Institut Européen de Chimie et Biologie

European Institute of Chemistry and Biology

I E C B

Scientific Report

2015

université de BORDEAUX

Inserm

cnrs

In september 2015, the iGEM Bordeaux team supervised by D. Dupuy obtained a Gold Medal at the giant Jamboree of the IGEM competition in Boston.

The team composed of 28 students from Bordeaux University and ENSTBB proposed an eco-friendly alternative treatment to prevent Downy Mildew: replacing copper sulfate by Curdlan, a sugar biopolymer which stimulates the plant natural defenses.

The plant naturally defends itself against pathogens through two distinct levels of defenses, an active and a passive defense which both cause a depolarization of the infected cell membrane and trigger the production of antimicrobial metabolites. Curdlan is recognised by the passive defense and activates it, with mechanisms similar to modern day vaccines.

Publication director: Jean-Louis Mergny **Graphic design:** Little Big Studio, A to B communication **Photo credits:** Cameron Mackereth & Gilles Guichard (front cover: biomimetic helices with the ability to self-assemble into homogeneous protein like architectures in aqueous conditions - published in 2015, in Nature Chemistry), Yves Théobald (building, portraits), François Quenet (portraits), Lionel Lizet (IECB-CGFB technology platform), Pierre-Emmanuel Gaultier (portraits), Elodie Emaille (portraits), Céline Charrier (portraits).

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Director's Foreword

Dr. Jean-Louis Mergny
Executive Scientific Director of the IECB
Research Director (DR) at Inserm (U1212)

Many subjects have paved the life at IECB in 2015 and deserve to be highlighted: new group leaders, seminal papers, exciting workshops and symposia, a prestigious award to I. Huc from the French Academy of Sciences, the creation of an international laboratory (LIA) with Japan... A quick look at the « News » page of our web site will give the reader a flavour of past events.

Year after year, IECB group leaders are awarded grants from highly competitive calls: an indisputable indication of the first rate quality of our scientists. Individual teams have made several seminal contributions in high impact journals. I would like to congratulate the teams of G. Guichard, C. Mackereth and V. Gabelica who published a common contribution on assemblies of water-soluble non-peptide helical foldamers. This article made the front cover of the November 2015 issue of Nature Chemistry… and the front cover of this annual report as well!

The platform for structural biophysico-chemistry of the institute now benefits from a new ion mobility mass spectrometer, a powerful instrument for structural investigation that was previously unavailable in Bordeaux. We have also rejuvenated our NMR platform and should host in 2016 a new FEI Arctica electron microscopy device. Several of our platforms are becoming a showcase for suppliers, with mutually beneficial consequences including an increased visibility.

The development of IECB continues to contribute to the strategy of the University of Bordeaux. For instance, both research teams and the structural biophysico-chemistry platform take an active part into the BRIO network dedicated to translational research on cancer, and also the university Action Thematique Transversale (ATT) focussing on Synthetic Biology. Of note, the iGEM team hosted at IECB earned a Gold Medal in Boston for the first time. Even though IECB is not (yet) an official actor of the IdEx (« Initiative d'excellence ») of Bordeaux, the quality of the science performed by our teams, their international visibility, the validated attractivity of our institute, our demonstrated interest for technology transfer that translated into the creation of several companies, make IECB a key player of this ambitious project. I sincerely wish that links are strengthened with IdEx in the near future for mutual benefit.

A number of scientific events were organized in IECB (or by IECB members) in 2015. Some of them are annual events, such as the Young Scientists Symposium (YSS) or RNA club. Others were exceptional, one of kind events: two IECB teams have organized the Fifth International Meeting on G-quadruplexes in May. Initially scheduled in IECB, we had to change venue as nearly 300 participants registered to this event. A meeting report was recently published in Cell Chemical Biology: according to this report, and from the feedback we received from participants, it was considered as a great success. We were also delighted to host Professor Yves Levy, Head of Inserm, for a visit of the Bordeaux Campus and our Institute on July 7th.

Did I forget anything? Oops: Yes! IECB has a new director since January 2015. It was a great (but scary!) honor to be appointed Director in January 2015. Jean-Jacques Toulmé decided to step back from this mission after 15 years of sacerdoce. He was part of the institute from its very early days and played a very important role in the growth of IECB, particularly during the challenging period when the concept of this new institute was not as widely accepted as today. Jean-Jacques was (and still is) incredibly supportive and he always encouraged me to move forward. Let me – on behalf of the whole Institute – thank him for the time and energy spent on making what the institute is today.

I hope the reader will find a wide range of useful information in the 2015 IECB scientific report and even, perhaps, reasons to collaborate or to join!

Dr Jean-Louis Mergny

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 Université de 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 12 research teams accounting for 120 researchers and expert technicians.

Two companies - Fluofarma Porsolt, created by former IECB team leaders, and Ureka (Immupharma Group) - are hosted at the Institute.

Contents

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

Dr. Moshe YANIV
Institut Pasteur, Paris, France

Dr. Witold FILIPOWICZ
Institut Friedrich Miescher,
Basel, Switzerland

Prof. Dinshaw PATEL
Memorial Sloan-Kettering
Cancer Center, New York, USA

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

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

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

Dr. Daniel SCHIRLIN
Sanofi Aventis, Paris, France

Pr. Roeland NOLTE
Radboud University Nijmegen,
Netherlands

Organisational Structure

Board Members

International scientific advisory board (ISAB)

Dr. Moshe YANIV President
Institut Pasteur, Paris, France

Dr. Witold FILIPOWICZ
Institut Friedrich Miescher, Basel, Switzerland

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

Pr. Roeland NOLTE
Radboud University Nijmegen, Netherlands

Prof. Dinshaw PATEL
Memorial Sloan-Kettering Cancer Center, New York, USA

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

Dr. Daniel SCHIRLIN
Sanofi Aventis, Paris, France

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

Former ISAB members

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. Jean-Louis MERGNY Executive Scientific Director
Research director, U1212 (Inserm - Université de Bordeaux)

Dr. Ivan HUC Deputy Scientific Director
Research director, UMR5248 (CNRS - Université de Bordeaux)

Mrs. Sylvie DJIAN Administrative Director (CNRS)

Former directors

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

Mrs. Sylvie DJIAN Administrative Director (CNRS)

Dr. Gilles GUICHARD Team leader
Research Director, UMR5248 (CNRS - Université de Bordeaux)

Dr. Ivan HUC Deputy Scientific Director
Research Director, UMR5248 (CNRS - Univ. Bordeaux)

Dr. Brice KAUFFMANN Head of IECB's technology platforms
Engineer, UMS3033 (CNRS - Université de Bordeaux)

Dr. Cameron MACKERETH Team leader
Senior Research Associate, U1212 (Inserm - Univ. Bordeaux)

Dr. Jean-Louis MERGNY Executive Scientific Director
Research Director, U1212 (Inserm - Univ. Bordeaux)

Dr. Anne ROYOU Team leader
Senior Research Associate, UMR5095 (CNRS - Univ. Bordeaux)

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

Université de Bordeaux
35 Place Pey Berland, 33000 Bordeaux

Organisational Chart

Research teams

- Pole 1 - Structural biology & biophysics
  - Translation regulation of gene expression — Dr. Axel Innis
  - Solid-state NMR of molecular assemblies — Dr. Antoine Loquet
- Pole 2 - Organic & bioorganic chemistry
  - Supramolecular bioorganic & biomimetic chemistry — Dr. Ivan Huc
  - Peptidomimetic chemistry — Dr. Gilles Guichard
  - Peptide-based polymer assemblies — Dr. Élisabeth Garanger
  - Chemical neuroglycobiology — Dr. Frédéric Friscourt
- Pole 3 - Molecular recognition
  - NMR spectroscopy of protein-nucleic acid complexes — Dr. Cameron Mackereth
  - Unusual nucleic acid structures — Dr. Jean-Louis Mergny
- Pole 4 - Molecular & cellular biology
  - Dynamics of cell growth & cell division — Dr. Derek McCusker
  - Genome regulation & evolution — Dr. Denis Dupuy
  - Control & dynamics of cell division — Dr. Anne Royou
  - Metabolism & cell signaling — Dr. Raul Duran
- Visiting scientist
  - Organic & medicinal chemistry — Pr. Léon Ghosez
  - Mass spectrometry of nucleic acids and supramolecular complexes — Dr. Valérie Gabelica

Board of directors

Steering committee

Institut Européen de Chimie et Biologie

I E C B

Board of trustees

International scientific advisory board

Administrative services
UMS3033 & US001

Technology platforms
UMS3033 & US001

- Structural biology
- Preparative & analytical techniques

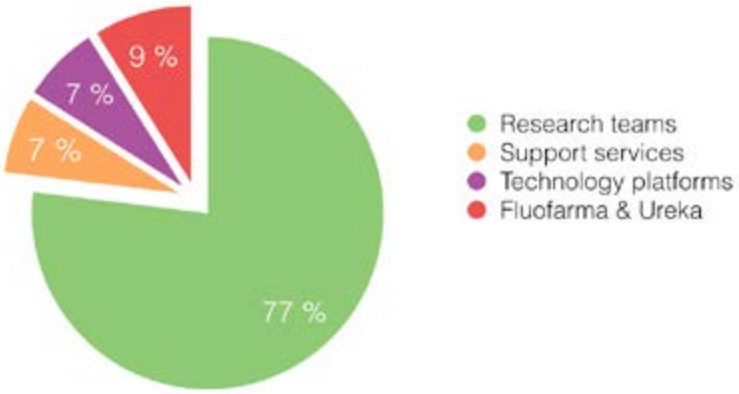
Technology transfer & start-ups

- Fluofarma — A Ponsolt Company
- UREkA — ImmuPharma Group

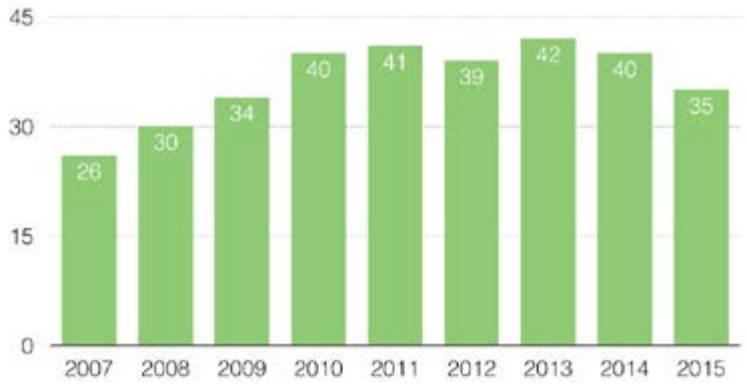
2015 Key Figures

In 2015, 156 people were part of the IECB : 120 research staff, 22 employees within the IECB's support services unit and 14 employees of the companies Fluofarma and Ureka. Young researchers (Master and PhD students, postdoctoral researchers) represent 65% the IECB research staff. This population largely contributes to gender equality and internationalization at IECB. It also testifies to the attractiveness of the institute.

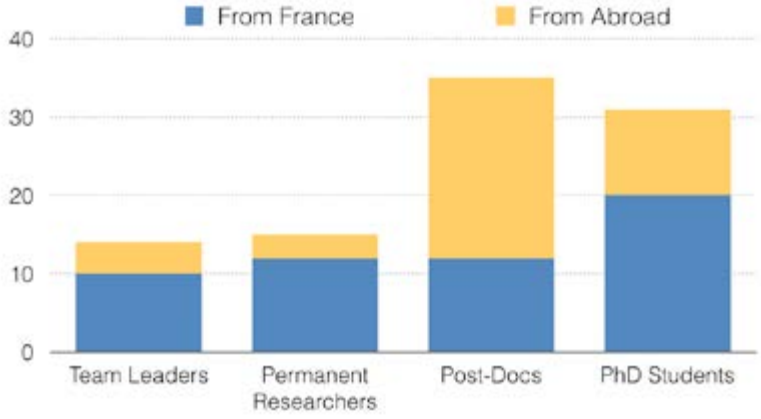
IECB staff by professionnal category



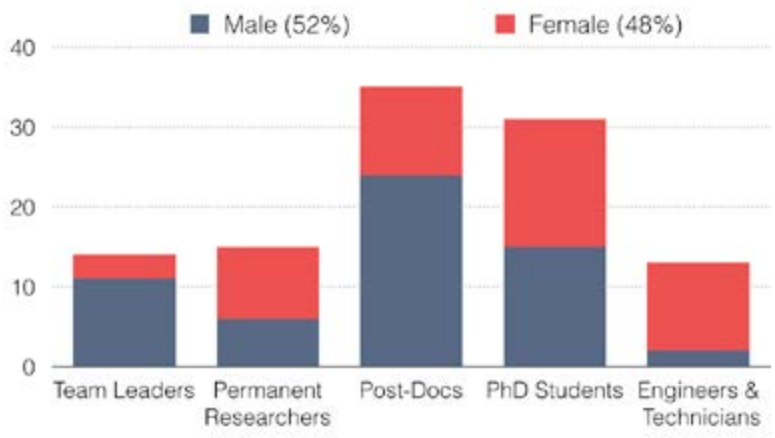
Number of postdoctoral researchers over the past 9 years



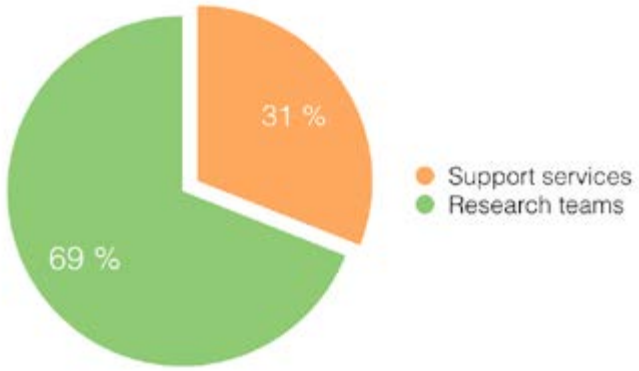
Number of postdoctoral researchers over the past 9 years



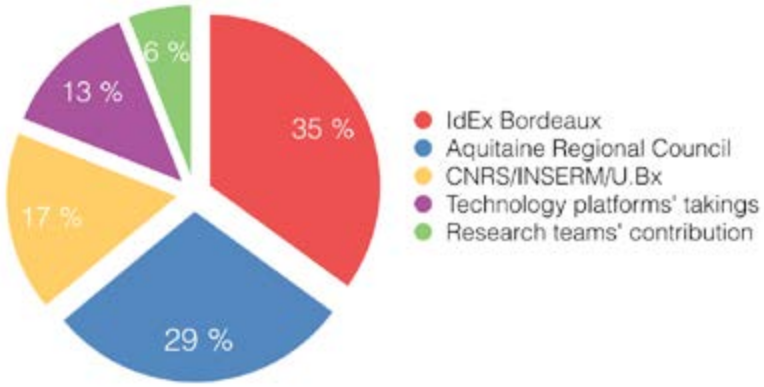
IECB research staff by gender & professional category



IECB's 2015 budget



Support services funding



The budget of the institute, which amounts to 10,1 millions euros including salaries, can be divided into two separate parts: the budget of the support services (UMS3033/US001) and the research teams' own resources.
The first one is mainly granted by the trustees (CNRS, Inserm, Université de Bordeaux), while the other comes from public and private research grants and contracts.

SUPPORT SERVICES (UMS3033 & US001)

Support services at IECB consist of staffs in administration and finance, infrastructure and maintenance, as well as 11 engineers and technicians dedicated to IECB's technology platforms. The support services unit UMS3033 & US001 is jointly funded by the CNRS, the Inserm and the Université de Bordeaux, and receives financial support from the Aquitaine Regional Council. Research teams also contribute to financing those general services.

Administration and finance

Administrative director
Sylvie DJIAN, IE, CNRS
Executive assistant officer
Claire-Hélène BIARD, AI, Inserm
Accounting and administration officers
Catherine DUPRAT, AJT, Inserm
Sandra LAVENANT, Tech., Univ. Bordeaux
Laurent KUBICKI, Tech., Inserm
Patricia MARTIN, Tech., Inserm
Amélie STOTZINGER, CDD, CNRS (IECB store)
Communication officer
Céline CHARRIER, CDD, CNRS
IT management
Gérald CANET, IE, Inserm
Eric ROUBIN, Tech., Inserm
Infrastructure officer
Patrice DUBEDAT, AJT, Univ. Bordeaux

Structural Biology facilities

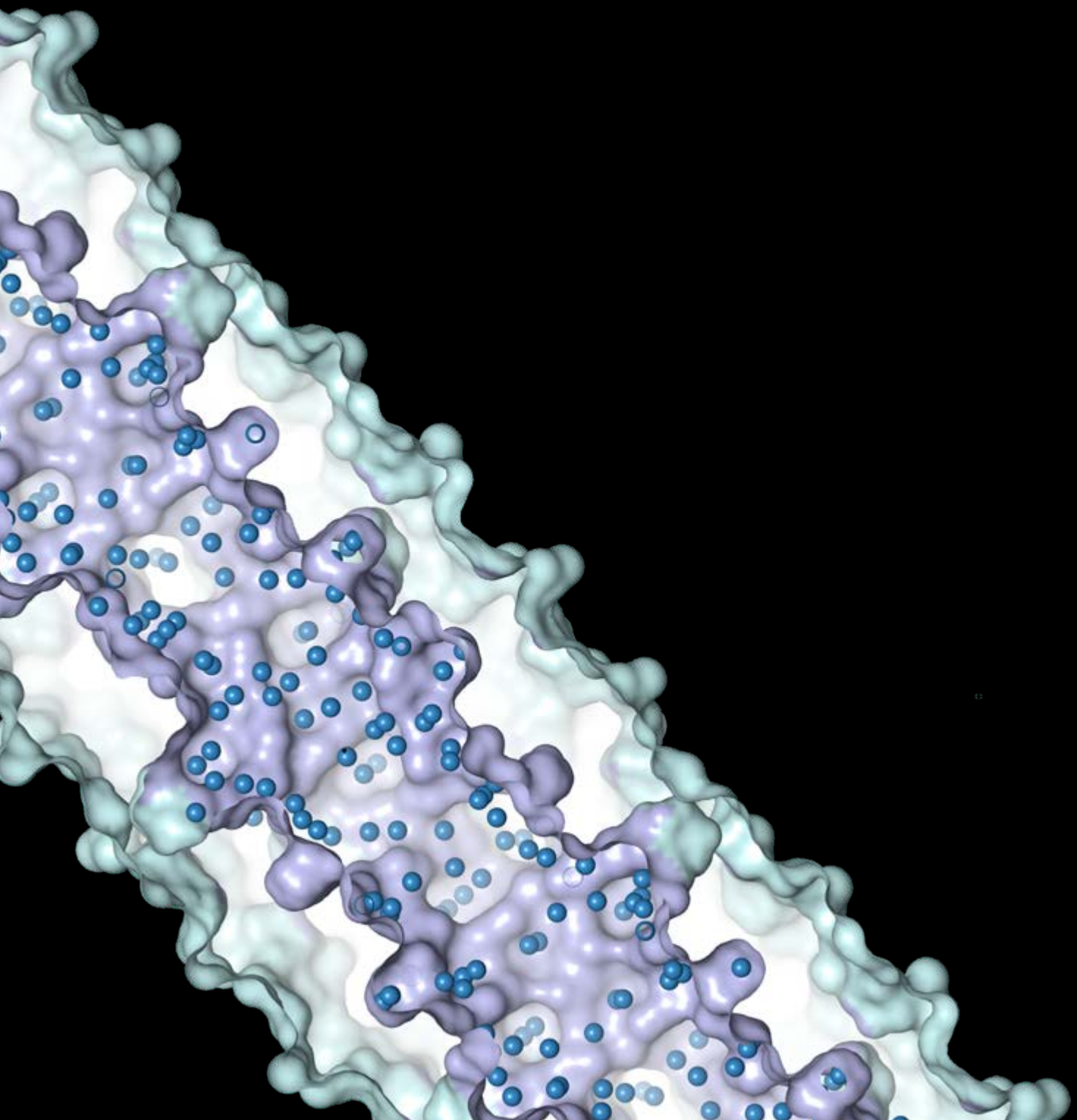
Head of structural biology facilities and crystallography engineer
Brice KAUFFMANN, IR, CNRS
NMR engineer
Estelle MORVAN, IE, CNRS
Mass spectrometry engineer
Frédéric ROSU, IR, CNRS
Mass spectrometry technician
Loïc KLINGER, Tech., Univ. Bordeaux
Crystallography engineer
Stéphane MASSIP, IE, Univ. Bordeaux
Surface plasmon resonance engineer
Laetitia MINDER, AI, Institut Bergonié
Quality approach
Julie KOWALSKI, Apprentice, Inserm

Analytical and preparative techniques facilities

Head of the analytical and preparative techniques facilities
Lionel BEAUREPAIRE, CDD IE, Inserm
High performance liquid chromatography assistant engineer
Yannick CHOLLET, AI, CNRS
Biochemistry and molecular biology engineer
Thierry DAKHLI, Tech., INSERM
Laundry
Myriam MEDERIC, AJT, Inserm

A collaboration of IECB teams led by the Guichard group (chemistry) and aided by the teams of Mackereth (structural biology) and Gabelica (mass spectrometry) have worked together to develop and characterize biomimetic helices with the ability to self-assemble into homogeneous protein like architectures in aqueous conditions. These results were published in 2015, in the journal Nature Chemistry.

Collie GW, Pulka-Ziach K, Lombardo CM, Fremaux J, Rosu F, Decossas M, Mauran L, Lambert O, Gabelica V, Mackereth CD, Guichard G. Shaping quaternary assemblies of water-soluble non-peptide helical foldamers by sequence manipulation. Nat Chem. 2015 Nov;7(11):871-8.



Research Teams & Output

Dr. Axel Innis

Senior Research Associate (CR1), INSERM

Axel Innis did his PhD in structural biology at the University of Cambridge, under the supervision of Prof. Sir Tom Blundell (1998-2002). He then joined the group of Dr. R. Sowdhamini at the National Centre for Biological Sciences in Bangalore as a visiting fellow (2002-2004), where he developed a computational method for identifying functionally important sites in proteins. Following his time in India, Dr. Innis joined the laboratory of Prof. Thomas A. Steitz at Yale University (2004-2012). There, he chose to tackle what was, at the time, a little-known form of translational control: the regulation of ribosomal protein synthesis by the nascent polypeptide. He joined IECB as a group leader in January 2013 and was recruited as an Insem senior research associate (CR-1) the same year.

Research team

Dr Britta SEIP Postdoctoral fellow (Université de Bordeaux)
Natacha PEREBASKINE ITA (Université Bordeaux)
Caroline SEEFELDT PhD student (Inserm)

This team is part of ARNA laboratory / Inserm U1212 - CNRS UMR5320

Translational Regulation of Gene Expression

Ribosomes are the large macromolecular complexes responsible for translating genetic information contained within a messenger RNA into protein in all living organisms. As part of the process of translation, nascent polypeptides transit through a long molecular cavity spanning the large subunit of the ribosome - known as the exit tunnel - before they are released into the cytoplasm or delivered to the protein translocation machinery.

Our lab uses combined biochemical, structural and computational approaches to study some of the key events that take place within the functional nano-environment of the exit tunnel, including:

1. Peptide bond formation, which is catalyzed by the peptidyl transferase center located at the tunnel entrance.
2. Nascent chain-mediated translational arrest, a process whereby signals encoded in certain nascent polypeptides termed arrest peptides bring protein synthesis to a halt.
3. Translation inhibition by antimicrobial peptides or antibiotics that target the exit tunnel and the peptidyl transferase center of the ribosome.

Peptide Bond formation

In order to understand how peptides or antibiotics inhibit peptide bond formation, we must first have a clear picture of the mechanism by which ribosomes catalyze peptidyl transfer. Peptide bond formation takes place within an active site that is composed primarily of RNA. Our high-resolution structures of the bacterial ribosome in complex with full-length tRNA substrates reveal a network of hydrogen bonds (or "proton wire") along which proton transfer could take place to assist catalysis (Polikanov et al., 2014). This has led us to propose a mechanism for peptide bond formation in which the ribosome together with the A- and P-tRNAs trigger the reaction by activating a water molecule (Fig. 1). As this proposed catalytic water is cut off from the bulk solvent by the N-terminus of ribosomal protein L27 in bacteria, we are currently investigating a possible regulatory role for this protein during translation.

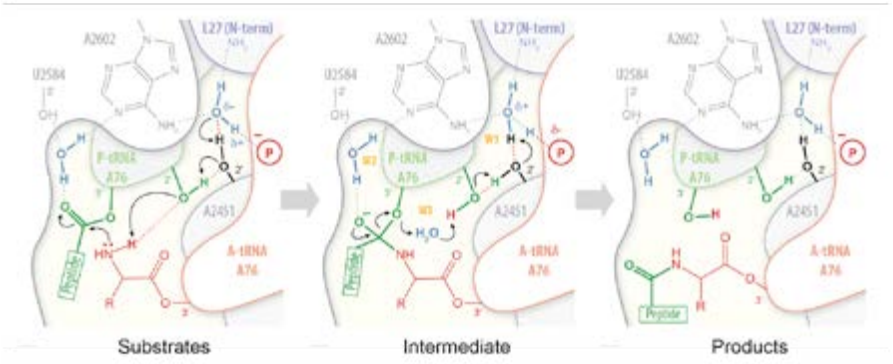


Figure 1 - Proton wire for peptide bond formation. In our proposed mechanism for peptide bond formation, nucleophilic attack is facilitated through the deprotonation of the α-amine of the incoming amino acid by a catalytic water molecule (W1) positioned at the extremity of a "proton wire" (Polikanov et al. 2014).

Nascent chain-mediated translational arrest

Translation inhibition by arrest peptides is critically dependent on their amino acid sequence, but often requires an additional low molecular weight ligand, such as a drug or a metabolite, to be sensed by the ribosome nascent chain complex. Thus, arrest peptides are used for metabolite-dependent gene regulation in both prokaryotes and eukaryotes. Biological processes that are regulated by arrest peptides in bacteria include the induction of erm resistance genes by macrolide antibiotics (e.g. erythromycin), the sensing of soluble tryptophan by a ribosome-associated TnaC peptide, targeting of the expression of the SecA pre-protein translocase to the cell membrane by the nascent SecM polypeptide, the expression of the YidC2 membrane insertase by the MifM peptide (Sohmen et al. 2015) and the regulation of SecDF2 in low-salinity environments by the arrest peptide VemP.

