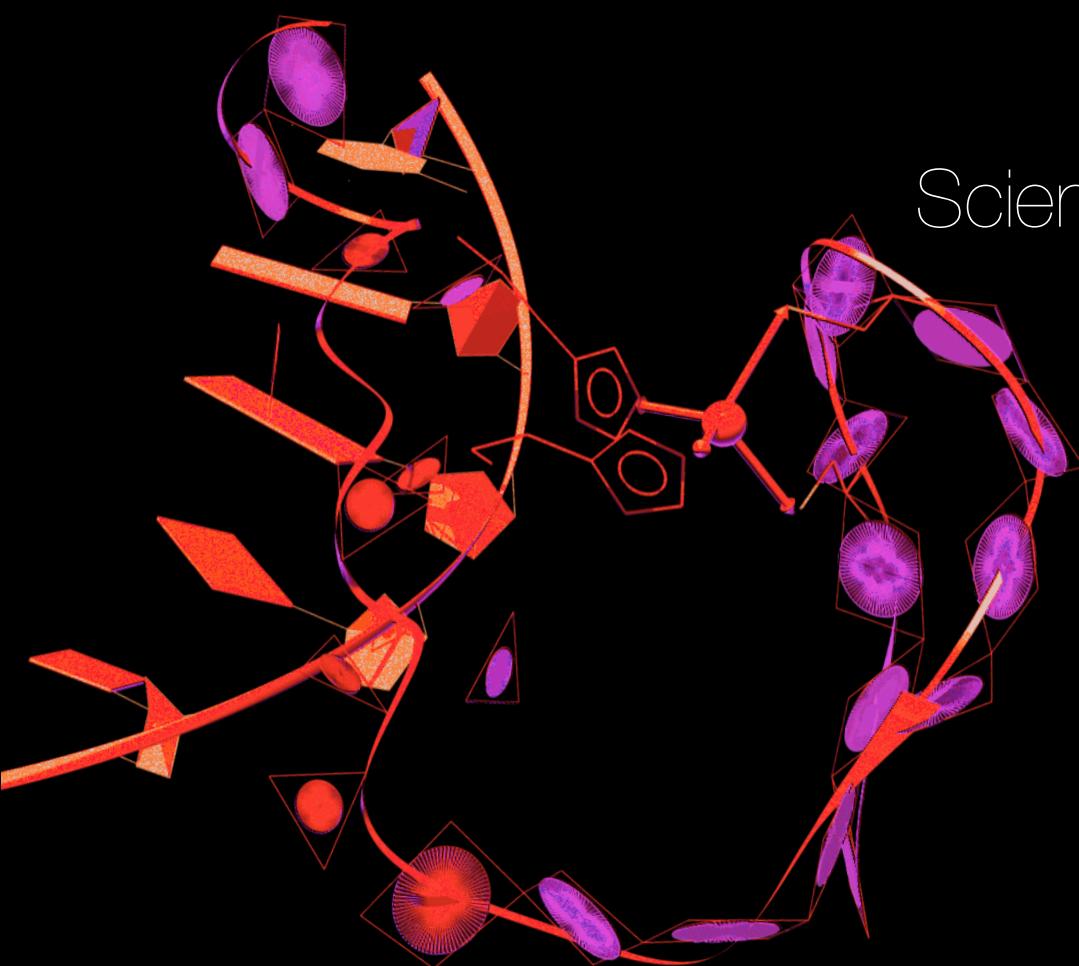




Institut Européen de Chimie et Biologie  
European Institute of Chemistry and Biology



Scientific Report  
2018

IECB celebrated its 20-year anniversary in 2018. A special symposium entitled "Science, Culture and Society" was held on April 9<sup>th</sup> to salute Léon Ghosez's awarding of the "Légion d'honneur". Léon Ghosez acted as Deputy director of IECB and is still involved in the institute as an associate member. IECB was honored to host Alain Rousset, President of the Nouvelle-Aquitaine region, who played a key role in the foundation of IECB. (From left to right : Jean-Jacques Toulmé, Alain Rousset, Léon Ghosez and Jean-Louis Mergny).



**Publication director:** Jean-Louis Mergny **Graphic design:** A to B communication **Photo credits:** Gilmar Salgado (front cover), Hugette Vanlierde, Yves Théobald (building, portraits), François Quenet (portraits), Lionel Lizet (IECB-CGFB technology platform), Pierre-Emmanuel Gaultier (portraits), Elodie Emaille (portraits), Céline Charrier (portraits), CNRS.



