represents an attractive target for the development of new antibacterials with innovative mode of action. Our previous research revealed €-4-amino-3-methylbut-2-enyl diphosphate (AMBPP) as one of the best inhibitors of IspH, with inhibition constant in the nanomolar range. Nevertheless, due to its low metabolic stability, its antibacterial effect has not been demonstrated. Here, we investigated the replacement of the diphosphate moiety of AMBPP by more stable substitutes such as sulfonate, phosphonate or phosphinophosphonate. After synthesis of the corresponding analogs, enzymatic assays highlighted the importance of the diphosphate moiety within AMBPP, emphazing its pivotal role in conferring and sustaining IspH inhibition.

Keywords: MEP pathway, IspH, antimicrobial resistance, (E), 4-amino-3-methylbut-2-enyl diphosphate (AMBPP), Structure, Activity Relationships

P15

Graphene nanodots as SEIRAS and SERS substrate for the study of membrane proteins

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Surface-Enhanced Infrared Absorption Spectroscopy (SEIRAS) and Surface-Enhanced Raman spectroscopy (SERS) are surface sensitive techniques that exploit the electromagnetic properties of nanostructured metal films to enhance the signal intensity of vibrational bands. This enhanced effect strongly depends on the metal-film type, its morphology and density. The ability of graphene nanostructures to support strong plasmonic resonances in the infrared part of the spectrum makes them an ideal platform for this spectroscopy techniques.

One application of SEIRAS and SERS is the study of proteins at very low concentrations. The proteins have to be immobilized close to the surface and maintain their structural and functional integrity.
In this study, we probe graphene nanodots deposited by drop casting or spray coating techniques on a silicon crystal for the study of cytochrome bd I oxidase from E. coli, a membrane protein that is present in the respiratory chains of many pathogenic bacteria. The protein was successfully immobilized on the graphene nanodots. The amide I signal confirms the structural integrity of the protein. SEIRAS and SERS experiments reveal a small but reproducible enhancement of the protein signals. This highly stable substrate is very promising for the use in biosensors.

Keywords: Cytochrome bd oxidase, graphene nanodots, biosensors, infrared spectroscopy, raman spectroscopy, surface, enhancement

P17

Human cerebellar organoid model to study region-specific neuropathology

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Pontocerebellar hypoplasia type 2a (PCH2a) is a rare neurogenetic disorder characterized by severe neurological impairment, particularly affecting the cerebellum and pons. PCH2a is caused by homozygous mutations in tRNA splicing endonuclease complex subunit (TSEN). Although the TSEN genes are widely expressed, the tissue-specific pathological mechanism of PCH2a remains unclear due to the absence of suitable model system. Brain organoids, derived from induced pluripotent stem cells (iPSCs), offer unique platform to study neurodevelopmental disorders with region-specific manifestations. Using different small molecules we can recapitulate region-specific brain development generating neuronal and glial pro- genitors and differentiated cells. We have recently used PCH2a patient-derived iPSCs and differentiated neocortical and cerebellar organoids and found that they recapitulate brain region-specific pathology. To extend this research, we aim to increase the reproducibility of cerebellar organoid differentiation derived from different cell lines and to further enhance and upscale brain organoid culture to improve reproducibility, enable live analysis of differentiation processes, and automate experimentation for pharmacological assays. By comparing our findings with published single-cell RNA sequencing data and histological stainings of the developing human cerebellum, our goal is to further establish cerebellar organoids as a human-specific model for prenatal cerebellar development and elucidate the pathological mechanisms underlying PCH2a.