Biochemical and structural studies have shown that interactions between nascent peptides and the ribosome that induce translational arrest do so by impairing tRNA accommodation, peptide bond formation or peptide release. However, the arrest code dictating whether a given nascent peptide is prone to inhibiting its own synthesis is yet to be elucidated, the range of metabolites that can be sensed by the nascent peptide is unknown and the molecular bases of the arrest mechanism itself are only partially understood. As a result, we are developing new high-throughput tools to systematically address these issues on an unprecedented scale.

Antimicrobial peptides

The threat posed by multidrug-resistant bacteria presents a major public health challenge that requires immediate and coordinated action on a global scale. The bacterial ribosome is a major target for antibiotics, many of which bind to the exit tunnel. This includes drugs that inhibit peptide bond formation (e.g. chloramphenicol), as well as compounds that selectively interfere with the movement of the nascent peptide down the exit tunnel (e.g. erythromycin).

In addition, we have recently shown that proline-rich antimicrobial peptides (PrAMPs) produced by the host immune response of insects and mammals inhibit translation by blocking the exit tunnel and peptidyl transferase center of the ribosome (Seefeldt et al. 2015; Seefeldt et al. 2016) (Fig. 2). These natural compounds share structural similarities with arrest peptides, indicating that the latter could help steer the search for new peptide-based antimicrobials that are effective against antibiotic-resistant pathogens.

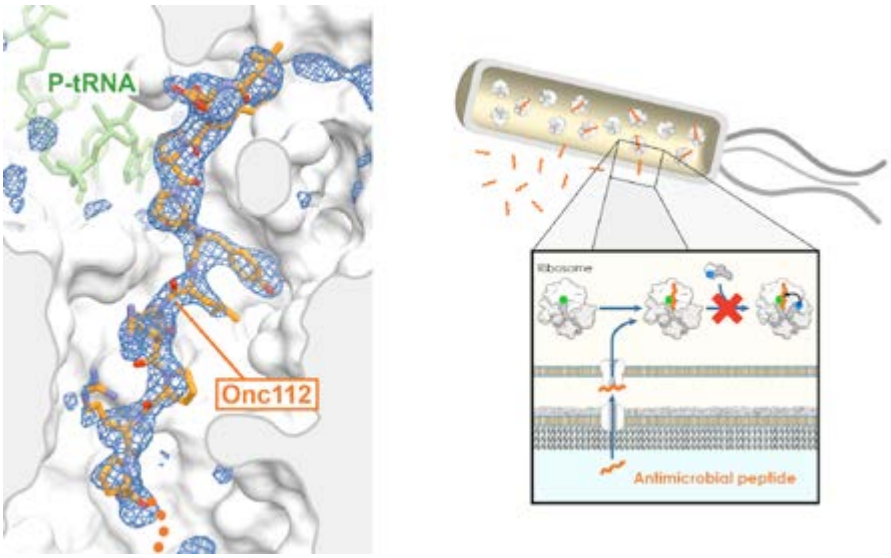


Figure 2 – Ribosome inhibition by antimicrobial peptides. The insect-derived proline-rich antimicrobial peptide Onc112 inhibits bacterial protein synthesis by blocking and destabilizing the translation initiation complex (Seefeldt et al. 2015). Other PrAMPs like Bac7, Metalnikowin or Pyrrhocoricin operate through a similar mechanism (Seefeldt et al. 2016).

Selected publications

Seefeldt, A.C., Graf, M., Nguyen, F., Pérébaskine, N., Arenz, S., Mardirossian, M., Scocchi, M., Wilson, D.N. †, Innis, C.A.† (2016). Structure of the mammalian antimicrobial peptide Bac7(1-16) bound within the exit tunnel of a bacterial ribosome. Nucleic Acids Res. 44, 2429-2438.

Seefeldt, A.C., Nguyen, F., Antunes, S., Pérébaskine, N., Graf, M., Arenz, S., Inampudi, K.K., Douat, C., Guichard, G., Wilson, D.N. †, Innis, C.A.† (2015). The proline-rich antimicrobial peptide Onc112 inhibits translation by blocking and destabilizing the initiation complex. Nat. Struct. Mol. Biol. 22, 470-475.

Sohmen D, Chiba S, Shimokawa-Chiba N, Innis CA, Berninghausen O, Beckmann R, Ito K, Wilson DN. (2015). Structure of the Bacillus subtilis 70S ribosome reveals the basis for species specific stalling. Nat. Commun. 6, 6941.

Polikanov, Y.S., Steitz, T.A.†, Innis, C.A.† (2014). A proton wire to couple aminoacyl-tRNA accommodation and peptide bond formation on the ribosome. Nat. Struct. Mol. Biol. 21, 787-793.

* Equal contribution † Corresponding author

Dr. Antoine Loquet
Senior Research Associate (CR1), 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. His current research concentrates on the structural investigation of molecular assemblies using Solid-State NMR.

Research team

Julie GEAN MUC (U. Bordeaux, IUT Perigueux)
Axelle GRÉLARD Research Engineer IR1 (CNRS)
Birgit HABENSTEIN Research Associate (CR2, CNRS)
Denis MARTINEZ Postdoctoral fellow (CNRS)
Ahmad SAAD PhD student (U. Bordeaux)
Mélanie BERBON Engineer (CNRS)

The team is part of the unit "Chimie et Biologie des Membranes et Nanoobjets" (CBMN), CNRS/ Université Bordeaux/UNITAB (UMR CNRS 5248)

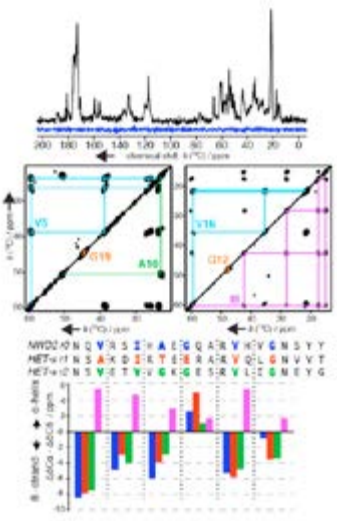
NMR of Molecular Assemblies

European Research Council

Self-assembly is a fundamental process by which individual subunits assemble into ordered macromolecular entities, such as filaments, fibrils, oligomers, tubes or nanomachines. In biology, protein assemblies are involved in crucial cellular processes, ranging from the propagation of neurological disorders to viral and bacterial infections. The group aims at investigating atomic structures, and assembly processes of such sophisticated assemblies. We develop and apply solid-state NMR to capture structural and dynamic details at the atomic scale. Our group is also involved in the production of large protein assemblies to solve their structures based on solid-state NMR methods. Molecular assemblies either involved in cellular processes or engineered by supramolecular chemistry constitute the current research activities.

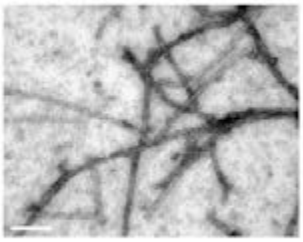
Study of an amyloid fold involved in signal transduction

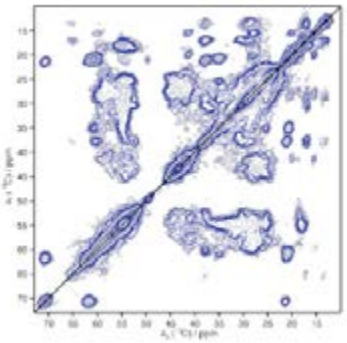
In the fungus Podospora anserina, the [Het-s] prion induces programmed cell death by activating the HET-S pore-forming protein. The HET-s β-solenoid prion fold serves as a template for converting the HET-S prion-forming domain into the same fold. This conversion, in turn, activates the HET-S pore-forming domain. The gene immediately adjacent to het-S en- codes NWD2, a Nod-like receptor (NLR) with an N-terminal motif similar to the elementary repeat unit of the β-solenoid fold. NLRs are immune receptors controlling cell death and host defense processes in animals, plants and fungi. We have proposed that, analogously to [Het-s], NWD2 can activate the HET-S pore-forming protein by converting its prion-forming region into the β-solenoid fold. Here, we analyze the ability of NWD2 to induce formation of the β-solenoid prion fold. We show that artificial NWD2 variants induce formation of the [Het-s] prion, specifically in presence of their cognate ligands. The N-terminal motif is responsible for this prion induction, and mutations predicted to affect the β-solenoid fold abolish templating activity. In vitro, the N-terminal motif assembles into infectious prion amyloids that display a structure resembling the β-solenoid fold. In vivo, the assembled form of the NWD2 N-terminal region activates the HET-S pore-forming protein. This study documenting the role of the β-solenoid fold in fungal NLR function further highlights the general importance of amyloid and prion-like signaling in immunity-related cell fate pathways.



Characterization of a novel cell death-inducing amyloid.

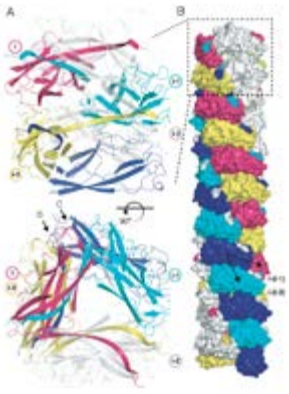
Recent findings have revealed the role of prion-like mechanisms in the control of host defense and programmed cell death cascades. In fungi, HET-S, a cell death-inducing protein containing a HeLo pore-forming domain, is activated through amyloid templating by a Nod-like receptor (NLR). Here we characterize the HELLP protein behaving analogously to HET-S and bearing a new type of N-terminal cell death-inducing domain termed HeLo-like (HELL) and a C-terminal regulatory amyloid motif known as PP. The gene encoding HELLP is part of a three-gene cluster also encoding a lipase (SBP) and a Nod-like receptor, both of which display the PP motif. The PP motif is similar to the RHIM amyloid motif directing formation of the RIP1/RIP3 necrosome in humans. The C-terminal region of HELLP, HELLP(215-278), encompassing the motif, allows prion propagation and assembles into amyloid fibrils, as demonstrated by X-ray diffraction and FTIR analyses. Solid-state NMR studies reveal a well-ordered local structure of the amyloid core residues and a primary sequence that is almost entirely arranged in a rigid conformation, and confirm a β-sheet structure in an assigned stretch of three amino acids. HELLP is activated by amyloid templating and displays membrane-targeting and cell death-inducing activity. HELLP targets the SBP lipase to the membrane, suggesting a synergy between HELLP and SBP in membrane dismantling. Remarkably, the HeLo-like domain of HELLP is homologous to the pore-forming domain of MLKL, the cell death-execution protein in necroptosis, revealing a transkingdom evolutionary relationship between amyloid-controlled fungal programmed cell death and mammalian necroptosis.





Structure determination of bacterial filamentous appendages

Our group is involved in the methodological development of new approaches based on solid-state NMR to solve 3D structures of complex biological assemblies. Notably, with Prof. Adam Lange at FMP Berlin, we have applied solid-state NMR to decipher the atomic architecture of the E. coli type 1 pilus. We described an approach for hybrid-structure determination that is based on data from solution-state NMR spectroscopy on the soluble subunit and solid-state NMR spectroscopy and STEM data on the asembled pilus. Our approach is based on iterative modeling driven by structural information extracted from different sources and provides a general tool to access pseudo atomic structures of protein assemblies with complex subunit folds. By using this methodology, we determined the local conformation of the FimA pilus subunit in the context of the assembled type 1 pilus, determined the exact helical pilus architecture, and elucidated the intermolecular interfaces contributing to pilus assembly and stability with atomic detail.



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Dr. Ivan Huc
Research Director (DR1), CNRS

Ivan Huc was born in Besançon, France, in 1969. He studied chemistry at the Ecole Normale Supérieure (Paris, France) and received his PhD in 1994 from the Univ. Pierre & Marie Curie (Paris) for research work carried out both at the Ecole Normale Supérieure and at the Massachusetts Institute of Technology (Cambridge, USA). He spent one year as a post-doc in Strasbourg Univ., then was offered a tenured CNRS researcher position and later obtained his habilitation there. Since 1998, he has been a group leader at the European Institute of Chemistry and Biology (Univ. of Bordeaux, France) where he holds a CNRS research director position. In 2008, he started to serve as co-director of IECB. His current research interests are foldamers and the biomimetic chemistry of peptides and nucleotides.

Research team

Dr. Yann FERRAND Senior Research Associate (CR1, CNRS)
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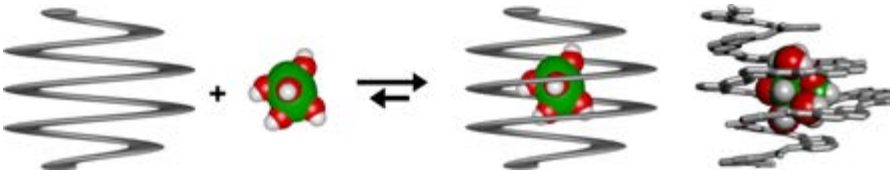
This team is part of the joint research unit "Chimie et Biologie des Membranes et Nanoobjets" (CBMN), CNRS/Univ. Bordeaux/IPB (UMR CNRS 5248)

Biomimetic Supramolecular Chemistry

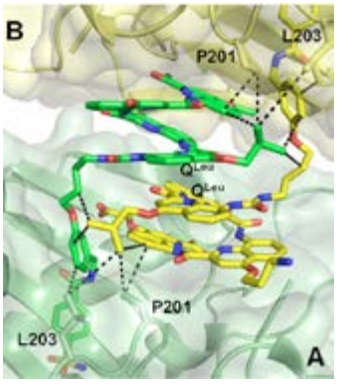
Foldamers – artificial folded molecular architectures – have shifted our knowledge of biopolymer folding in showing that molecular backbones chemically remote from those that nature uses are also able to adopt secondary and tertiary structures. Our group has developed several families of aromatic oligoamides which fold into exceptionally stable, predictable, and tunable conformations. Our current efforts aim at exploring how these aromatic oligoamides may mimic protein tertiary structures and functions, and nucleic acids hybridized architectures, and at investigating their molecular recognition properties and potential biological applications as, for example, ligands for G-quadruplex DNA or protein-protein interaction inhibitors.

Monosaccharide encapsulation

The group routinely prepares a number of heterocyclic amino acid monomers (quinolines, pyridines, naphthyridines, aza-anthracenes…) for the synthesis of aromatic amide foldamers. Monomers notably differ from one another in that they code for helices of various diameters. We have introduced the concept of molecular containers built from the folding of an oligomer into a helix whose diameter is large in the center and small at the ends, and investigated the diastereoselective recognition of chiral guests within these containers. This work recently culminated in the production of specific hosts for monosaccharides (Nat. Chem. 2015). We described the first crystal structures of host-guest complexes involving unsubstituted monosaccharides. Furthermore, these structures allowed to iteratively improve the receptors and reach unprecedented selectivity and atomic scale complementarity for the guests.



Foldamer-protein recognition



In a joint effort with biocrystallographers at CBMN (CNRS-Univ. Bordeaux, France), and biomolecular NMR specialist Dr. C. Mackereth at IECB, we identified a foldamer that interacts with a protein surface and characterized the structure of the protein-foldamer complex by single crystal x-ray diffraction (Angew. Chem. Int. Ed. 2014) and in solution (ChemBioChem 2016). We used carbonic anhydrase as a model protein. Foldamers were tethered to the protein surface through the covalent attachment of a nanomolar ligand of the protein active site and foldamer-protein interactions were screened by detecting induced circular dichroism, i.e. the emergence of a preferred foldamer helix handedness induced by interactions with chiral groups at the protein surface. The structure revealed an unexpected dimeric assembly mediated by foldamer-foldamer, foldamer-protein and protein-protein contacts. This ensemble of results represents a major milestone towards the design of medium-sized synthetic ligands for protein surface.

Nanosized foldamers

Until recently, the synthesis of very long helical aromatic amide foldamers was thought to be limited by steric hindrance associated with stable folded conformations in solution. We showed that this difficulty may be overcome by using pure reagents, relatively high concentrations, and long reaction times (Org. Lett. 2016). Careful identification and elimination of byproducts greatly improve chromatographic purification, giving access to pure products amenable to a segment-doubling synthesis of sequences composed of up to 96 monomers (ca 25 kDa). Compounds as long as 32 units could be prepared on a multigram scale. These results represent a great advance in the availability of foldamers of nanometer size. The physical properties of these compounds are being investigated, including their ability to transport electrons and their nanomechanical properties.

Disulfide bridged abiotic foldamer helices

Macrocyclization is a common approach to restrict the conformations available to an otherwise flexible molecular structure. In proteins macrocyclization through disulfide bridges between cysteines far apart in the primary sequence stabilizes folded conformations and contributes to resistance to proteolytic degradation. Disulfide bridge formation was investigated in helical aromatic oligoamide foldamers. Depending on the position of thiol-bearing side chains, exclusive intramolecular or intermolecular disulfide bridging may occur. The two processes are capable of self-sorting, presumably by dynamic exchange. We found that great stabilization of helical structures results, and that helix handedness communication emerges in macrocycles composed of two helices. These results provides an original example of long range conformational coupling that could be useful in synthetic molecular signaling systems and also a powerful tool to design elaborate multi-helical, tertiary-like abiotic architectures (Ang. Chem. Int. Ed. 2016, front cover).

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Dr. Gilles Guichard
Research Director (DR1), CNRS

Gilles Guichard graduated in chemistry from the Ecole Nationale Supérieure de Chimie in Toulouse (1991) and University of Montpellier (1992) in France. He received his PhD from the University Louis Pasteur in Strasbourg (1996), working on immune recognition of pseudopeptides and synthetic vaccines. Following post-doctoral research with Prof. Dieter Seebach at the ETH in Zürich (1997) in the field of β-peptide foldamers, 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 as a new group leader to the Institut Européen de Chimie et Biologie (IECB) in Bordeaux. His current research focuses on biomimetic chemistry of peptides, foldamer chemistry, self-assembly and biomolecular recognition.

Research team

Dr. Céline DOUAT Senior Research Associate (CR1, CNRS)
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Dr. Morgane PASCO Research Associate (CR2, CNRS)
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Dr. Vincent DIEMER Postdoctoral fellow (CNRS)
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Diane BÉCART PhD student (Université Bordeaux)
Johanne MBIANDA PhD student (Université Bordeaux)
Léonie CUSSOL PhD student (Université Bordeaux)

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

Peptidomimetic Chemistry

The ability of the polypeptide chain to fold correctly into well-ordered tertiary structures that can ultimately assemble into defined quaternary arrrangments is a major determinant of protein function. Multiple approaches, at the interface between biology, synthetic organic and polymer chemistries are currently being explored to elaborate synthetic systems with protein-like structures and functions. By using peptidomimetic chemistry, the general aims of our research are (i) to understand how to program molecules with the necessary information for self-ordering into complex and functional architectures, (ii) to create folded systems mimicking protein secondary and tertiary structure elements (e.g. helices), (iii) to study molecular recognition processes and to develop biomedical applications.

Our research program focuses on Peptidomimetic and Foldamer Chemistry and more specifically on aliphatic urea oligomers which adopt well defined and stable helical secondary structures. Over the last five years, the group has thoroughly explored the requirements for secondary structure formation, expanded the monomer repertoire and improved synthesis by generalizing solid-phase methods. The development of functional folded architectures has now become a major objective. Our early work in this direction was mainly dedicated to the design of cationic amphiphilic helices with antibacterial activities and was recently extended to sequences that interact with plasmid DNA (Highlight #1). The finding that oligourea foldamers can be interfaced with peptide helices is another feature of particular significance in the context of peptide and protein mimicry (Highlight #2). Finally, we have started to explore the possibility to design foldamer units for the precise construction of nanometer scale assemblies mimicking protein quaternary structures (Highlight#3).

2015 HIGHLIGHTS:

Highlight #1 : A Cell-Penetrating Foldamer for Intracellular Delivery of DNA

Peptide mimics based on artificial backbones may combine useful properties such as diminished susceptibility to degradation by proteases, high control over secondary structures, and a propensity to form assemblies in aqueous solution. Despite significant advances in foldamer chemistry, tailored delivery systems based on foldamer architectures, are curiously rare among non-viral technologies for transporting nucleic acids into cells. In this work, we sought to develop a urea-based cell-penetrating foldamer system for gene transfection that would enable endosomal escape and release of DNA into the cytoplasm. We prepared pH-responsive and bioreducible cell-penetrating foldamers (CPF) through covalent dimerization of a short (8-mer) amphipathic oligourea sequence bearing histidine-type units. This CPF was found to assemble with pDNA and to mediate efficient delivery of nucleic acids into the cell (Angew. Chem. Int. Ed. 2015).

Highlight #2 : Chimeric α-Peptide/Oligourea Helices

We have obtained very promising results trying to interface urea-based foldamers with α-peptides (Angew Chem Int Ed 2015 & C R Chimie 2016). The rationale was that the oligourea helix shares a number of features with the α-helix such as helix polarity and pitch. In this work (see Figure 1), we have investigated the ability of aliphatic oligoureas fused to short peptide segments to nucleate α-helical structures. We found that the resulting chimeras were fully helical in the solid state as well as in polar solvents, with as few as 2 (or 3) urea units sufficient to propagate an α-helical conformation in the fused peptide segment. The remarkable compatibility of α-peptide and oligourea backbones, along with the simplicity of the technology may suggest a general approach for the mimicry of peptide and protein helices for various applications.

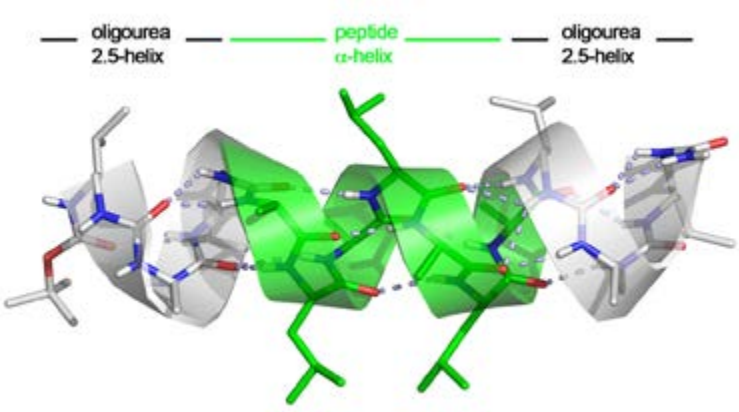

Fig. 1. Crystal structure of a α-helix (green) stabilized by two short adjacent accessory foldamers (grey).

Highlight #3 : Self-assembly of Amphiphilic Non-peptide Helical Foldamers

Taking inspiration from protein tertiary and quaternary structures, we have successfully transposed folding and assembly processes to artificial (non-peptide) molecular chains to create nanostructures with unusual shapes (e.g. bundles or nanotubular assemblies) in aqueous conditions (Nature Chem, 2015 & Chem Commun 2016). Four high-resolution crystal structures of unique foldamer quaternary arrangements have been described, supported by high-field NMR, electron microscopy and additional solution studies (Figure 2). The sequences of these oligomers were designed to contain a certain proportion of residues with polar and nonpolar side chains which depending on their arrangement at the surface of the helix determine how the helices self-assemble in water. Similar to soluble proteins, the hydrophobic effect (which leads to the burial of nonpolar side chains) is predominant. Due to (i) the simplicity of the design hypothesis, (ii) the small size of helical components and (iii) the tunability of the reported assemblies, this approach could be implemented for the creation of structures with a wider range of topologies, functional properties and, consequently, applications.

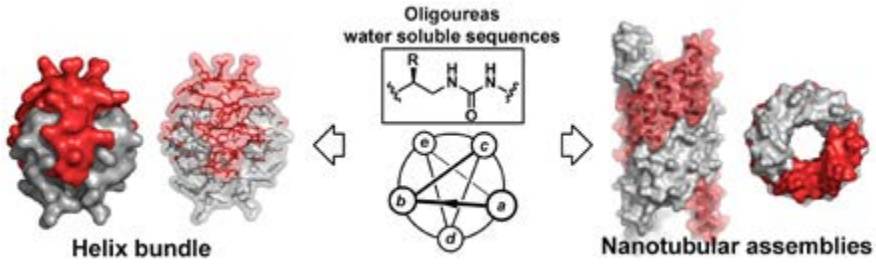

Fig. 2. Assemblies obtained in aqueous conditions from amphiphilic oligourea sequences.

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Dr. Élisabeth Garanger
Research Associate (CR2) CNRS

Trained as a chemist, Elisabeth Garanger graduated in 2001 as a Chemical Engineer from ENSC Clermont-Ferrand and obtained simultaneously a Master's degree in Biological Organic Chemistry. In 2005, she received her PhD in Chemistry and Biology from the University of Grenoble achieving a comprehensive study on peptide-based nanocarriers targeting tumors and their associated neoangiogenesis under the supervision of Profs. P. Dumy and M.-C. Favrot. She then joined the Center for Molecular Imaging Research (Massachusetts General Hospital, Harvard Medical School, Boston, USA) as a post-doctoral fellow in the group of Prof. L. Josephson and designed contrast agents for multimodal molecular imaging. In 2009, she joined the group of Prof. S. Lecommandoux at LCPO to work on self-assembled nanoparticles from amphiphilic block copolymers for biomedical applications, namely cancer theranostics. She was appointed as a junior group leader at IECB in 2010 and as a junior researcher at CNRS in 2012.

