Institut Européen de Chimie et Biologie

European Institute of Chemistry and Biology

I E C B

Scientific Report

2023

université de BORDEAUX

Inserm

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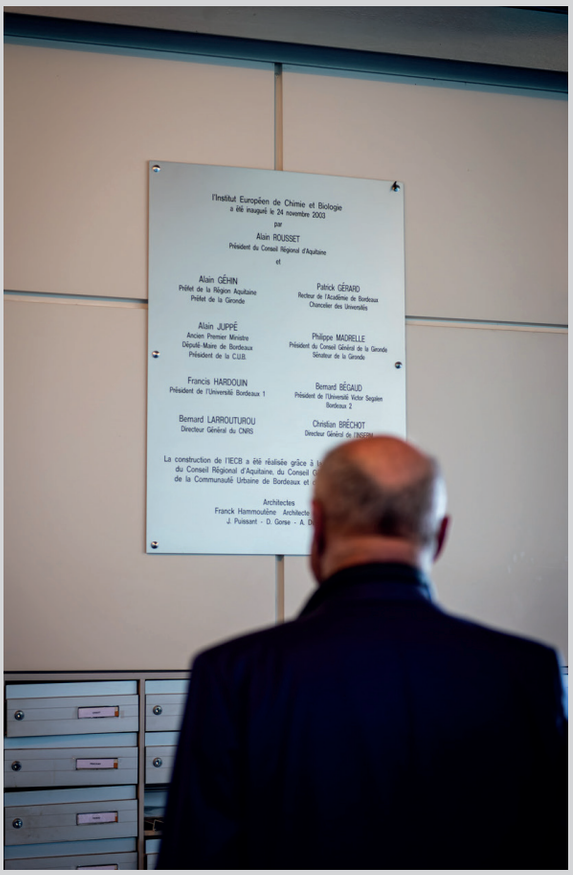
On April 16, 2023, IECB had the immense privilege of receiving a visit from the President of the Conseil Régional de la Nouvelle Aquitaine, Alain Rousset, and his delegation.
He had inaugurated the institute on November 24, 2003.
Representatives of the IECB's trustees, Inserm, CNRS and the University of Bordeaux were also present, accompanied by their regional delegates. The acquisition of an ultra-high field NMR instrument at the IECB has been presented and discussed with the President A. Rousset (project ENAMAR).



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Yves Théobald (building), Marc Grémillon (portraits), Lionel Lizet (UAR3033/US01 IECB technology platform).

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European Institute of Chemistry and Biology

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Scientific Report

2023

Director's Foreword

Dr. Gilles GUICHARD
Director of the IECB Research Team Incubator

Dr. Antoine LOQUET
Director of the Unit UAR3033/ US01 IECB

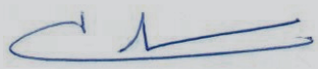
25 years... The IECB was inaugurated 25 years ago to propose a multidisciplinary environment for chemists, biologists and biophysicists to develop their independent projects. In 2023, the IECB hosted 13 research teams selected by our International Scientific Advisory Board (SAB) and the Trustees – Univ. Bordeaux, the CNRS and the Inserm. With the strong support of our partner Units (UMRs ARNA, CBMN, ISM, MFP and LBM), IECB continue to act as a powerful catalyst to attract talented researchers in the Bordeaux area.

The team of Dr. Valérie Gabelica, Director of the IECB (2021-2023), arrived in Bordeaux in 2013. She developed at IECB cutting-edge research in mass spectrometry for biology and chemistry. I would like to underline her scientific achievements, notably awarded by the Prix de la Recherche Inserm in 2022. One of the primary principles of IECB is the non-lifelong nature of IECB teams, who would have to move from the institute after some years. Valérie decided to move to the University of Geneva end of 2023, and I wish her to continue the development of innovative methods in biophysics and analytical chemistry at the chemistry-biology interface. For more than two years, I had the privilege, as a Deputy Director, to work with Valérie at the Direction of the IECB. A challenging and arduous task, the IECB being a research team incubator and a support Unit of the CNRS, Univ. Bordeaux and Inserm (UAR3033/US01), while as both IECB group leaders we wanted to maintain a competitive international scientific level despite the Direction load. I agreed to ensure the function of IECB Director in the interim (Mid 2023-2024). This period of one year was used to engage many fruitful discussions with former IECB group leaders (thank you Léon Ghosez for your advices), current group leaders, and the Trustees on the role of the IECB Direction. In the meantime, Gilles Guichard agreed to become the scientific Director of IECB. I am delighted that Gilles volunteered to take part of the IECB Direction, as we share the same vision of the founding principles of this institute. Starting September 2024, Gilles will act as the new Director of the IECB research team incubator, while I will take the Direction of the Unit UAR3033/US01. I'm grateful to Brice Kauffmann to join me as a Deputy Director.

Dr. Antoine Loquet
Director of the Unit UAR3033/ US01 IECB

2023 has been a year of transition, and I want to sincerely thank Valérie Gabelica for her leadership and dedication as director of the IECB, as well as Antoine for stepping in as interim director until September 2024. I look forward to my role as director of the IECB research team incubator next September, working alongside Frédéric Friscourt as Deputy Director. We are fully committed to uphold the core values of scientific excellence, interdisciplinarity, and collegiality that define our institute. This year, we are particularly proud to announce that Yaser Hashem has been awarded an ERC Consolidator Grant for his project entitled « Species-specific aspects in eukaryotic mRNA translation modulation and their implications in diseases » (2022 call) following his successful ERC Starting Grant in 2017. The IECB continues to attract new talents and we are thrilled to welcome Elia Stahl, a plant biologist selected by the ISAB in 2022, who will officially launch his group early January 2024. In the meantime, Elia Stahl has secured a CNRS chargé de recherche position in 2023 and received funding from the ATIP-Avenir program to develop his project on plant immune signaling. As we look to the future, we aim to attract more group leaders on the Bordeaux campus, and together with Frédéric and in collaboration with Antoine, enhance the influence of the institute at the intersection of chemistry and biology, both in France and beyond.

Dr. Gilles Guichard
Director of the IECB Research Team Incubator



The Institut européen de chimie et biologie (IECB) is a research team incubator placed under the joint authority of the CNRS, the Inserm and the Univ. Bordeaux. It was created in 1998 with the support of the Aquitaine Regional Council to provide promising European chemists and biologists with an environment designed to facilitate the development of first-class interdisciplinary research programs, in collaboration with international public and private research centres.

IECB's International Scientific Advisory Board guides the selection and periodic evaluation of the team leaders. After a probative period of two years, research teams are then hosted for a maximum of 10 years. During their stay at IECB, teams enjoy full financial and managerial autonomy and benefit from state-of-the-art facilities and dedicated technical expertise through IECB's technology platforms in structural biology and preparative and analytical techniques.

The IECB is the largest research team incubator in France, with 13 research teams accounting for 137 researchers and expert technicians.

The IECB hosts a Unit (UAR3033, US01, CNRS, Inserm, Univ. Bordeaux) composed of 17 people, managing the platforms of the building (X-ray diffraction, NMR, mass spectrometry, electron microscopy, biophysics and biochemistry).

ImmuPharma Biotech & AelisFarma are hosted at the institute.

Contents

The IECB International Scientific Advisory Board, chaired by Dr Moshe YANIV, interviewed candidates from all over the world for group leader positions.

Dr. Moshe YANIV
Chairman, Institut Pasteur,
Paris, France

Dr. Anne BERTOLOTTI
MRC-LMB, Cambridge, UK

Dr. Stephen CUSACK
EMBL, Grenoble, France

Dr. Witold FILIPOWICZ
Friedrich Miescher Institute for
Biomedical Research, Basel, Switzerland

Dr. Anne HOUDUSSE JUILLE
Institut Curie, Paris, France

Dr. Jesús JIMENEZ-BARBERO
CIC bioGUNE, Bizkaia, Espagne

Pr. Yves POMMIER
National Cancer Institute,
Bethesda, USA

Dr. Claude SARDET
Institut de Recherche en Cancérologie
de Montpellier, France

Pr. Helma WENNEMERS
ETH, Zurich, Switzerland

Organisational Structure

Board Members

International scientific advisory board (ISAB)

Dr. Moshe YANIV President
Institut Pasteur, Paris, France

Dr. Stephen CUSACK
EMBL, Grenoble, France

Dr. Witold FILIPOWICZ
Institut Friedrich Miescher, Basel, Switzerland

Dr. Bernd GIESE
Departement of Chemistry, University of Basel, Switzerland

Dr. Anne HOUDUSSE JUILLE
Institut Curie, Paris, France

Pr. Yves POMMIER
National Cancer Research, NIH, Bethesda, USA

Dr. Claude SARDET
Institut de Recherche en Cancérologie de Montpellier (IRCM), France

Pr. Helma WENNEMERS
ETH Zurich, Suisse

Dr. Anne BERTOLOTTI
MRC-LMB, Cambridge, UK

Former ISAB members

Pr. Roeland NOLTE
Radboud University Nijmegen, Netherlands

Dr Herbert WALDMANN
Max Planck Institute of Molecular Physiology, Dortmund, Germany

Dr. Daniel SCHIRLIN
Sanofi Aventis, Paris, France

Prof. Dinshaw PATEL
Memorial Sloan-Kettering Cancer Center, New York, USA (2009-2016)

Dr. Daniel LOUVARD
Institut Curie, Paris, France (1999-2014)

Pr. Iain D. CAMPBELL
Departement of Biochemistry, University of Oxford, UK (1999-2013)

Dr. Simon CAMPBELL
Royal Society of Chemistry, London, UK

Pr. Claude HÉLÈNE
Muséum National d'Histoire Naturelle, Paris, France (1999-2003)

Pr. Georges HUEZ
Université Libre de Bruxelles, Brussels, Belgium (2000-2005)

Pr. Steven LEY
Departement de Chemistry, University of Cambridge, UK (1999-2005)

Pr. Helmut RINGSDORF
Institut für Organische Chemie, Johannes Gutenberg Universität, Mainz, Germany (1999-2006)

Pr. Fritz ECKSTEIN
Max Planck Institute for Experimental Medicine, Göttingen, Germany (2003-2006)

Pr. Jack BALDWIN
Departement of Chemistry, University of Oxford, UK (2005 - 2007)

Pr. Wilfred van GUNSTEREN
Laboratory of Physical Chemistry, ETH, Zürich, Switzerland (1999-2007)

Pr. François DIEDERICH
Department of Chemistry and Applied Biosciences, ETH, Zürich, Switzerland (2006-2008)

Pr. Jean-Yves LALLEMAND
Institut de Chimie des Substances Naturelles, CNRS Gif-sur-Yvette, France (1999-2010)

Board of directors

Dr. Valérie GABELICA Executive Scientific Director, Research Director, team leader U1212 (Inserm), until August 2023

Dr. Antoine LOQUET Deputy Scientific Director, Research Director, team leader (CNRS), UMR5248

Dr. Antoine LOQUET & Dr. Gilles GUICHARD Scientific Directors (interim 2023-2024)

Former directors

Dr. Valérie GABELICA Executive Scientific Director (2020 until August 2023)

Dr. Rémi FRONZES Former Executive Scientific Director (2019-2020)

Dr. Jean-Louis MERGNY Former Executive Scientific Director (2015-2018)

Dr. Jean-Jacques TOULMÉ Former Executive Scientific Director (2001-2014)

Pr. Jean-Yves LALLEMAND Former Executive Scientific Director (1998-1999)

Pr. Léon GHOSEZ Former Deputy Scientific Director (1998-2008)

Steering committee

Fabienne Lastere-Itcaina Administrative Director (CNRS)

Dr Frédéric FRISCOURT Team leader
Associate professor (Univ. Bordeaux), UMR5255

Dr. Rémi FRONZES Team leader
Research Director (CNRS), UMR5234

Dr. Valérie GABELICA, Team leader (until September 1st 2023)
Research Director (Inserm), U1212

Dr. Gilles GUICHARD Team leader
Research Director (CNRS), UMR5248

Dr Yaser HASHEM Team leader
Research Director (Inserm), U1212

Dr. Brice KAUFFMANN Deputy Director of the UAR3033/US01 Unit

Dr. Antoine LOQUET Team leader (IECB-UAR/US acting director from September 1st 2023). Research Director (CNRS), UMR5248 (Director of the UAR3033/US01 Unit)

Board of trustees

Centre National de la Recherche Scientifique
3 rue Michel-Ange, 75794 Paris CEDEX 16

Institut National de la Santé et de la Recherche Médicale
101 rue de Tolbiac, 75654 Paris CEDEX 13

Univ. Bordeaux
35 Place Pey Berland, 33000 Bordeaux

Organisational Chart

Research teams

- Structure and Function of Bacterial Nanomachines
  Dr. Rémi Fronzes
- RNA Processing and translation regulation in pathogens and hosts
  Dr. Yaser Hashem
- Structural Biology of Biofilms
  Dr. Petya Krasteva
- Structural Biology of Signaling proteins
  Dr. Pierre Maisonneuve
- Membrane Protein Mechanisms
  Dr. Nicolas Reyes
- Chemical Neuroglycobiology
  Dr. Frédéric Friscourt
- Peptidomimetic Chemistry
  Dr. Gilles Guichard
- Chemical Biology of membrane proteins
  Dr. Emmanuelle Thinon
- Single-molecule Biophysics
  Dr. Mikayel Aznauryan
- Structure, Mechanism and RNA Therapeutics
  Dr. Sebastien Campagne
- Molecular mechanisms of amyloid diseases
  Dr. Yann Fichou
- Mass Spectrometryof Nucleic Acids & Supramolecular Complexes (until Sep. 2023)
  Dr. Valérie Gabelica
- Solid-state NMR of Molecular Assemblies
  Dr. Antoine Loquet

- Organic & medicinal chemistry
  Pr. Léon Ghosez

Board of directors

Steering committee

Institut Européen de Chimie et Biologie

I E C B

Board of trustees

International scientific advisory board

Administrative services
UAR3033 & US001

Technology platforms
UAR3033 & US001

- Structural biology
- Preparative & analytical techniques

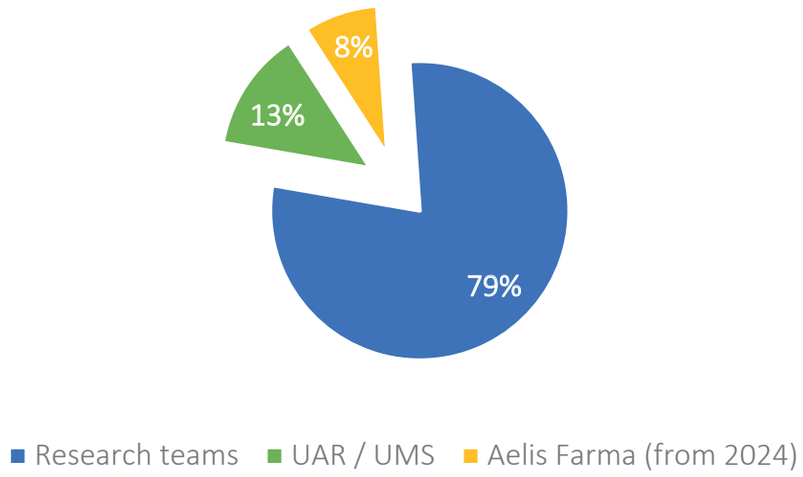
Technology transfer & start-ups

- ImmuPharma
- AELIS FARMA

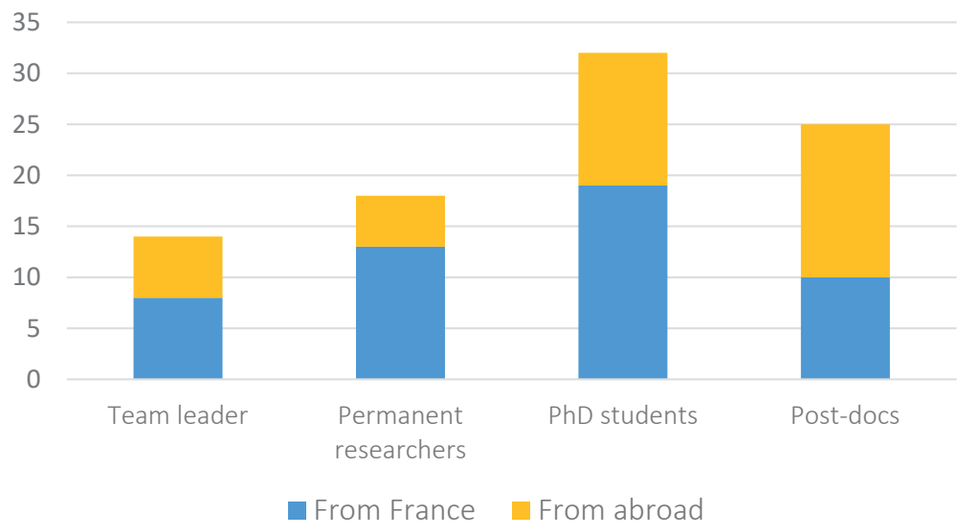
2022 Key Figures

In 2023, 137 people are part of the IECB : 108 research staff, 18 employees within the IECB's support services unit and 11 startup's employees.
Young researchers represent a big part of the IECB research staff and contributes to gender equality and internationalization at IECB. It also testifies to the attractiveness of the institute.

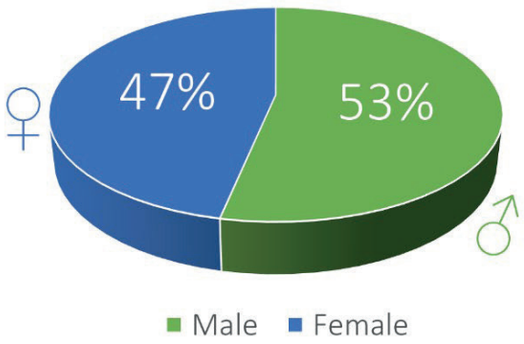
IECB research staff by gender & professional category

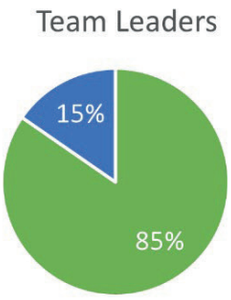


IECB researchers and students by nationality & Professional category



Male/Female Distribution within IECB (& among Team Leaders)





SUPPORT SERVICES (UAR3033 & US01)

Support services at IECB consist of staff in administration and finance, infrastructure and maintenance, as well as engineers and technicians dedicated to IECB's technology platforms. The support services unit UAR3033 & US01 is jointly funded by the CNRS, the Inserm and the Univ. Bordeaux, and receives financial support from the Nouvelle Aquitaine Regional Council. Research teams also contribute to financing those general services.

Administration and infrastructure

Administrative director
Fabienne LASTERE-ITCAINA, IE, CNRS
Executive assistant officer
Claire-Hélène BIARD, AI, Inserm
Accounting and administration officers
Sandra LAVENANT, Tech, Univ. Bordeaux
Amélie STOTZINGER, Tech, Inserm
IT management
Eric ROUBIN, AI, Inserm

Structural biology facilities

Head of structural biology facilities and crystallography engineer
Brice KAUFFMANN, IR, CNRS
Crystallography engineer
Stéphane MASSIP, IE, Univ. Bordeaux
Nuclear magnetic resonance engineer
Estelle MORVAN, IE, CNRS
Mass spectrometry engineer
Corinne BURE, IR, CNRS
Frédéric ROSU, IR, CNRS
Surface plasmon resonance engineer
Jean-Michel BLANC, IE, Inserm
Electron microscopy engineer
Axel SIROY, IR, Inserm

Biochemistry and molecular biology engineer
Laure BATAILLE, IR, Univ. Bordeaux
Jean-Michel BLANC, IE, Inserm
Biochemistry and molecular biology technicians
Thierry DAKHLI, Tech, Inserm
Myriam MEDERIC, Tech, Inserm
Quality approach and peptide synthesis
Loïc KLINGER, AI, CNRS

Dr. Elia Stahl joined the IECB as a group leader in January 2024.

In my scientific work, I have always been interested in plant innate immunity. We previously found that phospholipids released form insect eggs are perceived as immunogenic patterns by plants. Our current work focusses on the identification of novel microbial derived lipidic elicitors of plant immune signalling and their perception mechanism in Arabidopsis thaliana. In order to achieve this, we use analytical chemistry methods (chromatography, lipidomics, MS, NMR) and classical molecular biology and biochemistry methods. We are moreover interested in how plant endogenous lipid homeostasis in the plasma membrane and lipid signalling affect and contribute to plant immunity.

Elia Stahl received his PhD from the Heinrich-Heine-University (Düsseldorf, Germany) under the supervision of Jürgen Zeier. In his PhD he worked on functional and regulatory aspects of plant stress-inducible metabolic pathways. His PhD project was embedded in the CEPLAS (Cluster of Excellence on Plant Science) graduate school. He afterwards joined the laboratory of Philippe Reymond in the Department of Plant Molecular Biology (DBMV) at the University of Lausanne (Switzerland) as a postdoctoral fellow. During his PostDoc he worked on how plants perceive insect eggs and respond to insect oviposition.

Since December 2023, Elia Stahl is a CNRS Chargé de Recherche at the Laboratory of Membrane Biogenesis (LBM, UMR5200). His research is currently funded by the ATIP-Avenir program and the Grand Programme de Recherche Bordeaux Plant Science (GPR-BPS).

Research Teams & Output

European Research Council

Structure and Function of Bacterial Nanomachines

Dr. Rémi Fronzes
Research Director (DR1), CNRS

Rémi Fronzes has a long-term research experience in biochemistry and structural biology of macromolecular assemblies. He trained as a membrane protein biochemist during his PhD in Bordeaux (France). In 2005, he moved to Gabriel Waksman's laboratory at the Institute of Structural and Molecular Biology in London (UK) to work as a postdoctoral research associate. In 2009, he was appointed as a junior research scientist at the CNRS and as a group leader at institut Pasteur, in Paris (France). In 2011, RF was awarded an ERC (European Research Council) starting grant. In 2015, Rémi Fronzes was awarded a "Chaire d'excelence Senior" by the university of Bordeaux and Aquitaine regional Council. He moved his research group to IECB and CNRS unit UMR 5234 « Microbiologie Fondamentale et Pathogénicité in 2016. In 2017, RF was awarded an ERC consolidator grant. He is the coordinator of the EquipEx+ project NanoCryoCLEM awarded in 2020.

Research team

Dr. Rémi FRONZES Research Director DR1, (CNRS)
Dr. Esther MARZA Maître de conference (Univ. Bordeaux)
Robin ANGER PhD student (ERC)
Nina LOPEZ-LOZANO PhD Student (Université de Bordeaux)
Dr. Gabriel OKA Post-doc (ANR)
Nathanaël Benoit PhD Student (Université de Bordeaux)
Marie MANDART Research assistant AI (ANR)

This team is part of the unit "Microbiologie fondamentale et pathogénicité" (MFP), CNRS UMR5234/Univ. Bordeaux

Bacteria are extremely adaptable and able adjust their lifestyle very quickly when these changes occur. One dramatic illustration of this capacity is the spread of antibiotic resistance among bacterial pathogens. During the last decade, the emergence of multi-resistant bacteria, which are resistant to several treatments, led to increase mortality caused by common infections. The 2014 report on antimicrobial resistance from the World Health Organization warns against the beginning of a "post-antibiotic" era, when most of the bacterial pathogens will become resistant to all treatments available.

In this context, it is crucial to fully understand the molecular mechanism of bacterial adaptability to ultimately target and limit this ability. To survive in a changing environment, bacteria have to resist to stresses induced by these changes and ultimately to adapt their lifestyle if these changes persist. These two processes are almost contradictory since the first aims at maintaining cell integrity while the second allows long term variability through the acquisition of new traits.
For 10 years, the team engaged several lines of research on this topic in the lab, first at institut Pasteur and from 2016 within the MFP unit and at the Institut Européen de Chimie et Biologie (IECB) in Bordeaux. Over the last 5 years, we focused our research on the main projects listed below. The lab has also been instrumental in setting up a state of the art cryo-electron microscopy (CryoEM) facility at IECB. We have several on-going collaborations related to our expertise in CryoEM. We are also involved in technological development projects such as the implementation of super-resolution correlative microscopy in cryo conditions.