Institut Européen de Chimie et Biologie  
European Institute of Chemistry and Biology

Scientific Report  
2018

# Director's Foreword



"On n'a pas tous les jours 20 ans!"<sup>1</sup>

2018 has been a very rich year for IECB and many events deserve to be highlighted: its 20-year anniversary, a new group leader, seminal papers, exciting workshops and symposia, ERC awardees... 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. No less than 7 current or former IECB members got an ERC grant while working in the Institute! I hope this may convince potential candidates to dare apply...

Regarding our technical facilities, I am very glad to count Laetitia Member as a new Inserm permanent employee for the Surface Plasmon Resonance platform.

The publication output is steady, with a flurry of nice papers in Cell, Nature Microbiol, Nature comm., Nucleic Acids Research, EMBO Journal, Cancer Research... and a very recent front cover for the Journal of the American Chemical Society. In addition, Group leaders received awards and distinctions such as the Ruffec Rotary Club for F. Friscourt and the Dr. et de Mme Henri Labbé award from the "Académie des Sciences" to V. Gabelica

### Dr. Jean-Louis Mergny

Executive Scientific Director of the IECB  
Research Director (DR) at Inserm (U1212)

<sup>1</sup> One is 20 years old only once (and so is the institute!)

The development of IECB continues to contribute to the strategy of the University of Bordeaux. For instance, several research teams took an active part into the BRIO network dedicated to translational research on cancer, and participated in the preparation of the future organization of the University. 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 strong 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.

A number of scientific events were organized or hosted at IECB in 2018. Some of them are recurrent events, such as the Young Scientists Symposium (YSS), the Foldamer symposium or the 10<sup>th</sup> RNA club. In addition, monthly internal seminars "Chemistry meets Biology" are now a tradition... which is highly appreciated given that free drinks are provided after the talks. IECB also contributes to the success of "La fête de la science".

In addition, we organized a special Symposium entitled "Science, Culture and Society" to celebrate L. Ghosez's Légion d'honneur. Leon acted as Deputy director of IECB and is still very active in the Institute as an Associate Member. This event was coupled with the celebration of 20 years of existence of IECB. We were honored to host Alain Rousset, President of Nouvelle-Aquitaine, who was a major actor in the creation of IECB.

I hope the reader will find a wide range of useful information in the 2018 IECB scientific report and even, perhaps, reasons to collaborate or to join! Mikayel Aznauryan is our latest recruit: welcome aboard!

So... what's next? Well, how about a new director? As my 10-year term at IECB is ending soon, I have decided to step down in December 2018. These four years at the head of the Institute have been everything but boring... it was an honor and pleasure to lead this institute. I am especially pleased that Rémi Fronzes accepted to take this role, with Gilles Guichard as Executive director.

There are plenty of projects, and plans for changes for the forecoming years: a new boss, new instruments to be installed, new groups, lab space to be refurbished... no time to rest!

Dr Jean-Louis Mergny

A handwritten signature in black ink, appearing to read "JL 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 Univ. Bordeaux. It was created in 1998 with the support of the Aquitaine Regional Council to provide promising European chemists and biologists with an environment designed to facilitate the development of first-class interdisciplinary research programs, in collaboration with international public and private research centres.

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

The IECB is the largest research team incubator in France, with 15 research teams accounting for 200 researchers and expert technicians.

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



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



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



**Dr. Witold FILIPOWICZ**  
Institut Friedrich Miescher,  
Basel, Switzerland



**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



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

# 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

**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

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

## Former ISAB members

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

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

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

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

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

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

**Pr. Steven LEY**  
Departement of 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 – Univ. Bordeaux)

**Mrs. Sylvie DJIAN** Administrative Director (CNRS)

**Dr. Rémi FRONZES** Deputy Scientific Director  
Research Director, team leader UMR5234 (CNRS, Univ. Bordeaux)

**Dr. Gilles GUICHARD** Deputy Scientific Director  
Research Director, team leader UMR5248 (CNRS, Univ. Bordeaux)

## 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. Rémi FRONZES** Team leader  
Research Director, team leader UMR5234 (CNRS, Univ. Bordeaux)