Research team

Rosine PETITDEMANGE PhD student (Université Bordeaux)
Laura RODRIGUES PhD student (Université Bordeaux)
Léna GUYON Master 2 Student (ENSCBP Bordeaux)
Sarah FONTAINE Master Student (Albert-Ludwigs University Freiburg)

This team is part of the unit "Laboratoire de Chimie des Polymères Organiques" (LCPO) UMR5629 CNRS, Université Bordeaux, IPB

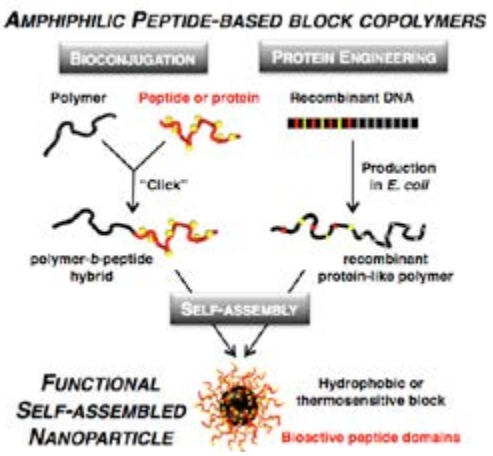
Self-Assemblies from Chimeric Polymer-Peptide Materials

Our main objective is the production of innovative polymer-based materials fulfilling prerequisites of precision, functionality and sustainability. We particularly focus on well-defined polymer materials featuring self-assembly and bioactivity properties encoded at the molecular level using two distinct synthetic approaches. Amphiphilic molecular chimeras featuring a synthetic polymer block conjugated to a peptide segment are chemically synthesized, while recombinant DNA and protein engineering techniques are used to produce recombinant polymers based on elastin motifs. Self-assembly mechanisms are studied and biological activities assessed with the ultimate goal of preparing biofunctional nanomaterials. This project is developed in relation with the LCPO team "Polymer Self-Assembly & Life Sciences" headed by Prof. S. Lecommandoux.

The design of functional self-assembled materials is currently a major challenge of micro- and nano-technologies and concerns domains as broad as health, communication and energy. Synthetic block copolymers possess tremendous self-assembling propensities that hence prompted their use for the preparation of self-assembled nanoobjects for various applications. However, in the specific field of biomimetic nanotechnologies, despite the huge number of chain lengths, sizes, architectures and chemical characters available, most synthetic polymers are inherently devoid of biological activity. This translates into a weak diversity of nanomaterials obtained from solely synthetic block copolymers as compared to highly complex and diverse natural self-assembled structures (e.g. proteins, ribosomes, molecular motors, viruses) obtained from natural biopolymers. Conversely, self-assembly of peptides and proteins, that are extraordinarily rich in terms of secondary/tertiary structures and biological functions, is sometimes difficult to control by synthetic chemists. One of today's consensuses thus relies on the association of natural biopolymers with synthetic polymer blocks at the molecular level in order to integrate the advantages of both materials and overcome the limitations inherent to each one separately. Towards this goal, our group is investigating two different approaches to access biofunctional precision block copolymers:

i) a synthetic approach involving the conjugation of functional peptides with synthetic polymers leading to amphiphilic polymer-b-peptide molecular chimera,

ii) a recombinant approach based on recombinant DNA and protein engineering technologies to produce amphiphilic biofunctional recombinant protein-like polymers.

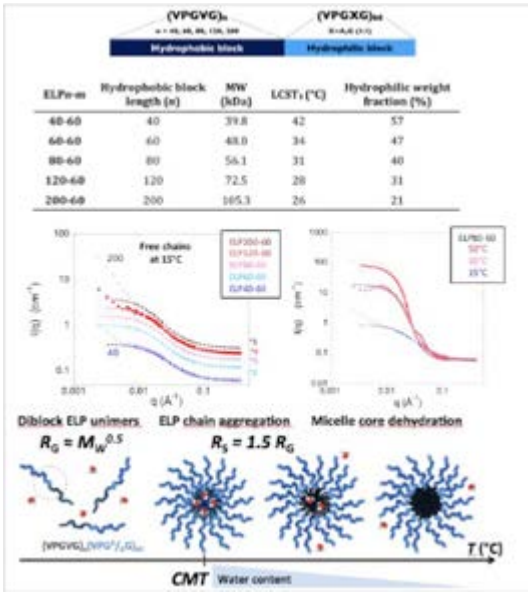


While our work in the past years had mainly focused on the study of amphiphilic polymer-b-peptide molecular chimera, our activities transitioned smoothly in the past year to the study of recombinant protein-like polymers.
Recombinant DNA and protein engineering techniques constitue an attractive alternative to synthetic polymerization methods for accessing monodisperse macromolecules

with a perfectly defined primary structure, namely a defined monomer sequence, chain length and therefore molecular weight. Control of these parameters is essential to govern the molecular, supramolecular and macroscopic properties of a polymer as well as a prerequisite for the establishment of structure-property relationships. Developed in the 70's, these techniques have greatly benefited from advances in molecular biology over the past 40 years. They are currently widely used in research laboratories, biotech companies and pharmaceutical industries to produce recombinant proteins. Our group has started to explore these techniques to produce precision protein-like polymers based on elastin motifs. Elastin-like polypeptides (ELPs) are biopolymers of (-Val-Pro-Gly-Xaa-Gly) pentapeptides (the guest residue Xaa being any amino acid other than Pro). These are characterized by a lower critical solubility temperature (LCST) which constitutes a major advantage for their purification from cell lysates as well as for the control their self-assembly.

Self-assembly study of diblock ELPs

To efficiently start working on this strategy in which she had no previous experience, the GL has initiated a collaboration with A. Chilkoti from Duke University, an internationally established scientist In the design and applications of ELPs. In this first project, we have studied the behavior and temperature-triggered self-assembly of a series of diblock ELPs with the goal of elucidating the mechanism of their self-assembly into nano-meter-sized particles. Diblock ELPs were designed to contain a hydrophilic ELP block of fixed size at the C-terminal end ((VPGXG)60, X being alternatively A or G) and a more hydrophobic (VPGVG)n block of variable length (n= 40-200) at the N-terminal end so as to cover a range of hydrophilic weight fractions from 21 to 57%. Aqueous solutions of diblock ELPs were studied below and above their critical micellar temperature (CMT at which the hydrophobic block aggregates) by multi-angle light scattering and small-angle neutron scattering techniques. Below the CMT, the radius of gyration of soluble ELP chains was found to follow a power law as a function of molecular weight with an exponent value close to 0.5 that is characteristic of Gaussian coil conformations. As the temperature reaches the CMT, attractive interactions between the more hydrophobic block of diblock ELP chains leads to the self-assembly of monodisperse spherical micelles at thermodynamic equilibrium. Above the CMT, micelles were found to expel water molecules from their core whose densification was evidenced by the monotonic increase in the light and neutron scattering intensities as a function of temperature. The behaviors of these different diblock ELPs in solution and as self-assembled nanoparticles above the CMT following universal experimental scaling laws make them analogous to synthetic amphiphilic diblock copolymers (star-like vs. crew-cut micelle models). These studies shed light on the important role of water in the thermal behavior of these thermally-responsive self-assembling diblock.



Chemoselective post-modifications of ELPs

With the goal of performing "post-polymerization modifications" of ELP backbones to introduce new functionalities and properties, we have started a project on the production of methionine-containing ELPs and their chemoselective alkylation. Involving the nucleophilic thioether group of the methionine side chain under acidic conditions, this reaction has recently gained significant interest as it shows full selectivity with respect to the primary amines of the lysine side chain and of the N-terminal end. Different chemical groups have already been attached onto an ELP backbone and showed that the LCST of the ELP can be fine tuned by post-polymerization alkylation.

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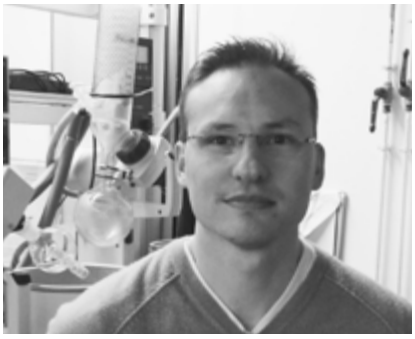


Dr. Frédéric Friscourt
Junior Chair of Excellence, Université Bordeaux

Frédéric Friscourt received his PhD from the University of Glasgow, UK in 2009, under the guidance of Prof. Pavel Kočovský, on the development of novel chiral ligands for enantioselective catalysis. He then joined the group of Prof. Geert-Jan 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 and synthesis of bioorthogonal 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. His current research focuses on using organic chemistry to develop novel tools that can probe the influence of glycans in the brain, notably in neurodegenerative diseases.

Research team

Dr. Jürgen SCHULZ Research Engineer (IR2) (CNRS)
Dr. Meriem SMADHI Postdoctoral fellow (Université Bordeaux)
Camille FAVRE PhD Student (Université Bordeaux)
Lucie de CREMOUX IUT Student (Université Paris Sud)

This team is part of the "Institut de Neurosciences Cognitives et Intégratives d'Aquitaine" (INCIA), CNRS/Université Bordeaux (UMR5287)

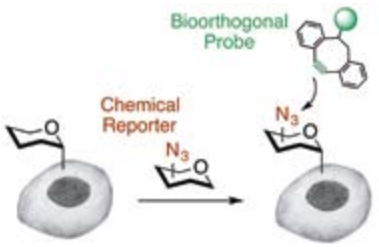
Chemical Neuroglycobiology

Glycans are chains of monosaccharides that are covalently linked to cell surface proteins and lipids. They have been recognized as key participants in cell-cell communications and for instance, in the brain, are crucial mediators in neurite outgrowth, synapse formation and plasticity. From a pathological point of view, changes in the neuro-glycome of cells are associated with developmental disorders, can mark the onset of glioma and neuro-inflammation. Despite these intriguing observations, the molecular mechanisms by which these complex carbohydrates influence neural cells are not well understood due to a lack of suitable biochemical methods. We aim at unravelling the functional roles of glycans in the nervous system by exploiting organic chemistry to develop novel tools that can probe glycans in the brain.

Imaging glycans: a daunting task

Although protein tracking in living cells has become routine experiments in cell biology laboratories thanks to the utilization of genetic reporters (i.e., fusion proteins such as GFP), glycans are, unfortunately, not amenable to these imaging techniques, as they are not directly encoded in the genome. Instead, complex glycans are the results of stepwise additions and abstractions of monosaccharides by various enzymes such as glycosyltransferases and glycosidases.
Previous efforts towards glycans imaging have been relying on the use of lectins (glycan-binding proteins) and monoclonal antibodies (mAbs). While, lectins have been used extensively for the detection of both monosaccharides and oligosaccharides, they typically have low affinity for their glycan epitopes. mAbs are viable options but due to their high molecular weight, they are often too large to cross the blood-brain barrier, significantly limiting their utilization for non-invasive in vivo brain imaging.

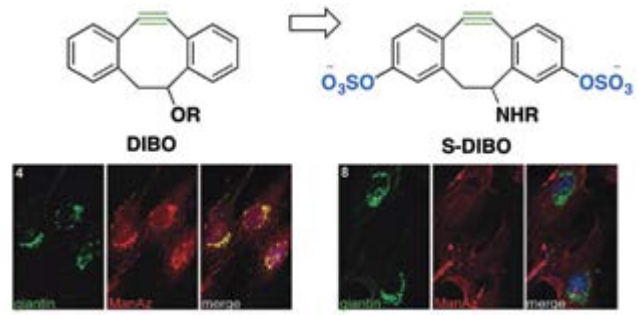
As an emerging alternative, the bioorthogonal chemical reporter strategy, which elegantly combines the use of metabolically labeled azido sugars and highly reactive cyclooctyne probes, through strain-promoted alkyne azide cycloadditions (SPAAC), is a versatile technology for labeling and visualizing glycans. However, cyclooctyne probes are often highly hydrophobic, which can promote their sequestration by membranes and nonspecific binding to serum proteins, thereby increasing background signal.



To address these difficulties, we have developed two novel dibenzocyclooctynes: 1) a highly polar O-sulphated-dibenzocyclooctyne (S-DIBO) and 2) a fluorogenic cyclooctyne (Fl-DIBO) that generate strongly fluorescent labeled products.

S-DIBO: the first water soluble cyclooctyne probe

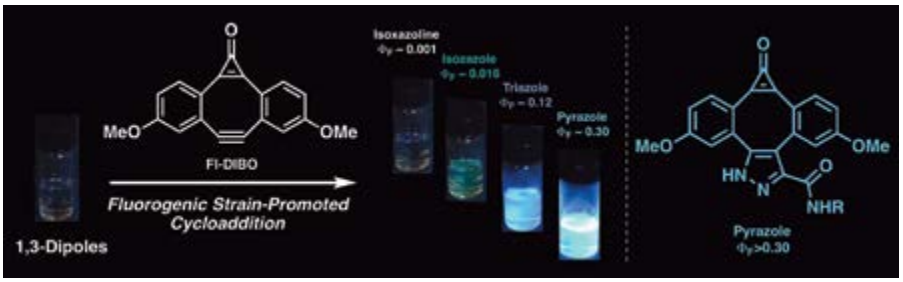
Sulfate esters of phenols have excellent stabilities under moderately acidic and basic conditions and are found in nature as post-translational modifications of tyrosine. Consequently, we designed an efficient synthetic route for introducing O-sulfate functionalities onto the aromatic rings of the parent dibenzocyclooctyne probe (DIBO). The novel highly polar sulfated dibenzocyclooctynylamide probe (S-DIBO) (J. Am. Chem. Soc. 2012) was found to be fully soluble in aqueous medium, making its utilization optimum for biological applications. While employing biotinylated S-DIBO for the labeling of azido-containing glycoconjugates in living cells, we uncovered that the substitution pattern of the dibenzylcyclooctyne probes can strongly influence their subcellular location. In particular, using an elegant confocal microscopic study, we showed that DIBO can enter cells, thereby labeling intra- and extracellular azido-modified glycoconjugates, whereas S-DIBO cannot pass the cell membrane and therefore is ideally suited for selective labeling of cell surface molecules.



Human fibroblasts labeling experiment. Green: Golgi marker; Red: Azido-glycans labeled with DIBO/S-DIBO; Blue: Nucleus staining

Fl-DIBO: a fluorogenic cyclooctyne probe

Due to the slow rates of strain-promoted alkyne-azide cycloadditions, large amount of probes is often required to achieve sufficient labeling of azido-glycans in living cells. Consequently, probe washouts are necessary for increasing the signal to background ratio. Fluorogenic bioorthogonal reactions, in which non- or weakly fluorescent reagents produce highly fluorescent products, offer therefore the unique opportunity to label biomolecules without the need for probe washout. We have recently developed a fluorogenic cyclooctyne Fl-DIBO (J. Am. Chem. Soc. 2012), which upon reaction with an azide, can produce a cycloaddition product that is more than 1000-fold brighter compared to the unreacted reagent. Interestingly, where cycloadditions of Fl-DIBO with other dipoles such as nitrones, nitrile oxides or di-substituted diazo reagents mostly generate quenched cycloadducts, reactions of mono-substituted diazo compounds with Fl-DIBO give highly fluorescent 1H-pyrazoles (10,000 times brighter than Fl-DIBO) (Chem. Eur. J 2015).



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Dr. Cameron Mackereth

Senior Research Associate (CR1), INSERM

Cameron Mackereth began his scientific training at the University of Waterloo (Canada) where he completed a degree in Biochemistry in 1996. His Ph.D. at the University of British Columbia (Canada) under the supervision of Dr. Lawrence McIntosh dealt with the structural investigation of a domain common to several protein families involved in transcription and cellular signaling. He continued to use nuclear magnetic resonance (NMR) spectroscopy at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, where he looked at domain arrangements of large protein-RNA splicing complexes in the group of Dr. Michael Sattler. In the fall of 2007, he joined the IECB as a group leader. In 2011 he was also recruited as a senior research associate within the French National Institute of Health and Medical Research (Inserm).

Research team

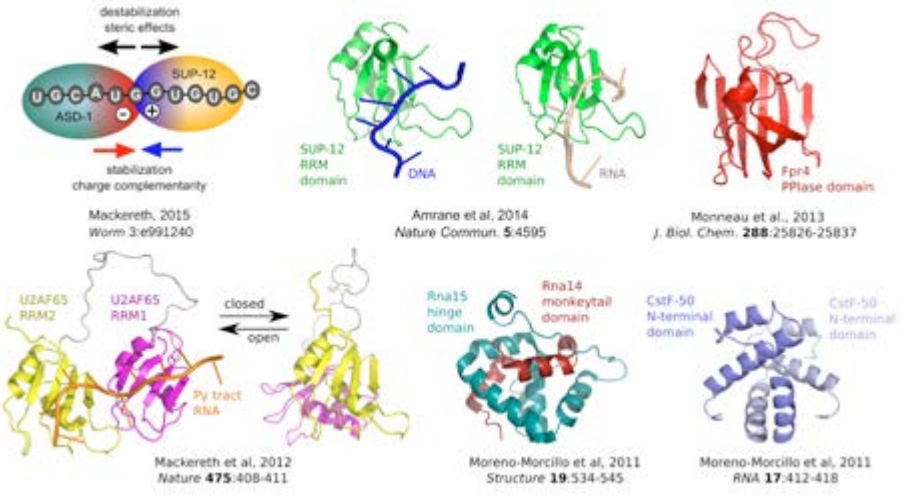
Dr. Pierre BONNAFOUS Associate professor, MdC (Univ. Bordeaux)
Sabrina ROUSSEAU, Engineer, IE (Inserm)
Dr. Xiaoqian XU, Postdoctoral fellow (ANR/Aquitaine Region/Inserm)
Dr. Kashyap MARUTHI, Postdoctoral fellow (ANR/Inserm)
Heddy SOUFARI PhD student (Inserm/Aquitaine Region)

This team is part of the unit "ARN : Regulation Naturelle et Artificielle" (ARNA), INSERM U869 (now U1212 since Jan 2016).

NMR Spectroscopy of Protein-Nucleic Acid Complexes

The lab studies molecular details of large protein-nucleic acid macromolecules and other complexes using a variety of new NMR techniques as well as established biophysical approaches. For large complexes, we combine small angle neutron or X-ray scattering (SANS/SAXS), NMR paramagnetic spin labeling to acquire information on long-range contacts, as well as in vitro mutational analysis and other binding assays. Equally important to the lab is the traditional strength of NMR as a tool to probe the dynamics of biological samples, the characterization of transient interactions, and the possibility to look at structures that exhibit a significant amount of unstructured elements.

Molecular basis of alternative splicing in muscle and neuron development.
A main goal of the group is to determine the atomic basis by which splicing factors have a selectivity for specific mRNA, and to also look at how they regulate splicing patterns of key genes during tissue development. We use this information to design strategic tools for in vivo work, to predict functional interactions with other splicing proteins, and to understand the role of abnormal splicing in disease. Recent studies include the investigation of the alternative splicing factor SUP-12 that functions in a muscle-specific manner to produce an isoform of the fibroblast growth factor receptor (egl-15). In this study, as well as several others currently in progress, we rely on the model organism C. elegans as a powerful tool to correlate in vitro findings with splicing observation in a live multi-cellular organism. This work involves close collaboration with the group of Denis Dupuy, also at the IECB. We have used NMR spectroscopy to determine the atomic structure of the RNA-binding domain from SUP-12 in complex with a high affinity RNA ligand derived from the egl-15 gene. The atomic details were used to design and test precise mutants in the protein and also the target pre-mRNA, and to look at the consequence of these mutations with in vivo fluorescent mini-gene reporters.



Complexes involved in pre-mRNA 3' processing

In collaboration with the lab of S. Fribourg at IECB, we are investigating the structure and dynamics of the yeast cleavage/polyadenylation factor IA (CF IA) and metazoan cleavage stimulation factor (CstF) complexes, both involved in the removal of the terminal sequence of the pre-mRNA prior to the addition of multiple adenosine to form the poly(A) tail. The current research in the laboratory deals with the structural characterization of the complete set of folded domains involved in protein-protein and protein-RNA interactions within CstF and CF IA, as a step toward looking at the architecture of the larger assembled complexes. We have recently used NMR spectroscopy to determine the atomic details of a new domain found in yeast Pcf11. The data indicate that this small but important domain, required for normal growth in yeast, is composed of three helical regions that directly follows the previously characterized N-terminal CID domain involved in RNA-binding and interaction with the large subunit of RNA polymerase II. We are continuing our investigations with additional and previously uncharacterized domains from the CF IA complex.

Solution studies of synthetic capsules designed to selectively bind fructose

Sugars such as glucose, fructose, mannose or galactose exist in different forms in solution, and are particularly difficult to discriminate. In collaboration with the group of Ivan Huc at IECB we have investigated modular artificial strands that are able to fold into well-defined conformations, and these foldamers can be designed to form cavities complementary to small molecules such as monosaccharides. To complement other analytical techniques in we have used NMR spectroscopy to obtain high resolution structural information of one such foldamer capsule able to bind to a single conformation of fructose. The incorporation of NMR tricks originally designed for biomolecular study has made this solution structure possible, and the resulting atomic information highlights the specific formation of hydrogen-bonds and molecular shape recognition crucial for fructose recognition by the capsule.

A new trick for oligoureas

We have added our expertise in solution NMR spectroscopy to a project from the group of Gilles Guichard (also at the IECB) in order to help in the characterization of a series of oligoureas that form different stable structures. The oligourea molecule resembles a peptide except for the nature of the backbone which has an urea linkage between each residue to replace the normal amide. The resulting polymer can form a stable regular helix with sidechains protruding on five sides. With a small change in the sequence to alter the pattern of hydrophobic and hydrophilic side chains, it was found that a certain set of oligoureas can exist as either a hexamer bundle or an extended channel. The extra properties of pH-sensitivity and, for the hexamer, a central hydrophobic cavity suggest that these oligoureas will have many interesting future uses.

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Dr. Jean-Louis Mergny

Research Director (DR1), INSERM

Jean-Louis Mergny graduated from Ecole Normale Supérieure de la rue d'Ulm (Paris) and got his PhD in Pharmacology (University Paris VI) in 1991 under the supervision of T. Garestier & M. Rougée (Triple-helices: spectroscopic studies). He went for a postdoctoral position in Basel, Switzerland with W. Gehring (Biozentrum). Afterwards he was hired by INSERM in 1993 in the Muséum National d'Histoire Naturelle, where he worked mainly on nucleic acids structures from a biophysical point of view. He was promoted Research Director in 2002. JL Mergny joined the IECB at the end of 2009 and became IECB director in January 2015.

Research team

Dr. Anne BOURDONCLE Teaching Assistant (MdC, Université Bordeaux)
Dr. Gilmar SALGADO Teaching Assistant (MdC, Université Bordeaux)
Dr. Carmelo DI PRIMO Senior Research Associate (CR1, Inserm)
Dr. Samir AMRANE Research Associate (CR2, Inserm)
Aurore GUÉDIN Tech. assistant (AI, Inserm)
Marion PETITET Tech. assistant (Inserm/ Aquitaine Region)
Dr. Souheila AMOR Postdoctoral fellow (Fondation ARC)
Dr. Aurore DE RACHE Postdoctoral fellow (ANR)
Dr. Vasantha KUMAR Postdoctoral fellow (ANR)
Dr. Eric LARGY Postdoctoral fellow (ANR)
Dr. Oscar MENDOZA Postdoctoral fellow (Fondation ARC)
Amina BEDRAT PhD student (Université Bordeaux)
Nassima GUEDDOUDA PhD student (Université Bordeaux)
William PALAU PhD student (Université Bordeaux)
Adrien BOUSSEBAYLE M2 student (Université Bordeaux)
Stefaniia IVASHCHENKO M2 student (Université Bordeaux)
Caitlin MIRON Visiting PhD student (Queens University, Canada)
Pr. Liliya YATSUNYK Visiting Professor (Swarthmre College, PA, USA)

This team is part of the unit "ARN : Regulation Naturelle et Artificielle" (ARNA), INSERM U869 (now U1212 since Jan 2016).

Unusual Nucleic Acid Structures

Nucleic acids are prone to structural polymorphism: in addition to the well-known double helix, a number of alternative structures may be formed. However, most non-canonical conformations are stable only under non-physiological conditions and have been considered as simple curiosities. Among these oddities, a family of nucleic acid secondary structures known as G-quadruplexes (G4) has emerged as more than a novelty. These structures can be formed by certain guanine-rich sequences and are stabilized by G-quartets. G-quadruplexes can be stable under physiological conditions and the evidence for quadruplex formation in vivo is now compelling. Our goals are to i) to apply these oddities to nanotechnologies and biotechnologies; ii) to understand their structures, rules of recognition and formation; iii) to conceive new biochemical, bioinformatics, and physico-chemical tools and finally iv) to apply G4-based strategies to various pathologies.

Our objectives are to answer the following questions:

Where and when ?

High-throughput sequencing methods and whole genome approaches are now being used to generate massive amounts of sequence data. Sometimes, statistical analyses point out the potential role of G-rich DNA or RNA motifs. However, the answer to the seemingly simple question "Is my sequence G4-prone?", based on somewhat flawed or oversimplified search algorithms, is often inaccurate. For example, we previously demonstrated that stable quadruplexes may be formed by sequences that escape the consensus used for bioinformatics. We have built a new prediction algorithm (G4Hunter, recently published in Nucleic Acids Research) that we are experimentally testing first on DNA. We validated an experimental procedure to demonstrate G4 formation for a large set of sequences.

G-quadruplexes: Friends or foes?

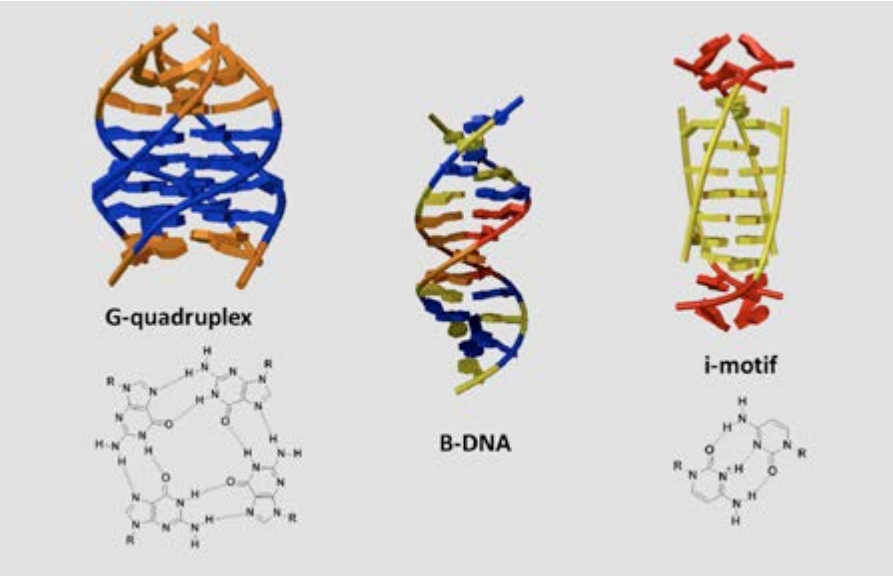
Comparison of sequencing data with theoretical sequence distributions suggests that there is a selection against G-quadruplex prone sequences in the genome, probably as they pose real problems during replication or transcription and generate genomic instability (see below). Nevertheless, "G4-hot spots" have been found in certain regions of the genome: in telomeres, in repetitive sequences such as mini and microsatellite DNAs, in promoter regions, and in first exons of mRNAs. There might be a specific positive role for these sequences that compensates for the general selection against G4 forming sequences. Our goals are to understand the factors that modulate these effects. A number of proteins that interact with these unusual structures have been identified, including DNA binding proteins, helicases, and nucleases. We are currently developing a fluorescent-based assay to follow the activity of helicases in real time (Mendoza, Nucleic Acids Res. 2015).