Keywords: neurogenetic disorder, brain organoids, iPSCs, single, cell RNA sequencing

P18

Immunosuppressive functions of CAFs in pancreatic cancer are modulated by CD44

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Pancreatic cancer is the deadliest type of cancer due to its invasive and fast metastasizing nature. In various pancreatic cancer models, we could show that blocking of CD44v6 with species-specific peptides, not only on human cancer cells (L3.6pl) but also on endogenous murine (host) cells, reduced tumor volume and metastases. We are currently investigating the role of CD44 on CAFs that influence tumor progression by interactions with stromal and cancer cells. Preliminary results show that the knockout of Cd44 leads to CAF inactivation, reflected in decreased marker expression and altered morphology. CAFs constitute a heterogenous cell population including myofibroblastic and inflammatory CAFs (iCAFs), influencing immunosuppression and fibrosis during tumor progression. Especially regarding the widely emerging field of immunotherapies, understanding the modulation of antigen- presenting cells and T cell response by iCAFs is of great interest. Deactivation of CAFs through the knockout of CD44 influences their inhibitory effect on dendritic cells, resulting in a decreased expression of immunesuppressive cytokines. To investigate the role of CD44 in the whole CAF population in vivo, we have removed Cd44 in Cd44fl/fl;PDGFRβCreERT2 mice to examine the consequences of the absence of all CD44 isoforms in CAFs on tumor growth, tumor composition, immune escape and metastasis.

Keywords: CAFs, CD44, CD44v6, pancreatic cancer, tumor progression, immunosuppression, metastasis

P19

Influencing tomato root development by genetic modification of MIG (mycorrhiza induced GRAS) transcription factors

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The arbuscular mycorrhiza symbiosis (AMS) can be established by over 80% of all land plants. To accommodate the fungal structures inside the root cortex cells the plant undergoes major transcriptional reprogramming to ensure the maintenance of the AMS. Many of the genes involved belong to the family of GRAS transcription factors. Members of the MIG1 (mycorrhiza-induced gene 1) clade are induced upon mycorrhization and play an important role in mycorrhizal root development by adjusting the cortical cell size. This is necessary to adequately harbor the fungus in the cortical root cells during colonization. MIG1 hereby acts as a positive regulator by increasing the size of cortex cells whereas MIG3 shows an antagonistic function. In the agronomic important model organism tomato four putative homologues have been identified. We are using these homologues as targets for genetic engineering of tomato root development to gain enhanced access to limited nutrients in the soil. To achieve this, we try to either overexpress the MedicagoMIG1 homolog in tomato as a positive regulator of radial cell expansion to enhance the cell size or downregulate negative regulators like MIG3 and SCL3 (scarecrow-like 3) by using the CRISPR/Cas12a technology to abolish their negative effects on cortex cells.

Keywords: AM symbiosis, GRAS transcription factors, root development, genetic engineering, CRISPR/Cas

P20

Inhibition of CD44 signaling impact colorectal cancer cell plasticity in tumor organoids

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Incidence of colorectal cancer (CRC), the third most frequently diagnosed cancer world- wide, is still rising. Early-stage CRC is often curable, while effective therapies for later and already metastatic stages, are lacking. Therefore, new approaches for treatment of CRC are needed. One finding that revolutionized our understanding of molecular aspects of CRC, is a phenomenon called plasticity, a process by which cancer cells perform a dynamic switch from a differentiated to an undifferentiated cancer stem cell (CSC) stage. This switch is required for the maintenance of metastases. One prominent CSC marker is CD44, a family of proteins highly expressed in intestinal stem cells (ISCs) and CR-CSCs. Using CRC organoids derived from LGR5DTR/eGFP mice, the influence of CD44 on the plastic process was investigated. To observe the plastic process, differentiated cancer cells (GFP-) were FACS sorted, and the reappearance of eGFP, reflecting the reappearance of CSCs, was followed. Here, the treatment of LGR5- CRC cells with an isoform specific peptide, targeting CD44v6, resulted in an impaired organoid formation, a process dependent on the presence of CSCs. Due to its role along the dynamic switches occurring during metastasis, CD44 represents a valuable therapeutic target for treatment of metastatic CRC.

Keywords: colorectal cancer, organoids, CD44, plasticity, cancer stem cells

P21

Investigating the Role of Respiratory Terminal Cytochrome bd Oxidases in Resistance Mechanisms.