Project 1: Natural transformation and gene repair in bacterial pathogens (Funded by ERC)

In this project, we want to understand how DNA can be uptaken and recombined in the bacterial genome during bacterial transformation. Natural genetic transformation, first discovered in *Streptococcus pneumoniae* by F. Griffith in 1928, is observed in many Gram-negative and Gram-positive bacteria. This process promotes genome plasticity and adaptability. In particular, it enables many human pathogens such as *Streptococcus pneumoniae*, *Neisseria gonorrhoeae* or *Vibrio Cholerae* to acquire resistance to antibiotics and/or to escape vaccines through the binding and incorporation of new genetic material. While it is well established that this process requires the binding, internalization of external DNA and its recombination in the bacterial genome, the molecular details of these steps are unknown. In this project, we aim at acquiring a detailed understating of each of these steps. We discovered a new appendage at the surface of *S. pneumoniae* cells and showed that this appendage is similar in morphology and composition to appendages called Type IV pili commonly found in Gram-negative bacteria. We demonstrated that this new pneumococcal pilus is essential for transformation and that it directly binds DNA **(PLOS Pathogens 2013 and 2015).** We are also actively studying the DNA translocation apparatus. We isolated most of its components and are in the process of determining their structure and studying their function *in vitro* and *in vivo*. Finally, we identified a new key ATPase involved in the recombination process. We determined the crystal structure of this protein and identified its function in vitro and in vivo in collaboration with Patrice Polard's team in Toulouse (France) **(Nature communications, 2017)**. We also explored the initiation and molecular mechanism of the recombination event. We determined the structure of RecA filaments from *S. pneumoniae* and revealed the structural basis of its interaction with its loader on ssDNA during transformation (called DprA) **(Manuscripts in preparation)**. Finally, we are also exploring the architecture of the transformation apparatus in its native cellular environment using Cryo-tomography and correlative microscopy approaches.

Project 2: Bacterial competition systems (Type 6 and type 7 secretion systems) (funded by the IDEX/regional Chair).

The bacterial Type 6 secretion (T6S) system is one of the key players for microbial competition, as well as an important virulence determinant during bacterial infections. It assembles a nano-crossbow-like structure that propels an arrow made of Hcp tube and VgrG spike into the cytoplasm of the attacker cell and punctures the prey's cell wall. The nano-crossbow is stably anchored to the cell envelope of the attacker by a membrane core complex. In collaboration with Eric Cascales' laboratory in Marseille (France), we recently have shown that this membrane complex is assembled by the sequential addition of three proteins -TssJ, TssM and TssL- and presented a structure of the fully assembled complex **(Nature 2015)**. Since our arrival at IECB and MFP, we solved the cryoEM structure of this complex **(EMBO J. 2019)**. We also solved the cryoEM structure of another key element of the T6S system, the baseplate **(Nature microbiology 2018)** and of the T6SS substrate from pathogenic *Escherichia coli* in complex with the T6SS spike **(EMBO J. 2020)**.

While at institut Pasteur, our group started to work on type 7 secretion systems (T7SS). These systems are mostly found in mycobacteria and other Gram-positive bacteria such as *Staphylococcus aureus* or *Bacillus subtilis*. While it is well established that mycobacterial T7SS are directly used in virulence, their exact function in other Gram-positive bacteria was unclear. We recently revealed that the T7SS found in B. subtilis is an anti-microbiobal device used by these bacteria to kill other Gram-positive bacteria (BioRviv 2020). We also performed an in-depth biochemical study and solved the crystal structure of a key component of this 4/12 system (YukC). Overall, our work shows that *B. subtilis* Yuk T7SS is a bona fide and functional T7SS that can be used a model system to study T7SSs.

Project 3: Metabolic adaptability of bacterial pathogens (funded by the ERC)

Acetaldehyde-alcohol dehydrogenase (AdhE) enzymes are a key metabolic enzyme in bacterial physiology and pathogenicity. They convert acetyl-CoA to ethanol via an acetaldehyde intermediate during ethanol fermentation in an anaerobic environment. This two-step reaction is associated to NAD+ regeneration, essential for glycolysis. The bifunctional AdhE enzyme is conserved in all bacterial kingdoms but also in more phylogenetically distant microorganisms such as green microalgae. It is found as an oligomeric form called spirosomes, for which the function remains elusive. We used cryo-electron microscopy to obtain structures of *E. coli* spirosomes in different conformational states. We showed that spirosomes contain active AdhE monomers, and that AdhE filamentation is essential for its activity *in vitro* and function *in vivo*. The detailed analysis of these structures provides insight showing that AdhE filamentation is essential for substrate channeling within the filament and for the regulation of enzyme activity. This work was published in **Nature communications in 2020**.

Project 4: Structure and function of a mycoplasma antibody cleavage device (funded by the ANR, in collaboration Yonathan Arfi, INRA, Bordeaux)

Mycoplasmas cause various chronic diseases in animals and humans. They have evolved strategies to evade the host immune response, including the Mycoplasma Ig Binding (MIB)- Mycoplasma Ig Protease (MIP) antibody degrading system. The Fab domain of many types of immunoglobulins is recognized by MIB. This interaction allows the recruitment of the serine protease MIP, which cleaves the VH domain of the antibody. To understand the molecular basis of this system, we have solved the structure of the ternary complex Fab-MIB-MIP antibody degrading system by cryoelectron microscopy. The structure of the complex between MIB, MIP and the Fab fragment of a goat IgG has been solved to a 3 Å resolution, by single particle cryoEM. Together with biochemical and in vivo data, our work reveals very original binding mechanism of the complex to the antibody **(Science Advances, 2020)**.

Project 5: Development of super-resolution cryo-correlative microscopy

The project 5 started very recently in collaboration with the laboratories of Daniel Choquet (IINS), Brahim Lounis, (LP2N) Gregory Giannone (IINS), Bordeaux imaging center and the UMS of the IECB. The major challenge in cell and structural biology today is to combine two cutting-edge technologies, super-resolution fluorescence microscopy and cryoEM, to enable a new revolution in the determination of atomic structure and the understanding of the function of molecules in their natural context. Multimodal or correlative microscopy approaches combining the power of high-resolution optical and electronic microscopy are at the forefront of technology at the national and international level. This technological development will make it possible to go beyond the limits of existing technologies and will revolutionize our understanding of the molecular mechanisms of living organisms, particularly in the fields of neurobiology, cancerology and the study of pathogens such as parasites, bacteria that are multi-resistant to antibiotics or emerging viruses. Rémi Fronzes is the coordinator of an EquipEx proposal awarded in 2020 focusing on this project. He is also the coordinator of a CPER project for IECB, including equipment that will be essential to this project.

Selected publications

1. Tassinari, M.; Doan, T.; Bellinzoni, M.; Chabalier, M.; Ben-Assaya, M.; Martinez, M.; Gaday, Q.; Alzari, P. M.; Cascales, E.; Fronzes, R.; Gubellini, F. The Antibacterial Type VII Secretion System of Bacillus Subtilis: Structure and Interactions of the Pseudokinase YukC/EssB. *mBio* **2022**, 13 (5), e0013422. https://doi.org/10.1128/mbio.00134-22.

2. Nottelet, P.; Bataille, L.; Gourgues, G.; Anger, R.; Lartigue, C.; Sirand-Pugnet, P.; Marza, E.; Fronzes, R.; Arfi, Y. The Mycoplasma Surface Proteins MIB and MIP Promote the Dissociation of the Antibody-Antigen Interaction. *Sci Adv* **2021**, 7 (10), eabf2403. https://doi.org/10.1126/sciadv.abf2403.

3. Jurėnas, D.; Rosa, L. T.; Rey, M.; Chamot-Rooke, J.; Fronzes, R.; Cascales, E. Mounting, Structure and Autocleavage of a Type VI Secretion-Associated Rhs Polymorphic Toxin. *Nat Commun* **2021**, 12 (1), 6998. https://doi.org/10.1038/s41467-021-27388-0.

European Research Council

Dr. Yaser Hashem
Research Director (DR2), Inserm

Yaser Hashem obtained his PhD in 2010 in Strasbourg (France) in computational structural biology where he developed computational approaches for the study of bacterial ribosomal RNA interactions with several antibiotics. After his PhD he went on for a Postdoc at Columbia University in the city of New York with Prof. Joachim Frank (Nobel Laureate for Cryo-EM, 2017) where he worked on understanding the mRNA translation regulation using Cryo-EM and more specifically the translation initiation step in mammals. In 2014, Y. Hashem started his research group in Strasbourg (France) where he became expert in translation regulation in pathogenic parasites and their mammalian hosts. In 2017, Y. Hashem was awarded with the ATIP-Avenir grant, the ERC (European Research Council) starting grant and the "Chair d'Excellence Junior" from the University of Bordeaux and joined the IECB as a Group Leader. More recently, Y. Hashem was awarded with the ERC (European Research Council) Consolidator Grant 2022.

Research team

Dr. Yaser HASHEM Research Director, DR2, (Inserm)
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Dr Ewelina GUCA Postdoc (INSERM)
Dr Mayara DEL CISTIA Postdoc (INSERM)
Dr Trung NGUYEN Postdoc (INSERM)
Ms Sramona BARUA PhD student (INSERM)
Ms Jessica DA CRUZ PhD student (INSERM)
Dr Rafael ROCHA Postdoc (INSERM)

This team is part of the unit "Acides Nucléiques: Régulations Naturelles et Artificielles" (ARNA), Inserm U1212/CNRS UMR5320/Univ. Bordeaux

RNA Processing and translation regulation in pathogens and hosts (RNA-PT)

The "mRNA translation regulation in pathogens and hosts" group endeavors to study at the molecular level the mRNA translation regulation in several species of pathogens, mainly eukaryotic (both cytosolic and mitochondrial mRNA translation), and their hosts. For several years already, the group has studies existing structural differences in the translation machinery between kinetoplastids and their mammalian hosts in order to discover new and more specific potential therapeutic targets that can be used for the development of safer therapeutic strategies against this family of dangerous parasites. One of the main focuses of the group is the translation initiation step that presents various important structural differences in kinetoplastids, when compared to humans. The group is mainly specialized in cryo-electron microscopy, a technique that allows in principle to resolve molecular structures of large sizes to atomic resolutions.

Translation initiation in mammals:

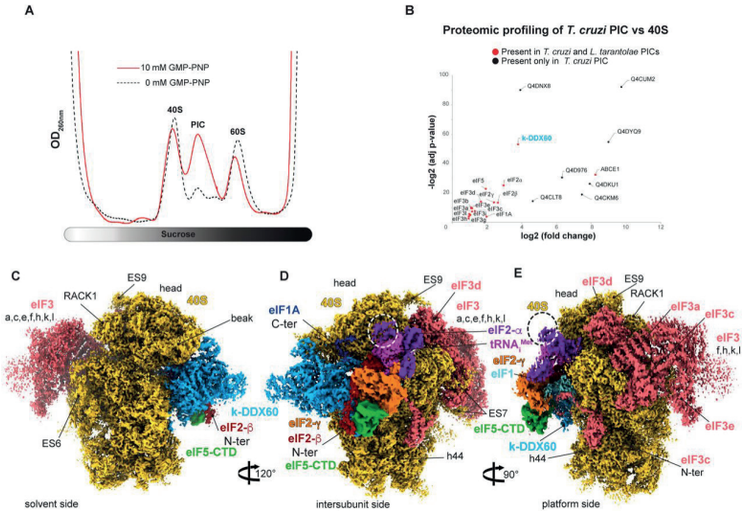

Figure1. ***Late-stage 48S initiation complexes (48SIC) from mammals****. Thanks to grad-cryo protocol we were able to purify native IC in native conditions. A, b-globin IC. B, histon 4 IC. In boxes a blow up on the start-initiation codons for both complexes. From Simonetti & Guca at al. Cell Reports 2020.*

We have solved the structures of two native translation initiation complexes with two archetype abundant cellular mRNAs, the β-globin and histon 4. Our structures are at near-atomic resolution (3.0 to 3.5 Å, respectively, Figure1) and reveal that depending on the mRNA sequence, its interactions with different components of the initiation complex such as eukaruotic initiation factors (eIFs) 1A, 2 and 3 can vary. These complexes can be

directly compared with those from several species of pathogenic protozoa.

Translation initiation in kinetoplastids: The initiation stage is expected to represent numerous variations in pathogenic protozoa such as kinetoplastids (like *T. cruzi, T. brucei and L. major)* compared to its mammalian counterpart because of the presence of several large rRNA expansion segments at the binding site of several initiation factors such as eIF3. Protozoa like kinetoplastids present a complex life cycle where the parasite spends most of its life in an insect vector before being transmitted to a mammalian host upon bitting. Moreover, *in vitro* growth of the parasite reveals various population regulation points aimed at optimizing the environmental resources such as oxygen and carbon resources. Therefore, we first attempted to study their *in vitro* growth in order to retrieve the best conditions allowing the purification of canonical translation initiation complexes.

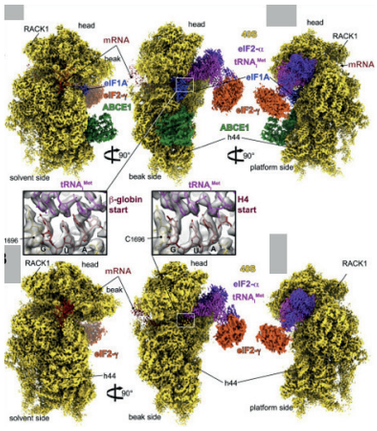

Figure2. ***Composition and cryo-EM structure of the T. cruzi 43S PIC.*** *(A) The effect of the GMP-PNP treatment on the 43S PIC stabilization in the T.cruzi lysate assessed by UV absorbance profile analyses (B) Proteomic profiling of the endogenous pre-initiation complex in comparison with native 40Ss purified from the T. cruzi cell lysate (see methods for the validation). (C) The overall structure of the T. cruzi 43S PIC shown from the intersubunit side. The initiation factors are colored variably. (D) The 43S PIC recons-truction focused on the solvent side. Extra density of eIF2α corresponding to the kinetoplastidian specific N-terminal insertion is encircled by a dashed line. (E) The 43S PIC reconstruction focused on eIF3 and the 40S platform. From Bochler et al. 2020 (Cell Reports).*

The study of the dynamics of growth of epimastigote forms from trypanosoma cruzi and Leishmania tarentolae was carried out. After establishing the best growth conditions for both parasites, we have attempted the purification of initiation complexes using our grad-cryo protocol at different time-points of the growth curves and only at the 3rd growth day we were able to harvest the (pre) initiation complexes in sufficient yield to obtain a cryo-EM structure, the reason of which remains unknown. The purified complexes were solved by cryo-EM at 3.3Å revealing the presence of several kinetolastids-specific features such as the presence of an additional helicase involved in the initiation process that we have termed DDX60-like because of its faint homology to mammalian DDX60 (Figure2).

Mitochondrial translation regulation: In the past years the team has heavily invested in investigating translation regulation in mitochondria in both pathogens and hosts. Thus, we have recently published the cryo-EM structure of the plant mitoribosome, as plants are also known to be hosts for several species of kinetoplastids (Waltz et al. Nature plants 2019, Waltz & Soufari et al. Nature plants 2020, Figure 3), but also from green algae *Chlamydomonas reinhardtii* (Waltz et Salinas, Nature Comm. 2022) and *T. cruzi* and *L. tarentolae* (Soufari et al. PNAS plants 2020).

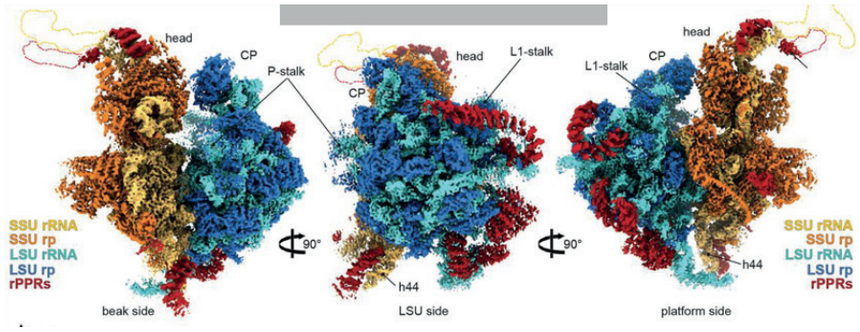

Figure3. ***Overall structure of the plant mitochondrial ribosome.***
rRNAs are colored in light blue (LSU) and yellow (SSU) and ribosomal proteins in blue (LSU) or orange (SSU). A dozen pentatricopeptide repeats proteins (PPR), specific to the plant mitoribosome were discovered and termed ribosomal PPR (rPPR), shown in red. From Waltz & Soufari et al. Nature plants 2020.

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European Research Council

Structural Biology of Biofilms

Dr. Petya Violinova Krasteva
Research Director (DR2), CNRS
UMR5248 CBMN

Dr. Petya V. Krasteva joined the CBMN as an IECB group leader in October 2019.
Her research focuses on cyclic dinucleotide signaling and extracellular matrix secretion in bacterial biofilm formation and pathogenesis. Combining X-ray crystallography, biophysical and biochemical assays, cryoelectron microscopy and in cellulo functional studies, her 'Structural Biology of Biofilms' team aims to provide a comprehensive view of bacterial social networks that spans the different resolution levels and present molecular blueprints for the development of novel anti-infectives.
Petya Krasteva completed her PhD in Molecular and Cell Biology at Ivy League's Cornell University in January 2011, after which she joined the editorial team of Nature Methods at Nature Publishing Group, New York. For her postdoc, she moved to the Institut Pasteur in Paris in 2012 and started her independent team as a CNRS CRCN and an ATIP-Avenir laureate in the end of 2016 at the I2BC, Gif-sur-Yvette.
For her work on bacterial signaling and biofilm formation, Petya Krasteva is the recipient of the Prix Jacques Monod (Fondation de France, 2016), the CNRS Médaille de Bronze (2019) and an ERC Starting Grant (BioMatrix, 2018-2023).

Research team

Dr. Petya V. KRASTEVA PhD, HDR, DR2 CNRS, Principal Investigator / Group Leader (CNRS)
Thibault SANA Research engineer (CNRS)
Baptiste FISCHER Lecturer (Univ. Bordeaux)
Areti NOTOPOULOU ERASMUS visiting scholar (CNRS)
Itxaso ANSO PostDoc(CNRS)
Clémence CAILLAUD Intern M1 (CNRS)
Lola LE BARS Intern BTS (CNRS)

This team is part of the unit "Chimie et Biologie des Membranes et des Nano-objets" (CBMN), CNRS UMR5248/INP/Univ. Bordeaux

The Krasteva Lab's research focuses on cyclic dinucleotide signaling and extracellular matrix secretion in bacterial biofilm formation and pathogenesis. Combining X-ray crystallography, biophysical and biochemical assays, cryo-EM and in cellulo functional studies, the 'Structural Biology of Biofilms' (SBB) team aims to provide a comprehensive view of bacterial social networks that spans the different resolution levels and presents molecular blueprints for the development of novel anti-infectives.

Currently the team's research is focused on two main scientific questions: i) what are the intracellular signaling mechanisms that regulate bacterial biofilm formation and, ii) what are the structure, function and dynamics of the membrane-embedded biosynthetic platforms for the secretion of extracellular matrix components.

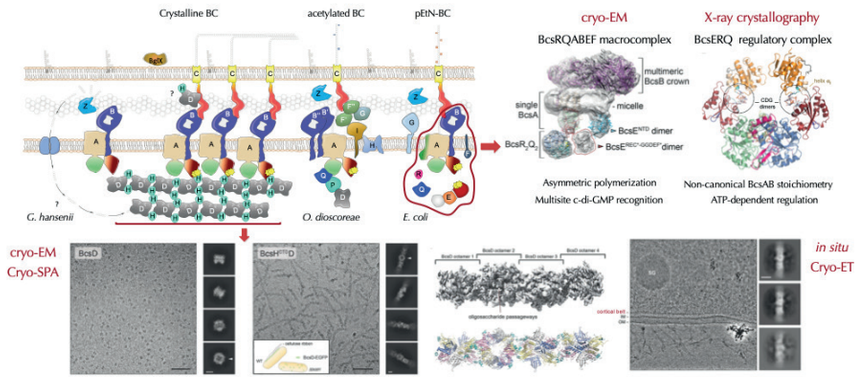
Recently, the 'Structural Biology of Biofilms' team provided unprecedented insights into the structural biology of bacterial cellulose secretion (BCS) systems in bacterial biofilms with complete structure-function analyses of the megadalton-sized membrane-embedded Bcs secretion macrocomplex of E. coli and other enterobacteria, as well as multiple regulatory subcomplexes (Zouhir *et al.* ***mBio*** 2020 and Abidi *et al.* ***Science Advances*** 2021). In a separate studies, the group also deciphered the mechanism of synthase array assembly in the cellulose superproducer *Gluconacetobacter hansenii* and in a wide array of plant-colonizing Proteobacteria which is of substantial interest for industrial, agricultural and biomedical applications (Abidi et al. ***Science Advances*** 2022; Sana et al. Current Biology 2023). Finally, the team also deciphered the mechanisms of transcription regulation of motility and biofilm formation in the ESKAPE pathogen P. aeruginosa (Torres-Sánchez et al. ***PNAS*** 2023)

Cellulose is the most abundant biopolymer on Earth and while it is the predominant building constituent of plants, it is also a key extracellular matrix component in the biofilms of many bacterial species. Importantly, cellulose secretion is key to the ecological success and host tissue colonization of both symbiotic and pathogenic bacteria that live in close association with plants, and can thus have significant economic impact as biocontrol microorganisms, cellulose superproducers of biotechnological interest or detrimental agricultural pathogens. While BC was first described in the 19th century, it was not until this last decade that insights were provided into how the bacterial cellulose synthase BcsA, assisted by an inner-membrane partner BcsB, senses the intracellular second messenger c-di-GMP to simultaneously polymerize UDP-activated glucose and extrude the nascent polysaccharide across the inner bacterial membrane. At the molecular level, it is now well established that biofilm-promoting BC can be produced by several distinct types of Bcs secretion systems and that in addition to the well-studied BcsAB duo, they can feature multiple accessory subunits, often indispensable for polysaccharide production. However, the roles of many of these key actors and how they assemble with each other remain to be examined.

We demonstrated recently that in *Escherichia coli,* the BcsAB tandem assembles into a stable megadalton-sized macrocomplex with four accessory subunits, which are either essential for (BcsR and BcsQ) or enhance (BcsE and BcsF) cellulose secretion. A yet distinct Bcs subunit, BcsG, was shown to covalently decorate the biomatrix polymer

with phosphoethanolamine (pEtN) residues, most likely via transient interactions with the secretion macrocomplex. Our structure-function analyses combining global architecture studies by cryo-EM with atomicresolution structures of multiple regulatory subcomplexes and a plethora of functional assays uncovered mechanisms for periplasmic BcsB polymerization and cell-pole targeting in the early stages of biofilm formation, and revealed unexpected subunit stoichiometry, multisite c-di-GMP recognition and ATP-dependent regulation. The cellulose biogenesis components of E. coli share similar coding operons and, likely, secretion system architecture with many plant-colonizing bacterial species including both food-borne enterobacterial pathogens (e.g. *Salmonella enterica* serovar Typhimurium) and beneficial biocontrol microorganisms (e.g. *Pseudomonas putida.*

Despite strong conservation of the BcsAB tandem across species, in the economically relevant BC superproducer G. hansenii cellulose is secreted in a drastically different manner: a longitudinal nanoarray of synthase terminal complexes (TCs) assembles the polysaccharide strands into a crystalline cellulose ribbon with implications in cell motility, flotation and substrate colonization. Crystalline BC secretion is dependent on two accessory subunits earlier proposed to interact in the periplasm: BcsD, a donut-shaped octamer with 4 luminal passageways proposed to guide and prevent aggregation of the nascent polysaccharide, and BcsH, previously proposed to be a short, 8 kDa peptide mediating the linear BcsD arrangement necessary for cellulose ribbon formation. We were recently able to provide the first atomic-resolution insights BcsHD mediated BC crystallinity. We showed that BcsH is in fact a 37 kDa protein that assembles into SDS- and heat-resistant dimers to drive the oligomerization of BcsD octamer into a three-dimensional supramolecular scaffold. We showed that, in situ, the BcsHD assemblies share remarkable morphological similarities with the recently discovered cortical belt, namely an intracellular cytoskeletal element that spatially correlates with the cellulose exit sites and the assembled crystalline cellulose ribbon. Finally, we detected specific protein-protein interactions between the BcsHD components and the regulatory BcsAPilZ module, further supporting that BcsHD features an unexpected intracellular localization for inside-out control of TC array formation and crystalline cellulose secretion.



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2. Krasteva, P. V. Bacterial Synthase-Dependent Exopolysaccharide Secretion: A Focus on Cellulose. *Curr Opin Microbiol* **2024**, 79, 102476. https://doi.org/10.1016/j.mib.2024.102476.