G-quadruplex ligands: Treats or tricks?

One may achieve structure-specific rather than sequence-specific recognition of DNA. Because of their particular geometric configuration and electrostatic potential, G-quadruplexes may indeed specifically accommodate small artificial ligands, such as planar molecules, and an impressive number of candidates have been evaluated. Together with chemists we successfully identified a variety of G4 ligands and we wish to improve and functionalize these compounds, analyse their biological effects, and ultimately find new classes of anti-proliferative agents with anticancer properties.

Beyond biology

Quadruplexes may well be biologically relevant, but they could also be used for various applications that are disconnected from cells. DNA is an attractive material for nanotechnologies because of its self-assembly properties. The ability of nucleic acids to self-assemble into a variety of nanostructures and nanomachines is being exploited by a growing number of researchers. Extremely sophisticated structures and nanodevices may be constructed with DNA. We believe that quadruplex structures offer interesting new possibilities and we have demonstrated that quadruplexes can be incorporated into nanodevices.



DNA double-helix (center); G-quadruplex and corresponding G-quartet (left) and i-motif and C.C+ base pair (right)

Selected publications

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Dr. Derek McCusker

Senior Research Associate (CR1), CNRS

Derek McCusker studied Immunology at Glasgow University and focused on the role of the proteasome in antigen presentation in Prof. John Trowsdale's lab at Cancer Research UK during his thesis. During postdoctoral work with Dr. Robert Arkowitz at the Laboratory of Molecular Biology in Cambridge, he became interested in the control of cell growth. He then joined Prof. Douglas Kellogg's group at the University of California, Santa Cruz, where he investigated how cells coordinate cell growth and cell division, a key problem in cell biology. He was recruited by CNRS in September 2009 and joined IECB as a group leader. The group uses interdisciplinary approaches to study how cell growth is coordinated with progression through the cell cycle.

Research team

Aurélie MASSONI-LAPORTE Assistant Engineer (AI, CNRS)
Dr. Peter RAPALI Postdoctoral fellow (Aquitaine Region)
Dr. Elodie SARTOREL Postdoctoral Fellow (CNRS)
Dr. Çaner ÜNLU Postdoctoral Fellow (CNRS)
Julien MECA PhD student (University of Bordeaux)

This team is part of the unit "Institut de Biochimie et Genetique Cellulaire" (IBGC), CNRS UMR 5095

Dynamics of Cell Growth & Cell Division

Cells grow, duplicate their genome and divide via a series of events collectively termed the cell cycle. Coordination between the cell cycle machinery and proteins that regulate cell growth ensure the fidelity of cell division; however, the underlying mechanisms are unclear. Failure of these control mechanisms has been directly linked to tumour formation. The goal of the Cell Growth and Division Laboratory is to understand how cell growth is controlled and how growth is coordinated with cell cycle progression. We address these fundamental questions using cutting edge interdisciplinary approaches.

Robust polarity establishment via an endocytosis-based cortical corralling mechanism

The size and shape that cells adopt is governed in part by the rate and location of plasma membrane growth. This growth is largely driven by exocytic vesicle fusion, while endocytosis removes membrane. The relative rates of these two processes therefore contributes to cell size. Moreover, the spatial organiaztion of these pathways contributes to cell shape and function. In budding yeast, endocytic and exocytic vesicles localize to growth sites in the bud. Given the antagonistic relationship of these processes, this arrangement could be incompatible with the membrane efflux required for polarized growth of the bud. Our previous work demonstrated that endocytic vesicles form a ring around exocytic sites at the cortex. To address whether this might facilitate the formation of a stable polarity axis that contributes to polarized growth, we studied the dynamics of endo- and exocytic vesicles using high resolution in vivo imaging and in silico mathematical modeling (Figure 1).

We made the following observations that were published in the Journal of Cell Biology:

- Robust polarity establishment involves dynamic changes in exocytic and endocytic trafficking systems (Figure 1).
- Robust polarity establishment involves the generation of a specific endocytic signature.
- Endocytic cortical corralling is required for robust polarity establishment.

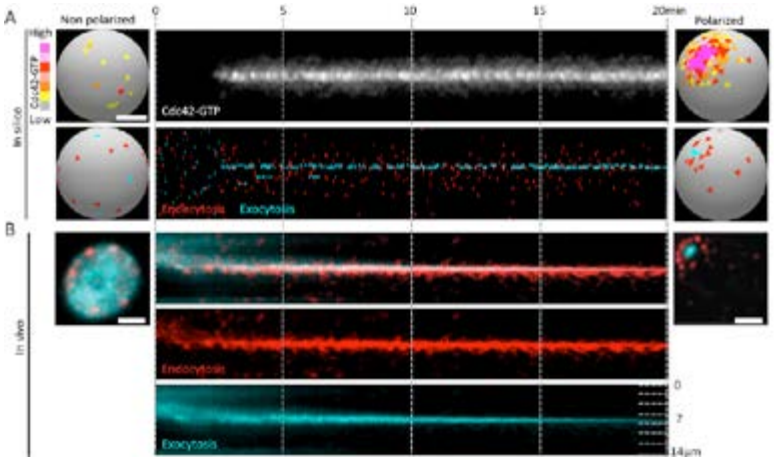

Figure 1: Robust polarity establishment involves dynamic changes in exocytic and endocytic trafficking systems. (A) Transition of an "in silico" cell from a non-polarized (left) to a polarized state. Membrane-bound active Cdc42 depolarized over the plasma membrane (top left) polarizes to a unique cluster of active Cdc42 over time (top right). The Cdc42 kymograph (upper panel) shows active Cdc42 during polarization. The kymograph in the lower panel shows individual endocytic and exocytic events over time (x-axis) along the cortex (y-axis). A tight pole of exocytosis develops (cyan) overlapping with the active Cdc42, and is corralled by a ring of endocytosis (red, bottom right). (B) Random endocytic and exocytic distributions in vivo in a non-polarized cell (left) change to an organized 'bull's-eye-pattern' in a polarized cell (right) with a tight exocytic zone surrounded by endocytic vesicles.

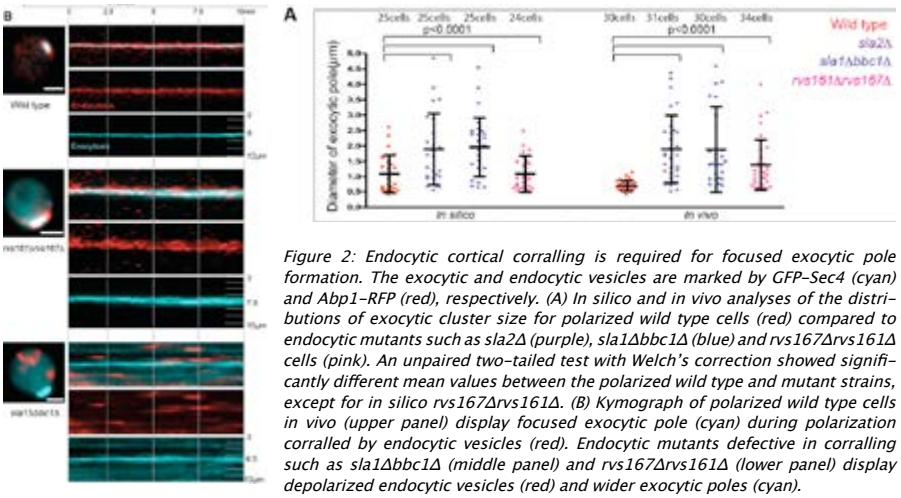

Figure 2: Endocytic cortical corralling is required for focused exocytic pole formation. The exocytic and endocytic vesicles are marked by GFP-Sec4 (cyan) and Abp1-RFP (red), respectively. (A) In silico and in vivo analyses of the distributions of exocytic cluster size for polarized wild type cells (red) compared to endocytic mutants such as sla2Δ (purple), sla1Δbbc1Δ (blue) and rvs167Δrvs161Δ cells (pink). An unpaired two-tailed test with Welch's correction showed significantly different mean values between the polarized wild type and mutant strains, except for in silico rvs167Δrvs161Δ. (B) Kymograph of polarized wild type cells in vivo (upper panel) display focused exocytic pole (cyan) during polarization corralled by endocytic vesicles (red). Endocytic mutants defective in corralling such as sla1Δbbc1Δ (middle panel) and rvs167Δrvs161Δ (lower panel) display depolarized endocytic vesicles (red) and wider exocytic poles (cyan).

A quantitative imaging-based screen reveals the exocyst vesicle tethering complex as a network hub connecting endo and exocytosis

Having identified a requirement for the spatial organization of endocytic sites around a developing exocytic pole in order to establish and maintain a robust polarity axis, we performed an imaging-based mutant screen to identify proteins required for this striking organization. Surprisingly little is known about the mechanisms linking these two essential trafficking pathways, despite intensive study of each individual pathway during the past 30 years. Developing methods in yeast cells that enable the tracking of vesicle dynamics, our studies identified many new players involved in the organization of endo- and exocytic trafficking domains.

In brief:

- We performed a candidate screen in over 400 deletions or temperature sensitive mutants and identified 120 mutants in which either endocytosis, exocytosis or both pathways are depolarized (Figure 3A).
- A functional interaction map of components affecting the spatial organization of endo- and exocytic sites revealed the exocyst vesicle-tethering complex as a hub linking the two processes.
- Exocyst mutants display a striking phenotype in which the organization of endo- and exocytic sites seen become interspersed.
- We introduce the use of super-resolution vesicle imaging and high density tracking to provide a novel quantitative view of vesicle dynamics in live cells (Figure 3B).

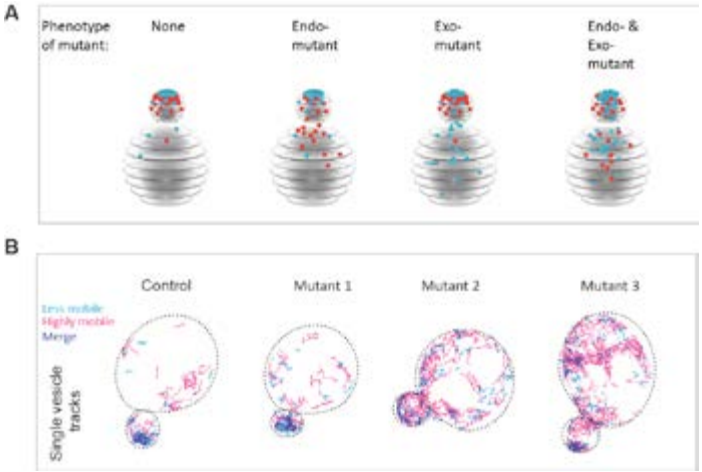

Figure 3: An imaging-based screening approach to identify proteins required for the spatial organization of endo- and exocytic trafficking domains. A Schematic representation of the mutant phenotypes identified by our screen. Endocytic vesicles are sown in red, while exocytic vesicles are shown in cyan. B Super-resolution imaging and very high density tracking to monitor exocytic vesicle dynamics in the mutants identified by the screen. Using this approach, thousands of vesicle movements can be monitored in each cell.

Selected publications

Jose M, Tollis S, Nair D, Mitteau R, Massoni-Laporte A, Velours C, Sibarita JB and McCusker D. A quantitative imaging-based screen reveals the exocyst complex as a network hub linking endo- and exocytosis. Molecular Biology of the Cell. 2015. 26: 2519-2534.

Derive N, Landmann C, Montembault E, Claverie MC, Pierre-Elies P, Goutte-Gattat D, Founounou N, McCusker D, Royou A. Bub3-associated BubR1 sequesters Fizzy/Cdc20 at DNA breaks and promotes the correct segregation of broken chromosomes. The Journal of Cell Biology. 2015. 211: 517-32.

Jose M, Tollis S, Nair D, Sibarita JB and McCusker D. Robust polarity establishment occurs via an endocytosis-based cortical corralling mechanism. The Journal of Cell Biology. 2013. 200: 407-418.

McCusker D and Kellogg D. Membrane growth during the cell cycle: Unsolved mysteries and recent progress. Current Opinion in Cell Biology. 2012. 24: 845-851.

Kellogg, D.* Royou, A. and McCusker, D.* Cdk1-dependent control of membrane trafficking dynamics. Molecular Biology of the Cell. 2012. July 5. 3336-3347. (* Shared senior co-authorship).

Dr. Denis Dupuy

Senior Research Associate (CR1), INSERM

Denis Dupuy initially trained in Biology at University of Pau and got his Master of Science in Molecular and Cell Biology at Université Bordeaux Segalen. He did his Ph.D. thesis in human genetics in the laboratory of Dr. Benoit Arveiler at the University of Bordeaux (1998-2001) working on positional cloning of schizophrenia susceptibility gene. He then joined the group of Dr Marc Vidal, at the Dana-Farber Cancer Institute (Harvard Medical School, Boston, Ma) for a Post-Doctoral training in systems biology. There he acquired the tools and methods needed to perform systematic analysis of spatiotemporal gene expression in vivo in C. elegans.

Research team

Sabrina ROUSSEAU Engineer (INSERM)
Jonathan MILLET PhD student (INSERM-MNRT)
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This team is part of the unit "ARN : Regulation Naturelle et Artificielle" (ARNA), INSERM U869 (now U1212 since Jan 2016).

Genome Regulation & Evolution

The major goal of our group is to generate an integrative model of tissue-specific post-transcriptional regulation processes in Caenorhabditis elegans. Many cis-acting elements and trans-acting factors involved in the regulation of these processes have been characterized. However, integrative models of the molecular mechanisms underlying the sophisticated cell- and stage-specific patterns of regulation are yet to be developed due to difficulties in following these events in vivo. Post-transcriptional regulation represents a critical aspect of genetic regulatory networks in eukaryotes. To dissect the genetic requirements for these mechanisms we will generate the first quantitative genome-scale dataset of post-transcriptional regulation in vivo during C. elegans development.

We focus our effort on two major aspects of post-transcriptional regulation and in particular the analysis of alternative splicing.

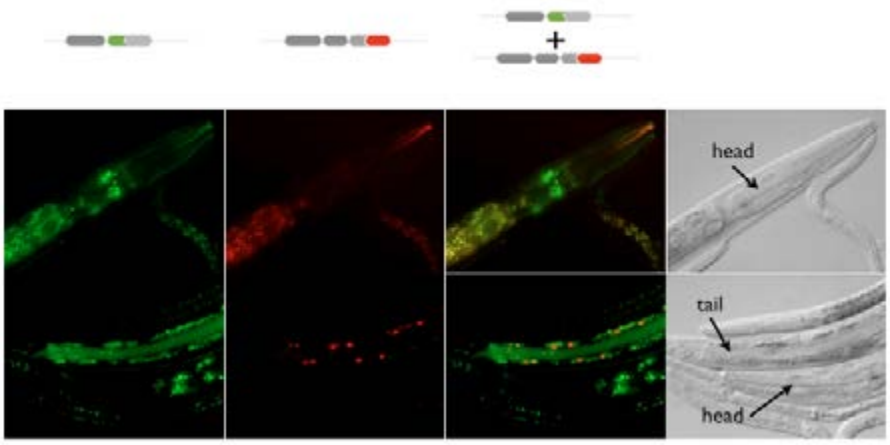

Figure 1: Two-color reporters for in vivo post-transcriptional regulation studies.

Alternative splicing of pre-mRNAs is a widespread mechanism that contributes to the spatiotemporal diversity of gene expression in metazoans. In Caenorhabditis elegans, it has been estimated that ~10% of genes are subjected to alternative splicing. To date, there is no information about global regulation of alternative splicing during worm development. In a recent study using a custom-made microarray, only ~20% of the tested genes showed a significant change in isoform ratio in the course of development. For the majority of the genes, for which EST data indicates alternative splicing events, no variation has been observed. This might indicate that most alternative isoforms are regulated in a tissue-specific rather than stage-specific manner. Such tissue- or cell-specific events are notoriously difficult to follow using microarray analyses. We will use a variation of the two-color reporter system pioneered by our collaborator H. Kuroyanagi (Tokyo) in which two fluorescent reporters are respectively fused to mutually exclusive alternatively spliced exons (Figure 1b), to characterize the alternative splicing patterns of 200 genes. This will provide the first large-scale overview of alternative splicing regulation in vivo in a metazoan organism.

In summary

To build dynamic models of cell differentiation it will be important to integrate comprehensive datasets of expression information and physical relationships between regulators and their targets within the system of interest. Tremendous efforts are underway to collect such datasets in C. elegans which make it the ideal model organism to reach this objective. Our goal is to complement these approaches with a systematic quantitative analysis of major spatiotemporal post-transcriptional regulation processes in vivo in C. elegans.

IGEM 2015

In 2012 D. Dupuy launched the first Bordeaux-based team to participate in the International Genetically Engineered Machine (IGEM) competition. For the fourth participation a team of twenty eight students gathered every week for evening sessions of discussions and planning for a new synthetic biology project to be carried out over the summer. Fourteen undergraduate students represented the « Cured vine » project at the IGEM Giant Jamboree in Boston in September 2015 and were awarded a Gold medal in the Environment track.

Selected publications

Cornes E, Porta-De-La-Riva M, Aristizábal-Corrales D, Brokate-Llanos AM, García-Rodríguez FJ, Ertl I, Díaz M, Fontrodona L, Reis K, Johnsen R, Baillie D, Muñoz MJ, Sarov M, Dupuy D, Cerón J. Cytoplasmic LSM-1 protein regulates stress responses through the insulin/IGF-1 signaling pathway in Caenorhabditis elegans. RNA 2015; 21 (9), 1544-1553

Marza E, Taouji S, Barroso K, Raymond AA, Guignard L, Bonneu M, Pallares-Lupon N, Dupuy JW, Fernandez-Zapico MX, Rosenbaum J, Palladino F, Dupuy D, Chevet E. Genome-wide screen identifies a novel p97/CDC-48-dependent pathway regulating ER-stress-induced gene transcription. EMBO reports. 2015; 16 (3), 332-340

Cornes E, Quéré CAL, Giordano-Santini R, Dupuy D. Applying antibiotic selection markers for nematode genetics. Methods. 2014; 68(3) 403-408

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Dr. Anne Royou

Senior Research Associate (CR1), CNRS

Following a bachelor degree in physiology and cell biology, Anne Royou did a post-graduate degree in molecular and cellular genetics at the Université Paris XI. She did her PhD thesis under the guidance of Dr. Roger Karess, at the Centre de Génétique Moléculaire in Gif-sur-Yvette, studying the role of non-muscle myosin II during development in Drosophila. Following her PhD, she joined Dr. William Sullivan's lab at the University of California, Santa Cruz, as a post-doctoral fellow. There, she became interested in the mechanisms that preserve genome integrity during cell division. She obtained a CNRS permanent position in 2009, an ATIP/Avenir grant in 2010 and was recruited as a team leader at IECB in 2011. In 2014 she was awarded an ERC starting grant.

Research team

Dr. Emilie MONTEMBAULT Researcher (CNRS)
Lou BOUIT Assistant Engineer (ANR retour post-doc)
Marie-Charlotte CLAVERIE Assistant Engineer (Université Bordeaux)
Priscillia PIERRE-ELIES Assistant Engineer (ERC-STG-2012 NoAneuploidy)
Yoann PLANCHENAULT Assistant Engineer (CNRS)
Dr. Damien GOUTTE-GATTAT Postdoctoral fellow (ERC-STG-2012 NoAneuploidy)
Cédric LANDMANN PhD student (Région Aquitaine/CNRS)
Enzo CAMARA, Master 2 (CNRS)
Camille VACHON, Master 2 (CNRS)
Jérôme TOUTAIN Visiting scientist (CHU Bordeaux/CNRS)

This team is part of the "Institut de Biochimie et Génétique Cellulaire" (IBGC), CNRS/Université Bordeaux (UMR5095)

Control & Dynamics of Cell Division

The mechanisms that safeguard cells against aneuploidy are of great interest as aneuploidy contributes to tumorigenesis. Using live imaging approaches, we have identified two novel mechanisms that permit the accurate transmission of chromosomes during cell division. The first mechanism involves the faithful segregation of damaged chromosomes. Our studies reveal that chromosome fragments segregate properly to opposite poles. This poleward motion is mediated through DNA tethers that connect the chromosome fragments. The second mechanism involves the coordination of chromosome segregation with cell cleavage. We found that cells can adapt to a four-fold increase in chromatid length by elongating transiently during anaphase. This mechanism ensures the clearance of chromatids from the cleavage plane at the appropriate time during cytokinesis, thus preserving genome integrity.

Mitosis is the final stage of the cell cycle where a copy of the duplicated genome condensed into chromosomes is transmitted to each daughter cell. Failure to do so produces daughter cells with an inappropriate genome content, also called aneuploidy. The mechanisms that safeguard cells against aneuploidy are of great interest as aneuploidy contributes to tumorigenesis. Our group has identified two novel mechanisms that permit the accurate transmission of chromosomes during cell division. The first mechanism involves the faithful segregation of damaged chromosomes. The second mechanism coordinates chromosome segregation with cell cleavage.

Mechanism that permits faithful transmission of broken chromosomes

The presence of DNA double-strand breaks during mitosis is particularly challenging for the cell as it produces broken chromosomes lacking a centromere. This situation can cause genomic instability due to improper segregation of the broken fragments into daughter cells. We have recently uncovered a process by which broken chromosomes are faithfully transmitted, via the BubR1-dependent tethering of the two broken chromosome ends. However, the mechanisms underlying BubR1 recruitment and function on broken chromosomes were largely unknown. Here, we show that BubR1 requires interaction with Bub3 to localize on the broken chromosome fragments and to mediate their proper segregation. We also find that Cdc20, a co-factor of the E3 ubiquitin ligase Anaphase-Promoting-Complex/Cyclosome (APC/C), accumulates on DNA breaks in a BubR1 KEN box-dependent manner. A biosensor for APC/C activity demonstrates a BubR1-dependent local inhibition of APC/C around the segregating broken chromosome. We therefore propose that the Bub3/BubR1 complex on broken DNA inhibits the APC/C locally via the sequestration of Cdc20, thus promoting proper transmission of broken chromosomes.

Mechanism that coordinates chromosome segregation with cell cleavage

Chromosome segregation must be coordinated with cell division to ensure proper transmission of the genetic material into daughter cells. Our group identified a novel mechanism by which Drosophila neuronal stem cells coordinate chromosome segregation with cell division. Cells adapt to the presence of chromatid arms at the cleavage site by transiently, but dramatically, elongating during anaphase, thus increasing the rate at which the long chromatids clear the cleavage plane. This adaptive elongation depends on myosin activity and the Rho Guanine-nucleotide exchange factor, Pebble. To understand how the cell deforms when chromatids are present at the cleavage plane, we studied the dynamics of myosin during cytokinesis in cells with or without long chromosomes. Surprisingly, halfway through cytokinesis, myosin undergoes flux from the cytokinetic ring and invades the entire cortex. In control cells, myosin efflux is transient, as myosin

dissociates from the cortex upon reformation of the nuclear envelope. However, cells with long chromatids exhibit an extended period of myosin efflux associated with a delay in nuclear envelope formation (NEF). During this prolonged myosin efflux, cortical myosin forms extra rings that deform the nascent daughter cells, permitting the clearance of chromatids from the cleavage plane. We have previously shown that adaptive cell elongation depends on Pebble. Consistently myosin does not undergo efflux in pebble mutant cells with or without long chromatids. Since Pebble accumulates in the nucleus at telophase at the time myosin dissociates from the cortex, we hypothesized that the translocation of Pebble into the nucleus induces myosin dissociation from the cortex via the inactivation of RhoA. Consistently, the expression of a pebble mutant lacking a nuclear location signal induces prolonged myosin efflux associated with cell elongation and extensive blebbing, even in the absence of long chromatid arms at the cleavage site. We propose that the coordination between chromatid segregation, myosin efflux and NEF allows adaptive cell elongation to clear chromatid arms from the cleavage plane before the completion of cytokinesis.