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Heme-copper oxidase and bd-type oxidases catalyse the reduction of molecular oxygen to water using different substrates. Current studies also reveal that cytochrome bd oxidase could additionally have a role as a defence factor since it interacts with signalling molecules (NO, CO, H_2S). The absence of bd oxidases in Eukaryotes and their expression in some pathogenic bacteria such as the Mycobacteria tuberculosis creates the need for a better understanding of this enzyme in relation to drug targeting.

The main objective is to reveal the amino acids in the proton channel that are important for oxygen reduction. In addition, to identify the role of cytochrome bd in signaling molecules (NO). Furthermore, to unravel the oxygen reaction mechanism by identifying the intermediates. The electrochemical and spectroscopic (UV-visible, Infrared, Raman) analysis will be carried out. The catalytic reaction of wild-type cytochrome bd oxidase and mutants was studied electrochemically at different pH values using thin film protein voltammetry. The NO binding of several selected mutants by UV visible spectroscopy was performed. The protonation state of the amino acids was identified using spectroelectrochemistry in IR. The data obtained provide information about the pH-dependent catalytic activity of the created mutants pointing to their role in the proton channel.

Keywords: Cytochrome bd oxidase, Electrochemistry, spectroelectrochemistry, protonchannels, drug resistance

P22

Lignin-based non-isocyanate polyurethanes, towards greener and safer to produce materials.

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We present original work on lignin valorization to non-isocyanate polyurethanes (NIPU). Polyurethanes are one of the most used polymer family for high value applications (foams, adhesives, elastomers, ...). Their production relies on fossil-based and toxic isocyanates. On the other hand, lignins are relatively unused bio-based polyphenols, by-product of lignocellulose processing in pulp and paper and bioethanol industries. In this study, we aimed at killing two birds with one stone by producing lignin-based polyurethanes without using isocyanates.

We developed new functionalization of lignins to reactive polyfunctional molecules (alcohols, amines and cyclic carbonates) through green chemistry using safe to handle chemicals. Then, modified lignins were used as building-blocks for polymer synthesis. Two different reactions of polymerization to polyurethanes were tested : aminolysis (reaction between a polyamine and a polycyclic carbonate) and transurethanization (reaction between a polyol with a short chain urethane). The thermomechanical studies of the materials are ongoing. This work opens new pathways towards easier valorization of lignins, a relatively untapped bio-based chemical pool. The production of high-value materials from lignin using only safe and low environmental impact methodologies pave the way towards sustainable polymer materials.

Keywords: Lignin, Functionalization, Non, isocyanate polyurethanes.

P23

Mechanism of action of LNP509, a new AMPK activator

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Introduction: We previously reported that LNP molecules improve insulin resistance and cardio-metabolic disorders in obese animals. We also observed an activation of AMPK in animal tissues, with an increased phosphoAMPK/AMPK ratio.

Objective: Since AMPK may be activated allosterically and through phosphorylation by up-stream kinases (LKB1 and CamKK), our objective was to clarify the interaction between LNP509 and AMPK and determine how LNP509 activates this enzyme.

Methods: A cell-free model with human recombinant enzyme isoforms was used to determine if LNP509 interacts directly and with isoselectivity with AMPK. To evaluate the role of up-stream kinases, we used LKB1-deficient Hela cells and HepG2 cells treated with LKB1 or CamKK inhibitors. Finally, co-treatments with metformin were performed to determine if LNP509 binds on the AMP-binding site of AMPK.

Results: We demonstrated that LNP509 can directly activate AMPK (+27% at 10-5M) without isoselectivity. The increase in AMPK phosphorylation observed in cells upon LNP509 treatment was LKB1- but not CamKK-dependent. Additivity of LNP509 and metformin effects suggested that LNP509 does not bind on the AMP-binding site of the enzyme.

Conclusion: These data show that LNP509 binds to and activates AMPK. The interaction with LNP509 seems to sensitize the enzyme to the phosphorylating action of LKB1.

Keywords: AMPK, LNP, metabolism

P24

Microfluidic chips for biomolecular crystal growth and serial crystallography

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Twenty years ago, microfluidics opened up new possibilities and brought many benefits for the crystallization of biomolecules. Indeed, microfluidic systems facilitate the manipulation of nano-volumes of sample solutions, as well as extreme miniaturization and parallelization of crystallization assays. In addition, they provide a convection-free environment that favors the growth of high-quality crystals (1).