3. Abidi, W.; Decossas, M.; Torres-Sánchez, L.; Puygrenier, L.; Létoffé, S.; Ghigo, J.-M.; Krasteva, P. V. Bacterial Crystalline Cellulose Secretion via a Supramolecular BcsHD Scaffold. *Sci Adv* **2022**, 8 (50), eadd1170. https://doi.org/10.1126/sciadv.add1170.

4. Torres-Sánchez, L.; Sana, T. G.; Decossas, M.; Hashem, Y.; Krasteva, P. V. Structures of the P. Aeruginosa FleQ-FleN Master Regulators Reveal Large-Scale Conformational Switching in Motility and Biofilm Control. *Proc Natl Acad Sci U S A* **2023**, 120 (50), e2312276120. https://doi.org/10.1073/pnas.2312276120.

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6. Abidi, W.; Torres-Sánchez, L.; Siroy, A.; Krasteva, P. V. Weaving of Bacterial Cellulose by the Bcs Secretion Systems. *FEMS Microbiol Rev* **2022**, 46 (2), fuab051. https://doi.org/10.1093/femsre/fuab051.

7. Abidi, W.; Decossas, M.; Torres-Sánchez, L.; Puygrenier, L.; Létoffé, S.; Ghigo, J.-M.; Krasteva, P. V. Bacterial Crystalline Cellulose Secretion via a Supramolecular BcsHD Scaffold. *Sci Adv* **2022**, 8 (50), eadd1170. https://doi.org/10.1126/sciadv.add1170.

Dr. Pierre Maisonneuve
Research Scientist (CNRS)

Pierre Maisonneuve has completed his PhD in 2014 at the Pasteur institute in Paris. He then performed a postdoc at the Lunenfeld-Tanenbaum research Institute in Toronto (Canada) where he was supported by a postdoctoral fellowship from the Canadian Institutes of Health Research. In 2022, he was awarded a starting grant "Amorçage de Jeunes Équipes" from the "Foundation pour la Recherche Médicale" (FRM) to join the CBMN in Bordeaux and started as a group leader in the IECB. In 2023, he obtained a permanent position as a research scientist (CRCN) at the CNRS..

Research team

Dr. Pierre MAISONNEUVE Research Scientist (CNRS)
Dr. Marion DECOSSAS Research engineer (CNRS)
Dr. Margaux LUSTIG Postdoctoral fellow (CNRS)
Marroussia AUBOUIN Master 2 Student (UB)

This team is part of the unit: "Chemistry and Biology of Membranes and Nano-objects" (CBMN), CNRS UMR 5248/INP/Univ. Bordeaux

Structural Biology of Signaling proteins

Pseudokinases are inactive kinases that influence cell signaling through non-catalytic mechanisms. Pseudokinases represent ~10% of all human protein kinases. Their dysregulation contributes to human diseases, including cancers. They represent a promising niche of therapeutic targets. Indeed, the first drug targeting a pseudokinase protein, i.e. Deucravacitinib, was approved by the FDA in 2022, paving the way for the development of new therapeutics targeting pseudokinases. However, pseudokinases remain challenging targets due to their lack of catalytic activity and our lack of understanding of how they function. Therefore, uncovering the molecular mechanisms of pseudokinases would not only improve our understanding of human signaling in health and disease, but would also allow us to better target them in the clinic.

Our research interest is to decipher the molecular mechanisms of protein pseudokinases in human signaling and to understand how their dysregulation is involved in diseases. To this end, we mainly focus on two family of pseudokinase proteins, 1) the pseudokinase proteins KSR and 2) a particular pseudokinase-containing family of receptors, for which the molecular mechanisms are yet to be uncovered.

1) The pseudokinase KSR is a member of the RAF family kinases, which are mutated in 8% of human cancers. RAF kinases are regulated by dimerization of their kinase domains, and this underpins the majority of acquired resistance mechanisms against RAF therapeutics. KSR plays an important role in regulating RAF kinase dimerization, but its precise mechanism of action is not fully understood.

2) The particular family of pseudokinase-containing receptors are implicated in numerous human diseases, such as intestinal inflammatory diseases, affecting millions of people worldwide. Therefore, they are very promising therapeutic targets. However, much remains to be learned about the mechanism by which they transduce external signals across the membrane to trigger intracellular downstream signaling and affect the cell function.

To shed light on how these pseudokinase proteins work, our group combines integrative structural biology approaches (cryo-EM, X-Ray crystallography and NMR), biophysics characterization, functional assays (*in vitro* and *in cell*) and development of pseudokinasetargeting small molecules. Such molecules are exploited as chemical tools to decipher the molecular mechanism of pseudokinase proteins but also to address key questions about their biological function. These molecules may also represent proof-of-concept pre-clinical chemical tools and set the stage for translational research to develop therapeutic lead compounds against various diseases.

Selected publications

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2. Mishra, V.; Sharma, K.; Bose, A.; Maisonneuve, P.; Visweswariah, S. S. The Evolutionary Divergence of Receptor Guanylyl Cyclase C Has Implications for Preclinical Models for Receptor-Directed Therapeutics. *J Biol Chem* **2024**, 300 (1), 105505. https://doi.org/10.1016/j.jbc.2023.105505.

3. Maisonneuve, P.; Sahmi, M.; Bergeron-Labrecque, F.; Ma, X. I.; Queguiner, J.; Arseneault, G.; Lefrançois, M.; Kurinov, I.; Fronzes, R.; Sicheri, F.; Therrien, M. The CNK-HYP Scaffolding Complex Promotes RAF Activation by Enhancing KSR-MEK Interaction. *Nat Struct Mol Biol* **2024**. https://doi.org/10.1038/s41594-024-01233-6.

4. Ignatov, M.; Jindal, A.; Kotelnikov, S.; Beglov, D.; Posternak, G.; Tang, X.; Maisonneuve, P.; Poda, G.; Batey, R. A.; Sicheri, F.; Whitty, A.; Tonge, P. J.; Vajda, S.; Kozakov, D. High Accuracy Prediction of PROTAC Complex Structures. *J Am Chem Soc* **2023**, 145 (13), 7123–7135. https://doi.org/10.1021/jacs.2c09387.

Dr. Nicolas Reyes
Research Director (DR2),
CNRS/Univ. Bordeaux

My work focuses on the molecular mechanisms of human membrane proteins. I have a multidisciplinary background in membrane protein biophysics spanning from single-molecule electrophysiological measurements (*Nature* 2006; visiting PhD student at The Rockefeller University, USA) to atomic-resolution structure determination (*Nature* 2009; Postdoc at Weill Cornell, USA).
As an early-career independent researcher, my laboratory determined the first 3D structures of an essential synaptic component in the human brain, namely excitatory amino acid transporters, and a first-in-class allosteric inhibition mechanism (*Nature* 2017).
More recently, we studied receptor (*Science* 2020; *Nature* 2022; *Nat. Struct. Mol. Biol.* 2022) and transport (*EMBO J.* 2022) mechanisms of different membrane protein systems with a focus on human solute carriers.
Research in my lab has mainly been funded by international grants including ERC Starting and Consolidator grants.

Research team

Dr. Nicolas REYES Research Director, DR2 (CNRS)
Dr. Juan CANUL-TEC Postdoc (CNRS)
Dr. Miryam VILLALBA Postdoc (CNRS)
Dr. Sandeep MULAKALA Postdoc (CNRS)
Shashank KHARE PhD Student (CNRS)

This team is part of the unit: "Fundamental microbiology and pathogenicity" (MFP), CNRS UMR5234/Univ. Bordeaux

Membrane Protein Mechanisms

Human solute carriers (hSLC) form a superfamily of integral membrane proteins that transport essential molecules and ions across membranes, and are the cellular receptors of human and pathogenic proteins. Their transport and receptor functions are involved in a wide range of pathological conditions, making hSLCs important emerging drug targets in neurodegeneration, cancer, and infectious diseases, among others.
Our research program aims to unravel novel transport, receptor and pharmacological mechanisms of medically important hSLCs using a multidisciplinary biophysical approach.
To achieve this, we combined high-resolution cryo-electron microscopy with functional approaches to probe hSLC complexes' structures, dynamics, and thermodynamics.

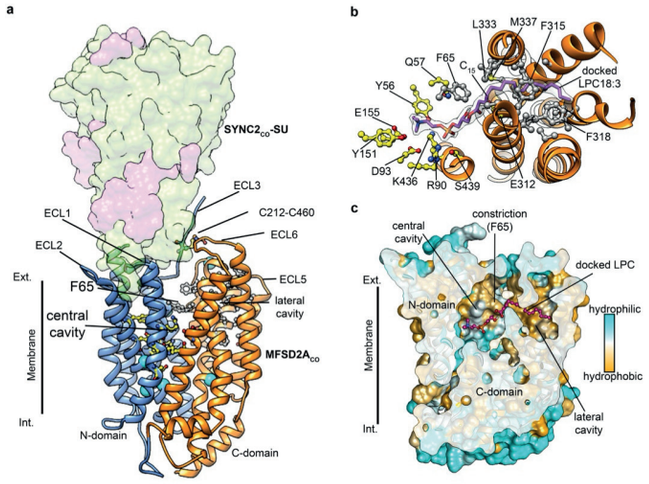

Figure 1. Outward-facing occluded MFSD2A. a, Membrane view of MFSD2ACO:SYNC2CO-SU complex. N- (blue) and C-domains (orange) form an outward-facing cavity in MFSD2ACO displaying clusters of conserved-polar residues (yellow), and -hydrophobic (gray) residues. Human disease-causing MFSD2A mutations are mapped on the structure (alpha-carbon, cyan spheres). b, Extracellular view of MFSD2ACO with docked LPC 18:3 molecule (purple, and pseudo-transparent molecular surface) burying lipid-tail C1-C14 atoms within the C-domain (orange ribbons). Residue sidechains likely involved in binding of LPC headgroup (yellow), and lipid-tail (grey) are shown. N-domain TMs are not shown for clarity of display. c, MFSD2A molecular surface colored by residue hydrophobicity shows central and lateral cavities connected through a constriction around F65. SYNC2CO-SU is not shown.

Transport and retroviral receptor mechanisms of an essential omega-3 fatty acid human carrier.

Brain, and blood-brain barrier (BBB) development and function require uptake of docosahexaenoic omega-3 fatty acid in the form of lysophosphatidylcholine. The majorfacilitator superfamily transporter MFSD2A is the main uptake route of that molecule into the brain, and a potential pharmaceutical target to facilitate passage of therapeutic molecules across the BBB. MFSD2A also functions as the receptor of endogenous-retroviral envelope syncytin-2 (SYNC2) in human placenta, where it mediates cell-cell fusion and formation of the maternal-fetal interface. In this project, we aim to understand the molecular mechanisms underlying We human MFSD2A transport and receptor functions. To this goal, we determined the cryo-electron microscopy structure of the MFSD2A-SYNC2 complex (Fig. 1). The structure reveals MFSD2A in a novel state of the transport cycle that enables occlusion of a lysophosphatidylcholine molecule within the protein core, and displays a large hydrophobic cavity in the transporter

C-terminal domain to occlude long aliphatic chains. This particular architecture suggests an adapted alternating-access transport mechanism for lipid substrates in mammalian MFS transporters. We further demonstrate that SYNC2 establishes an extensive binding-interface with MFSD2A, and that a SYNC2-soluble fragment acts as long-sought after inhibitor of MFSD2A transport, and we have filed a patent to protect engineered SYNC2 fragments. Our results have so far uncovered molecular mechanisms important to brain and placenta development and function. The inhibitory effect of SYNC2 on MFSD2A transport further suggests strategies to aid delivering therapeutic macromolecules across the BBB.

Transport and hepatitis-B-virus receptor mechanisms of a central liver carrier.

Bile salts could be regarded as detergent molecules secreted by our body to help us solubilize and absorb lipidic nutrients from the diet (fat and hydrophobic vitamins, for example vitamin D). However, they are a unique detergent type, as bile salts are made out of cholesterol, and therefore contribute to control cholesterol levels in our body. To act as efficient detergents, bile salts are concentrated in bile, a dark-green liquid produced in the liver, and then stored in the gallbladder for release into the intestine to aid our digestion. In order to avoid wasting energy to produce new bile salt molecules after their use in the intestine, our body recycles bile salts by transporting them back into the liver from blood.

This transport function is mainly carried out by a membrane protein called Na+-taurocholate co-transporting polypeptide (NTCP), that uses the energy stored in the sodium transmembrane gradient to efficiently take up bile salts into the liver for bile production. Importantly, NTCP plays a fundamental role in liver pathology, as it is the cellular entry receptor of human hepatitis B and D viruses (HBV/HDV). Despite efficient vaccination programs, chronic HBV infection is a major cause of hepatocellular carcinoma and liver cirrhosis that affects ~250 million people globally. NTCP has emerged as an important target to develop viral entry inhibitors.

In this project we aim to understand the molecular mechanisms underlying NTCP transport and HBV receptor functions. To his aim, we combine high-resolution cryo-EM and transport functional assays. Cryo-EM only works for relatively large proteins (> 50 kDa), and NTCP is only ~38 kDa. To overcome this problem, in collaboration with the laboratory of Jan Steyaert at VIB Brussels, we developed selective antibody fragments against NTCP that recognize its extracellular surface, and provide molecular features that enable cryo-EM structure determination. These antibody fragments, namely nanobodies, have an added advantage, as they stabilize different conformations of NTCP transport cycle.

Our results constitute the first structural characterization of the human bile acid transporter and HBV/HDV receptor NTCP, and provide unprecedented molecular insights into its “gatedpore” transport, as well as HBV/HDV receptor-recognition mechanisms (Fig. 2).

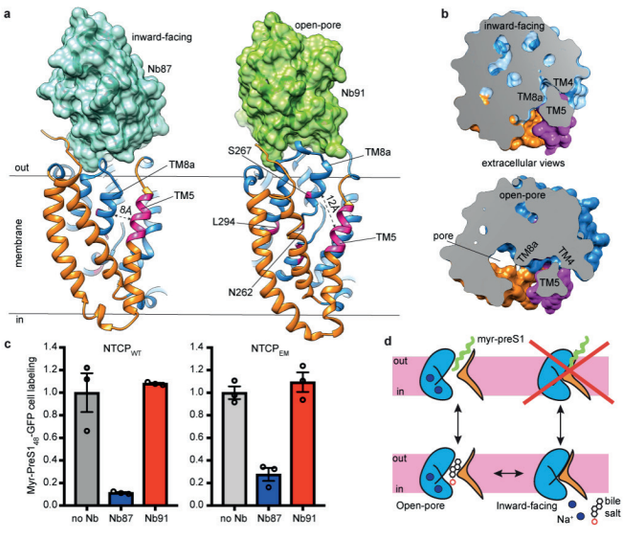

Figure 2. Structures of NTCP complexes with Nb87 and Nb91 a, Nb87 (left, cyan surface) and Nb91 (right, green surface) bind overlapping 3D epitopes on the extracellular surface of the core domain, distant from myr-preS1 binding-determinant TM5 region, and residues within the pore (highlighted in pink). In the inward-facing state (left) TM5 packs against the core domain (blue). In the open-pore state (right), the core domain moves outward and away from TM5 exposing important residues for myr-preS1 binding (pink). b, Extracellular view of cross-sections passing through the myr-preS1 binding determinant region in TM5 (highlighted in pink). Inward-facing (top), and open-pore (bottom) show TM5-core domain (blue) interfaces. c, Myr-preS148-GFP labelling of cells expressing NTCPWT (left) and NTCPEM (right), respectively. Pre-incubation with Nb87, but not with Nb91, impaired myr-preS148-GFP labelling. Plots depict average of n=3 biologically independent experiments, and circles represent values from individual experiments. Error bars represent SEM. d, Cartoon representation of NTCP “gated-pore” transport mechanism and the relative movements of core (blue), and panel (orange) domains. Myr-preS1 domain of HBV/HDV (green) preferentially binds to open-to-outside states of NTCP transport cycle.

Selected publications

1. Goutam, K.; Ielasi, F. S.; Pardon, E.; Steyaert, J.; Reyes, N. Structural Basis of Sodium-Dependent Bile Salt Uptake into the Liver. *Nature* **2022**, 606 (7916), 1015-1020. https://doi.org/10.1038/s41586-022-04723-z.

2. Martinez-Molledo, M.; Nji, E.; Reyes, N. Structural Insights into the Lysophospholipid Brain Uptake Mechanism and Its Inhibition by Syncytin-2. *Nat Struct Mol Biol* **2022**, 29 (6), 604-612. https://doi.org/10.1038/s41594-022-00786-8.

3. Canul-Tec, J. C.; Kumar, A.; Dhenin, J.; Assal, R.; Legrand, P.; Rey, M.; Chamot-Rooke, J.; Reyes, N. The Ion-coupling Mechanism of Human Excitatory Amino Acid Transporters. *The EMBO Journal* **2022**, 41 (1), e108341. https://doi.org/10.15252/embj.2021108341.

Dr. Frédéric Friscourt
Associate Professor, ATIP-Avenir Fellow, Univ. Bordeaux

Frédéric Friscourt received his PhD from the University of Glasgow, UK in 2009, under the guidance of Prof. P. Kočovský, on the development of novel chiral ligands for enantioselective catalysis. He then joined the group of Prof. G-J. Boons at the Complex Carbohydrate Research Center, GA, USA, as a post-doctoral research associate (2009-2014) in order to transition to chemical biology research. There, he became involved in the design of probes for imaging the glycome. In 2014, he obtained a Junior Chair of Excellence from the University of Bordeaux and was soon after recruited as a group leader at the IECB in Bordeaux. He received the prestigious CNRS-ATIP-Avenir award (2017) and was recently promoted to Associate Professor in Chemical Biology at the University of Bordeaux, France (2021). His current research focuses on using organic chemistry to develop novel tools that can probe and control the influence of mammalian glycans physiologically and pathologically.

Research team

Dr. Frédéric FRISCOURT Associate Professor, (Univ. Bordeaux)
Dr. Zoeisha CHINOY CRCN (CNRS)
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Khalaf TAREK PhD Student (Univ. Bordeaux)
Luka PERRIN Master student (M2) (Univ. Bordeaux)
Mathilde WILLIGENS Master student (M1) (Univ. Bordeaux)
Aymeric LAVALADE Undergraduate student (BTS – Lycée St Louis, Bordeaux)
Léa JARLET Undergraduate student (L3) (Univ. Bordeaux)

This team is part of the unit "Institut des Sciences Moléculaires" (ISM), CNRS UMR5255/ Univ. Bordeaux

Chemical Glycobiology

Glycans are chains of monosaccharides that are covalently linked to cell surface proteins and lipids. They have been recognized as key participants in a variety of physiological processes, including angiogenesis, fertilization, cell adhesion and host-pathogen interactions. From a pathological point of view, changes in the glycome of cells are associated with developmental disorders, can mark the onset of cancer and inflammation. Despite these intriguing observations, the molecular mechanisms by which these complex carbohydrates influence cell functions are not well understood due to a lack of suitable biochemical methods. We aim at unravelling the functional roles of mammalian glycans by exploiting organic chemistry to develop novel tools that can probe and control them in living systems.

Tagging glycans.

The **bioorthogonal chemical reporter strategy**, which elegantly combines the use of metabolically labeled azido sugars and highly reactive cyclooctyne probes, through strain-promoted alkyne azide cycloadditions (SPAAC), is a versatile technology for labeling and visualizing glycans. However, the biological stability and chemical diversity of current bioorthogonal reporters is not always up to par. To address these shortcomings, we are developing novel bioorthogonal reporters while maintaining high reactivity towards cyclooctyne probes, and exploit them in order to **control glycan-protein interactions**.

Sydnones as novel bioorthogonal chemical reporters.

Over the past few years, we have exploited **sydnones** (Figure 1), highly stable mesoionic 1,3-dipoles, as novel bioorthogonal chemical reporters for the challenging detection of modified-proteins in complex cellular extracts (*J. Org. Chem.* **2018**, 83, 2058), for the fast tagging of single-stranded DNAs both in vitro and in cells (*Chem. Eur. J.* **2021**, 27, 16093), as well as for the labeling of complex glycans in living cells (*Angew. Chem. Int. Ed.* **2019**, 58, 4281).
More recently, we started to investigate the impact of bioorthogonal tags on the activity of metabolic enzymes.

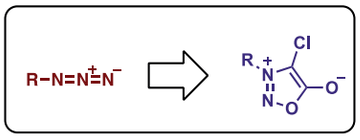


Figure 1. Bioorthogonal chloro-sydnone 1,3-dipole as opposed to the common azido-tag.

Impact of chemical reporters on the activity of glycan-processing enzymes.

Impact on Sialyltransferases

We recently showed that while sydnones could be employed for **tagging complex sialo-glycans in living mammalian cells,** their positioning on the sialic acid residue had a strong influence on sialyltransferases substrate recognition (*Angew. Chem. Int. Ed.* **2019**, 58, 4281). Unlike azido-sialic acid, which is well processed by all human sialyltransferases (hST), 9-sydnone modified sialic acid was found to be a good substrate for hST6GAL1 but not at all for hST3GAL4, consequently leading to the selective incorporation of the tag into linkage-specific a2,6-N-linked sialoproteins.

Impact on Sialidases

We next turned our attention to exploit the impacted recognition of sydnone-modified sugars in a pathological context. We focused our attention on studying the activity of **bacterial sialidases**, enzymes expressed by bacteria during pathogenesis for cleaving sialic acid sugars from mammalian cell-surface glycans in order to adhere and infect the host.

By employing a multidisciplinary approach, including chemo-enzymatic synthesis for generating the unnatural sugars, enzymatic assays for probing in vitro the sialidase activity, cell imaging for visualizing glycans in living cells, and *in silico* modelling for rationalizing the observed molecular effects, we recently identified that pathogenic bacterial sialidases were unable to cleave sialosides displaying a sydnone in vitro as well as in living cells (*ACS Chem. Biol.* **2021**, 16, 2307) (Figure 2). We are currently studying the potential use of this novel strategy for protecting mammalian cells against bacterial invasion.

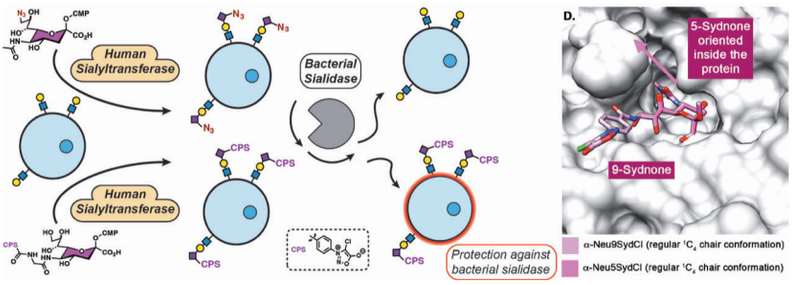
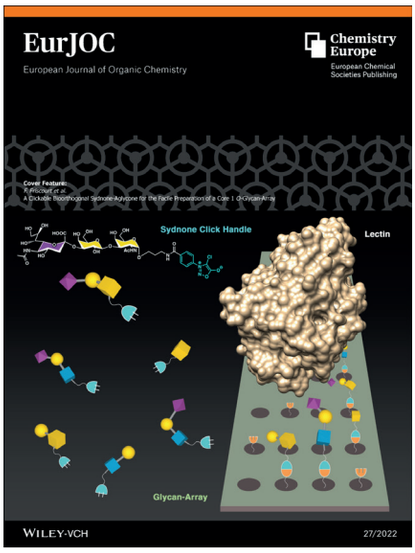


Figure 2. Glyco-edited mammalian cells with azide- or sydnonemodified sialic acids are not recognized similarly by bacterial sialidases and consequently exhibit different level of protecting effects against them. D. Sydnone-modified sialic acids modeled into the active site of C. perfringens sialidase

Exploiting sydnone tags for the facile preparation of a glycan-array.

At the molecular level, glycans have been shown to exert their functions through glycan-protein interactions. However, our understanding of the molecular cues that control these interactions is still in its infancy. Glycan-microarrays have revolutionized our knowledge of functional glycomics by allowing high-throughput study of glycan-protein recognition. However, their generation remains laborious.

Accordingly, we have recently exploited sydnone tags as an innovative technology for the facile preparation of glycan-microarray via Strain-Promoted Sydnone-Alkyne Cycloadditions (SPSAC) (*Eur. J. Org. Chem.* **2022**, 27, e202200271). We showed that sydnones, unlike azides, can be incorporated as an aglycon into core 1 O-glycans early-on in their synthesis since they are compatible with carbohydrate chemistry and enzymatic glycosylations. The sydnone-aglycon was then utilized for the preparation of an O-glycan array via SPSAC, which in turn was employed for the high-throughput screening of O-glycan-lectin interactions.