**Dr. Gilles GUICHARD** Team leader  
Research Director, UMR5248 (CNRS – Univ. Bordeaux)

**Dr. Brice KAUFFMANN** Head of IECB's technology platforms  
Engineer, UMS3033 (CNRS – Univ. 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

## Univ. Bordeaux

35 Place Pey Berland, 33000 Bordeaux

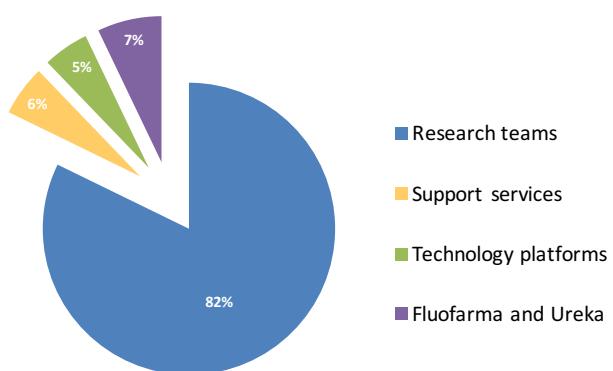
# Organisational Chart



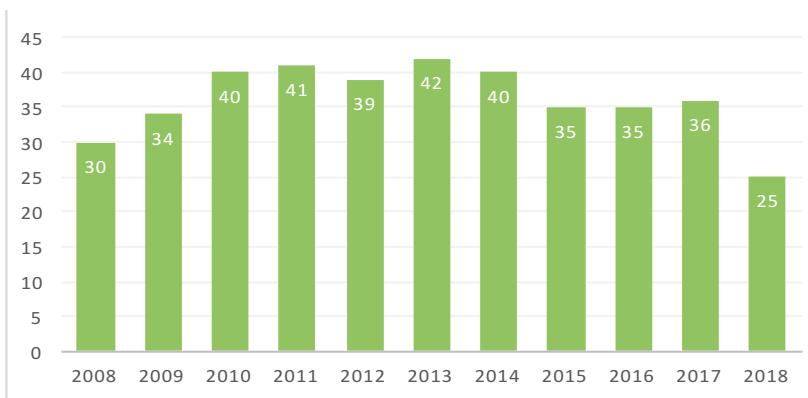
# 2018 Key Figures

In 2018, 197 people were part of the IECB: 162 research staff, 21 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 67% the IECB research staff. This population largely contributes to gender equality and internationalization at IECB. It also testifies to the attractiveness of the institute.

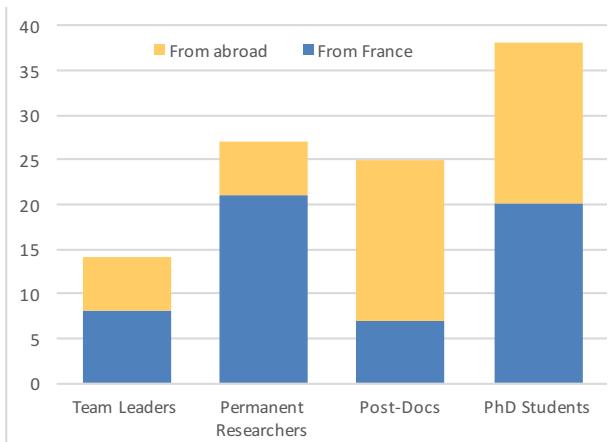
IECB staff by professional category



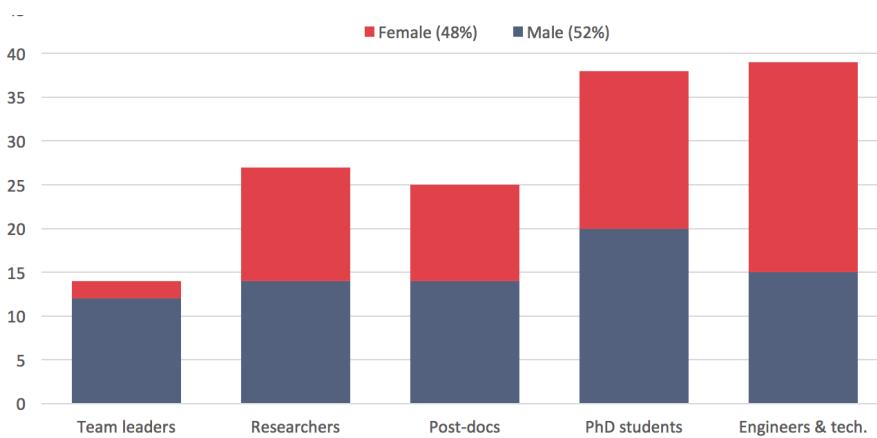
Number of postdoctoral researchers over the past 10 years