As an illustration, a new multifunctional microchip will be presented that combines 1) the search and optimization of crystallization conditions of biomolecules by the counter diffusion method, 2) crystal identification by fluorescence microscopy, 3) microcrystalline seeding, 4) derivatization of crystals by substrate soaking, and 5) routine in situ crystal analysis and ligand/fragment screening at room temperature. The concept was already tested on a large panel of biomolecules including RNA and various soluble or membrane proteins (2-3). A new chip design and our latest results in microcrystallization and in situ serial synchrotron crystallography at room temperature (RT-SSX) will be presented.

(1) Sauter et al. (2007). Crystal Growth & Design, 7, 2247. (2) de Wijn et al. (2019). IUCrJ, 6, 454.

(3) de Wijn et al. (2021). JoVE, 169, e61972.

Keywords: microfluidics, structural biology, biotechnology, serial crystallography, ligand screening

P25

Next Generation BiOactiVe NAnocoatings - NOVA

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The NOVA project aims to develop a streamlined, holistic process to implement innovative antimicrobial coatings in everyday settings. Any material/device/product that needs to be handled by individuals and that will stay in use after this manipulation has the potential to act as a fomite. This can be via direct contact or by the settling of the aerosols. Thus, manufacturers need to consider having safety measures to prevent disease transmission by their products.

Four coating technologies (3 light activation based, 1 antimicrobial biopolymer based) form the basis of the technological toolset in NOVA for resolving the risks associated with the presence of potential pathogens in a wide range of environments with multi-material type surface presence (metals, glass, ceramic, polymers). New advanced test methods for bio-compatibility and immunocompatibility to conduct in-depth are being developed as well as novel antibacterial, antifungal and antiviral test methods that support the various stages of coating development to predict their performance under conditions of actual use. Data science and machine learning methodologies is using to develop robust in-silico models for coating risk management and future coating development.

Finally, NOVA will develop a “Biocide-Safe and Sustainable by Design (SSbD)” strategy, specifying the general SSbD concept for biocidal coatings.

Keywords: nanocoating, antimicrobial, pathogens, biocompatibility, SSbD predictionmodel

P26

On the role of natural products as virulence factors in fungi with a predatory lifestyle

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An intriguing and fascinating inter-kingdom interaction occurs between nematodes and fungi that trap and prey on them. Nematode-trapping fungi are soil microbes which can switch from a saprotrophic lifestyle to a predatory behavior in the presence of nematodes. Among them, Arthrobotrys flagrans is a typical member of the soil microbiome and is able to form sticky traps to catch nematodes. Using Caenorhabditis elegans as model, we previously showed that secondary metabolites produced by A. flagrans are crucial for attracting the nematodes into fungal colonies and for controlling trap formation. Bioinformatic analysis has revealed that A. flagrans only encodes 9 biosynthetic gene clusters, which is a low compared to other fungi. Therefore, the A. flagrans - C. elegans interaction offers the perfect opportu- nity to elucidate the entire secondary metabolism of A. flagrans, as well as the importance of the produced compounds. Here we focus on the two uncharacterized PKS-encoding genes of A. flagrans and show that they are expressed exclusively in the fungal traps and in trophic hyphae inside the nematode. Chemical analysis revealed that the two PKSs work in a concerted fashion and biosynthesize volatile natural products with synergistic effects, increasing the attraction of nematodes into the hyphal traps.

Keywords: polyketide, volatiles, nematodes, natural products, secondary metabolites, fungus

P27

PROTEOLYTIC ACTIVITY OF VIPERA BERUS BERUS AND BERUS NIKOLSKII VENOM ON LUNG TISSUE

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Viper's venoms have the ability to activate proteolytic processes, which can be evidenced by an increase in the number of active enzyme molecules and their degraded active forms. In order to study proteolytic activity, we analyzed active enzyme molecules - proteases, using the enzyme-electrophoresis method using gelatin, fibrinogen and collagen as substrates. For the study, we took white rats lung tissues in three groups: the control group, and with the introduction of venom of vipers berus berus and berus nikolskii.