Selected publications

1. Chinoy, Z. S.; Moremen, K. W.; Friscourt, F. A Clickable Bioorthogonal Sydnone-Aglycone for the Facile Preparation of a Core 1 O -Glycan-Array. *Eur J Org Chem* **2022**, 2022 (27), e202200271. https://doi.org/10.1002/ejoc.202200271.

2. Chinoy, Z. S.; Friscourt, F. Expanding the Strain-Promoted 1,3-Dipolar Cycloaddition Arsenal for a More Selective Bioorthogonal Labeling in Living Cells. *Israel Journal of Chemistry* **2023**, 63 (1-2), e202200055. https://doi.org/10.1002/ijch.202200055.

Dr. Gilles Guichard
Research Director (DR1), CNRS

Gilles Guichard graduated in chemistry from the Ecole Nationale Supérieure de Chimie in Toulouse (1991) and Univ. Montpellier (1992) in France. He received his PhD from the Univ. Strasbourg (1996) in the field of peptide science. Following post-doctoral research with Prof. Dieter Seebach at the ETH in Zürich (1997) working on the synthesis of β-amino acids and β-peptides, he joined the Institut de Biologie Moléculaire et Cellulaire (IBMC) in Strasbourg as a CNRS Chargé de Recherche (1998). Since 2006, he has been a CNRS Research Director. In 2009, he moved to Bordeaux and joined the Institut de Chimie et Biologie des Membranes et Nanoobjets (CBMN) and the Institut Européen de Chimie et Biologie (IECB). In 2019, he received the Grammaticakis-Neuman award from the Académie des Sciences for his work on foldamers and has been a member of the advisory board of Peptide Science since 2022. His research focuses on the biomimetic chemistry of peptides.

Research team

Dr. Gilles GUICHARD DR1 (CNRS)
Dr. Christel DOLAIN MCU (Univ. Bordeaux)
Dr. Morgane PASCO CRCN (CNRS)
Dr. Guillaume COMPAIN MCU (Univ. Bordeaux)
Dr. Claire SARAGAGLIA AI (CNRS)
Dr. Bo LI Postdoctoral fellow (CNRS)
Dr. Santu BERA Postdoctoral fellow (Univ. Bordeaux)
Dr. Sandeep Mummadi Postdoctoral fellow (CNRS)
Naveen Gupta Postdoctoral fellow (CNRS)
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Jiao WANG PhD student (CSC)
Laetitia VARAJAO PhD student (Univ. Bordeaux)
Fabyan SOULARD PhD student (Univ. Bordeaux)

This team is part of the unit "Chimie et Biologie des Membranes et Nanoobjets" (CBMN), CNRS – Université de Bordeaux – Bordeaux INP (UMR 5248)

Peptidomimetic Chemistry

Our main line of research is biomolecular chemistry. We are interested in designing synthetic molecular systems with protein like structure and functions and to investigate their molecular recognition properties and biomedical applications. Although centered on chemical synthesis, our research program is based on a multidisciplinary approach involving spectroscopic studies, structural analyses, combinatorial techniques, and binding studies. NMR and X-ray crystallography have played a major role in the advancement of our research, allowing atomic description and facilitating the design of foldamer-based protein mimics and nanostructures. In recent years, our group has also gained interest in foldamer-based catalysis and in the structure-guided design of peptidomimetics and foldamers as inhibitors of protein-protein interactions with a focus on cancer-related and bacterial targets.

Our current research primarily focuses on the chemistry of amino acids, peptidomimetics and foldamers. We specifically concentrate on the development of oligourea-based α-helix mimics to disrupt protein-protein interactions (PPIs), with a particular emphasis on targets relevant to cancer biology (*Sci Adv* 2021 & *Chem Commun* 2023, **Highlight #1**). Another research direction is mimicry of protein tertiary and quaternary structure motifs. Building upon previous achievements, we reported the synthesis of mimics of helix-turn-helix (HTH) motifs by using diamine-type connectors to link foldamer helices in a head-to-head manner (*Chem Eur J*, 2023, **Highlight #2**). Finally, we have initiated a project aimed at engineering foldamer sequences for self-assembly into membranes, with a particular interest to generate new systems for water and ion transport (**Highlight #3**).

Highlight #1: Unexpected binding modes of inhibitors to the histone chaperone ASF1 revealed by a foldamer scanning approach (*Chem Commun* 2023)

One objective is to design high-affinity binders for protein surfaces by combining foldamer-based strategies and structure-guided approaches. In this particular study conducted in collaboration with Francoise Ochsenbein from I2BC, Univ. Paris-Saclay, we employed a 3-urea scanning approach on a previously reported short α-helical sequence known to interact with the histone chaperone ASF1 (Anti-Silencing Function 1) and investigated how the helical conformation of the resulting α/u chimeras adjusts to the protein surface to optimize binding. ASF1 is a key regulator of chromatin dynamics and a promising PPI target for cancer. Through a comprehensive analysis of various foldamer substitutions along the peptide chain, we have elucidated different binding modes exhibited by the peptide-urea chimeras when interacting with ASF1 (see Fig. 1). The structures obtained here will likely inspire the design of new foldamer-based ASF1 inhibitors with increased resistance to proteolysis.

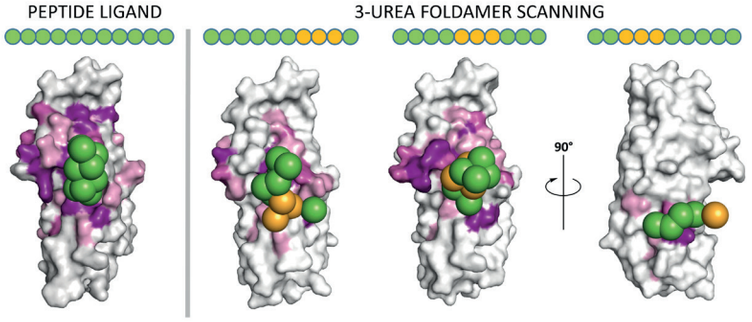

Fig. 1.

Highlight #2: Synthesis and Crystallographic Characterization of Helical Hairpin Oligourea Foldamers (*Chem Eur J*, 2023)

Synthetic, sequence-specific, helically folded molecules have attracted considerable interest in part because of their potential applications in various areas (e.g. as α-helix or DNA mimics, as receptors for molecular guests, or as catalysts). Functional foldamer sequences generally correspond to isolated helices. To expand the recognition potential of foldamers and improve their functions, we designed supersecondary structures inspired by the protein HTH motif by connecting two helical foldamers together using appropriate linkers. Crystallization efforts including racemic crystallization to improve crystal growth and phasing led to the structural characterization of several such helical hairpins and to the precise description of the relative arrangement of individual helices within the HTH motif (see Fig. 2).

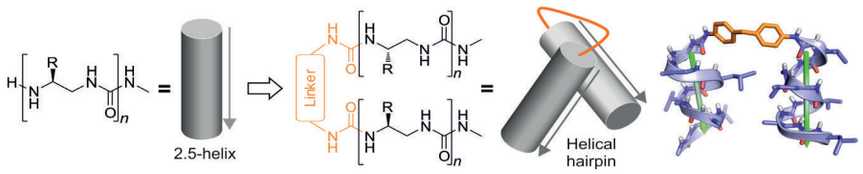

Fig. 2.

Highlight #3: Application of urea-based foldamers for water transport (*Chem*, 2023)

In this work conducted in collaboration with the National University of Singapore (NUS) and Mihail Barboiu at the Institut Européen des Membranes (IEM) in Montpellier, we developed oligourea foldamers as artificial water channels (AWCs). We discovered that amphipathic oligourea sequences known to self-assemble into nanotubes with hydrophilic interior in aqueous environment could insert and self-assemble into lipid membranes. Solid-state NMR (coll. Antoine Loquet), cryo-EM and molecular dynamics analyses confirmed insertion into lipid vesicles. Two foldamer sequences demonstrated water permeability and almost total salt rejection across lipid membranes (Fig. 3). New developments of this project in the context of water transport received funding from ANR in 2023.

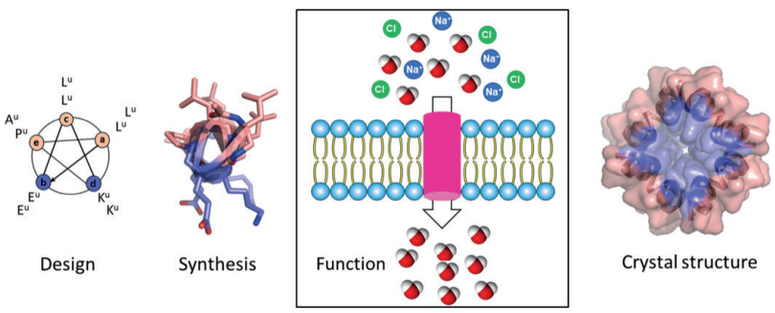

Fig. 3.

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1. Zaky, M. S.; Guichard, G.; Taton, D. Structural Effect of Organic Catalytic Pairs Based on Chiral Amino(Thio)Ureas and Phosphazene Bases for the Isoselective Ring-Opening Polymerization of Racemic Lactide. *Macromolecules* **2023**, 56 (10), 3607-3616. https://doi.org/10.1021/acs.macromol.3c00462.

2. Yoo, S. H.; Buratto, J.; Roy, A.; Pasco, M.; Pulka-Ziach, K.; Collie, G. W.; Guichard, G. Oligourea Helix Bundle Binds Detergents with Diverse Polar Head Groups. *Org. Biomol. Chem.* **2024**, 22 (4), 731-734. https://doi.org/10.1039/D3OB01873C.

3. Perrin, M. E.; Li, B.; Mbianda, J.; Bakail, M.; André, C.; Moal, G.; Legrand, P.; Ropars, V.; Douat, C.; Ochsenbein, F.; Guichard, G. Unexpected Binding Modes of Inhibitors to the Histone Chaperone ASF1 Revealed by a Foldamer Scanning Approach. *Chem. Commun.* **2023**, 59 (56), 8696-8699. https://doi.org/10.1039/D3CC01891A.

4. Dutta, C.; Krishnamurthy, P.; Su, D.; Yoo, S. H.; Collie, G. W.; Pasco, M.; Marzinek, J. K.; Bond, P. J.; Verma, C.; Grélard, A.; Loquet, A.; Li, J.; Luo, M.; Barboiu, M.; Guichard, G.; Kini, R. M.; Kumar, P. P. Nature-Inspired Synthetic Oligourea Foldamer Channels Allow Water Transport with High Salt Rejection. *Chem* **2023**, 9 (8), 2237-2254. https://doi.org/10.1016/j.chempr.2023.04.007.

5. Pendem, N.; Nelli, Y.; Cussol, L.; Didierjean, C.; Kauffmann, B.; Dolain, C.; Guichard, G. Synthesis and Crystallographic Characterization of Helical Hairpin Oligourea Foldamers. *Chemistry A European J* **2023**, 29 (39), e202300087. https://doi.org/10.1002/chem.202300087.

6. Naulet, G.; Delamare, A.; Guichard, G.; Compain, G. In Situ Generated DBU□HF Acts as a Fluorinating Agent in a Hexafluoroisobutylation Tandem Reaction: An Effective Route to 5,5,5,5',5',5'-Hexafluoroleucine. *Eur J Org Chem* **2023**, 26 (10), e202201148. https://doi.org/10.1002/ejoc.202201148.

7. Compain, G.; Monsarrat, C.; Blagojevic, J.; Brillet, K.; Dumas, P.; Hammann, P.; Kuhn, L.; Martiel, I.; Engilberge, S.; Oliéric, V.; Wolff, P.; Burnouf, D. Y.; Wagner, J.; Guichard, G. Peptide-Based Covalent Inhibitors Bearing Mild Electrophiles to Target a Conserved His Residue of the Bacterial Sliding Clamp. *JACS Au* **2024**, 4 (2), 432-440. https://doi.org/10.1021/jacsau.3c00572.

Dr. Emmanuelle Thinon
Research scientist (CRCN), CNRS

Emmanuelle Thinon completed her PhD in Chemical Biology at Imperial College London in 2014, under the supervision of Prof. Ed Tate. For her postdoc, thanks to a Marie Skłodowska-Curie Global fellowship, she worked at the Rockefeller University (USA) with Prof. Howard Hang and The Francis Crick Institute (UK) with Dr. Sharon Tooze. In 2019, she was recruited as a research associate (chargé de recherche, CRCN) within the French National Centre for Scientific Research (CNRS), to join the CBMN (Institute of Chemistry & Biology of Membranes & Nanoobjects) in Bordeaux. In November 2019, she joined IECB as a group leader.

Research team

Dr. Emmanuelle THINON Research scientist CRCN, (CNRS)
Chloé FREYERMUTH PhD student (CNRS)
Santiago LEIVA Postdoctoral scientist (UB)
Yasmine YASSAD BTS (CNRS)

This team is part of the unit "Chimie des membranes et des nanoobjets" (CBMN), CNRS UMR5248/INP/ Univ. Bordeaux

Chemical Biology of membrane proteins

The study of small transmembrane proteins can often be challenging. In particular, it can be difficult to tag these proteins with a fluorophore in cellulo without perturbing the proteins localization and function, or to extract and purify them from membranes, without disturbing their structure or interactions with other proteins, for structure determination or for mass spectrometry interaction proteomics. Additionally, these proteins can be post-translationally modified by lipids, but proteomics methods to precisely identify and quantify some of these modifications are noticeably lacking. The "Chemical Biology of membrane proteins group" endeavours to develop and/or apply a combination of chemical and biological approaches to facilitate the study of these small membrane proteins.

The first aim of our work is to use a combination of chemical approaches (site-specific chemical labelling, crosslinking interaction proteomics, chemical proteomics, genetic code expansion, solid state NMR) to characterize small transmembrane proteins involved in viral infections. Some of these proteins are post-translationally modified by S-palmitoylation, which corresponds to the reversible addition of a C16 fatty acid to Cys, often adjacent to the protein transmembrane domain. S-palmitoylation is essential for protein localization and regulation, but its precise function, notably during viral infection, remains unknown for some proteins.
Using a combination of methods, we are currently characterising a small protein involved in viral infections by studying the role and regulation of its S-palmitoylation, its structure in interaction with membranes and by identifying its interaction partners. These studies will help us to understand if this protein could be new antiviral drug target.

The second aim of our work is to develop new methods to tag proteins at the endogenous level (no overexpression). The addition of a tag to a protein, such as GFP (Green Fluorescence Protein) for immunofluorescence studies, can sometimes perturb the protein biophysical properties, localization and/or function. The tag is often added by overexpressing the protein of interest, which can sometimes lead to toxicity, hence the development of new methods to tag proteins at the endogenous level is essential. The tag could be a small fluorophore (BODIPY etc) for live cell imaging studies or with a crosslinking moiety to enable the identification of the interactome of the protein of interest by mass spectrometry-based proteomics. These new methods will be applied to facilitate the study of small membrane proteins.

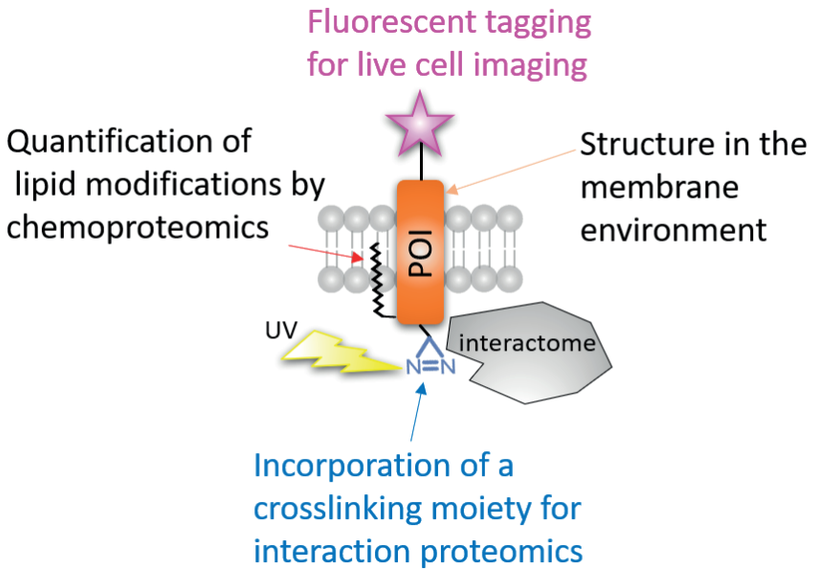


Figure 1. Characterization of small membrane proteins using a combination of chemical and biological methods.

Selected publications

1. Thinon, E.; Hang, H. C. Chemical Proteomic Analysis of S-Fatty Acylated Proteins and Their Modification Sites. *Methods Mol Biol* **2019**, 2009, 45-57. https://doi.org/10.1007/978-1-4939-9532-5_4.

2. Tapodi, A.; Clemens, D. M.; Uwineza, A.; Jarrin, M.; Goldberg, M. W.; Thinon, E.; Heal, W. P.; Tate, E. W.; Nemeth-Cahalan, K.; Vorontsova, I.; Hall, J. E.; Quinlan, R. A. BFSP1 C-Terminal Domains Released by Post-Translational Processing Events Can Alter Significantly the Calcium Regulation of AQP0 Water Permeability. *Exp Eye Res* **2019**, 185, 107585. https://doi.org/10.1016/j.exer.2019.02.001.

3. Spence, J. S.; He, R.; Hoffmann, H.-H.; Das, T.; Thinon, E.; Rice, C. M.; Peng, T.; Chandran, K.; Hang, H. C. IFITM3 Directly Engages and Shuttles Incoming Virus Particles to Lysosomes. *Nat Chem Biol* **2019**, 15 (3), 259-268. https://doi.org/10.1038/s41589-018-0213-2.

Dr. Mikayel Aznauryan,
Research scientist (CRCN), Inserm

Mikayel Aznauryan obtained his PhD from Yerevan State University in Armenia (2008–2011). Then, he moved to Switzerland (2012–2014) as a postdoctoral researcher at the Department of Biochemistry of the University of Zurich (Group of Prof. B. Schuler), to work on protein folding and dynamics with single-molecule FRET spectroscopy. Afterwards, Mikayel Aznauryan did a second postdoc (2014–2018) at the Department of Chemistry and the Interdisciplinary Nanoscience Center of Aarhus University in Denmark, where he used single-molecule methods to study the dynamics of nucleic acid structures.
Mikayel Aznauryan has joined IECB at the end of 2018 and has been awarded FRM Jeune equipe and IdEx Chaire Junior grants to start his group. Shortly after, he obtained INSERM researcher position (CRCN) within ARNA laboratory.

Research team

Dr. Mikayel AZNAURYAN Research associate CRCN (Inserm)
Dr. Carmelo DI PRIMO Research associate CRHC (Inserm)
Mme. Sabrina ROUSSEAU Engineer, IE (Inserm)
Dr. Bikash Chandra SWAIN Postdoc (Inserm)
Mme Pascale SARKIS PhD student (Univ. Bordeaux)
Mme Paramita CHAUDHURI M1 student (UBdx/BBM)
Lelaud ESNAULT M1 student (UBdx/BBM)
Thania HAMMOUM M1 student (UBdx/BBM)
Valentin RINALDO M1 student (UBdx/BBM)

This team is part of the unit: "Acides Nucléiques: Régulations Naturelles et Artificielles" (ARNA), Inserm U1212/CNRS UMR5320/Univ. Bordeaux

Single-molecule spectroscopy of disordered protein dynamics and interactions

Intrinsically disordered proteins (IDPs) or proteins containing intrinsically disordered regions (IDRs) are ubiquitous in eukaryotic proteome. They typically lack persistent structure in their native form and do not necessarily require defined structure for molecular recognition and specific function. They are frequently involved in liquid-liquid phase separation (LLPS) driven assembly of various cellular condensates. We use a large variety of biochemical and biophysical tools, among which particularly single-molecule FRET spectroscopy, in order to understand the mechanisms of IDP interactions and to reveal the basis of specificity for molecular recognition and particular function of IDPs, as well as uncover how certain IDP interactions define and modulate the LLPS and formation of cellular condensates.

The key expertise of the group is centered on *in vitro* and *in-cell* single-molecule FRET spectroscopy, which is our main tool to look at IDPs and their interaction. For this purpose, we also use a variety of other state-of-the-art biochemical and biophysical techniques, such as biomolecular nuclear magnetic resonance (NMR) spectroscopy, surface plasmon resonance (SPR), isothermal titration calorimetry (ITC), live-cell imaging and others, to obtain a comprehensive picture of mechanisms of IDP interactions and to reveal the basis of specificity for molecular recognition and particular function of IDPs.

Currently, in the group we are working on the following research projects:

- investigation of eukaryotic translation initiation and especially the role of disordered translation initiation factors in this process;
- understanding the behavior and molecular mechanisms of function of disordered RNA-binding proteins in LLPS and cellular condensates.

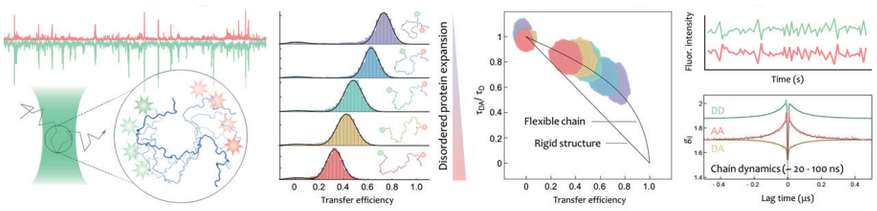


Figure 1. From detection of single biomolecules to characterization of their conformational distributions, fluctuations and dynamics

Disordered initiation factors – fine-tuners of the early steps of translation initiation

Translation initiation is directly regulated by the cap-binding complex (eIF4F), which recognizes and associates with the 5' terminal cap of mRNA and prepares it for the recruitment of the ribosome. eIF4F consists of three different proteins, so called translation initiation factors eIF4E, eIF4G and eIF4A. eIF4E is responsible for direct recognition of mRNA methyl-guanosine cap. eIF4A is an ATP-driven RNA helicase that unwinds secondary structures surrounding the 5'-end of mRNA. eIF4G serves as a scaffold for assembly of eIF4F, directly interacting with both eIF4E and eIF4A (Jackson, Hellen et al. 2010). In addition, eIF4F complex associates with eIF4B and eIF4H, which possess several crucial regulatory roles in translation initiation (Parsyan 2014). In a concerted action, these factors prepare the mRNA and facilitate the recruitment of the 43S pre-initiation complex to it, followed by scanning the mRNA towards the start-codon recognition. Despite the large number of binding partners (initiation factors, mRNA,

rRNA) and important function, eIF4B (and eIF4H) are predicted to be predominantly disordered (Uversky 2014) and can be termed as disordered translation initiation factors (DisIFs). We focus on investigation of these proteins, and aim at understanding their behavior, interactions and mechanistic basis for function in translation initiation.

Disordered initiation factors and their relation to LLPS and stress granules

It is currently emerging that many aspects of intracellular organization are performed through formation of membrane-less condensates (Banani, Lee et al. 2017). The main driving force for condensate assembly is believed to be the intracellular LLPS (Shin and Brangwynne 2017). Currently many independent observations point that IDPs or proteins with long IDRs can contribute to the cellular LLPS (Dignon, Best et al. 2020).

Cellular condensates form under action of various stimuli. For example, stress granules (SGs) form during cellular stress and are responsible for subcellular storage of stress-inhibited translation machinery and stabilization of naked mRNAs (Protter and Parker 2016).

Recent evidences indicate an enrichment of translation initiation factors, among which DisIFs (eIF4B, eIF4H, eIF4G, etc.), within the proteome of SGs (You, Huang et al. 2020), nevertheless their exact roles therein are currently unknown. We primarily focus on understanding of the behavior and function of DisIFs in LLPS and assembly of SGs. Our recent work shows that eIF4B is able to undergo LLPS in vitro at close to physiological conditions, i.e. at protein concentration comparable to endogenous levels and physiological ionic strength. Interestingly, prior to phase separation, eIF4B forms a range of high-molecular "fuzzy" oligomers. Our single-molecule and bulk phase separation assays allow to map the eIF4B self-association landscape both at the nanoscale and the mesoscale.