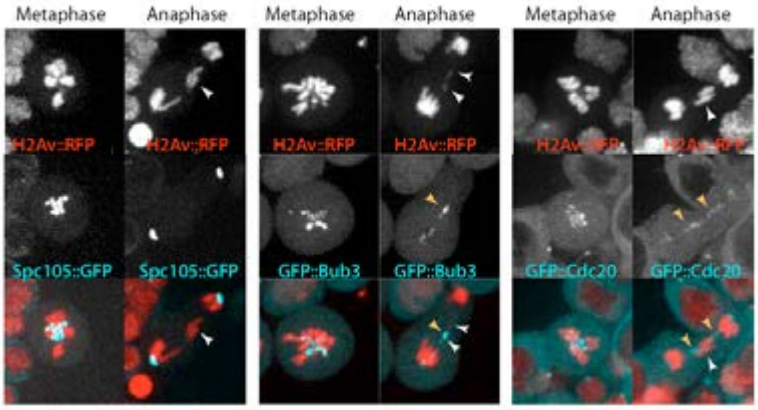


Figure 1: Bub3 and Cdc20 but not Spc105 localize on the tether. *Third instar larval neuro- blasts expressing H2Av::RFP (Red) and Spc105::GFP (Cyan), GFP::Bub3 (Cyan) or GFP::Cdc20 (Cyan) were monitored by time lapse spinning disk confocal microscopy. Spc105::GFP signal accumulated on the kinetochore at metaphase and anaphase. However, no signal was detected on the tether connecting the lagging acentric chromatid (white arrowhead) to their centric partners during anaphase. Both GFP::Bub3 and GFP::Cdc20 signals were found on the kinetochore at metaphase and faded away during anaphase. Stretched GFP-Bub3 and GFP- Cdc20 signals (gold arrowheads) were detected on the lagging acentric (white arrowheads).*

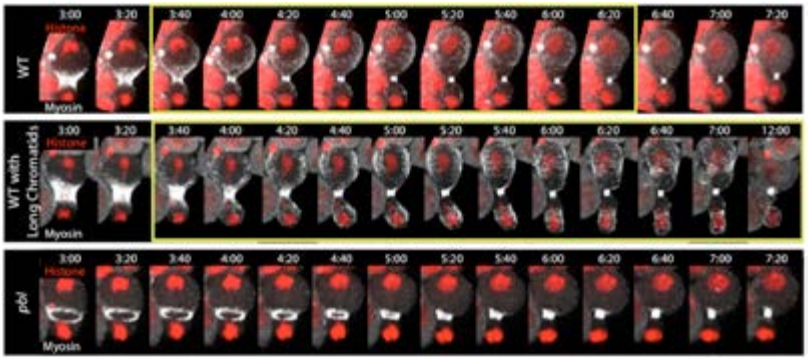


Figure 2: Myosin efflux during cytokinesis is prolonged in the presence of long chromatids and absent in pbl mutants. *Time-lapse images of wild type cells with normal chromosomes (top row), wild type cells carrying an abnormally long chromosome (second row), and cells mutant for the Rho-GEF Pebble (pbl, bottom row). The chromosomes are marked with H2Av::RFP (red) and myosin with Sqh::GFP (Gray). In control cell, half way through cytokinesis, myosin undergoes flux from the contractile ring and invades transiently the whole cortex (yellow rectangle) before dissociating from the cortex. This myosin efflux is prolonged during the segregation of long chromatids (yellow rectangle). No myosin efflux is detected in the pebble mutant. Time=min:second.*

Selected publications

Derive N*, Landmann C*, Montembault E, Claverie MC, Pierre-Elies P, Goutte-Gattat D, Founounou N, McCusker D and Royou A (2015) Bub3/BubR1-dependent sequestration of Cdc20Fizzy at DNA breaks facilitates the correct segregation of broken chromosomes. J Cell Biol. 211(3):517-32. * denotes equal contribution

Jose M, Tollis S, Nair D, Mitteau R, Velours C, Massoni-Laporte A, Royou A, Sibarita JB, McCusker D (2015) A quantitative imaging-based screen reveals the exocyst as a network hub connecting endocytosis and exocytosis. Mol. Biol. Cell. 26(13):2519-34

Kotadia, S*, Montembault, E*, Sullivan, W and Royou A (2012) Cell elongation is an adaptive response for clearing long chromatid arms from the cleavage plane. J Cell Biol. 199(5):745-53. * denotes equal contribution, # denotes corresponding author

McCusker D*, Royou A, Velours C, Kellogg D* (2012) Cdk1-dependent control of membrane trafficking dynamics. Mol Biol Cell. Sep;23(17):3336-47. * denotes equal contribution.

Royou, A., Gagou, M., Karess, R., D., Sullivan, W. (2010) BubR1 and Polo-coated DNA tethers facilitate the segregation of acentric chromatids. Cell 140(2) : 235-45.

Royou, A., McCusker, D., Kellogg, D., Sullivan, W. (2008) Grapes(Chk1) prevents nuclear Cdk1 activation by delaying Cyclin B nuclear accumulation. J. Cell Biol. 183(1):63-75

Dr. Raul V. Duran

Senior Research Associate (CR1), INSERM

Raul V. Duran obtained his PhD at the University of Seville (Spain) in 2005 on cellular bioenergetics under the supervision of Prof. Miguel Angel de la Rosa. Then, he joined the lab of Prof. Eyal Gottlieb at Cancer Research UK (Glasgow, UK) as a postdoctoral researcher (2006-2009). During this period, he worked on the metabolism of cancer cells, with especial emphasis on the role of prolyl hydroxylases as regulators of cell metabolism. Later, he moved to the lab of Prof. Michael N. Hall at the Biozentrum (University of Basel, Switzerland) as a senior postdoc (2010-2013) to study the role of the metabolism of glutamine in the control of cell growth. In June 2013, he joined the IECB as a Junior Group Leader, focusing on the cross-talk between metabolism and cell signaling in cancer cells. In 2015 he obtained a CR1 position at INSERM.

Research team

Dr. Victor H. VILLAR Postdoctoral fellow (SIRIC - U. Bordeaux)
Tra Ly NGUYEN PhD student (CRA)
Clement BODINEAU M2 Student (U. Bordeaux)
Marion MULLER Undergraduate Student (U. Bordeaux)
Cynthia ABANE Medicine Master Student (U. Bordeaux)
Sarah COURTOIS Visitor PhD (U. Bordeaux)
Angela RUBIO Visitor PhD (U. Salamanca)

This team is part of the unit ACTION U1218, INSERM - Université de Bordeaux

Metabolism & Cell Signaling

We study the mechanisms by which the de-regulation of cell signaling contributes to metabolic transformation in cancer. Particularly, we focus our research on the regulation of glutamine addiction by the mTORC1 pathway in cancer cells. First, we investigate the biochemical and cellular mechanisms of the interaction between glutaminolysis and mTORC1. Second, we study the interplay between glutamine metabolism and mTORC1 in cancer models of lymphoblastic leukemia driven by Notch upregulation. Third, we analyze the role of glutamine-dependent activation of mTORC1 in cell death and senescence in cancer models. Those investigations will permit, in collaboration with the Institut Bergonié, the implementation of clinical trials evaluating glutamine and mTOR as potential therapeutic co-targets against cancer.

mTOR is a serine/threonine kinase highly conserved from yeast to human, which integrates several stimuli to regulate cell growth, metabolism and aging. mTOR forms two functionally and structurally distinct complexes termed mTORC1 (comprising mTOR, Raptor and mLST8) and mTORC2 (comprising mTOR, Rictor, mSIN1, PRR5 and mLST8) (Durán & Hall, EMBO Rep 2012). Four main inputs regulate mTORC1: nutrients, growth factors, cellular bioenergetics (controlled by the AMPK pathway), and oxygen availability. Thus, mTORC1 regulates protein synthesis, ribosome biogenesis, nutrient uptake and autophagy in response to growth factors, amino acids, and cellular energy. The Rag GTPases, members of the Ras GTPase superfamily, activate mTORC1 in response to amino acids, especially leucine. The activation of Rag GTPases by amino acids is mediated by a GEF complex termed Ragulator, any by a double GAP component, termed GATOR1 and GATOR2. The addition of amino acids allows the Rag heterodimer to bind and thereby recruit mTORC1 to the lysosome, where mTORC1 is activated (Figure 1). Therefore, according to the current model, the activation of the catalytic GEF activity of Ragulator and the inhibition of the GATOR system are two key steps in the activation of mTORC1 by amino acids. To date, the molecular mechanism leading to the activation of Ragulator and GATOR by amino acids is not well understood. Of note, glutaminolysis, the deamination of glutamine to produce α-ketoglutarate (αKG), is a critical step in the Rag-dependent recruitment of mTORC1 to the lysosome (Durán et al., Mol Cell 2012), but the molecular mechanism connecting glutaminolysis and mTORC1 has not been clarified yet.

Glutamine, plays a particularly important role in cell growth and metabolism as a precursor for αKG of the tricarboxylic acid cycle, for nucleotides and for other amino acids. Glutamine is metabolized through glutaminolysis, which consists of two steps. The first step, catalyzed by the enzyme glutaminase (GLS), converts glutamine to glutamate. The second step, catalyzed by glutamate dehydrogenase (GDH), converts glutamate to αKG. In the past, we demonstrated that glutaminolysis activates mTORC1 by enhancing glutaminolysis and αKG production (Durán et al., 2012; Durán & Hall, Cell Cycle 2012). We also described that the prolyl hydroxylases domain (PHD) proteins are necessary to induce mTORC1 activation by glutaminolysis (Duran et al., Oncogene 2013). Thus, αKG produced by glutaminolysis activates PHD, which in turn induce the lysosomal translocation of mTORC1 and its subsequent activation (Figure 2).

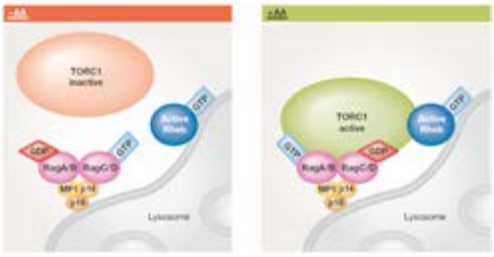


Figure 1. Regulation of mTORC1 by amino acids (from Durán & Hall, EMBO Rep. 2012).

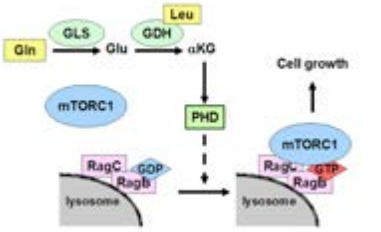


Figure 2. PHDs mediate the activation of mTORC1 by glutaminolysis (Durán et al., 2012; Durán et al., 2013).

Unbalanced activation of glutaminolysis and cell death

Despite the role of both glutaminolysis and mTORC1 in the promotion of cell growth, we recently observed that the unbalanced activation of the glutaminolysis/mTORC1 pathway in the absence of other amino acids induced apoptotic cell death in human cells. Indeed, the long-term production of glutaminolysis-derived αKG in the absence of other amino acids was sufficient to activate mTORC1 and to inhibit autophagy, but concomitantly reduced cell viability and activated apoptosis. Inhibition of mTORC1 or re-activation of autophagy were sufficient to suppress the glutaminolysis-induced apoptosis (Figure 3). We additionally observed that the ability of rapamycin to prevent apoptosis resides in its pro-autophagic potential (Villar et al., Autophagy 2015): re-inhibition of autophagy prevented cell survival in rapamycin-treated cells. In agreement with our results, previous reports have shown that increasing intracellular αKG levels induces apoptosis, although no clear mechanism was provided (Tennant et al., Oncogene 2009; Tennant and Gottlieb, J Mol Med 2010). In the other hand, a recent report has shown that glutaminolysis is crucial for the induction of ferroptosis, a non-apoptotic type of cell death (Gao et al., Mol Cell 2015). The surprising role of glutaminolysis as a cell death inducing mechanism during nutrient restriction points at the importance of nutritional imbalance in the control of cell viability and the potential use of this metabolic disequilibrium to identify new metabolic components and targets with potential implication in the treatment of nutrition-related diseases, such as obesity, diabetes, cancer, or cardiovascular diseases. In any case, whether the activation of apoptosis by the unbalanced activation of glutaminolysis and mTORC1 plays an active role in the biochemical basis of those diseases is a question that remains to be elucidated.

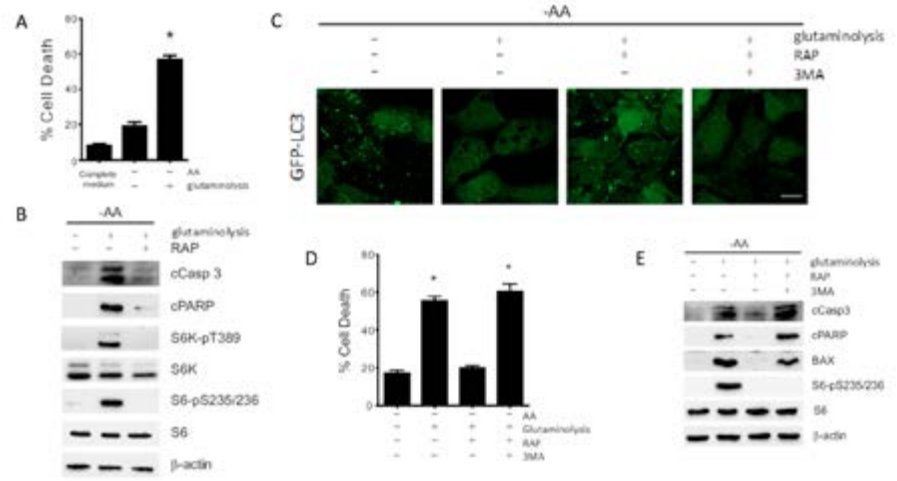


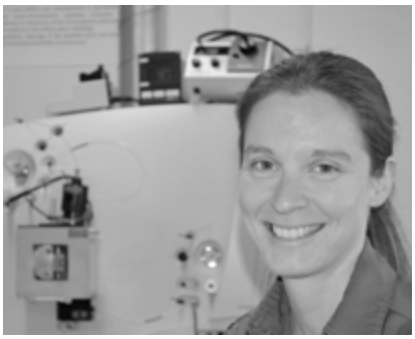
Figure 3. Activation of glutaminolysis in otherwise amino acid starved cells increased apoptotic cell death (A, B), activated mTORC1 (B) and inhibited autophagy (C). Inhibition of mTORC1 using rapamycin restored both autophagy and cell viability, preventing apoptosis (B, C, D, E). Re-inhibition of autophagy using 3MA was sufficient to induce apoptosis even in rapamycin treated cells (C, D, E).

Selected publications

Terés S, Nguyen TL and Durán RV (2016) Metabolic transformation in Notch-driven acute lymphoblastic leukemia, Int. J. Mol. Biol. Med., in press.

Klionsky DJ et al. (2016) Guidelines for the use and interpretation of assays for monitoring autophagy, Autophagy 12, 1-222.

Villar VH, Mehri F, Djavaheri-Mergny M and Durán RV (2015) Glutaminolysis and autophagy in cancer, Autophagy 11, 1198-208.



Dr. Valérie Gabelica

Research Director (DR2), 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 an FNRS research associate position in October 2005. She joined the IECB in 2013 with the support of an Atip-Avenir grant, and became an Inserm research director (DR2) in December 2013. Her main research interests are fundamental aspects of mass spectrometry and its application to non-covalent complexes in general and nucleic acid complexes in particular, with research themes spanning from physical chemistry to biophysics and structural chemistry and biology.

Research team

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Dr Massimiliano PORRINI Postdoctoral fellow (INSERM)
Dr Dabrabata PAUL Postdoctoral fellow (INSERM)
Adrien MARCHAND PhD Student (INSERM)
Clémence RABIN PhD Student (INSERM)
Stefano PICCOLO PhD student Inserm

This team is part of the unit "RNA: Natural and Artificial Regulation" (ARNA), Inserm U1212/CNRS UMR5320/Univ. Bordeaux

Mass Spectrometry of Nucleic Acids & Supramolecular Complexes

European Research Council

There is now increasing evidence that specific nucleic acid structures modulate gene expression. Our objectives are to understand the structure-function relationships in nucleic acids, and specifically to detect, quantify and characterize all the assemblies and tridimensional structures formed by nucleic acids in solution. For that, we develop tailor-made mass spectrometry-based approaches. Our strength is to integrate a multidisciplinary approach, from physical and analytical chemistry (mass spectrometry fundamentals and instrumentation) to molecular biology. In particular, our goal is to reveal the mechanisms of ligand-induced conformational changes in important regulatory structures such as G-quadruplex or riboswitches. The approaches and concepts developed here are also transferrable to other supramolecular and biological complexes.

Mass spectrometry of intact non-covalent complexes

To characterize the variety of intermediates or the variety of end products that can be produced on the folding and assembly pathways of complexes, we use electrospray mass spectrometry (MS) operated in non-denaturing conditions. Thanks to delicate instrument tuning, supramolecular complexes can be preserved and separated according to their mass. Characterizing the various species present in mixtures is the definite advantage of mass spectrometry as a biophysics method.

The interplay between cation and ligand binding in telomeric DNA G-quadruplexes

For nucleic acid complexes, the measured mass indicates how many strands of each sort assemble together, with how many cations and how many ligands. In the presence of mixtures, we obtain this information for each and every complex. This led us to an interesting recent discovery on ligand binding mode to telomeric DNA G-quadruplexes. G-quadruplex structures are formed by cation-mediated stacking of tetrads of guanines. After developing a protocol to study G-quadruplexes by mass spectrometry from potassium solutions, we found in our ligand binding studies that some previously well-known high affinity ligands did actually bind not by simply stacking on the pre-formed G-quadruplex structure, but ligand binding was accompanied by cation ejection, indicating the rupture of at least one G-quartet (Figure 1B). We are currently investigating more in-depth the nature of this ligand-induced conformational change. We also currently investigate the general occurrence of 1-cation/2-tetrad intermediates in G-quadruplex folding pathways.

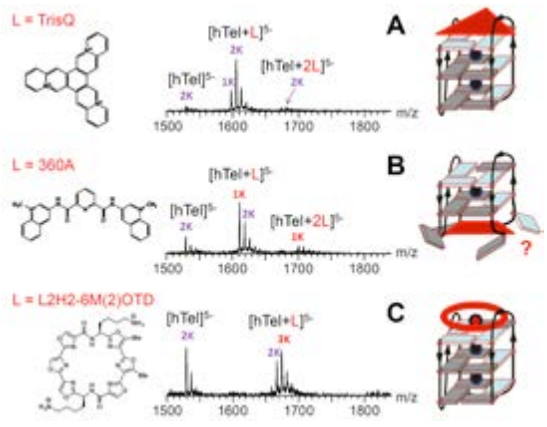

Figure 1: Potassium and ligand binding to G-quadruplexes: ligand binding occurs either without cation displacement (A), with cation ejection indicating the rupture of a G-quartet (B) or with coordination of an extra cation (C). (Marchand et al., JACS, 2015)

Ion mobility spectrometry

In addition to stoichiometry determination and quantitation, we also aim to structurally characterize each complex in the mixture, in order to investigate the binding mode of ligands for a variety of DNA and RNA targets. The originality and challenge is to carry out structural characterization inside the mass spectrometer in order to benefit from the simultaneous separation of the stoichiometries. A new drift tube ion mobility spectrometer (IMS, a technique based on the electrophoretic movement of ions in gases) operated in helium provides high separative power and accurate collision cross section (CCS) measurements. Over the last year, we developed the molecular dynamics simulations of multiply charged nucleic acid structures in the gas phase, in order to correlate experimental collision cross sections (CCS) inferred from IMS with theoretical CCS issued from modeling (Figure 2). The ultimate goal is to infer solution phase structures from CCS measurements. IMS will be crucial for studying the conformational adaptability of the target, and ligand-induced conformational changes. We also plan to explore ion mobility spectrometry for the characterization of folding and multimerization properties of other nucleic acids (in particular, aptamers and riboswitches) and of foldamers.

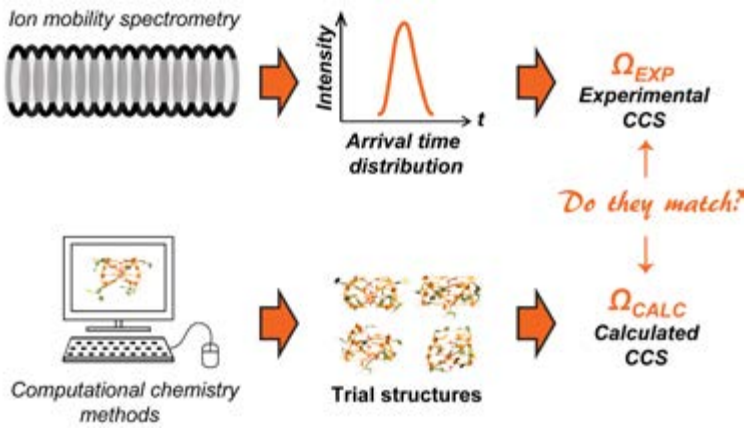

Figure 2: Workflow for assigning structures using ion mobility spectrometry.

Ion spectroscopy

We also combine ESI-MS with traditional spectroscopy approaches, mainly circular dichroism in solution, to ascertain the base stacking topology of nucleic acids. One ambitious objective of the ERC-CoG project "DNAFOLDIMS" (2014-2019) is to develop ion spectroscopy, and in particular, circular dichroism of ions sorted in mass and shape, to characterize the secondary structures and chirality of biomolecules.

Selected publications

Largy E, Mergny JL, Gabelica V. Role of Alkali Metal Ions in G-Quadruplex Nucleic Acid Structure and Stability. Met Ions Life Sci. 2016;16:203-58.

D'Atri V, Porrini M, Rosu F, Gabelica V. Linking molecular models with ion mobility experiments. Illustration with a rigid nucleic acid structure. J Mass Spectrom. 2015 May;50(5):711-26.

Marchand A, Granzhan A, Iida K, Tsushima Y, Ma Y, Nagasawa K, Teulade-Fichou MP, Gabelica V. Ligand-induced conformational changes with cation ejection upon binding to human telomeric DNA G-quadruplexes. J Am Chem Soc. 2015 Jan 21;137(2):750-6.

Arcella A, Dreyer J, Ippoliti E, Ivani I, Portella G, Gabelica V, Carloni P, Orozco M. Structure and dynamics of oligonucleotides in the gas phase. Angew Chem Int Ed Engl. 2015 Jan 7;54(2):467-71.

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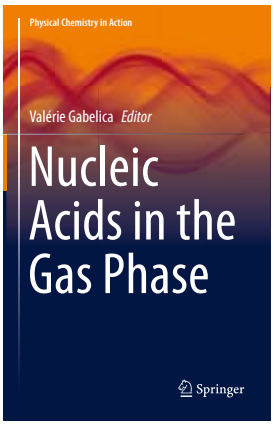
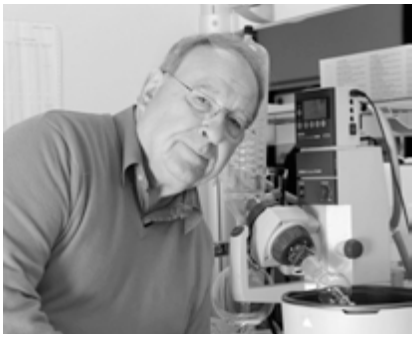




Pr. Léon Ghosez

Prof. Emer., Invited Scientist, University of Bordeaux

Léon Ghosez was born in Aalst, Belgium, in 1934. He got a PhD in polymer chemistry at the University of Louvain in 1958 under the supervision of Prof. G. Smets. He then spent 2 years as postdoctoral researcher at Harvard University (Prof. R.B. Woodward). He also collaborated for a few months with Prof. R. Huisgen at the University of Munich. He got his "Habilitation" in 1969 at the age of 32 and became Professor at the University of Louvain. During his career in Louvain (1963-1999) he supervised the research of 125 PhD students and 135 postdoctoral associates. He also held appointments at the University of Liège (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 and from 2000 till the end of 2009, he shared the directorship of IECB with Dr. J.J. Toulmé. Léon Ghosez is an Emeritus Member of the Royal Academy of Sciences, Literature & Fine Arts of Belgium. He recently received the Medal of the French Chemical Society.

Research team

Dr. Eduard BADARAU Postdoctoral fellow (Université Bordeaux)
Elsom Michael Master (Erasmus Univ. Aberdeen)
Magdalen PLUCIENNIK Erasmus student (Erasmus Polit. Wroclawska)

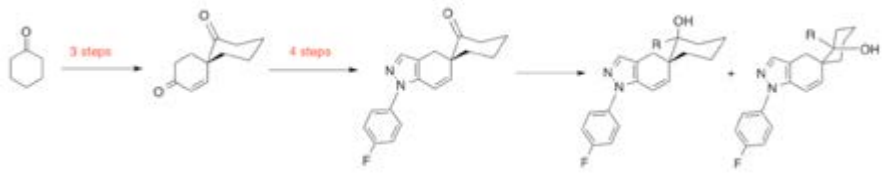
The team is part of the unit "Chimie et Biologie des Membranes et Nanoobjets" (CBMN), CNRS/ Université Bordeaux (UMR 5248)

Organic & Medicinal Chemistry

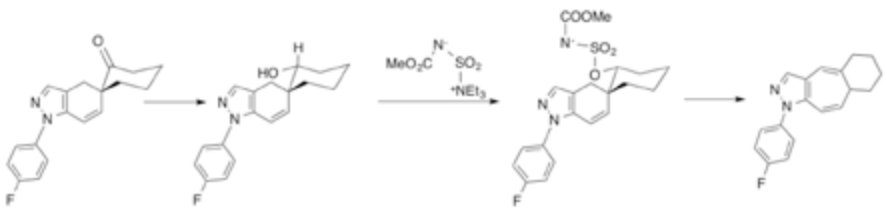
Project 1 : Small natural molecules have been shaped and optimized by evolution and are therefore perfectly tailored to interact with natural macromolecules and induce a biological response. Our first research project consists in designing and producing privileged scaffolds by short sequences of reactions. These should be readily transformed into a wide diversity of natural product analogs of therapeutic interest. This provides an entry into the drug discovery process at a much more advanced stage that does the screening of standard diversity libraries.
Project 2 : Our goal is to develop new ionic solvents and silicon-derived Lewis superacids which are both derived from strong Brönsted acids of rather low molecular weight. These are used as functionally tolerant though highly electrophilic solvents or catalysts for reactions highly functionalized molecules. These solvents and catalysts are free of toxic metals and leave little waste allowing for sustainable processes

Synthesis and evaluation of new ligands of the glucocorticoid receptor

Spirocyclic glucocorticoids were designed, synthesized and evaluated for their activity toward hGRs and IL1/IL6 receptors. A diastereoselective approach was conducted in order to evaluate the biological activity of specific diastereoisomers. The synthetic sequence, without details, is shown in scheme 1. The replacement of fused- by spiranic rings give more conformational freedom to ring C. Thus both diastereomeric alcohols were shown to have an axial hydroxyl group in the most stable conformation. The homologues in 5-, 6- and 7-series have different conformations with huge impact on their binding properties. Our synthetic studies were supported by several single crystal X-rays analysis and DFT calculations performed by Dr. F. Robert of ISM, Univ. Bordeaux. This project led to interesting biological findings. Compounds with nanomolar ranges of activities were obtained and, more interestingly, we found dissociation of the activity profile (hGRs vs IL1/IL6 receptors) for some compounds. This study also led to an unprecedented application of Burgess reagent (Scheme 2) which led an interesting expansion of ring B.