When using each three substrates, the presence of additional enzyme bands with different molecular weights was observed in the studied lung tissue samples. At the same time, in the study of the vipers berus berus and berus nikolskii venoms effects, fragments of 100-67 kDa in gelatin and 67-35 kDa in fibrinogen and collagen prevail. Fragments of three dimensions like 100-67 kDa, 67-35 kDa and 35-10 kDa are observed in both cases. Considering the molecular weight of these additional bands, it is possible to assume the appearance of native enzymes degraded forms present in the control sample.

Thus, the studied poisons by vipers berus berus and berus nikolskii venoms showed effects on the functioning of proteolytic systems of lung tissue.

Keywords: lung, proteolytic activity, Vipera, venom, poison

P28

PROTOCOL OPTIMIZATION FOR NEUROHISTOLOGYCAL HIPOCAMPUS ANALYSIS

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Astrocytes exhibit a complex response to damage and disease within the central nervous system (CNS), known as astrogliosis, marked by heightened proliferation and hypertrophy. To comprehensively understand these processes, precise protocols for quantitatively assessing changes in cellular density and morphology are indispensable.

In this study, we introduce a protocol designed to offer detailed analyses of astrocyte profiles and conduct a layer-by-layer investigation of cytoarchitectural organization in the dorsal hippocampus of wild-type mice. To achieve this, we employed immunostaining of astrocytes using antibodies targeting glial fibrillary acidic protein (GFAP), a key intermediate filament protein. The hippocampus was segmented according to different layers as outlined in the Mouse Brain Paxinos Atlas (Hof et al.): Oriens, Pyramidale, Radiatum, Lacunosum, Granulosum, Polymorphic, and Moleculare using Fiji/IMAGEJ routines.

For each hippocampal layer, we quantified the percentage area of GFAP staining across brain samples from wild-type C57Bl6 mice, providing preliminary data at different ages through- out mice lifespan (3 months, 6 months, 9 months, and 12 months). Following analyses of astrocytic branches and soma, parametric indices were utilized in an attempt to characterize morphological features within this cell population. This optimized protocol will be tailored for the characterization of samples derived from models of CNS disorders.

Keywords: Hippocampus, astrosytes, GFAP, density

P29

Role of N-Glycosylation for the Activation of the Wnt Co-Receptor LRP6

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Wnt signaling is an evolutionarily conserved cell-cell communication network that operates throughout development and adult tissue homeostasis to establish the primary (A- P) body axis, regulate cell migration, shape and polarity. Alteration in levels or function of Wnt/β-catenin pathway components are associated with disorders including cancer, osteoarthritis, Alzheimer disease and diseases of the eye, bone and heart.

Post-translational modifications (PTMs) of Wnt pathway components are essential for the relay-like activation events that transduce Wnt/β catenin signals within and between cells. Indeed, Wnt signaling is well known to be regulated by phosphorylation, ubiquitination, sumylation and PARsylation events. The relevance of glycosylation events and their role in Wnt signaling is, by contrast, relatively uncharacterized.
We have identified the glycosyltransferase B3GnT2 as a regulatory modifier of N-glycan antennae on the extracellular domain (ECD) of the Wnt/β-catenin co-receptor, LRP6 that promotes Wnt Signaling. My work focuses on studying the molecular mechanisms underlying the regulation of ligand-receptor interactions mediated by B3GnT2. Our main focus is to understand the effect of LRP6 glycosylation on its ability to interact with different ligands (DKK and Wnts), Wnt-FZD-LRP6 trimetric complex formation, aggregation of higher order LRP6/FZD/Wnt receptor complexes (signalosome formation) and their functional relevance to Wnt signaling.

Keywords: B3GnT2, LRP6, Wnt signalling, Wnt/βcatenin, Glycosylation, Glycans.