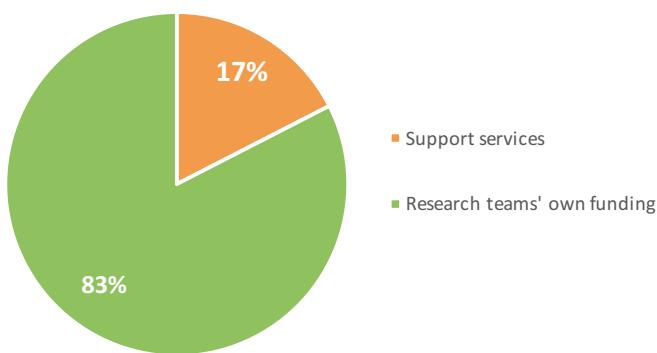
IECB researchers and students by nationality & professional category



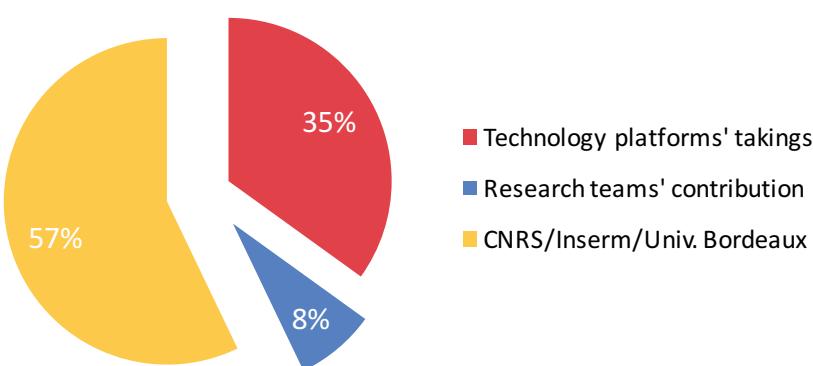
## IECB research staff by gender & professional category



## IECB's 2018 budget



## Support services funding



The budget of the institute, which amounts to 10.7 million 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 staff 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 Univ. Bordeaux, and receives financial support from the Nouvelle - 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, Tech, Inserm

Sandra LAVENANT, Tech., Univ. Bordeaux

Laurent KUBICKI, Tech., Inserm

Patricia MARTIN, Tech., Inserm

Amélie STOTZINGER, AJT, Inserm

#### 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

#### Nuclear magnetic resonance engineer

Estelle MORVAN, IE, CNRS

#### Mass spectrometry engineer

Frédéric ROSU, IR, CNRS

#### Mass spectrometry technician

Loïc KLINGER, AI, CNRS

#### Crystallography engineer

Stéphane MASSIP, IE, Univ. Bordeaux

#### Surface plasmon resonance engineer

Laetitia MINDER, AI, Institut Bergonié

#### Electron microscopy engineer

Armel BEZAULT, IE, CNRS

#### Quality approach

Julie KOWALSKI, Apprentice, Inserm

Loïc KLINGER, AI, CNRS

### Analytical and preparative techniques facilities

#### Head of the analytical and preparative techniques facilities

Jean-Michel BLANC, IE, Inserm

#### Biochemistry and molecular biology engineer

Thierry DAKHLI, Tech., Inserm

#### Laundry

Myriam MEDERIC, AJT, Inserm



**Dr. Mikayel Aznauryan** joined the IECB as Group Leader in November 2018.

The research interests of Mikayel Aznauryan are centered on *molecular biophysics of proteins and nucleic acids and probing the conformations, molecular motions and interactions in these systems*. The main focus of his group is on intrinsically disordered proteins (IDPs) involved in translation initiation and revealing the molecular mechanisms of their function in eukaryotes. For that, he is utilizing and further developing state-of-the-art single-molecule fluorescence microscopy methods for investigation of these complex biomolecular systems *in vitro* and more importantly in live cells.