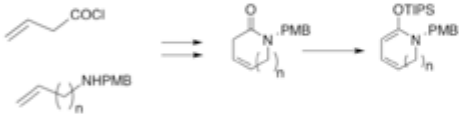
Scheme 1. A short synthesis of new spirocyclic modulators of the glucocorticoid receptor.



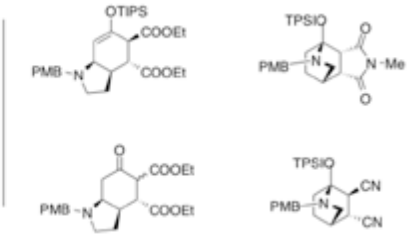
Scheme 2. An unprecedented application of Burgess reagent.

A versatile and productive Diels-Alder route to NPs-inspired privileged scaffolds

The group has pursued its effort towards the synthesis of privileged scaffolds designed after natural products templates. This chemistry-driven approach to drug design relies upon the availability of the complex scaffolds : the challenge is thus to make accessible complex molecules in a short number of steps to allow preparation of multigram quantities of the scaffold and build chemical libraries therefrom. We have completed our studies of a new class of cyclic dienes which could lead to scaffolds designed after natural products such as ottelione A, mesembrenone or lycorine. This class of activated and functionalized dienes should be of general interest to build complex nitrogen-containing molecules. They are readily accessible from the corresponding unsaturated lactames (Scheme 3).



Scheme 3. Practical synthesis of the dienes



Scheme 4. Examples of complex structures available from dienes

The search for new ionic solvents and silicon-derived Lewis super acids

A few more applications of our silylated triflimides superacids and of the corresponding ionic solvents (concentrated solutions of LiNTf2 in ethers, acetone, acetonitrile, ethyl acetate) have been found.

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Other Publications

1. D'Atri V, Porrini M, Rosu F, Gabelica V. Linking molecular models with ion mobility experiments. Illustration with a rigid nucleic acid structure. J Mass Spectrom. 2015 May;50(5):711-26.
2. Dumas P, Ennifar E, Da Veiga C, Bec G, Palau W, Di Primo C, Piñeiro A, Sabin J, Muñoz E, Rial J. Extending ITC to Kinetics with kinITC. Methods Enzymol. 2016;567:157-80.
3. Habenstein B, Loquet A. (2015) Solid-state NMR: An emerging technique in structural biology of self-assemblies. Biophys Chem., 210:14-26
4. Hennig J, Warner LR, Simon B, Geerlof A, Mackereth CD, Sattler M. Structural Analysis of Protein-RNA Complexes in Solution Using NMR Paramagnetic Relaxation Enhancements. Methods Enzymol. 2015;558:333-62.
5. Largy E, Mergny JL, Gabelica V. Role of Alkali Metal Ions in G-Quadruplex Nucleic Acid Structure and Stability. Met Ions Life Sci. 2016; 16: 203-58.
6. Mackereth CD. Splicing factor SUP-12 and the molecular complexity of apparent cooperativity. Worm. 2015 Jan 30;3(4):e991240.
7. Wilson, D. N.; Guichard, G.; Innis, C. A. Antimicrobial peptides target ribosomes. Oncotarget. 2015, 6, 16826-16827.
8. Wilson, D.N., Guichard, G., Innis, C.A. (2015). Antimicrobial peptides target ribosomes. Oncotarget. 6, 16826-16827.

Patents

1. S. Amrane, A. Bedrat, J.L. Mergny. Methods and pharmaceutical compositions for the treatment of filovirus infection EP 15 305 367.3, filed on March 24, 2015.
2. S. Amrane, M.L. Andreola, G. Pratviel, J.L. Mergny. Derivatives of porphyrines, their process of preparation and their use for treating viral infections. EP15306737.6, filed on October 30, 2015
3. S. Amrane, ML Andreola, A. Bedrat, J.L. Mergny. Methods and pharmaceutical compositions for the treatment of HIV infection. EP 15 305 329.3, filed on March 24, 2015.
4. S. Lecommandoux, E. Garanger, T. Deming. Derivatives of elastin-like polypeptides and uses thereof. Application #15 306 247.6

Prizes, Awards

- Great Prize "Mme Victor Noury", French Academy of Sciences, I. Huc
- Glasser Visiting Professorship, Univ. of the Sciences, Philadelphia, USA, I. Huc
- Prix SCT-EFMC 2015, Société de Chimie Thérapeutique, S. Antunes

Journal & Scientific Society Boards

- President, Groupe Français des peptides et des proteins (GFPP) C. Douat
- Editor, PLoS One, D. Dupuy
- Reviewer of Autophagy, Nature Cell Biology, Biochimie, Oncogenesis, Anti-caner Drugs R.V. Duran
- Editoral Board Member, Journal of the American Society for Mass Spectrometry, V. Gabelica
- Board member and Secretary, Société Française de Spectrométrie de Masse, V. Gabelica
- Management committee member for France, Co-leader of WG4 COST Action BM1403 "Native Mass Spectrometry and Related Methods for Structural Biology", V. Gabelica
- Expert of the group Micro- and NanoMedicine, OMNT (Observatoire des Micro- et NanoTechnologies) E. Garanger
- Regional Editor, Tetrahedron, L. Ghosez
- Scientific advisor, Société de Chimie Thérapeutique (SCT) G. Guichard
- Vice President, Société Chimique de France - Section Aquitaine, G. Guichard
- Vice-President of the Bordeaux Association for Crystallography, I. Huc
- Member of the International editorial advisory board of the European Journal of Organic Chemistry and of ChemPlusChem I. Huc
- Reviewer for EMBO Journal & PNAS, A. Innis
- Associate Editor of Biochemistry and Cell Biology, C. Mackereth
- Reviewer of PLoS, D. McCusker
- Editor of Biochimie (Elsevier) and Methods (Elsevier) J.L. Mergny
- Academy Member, Faculty of 1000, J.L. Mergny
- Reviewer, Nature communication, Anne Royou

Evaluation Boards

- Grant Revision Committee Member, Welcome Trust-DBT India Alliance, India, R.V. Duran
- Grant Revision Committee Member, Kidney Research UK, R.V. Duran
- Grant Revision Committee Member, Université Sorbonne Paris Cité, France, R.V. Duran
- Award selection Committee, Hites Award (year's best paper in J. Am. Soc. Mass Spectrom.) V. Gabelica
- Chairman, Scientic Board of iCFRC, Strasbourg, France, L. Ghosez
- Member of the Japanese Committee, ANR-JST programme on Molecular Technology, L. Ghosez
- Member of Tetrahedron Prize and Young Research Award committees, L. Ghosez
- Member of the CN4 committee, Fondation ARC, G. Guichard
- Comité de Pilotage Axe 1, Cancéropôle Grand Sud-Ouest, G. Guichard
- Board member, Czech Academy of Sciences, J.L. Mergny
- Board Member, CCRRDT, J.L. Mergny

Teaching

- "Nascent peptide-mediated gene regulation" (1 hour) metaRNA ITN course, A. Innis
- Structural Biochemistry (43 hours) – First year undergraduate (License 1), Université de Bordeaux, P. Bonnafous
- Methodology (40 hours) – Second year undergraduate (Licence 2), Université de Bordeaux, P. Bonnafous
- Bioinformatics (40 hours) Third year undergraduate (Licence 3), Université de Bordeaux, P. Bonnafous
- Spectroscopy (12 hours) Third year undergraduate (Licence 3), Université de Bordeaux, P. Bonnafous
- Bioinformatics (50 hours) First year Masters (M1), Université de Bordeaux, P. Bonnafous
- Molecular Interactions (4 hours), Second year Masters (M2), Université de Bordeaux, C. Mackereth
- Irreversibility and switch-like characteristics of the celll cycle. (4 hours) Cell Cycle class Master 2 program, University of Bordeaux D. McCusker
- Cancer Metabolism (4 hours) Second year Masters (M2), Université de Bordeaux R.V. Duran
- Chimie, Méthodologie, Chimie-Biochimie (L1, L2: 172h) – Nanosciences et Chimie du Vivant (M1: 20h), Université de Bordeaux, C. Dolain
- Thermodynamique-cinétique-enzymologie, Méthodologie, Instrumentation et appareillages, Biophysique (107h), Université de Bordeaux, A. Bourdoncle
- Chemistry, thermodynamics, biochemistry, biophysics (86h/year) L1, L2, L3, M1, M2, Université de Bordeaux, G. Salgado
- RNA structure and function (6 hours) M1, Université de Bordeaux, JL Mergny
- Surface Plasmon Resonance (20 hours) M1/M2, ENSTBB, C. Di Primo
- Checkpoints, Aneuploidy and Cancer (4 hours) Cell cycle class – Master 2 program, A. Royou
- Organic Chemistry (2 hours), PhD program, University of Barcelona, Spain, V. Gabelica

PhD Theses

- Christos TSIAMANTAS "Synthesis and structure-stability relationship of aromatic helical foldamers", I. Huc, Victor Maurizot, Univ. Bordeaux, FP7-ITN-Dynamol, 2015
- Stéphanie ANTUNES " Agents antimicrobiens innovants de type foldamère pour le contrôle de l'infection par des pathogènes du risque biologique : application à bacillus anthracis", G. Guichard/C Douat, Univ. Bordeaux, Regional Council/DGA, 2015
- Heddy SOUFARI "Structure and function study of the tissue-specific alternative splicing factor MEC-8 from C. elegans", C. Mackereth, Univ. Bordeaux, Inserm, Regional Council, 2015
- Amina BEDRAT, "G4-Hunter : un nouvel algorithme pour la prédiction des G-quadruplexes" J.L. Mergny Un. of Bordeaux, ANR, region, 2015
- Eric CORNES, "Functional analysis of LSM protein family in C. elegans" D. Dupuy/ J. Ceron, University Pompeu Fabra, 2015
- Jonathan MILLET "In vivo analysis of alternative splicing regulation in C. elegans" D. Dupuy, Université de Bordeaux, Ministry of research, 2015
- Xuesong LI "Synthesis and physical properties of helical nanosized quinoline-based foldamers", I. Huc, V. Maurizot, Univ. Bordeaux, Erasmus Mundus, 2016

Science & Society

- TV documentary on folding related to Science, arts (origami) and nature, France and Germany, Aug. 2015, I. Huc
- Radio interview on foldamers and biomimetism, Bordeaux, France Dec. 2015, I. Huc, G. Guichard
- iGEM 2015, Boston, USA, September 2015, D. Dupuy
- « Recherche : défis et aventures » : à l'invitation de Najat Vallaud-Belkacem, Ministre de l'Éducation nationale, de l'Enseignement supérieur et de la Recherche, participation à la table ronde « paroles de chercheurs » lors de la remise de la stratégie nationale de recherche au premier ministre. Paris, France, Dec. 2015 V. Gabelica

Team Funding

European Research Council funding

Coordinated by IECB researchers

IECB Researcher(s)	Funding body	Research project	Period
I. Huc	FP7-Ideas-ERC advanced	Functional Aromatic Amide Foldamers: Beyond Biolpolymers	2013-2018
V. Gabelica	ERC - 2013 - CoG	Advanced mass spectrometry approaches to reveal nucleic acid folding energy landscapes	2014-2019
A. Loquet	ERC Starting Grant	Weak interactions in self-organizations studied by NMR spectroscopy in the supramolecular solid-state	2015-2019
A. Royou	ERC	Mechanisms that prevent aneuploidy	2013-2017

International funding

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher(s)	Funding body	Research project	Period
V. Gabelica	Marie Curie 2012-CIG (Career Integration Grant)	Mass spectrometry for nucleic acids biophysics dealing with diversity	2013-2017
V. Gabelica	H2020-MSCA-ITN-2014	MetaRNA: RNA-based technologies for single-cell metabolite analysis	2015-2018
G. Guichard	FP7 Marie Curie IEF	LXSWAP : Composite proteins	2013-2015
G. Guichard	H2020 Marie Curie IF	FOLDASYNBIO : Bioinspired nanostructures	2015-2017
I. Huc	China Scholarship Council	Foldamer based molecular motors	2012-2016
I. Huc	China Scholarship Council	Amphipathic foldamers	2013-2017
I. Huc	Polish Government	Foldamer based protein recognition	2014-2016
I. Huc	H2020 - People - IEF	Aryl amide metallo-foldamers as selective saccharide sensors	2015-2017
I. Huc	H2020 - People - IEF	RMulti-stimuli responsive molecular systems	2015-2018
I. Huc	China Scholarship Council	Self-assembly of foldamers - applications in electron transport	2015-2019
A. Innis	Marie-Curie CIG (Career Integration Grant)	transARREST : Translational regulation of gene expression by the nascent polypeptide chain	2014-2018
A. Loquet	Marie-Curie CIG (Career Integration Grant)	SecsysNMR	2014-2016
JL. Mergny	ANR-internationale	G4 ligands (with Hong Kong/Prof. E. Ma)	2013-2016

National funding

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Funding body	Research project	Period
S. Amrane	ANRS	Rôle des G-quadruplexes dans le cycle de réplication du VIH	2016-2017
F. Friscourt	IdEx Bordeaux	Bioorthogonal Probes for Chemical Glycobiology	2014-2017
V. Gabelica	Inserm ATIP Avenir	Mass spectrometry for nucleic acids biophysics dealing with diversity	2013-2015

IECB Researcher	Funding body	Research project	Period
E. Garanger	ANR	Recombinant Elastin-like Polypeptides as Precision Polymer Scaffolds towards Synthetic Glycoconjugates	2015-2018
G. Guichard	ANR ASTRID	NEOTHERAPEUTICS : Antimicrobial foldamers against Bacillus anthracis	2013-2016
G. Guichard	ANR-SIMI7	FOLDART : Composite proteins	2013-2016
G. Guichard	ANR Generic call	RiboFLEX : Structural studies of arrested ribosome nascent chain complexes	2014-2017
G. Guichard	IMMI / INSERM/ AstraZeneca	AnBRe : Antibiotics against Bacterial Replication	2015-2017
G. Guichard	Université Bordeaux	PPI Inhibitors	2015-2018
G. Guichard	ANR Generic call	CHIMPP2I -PPI inhibitors	2015-2019
G. Hemery	Ministry of research	Greffage de polymères synthétiques et protéiques thermosensibles sur des nanoparticules magnétiques d'oxyde de fer comme sondes locales de température pour l'IRM et l'hyperthermie magnétique	2014-2017
I. Huc	ANR-Blanc	Aromatic Amide Nucleic Acid Mimics	2011-2015
I. Huc	ANR-Blanc	Foldamers Scaffolds for Electron Transport	2012-2016
I. Huc	Ministry of research	Pre-doctoral Fellowship	2013-2016
I. Huc	Ministry of research	Pre-doctoral Fellowship	2014-2017
A. Innis	ANR Generic call	riboFLEX : Structural studies of arrested ribosome nascent chain complexes prepared using a flexizyme-based approach	2014-2018
A. Innis	Université de Bordeaux (IdEx)	The nascent peptide as a natural and artificial regulator of gene expression	2015-2017
A. Loquet	ANR	NanoSSNMR	2015-2017
C. Mackereth	ANR	Structural and functional analysis of yeast cleavage and polyadenylation factors	2012-2016
C. Mackereth	ANR	Chemical tools for the modulation and monitoring of protein-protein interactions at the synapse	2013-2016
D. McCusker	ANR Blanc	Regulation and dynamics of a Rho-GTPase signaling module	2014-2017
JL. Mergny	PIA-Nanobiotech	VIBBNano	2011-2015
JL. Mergny	ANR-Blanc	T-Kinet	2012-2015
JL. Mergny	ANR-Blanc	Quarpdiem	2012-2015
JL. Mergny	ANR-Blanc	Foldart	2013-2016
J. Millet	Ministry of research	In vivo analysis of alternative splicing regulation in C. elegans	2012-2015
E. Montembault	ANR	Adaptive response of the cell to coordinate chromosome segregation with cell division	2012-2015
C. Parrot	MENRT	Functional analysis of human RNA polymerase III in pluripotent cells	2013-2016
C. Di Primo	ANRS	Dimérisation du génome du VHC : etudes structurales et dynamique fonctionnelle	2014-2015
C. Di Primo	ANRS	Phosphorylation de l'integrase du VIH-1 et integration	2015-2016
G. Salgado	ANR Blanc	BacTox1	2014-2016
C. Seefeldt / A. Innis	INSERM	Structural studies of arrested ribosome nascent chain complexes	2014-2017

Regional funding

Coordinated by IECB researchers

IECB Researcher	Funding body	Type of funding	Period
S. Amrane	Aquitaine Regional Council	Les G-quadruplexes dans les virus : fonctions et applications thérapeutiques	2015-2018
C. Douat	PEPS/IDEX	Foldamer-Functionalized Gold Nanoparticules for Nucleic Acid Delivery	2015-2016
R.V. Duran	Aquitaine Regional Council	Interaction entre la signalisation TOR et le métabolisme de la glutamine dans les cellules cancéreuses	2013-2015
F. Friscourt	Canceropole GSO (Emergence program)	Radiolabeling of bioorthogonal probe	2015-2016
V. Gabelica	Aquitaine Regional Council	Mass Spectrometry for nucleic acids biophysics: innovative approaches to study nucleic acid structure sefl assembly and interactions with anticancer drugs	2013-2016
E. Garanger	BXCRM (ATT UB)	Novel composite biomaterials for bone neurotization	2015-2017
G. Guichard	Aquitaine Regional Council	Bioinspired catalysis	2014-2017
G. Guichard	IDEX Université Bordeaux	Bioinspired catalysis	2014-2017
I. Huc	Aquitaine Regional Council	Ingénierie moléculaire : foldamères amides aromatiques pour la reconnaissance moléculaire	2015-2017
A. Innis	Aquitaine Regional Council	La régulation de la synthèse des protéines par les peptides naissants/ Regulation of Protein Synthesis by the Nascent Polypeptide Chain	2012-2016
A. Innis	Aquitaine Regional Council	The exit tunnel of the ribosome as a high-throughput selection platform for the development of novel antibiotics	2015-2019
A. Loquet	PEPS	PrioNMR : NMR of amyloid prions	2015
A. Loquet	Aquitaine Regional Council	NMR of nanotubes	2015
T.L. Nguyen	Aquitaine Regional Council	Caractérisation biochimique de l'interaction entre le métabolisme de la glutamine et la signalisation de mTOR	2014-2017
C. Mackereth	Aquitaine Regional Council	Characterization of a protein that helps an anti-cancer gene protect the cell against DNA damage	2012-2015
C. Mackereth	Université Bordeaux	Replacing protein flexible linkers with rigid synthetic foldamers	2014-2015
C. Mackereth	Aquitaine Regional Council	Biomimetics of synaptic proteins	2015-2016
J.L. Mergny	Aquitaine Regional Council	Programme Maturation	2014-2016
A. Royou	Aquitaine Regional Council	Mechanisms that control chromosome transmission	2014-2017
G. Salgado	Inserm & Université Bordeaux	Chaire Inserm-Université	2010-2015
G. Salgado	CNRS	Probing G-quadruplex structure by NMR inside cells	2014-2015
C. Seefeldt / A .Innis	Aquitaine Regional Council	Structural studies of arrested ribosome nascent chain complexes	2014-2017
H. Soufari	Aquitaine Regional Council & Inserm	Protein characterization	2012-2015

Charity-funded research projects

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Charity	Research project	Period
S. Amor	ARC	Effets biologiques ligands (Post-doctoral fellowship)	2012-2015
P. Ciufici	FRM	Etude du rôle de la protéine Fgd1 dans l'invasion des carcinomes mammaires	2014
C. Di Primo	Ligue régionale contre le cancer	Régulation de la béta-caténine par une structure en triple hélice ARN : rôle dans l'hépatoblastome, un cancer pédiatrique du foie.	2014-2015
R.V. Duran	FRM	Crosstalk between cell growth signaling and metabolism in cancer cells	2013-2015
R.V. Duran	ARC	Role of mTOR and glutaminolysis in cancer cell death	2014-2016
R.V. Duran	Ligue contre le Cancer	Analyse métabolique des leucémies aigües lymphoblastiques causées par la dérégulation de la voie de la signalisation Notch1	2014-2015
G. Guichard / C. Douat	Ligue contre le Cancer	Foldamers for inhibiting PPIs	2014-2017
A. Loquet	FRM	NMR of assemblies	2014-2016
O. Mendoza	ARC	New Helicase based technique for screening of G4 ligands (Post-doctoral fellowship)	2013-2015
L. Rodrigues	Ligue contre le Cancer	CXCR3-targeting polymer nanoparticles: synthesis and evaluation on tumor models	2014-2017
G. Salgado	Ligue régionale contre le cancer		2014-2015
W. Signac	FRM	Etude du rôle de la protéine Fgd1 dans l'invasion des carcinomes mammaires	2013-2015

Contracts with the industry

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Company	Research contract	Period
E. Badarau	undisclosed	undisclosed	2015-2016
G Guichard	ANRT / Ureka	Folddamers for inhibiting PPIs	2014-2017
G Guichard	Ureka	Collaboration agreement (research and post-doc)	2014-2017
I. Huc	CIVB	New fluorescent probes for the simultaneous analysis of wine acids	2014-2017

IECB funding

Coordinated by IECB researchers

IECB Researcher	Funding body	Research contract	Period
R.V. Duran	IECB	Complementary support of the IECB, Mission pour l'Interdisciplinarité - soutien à l'installation	2014-2015
F. Friscourt	IECB	Complementary support of the IECB, Mission pour l'Interdisciplinarité - soutien à l'installation	2014-2015
A. Loquet	IECB	Complementary support of the IECB, Mission pour l'Interdisciplinarité - soutien à l'installation	2014-2015

Collaborations

Pole 1 – Structural biology & biophysics

Translation regulation of gene expression
Dr. Axel Innis

1. Dr. Gilles Guichard, IECB – CBMN UMR 5248, Bordeaux, France
2. Prof. Daniel Wilson, Gene Center, LMU (U. of Munich), Munich Germany

NMR of Molecular Assemblies
Dr. Antoine Loquet

1. Dr. Sven Saupe, IBGC, UMR5095 CNRS, Bordeaux, France

Pole 2 – Organic & bioorganic chemistry

Biomimetic Supramolecular Chemistry
Dr. Ivan Huc

1. Pr. Didier Dubreuil, Université de Nantes, Nantes, France
2. Dr. Bernard Gallois, CBMN, CNRS Université de Bordeaux, Bordeaux, France
3. Prof. Makoto Takafuji, Kumamotot University, Kumamoto, Japan
4. Prof. Aya Tanatani, Ochanomizu University, Tokyo, Japan
5. Prof. Nils Metzler-Nolste, Buchum University, Bochum Germany
6. Dr. Nathan McClenaghan, CNRS-Univ. Bordeaux, Bordeaux, France
7. Dr. Cameron Mackereth, INSERM-Univ. Bordeaux, Bordeaux, France

Peptidomimetic chemistry
Dr. Gilles Guichard

1. Pr. Jonathan Clayden, School of Chemistry, University of Manchester, Manchester, UK
2. Dr. Stéphane Bellemin-Laponnaz, IPCMS, UMR 7504, Strasbourg, France
3. Dr. Dominique Burnouf, IBMC, Strasbourg, France
4. Dr. Burkhard Bechinger, Université de Strasbourg, Strasbourg, France
5. Prof. Sylvie Fournel, Faculté de Pharmarcie, Illkirch, France
6. Dr. Hinrich Gronemeyer, IGBMC, Illkirch, France
7. Dr. Antoine Kichler, Faculté de Pharmacie, Illkirch, France
8. Dr. Benoit Odaert, CBMN, Pessac, France
9. Dr. Olivier Lambert, CBMN, Pessac, France
10. Dr. Axel Innis, ARNA, Pessac, France
11. Dr. Valérie Gabelica, ARNA, Pessac, France
12. Dr. Cameron Mackereth, ARNA, Pessac, France

Self-assemblies from chimeric polymer-peptide materials
Dr. Élisabeth Garanger

1. Pr. Sébastien Lecommandoux, LCPO, CNRS UMR 5629, Pessac, France
2. Dr. Olivier Sandre, LCPO, CNRS UMR 5629, Pessac, France
3. Pr. Bertrand Garbay, EA 4135, Université de Bordeaux, Bordeaux, France
4. Dr Katell Bathany, CBMN, CNRS UMR 5248, Pessac, France
5. Pr. Chilkoti Ashutosh, Duke University, Durham (NC), US
6. Pr. Timothy Deming, UCLA, Los Angeles (CA), USA
7. Pr. Gerard Wong, UCLA, Los Angeles (CA), USA

Chemical Neuroglycobiology
Dr. Frédéric Friscourt

1. Prof. Christoph J. Fahrni, Georgia Institute of Technology, Atlanta, USA
2. Prof. Binghe Wang, Georgia State University, Atlanta, USA

Pole 3 – Molecular recognition

NMR spectroscopy of protein-nucleic acid complexes
Dr. Cameron Mackereth

1. Dr. Michael Sattler, Helmholtz Zentrum / TUM, Munich, Germany
2. Dr. Ivan Huc, IECB, CNRS UMR 5248, Pessac, France
3. Dr. Gilles Guichard, IECB, CNRS UMR 5248, Pessac, France
4. Dr. Sebastien Fribourg, Inserm U1212, Bordeaux, France
5. Dr. Lionel Minvielle-Sebastia, Inserm U1212, Bordeaux, France
6. Dr. Janosch Hennig, EMBL, Heidelberg, Germany