P30

Structural studies of CBP/p300 complexes and characterization of peptide based CBP inhibitors

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Intrinsically disordered proteins are crucial for cellular processes, as they are highly flexible and can bind to multiple targets. ACTR and CBP/p300 are coactivators that regulate gene expression of highly regulated genes by interacting with many transcription factors. However, overexpression of these proteins has been linked to various diseases, including cancer and metabolic disorders. My PhD project aims to study a new therapeutical strategy to target the interacting disordered domains of ACTR and CBP/p300, characterizing them bio- chemically and structurally within a transcription factor complex to gain insights into their function. A library of synthesised peptide AD1 domain of ACTR, containing non-canonical amino acid modifications, such as α-methylated leucine and D-amino acids, is used to specifi- cally interact with the NCBD domain of CBP/p300, stabilising the formation of the complex. The project aims to characterize the biological effects of these modified ACTR peptides on CBP/p300-mediated activities, transcription activation of nuclear receptors and acetylation activity, as well as to study the three-dimensional structure of CBP/P300 functional complexes with the nuclear receptors PPARγ2/RXRα. To this end, we have developed a set of approaches combining expertise in biochemistry, biophysics and Cryo-EM.

Keywords: CBP/p300, nuclear receptor, coregulators, Cryo, EM, gene transcription

P31

Systems approaches identify new drug targets for vascular therapies

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Selective targeting of the vascular growth process is crucial to alleviate hypoxia in pa- tients with cardiovascular disease. VEGF-based therapies require strategies for the precise titration of VEGF signaling output. Bulk and single-cell sequencing analysis of WT and zebrafish mutants with a VEGF gain-of-function scenario identified several pathways reg- ulating VEGF signaling output. We found that Vegfa bioavailability is fine-tuned by the opposing actions of Vegfa decoy receptor Flt1 and Esm1 produced by parenchymal cells. Vegf signaling strength controls EC size to determine lumen diameter in developing vessels. Additionally, parenchymal Vegfa and Apelin act in synergy to titrate endothelial VEGF sig- naling strength in venous ECs to induce sprouting. Single-cell sequencing of FACS-sorted ECs identified a subset of venous ECs expressing the Apelin-receptor (Aplnr) and VEGF receptor-2/Kdrl. Upon exposure to both parenchymal Apelin and Vegfa, the activated Aplnr and Kdrl genetically interact to amplify VEGF signaling output, promoting the formation of a specialized venous angiogenic cell. We conclude that precise titration of VEGF sig- naling output is achieved by regulating VEGF ligand level and VEGFR2 signaling strength via genetic interaction with others receptors activated by a combination of tissue-derived cues. This opens novel therapeutic avenues for interfering with vascular remodeling defects in disease conditions.

Keywords: angiogenesis, VEGF

P32

The Chemotion ELN and Chemotion Repository as FAIR solutions for digitalizing research data

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The Chemotion ELN is an open source, web-based application designed to provide FAIR solutions for digitalizing chemical data, with a primary focus on Organic Chemistry. It was developed at the Karlsruhe Institute of Technology and is part of the National Research Data Infrastructure in Germany (NFDI) now. The Chemotion ELN facilitates the acquisition of relevant data, from the design and documentation of experiments, the drawing of chemical structures and reactions, to the storage and analysis of analytical data files. All information is stored completely and without great effort, linked to each other and made available digitally. The generic extension of the Chemotion ELN, LabIMotion, allows the design of customizable modules, providing flexibility in utilizing the software with or without chemistry-specific features. Chemotion ELN can be used in combination with the open access repository Chemotion. These two interoperable systems guarantee an easy process for the disclosure of information and the availability of comprehensive data. Furthermore, sample information in the Chemotion repository is linked to the physical presence of compounds in the Molecule Archive of the Compound Platform, ensuring that a physically available sample is not only made FAIR through metadata but also becomes accessible and reusable as a material for others.