Mikayel Aznauryan has completed his PhD from the Department of Chemistry of the Yerevan State University in Armenia. After this, he moved to Switzerland as a postdoctoral researcher at the Department of Biochemistry of the University of Zurich (Group of Prof. Benjamin Schuler), followed by a second postdoc at the Department of Chemistry and the Interdisciplinary Nanoscience Center of Aarhus University in Denmark.

His team is affiliated to the ARNA laboratory (Inserm - U1212, CNRS - UMR5320, University of Bordeaux).

# Research Teams & Output



Dr. Axel Innis

Research Director (DR2), Inserm

Axel Innis did his PhD in structural biology at the University of Cambridge, under the supervision of Prof. 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, Axel joined the laboratory of Prof. Thomas Steitz at Yale University (2004–2012). There, he chose to tackle what was, at the time, a little-known form of translational control: gene regulation by nascent polypeptides. He joined IECB as a group leader in January 2013, was awarded the 2017 Coups d'Elan Prize for French Research from the Bettencourt-Schuller Foundation and was selected as a 2017 EMBO Young Investigator.

## Research team

**Dr. Mecit GÖKÇE** Postdoctoral Fellow (Inserm)  
**Dr. Aitor MANTECA** Postdoctoral Fellow (Inserm – EMBO Long Term Fellow)  
**Dr. Britta SEIP** Postdoctoral Fellow (Inserm)  
**Dr. Anne-Xander VAN DER STEL** Postdoctoral Fellow (Inserm)  
**Guénael SACHEAU** Assistant Engineer (Inserm)  
**Mélanie GILLARD-BOCQUET** Project Engineer (Inserm / Univ. Paris Descartes)  
**Natacha PEREBASKINE** Assistant Engineer (CNRS)  
**Elodie LEROY** PhD Student (Inserm)  
**Alba HERRERO DEL VALLE** PhD Student (Univ. Bordeaux)  
**Carolin SEEFELDT** PhD Student (Inserm)

This team is part of Inserm U1212 / CNRS UMR 5320 (ARNA).

# Translational Regulation of Gene Expression

During the translation of genetic information into protein by the ribosome, nascent peptides sometimes block their own synthesis by interacting with the ribosomal interior. Although this process mainly depends on the amino acid sequence of the nascent peptide, it can also require the additional presence of a small molecule, explaining its use for metabolite-dependent gene regulation in bacteria and in eukaryotes. Biochemical and structural studies of ribosomal complexes containing such arrest peptides have yielded key insights into their mode of action, but their ability to sense different types of small molecules, their impact as regulators of gene expression and the molecular mechanisms underlying metabolite binding are still largely unexplored.

The aim of our group is to decipher the arrest code governing nascent chain-mediated translational arrest in bacteria. We seek to achieve this overall aim through four complementary objectives :

1. To assess the extent to which arrest peptides can act as small molecule sensors
2. To identify naturally occurring arrest peptides in bacteria
3. To develop inhibitory peptides that block protein synthesis by targeting the ribosome
4. To uncover the modes of action of arrest or ribosome-targeting antimicrobial peptides through structural and biochemical characterization.

Addressing the natural diversity and molecular bases of the arrest process will be the key to understanding a unique form of gene regulation and a fundamental aspect of ribosome function. It will also provide a handle for designing next-generation antimicrobials.

### 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 (RNC). Thus, arrest peptides are used for metabolite-dependent gene regulation in both prokaryotes and eukaryotes (Seip & Innis (2016)). (Fig. 1). Biological processes that are regulated by arrest peptides in bacteria include the induction of the 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 and the regulation of SecDF2 in low-salinity environments by the arrest peptide VemP.

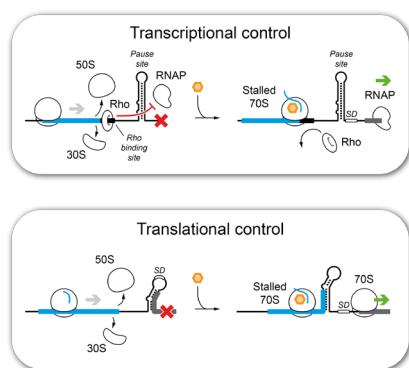
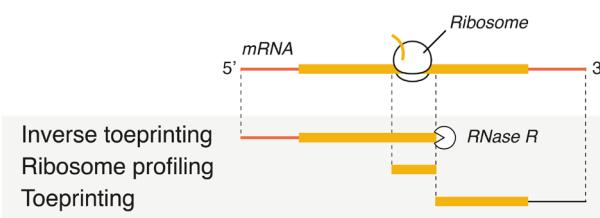


Figure 1 : Arrest peptides regulate gene expression in bacteria. Nascent peptides sometimes block translation by interacting with the exit tunnel of the large ribosomal subunit. This often requires a small ligand – such as a drug or a metabolite (orange hexagon) – to be sensed by a ribosome nascent chain complex carrying a specific arrest peptide (blue). As a result, arrest peptides regulate gene expression in a metabolite-dependent manner in bacteria, using transcriptional or translational mechanisms.