Unusual nucleic acid structures
Dr. Jean-Louis Mergny

1. Dr. Iyer K Swaminathan, School of Chemistry and Biochemistry, The University of Western Australia, Crawley, Australia
2. Dr. Jean-Baptiste Boulé, Dr. Patrizia Alberti, Prof. Jean-Francois Riou MNHN – CNRS UMR 7196 / INSERM U1154 – Sorbonne Universités, Paris, France
3. Dr. Isabel Alves, CNRS, Bordeaux, France
4. Dr. Eric Ennifar, University of Strasbourg, CNRS, Strasbourg, France
5. Dr. Philippe Dumas, University of Strasbourg, CNRS, Strasbourg, France
6. Dr. Michel Ventura, University of Bordeaux, CNRS, Bordeaux, France
7. Dr. Jean-Luc Taupin, APHP, Hôpital Saint Louis, Paris, France
8. Dr. Jonathan Visentin, CHU Bordeaux, University of Bordeaux, Bordeaux, France
9. Dr. Anny Slama-Schwok, INRA, Jouy-en-Josas, France
10. Dr. Macha Nikolski, University of Bordeaux, Bordeaux, France
11. Dr. Marie-Line Andreola, CNRS UMR5234, Bordeaux, France
12. Dr. Jean-Pierre Aimé, CBMN, Pessac, France
13. Dr. Valérie Gabelica, IECB – ARNA, Pessac, France
14. Dr. Eric Defrancq, Pr. Fabrice Thomas, DCM, Université de Grenoble, France
15. Dr. Geneviève Pratviel, Université de Toulouse, Toulouse, France

Pole 4 – Molecular & cellular biology

Dynamics of cell growth & cell division
Dr. Derek McCusker

1. Dr. Jean-Baptiste Sibarita, Institute of Intdisciplinary Neuroscience, Bordeaux, France

Genome regulation & evolution
Dr. Denis Dupuy

1. Dr. Chevet Eric, Inserm, Université de Rennes 1, Rennes, France
2. Dr. Ceron Madrigal Julian, Catalan Institute of Oncology (ICO), Barcelona, Spain

Control and dynamics of cell division
Dr. Anne Royou

1. Dr. McCusker Derek, UMR5095, Bordeaux, France

Visiting Scientists

Mass spectrometry of nucleic acids ans supramolecular complexes

Dr. Valérie Gabelica

1. Pr. Stephen J. Valentine, West Virginia University, Morgantown, USA
2. Pr. Kazuo Nagasawa, Tokyo University of Agriculture and Technology, Tokyo, Japan
3. Pr. Modesto Orozco, Institute for Research in Biomedicine (IRB Barcelona), Barcelona, Spain
4. Pr. Carlos Gonzales, University of Madrid, Madrid, Spain
5. Prof. Giovanni Di Fabio, Federico II University of Napoli, Naples, Italy
6. Dr. Marie-Paule Teulade-Fichou, Institut Curie, CNRS UMR176, Centre Universitaire Paris XI, Orsay, France
7. Dr. Jean-Louis Mergny, IECB, U1212 ARNA, Pessac, France
8. Dr. Gilles Guichard, IECB, UMR 5248 CBMN, Pessac, France
9. Dr. Jean-Jacques Toulmé, U1212 ARNA, Bordeaux, France
10. Pr. Pradeepkumar P.I., Indian Institute of Technology Bombay, Mumbai, India
11. Pr. Terry McMahon, University of Waterloo, Waterloo, Canada
12. Pr. Scott Hopkins, University of Waterloo, Waterloo, Canada

Organic & medicinal chemistry

Pr. Léon Ghosez

1. Dr Frédéric Robert, ISM, CNRS-Univ. Bordeaux, Bordeaux France
2. Pr Houk Ken, UCLA, Los Angeles, USA
3. Pr Cossy Janine, ESPCI, Paris, France
4. Dr Breton Philippe, Institut Servier, Paris, France
5. Dr Lesur Brigitte, Institut Servier, Paris, France
6. Dr Frormann Sven, Grûnenthal GMBH, Aachen, Germany
7. Dr. Massip, Stephan, Grünenthal GMBH, Aachen, Germany
8. Dr. Renard Pierre, Institut Servier, Paris, France
9. Dr. Rosse Gérard, DART Neurosciences, San Diego, Cal, USA

Invited Conferences

Pole 1 – Structural biology & biophysics

Translation regulation of gene expression

- Metacode Satellite Meeting of the 10th European Biophysics Congress, Dresden, Germany, July 2015, A. Innis

NMR of Molecular Assemblies

- LIA Bordeaux-Kumamoto, Bordeaux, France, October 2015, A. Loquet
- 2nd school of Integrative Structural Biology, Oléron, France, June 2015, A. Loquet
- 2nd Kyoto-Bordeaux Symposium Kyoto, Japan, May 2015, A. Loquet
- 2nd Joint Seminar Technical University of Darmstadt / University of Bordeaux, Bordeaux, France, May 2015, A. Loquet
- Invited Seminar, Sanofi-Pasteur, Lyon, France, February 2015, A. Loquet
- TGIR meeting, Paris, France, October 2015, A. Loquet
- Chemical Complexity and Biology meeting, Strasbourg, France, January 2015, A. Loquet

Pole 2 – Organic & Bioorganic Chemistry

Biomimetic Supramolecular Chemistry

- Gordon Research Conference on Protein Folding Dynamics, Galveston, USA, January 2016, I. Huc
- 7th Peptide Engineering Meeting, Pune, India, Dec. 2015, I. Huc
- Ludwig Maximilians Universität, Deparment seminar, Munich, Germany, Dec. 2015, I. Huc
- Nagoya Univ. Department Seminar, Nagoya, Japan, Nov. 2015, I. Huc
- Ochanomizu Univ. Department Seminar, Tokyo, Japan, Nov. 2015, I. Huc
- Tokyo Univ. Department Seminar, Tokyo, Japan, Nov. 2015, I. Huc
- Kyoto Univ. Department Seminar, Kyoto, Japan, Nov. 2015, I. Huc
- Univ. of Duisburg-Essen Welderman Lectures, Essen, Germany, Nov. 2015, I. Huc
- Journées André Collet de la Chiralité, Lyon, France, Oct 2015, I. Huc
- 16th Blue Danube Symposium on Heterocyclic Chemistry, Balatonalmadi, Hungary, June 2015, I. Huc
- Univ. of the Sciences Glasser visiting Professor lectureship, Philadelphia, USA, May 2015, I. Huc
- Nantes Univ. Department Seminar, Nantes, France, April 2015, I. Huc
- CNRS Chemistry Institute introductory lecture, Meudon, France, March 2015, I. Huc
- Symposium on Grand Challenges at the Chemistry-Biology Interface, Heidelberg, Germany, March 2015, I. Huc
- Bordeaux 2015 symposium on Foldamers, Bordeaux, France Jan. 2015, I. Huc
- ISIS, Strasbour Univ. Department Seminar, Strasbourg, France 05/2015, I. Huc

Peptidomimetic chemistry

- 7th International Peptide Meeting (IPS2015), Singapore, Dec. 2015, G. Guichard
- PEM7-The Seventh Peptide Engineering Meeting, Pune, India, Dec. 2015, G. Guichard
- Minisymposium Recent Advances in Foldamer Research, Copenhagen, Denmark, June 2015, G. Guichard

Chemical Neuroglycobiology

- Cancéropôle Grand Sud Ouest – Cancer & Technologies pour la Santé, Toulouse, France, Sept. 2015, F. Friscourt
- 18th European Carbohydrate Symposium, Moscow, Russia, Aug. 2015, F. Friscourt

Pole 3 – Molecular Recognition

NMR spectroscopy of protein-nucleic acid complexes

- 9th NMR retreat of Protein-RNA interactions, Parpan, Switzerland, March 2015, C. Mackereth, H. Soufari
- International Society of Magnetic Resonance, Shanghai, China, Aug. 2015, C. Mackereth
- Wuhan Institute of Physics and Mathematics, Wuhan, China, Aug. 2015, C. Mackereth
- 4th Aquitaine NMR Network, Bordeaux, France, June 2015, C. Mackereth

Unusual nucleic acid structures

- Pacifichem Conference, Honolulu, HI, USA Dec 2015, J.L. Mergny
- 51st International Conference on Medicinal Chemistry, Avignon, France, July 2015, G. Salgado
- Gordon Research Conference, Newport, RI, USA, June 2015, J.L. Mergny
- Canceropôle Grand Sud Ouest, Toulouse, France, June 2015, J.L. Mergny
- 5th International Quadruplex Meeting Pessac, France, May 2015, J.L. Mergny, O. Mendoza
- 2nd ARBRE conference, London, England, Jan. 2015, C. Di Primo
- ISBOC Meeting Pune, India, Jan 2015, J.L. Mergny

Pole 4 – Molecular & Cellular Biology

Dynamics of cell growth & cell division

- American Society of Cell Biology, San Diego, USA, Dec. 2015, D. McCusker
- EMBO Cell Cycle meeting, Budapest, Hungary, October 2015, P. Rapali

Control and dynamics of cell division

- American Society for Cell Biology, San Diego, USA, Dec. 2015, A. Royou
- EMBO workshop on Cell cycle, Budapest, France, Sept. 2015, A. Royou

Metabolism and Cell Signaling

- Journée Scientifique Annuelle de la SFR TransBioMed 2015, Bordeaux, France, Dec. 2015, T.L. Nguyen, S. Teres, V.H. Villar, R. V. Duran
- 11èmes Journées du Canceropole GSO, Talence, France, Nov. 2015 T.L. Nguyen, S. Teres, V.H. Villar, R. V. Duran
- BIOSARC 2015 Paris, France, Oct. 2015, R. V. Duran
- 3rd Meeting of the Spanish Autophagy Group, Sevilla, Spain, June 2015, R. V. Duran
- XVI Congress of the Spanish Society for Cell Biology (SEBC) Sevilla, Spain, June 2015, R. V. Duran
- 1st Meeting of the Club of Autophagy of Bordeaux, Pessac, France, May 2015, R. V. Duran
- CIB Madrid, Spain, April 2015, R. V. Duran
- Genes and Cancer 31st Meeting, Cambridge, UK, April 2015, V.h. Villar, R. V. Duran
- IBFG Salamanca, Spain, April 2015, R. V. Duran
- IBGC Bordeaux, France, March 2015, R. V. Duran
- CRCL, Lyon, France, Feb. 2015, R. V. Duran

Visiting Scientists

Mass spectrometry of nucleic acids and Supramolecular complexes

- 28th Lake Louise Tandem Mass Spectrometry Workshop, Lake Louise, Canada, Dec. 2015, V. Gabelica
- Congrès Français de Spectrométrie de Masse et Analyse Protéomique (SMAP), Ajaccio, France, September 2015, V. Gabelica, A. Marchand, M. Porrini

- 19th Conversation in Albany, Albany, NY, USA, June 2015, M. Porrini
- Molecular Physics Workshop, Caen, France, July 2015, V. Gabelica
- IIIrd Mediterranean MS conference, Athens, Greece, July 2015, V. D'Atri
- Annual Conference of the Mass Spectrometry Society of Japan (MSSJ), Tsukuba, Japan, June 2015, V. Gabelica

Organic & medicinal chemistry

- Seminar DART Neurosciences, San Diego, Cal. USA, Sept. 2015, L. Ghosez
- Seminar Caltech, Pasadena, Cal. USA, Sept. 2015, L. Ghosez
- Seminar UCLA Los Angeles, Cal. USA, Sept. 2015, L. Ghosez
- Seminar Eli Lilly, Indianapolis, Indianapolis, Ind. USA, Sept. 2015, L. Ghosez
- Seminar Chubu UniversityNagoya, Japan, Sept. 2015, L. Ghosez
- Conf Franco-Ukrainienne (plenary Lect.),Toulouse, France, June 2015, L. Ghosez
- Seminar Univ. Sao Paulo, Sao Paulo, Brazil, April 2015, L. Ghosez
- Seminar Univ Campinas, Campinas, Brazil, April 2015, L. Ghosez
- Seminar Univ Ribeirao Preto, Ribeirao Preto, Brazil, April 2015, L. Ghosez
- Seminar Univ San Carlos, San Carlos, Brazil, April 2015, L. Ghosez
- Seminar Univ. Erlangen, Erlangen, Germany, April 2015, L. Ghosez
- Conf. on Multicomp. Reactions (plenary lecture), Brasilia, Brazil, March 2015, L. Ghosez
- Seminar Univ. Belo Horizonte, Belo Horizonte, Brazil, March 2015 L. Ghosez
- Seminar Univ. of Pensylvania, Philadelphia, USA, Jan.2015, L. Ghosez
- Seminar J&J, Spring House, Pen, USA, Jan. 2015, L. Ghosez

Conference Organisation

- Journée Scientifique Annuelle de la SFR TransBioMed 2015, Bordeaux, France, Dec. 2015, R. V. Duran
- Journée prix de these Société Chimique de France, Pessac, France Oct. 2015, G. Guichard
- JEOL Workshop, Bordeaux, France, July 2015, A. Loquet
- 7th Bordeaux RNA Club Workshop, Bordeaux, France, June 2015 A. Innis, C. Mackereth, C. Di Primo, D. Dupuy
- 6th European Conference on Chemistry for Life Sciences, G. Salgado
- IECB Young Scientist Symposium (JJC), Bordeaux, France, May 2015, B. Seip, C. Seefeldt, B. Habenstein
- 1st Meeting of the Club of Autophagy of Bordeaux, Pessac, France, May 2015 R. V. Duran
- Precision Polymer Materials (P2M) Final Meeting, Lacanau, France, May 2015, E. Garanger
- 5th International Quadruplex Meeting, all members of J.L. Mergny's group, V. Gabelica
- Bordeaux 2015 Symposium on Foldamers, Jan. 2015, I. Huc, G. Guichard, C. Douat, C. Dolain


OUT

Technology Platforms

Dr. Brice Kauffmann
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.

Selected publications

Douliez JP, Zhendre V, Grélard A, Dufourc EJ. Aminosilane/oleic acid vesicles as model membranes of protocells. Langmuir. 2014 Dec 16;30(49):14717-24

Furlan AL, Jobin ML, Buchoux S, Grélard A, Dufourc EJ, Géan J. Membrane lipids protected from oxidation by red wine tannins: a proton NMR study. Biochimie. 2014 Dec;107

Fremaux J, Mauran L, Pulka-Ziach K, Kauffmann B, Odaert B, Guichard G. α-Peptide-Oligourea Chimeras: Stabilization of Short α-Helices by Non-Peptide Helical Foldamers. Angew Chem Int Ed Engl. 2015 Aug 17;54(34):9816-20

Chandramouli N, Ferrand Y, Lautrette G, Kauffmann B, Mackereth CD, Laguerre M, Dubreuil D, Huc I. Iterative design of a helically folded aromatic oligoamide sequence for the selective encapsulation of fructose. Nat Chem. 2015 Apr;7(4):334-41.

Collie GW, Pulka-Ziach K, Lombardo CM, Fremaux J, Rosu F, Decossas M, Mauran L, Lambert O, Gabelica V, Mackereth CD, Guichard G. Shaping quaternary assemblies of water-soluble non-peptide helical foldamers by sequence manipulation. Nat Chem. 2015 Nov;7(11):871-8.

D'Atri V, Porrini M, Rosu F, Gabelica V. Linking molecular models with ion mobility experiments. Illustration with a rigid nucleic acid structure. J Mass Spectrom. 2015 May;50(5):711-26.

Biophysical & Structural Chemistry

IECB's technology platform in Biophysical and Structural Chemistry aims at answering structural and functional questions on molecules/complexes of biomedical interest, with particular emphasis on topics related to biomembranes gene expression and biomimetic molecules (foldamers). IBiSA labelled since 2011, this open platform provides internal and external research teams with a privileged access to state-of-the-art instruments as well as dedicated scientific expertise from scientists located either at IECB or in other labs from Bordeaux. Since January 2008, IECB's technology platform has been part of Bordeaux Functional Genomics Center (CGFB), a network of technology platforms that brings together and makes available to public and private research centers a wide range of biotechnological facilities (bioinformatics, proteomics, metabolomics, …).

Services and expertise of IECB's Structural Biology Platform

- Liquid/Solid NMR
- Electron microscopy
- Mass spectrometry
- Surface plasmon resonance (SPR)
- Crystallogenesis
- X-ray diffraction and diffusion

Liquid/solid NMR

Services and expertise

- NMR of membrane lipids in the context of bicelles and membrane domains (rafts), atherosclerosis, and cellular
- signalling (e.g. nano-objects oriented by magnetic fields, sterols and phosphoinositids)
- NMR of peptides and membrane proteins involved in cancer, apoptosis or featuring particular antibiotic and anti-microbial properties (e.g.neu/erbB-2, Bax, Bcl-2, melittin, surfactin, cateslytin, etc.)
- NMR of colloids associated with the food or pharmaceutical industry (e.g. tannins with saliva proteins, lipopeptides with active nebulisable substances)
- Auto-assembly of amphiphilic molecules
- Synthesis and activity of natural substances of biological interest (e.g. phenols and quinols)
- Structures of nucleic acids, proteins, and protein/nucleic acid complexes
- Chemistry of solids, materials and alloys
- 2D, 3D and multidimensional NMR
- Residual dipolar coupling (RDC)
- Dynamics, 13C/15N relaxation

Equipment

- NMR 800 MHz, SB (TGIR CNRS : http://www.tgir-rmn.org/)
- NMR 700 MHz, SB, Ultra-shield
- NMR 500 MHz, WB, Ultra-shield
- NMR 300 MHz, WB, Ultra-shield
- Solid NMR, triple channel, MAS
- NMR 300 MHz, SB, Ultra-shield
- NMR 400 MHz, SB Ultra-shield

Technical contacts

Axelle Grélard, a.grelard@iecb.u-bordeaux.fr
Estelle Morvan, e.morvan@iecb.u-bordeaux.fr

Scientific expertise

Erick Dufourc, e.dufourc@iecb.u-bordeaux.fr
Antoine Loquet, a.loquet@iecb.u-bordeaux.fr
Cameron Mackereth, c.mackereth@iecb.u-bordeaux.fr
Gilmar Salgado, gfjsalgado@gmail.com

Electron microscopy

Services and expertise

- Samples preparation for MET and Cryo-MET experiments
- Preparation of biological samples and synthetic, organic and metallic assemblies
- Tissues, cells : Inclusion techniques in resin, ultramicrotomy
- Sub-cellular preparation of proteins, protein-membrane complexes : negative coloration, CryoMET of thin layers
- MET cryoMET and Tomography of biological samples, inorganic nanoparticules, polymers, natives or functionalized
- AFM (Atomic force microscopy) of functionalized materials (nanobiotechnology)
- AFM of lipids and proteins assemblies

Equipment

- Tecnai-F20 200kV-FEG (FEI)
- CM-120 120 kV (FEI)
- Nanoscope-IV AFM (Veeco)

Technical contact

Marion Decossas, m.decossas@cbmn.u-bordeaux.fr

Scientific expertise

Alain Brisson, a.brisson@iecb.u-bordeaux.fr
Olivier Lambert, o.lambert@cbmn.u-bordeaux.fr

Surface plasmon resonance (SPR)

Services and expertise

- Informations : interactions (yes or no answer), affinity, binding kinetics, thermodynamics (5°C to 40°C), stoichiometry and active concentrations.
- Samples : proteins, nucleic acids, small molecules (>180 Da), liposomes, bacteria, extracts.
- Recovery function: the instrument can recover compounds bound to the functionnalized surface.
- Sensorchips are available for the immobilisation of compounds via thiol, amines, aldehyde functions, for streptavidin/biotin coupling, Tag-HIS and liposomes capturing.
- Measured parameters : association rates 10^3 to 10^7 $M^{-1}s^{-1}$, dissociation rates : 5 10^{-6} to $10^{-1}s^{-1}$, equilibrium constant 10^4 to 2.10^{10} M^{-1}, concentration: 10^{-3} to 10^{-11} M.

Equipment

Biacore™ T200
Biacore™ 3000

Technical contact

Laetitia Minder, l.minder@iecb.u-bordeaux.fr

Scientific expertise

Carmelo Di Primo, carmelo.diprimo@inserm.fr

Mass spectrometry

Services and expertise

- Synthesis or process verification, either with low resolution or with accurate mass measurement of small molecules (polyphenols, lipids, antimicrobial molecules, various synthetic compounds,…) and biomolecules (peptides, proteins and nucleic acids)
- Elementary composition determination (via the accurate mass) for small molecules (M < 1000 Da)
- Fragmentation spectra for structural elucidation of small molecules
- Native Mass Spectrometry: investigation of non-covalent complexes (stoichiometry determination, relative quantification, detection of minor complexes in mixtures).
- Ligand binding analysis. We design mass spectrometry experiments to characterize ligand binding to biomolecule or biomimetics targets, for ligand binding equilibrium constants (KD) determination, or monitor complex formation (min time scale and longer).

Equipment

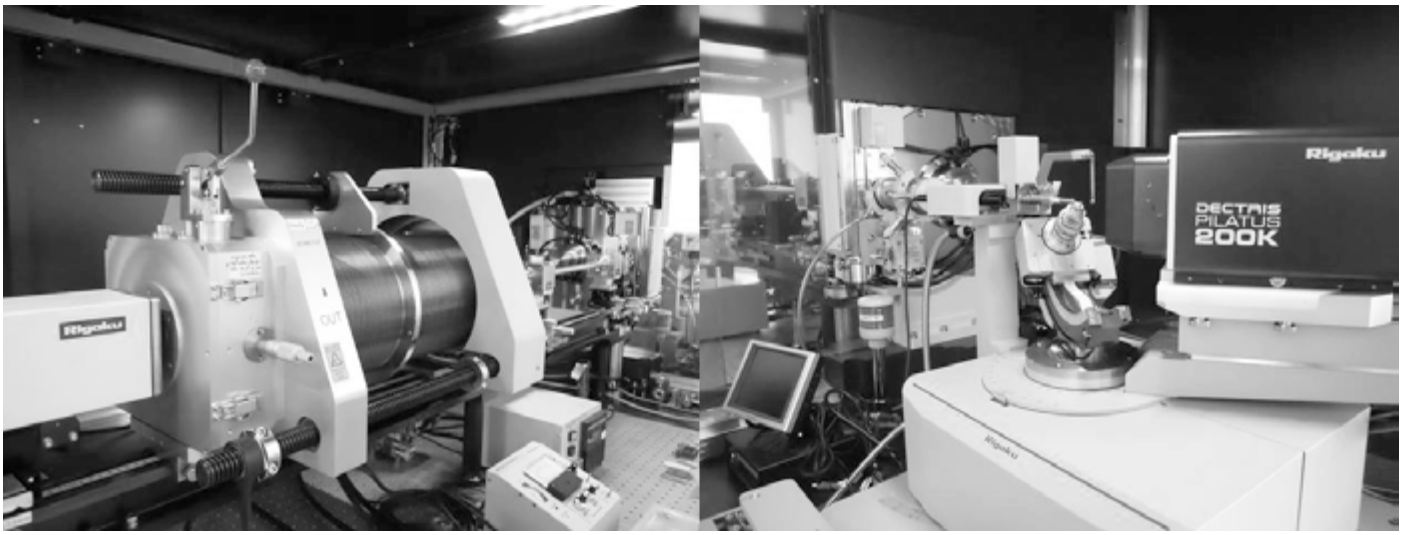
- LCT Premier (Waters): optimized for large masses
- LCQ Advantage (Thermo): available for external users 50% of its operation time
- Orbitrap Exactive (Thermo)
- Waters Q-TOF Ultima Global : optimized for non-covalent complexes
- Agilent 6560 ESI-IMS-Q-TOF
- Modified Bruker Amazon ESI-IMS-Trap

Technical contact

Frédéric Rosu, f.rosu@iecb.u-bordeaux.fr
Loïc Klinger, l.klinger@iecb.u-bordeaux.fr

Scientific expertise

Valérie Gabelica, v.gabelica@iecb.u-bordeaux.fr - Nucleic acids and supramolecular assemblies



Crystallogenesis

Services and expertise

- Robotised Cristallogenesis (screening and opitmization of cristallization conditions)
- Cristallogenesis of membrane proteins in mesophase
- Cristallogenesis of supramolecular self-assemblies

Equipment

- Robot Cartesian Honeybee 961 Genomic solutions
- Robot Mosquito TTP Labtech
- Robot Beckman Coulter Biomek NX
- Robot Beckman Coulter Biomek 3000 equipped with a micro-seringe for pipeting small volumes of viscous solutions (cristallization in mesophase...)
- Robot Xtal Focus from Explora Nova for automatically images crystallization experiments and links images with crystallization conditions

Technical contact

Brice Kauffmann, b.kauffmann@iecb.u-bordeaux.fr
Stéphane Massip, s.massip@iecb.u-bordeaux.fr

Scientific expertise

- Supramolecular assemblies/foldamers - Ivan Huc, i.huc@iecb.u-bordeaux.fr and Gilles Guichard, g.guichard@iecb.u-bordeaux.fr
- Macromolecules - Axel Innis, a.innis@iecb.u-bordeaux.fr

X-ray diffraction and diffusion

Services and expertise

- Diffraction intensities measurements on single crystals of small organic molecules and macromolecules (proteins, nucleic acids, complexes, supramolecular assemblies) : structure resolution
- Small and wide angle X-ray scattering (SAXS, WAXS) experiments (q range of 0.08 to 3 Å-1) : low resolution structures (shape of the molecules)
- Diffuse scattering measurements on single crystals

Equipment

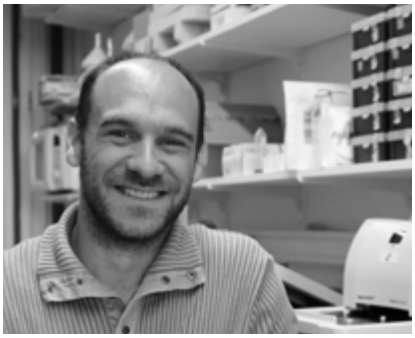
- Microfocus rotating anode Rigaku FRX 3kW with Dectris Pilatus detector
- Microfocus rotating anode Rigaku MM007 1.2kW with Spider IP detector

Technical contact

Brice Kauffmann, b.kauffmann@iecb.u-bordeaux.fr
Stéphane Massip, s.massip@iecb.u-bordeaux.fr

Scientific expertise

- Small organic molecules/foldamers - Ivan Huc, i.huc@iecb.u-bordeaux.fr
- SAXS/WAXS - Reiko Oda, r.oda@iecb.u-bordeaux.fr
- Macromolecules - Axel Innis, a.innis@iecb.u-bordeaux.fr



Lionel Beaurepaire
Head of IECB's technology platform in preparative and analytical techniques (IE), INSERM, UMS 3033/US001

Lionel Beaurepaire graduated from the Conservatoire des Arts et Métiers (CNAM) with a Master of Biological Engineering in 2009. He joined the European Institute of Chemistry and Biology in October 2015 as manager of the preparative and analytical facility in biology.