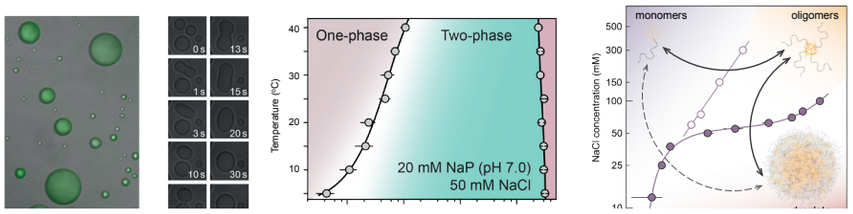


Figure 2. The self-association behavior of eIF4B at nanoscale and mesoscale

Selected publications

1. Mondal, S.; Rousseau, S.; Talenton, V.; Thiam, C. A. B.; Aznauryan, M.; Mackereth, C. D. Backbone Resonance Assignments of the C-Terminal Region of Human Translation Initiation Factor EIF4B. *Biomol NMR Assign* **2023**, 17 (2), 199-203. https://doi.org/10.1007/s12104-023-10141-7.

2. Dobrovodský, D.; Di Primo, C. Do Conformational Changes Contribute to the Surface Plasmon Resonance Signal? *Biosens Bioelectron* **2023**, 232, 115296. https://doi.org/10.1016/j.bios.2023.115296.

3. Aznauryan, M.; Birkedal, V. Dynamics of G-Quadruplex Formation under Molecular Crowding. *J Phys Chem Lett* **2023**, 14 (46), 10354-10360. https://doi.org/10.1021/acs.jpclett.3c02453.

Dr. Sébastien Campagne

Research scientist (CRCN), Inserm

Sébastien Campagne undertook his PhD on the structural biology of a novel family of human transcription factors, the THAP protein family at the Institute of Pharmacology and Structural Biology and the University of Toulouse under the supervision of Prof. Alain Milon and Dr. Virginie Gervais. He then joined ETH Zurich in the group of Prof. Julia Vorholt to identify the molecular mechanisms triggering transcription rewinding in α-proteobacteria. In 2014, he joined the group of Prof. Frédéric Allain at ETH Zurich to start working on the regulation of mRNA splicing where he did important contributions in the field of RNA splicing correction. He joined IECB in October 2021 as Research officer in the group of Cameron Mackereth and was appointed group leader in February 2023.

Research team

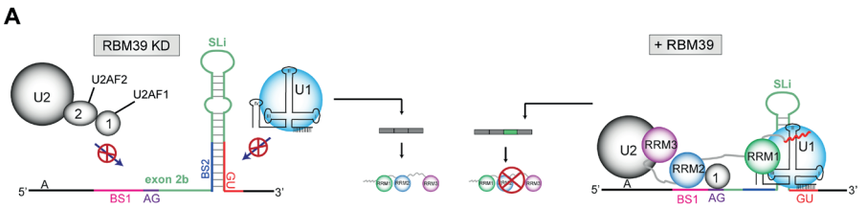
Dr. Sébastien CAMPAGNE Research scientist CRCN (INSERM)
Dr. Florian MALARD Post-doctoral fellow (Inserm)
Léa BOUTON PhD student (INSERM)
Agathe ECOUTIN Technical assistant (industrial collaboration) (INSERM)

This team is part of the unit: "Acides Nucléiques: Régulations Naturelles et Artificielles" (ARNA), Inserm U1212/CNRS UMR5320/Univ. Bordeaux

Structure, Mechanism and RNA Therapeutics

RNA splicing is key step of gene expression that shapes the transcriptional output by regulating mRNA translation, localization and decay. This process is tightly regulated and from a given precursor messenger RNA, different mRNA associated with different proteins can be generated via alternative splicing. Although the splicing cycle has been deciphered at atomic level, splicing regulation is still poorly understood. Furthermore, many human diseases are linked to non-physiological splicing patterns. In this context, the SMaRT lab aims to decipher the molecular mechanisms controlling RNA splicing regulation and design synthetic splicing switches to correct rationally RNA splicing with therapeutic purposes in the context of inherited diseases and cancers.

Fundamental insights into RNA splicing regulation and anti-cancer applications.
Regulation of splicing mainly occurs during the initial stages of spliceosome assembly, notably when U1 snRNP and U2 snRNP/U2AFs define the splice sites. In this context, we studied the role of RNA Binding Motif 39 (RBM39) in splicing regulation since it was previously described that RBM39 is essential for the survival of several types of cancer cells. In a collaborative work, we found that the three globular domains of RBM39 have specific functions. The RNA Recognition Motif 1 (RRM1) binds to RNA stem loop structures with poor selectivity, the RRM2 domain of RBM39 binds specifically to a N(G/U)NUUUG motif embedded into single stranded RNA regions while the third domain of RBM39 interacts with U2 snRNP. Furthermore, by combining a transcriptomic analysis with cell-based assays, we identify that this cancer-associated splicing factor autoregulates at the splicing level through a negative feedback loop (Fig. 1A, Campagne S., *et al.*, Nat. Commun. 2023). According to the essential role play by RBM39 in the survival of cancer cells, we aim now to develop RNA therapeutics to manipulate the autoregulation pathway of RBM39 in order to induce the depletion of RBM39 in cancer cells and trigger their death. In this context, Léa Bouton (MSc) is performing her PhD thesis, embedded into the Cancer Biology Program of the University of Bordeaux. Interesting candidates have already been identified (Fig. 1B).



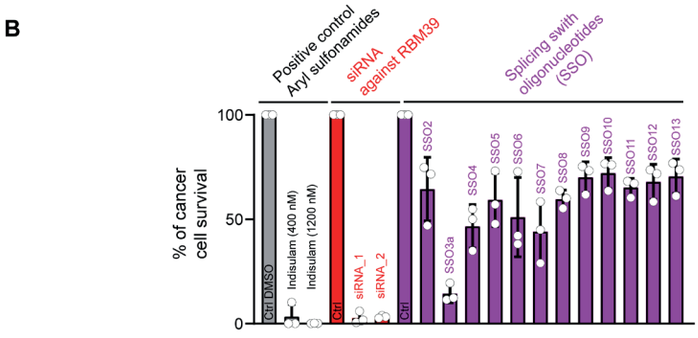


*Figure 1 – **RBM39 autoregulation and development of anti-cancer RNA therapeutics.** A) Schematic representation of the negative feedback loop mechanism controlling RBM39 autoregulation. B) HCT116 cell survival upon treatment with aryl sulfonamides, specific siRNA against RBM39 and a set of oligonucleotide splicing switches.*

***Exploring the diversity of small molecule splicing modifiers.** A major revolution in the field of specific splicing correction was the discovery of the first gene specific small molecule splicing modifier that switches the splicing of the* SMN2 *gene. The small molecule (SMN-C5) acts as a molecular glue between the first particle of the spliceosome (U1 snRNP) and the A-$_1$ bulged 5'-splice site of* SMN2 *exon 7. It binds the RNA duplex formed upon 5'-splice site recognition and stabilizes the unpaired adenine in position -1 to allosterically activate the inclusion of exon 7 in the* SMN2 *transcript (Fig. 2A,B). We coined this mechanism "5'-splice site bulge repair" (Campagne S.* et al., *Nat. Chem. Biol. 2019). However, SMN-C5 did not passed the clinical evaluation and raised a safety issue. Optimization of SMN-C5 triggers the discovery of other small molecules associated with similar activities and the molecule called risdiplam passed the clinical evaluation to become the first orally available treatment against Spinal Muscular Atrophy. To understand the chemical diversity of A-$_1$ splicing modifiers, we investigated whether risdiplam and three other A-1 splicing modifiers also act through the bulge repair mechanism. By solving the solution structures of the four small molecules bound to the RNA helix (U1:A-1 bulged 5'-splice site), we could show that the four small molecules bind the same cavity than SMN-C5 and act through the bulge repair mechanism (Fig. 2C-E; Malard F.* et al., *Nucleic Acids Res. 2024). These structures pinpointed the common pharmacophores required to correct splicing on an A-$_1$ bulged 5'-splice site and paves the way towards the rational development of novel splicing modifiers associated with different gene selectivity (project funded by the FRM, 2024-2027).*

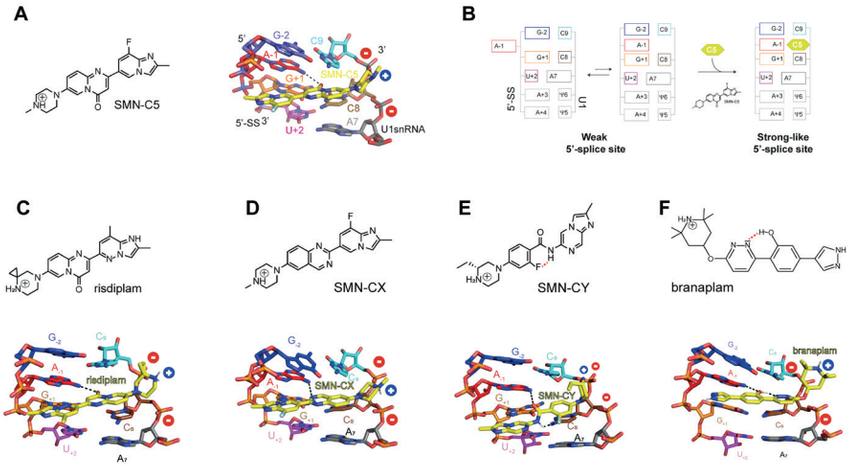


*Figure 2 – **Structures of A-1 splicing modifiers bound to the RNA epitope and concept of bulge repair.** A) structure of SMN-C5 bound to its RNA epitope. B) Schematic representation of the bulge repair mechanism. C-F) Structures of risdiplam C), SMN-CX D), SMN-CY E) and branaplam F) bound to the RNA epitope.*

Selected publications

1. Pokorná, P.; Krepl, M.; Campagne, S.; Šponer, J. Conformational Heterogeneity of RNA Stem-Loop Hairpins Bound to FUS-RNA Recognition Motif with Disordered RGG Tail Revealed by Unbiased Molecular Dynamics Simulations. *J Phys Chem B* **2022**, 126 (45), 9207-9221. https://doi.org/10.1021/acs.jpcb.2c06168.

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4. Campagne, S.; de Vries, T.; Allain, F. H.-T. Probing the Interactions of Splicing Regulatory Small Molecules and Proteins with U1 SnRNP Using NMR Spectroscopy. *Methods Mol Biol* **2022**, 2537, 247-262. https://doi.org/10.1007/978-1-0716-2521-7_15.

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European Research Council

Molecular mechanisms of amyloid diseases

Dr. Yann Fichou

Research Scientist (CRCN), CNRS

Yann Fichou got an engineering degree in physics and material sciences from the Institut National des Sciences Appliquées (INSA) in Rennes in 2011. He received in 2015 his PhD from the Université Grenoble Alpes where he studied protein and hydration dynamics by neutron scattering and MD simulations, under the supervision of Martin Weik at the Institut de Biologie Structurale (IBS). He carried out a first postdoc in the lab of Martina Havenith at Ruhr-Universität Bochum (RUB, Germany) before going to the University of California Santa Barbara (UCSB) in the group of Songi Han. Since 2020, Yann Fichou is a CNRS Chargé de Recherche at the institute de Chimie et Biologie des Membranes et Nano-objets (CBMN) in Bordeaux and he became group leader at the IECB after obtaining a ERC starting grant in 2021.

Research team

Dr. Yann FICHOU CRCN (CNRS)
Dr. Mélanie ROSSOTTI Engineer (CNRS)
Mr. Julien Broc-Casalengo PhD student (CNRS)
Mrs Clara PIERSSON PhD student (CNRS)

This team is part of the unit: "Chimie et biologie des membranes et nanoobjets" (CBMN), UMR5248 CNRS/UB

The aggregation of the protein tau is involved in several neurodegenerative diseases, termed tauopathies, such as Alzheimer's disease. In different tauopathies, tau aggregates adopt different structures, emphasizing a causal link between the nature of tau aggregates at a molecular level and the associated pathology. Our research aims at understanding the molecular rules governing aggregate structural differentiation and propagation. Using biophysical and biochemical techniques, we study the mechanisms of tau aggregation across different pathways. We investigate different modulators of tau aggregation such as disease-associated mutations and interaction with various biomolecular cofactors (GAG, nucleic acids and lipids...). We also study liquid-liquid phase separation and its relationship to protein aggregation. Although the group uses a multi-technique approach, we have a particular interest in applying advanced electron paramagnetic resonance (EPR) spectroscopy to address different biological and chemical questions.

We have investigated mechanisms through which the disease-associated single-point mutations promote amyloid formation. Tau is an intrinsically disordered protein (IDP) tau is involved in several diseases, called tauopathies. Some tauopathies can be inherited due to mutations in the gene encoding tau, which might favor the formation of tau amyloid fibrils. We combined biochemical and biophysical characterization, notably, small-angle X-ray scattering (SAXS), to study six different FTDP-17 derived mutations. We found that the mutations promote aggregation to different degrees and can modulate tau conformational ensembles, intermolecular interactions, and liquid-liquid phase separation propensity. In particular, we found a good correlation between the aggregation lag time of the mutants and their radii of gyration. We show that mutations disfavor intramolecular protein interactions, which in turn favor extended conformations and promote amyloid aggregation. This work proposes a new connection between the structural features of tau monomers and their propensity to aggregate, providing a novel assay to evaluate the aggregation propensity of IDPs. This study was published in JACS.

Julien Broc-Casalengo joined the group as a PhD student to characterize the composition and properties of tau aggregates extracted from different tauopathies. He will investigate their chemical properties with spectroscopic methods (IR, MS, raman), their capacity to trigger pathology and their structural features. Welcome Julien!

We have obtained an ANR and UB funding, in collaboration with the CRPP in Bordeaux, the IBS in Grenoble, UC Santa Barbara and Boston university, to study liqui-liquid phase separation of intrinsically disordered protein. LLPS is a physical process in which proteins split into a high-concentration phase, or dense phase, and a low-concentration phase (diffuse phase). The phenomenon has recently gained significant interest as it has been shown to be involved in both metabolic and pathological pathways, in particular in formation of amyloid. Here we will answer the following questions: what are the driving forces of tau and a-synuclein LLPS? What are the physico-chemical properties of tau and a-synuclein in LLPS droplets? How these properties are linked to the LLPS-to-amyloid transition?

Selected publications

1. Pounot, K.; Piersson, C.; Goring, A. K.; Rosu, F.; Gabelica, V.; Weik, M.; Han, S.; Fichou, Y. Mutations in Tau Protein Promote Aggregation by Favoring Extended Conformations. *JACS Au* **2024**, 4 (1), 92–100. https://doi.org/10.1021/jacsau.3c00550.

Dr. Valérie Gabelica
Research Director (DR1), INSERM

Valérie Gabelica studied Chemistry and obtained her PhD in Sciences in 2002 at the University of Liège. After a postdoc in Frankfurt as Humboldt fellow, she rejoined the Mass Spectrometry Laboratory in Liège where she obtained a permanent position as FNRS research associate in October 2005. She joined the IECB in 2013 with the support of an Atip-Avenir grant, became an Inserm research director (DR2) in December 2013 and was promoted DR1 in 2023. She served as the director of the IECB from 2021 to 2023. She obtained an ERC Consolidator grant in 2014, was awarded several research prizes (French Academy of Sciences in 2018, Liliane Bettencourt Prize for Life Sciences in 2021, Heinrich Emanuel Merck Award for Analytical Sciences as well as INSERM research prize in 2022). In January 2024, she was appointed as Full Professor in Analytical Chemistry at the University of Geneva, in the School of Pharmaceutical Sciences.

Research team

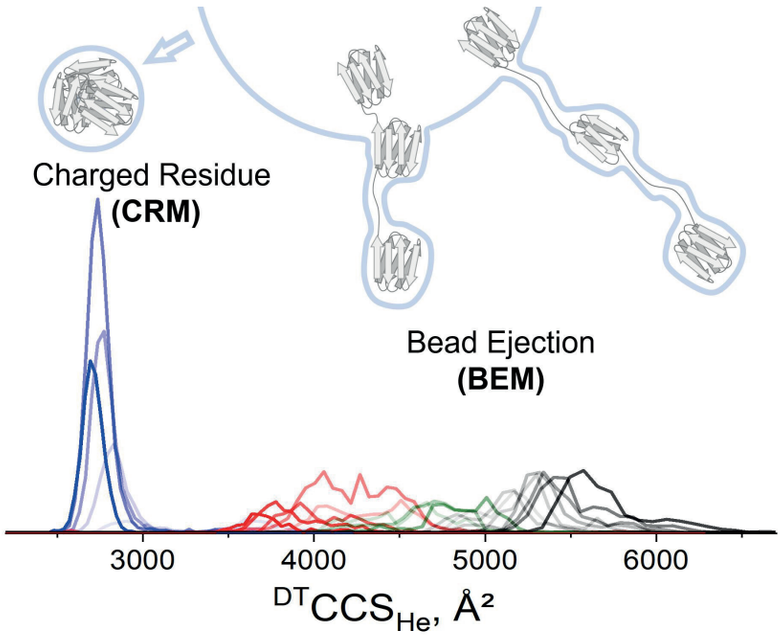
Dr. Valérie GABELICA Research Director DR1 (INSERM)
Dr. Eric LARGY Maître de Conférences (Univ. Bordeaux)
Dr. Dominika STRZELECKA Post-doc (INSERM)
Dr. Debasmita GHOSH Post-doc (INSERM)
Alexander KÖNIG PhD student (Univ. Bordeaux)
Matthieu RANZ PhD student (INSERM)

This team is part of the unit "Acides Nucléiques: Régulations Naturelles et Artificielles" (ARNA), Inserm U1212/CNRS UMR5320/Univ. Bordeaux

Mass Spectrometry of Nucleic Acids & Supramolecular Complexes

Our team focuses on the measurement sciences applied to non-covalent interactions. Nucleic acids (and more recently, foldamers and protein therapeutics) are our model systems and systems on which we learn new things. Our aim is to decipher the relationships between structures and energetics—Angstroms and Calories—in non-covalent complexes. Non-covalent interactions govern the structure and function of myriads of systems, from supramolecular assemblies to biological complexes. High-resolution structural methods help to understand what interactions are at stake in specific states of well-defined assemblies. Yet function is linked to energetics: How prevalent is a structural form? How does it switch to other states? How fast? To bridge the gap between structure and energetics, our team develops new mass spectrometry approaches to separate, quantify, and structurally characterize the different ensembles of structures (the different states) simultaneously present in solution.

In mass spectrometry, our team contributes to establish more solid ground to interpret ion mobility spectrometry experiments in terms of structure. Unexpected results have led us to challenge the paradigm claiming that non-covalent interactions are always well maintained in the gas phase. It turns out that this assertion was based on a bias favoring the publication of positive results. We highlighted the importance of structural changes related to the electrospray ionization process. Recently, based on a study of therapeutic proteins in collaboration with Merck Biodevelopment SAS, we formulated a new electrospray ion production mechanism called the bead ejection mechanism (BEM). This mechanism (*Khristenko et al., JACS 2023*) accounts for the formation of charge states and conformations larger than those produced by the charged residue mechanism (CRM), but lower than those produced by a pure chain ejection mechanism (CEM).



A new electrospray mechanism: The bead ejection mechanism of therapeutic proteins (folded domains tethered by intrinsically disordered linkers) accounts for intermediate charge states and gas-phase conformations, as indicated by ion mobility mass spectrometry.

In the field of nucleic acid biophysics, our team demonstrated the feasibility of probing nucleic acid structures by in-solution hydrogen/deuterium exchange mass spectrometry (*Largy & Gabelica, Anal. Chem. 2020*). The highlight of 2023 was the publication of a detailed framework to interpret HDX-MS data for G-quadruplex folding biophysics (*Largy et al., JACS 2023*).

Selected publications

1. Largy, E.; Ranz, M.; Gabelica, V. A General Framework to Interpret Hydrogen-Deuterium Exchange Native Mass Spectrometry of G-Quadruplex DNA. *J Am Chem Soc* **2023**, 145 (49), 26843-26857. https://doi.org/10.1021/jacs.3c09365.

2. Largy, E.; König, A.; Ghosh, A.; Ghosh, D.; Benabou, S.; Rosu, F.; Gabelica, V. Mass Spectrometry of Nucleic Acid Noncovalent Complexes. *Chem Rev* **2022**, 122 (8), 7720-7839. https://doi.org/10.1021/acs.chemrev.1c00386.

3. Khristenko, N.; Rosu, F.; Largy, E.; Haustant, J.; Mesmin, C.; Gabelica, V. Native Electrospray Ionization of Multi-Domain Proteins via a Bead Ejection Mechanism. *J Am Chem Soc* **2023**, 145 (1), 498-506. https://doi.org/10.1021/jacs.2c10762.

4. Juribašić Kulcsár, M.; Gabelica, V.; Plavec, J. Solution-State Structure of a Long-Loop G-Quadruplex Formed Within Promoters of Plasmodium Falciparum B Var Genes. *Chemistry* **2024**, 30 (36), e202401190. https://doi.org/10.1002/chem.202401190.

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6. Ghosh, D.; Rosu, F.; Gabelica, V. Negative Electrospray Supercharging Mechanisms of Nucleic Acid Structures. *Anal Chem* **2022**, 94 (44), 15386-15394. https://doi.org/10.1021/acs.analchem.2c03187.

7. Di Carluccio, C.; Cerofolini, L.; Moreira, M.; Rosu, F.; Padilla-Cortés, L.; Gheorghita, G. R.; Xu, Z.; Santra, A.; Yu, H.; Yokoyama, S.; Gray, T. E.; St Laurent, C. D.; Manabe, Y.; Chen, X.; Fukase, K.; Macauley, M. S.; Molinaro, A.; Li, T.; Bensing, B. A.; Marchetti, R.; Gabelica, V.; Fragai, M.; Silipo, A. Molecular Insights into O-Linked Sialoglycans Recognition by the Siglec-Like SLBR-N (SLBRUB10712) of Streptococcus Gordonii. *ACS Cent Sci* **2024**, 10 (2), 447-459. https://doi.org/10.1021/acscentsci.3c01598.

Dr. Antoine Loquet
Research Director (DR2), CNRS

Antoine Loquet graduated from the University of Lyon / Ecole Normale Supérieure de Lyon. He did his PhD (2006-2009) under the guidance of Anja Böckmann (IBCP Lyon), working on the development of Solid-State NMR to solve protein structures. In 2008 he joined the group of Beat Meier (ETH Zürich) to study prion fibrils by Solid-State NMR. He then focused his research on molecular assemblies by Solid-State NMR as an EMBO postdoctoral fellow with Adam Lange at the Max Planck Institute for Biophysical Chemistry (Göttingen, Germany). There, he developed Solid-State NMR methods to determine atomic structures of large biological supramolecular assemblies. He obtained a CNRS position in 2013 at the CBMN (Institute of Chemistry & Biology of Membranes & Nanoobjects) in Bordeaux. In 2014, he was recruited as a group leader at the IECB and since 2016, he is leading the group "NMR of Membranes and Protein Assemblies" at CBMN. He obtained an ERC Starting Grant in 2015. His current research concentrates on the structural investigation of biological assemblies using Solid-State NMR. He is CNRS Research Director since 2020 and current Director of the UAR3033/ US001 IECB.

Research team

Antoine LOQUET Research Director, DR (CNRS)
Axelle GRÉLARD Research Engineer, IR CNRS
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Dr. Corinne SANCHEZ McF U. Bordeaux (Univ. Bordeaux)
Dr. Birgit HABENSTEIN CR CNRS (CNRS)
Dr. Erick DUFOURC Emeritus Research Director, (CNRS)
Bilal MUHAMMED PhD (Univ. Bordeaux)
Loic DELCOURTE PhD (CNRS)
Laura DOMINGUEZ PhD (Malaga University)
Frank NGUETSOP PhD (CNRS)
Zeren XU PhD (CNRS)
Seamoon DEB PhD (UB)

This team is part of the unit "CBMN UMR5248 CNRS/Univ. Bordeaux /Bordeaux INP

NMR of Molecular Assemblies

The group aims at investigating atomic structures of biological assemblies, ranging from protein complexes (fibrils, amyloids, oligomers), biopolymers, lipid membranes and cell wall structures. We develop and apply solid-state NMR techniques to capture structural and dynamic details at the atomic scale.