Keywords: FAIR Data, Chemotion ELN, Chemotion Repository, Research data management

P33

The Molecule Archive of the Compound Platform: An Infrastructure to promote Open Science and the Sustainability of Chemical Research in Academia

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Established in 2009, the Molecule Archive serves as core facility of the German Research Foundation with the objective of gathering and preserving chemical substances originating from academic research. The substance collection is continuously expanding, currently comprising over 12,000 compounds contributed by 40 international research groups. The library is distinguished by its extensive structural diversity and highly sophisticated molecules un- available from commercial vendors.

Notably, several substance classes within the archive are recognized as privileged scaffolds in medicinal chemistry, encompassing natural products such as steroids and coumarins and numerous N-/S-heterocyclic compounds. Moreover, the archive extends beyond the chemical space of conventional drugs, offering the potential for identifying exotic chemotypes as bioactive agents.

Over time, the Molecule Archive has cultivated a robust network of scientists dedicated to exploring the biochemical potential of its collected substances. More than 45 inter- national research groups and seven screening centres test newly acquired compounds for anti-inflammatory, or antimicrobial properties, as well as their potential utility as cancer therapeutics.

In addition to its archival and exchange functions, the Molecule Archive provides partners with access to a diverse array of chemical analysis and automation techniques, along with expertise and personnel capable of resynthesizing or derivatizing identified screening hits.

Keywords: Open Science, Screening Library, Compound Screening, Academic Drug Discovery, Sustainability, Collaboration, Reference Samples

P34

The periplasmic domain of the cupric reductase CcoG is important for function

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CcoG is the first known bacterial membrane-bound cupric reductase that reduces cytosolic Cu(II) to Cu(I). CcoG is encoded in the ccoGHIS-operon of cbb3-type cytochrome oxidase (cbb3-Cox) assembly factors and required for full cbb3-Cox activity. CcoG consists of five transmembrane domains and a C-terminal immunoglobulin-like domain that is located in the periplasm. This domain is not present in all CcoG-homologues, and its function is unknown. A truncated CcoG variant that lacked the immunoglobulin-like periplasmic domain (PD) showed decreased cbb3-Cox activity and increased Cu sensitivity, which is similar to the phenotype of a ΔccoG strain, indicating its importance for the CcoG function. The low cbb3-Cox activity is explained by reduced protein levels of CcoN, the main subunit of cbb3-Cox. Moreover, the periplasmic domain of CcoG is also required for the stability of CcoG itself, because the truncated version undergoes enhanced proteolysis in the membrane. Although the exact function of the periplasmic domain is still unknown, it might be involved protein-protein interactions with the other cbb3-Cox assembly factors during cbb3-Cox maturation, which is currently under investigation.

Keywords: copper, cbb3, type cytochrome oxidase, CcoG, Rhodobacter capsulatus, membrane protein biogenesis

P35

The SP7 effector family of symbiotic arbuscular mycorrhizal fungi targets the plant mRNA processing machinery

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Most plants in natural ecosystems live in association with beneficial AM (arbuscular mycorrhizal) fungi to survive under poor nutrient conditions. To engage in symbiosis, AM fungi secrete effector molecules that, similar to pathogenic effectors, reprogram plant cells. Here we show that the AM SP7-like effector family impacts on the mRNA processing machinery of their hosts. We identified 13 members of this family within the genome of the model organism Rhizophagus irregularis. All members possess a unique repeat structure reminiscent of the plant DNA binding TAL effectors from phytopathogenic bacteria. In planta expression of SP7-like members revealed their localization in mRNA related nuclear and cytoplasmic condensates. Furthermore, we found multiple components of the plant mRNA processing machinery physically interacting with the SP7-effector family.

The variable amino acids of TAL effectors function as a versatile code for binding to specific DNA target sequences. We believe that, in a similar manner, the unique repeat amino acid pattern of the SP7-like family might encrypt a code for binding to specific RNA target sequences. Future approaches aim towards testing the ability of the effectors to directly bind RNA, the identification of specific plant mRNA effector targets as well as deciphering a putative effector-RNA sequence code.