Contact
lionel.beaurepaire@u-bordeaux.fr

Team
Myriam MEDERIC, Adj., Inserm
Thierry DAKHLI, Tech., Inserm

Preparative & Analytical Techniques

The "analytical and preparative techniques" facilities opened in November 2007 with the aim of providing services in biochemistry, cell biology and molecular biology. As an open platform, it provides technical support and scientific expertise to internal or external research teams. Its activities complement the ones of the technology platform in structural biology.

Services and expertise of IECB's technology platform in preparative and analytical techniques:

Molecular biology	Cloning Genotyping Directed site mutagenesis
Preparative biochemistry	Tests of protein expression Protein production and purification
Other services	Generation of cDNA libraries Purification of oligonucleotides

cgfb BIOLOGIE STRUCTURALE

Molecular biology

Services and expertise

- CLONING – 2 cloning methods are proposed : T4 DNA ligase or "In-Fusion Advantage PCR Cloning Kit" Clontech.
- GENOTYPING – This test allows the differentiation between homozygous or heterozygous animals for a gene of interest. This technique is performed on blood samples and is used for the genotyping in the FTA technical of Wathman.
- DIRECTED SITE MUTAGENESIS – It consists in introducing a specific mutation or deletion in a target gene. Two different PCR methods are used : high fidelity Taq polymerase or Lightning Quick Change mutagenesis kit from Stratagene.

Equipment

- Thermocycler: Mastercycler Pro (Eppendorf).
- Microvolume or cuvette determination: nanophotometer (Serlabo)

Technical contact

lionel.beaurepaire@u-bordeaux.fr

Preparative biochemistry

Services and expertise

- TESTS OF PROTEIN EXPRESSION – This test evaluates the level of expression and solubility of candidate proteins in different bacterial strains (8 strains of *E. coli* in total). A scaling is possible to evaluate the level of expression in different volumes. Plasmid constructs for expression assays may be provided either by the customer or performed by the facility.
- PROTEIN PRODUCTION AND PURIFICATION – This service offers the production and the purification of recombinant protein from a gene of interest. To allow easier purification, the gene of interest is cloned into a tagged vector. We carry out the expression of recombinant proteins in E. coli. Plasmid constructs containing sequence of interest may be provided either by the customer or by the facility.

Equipment

- Centrifuges:
  - AVANTI J26XP (Beckman coulter) equipped with rotors JLA 8.1000, JA25.50.
  - 5804R (Eppendorf) equipped with: Swing-bucker rotor for plates A-2-DWP, Standard rotor for 1,5/2ml tubes FA-45-30-11, Rotor F-34-6-38 (Adaptator for 15ml, 15-18ml or 50ml tubes).
  - 5418 (Eppendorf) equipped with Rotor for 1,5/2ml tubes FA-45-18-11
- Ultracentrifuges:
  - OPTIMA-L80XP (Beckman coulter) equipped with rotors SW 40Ti, 50.2 Ti.
  - OPTIMA MAX (Beckman coulter) equipped with rotors: TLA 120, MLS 80, MLA 80.
- Bacterial refrigerated incubator: MaxQ 6000 (Thermofisher).
- Bacterial incubator: StabiliTherm (Thermofisher).
- Benchtop Fermentor: Bioflo® 115 (New Brunswick).
- FPLC system : Akta – Purifier (GE)

Technical contact
lionel.beaurepaire@u-bordeaux.fr

Other services

Services and expertise

- GENERATION OF CDNA LIBRARIES – generation of various cDNA libraries based on mRNA isolated from organisms or organs upon request. The technique is based on addition of oligo nucleotides with the terminal transferase and amplification by PCR.
- PURIFICATION OF OLIGONUCLEOTIDES – performed on SDS-PAGE. The oligonucleotides can be deprotected.

Technical contact
lionel.beaurepaire@u-bordeaux.fr

Other laboratories

Services and expertise

- L1 Laboratory – For the manipulation of eukaryotic cells classified: biosafety level 1
- L2 Laboratory – For the manipulation of eukaryotic cells classified: biosafety level 2
- Radioactivity laboratory – For the manipulation of radionuclides: 32P, 33P, 35S and 3H

Equipment

- PSMII, Herasafe ™ KS (Thermo Scientific)
- CO2 incubator, Heracell 150i (Thermo Scientific)
- Centrifuge 3K18 (sigma)

Technical contact
Aurore Guedin-Beaurepaire (Radioactivity),
aurore.guedin-beaurepaire@u-bordeaux.fr

Scientific expertise
All access those laboratories are regulated.
For the L2 laboratory, all new demand will be considered by a management commitee.

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, Grünenthal, Ureka, Conseil Interprofessionnel du Vin de Bordeaux, ... Several key industry players work with IECB teams. In 2015, the institut totalized 4 on-going projects with industrial partners.

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 technology platform in stuctural biology and the preparative and analytical techniques facilities.

Technology transfer

IECB researchers are strongly encouraged to patent their discoveries. In 2015, 4 additional patents were submitted by team leaders, Elisabeth Garanger and Jean-Louis Mergny.

The technology transfer unit, Novaptech, that has been hosted at the IECB from 2008 to 2013 is now settled down in Bordeaux.

Incubating start-ups

IECB has a 300m^2 work space dedicated to start-ups. This area is presently occupied by Fluofarma, created in 2003 by two team leaders from the IECB, and Ureka, created in 2010 and located at the Institute since 2014.

Fluofarma
A Porsolt Company

Created in 2003 by former IECB team leaders, Fluofarma is a preclinical contract research organization specialized in providing tailored services in cell biology and high content analysis, an approach highly solicited in association with predictive tools and cell-based models, thereby fulfilling pharmaceutical industry requirements to optimize the drug discovery pipeline. Fluofarma's expertise include in vitro disease models, cell-cell interaction models, assay development, and tissue analysis, all combined with the latest technologies in automated flow cytometry, high content imaging, live imaging, and high content histology.

In 2015, Fluofarma has been acquired by Porsolt SAS, a long established preclinical CRO with an international reputation for expertise in physio-pathological models. The acquisition of Fluofarma complements Porsolt's extensive drug discovery portfolio of services and capabilities addressing multiple stages of the drug discovery process.

Fluofarma services & capacities in drug discovery:

Development of complex in vitro models & cell-based assays
- Generation of multi-cell type cultures & in vitro disease models in 384-well format
- Production & analysis of 3D microtissues based on cell lines & primary cells
- Development, multiplexing, miniaturization and automation of cellular assays

Cell-based high-content screening (over 100 validated cellular assays)
- High-throughput functional target validation: SiRNA screening
- Phenotypic & molecular screening of compound libraries, lead optimization services
- Preclinical proof-of-concept services : drug efficacy, predictive toxicology, mechanism of action studies

Quantitative biomarker analysis in blood & tissues
- Custom development of biomarker assays based on IF/IHC staining
- High-content histology: automated biomarker quantification in tissue microrrays (TMAs)
- Multiplexed detection of surface & intracellular biomarkers in whole blood samples by flow cytometry

Guillaume Froget, PhD
Porsolt / Fluofarma CEO

Year of creation 2003

Staff 9

2015 turnover Not disclosed

Website www.fluofarma.com

UREkA
ImmuPharma Group

Established in the region of Bordeaux in March 2014, UREkA, a subdivision of ImmuPharma, proposes to revolutionize the way we make peptide-based drugs.
Coming from the vision of Robert Zimmer, director of ImmuPharma and Gilles Guichard, Group Leader at the IECB, UREkA is the result of many years of research of foldamer chemistry in the laboratory of Gilles Guichard.
UREkA is now performing research programs to apply its UrelixTM technology for the discovery of innovative therapeutics still in close collaboration with Gilles Guichard's team.

Medicinal chemistry - diseases of interest
- Metabolic diseases: diabetes
- Viral infections
- Cancer

Collaborative research projects
- Implementation of UrelixTM technologies in partners projects.
- Design and synthesis of bioactive foldamers.
- Hit to lead
- SAR
- Development

Dr. Sébastien Goudreau
Ureka Research Director

Year of creation 2010

Staff 5 (4 CDI and 1 PhD student)

Collaborative projects with IECB teams in 2015 2

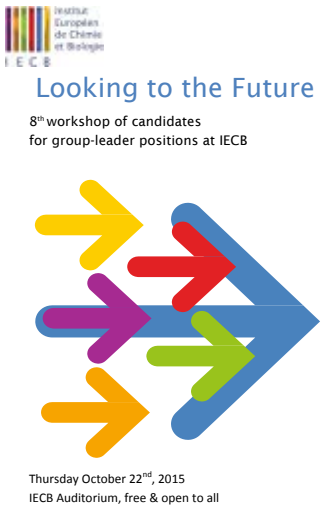
Website www.immupharma.com

Contact
sebastien.goudreau@immupharma.com

Two IECB team leaders - Jean-Louis Mergny and Valérie Gabelica - chaired the *5th International Meeting on Quadruplex Nucleic Acids : G4thering,* held in Bordeaux on May 26-28 2015. 280 participants from all over the world attended the conference.

Scientific Events

Workshops & symposia



IECB: Looking to the Future, June 10 & October 22.

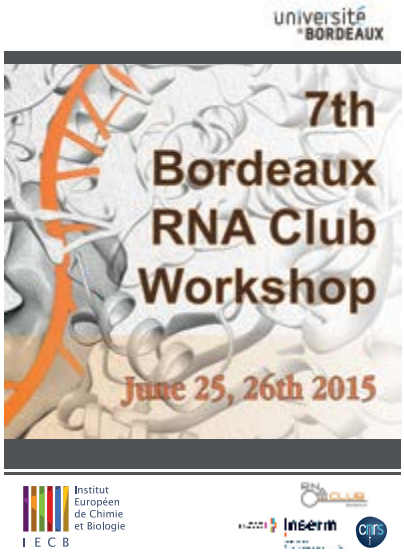
Two workshops of candidates for group leader positions at IECB took place in 2015.

Speakers of the 7th edition (June 10)

- Szilvia SOLYOM, John Hopkins University School of Medicine, Baltimore, MD, USA
- Antoine KARNOUB, Harvard Medical School, Boston, MA, USA
- Alexandre CALON, IRB, Barcelona, Spain
- David SANTAMARIA, CNIO, Madrid, Spain
- Hesso FARHAN, Univ. Konstanz, Germany

Speakers of the 8th edition (October 22)

- Dr. Nicolas Barry, Department of Chemistry, University of Warwick, UK
- Dr. Christian Hoppmann, Department of Pharmaceutical Chemistry, (UCSF), USA
- Dr. Natalià Carulla, Institute for Research in Biomedicine (IRB Barcelona), Barcelona, Spain
- Dr. Chao Xu, Structural Genomics Consortium (SGC) of the University of Toronto, Canada
- Dr. Hesso Farhan, Department of Biology, University of Konstanz and BITg, Germany
- Dr. Tanuj Sapra, University of Zürich, biochemistry Institute, Switzerland
- Dr. Guillermo Acuna, Institute of physical and theoretical chemistry, Braunschweig, Germany
- Dr. Anton Kuzyk, Max Planck Institute for Intelligent Systems, Stuttgart, Germany



7th annual workshop of the Bordeaux RNA Club, June 25-26

100 participants. Invited speakers :

- Martin Jinek, Department of Biochemistry, University of Zurich, Switzerland
- Centre de Génétique Moléculaire (UPR 3404), Gif sur Yvette Cedex, France
- Jan Karlseder, The Salk Institute for Biological Studies, Molecular and Cellular Biology Dept, La Jolla, USA
- Roland Beckmann, Gene Center and Department of Biochemistry, Ludwig-Maximilians-Universität, Munich, Germany
- Frederic Allain, Institute of Molecular Biology and Biophysics, Department of Biology, ETH Zurich, Switzerland

5th International Meeting on Quadruplex Nucleic Acids: G4thering in Bordeaux, May 26-28

280 participants from all over the world.

Conference chairs: Jean-Louis Mergny and Valérie Gabelica (IECB, France). 50 contributed talks organized in 10 sessions, and over 150 posters:

- G4 folding (chair: Nancy Maizels, University of Washington, Seattle, USA)
- G4 ligands part I (chair: Marie-Paule Teulade-Fichou, Institut Curie, France)
- G4s in cancer (chair : Lukas Trantirek, Masaryk University, Czech Republic)
- Novel G4 structures (chair: Antonio Randazzo, University of Napoli, Italy)
- G4s and replication or helicases (chair: Tracy Bryan, University of Sydney, Australia)
- Novel G4-based assemblies (chair: Anh Tuan Phan, Nanyang Technological University, Singapore)
- G4 ligands part II (chair: Dipankar Sen, Simon Fraser University, Canada)
- Finding new G4s or G4 interactions (chair: Paula Bates, University of Louisville, USA)
- Single molecule G4 studies (chair: Concetta Giancola, University of Napoli, Italy)
- The relation of G4 to disease (chair: J. Brad Chaires, University of Louisville, USA)

IECB Young Scientist Symposium, May 21-22

This event dedicated to young researchers' works has been organized since 2008 by PhD students and postdoctoral fellows of IECB. It promotes interdisciplinary exchanges between young chemists and biologists. In 2015, over 100 participants from France, UK, Spain, USA, Canada and Serbia attended the event. 21 oral communications & 17 poster were presented.

Y S S

Keynote speakers:

- Prof Roland riek, ETH Zurich
- Dr. Anne Vessière, Paris Chimie tech

Career session:

- Dr. Anne Nielsen, Scientific editor at the EMBO journal
- Dr. Helena González, Co-founder of The big van theory
- Dr. Edwin Kets, Director of Operations at MSD Animal Health

Symposium on Foldamers 2015 January 26-28 IECB, Bordeaux-Pessac, France

Program and Abstract Book

Bordeaux 2015 Symposium on Foldamers, January 26-28

120 participants. Co-chairmen : Gilles Guichard & Ivan Huc (IECB & CBMN, CNRS, Univ. Bordeaux)

Plenary Speakers:

- Prof. Kurt Vesterager Gothelf (Aarhus University, Denmark)
- Prof. Bert Meijer (Technical Univ. Eindhoven, The Netherlands)
- Prof. Vincent Pecoraro (Univ. Michigan, USA)
- Prof. Fraser Stoddart (Northwestern Univ., USA)
- Prof. Todd Yeates (UCLA, USA)

Keynote speakers:

- Prof. Luc Brunsveld (Technical Univ. Eindhoven, The Netherlands)
- Dr. Jeanne Crassous (Univ. Rennes, France)
- Prof Amar H Flood (Indiana University, USA)
- Prof. Fernando Formaggio (Univ. Padova, Italy)
- Ass. Prof. Seth Horne (Univ. Pittsburgh, USA)
- Prof. Kyu-Sung Jeong (Yonsei University, Korea)
- Prof. Ronald Micura (Univ. Innsbruck, Austria)
- Ass. Prof. Bradley Pentelute (Massachusetts Institute of Technology, USA)
- Prof. Alan Rowan (Univ. Nijmegen, The Netherlands)
- Prof. Michinori Suginome (Kyoto University, Japan)
- Prof. Dan Yang (Honk-Kong University)

Seminars

1. Mihail Barboiu, Adaptive Supramolecular Nanosystems Group, Institut Européen des Membranes, Montpellier, FRANCE: Molecular encapsulation of dynamic systems inside the crystalline cages
2. Luca Monticelli, Institut de Biologie et Chimie des Protéines, CNRS, Université C. Bernard, Lyon, France : Molecular simulations of lipid membranes
3. Jean-Christophe Baret, Centre de Recherche Paul Pascal, Université de Bordeaux, FRANCE : Microfluidic Ultra-High Throughput Screening.
4. Meriem Smadhi, Post-doctorant applicant in the Friscourt group : Novel polysulfurated glycoasterisks and molecular glasses : Synthesis and properties
5. Ryan Gilmour, Organic Chemistry Institute, Westfälische Wilhelms-Universität Münster, GERMANY: Physical organic principes in organic reaction design
6. Eugen Stulz, School of Chemistry and Institute for Life Sciences, University of Southampton, Highfield, Southampton, UK: Substituted Nucleotides: versatile building blocks in DNA bio-nanotechnology
7. Gaëlle Legube, Chromatin and DNA repair group, LBCMCP-CNRS UMR5088, University of Toulouse, FRANCE: Transcriptionally active chromatin recruits homologous recombination at DNA double strand breaks
8. Scott A. Snyder, Scripps Research Institute, Jupiter, FLORIDA, USA: Strategies to Create Diverse Collections of Natural Products
9. Tomonari Ogata Innovative Collaboration Organization, Kumamoto University, JAPAN: Photo-functional Polymeric Materials-multilayered polymer composite for photo-mechanical application
10. Hirotaka Ihara, Departement of Applied Chemistry and Biochemistry, Graduate School of Science and Technology, Kumamoto University, JAPAN: Supramolecular gel-functionalized polymer composite for optical use
11. Laurent Trembleau, School of Natural and Computing Sciences, University of Aberdeen, UK : Synthesis and biological characterisation of allosteric ligands of the CB1 cannabinoid receptor
12. Norbert Polacek, Department of Chemistry and Biochemistry, University of Bern, SWITZERLAND: The ribosome as novel target for stress-induced small regulatory RNAs
13. Christophe Lavelle Museum National d'Histoire Naturelle, Paris, FRANCE : Gene expression goes physical
14. Natacha Rochel Institute of Genetics and of Molecular and Cellular Biology (IGBMC), UMR7104, Illkirch, FRANCE: Molecular mechanisms of DNA and coactivator recognition by nuclear receptor heterodimers
15. Julien Marcoux, Institut de Pharmacologie et de Biologie Structurale, UMR 5089, Toulouse, France : Use of structural mass spectrometry for the study of soluble and membrane complexes
16. Andres Ramos, University College London, UK
17. Stephan Vagner, UMR3348, Institut Curie, Orsay, FRANCE: Translation and cancer
18. Itaru Hamachi, Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, JAPAN: Ligand-directed chemistry for endogenous protein labeling in live cells
19. Christophe Tribet, Ecole Normale Supérieure, Départment de Chimie, Paris, France : Strauggtfirward coating by polymer switches to manipulate lipid membranes anc cells
20. Roberto Milani, VTT Technical Research Centre of Finland, Espoo, FINLAND: Engineering the self-assembly of proteins and polymers with fluorous interphases and halogenated molecules
21. Guillaume Achaz, Université Pierre et Marie Curie, Paris, France : Assessing co-evolution among discrete traits
22. Robert Brosh, Laboratory of Molecular Gerontology, NIA, National Institutes of Health, NIH Biomedical Research Center, Baltimore, Maryland, USA: Human DNA repair helicases and their roles in genome stability and disease
23. Anne Imberty, CERMAV, CNRS and Université Grenoble Alpes, Grenoble, FRANCE: Bacterial lectins and dynamics of glycolipids in host membranes
24. Nicolas Giuseppone, ICS, University of Strasbourg, Institut Universitaire de France (IUF), Strasbourg, FRANCE: Supramolecular triarylamine self-assemblies as functional nanomaterials
25. Itaru Hamachi, Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, JAPAN: Ligand-directed chemistry for endogenous protein labeling in live cells
26. Shigeori Takenaka, Department of Applied Chemistry, Kyushu Institute of Technology, Kitakyushu, JAPAN: Development of new probing molecules connected with tetraplex DNA
27. Scott Hopkins, University of Waterloo, CANADA: Elucidating the Physicochemical Properties of Isolated Clusters
28. Vadim A. Frolov, Biophysics Unit (CSIC, UPV/EHU) University of the Basque Country and Ikerbasque, Basque Foundation for Science, Bilbao, SPAIN: Role of lipids in nanoscale membrane remodeling: from poration to nanoelasticity
29. Frank Sobott, University of Antwerp, BELGIUM : Native ion mobility-mass spectrometry : from flexible proteins to ion channels
30. Enrique de la Cruz, Yale University, New Haven, CT, USA: How cells use chemistry and physics to break the bones that power their movement
31. Jean-Philippe Lumb, McGill University, Montreal, Quebec, CANADA : Driving Synthesis by Oxidation
32. Robbie J. Loewith, University of Geneva, SWITZERLAND: Regulation of Rps6 Phosphorylation by TOR Complexes in Saccharomyces cerevisiae
33. Kazuhiko Nakatani, Osaka University, JAPAN : Modulation of RNA function by small ligands
34. Beatrix Suess, Technische Universität Darmstadt, GERMANY: Engineered riboswitches-an alternative means to control gene expression
35. Gérard Rosse, DART Neuroscience, San Diego, CA, USA
36. Frédéric Ducongé, Molecular Imaging Research Center (MIRCen), Fontenay-aux-Roses, FRANCE : Aptamers for in vivo sensing in biological systems
37. Jean-Pierre Perreault, Université de Sherbrooke, Québec, CANADA: Récent progrès dans l'étude des G-quadruplexes d'ARN comme motifs clés du transcriptome et utilisation en biologie de synthèse
38. Mike Boxem, Utrecht University, NETHERLANDS : Unraveling

the C. elegans interactome underlying cell polarity

39. Fernand Federici, Université Pontificale Catholique de Santiago et Université de Cambridge
40. Thierry Michon, UMR 1332 Biologie du Fruit et Pathologie, INRA, Université de Bordeaux, Villenave d'Ornon, France : Using virus particles scaffolds for imaging proteins at work
41. Jean-François Nieregarten, Laboratoire de Chimie des Matériaux Moléculaires, Université de Strasbourg et CNRS (UMR 7509), France : Fullerene and pillar[5]arene scaffolds for the preparation of bioactive multifunctional compounds
42. Cyril Dominguez, University of Leicester, UK: Structural studies of Bcl-x alternative splicing: Role of RNA structure, G-quadruplexes, and splicing factors
43. Ecaterina Lozan, CBMN/CGFB, Bordeaux, FRANCE: Analyse quantitative de l'Estradiol dans les tissus cérébraux et le plasma de souris
44. Benoit Pichon, Institut de Physique et de Chimie des Matériaux de Strasbourg, Université de Strasbourg, France : Assemblies of Magnetic Iron Oxide Nanoparticles with Tuneable Nanostructures and Magnetic properties
45. Matthias Pauly, Institut Charles Sadron, CNRS-Université de Strasbourg : Versatile large area alignment of anisotropic nanoparticles in layer-by-layer assembled films for plasmonics

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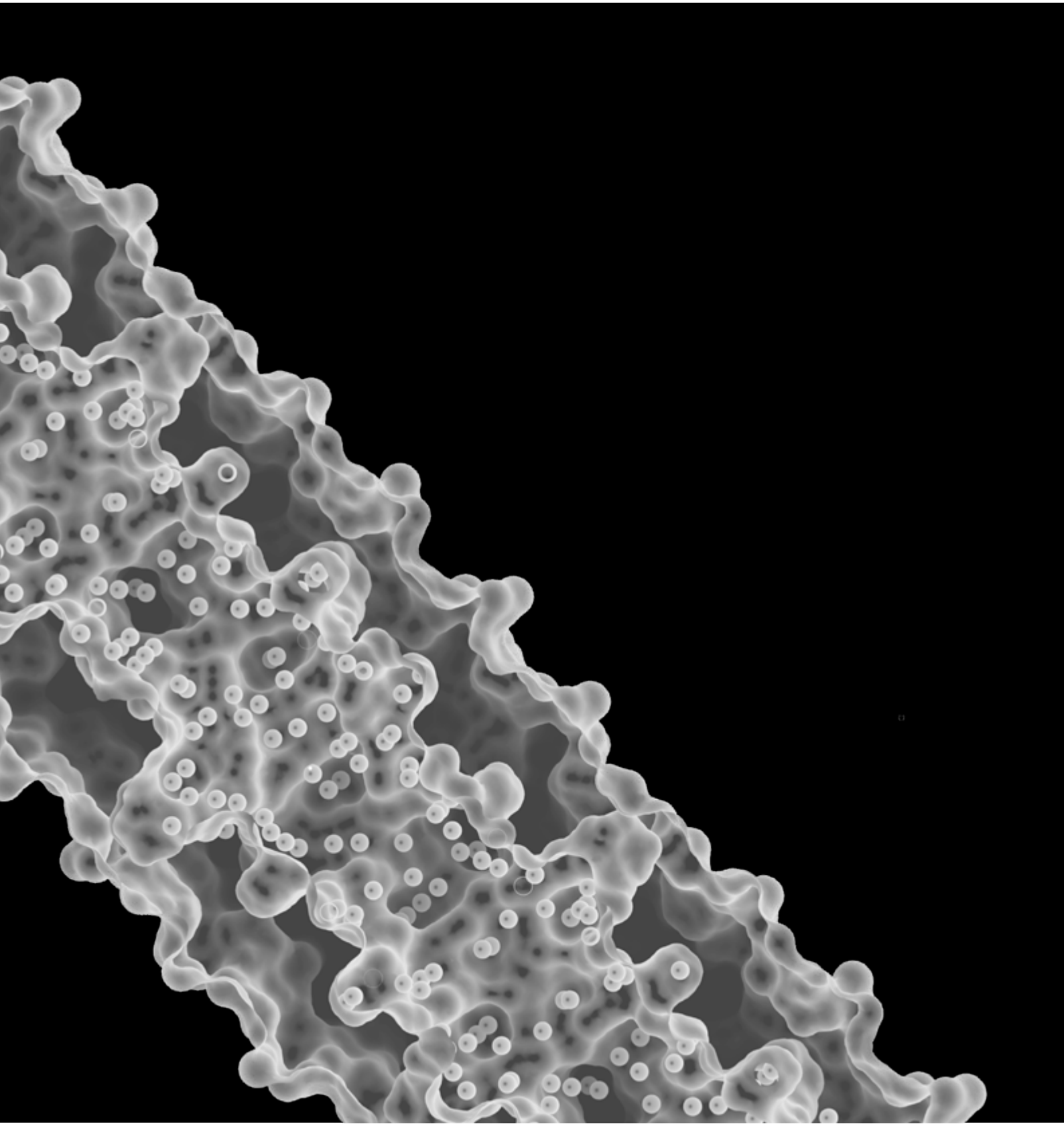

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