Research performed in 2023 has been focused on two thematic:

. Development of solid-state techniques to investigate the molecular organization of native cell wall (Lamon et al., PNAS 2023):

While establishing an invasive infection, the dormant conidia of Aspergillus fumigatus transit through swollen and germinating stages, to form hyphae. During this morphotype transition, the conidial cell wall undergoes dynamic remodeling, which poses challenges to the host immune system and antifungal drugs. However, such cell wall reorganization during conidial germination has not been studied so far. We explored the molecular rearrangement of Aspergillus fumigatus cell wall polysaccharides during different stages of germination. We took advantage of magic-angle spinning NMR to investigate the cell wall polysaccharides (Figure 1), without employing any destructive method for sample preparation. The breaking of dormancy was associated with a significant change in the molar ratio between the major polysaccharides β-1,3-glucan and α-1,3-glucan, while chitin remained equally abundant. The use of various polarization transfers allowed the detection of rigid and mobile polysaccharides; the appearance of mobile galactosaminogalactan was a molecular hallmark of germinating conidia. We also report for the first time highly abundant triglyceride lipids in the mobile matrix of conidial cell walls. Water to polysaccharides polarization transfers revealed an increased surface exposure of glucans during germination, while chitin remained embedded deeper in the cell wall, suggesting a molecular compensation mechanism to keep the cell wall rigidity. We complement the NMR analysis with confocal and atomic force microscopies to explore the role of melanin and RodA hydrophobin on the dormant conidial surface. Exemplified here using Aspergillus fumigatus as a model, our approach provides a powerful tool to decipher the molecular remodeling of fungal cell walls during their morphotype switching.

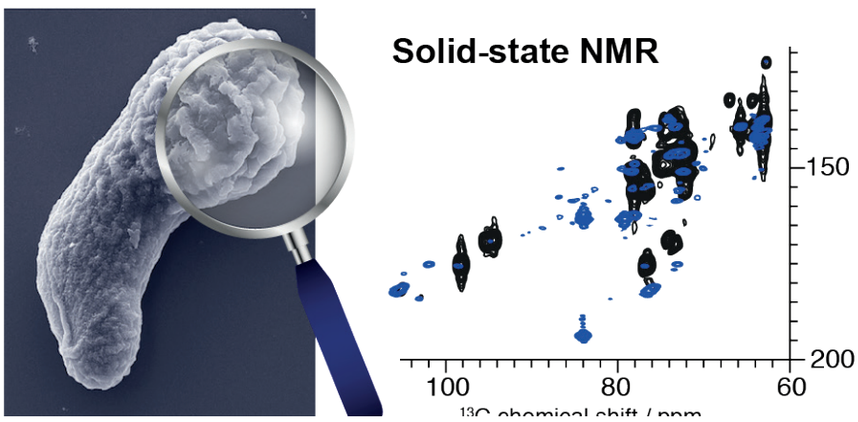

Figure 1: Solid-state NMR investigation of the cell wall organization of native fungal cells.

Solid-state NMR methods to investigate amyloid fibrils (Becker et al., Angewandte Chemie 2023; Lends et al., J. Biomol. NMR):

Aromatic side chains are important reporters of the plasticity of proteins, and often form important contacts in protein-protein interactions. In collaboration with the team of Paul Schanda (IST Vienna, Figure 2), we studied aromatic residues in the two structurally homologous cross-β amyloid fibrils HET-s, and HELLF by employing a specific isotope-labeling approach and magic-angle-spinning NMR. The dynamic behavior of the aromatic residues Phe and Tyr indicates that the hydrophobic amyloid core is rigid, without any sign of "breathing motions" over hundreds of milliseconds at least. Aromatic residues exposed at the fibril surface have a rigid ring axis but undergo ring flips on a variety of time scales from nanoseconds to microseconds. Our approach provides direct insight into hydrophobic-core motions, enabling a better evaluation of the conformational heterogeneity generated from an NMR structural ensemble of such amyloid cross-β architecture. With Prof. Kong Ooi Tan (ENS Paris), we show that high-field dynamic nuclear polarization (DNP), an NMR hyperpolarization technique typically performed at low temperatures, can slow down the protein dynamics to escape unfavorable NMR detection regime. We have successfully established an impressive enhancement factor of ε ~ 50 on amyloid fibrils using an 18.8 T/ 800 MHz magnet. The MAS DNP experiments revealed signals of flexible side chains in amyloid fibrils, previously inaccessible at conventional room-temperature experiments. These results demonstrate the potential of MAS-DNP NMR as a valuable tool for structural investigations of amyloid fibrils, particularly for side chains and dynamically disordered segments otherwise hidden at room temperature.

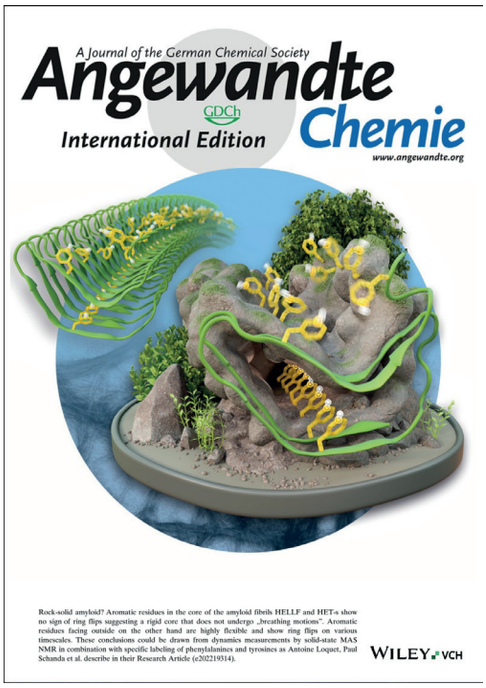

Figure 2: Solid-state NMR investigation of dynamics in amyloid fibrils.

Selected publications

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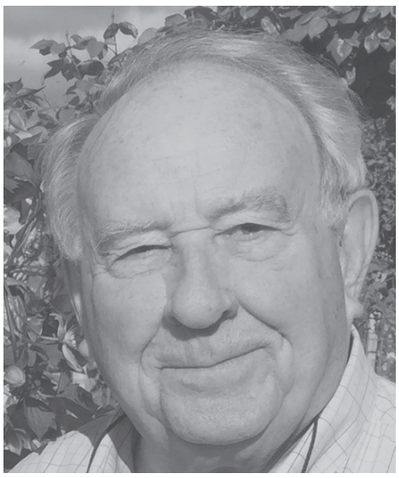

Pr. Léon Ghosez

Professor Emeritus UCL, Visiting Scientist IECB, Univ. Bordeaux

Léon Ghosez was born in Aalst, Belgium, in 1934. He studied at the University of Louvain where he got a PhD in 1958 under the supervision of Prof. G. Smets,. He then spent 2 years as postdoctoral researcher at Harvard University (Prof. R.B. Woodward) and also collaborated for a few months with Prof. R. Huisgen in the Department of chemistry of the University of Münich He got his "Habilitation" at the age of 32 for his independent work on the stereochemistry of synthesis and rearrangement of halocyclopropanes. In 1969 he became "Professeur Ordinaire" at the University of Louvain where he created the laboratory of organic synthesis. During his career in Louvain (1963-1999) he supervised the research of 125 PhD students and 135 postdoctoral associates. He also hold appointments at the University of Liége (1969-1999) and the Ecole Polytechnique in Palaiseau (1993-1999). He took an active part in the creation of IECB where he established a research group in 1998. Since 2000, he shared the directorship of IECB with Dr J.J. Toulmé. Since 2011 he is an invited scientist in the same Institute. His current research interests include the design and total synthesis of biologically active molecules and the search of mild, efficient and "green" Lewis acid catalysts. In 2007, he received the medal of the Société Française de Chimie as a recognition of his support to the development of organic chemistry in France. Léon Ghosez is an emeritus member of the Royal Academy of Sciences of Belgium and a fellow of the Royal Society of Chemistry. In 2017 he received the title of "Chevalier de la Légion d'Honneur".

Research team

Dr. Léon GHOSEZ Prof. Emeritus, Invited scientist (CNRS-Univ. Bordeaux)

The team is part of the CNRS/University of Bordeaux UMR 5144 CBMN.

Organic & Medicinal Chemistry

1. Sustainable electrophilic catalysts for the activation of highly functionalized and sensitive molecules

The project aims at finding solutions to the often encountered problems associated with the use of many electrophilic catalysts: chemoselectivity, low turnover, too high molecular weight, in particular for asymmetric catalysis, toxicity and generation of much waste. New ionic solvents and silicon-derived Lewis superacids have been found to provide solutions to these problems. New electrophilic catalysts for cycloaddition and alkylation reactioins involving highly functionalized acid-sensitive molecules have been developed.

2. Deoxysubstitution of hydroxyl-containing compounds under mild and sustainable conditions : a possible practical and sustainable substitute for the Mitsonobu reaction.

The project aims at finding milder conditions for the replacement of a hydroxyl group by a nucleophile. present methods often required acidic conditions or the use of toxic reagents or(and) lead much waste (eg Mitsonobu reaction) The concept is based on earlier findings of the group on the deoxychlorination-, bromination- and iodination reactions with the readily available haloenamines : conditions are mild, atom economy is high and no reagent is toxic. The reaction was recently extended to the often pharmacologically interesting replacement of an hydroxyl group by fluorine. The plan is to extend the method to a wide variety of nucleophilic reagents including carbon nucleophiles.

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38. Torres-Sánchez, L.; Sana, T. G.; Decossas, M.; Hashem, Y.; Krasteva, P. V. Structures of the P. Aeruginosa FleQ-FleN Master Regulators Reveal Large-Scale Conformational Switching in Motility and Biofilm Control. **Proc Natl Acad Sci U S A 2023**, 120 (50), e2312276120. https://doi.org/10.1073/pnas.2312276120.

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45. Malard, F.; Wolter, A. C.; Marquevielle, J.; Morvan, E.; Ecoutin, A.; Rüdisser, S. H.; Allain, F. H. T.; Campagne, S. The Diversity of Splicing Modifiers Acting on A-1 Bulged 5'-Splice Sites Reveals Rules for Rational Drug Design. **Nucleic Acids Res 202**4, 52 (8), 4124-4136. https://doi.org/10.1093/nar/gkae201.

46. Mishra, V.; Sharma, K.; Bose, A.; Maisonneuve, P.; Visweswariah, S. S. The Evolutionary Divergence of Receptor Guanylyl Cyclase C Has Implications for Preclinical Models for Receptor-Directed Therapeutics. **J Biol Chem 2024**, 300 (1), 105505. https://doi.org/10.1016/j.jbc.2023.105505.

47. Canul-Tec, J. C.; Kumar, A.; Dhenin, J.; Assal, R.; Legrand, P.; Rey, M.; Chamot-Rooke, J.; Reyes, N. The Ion-coupling Mechanism of Human Excitatory Amino Acid Transporters. **The EMBO Journal 2022**, 41 (1), e108341. https://doi.org/10.15252/embj.2021108341.

48. Mourer, T.; El Ghalid, M.; Pehau-Arnaudet, G.; Kauffmann, B.; Loquet, A.; Brûlé, S.; Cabral, V.; d'Enfert, C.; Bachellier-Bassi, S. The Pga59 Cell Wall Protein Is an Amyloid Forming Protein Involved in Adhesion and Biofilm Establishment in the Pathogenic Yeast Candida Albicans. **npj Biofilms Microbiomes 2023**, 9 (1), 6. https://doi.org/10.1038/s41522-023-00371-x.

49. Becker, L. M.; Berbon, M.; Vallet, A.; Grelard, A.; Morvan, E.; Bardiaux, B.; Lichtenecker, R.; Ernst, M.; Loquet, A.; Schanda, P. The Rigid Core and Flexible Surface of Amyloid Fibrils Probed by Magic-Angle-Spinning NMR Spectroscopy of Aromatic Residues. **Angew Chem Int Ed 202**3, 62 (19), e202219314. https://doi.org/10.1002/anie.202219314.

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Invited Peer-Reviewed Articles

1. Krasteva, P. V. Bacterial Synthase-Dependent Exopolysaccharide Secretion: A Focus on Cellulose. **Curr Opin Microbiol 2024**, 79, 102476. https://doi.org/10.1016/j.mib.2024.102476.

2. Morvan, E.; Taib-Maamar, N.; Grélard, A.; Loquet, A.; Dufourc, E. J. Bio-Membranes: Picosecond to Second Dynamics and Plasticity as Deciphered by Solid State NMR. Biochimica et Biophysica Acta (BBA) - **Biomembranes 2023**, 1865 (2), 184097. https://doi.org/10.1016/j.bbamem.2022.184097.

3. Chinoy, Z. S.; Friscourt, F. Expanding the Strain-Promoted 1,3-Dipolar Cycloaddition Arsenal for a More Selective Bioorthogonal Labeling in Living Cells. **Israel Journal of Chemistry 2023**, 63 (1-2), e202200055. https://doi.org/10.1002/ijch.202200055.

4. Lin, Y.; Fichou, Y.; Rauch, J. N.; Zhang, X.; Kosik, K. S.; Han, S. Mapping Phase Diagram of Tau-RNA LLPS Under Live Cell Coculturing Conditions. In **Protein Aggregation**; Cieplak, A. S., Ed.; Methods in Molecular Biology; Springer US: New York, NY, **2023**; Vol. 2551, pp 269-284. https://doi.org/10.1007/978-1-0716-2597-2_18.

5. Baron, L.; Hadjerci, J.; Thoidingjam, L.; Plays, M.; Bucci, R.; Morris, N.; Müller, S.; Sindikubwabo, F.; Solier, S.; Cañeque, T.; Colombeau, L.; Blouin, C. M.; Lamaze, C.; Puisieux, A.; Bono, Y.; Gaillet, C.; Laraia, L.; Vauzeilles, B.; Taran, F.; Papot, S.; Karoyan, P.; Duval, R.; Mahuteau-Betzer, F.; Arimondo, P.; Cariou, K.; Guichard, G.; Micouin, L.; Ethève-Quelquejeu, M.; Verga, D.; Versini, A.; Gasser, G.; Tang, C.; Belmont, P.; Linkermann, A.; Bonfio, C.; Gillingham, D.; Poulsen, T.; Di Antonio, M.; Lopez, M.; Guianvarc'h, D.; Thomas, C.; Masson, G.; Gautier, A.; Johannes, L.; Rodriguez, R. PSL Chemical Biology Symposia Third Edition: A Branch of Science in Its Explosive Phase. **ChemBioChem 2023**, 24 (8), e202300093. https://doi.org/10.1002/cbic.202300093.

6. Bouton, L.; Ecoutin, A.; Malard, F.; Campagne, S. Small Molecules Modulating RNA Splicing: A Review of Targets and Future Perspectives. **RSC Med. Chem. 2024**, 15 (4), 1109-1126. https://doi.org/10.1039/D3MD00685A.

7. Campagne, S. U1 SnRNP Biogenesis Defects in Neurodegenerative Diseases. **Chembiochem 2024**, 25 (9), e202300864. https://doi.org/10.1002/cbic.202300864.

8. Abidi, W.; Torres-Sánchez, L.; Siroy, A.; Krasteva, P. V. Weaving of Bacterial Cellulose by the Bcs Secretion Systems. **FEMS Microbiol Rev 202**2, 46 (2), fuab051. https://doi.org/10.1093/femsre/fuab051.

Prizes, Awards

- French Chemical Society (SCF-Chemical Biology division) award – Nomination to represent France at the European Chemical Society (EuChemS-Life Science) young investigator symposium in Helsinki, Finland, EuChemS-Life Science, Nominated by the French Chemical Society (SCF-Chemical Biology division), 2023, F. Friscourt

Journal & Scientific Society Boards

- Advisory Board Member, Peptide Science (Wiley), 2023, G. Guichard
- Scientific Council, Société de Chimie Thérapeutique (SCT), 2023, G. Guichard
- Member, SCT Young MedChem Forum – YMCF, 2023, G. Compain
- Member of the scientific society board, Société Chimique de France (SCF) – section Aquitaine, 2023-2024, E. Thinon
- Editorial board member, Proceedings of the Yerevan State University B: Chemical and biological sciences (Armenia), 2023, M. Aznauryan
- Associate editor, Frontiers in biomolecular Sciences, Nov 2022, S. Campagne
- Board member, French EPR society, 2022, Y. Fichou
- Associate Editor, Analytical Chemistry (ACS), 2021-2026, V. Gabelica

Evaluation Boards

- Scientific advisory board, Cancéropole GSO, Heath and Technologies, 2023, F. Friscourt
- Member of a focus group on how to improve interdisciplinary research at the University of Bordeaux, InterD at the University of Bordeaux, 2023, F. Friscourt
- Research Evaluation for HCERES, HCERES Evaluation panel, 2023, G. Guichard
- Panel chair, jury d'attribution de financements "ERC-Generator", IdEX de Lille, 2023, V. Gabelica
- International board member, SNSF, 2023-2024, A. Loquet
- Co-president of CE011, ANR, 2024, A. Loquet

Teaching

- Microbiology 2H, Cours de microbiologie génrale insititut Pasteur, 2020, R. Fronzes
- Chemical Biology class: Structure and biological roles of glycans and lipids, Master Level (M1 STS chimie), 2023, F. Friscourt
- Organic Chemistry Classes: Structure- reactivity in organic chemistry (Alkane, Alkene and Aromatic chemistry, SN, E, organometallic reagents, Alcohols, Thiols, Amines and Carbonyl reactivity) as well as thermodynamic and kinetic aspects of organic reactions, Total of 148h, BSc Level (L1-L3 STS chimie), 2023, F. Friscourt
- Atelier formation doctorale : Caractérisation de biomolécules, biomatériaux et matériaux inorganiques à l'échelle atomique par diffraction des rayons X et spectroscopie de RMN – 2h, The Contribution Of Nmr And Crystallography To Foldamer Chemistry : A Personal Account, 2023, G. Guichard
- Chimie générale, Chimie organique, RMN, Biomolécules du vivant, Biologie Chimique : 192 HETD, BSc Level (L1 SVSTC Chimie, L2 SVSTC Chimie), MSc Level (M1 MMF/COVAN Chimie du vivant, M2 COVAN biologie chimique, 2023-2024, C. Dolain
- Chimie générale, chimie organique, vectorisation, peptides bioactifs, sondes en imagerie, ciblage, chimie thérapeutique : 192 HETD, PASS (Parcours Accès Santé Spécifique) du collège santé, cursus pharmacie 2ème année et 3ème année, module chimie du double cursus "Ecole Santé Sciences" (equivalent M1 recherche) Coordinateur du module de chimie du double cursus "Ecole Santé Sciences", 2023, G. Compain
- 2nd year ENSTBB – 8h30, Characterization of biomolecules by SPR, 2023, C. Di Primo
- Master 1 Biochimie Univ. Bordeaux – 4h, Analysis of the interactions by SPR, 2023, C. Di Primo
- L3 TecSan Univ. Bordeaux – 14h, Instrumentations: SPTR technology, 2023, C. Di Primo
- Master 1 Biochimie Univ. Bordeaux – 4h, smFRET for biomolecular structure and interactions, 2023, M. Aznauryan
- Master 1 Chimie SiTH Univ. Bordeaux – 4h, Analysis of the biomolecular interactions by smFRET, 2023, M. Aznauryan

PhD Theses

- Pauline Pony, Etude structural et fonctionnelle des spirosomes bactériens, Université de Bordeaux, R. Fronzes, 2020
- Lucia TORRES-SANCHEZ, "Structure and regulation of exopolysaccharide secretion systems in Gram-negative bacteria", PV. Krasteva, ED ITFA, Université Paris-Saclay, 2022
- Shashank Khare, Universite Bordeaux, 2023, N. Reyes
- Tarek Khalaf, Novel Chemical Reporters for the Bioorthogonal Tagging of Biomolecules, University of Bordeaux, Lebanese Scholarship, 2023, F. Friscourt
- Aline Delamare, Elaboration de composés comportant des groupements hautement fluorés pour contrôler et stabiliser la formation d'assemblages supramoléculaires, Univ. Bordeaux, 2023, G. Guichard / G.Compain
- Alexander König, Elucidating the cation-dependent folding of DNA G-quadruplexes, and how to target specific topologies with synthetic ligands, Université de Bordeaux, MESRI, 2023, V. Gabelica
- Vincent Laffilé, Comprendre l'ionisation électrospray grâce aux foldamères d'oligoamides aromatiques, Université de Bordeaux, ANR, 2023, Y. Ferrand / F. Rosu
- Muhammed Bilal ABDUL SHUKKOOR, Structural studies of amyloid proteins by solid-state nuclear magnetic resonance spectroscopy, UB, 2023, A. Loquet
- Coralie ROBERT, Étude à l'échelle atomique du dépérissement de la vigne par spectroscopie de Résonance Magnétique Nucléaire, UB, CNIV/IFV/Regional Council, 2023, A. Loquet

Science & Society

- Fête de la science, Bordeaux, Octobre 2020
- Ask Me Anything – SCT Young MedChem Forum, Zoom, 10/2023, G. Guichard
- Fête de la Science, Pessac, 10/2023, M. Pasco
- Les Echappées inattendues (CNRS), Talence, 06/2023, M. Pasco
- Happy hour de la recherche en pharmacie, Bordeaux, 03/2023, G. Compain
- CNRS year of Biology : purification of a green fluorescent protein with high school teachers, Pessac, france, Oct 2022, E. Thinon
- Bureau des enquêtes, Cap sciences, Bordeaux France, Oct 2022, E. Thinon
- Half-day outreach activity at Lycée des Graves, Gradignan, organized through the association “Declics”, Gradignan, France, Nov 2022, E. Thinon
- Assemblé Générale de la ligue contre le cancer – comité 33, Bordeaux, France, 05/2022, S. Campagne

Team Funding

European and International fundings

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher(s)	Funding body	Research project	Period
R. Fronzes	ERC	Structure and Function of the Bacterial Transformasome	2017-2023
Y. Hashem	ERC	Translation regulation in eukaryotic pathogens and hosts	2018-2023
Y. Hashem	ERC	Species-specific aspects in eukaryotic mRNA translation modulation and their implications in diseases	2023-2028
P.V. Krasteva	ERC	BioMatrix	2018-2024
P.V. Krasteva	H2020 | ERASMUS	ERASMUS+	2022-2023
P.V. Krasteva	ERASMUS	Advancement Grant	2024-2025
N. Reyes	ERC	Transport and Receptor Mechanisms of Human Solute Carriers	2018-2023
N. Reyes	NIH	The mechanism of allosteric modulation of glutamate transporters	2019-2024
G. Guichard	EU	Metal-Foldamer Porous Frameworks	2021-2023
G. Guichard	EU	Bioinspired Foldamer-based Asymmetric Catalysis at low catalyst loading	2023-2026
G. Guichard	China Scholarship Council	Conception et synthèse de mimétiques enzymatiques à base de foldamères	2022-2026
C. Di Primo	Euskampus	LTC INCUBATOR	2023-2024
C. Di Primo	EIC	FUnctional Nucleic Acids as Versatile SMart BUilding BLocks in Non-ConventIonal SolvenTs	2023-2026
Y. Fichou	ERC	Cofactors at the core of tau prion behavior	2022-2027
Y. Fichou	FEBS	Tau protein structural differentiation guided by aggregation cofactors	2022-2025
V. Gabelica	Horizon Europe	Ion Mobility Mass Spectrometry Training Network	2024-2028
B. Habenstein	EU-SUDOE	RePo	2024-2027

National funding

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Funding body	Research project	Period
R. Fronzes	ANR	Dissecting the Antibody Cleavage System of Mycoplasmas	2018-2021
R. Fronzes	ANR	Structural basis of Helicobacter pylori type IV secretion system	2019-2022
R. Fronzes	ANR	Une approche multidisciplinaire pour comprendre la structure et la dynamique du système de sécrétion de type VI	2020-2024