Keywords: mycorrhiza, effectors, plant, microbe interactions, splicing, RNA binding, symbiosis

P36

Towards structurally complex aza-cyclic architectures merging 1-aza-spirocyclic and isoquinuclidine ring systems

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Constructing 3D aza-polycyclic architectures remains a big challenge in organic synthesis. In particular, much synthetic efforts have been devoted to 1-azaspirocyclic and isoquinuclidine ring systems, due to their presence in many natural products of biological relevance. Our goal is to go further in 3D structural complexity by accessing to unprecedented architectures merging these two aza-cyclic systems of high relevance. Herein, we wish to report our synthetic approach towards this complex azaspiro/isoquinuclidine hybrid skeleton from simple starting materials. Our approach starts with a 3-step sequence, including 2 steps under Cu(I)-zeolite catalysis (i.e., KA^2 coupling and enyne cycloisomerization reactions), that first furnishes 1-azaspirocyclic systems featuring a 1,2-dihydropyridine motif. The potential of the resulting 1,2-dihydropyridine motif as diene is finally exploited to construct the additional isoquinuclidine ring system via a formal cycloaddition process. DFT calculations are conducted in parallel to rationalize the reaction mechanism and energetic pathway of the cycloaddition process. Noteworthy is that this methodology is highly atom and step economical, with water as sole by-product during the whole 4-step sequence.

Keywords: 1-azaspirocycles, isoquinuclidine, cycloaddition, 3D complex architectures, 'green' chemistry, DFT calculations, biologically relevant structures

P37

TOXIC EFFECT OF HOMOCYSTEIN ON THE THYROID GLAND TISSUE

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Homocysteine metabolism is closely related to the thyroid gland, which regulates almost all types of metabolic activity of the body.

The aim: to examine biochemical parameters in the homogenate of the different age rat's thyroid gland with a model of hyperhomocysteinemia (HHC). The chronic HHC model was created on white outbred rats of three age groups: young, adult and old by administering D,L-thiolactone homocysteine hydrochloride (Acros Organics, Italy).

Total activity of matrix metalloproteinases (MMP) and their distribution, level and distribution of proteases and proinflammatory cytokines and protein composition of the thyroid gland were determined in homogenates of the thyroid gland.

We have determined that the accumulation of molecules of the middle mass in the thyroid gland with HHC, which may indirectly indicate the development of a state of endogenous intoxication. Elevated levels of pro-inflammatory cytokines were also observed, indicating the development of inflammation. The general proteolytic activity was found to be increased, there was an overexpression of MMP-2 and a change in the protein composition of the thyroid gland, which indicated the activation of proteolysis.

Thus, biochemical parameters of the thyroid gland of rats can be criteria for intoxication with HHC.

Keywords: homocysteine, inflammation, proteinase, cytokines, thyroid gland, age

P38

Unraveling the proteome and ubiquitin pathways by chemically induced proximity

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The proteome quality control is critical for the maintenance of cellular functions, and it is assured by the proteostasis network. This complex protein machinery that identifies, rescues or degrade polypeptides is important for biological pathways such as autophagy, protein quality control and proteostasis during stress, aging and diseases. Protein-protein interactions (PPIs) stabilization by small molecules (Glues, PROTACs, ...) has become an attractive approach to target disease-causing proteins for destruction and expand the druggable proteome.

A comprehensive Yeast Two-Hybrid screening platform, which allows to perform unbiased and exhaustive protein interaction screens of highly complex cDNA libraries (135+ libraries), has been adapted to support Targeted Protein Degradation (TPD) projects, and now allows to supports all aspects of this important research field: (1) Protein Interaction discovery to identify pathways for proteins, RNA and DNA; (2) E3 ligases-POI specific chemical inducers discovery or validation; (3) Molecular Glues, PROTACs interactions profiling, deconvolution including off-targets and validation.
The readout and the absence of any washing steps contributes to its high sensitivity. In addition, each putative interaction partner is tested individually, eliminating the competition by abundant or strong binders. Intergraded bioinformatics allow to delineate interacting domains and to attribute confidence scores. Few examples will be exposed.

Keywords: Chemically induced proximity, Drug target deconvolution, Targeted Protein Degradation, molecular glues, PROTACs, proteostasis, protein interactions, E3 ligases

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