IECB Researcher	Funding body	Research project	Period
R. Fronzes	EquipEX+	Microscopie corrélative à haute résolution en conditions cryogéniques	2021-2027
R. Fronzes	ANR	Nanoscale organization and dynamics of the molecular machinery that drives cell migration	2022-2026
Y. Hashem	ANR	Architecture of Algae MItochondria translation System and its interplay with mRNA maturation	2021-2025
Y. Hashem	ANR	Dynamic And regulation of the MItochondrial translational Apparatus in Arabidopsis	2020-2024
Y. Hashem	ANR	Deciphering the ABC-F protein mechanism of antibiotic resistance	2018-2022
Y. Hashem	Fondation ARC	Structural and molecular characterization of mRNA translation in colorectal cancer	2021-2023
Y. Hashem	Inserm	Rôle structural et régulatrice des G-quadruplexes dans le promoteur du proto-oncogène KRAS	2024-2028
P.V. Krasteva	ANR	Role Of C-di-GMP in the Kinetics of legionella Effector Translocation – ROCKET	2022-2025
P.V. Krasteva	ANR	CelluSec	2024-2027
F. Friscourt	ANR	Atypical N-glycosylation of the neuronal surface and its impact on synaptic transmission and plasticity	2022-2026
F. Friscourt	French Ministerial Scholarship	Development of unnatural sugars for controlling glycan-protein interactions in living cells	2023-2026
G. Guichard	ANR	Precise pore-forming Assemblies of bioinspired foldamers for selective water translocation	2024-2027
G. Guichard	ANR	Fragment-based design of Irreversible Inhibitors of the Bacterial Replication	2023-2027
G. Guichard	ANR	Mode d'action dual: Nouveaux antimicrobiens ciblant la réplication et la traduction	2022-2025
G. Guichard	ANR	Selective and directional supramolecular interactions based on highly polar fluorinated synthons	2021-2024
G. Guichard	ANR	Therapeutic targeting and chemical biology of histone chaperone using rationally designed medium-size inhibitors	2021-2025
G. Guichard	ANR	Low Loading Asymmetric Catalysis with Helical Chiral Oligoureas	2019-2024
E. Thinon	ANR	Chemical approaches to study the S-palmitoylation of a host factor in Influenza A virus infection	2021-2024
E. Thinon	AFAF- FRM	Protein palmitoylation in Friedreich ataxia	2024-2025
M. Aznauryan	ANR	Probing the molecular mechanisms of function of disordered translation initiation factors: from in vitro to in-cell	2021-2025
Y. Fichou	ANR	En route to amyloid formation: Protein and hydration-water dynamics under liquid-liquid phase separation	2024-2028
V. Gabelica	ANR	Understanding Native Electrospray of Artificial and Natural Polymers	2019-2023
V. Gabelica	ANR	Hydrogen-deuterium exchange mass spectrometry of nucleic acids	2021-2025
A. Loquet	ANR	Transkingamyloid	2021-2025
A. Loquet	ANR	Sorcelhub	2023-2027
B. Habenstein	ANR	BACDOMAIN	2023-2027
E. Dufourc	ANR	API-NMR	2022-2025

IECB Researcher	Funding body	Research project	Period
E. Dufourc	ANR	Ultimo	2022-2025
A. Loquet	ANR	ROSANE	2021-2025

Regional funding

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Funding body	Type of funding	Period
N. Reyes	IDEX	Membrane protein mechanisms	2019-2024
N. Reyes		Membrane protein mechanisms	2020-2025
F. Friscourt	Univ. Bordeaux / SMR Department	Synthesis of Siglec specific glycans for oncological therapies	2023
F. Friscourt	Univ. Bordeaux / InnovationS	Novel bioorthogonal fluorogenic probes for the fast and precise labeling of biomolecules	2023-2024
G. Guichard	Region Nouvelle Aquitaine	Nouveaux Antimicrobiens Ciblant La Réplication et la Traduction	2023-2025
G. Guichard	Region Nouvelle Aquitaine	Interactions supramoléculaires sélectives et directionnelles basées sur des synthons fluorés hautement polaires	2022-2024
G. Guichard	Region Nouvelle Aquitaine	Nouveaux outils pour l'optimisation et le développement de peptides thérapeutiques : Application au ciblage thérapeutique des chaperons d'histones	2022-2024
E. Thinon	University of Bordeaux	Chemical approaches to decipher the role of a host factor in Influenza A virus internalization	2019-2023
E. Thinon	Region Nouvelle Aquitaine	Caractérisation d'une nouvelle cible thérapeutique antivirale	2020-2025
M. Aznauryan	Region Nouvelle Aquitaine	Caractérisation des mécanismes moléculaires gouvernant la fonction d'eIF4B : vers de nouvelles cibles contre le cancer	2020-2025
S. Campagne	Regional council	Rational development of RNA therapeutics against AML	2023-2027
S. Campagne	AAP	DNA binding proteinomimetics with anti-cancer activity: inhibition of the JNK pathway by targeting c-Fos/c-Jun transcription factors	2023-2024
S. Campagne	AAP	Molecular basis for the interaction between Tau and U1 snRNP in the context of Alzheimer's disease	2024-2025
Y. Fichou	UB	Photoswitches for the Control of tau Protein Liquid-Liquid Phase Separation	2023-2025
Y. Fichou	UB	Molecular basis for the interaction between Tau and U1 snRNP in the context of Alzheimer's disease	2023-2024
V. Gabelica	Conseil Régional Aquitaine	Caractériser le repliement de protéines thérapeutiques recombinantes par spectrométrie de mobilité ionique	2019-2024
A. König / V. Gabelica	MESRI	PhD fellowship	2020-2023
A. Loquet	RRI (University Bordeaux)	PhD	2023-2025
A. Loquet	PSGAR	EMERG	2024-2028

Charity-funded research projects

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Charity	Research project	Period
P. Maisonneuve	Foundation pour la Recherche Médicale (FRM)	Uncovering the mechanism of action of pseudokinases in human health and diseases	2022-2025
G. Guichard	Ligue Contre le Cancer	Protéinomimétiques se liant à l'ADN avec une activité anticancéreuse	2024
E. Thinon	AFAF- FRM	Protein palmitoylation in Friedreich ataxia	2024-2025
M. Aznauryan	FRM	Probing interactions of eukaryotic initiation factor 4B (eIF4B): towards new anti-cancer targets	2022-2024
S. Campagne	LCC	Rational development of RNA therapeutics against AML	2022-2023
S. Campagne	Ligue Contre le Cancer	Splicing modulation of mTOR mRNA as a novel anti-cancer strategy	2024-2025
S. Campagne	FRM	Fundamental basis for specific splicing correction by small molecules	2024-2027
Y. Fichou	Fondation Vaincre Alzheimer	Tau aggregation cofactors	2023-2026
V. Gabelica	Fondation Bettencourt Schueller	New mass spectrometry approaches to reveal how covalent modifications modulate the stability of regulatory DNA or RNA	2021-2024

Contracts with the industry

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Company	Research contract	Period
G. Guichard	Ureka Pharma	Developpement de Peptidomimes Contraints Ciblant la Surface de Proteines	2022-2025
S. Campagne	Sardona Therapeutics	Target identification of Sardona compounds	2023-2024
A. Loquet	BioLaffort		2024-2027
A. Loquet	Lallemand		2023-2024

Collaborations

Pole 1 – Structural biology

Structure and Function of Bacterial Nanomachines
Dr. Rémi Fronzes

- Dr. Yonathan Arfi, INRAE, Biologie du Fruit et Pathologie, UMR 1332, Villenave D'ornon, France
- Dr. Eric Cascales, LISM CNRS UMR7255, Marseille, France
- Dr. Laure Journet, LISM CNRS UMR7255, Marseille, France
- Dr. Laurent Terradot, IBCP, Lyon, France
- Dr. Thomas Henry, CIRI, Lyon, France
- Dr. Gregory Giannone, IINS, Bordeaux, France
- Dr. David Perrais, IINS, Bordeaux, France
- Dr. Raffaele Ieva, CBI, Toulouse, France
- Dr. Patrice Polard, CBI, Toulouse, France
- Dr. Vladimir Pellicic, LCB, Marseille, France

RNA Processing and translation regulation in pathogens and hosts
Dr. Yaser Hashem

- Dr. Zoya Ignatova, University of Hamburg, Hamburg, Germany
- Dr. Jody Puglisi, Stanford University, Stanford, USA
- Dr. Gregory Boël, CNRS, Université de Paris, Paris, France
- Dr. Axel Innis, Inserm, Université de Bordeaux, Bordeaux, France

Structural Biology of Biofilms
Dr. Petya Krasteva

- Dr. Yaser HASHEM, IECB, Pessac, France
- Dr. Yoshiharu Yamaichi, I2BC, Gif-sur-Yvette, France
- Dr. Jean-Marc Ghigo, Institut Pasteur, Paris, France

Membrane Protein Mechanisms
Dr. Nicolas Reyes

- Prof. Jan Steyaert, VIB/VUB Brussel, Brussels, Belgium

Pole 2 – Organic & bioorganic chemistry

Chemical Glycobiology
Dr. Frédéric Fiscourt

- Prof. Kelley Moremen, University of Georgia, CCRC, Athens, GA, USA

Peptidomimetic Chemistry
Dr. Gilles Guichard

- Dr. Françoise Ochsenbein, Institute for Integrative Biology of the Cell (I2BC), CEA, CNRS, Université Paris-Saclay, Gif-sur-Yvette, France
- Prof. Prakash P. Kumar, National University of Singapore (NUS), Singapore
- Prof. R. Manjunatha Kini, National University of Singapore (NUS), Singapore
- Dr. Gavin Collie, Discovery Sciences, R&D, AstraZeneca, Cambridge, UK
- Dr. Céline Douat, Department of Pharmacy and Center for Integrated Protein Science, Ludwig-Maximilians-Universität, München, Germany
- Dr. Dominique Burnouf, Institut de Biologie Moléculaire et Cellulaire, Strasbourg France
- Prof. Daniel Taton, Laboratoire de Chimie des Polymères Organiques (LCPO), Université de Bordeaux, INP-ENSCBP, Pessac, France
- Prof. Philippe Carbonnière, IPREM, Univ Pau et des Pays de l'Adour, Pau, France
- Prof. Jean-Marc Sotiropoulos, IPREM, Univ Pau et des Pays de l'Adour
- Dr. Valérie Gabelica, Univ. Bordeaux, CNRS, INSERM, ARNA, UMR 5320, U1212, IECB, Pessac, France
- Dr. Frédéric Rosu, Univ. Bordeaux, CNRS, INSERM, IECB, UMS 3033, Pessac, France
- Brice Kauffmann, Univ. Bordeaux, CNRS, INSERM, IECB, UMS 3033, Pessac, France
- Dr. Cameron Mackereth, Univ. Bordeaux, CNRS, INSERM, ARNA, UMR 5320, U1212, IECB, Pessac, France
- Dr. Antoine Loquet, Univ. Bordeaux, CNRS, CBMN, UMR 5248, Pessac, France

Pole 3 - Biophysics

Single-molecule Biophysics
Dr. Mikayel Aznauryan

- Dr. Cameron D. Mackereth, ARNA, Bordeaux, France
- Prof. Victoria Birkedal, INANO, Aarhus University, Aarhus, Denmark
- Dr. Harald Wodrich, MFP, CNRS, Univ. Bordeaux, Bordeaux, France

Structure, Mechanism and RNA Therapeutics
Dr. Sébastien Campagne

- Prof. Frédéric HT Allain, ETH Zurich, Zurich, Switzerland
- Dr. Marc-David Ruepp, King's college, London, UK
- Prof. Jiri Spooner, Czech Academy of Sciences, Brno, Czech Republic
- Prof. Fedor Karginov, UC Riverside, Riverside, USA
- Prof. Jean-Marc Campagne, ENSCM, Montpellier, Montpellier, France
- Prof. Sophie Javerzat, Univ. Bordeaux, MGMR, Bordeaux, France
- Prof. Vanessa Desplat, Univ. Bordeaux, BRIC, Bordeaux, France
- Dr. Gilles Guichard, Univ. Bordeaux, IECB, CBMN, Bordeaux, France
- Dr. Yann Fichou, Univ. Bordeaux, IECB, CBMN, Bordeaux, France

• Molecular mechanisms of amyloid diseases
Dr. Yann Fichou

- Dr. Valerie Gabelica, IECB/ARNA, Bordeaux, France
- Dr. Sébastien Bonhommeau, CBMN, Bordeaux, France
- Dr. Sophie Lecomte, CBMN, Bordeaux, France

Mass Spectrometryof Nucleic Acids & Supramolecular Complexes
Dr. Valérie Gabelica

- Dr. Gilles Guichard, IECB, Pessac, France
- Dr. Yann Ferrand, UMR 5248 CBMN, Pessac, France
- Prof. Janez Plavec, National Institute of Chemistry, Ljublkana, Slovenia
- Prof. Jean Guillon, ARNA laboratory, Bordeaux France
- Dr. Cameron Mackereth, ARNA laboratory, Bordeaux France
- Dr. Valérie Blanchet, CELIA laboratory, Talence, France
- Dr. Yann Mairesse, CELIA laboratory, Talence, France
- Prof. Liliya Yatsunyk, Swarthmore College, USA
- Prof. Alba Silipo, University of Naples Federico II, Naples, Italie
- Dr. Yann Fichou, IECB, Pessac, France
- Dr. Cédric Mesmin, Merck Biodevelopment SA, Martillac, France

Solid-state NMR of Molecular Assemblies
Dr. Antoine Loquet

- Dr. Mathieu Chavent, IPBS, Toulouse, France
- Dr. Vishu Aimanianda, Institut Pasteur, Paris, France
- Dr. Chantal Abergel, IGS, Marseille, France
- Prof. Paul Schanda, IST, Vienna, France
- Dr. Jeanne Leblond-Chain, ARNA, Bordeaux, France
- Prof. Alex Buell, DTU, Copenhagen, Denmark
- Prof. Tan Kong, ENS Paris, Paris, France
- Prof. Romero, Malaga U., Malaga, Spain
- Prof. Fandrich, Ulm, Germany
- Prof. Smith, Leipzig U., Leipzig, Germany
- Prof. Ventura, Universitat Autoňoma de Barcelona, Barcelona, Spain

Invited Conferences

Pole 1 - Structural biology

RNA Processing and translation regulation in pathogens and hosts

- ZOMES XI CONFERENCE, Magdeburg, Germany, 2022, August 31-September 3, Y. Hashem
- The Ribosome Conference 2022, Bordeaux, France, 2022, Jully 10-14, Y. Hashem
- Translational Control Meeting CSH, Cold Spring Harbor, NY, USA, 2022, September 5-10, Y. Hashem
- Joachim Frank Honorary Symposium, Columbia Unversity, NYC, NYC, USA, 2022, September 5-5, Y. Hashem
- Brazil Symposium on Biocomputing, Buzios, Brazil, 2022, September 22nd-23rd, Y. Hashem
- The sifrARN 2022 Meeting, Bordeaux, France, 2023, October 3rd-5th, Y. Hashem
- Société Française des Microscopies, Rouen, France, 2023, July 3rd-7th, Y. Hashem
- FEBS 47th Meeting, Tour, France, 2023, July 8th-12th, Y. Hashem
- Israeli RNA Society Meeting, Weizmann Institute, Rehovot, Israel, 2023, October 16-18th, Y. Hashem
- INT. CONFERENCE ON MICROBIOLOGY & ONE HEALTH, Quy Nhon, Vietnam, 2024, AUGUST 11th - 14th, Y. Hashem
- ZOMES XII CONFERENCE, Shenzen, China, 2024, October 31-November 3, Y. Hashem

Structural Biology of Biofilms Group

- CSSB Symposium: Charting the landscape of infection, Hamburg, Germany, May 2023, P. V. Krasteva
- ASM Conference on Biofilms (Invited speaker), Charlotte, North Carolina, USA, November 2022, P. V. Krasteva
- SPP1879 Nucleotide Second Messenger Signaling in Bacteria, Berlin, Germany, May 2022, P. V. Krasteva

Membrane protein mechanisms

- Transmembrane Transporter Society International Meeting, Copenhagen, Denmark, June/2022, N. Reyes
- Gordon Research Conference "Ligand Recognition and Gating", Toscana/Italy, March/2022 , N. Reyes

Pole 2 - Organic & bioorganic chemistry

Chemical Glycobiology

- 3rd Young Investigators Workshop, European Chemical Society - Division Chemistry in Life Sciences, Selected and nominated by the Société Chimique de France, Helsinki, Finland, May, 2023, F. Friscourt
- 1st workshop "Chemistry and Cancer" of the Cancéropôle Grand-Sud-Ouest, Toulouse, France, June, 2023, F. Friscourt
- 21st European Carbohydrate Symposium (EuroCarb21), Paris, France, July, 2023, F. Friscourt

Peptidomimetic Chemistry

- CBID 2023:Chemistry Biology Interface Day, Bordeaux, France, November 2023, M. Pasco
- 28th French-Japanese Symposium on Medicinal and Fine Chemistry, Nice, France, October 1-4, 2023, G. Guichard
- Bio3Pharm - French - Portuguese Symposium, Bordeaux, France - Sept 13-15 2023, Bordeaux, France, September 13-15, 2023, G. Guichard
- Symposium IEM (Host Mihail Barboiu), Montpellier, France, June 22, 2023, G. Guichard
- 1er workshop du Groupe de travail « Chimie et Cancer », Toulouse, France , June 19-20 2023, G. Guichard
- 23rd International Symposium on Fluorine Chemistry (23rd ISFC), Québec city, Canada, July, 2023 , G. Compain
- 4th Microbiology Day 2023, Bordeaux, France, May, 2023, G. Compain

Chemical Biology of membrane proteins

- Biochemical Society: New Insights into Lipidation in Cell Biology, Liverpool, UK, September 2023, E.Thinon
- Chemical Biology and Bioorganic Group (CBBG) Community Meeting, Leeds, UK, E.Thinon
- 1st CBIC Chemical Biology Leadership Retreat, Newcastle, UK, E.Thinon

Pole 3 - Biophysics

Structure, Mechanism and RNA Therapeutics

- XXVII EFMC International Symposium on Medicinal Chemistry (September 2022), Nice, France, Scientific committee of EFMC, S. Campagne
- 18th NMR Winter retreat on Protein-RNA interactions (January 2023), Parpan, Switzerland, Frederic Allain, S. Campagne, F. Malard

- RNA society 2022, Boulder, USA, 31/05/2022 - 5/6/2022, S. Campagne
- 12eme SifrARN meeting, Bordeaux, France, 3/10/2022- 5/10/2022, S. Campagne, F. Malard
- 4th RNA'occ meeting, Montpellier, France, 13/06/2023, S. Campagne, L. Bouton, A. Ecoutin
- 4th meeting of the GDR ARN, Montpellier, France, 14, 15/06/2023, S. Campagne, L. Bouton, A. Ecoutin

Molecular mechanisms of amyloid diseases

- 5th International symposium on pathomechanisms of amyloid diseases, Bordeaux, France, Sept 2023, Y. Fichou
- Journées scientifiques de l'ARPE, Paris, France, Mars 2023, Y. Fichou
- EuroTau, Lille,France, April 2023, Y. Fichou
- European biophysical society meeting, Stockholm, Sweeden, July 2023, Y. Fichou

Mass Spectrometryof Nucleic Acids & Supramolecular Complexes

- G4 INTERACTION WINS 2023, online (international), 02/2023, V. Gabelica
- TULIP School on Modern Developments in Spectroscopy, Noordwijk, The Netherlands, 04/2024, V. Gabelica
- Analytical Technologies Europe: Symposium on Analytical Sciences and Regulatory Trends in the Biopharmaceutical Industry, Rotterdam, The Netherlands, 05/2024, V. Gabelica
- HPLC 2023, Düsseldorf, Germany, 06/2023, V. Gabelica
- Mass Spectrometry in Biotechnology and Medicine (MSBM 2023), Dubrovnik, Croatia, 07/2023, V. Gabelica
- 6th International Mass Spectrometry School, Cagliari, Italy, 09/2023, V. Gabelica
- Institut pour l'Avancée des Biosciences (IAB), Grenoble, France, Hélène Medjkane, V. Gabelica
- Sanofi Vaccins, Marcy-L'Etoile, France, Sébastien Peronin, V. Gabelica
- Merck KGgA, Darmstadt, Germany, Ulrich Betz, V. Gabelica
- Institute for Science and Technology Austria (ISTA), Klosterneuburg, Austria, Robert Seiringer, V. Gabelica
- Institut de génétique, biologie moléculaire et cellulaire (IGBMC), Stasbourg, France, Elodie Monsellier, V. Gabelica
- PROGRAMME DOCTORAL EN SCIENCES PHARMACEUTIQUES de l'Université de Genève, Leysin, Suisse, Leonardo Scapozza, V. Gabelica

NMR of Molecular Assemblies

- Microbial Cell Wall, Paris, 2024, A. Loquet
- Biomolecular Assemblies, Bordeaux, 2024, A. Loquet
- BSI 3rd edition, Marseille, A. Loquet
- Conference on Pathological Amyloids, Bordeaux, A. Loquet

Conference Organisation

- The Ribosome Conference 2022, Bordeaux, France, 2022, Jully 10-14, Y. Hashem
- Translational Control Meeting CSH, Cold Spring Harbor, NY, USA, 2022, September 5-10, Y. Hashem
- Joachim Frank Honorary Symposium, Columbia Unversity, NYC, NYC, USA, 2022, September 5-5, Y. Hashem
- The sifrARN 2022 Meeting, Bordeaux, France, 2023, October 3rd-5th, Y. Hashem
- EMBO Bacterial Morphogenesis, Survival and Virulence, Goa, India, February 2023, P. V. Krasteva
- 16th Plants-Bacteria meeting, Aussois, France, March 2023, P. V. Krasteva
- ASM Conference on Biofilms (Invited speaker), Charlotte, North Carolina, USA, November 2022, P. V. Krasteva
- BECM Bio Electron Cryogenic Microscopy meeting, Brussels, Belgium, September 2022, P. V. Krasteva
- Chemical Biology Tour de France of Prof. Laura Kiessling, Bordeaux, France, April, 2023, F. Friscourt
- Chemistry Biology Interface Day CBID 2023, Bordeaux, France, November, 2023, F. Friscourt
- Munich Symposium on Foldamers, Munich, Germany, 09/2023, G. Guichard
- Laura L Kiessling - Chemical Biology Tour & Mini Symposium, Bordeaux, France, 04/2023, G. Guichard
- CBID 2023: Chemistry Biology Interface Day, Bordeaux, France, November 2023, E.Thinon
- SifrARN, Bordeaux, France, 10/2022, C. Di Primo

Access to the platform:

The platform is accessible to researchers from the public and from the private sector. All information on available equipment and process to request services or contact experts can be found on the BPCS web page:
http://www.iecb.u-bordeaux.fr/index.php/en/structural-biophysico-chemistry

Three types of services are offered:

(1) Instrument access time: duly trained users can request machine time, perform the experiments, and interpret the data. Office space is available to accommodate external users.

(2) Routine services: samples are submitted, the platform personnel performs the assays and sends the analysis report to the user. Experiments for which the data interpretation is routine fall into this category.

(3) Collaborative projects: all requests that require the platform personnel's scientific expertise and/or methodological developments in instrumentation, experiment design, or data interpretation, fall into this category.

Technology Platforms

Dr. Brice Kauffmann
Head of IECB's Biophysical and Structural Chemistry platform, IR, CNRS

Head of IECB's Biophysical and Structural Chemistry platform, IR, CNRS After a PhD in protein crystallography (2003, University of Nancy I), Brice Kauffmann spent three years at the European Molecular Biology Laboratory (EMBL) in Hamburg (Germany) working on the development of a new macromolecular crystallography beamline (X12, DESY). He joined the European Institute of Chemistry and Biology in January 2006 as a staff Scientist. Since 2024, he is Deputy Director of the UAR3033/US01.

Selected publications

1. Koehler V, Bruschera G, Merlet E, Mandal PK, **Morvan E, Rosu F**, Douat C, Fischer L, Huc I, Ferrand Y. High-Affinity Hybridization of Complementary Aromatic Oligoamide Strands in Water. ***Angew Chem Int Ed Engl***. 2023 Nov 27;62(48.
2. Ruiz J, LoRicco JG, Soulère L, Castell MS, **Grélard A, Kauffmann B**, Dufourc EJ, Demé B, Popowycz F, Peters J. Membrane plasticity induced by myo-inositol derived archaeal lipids: chemical synthesis and biophysical characterization. ***Phys Chem Chem Phys.*** 2023 Jun 21;25(24):16273-16287.
3. Phan HT, Passos Gibson V, Guédin A, Ibarboure E, El Mammeri N, **Grélard A,** Le Meins JF, Dufourc EJ, **Loquet A**, Giasson S, Leblond Chain J. Switchable Lipids: From Conformational Switch to Macroscopic Changes in Lipid Vesicles. ***Langmuir***. 2023 Feb 28;39(8):3072-3082.
4. Kriat A, Pascal S, **Kauffmann B,** Ferrand Y, Bergé-Lefranc D, Gigmes D, Siri O, Kermagoret A, Bardelang D. A pH- and Metal-Actuated Molecular Shuttle in Water. ***Chemistry***. 2023 Jun 13;29(33).
5. Torres-Sánchez L, Sana TG, **Decossas M, Hashem Y,** Krasteva PV. Structures of the P. aeruginosa FleQ-FleN master regulators reveal large-scale conformational switching in motility and biofilm control. ***Proc Natl Acad Sci USA.*** 2023 Dec 12;120(50).
6. Cao M, Vial A, **Minder L,** Guédin A, Fribourg S, Azéma L, Feuillie C, Molinari M, **Di Primo** C, Barthélémy P, Jeanne LC. Aptamer-based nanotrains and nanoflowers as quinine delivery systems. ***Int J Pharm X.*** 2023 Feb 14;5:100172.20;144(15):6894-6906.

Biophysical & Structural Chemistry platform (BPCS)

IBiSA-labelled since 2011, IECB core facility provides privileged access to state-of-the-art instruments and dedicated scientific expertise from scientists leading research programs either at IECB, or for external academic and industrial users. The BPCS serves to nucleate the development of a supportive local community with expertise in structural biology, structural chemistry and biophysics to increase the attractiveness of the University of Bordeaux for talented scientist from all over the world.

In 2019, the IECB core facility has joined the new "Core Facilities" department at Bordeaux University. At the forefront of methodological developments in Structural (Bio) Chemistry and Biophysics, the facility is gathering on the same site a coherent set of techniques and expertise to investigate molecular recognition processes and structure of supramolecular assemblies from a structural and biophysical perspective.
Importantly, the facility stands at the frontiers between chemistry and biology, by focusing both on biological molecules and on synthetic molecules conceived to fold and self-assemble like biological molecules and/or interact with biological systems. It is indeed not sufficient to determine simply the structure and biochemical properties of macromolecules in vitro. In line with the trend towards systems biology and integrated structural biology initiatives in Europe (Instruct), a major challenge now is to understand how macromolecules functions dynamically within a larger macromolecular assembly or in a cellular pathway or even at the organism level. Understanding dynamical processes is not possible using a single technology, but becomes potentially accessible through the integration of a number of approaches, spanning different resolution scales.
The IECB facility follows that development strategy by regrouping expertise and state-of-the art instruments in Biochemistry (production and purification of recombinant proteins, peptide synthesis…), NMR spectroscopy (liquid and solid state with 8 spectrometers from 100 MHz to 800 MHz), X-ray crystallography (from crystallization to atomic resolution structure on single crystals or powder samples with a high flux X-ray source and Hybrid direct detector), Cryo-EM (with a 200kV FEI Talos Arctica microscope equipped with a GATAN K2 summit camera), mass spectrometry (Bruker SolariX 7T ETD), surface plasmon resonance and spectroscopy (absorption and circular dichroism spectroscopy, SPR exploiting a T200 instrument from Biacore and Octet8 BLI.

Access to the platform:
The platform is accessible to researchers from the public and from the private sector. All information on available equipment and process to request services or contact experts can be found on the BPCS web page:
https://www.iecb.u-bordeaux.fr/en/facilities

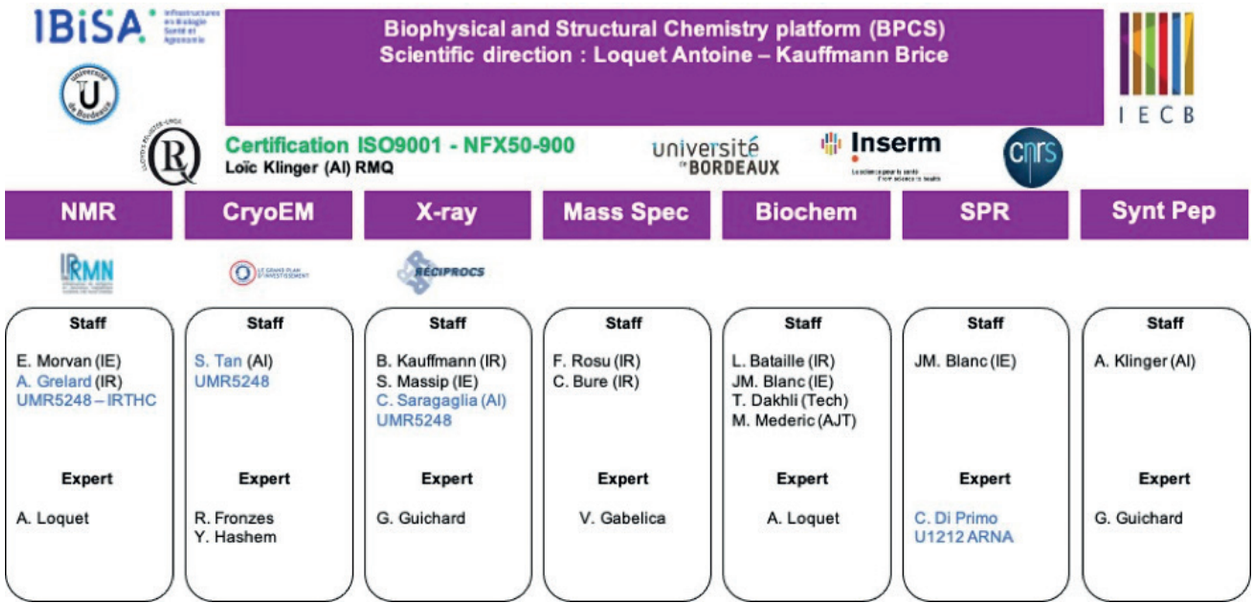
Three types of services are offered:
1. Instrument access time: duly trained users can request machine time, perform the experiments, and interpret the data. Office space is available to accommodate external users.
2. Routine services: sample conditioning, experimental data collection, data analysis and result reports. Experiments for which the data interpretation is routine fall into this category.
3. Collaborative projects: all requests that require the platform personnel's scientific expertise and/or methodological developments in instrumentation, experiment design, or data interpretation, fall into this category.

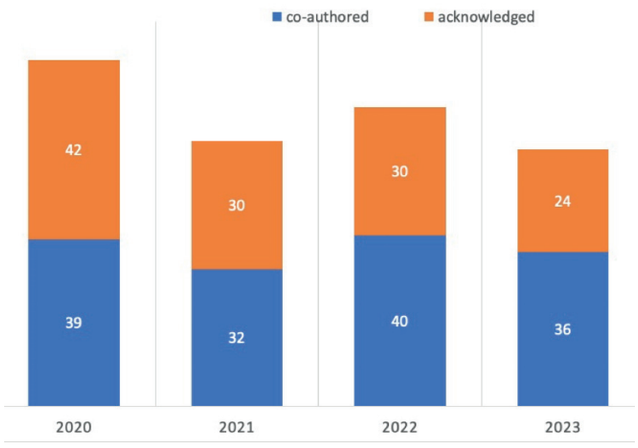
Scientific and Quality policies:

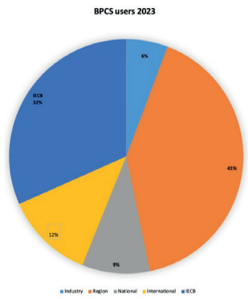
To fulfill these missions, the BPCS is committed to:

- Support the research of IECB teams by providing them with:
  - Privileged access to a high-level platform (instruments and expertise) for physico-chemical and structural characterization of synthetic molecules, biomolecules and their assemblies.
  - Opportunities for collaboration in methodological research.
- Pursue opening policy to external academic and industrial teams. In particular, the strategic objectives are to:
  - Strengthen the positioning of the structural chemistry cluster, focused on the characterization of biomolecules and bio-inspired assemblies.
  - Strengthen the structural biology cluster through developments in cryo-electron microscopy, at the interface with cellular imaging.
  - Restructure a biophysics cluster to characterize molecular interactions.
- Reinforce best practices related to scientific ethics in experimental research (traceability, reliability).
- Contribute to the training of students and scientific and technical staff in the platform's areas of expertise.
- Continue the improvement process following ISO 9001:2015 and NF-X50-900.

Organization







Users of the platform: In 2023, the platform contributed to 139 projects for more than 60 different public or private laboratories or companies.

Key figures:

- **More than 100** people **trained** per year (students, technicians, researchers)
- **60** publications with staff members as co-author or with acknowledgments for the BPCS.

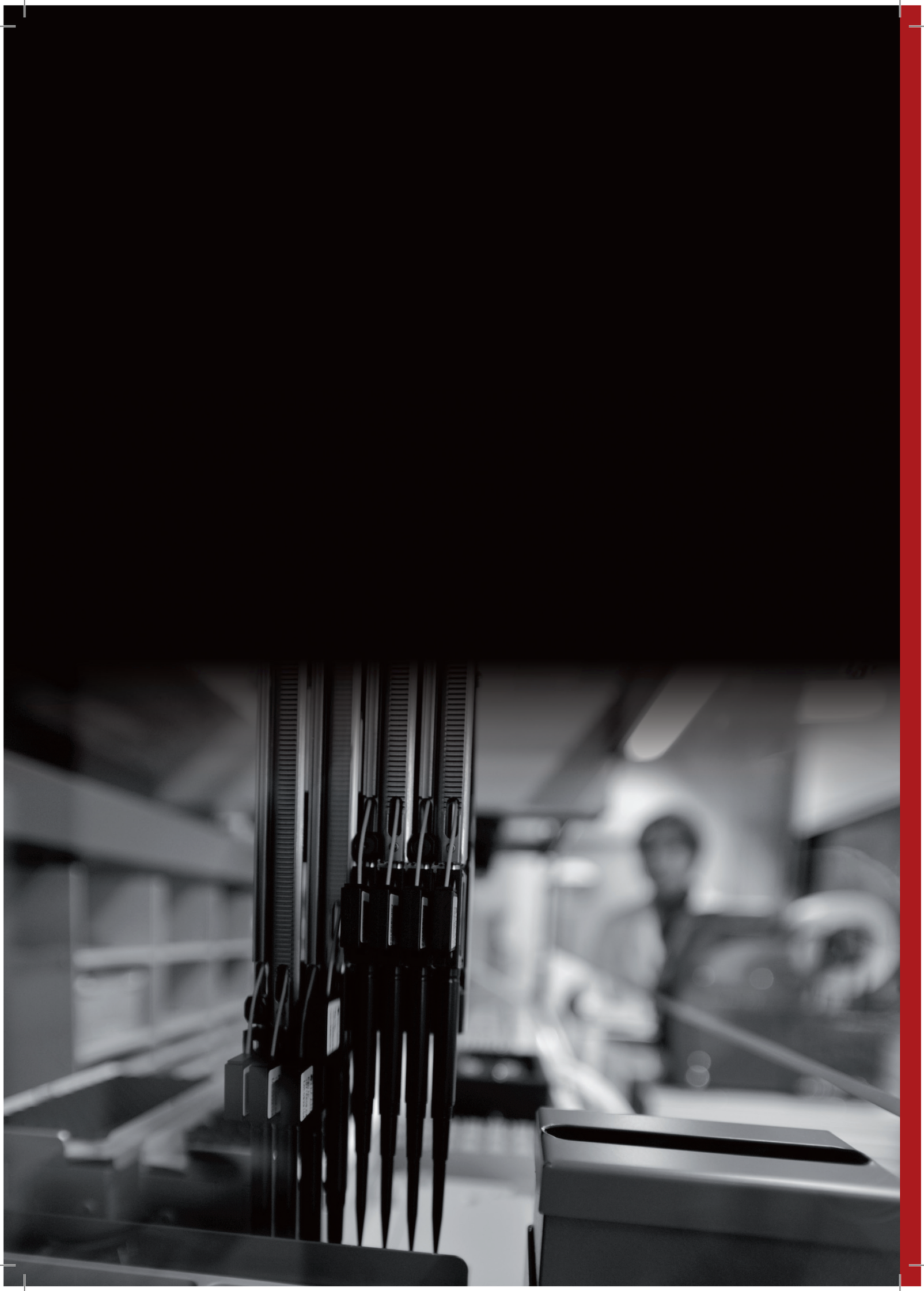
2023 Highlights:

A Bio-Layer Interferometry (BLI) instrument at the UAR/US to study biomolecular interactions.

Late 2023, the UAR/US, in collaboration with Dr. Carmelo Di Primo (UMR ARNA), acquired an instrument for characterizing biomolecular interactions using Bio-Layer Interferometry (BLI) : the Sartorius Octet R8. This technology can be used to study molecular interactions by determining the association/dissociation and affinity kinetic constants, and can also be used to quantify biological molecules. This instrument is used to characterize the molecular interactions of proteins, antibodies, peptides, DNA, RNA, liposomes and viruses in various media, including serum, DMSO-containing buffers, periplasmic fractions, untreated cell culture supernatants and crude cell lysates. The consolidated budget was assembled thanks to a great consortium of academic labs (ARNA, CBMN, IECB, IINS, BFP, ikerbasque POLYMAT) the Nouvelle-Aquitaine Region and private companies (Novaptech, CovalX, Surphase.

Renewal of ISO9001 and NF X50-900 certification.

Following the audit conducted by the independent agency LRQA in April, the BPCS platform has renewed its certifications for 3 years. Thanks to the great involvement of the staff, the platform continues its continuous improvement process.



Technology Transfer & Start-ups

The scientific breakthroughs achieved at IECB are meant to nurture technological innovation. The skills, knowledge and technologies developed at the institute are transfered to economic players via different routes:

Collaborative research

Servier, UreKa, DART Neurosciences... Several key industry players work with IECB teams.

Contract services and consulting

The IECB brings together a wide range of scientific equipments and expertise in chemistry and biology. Such resources are made available to public and private research centers through IECB's Biophysical and Structural Chemistry platform.

Technology transfer

IECB researchers are strongly encouraged to patent their discoveries.

The technology transfer unit Novaptech that was hosted at IECB in 2008-2013 is now a promising biotech company headquartered in Bordeaux.

Incubating start-ups

IECB has 300 m2 work space dedicated to start-ups. Ureka created in 2010 is located at the institute since 2014. Until 2018, a part of this area was also occupied by Fluofarma, created in 2003 by two team leaders from IECB.

Founded in Bordeaux in 2013, Aelis Farma is a biopharmaceutical company that is developing a new class of drugs, the Signaling-Specific inhibitors of the CB1 receptor of the endocannabinoid system (CB1-SSi). CB1- SSi have been developed by Aelis Farma based on the discovery of a natural regulatory mechanism of CB1 hyperactivity made by the team led by Dr. Pier Vincenzo Piazza, the Company's CEO, when he was the director of the Neurocentre Magendie of INSERM in Bordeaux.

By mimicking this natural mechanism, CB1- SSi appear to selectively inhibit the disease-related activity of the CB1 receptor without disrupting its normal physiological activity. CB1-SSi have consequently the potential to provide new safe treatments for several brain diseases.

Aelis Farma is currently developing two first-in-class clinical-stage drug candidates: AEF0117 for the treatment of cannabis related disorders, that has just completed a Phase 2B study in the United States in CUD, and AEF0217 for cognitive disorders, including those of Down syndrome (Trisomy 21), that has just completed recruitment in a Phase 1/2 study in Spain in people with Down syndrome, with results expected in Q4 2024.

The Company also has a portfolio of new innovative CB1-SSi for the treatment of other disorders associated with a dysregulation of the activity of the CB1 receptor. The different drugs developed by the Company belong to the same general pharmacological class, the CB1-SSi, but have distinct functional effects allowing to target different types of dysregulations of the CB1 receptor.

Aelis Farma draws on the talents of more than 25 highly qualified employees.

Scientific Events

Workshops & symposia held at IECB

CBID 2023: Chemistry Biology Interface Day

» A scientific meeting aiming at promoting research at the interface between chemistry and biology in the Nouvelle Aquitaine region.
» Open to all from master student to researcher.

November 13 th 2023
9h00-16h00

at IECB
2, rue Robert Escarpit
Pessac

Registration before November 3 rd
free but mandatory
https://framaforms.org/cbid2023-chemistry-biology-interface-day-1693904289

Organizers:
Frederic Friscourt (IECB/ISM)
Elisabeth Garanger (LCPO)
Jeanne Leblond-Chain (ARNA)
Nicolas Martin (CRPP)
Matthieu Sainlos (IINS)
Elia Stahl (IECB/LBM)
Emmanuelle Thinon (IECB/CBMN)

Contact:
e.thinon@iecb.u-bordeaux.fr

université de BORDEAUX

Chirality in Aquitaine (χ-NOA) day

25th of April 2023

INFORMATIONS : The kinoa-day will take place at IECB building.

All times include question time with typically 3min to 5min depending on the length of the interventions. Invited Conference (45 min) /Talks "Young Researchers" (15 min)/ Talk "Senior Researcher" (25 min) /Laboratory presentation (30 min)

PROGRAM :

- 8h50-9h05 : Welcome
- 9h05-9h50 : Laurent Nahon (SOLEIL-Paris-Saclay) :VUV circularly polarized synchrotron radiation in interaction with chiral matter @ SOLEIL
- 9h50-10h05 : Zikkawas Pasom (ISM) :Chiral-imprinted mesoporous metals for Enhancing Oxygen Reduction Reaction
- 10h05-10h20 : Serena Arnaboldi (ISM) : Enantioselective dynamic systems
- 10h20-10h35 : Wanmai Srisuwanno (ISM) : Autonomous chiral microswimmers for enantioselective synthesis

10h35 -11h00 : Coffee break/poster installation

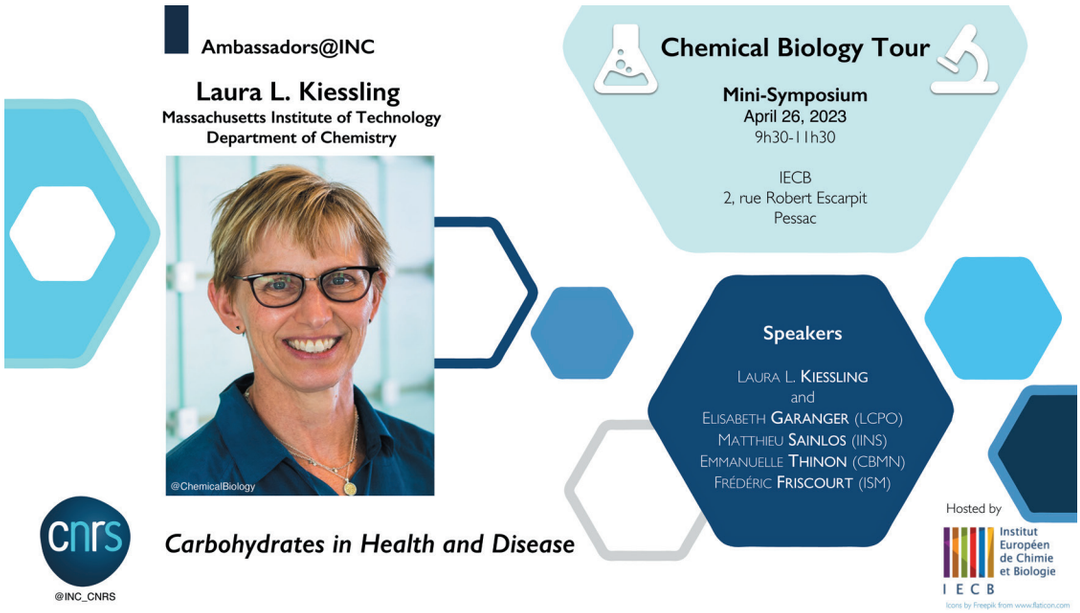
- 11h00-11h30 : Pierre Waffo Teguo (OENO) : How can the enantiomeric ratio of E-epsilon-viniferin, a dimer of resveratrol, be a new chemotaxonomic marker of grapevine ?
- 11h30-11h45: Marie Le Scanff (OENO) : How can stereochemistry influence the taste of wine ?
- 11h45-12h00: Rihab Fkiri (IC2MP) : New extraction derivatization protocol for amino acids chiralite measurement: one step one pot strategy
- 12h00-12h30: François Riobé (ICMCB) : Influence of temperature on circularly polarized luminescence

12h25-14h30 : lunch/discussions and poster's presentation

- 14h30-15h00 : Michel Rérat et Didier Bégué (Univ. Pau) : Etude théorique de l'hélicité orbitalaire et le calcul quantique de la chiralité de systèmes moléculaires et cristallins
- 15h00-15h25: Rémi Avriller (LOMA) : Chiral polaritonics: a road towards enhanced sensing
- 15h25-15h40 : Nicolas Bruni (LOMA) : Understanding the polar nature of laser-induced quasi-particles in chiral liquid crystal
- 15h40-15h55 : Maria João Álvaro Martins (ISM) : Influence of exciplex/excimer on the chiral properties of materials

16h00 -16h30 : Coffee break/posters

- 16h30-16h50: Olivier Sandre (LCPO) : Dichroïsme circulaire d'auto-assemblages de copolymères PEO-block-poly(L-amino acids) présentant des transitions de structures secondaires en pH, ainsi que des copolymères PEO-block-poly(e-caprolactone-co-L-lactide) semi-cristallins
- 16h50-17h15: Vincent Rodriguez (ISM) : Inverse magnetochiral birefringence in chiral liquids



Ambassadors@INC

Laura L. Kiessling - Chemical Biology Tour

April 26 - Chemical Biology - Mini-Symposium (9:30-11:30)

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9:30-9:35	Introduction (G. Guichard, CBMN/IECB)
9:35-9:50	**Elisabeth Garanger** (LCPO, Bordeaux) / *Post-Modifications of Recombinant Elastin-Like Polypeptides Towards Bioactive Materials and Self-Assemblies*
9:50-10:05	**Matthieu Sainlos** (IINS, Bordeaux) / *Protein Engineering for Endogenous Synaptic Proteins Investigation*
10:05-10:20	**Emmanuelle Thinon** (CBMN, Bordeaux) / *Chemical Biology Approaches to Identify the Protein Targets of an Inhibitor of Viral Infection*
10:20-10:35	**Frédéric Friscourt** (ISM, Bordeaux) /*Controlling the Activity of Bacterial Sialidases with Bioorthogonal Chemical Reporters*
10:35-11:30	**Laura Kiessling** (MIT, Boston, US) / *Carbohydrates in Health and Disease*

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Seminars

1. Prof. Nicola Pohl, Indiana University Bloomington USA.* Synthetic glycans on demand and the analysis of carbohydrates.

2. Prof. Thierry Brigaud from CY Cergy Paris Université & Université Paris-Saclay, CNRS, BioCIS. The title of his presentation is "Fluorinated amino acids incorporation into peptides: a tool for the tuning of biophysical properties and biological applications" (abstract attached)

3. Dr. Nadia El Mammeri (a Post-doc at MIT in the Dpt of Chemistry and a PhD from the Univ. Bordeaux). The title of her presentation is "Understanding Tau's Chemical code: microtubules, lipid membranes, anionic co-factors, and phosphorylation". (please find her asbtract attached)

4. Frédéric Allain ETH Zurich, D-BIOL, Institute of Biochemistry, Switzerland A solid beta-sheet structure is formed at the surface of FUS liquid droplets during aging

5. Prof John Klassen, from The University of Alberta, Canada, (see poster below), hosted by Valérie Gabelica at the IECB on Friday 30th of June, 11am. Native mass spectrometry tools for glycomics

6. Prof Daniela Verga, from Paris-Saclay, Orsay (see poster below), hosted by Valérie Gabelica at the IECB on Tuesday 13th of June, 10am. Targeting G-quadruplex structures: Design of Selective non-covalent and covalent G4 ligands

7. Prof. James Nowick, on Friday the 26th of May at 11 am in the IECB amphitheater. Dpt of Chemistry and Dpt of Pharmaceutival sciences, University of California, Irvine, USA Unlocking the mysteries of Alzheimer's disease with Macrocyclic beta-sheet peptides

8. Mini Symposium Chemical biology Tour: Laura Kiessling from MIT, Boston, US: Carbohydrates in Health and Disease ; Elisabeth Garanger from LCPO, Bordeaux: Post-Modifications of Recombinant Elastin-Like Polypeptides Towards Bioactive Materials and Self-Assemblies; Matthieu Sainlos from IINS, Bordeaux: Protein Engineering for Endogenous Synaptic Proteins Investigation; Emmanuelle Thinon from CBMN, Bordeaux: Chemical biology Approaches to identify the Protein Targets of an inhibitor of Viral Infection; Frederic Friscourt from ISM, Bordeaux : Controlling the Activity of Bacterial Sialidases with Bioorthogonal Chemical Reporters.

9. Ivan Huc (department of pharmacy, LMU Munich, Germany) He will give a seminar entitled: "Aromatic foldamers: engineering molecular shape".

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Cover image: Image credit: Florian Malard and Sébastien Campagne, image generated using DALL-E.

This illustration highlights the scientific progress in manipulating gene expression using small molecule splicing modifiers. In their manuscript published in *Nucleic Acids Research*, Malard F., Wolter AC, *et al.* demonstrated how FDA-approved SMN2 splicing modulator Risdiplam, along with other A-1 splicing modulators, function as molecular glues between U1 snRNP and the A-1 bulged 5'-splice site of *SMN2* exon 7. By correcting the splicing pattern of the *SMN2* gene, this orally available drug alleviates symptoms in patients with Spinal Muscular Atrophy (SMA), a devastating neuromuscular disease. Through a detailed examination of the atomic-level mechanism of A-1 splicing modifiers, the authors have uncovered key principles for guiding the rational design of new therapeutic splicing modulators.

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