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 has yet to be elucidated, the range of metabolites that can be sensed by the nascent peptide is unknown and the molecular mechanisms of metabolite binding and translational arrest by arrest peptides are only partially understood. As a result, we are developing high-throughput tools to systematically address these issues on a large scale. In particular, we have developed inverse toeprinting, a new method to map the position of ribosomes arrested on messenger RNAs during *in vitro* translation (Seip et al. (2018)) (Fig. 2). Unlike the widely used ribosome profiling approach, our method protects the entire coding region upstream of a stalled ribosome, making it possible to work with transcripts of unknown sequence. We used inverse toeprinting to characterize the pausing landscape of free and drug-bound bacterial ribosomes engaged in translation of a random transcript library. The high-throughput nature of inverse toeprinting resulted in a comprehensive list of arrest motifs along with a quantitative measure of their pause strength, in good agreement with prior *in vivo* data. Thus, our method provides a means to decipher the translational arrest code that can be adapted to other sequence-dependent translational processes.

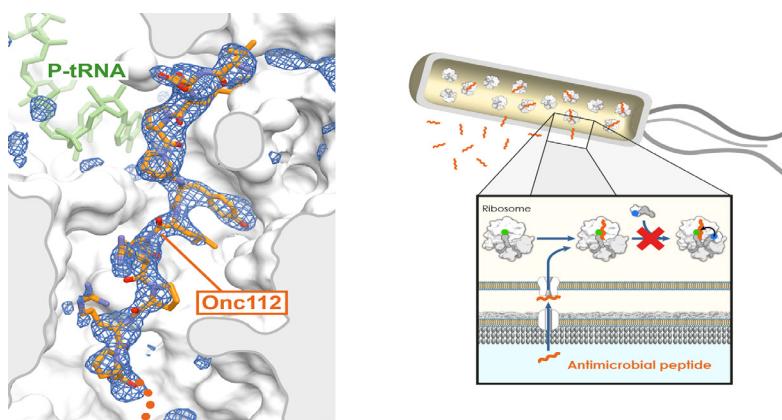
**Figure 2 – Inverse toeprinting locates stalled ribosomes on the mRNA with codon resolution. Comparison between inverse toeprinting, ribosome profiling and classical toeprinting.**



### 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 and other macrolides).

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; Mardirossian et al. 2018) (Fig. 3). 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 (Charon et al. 2019).



**Figure 3 – 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, Pyrrhocoricin or Tur1A operate through a similar mechanism (Seefeldt et al. 2016, Mardirossian et al., 2018).

### Selected publications

Charon J., Manteca A., Innis C.A. (2019). Using the Bacterial Ribosome as a Discovery Platform for Peptide-Based Antibiotics. *Biochemistry*, 58, 75.

Seip B., Sacheau G., Dupuy D., Innis C.A. (2018). Ribosomal stalling landscapes revealed by high-throughput inverse toeprinting of mRNA libraries. *Life Science Alliance*. 1(5):e201800148.

Mardirossian M., Pérubaskine N., Benincasa M., Gambato S., Hofmann S., Huter P., Müller C., Hilpert K., Innis C.A., Tossi A., Wilson D.N. (2018). The Dolphin Proline-Rich Antimicrobial Peptide Tur1A Inhibits Protein Synthesis by Targeting the Bacterial Ribosome. *Cell Chem Biol.* 25, 530.

Graf M., Mardirossian M., Nguyen F., Seefeldt A.C., Guichard G., Scocchi M., Innis C.A., Wilson D.N. (2017). Proline-rich antimicrobial peptides targeting protein synthesis. *Nat Prod Rep.* 34, 702.



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

### Research team

Julie GEAN Associate professor (Univ. Bordeaux, IUT Perigueux)  
 Axelle GRÉLARD Research Engineer IR1 (CNRS)  
 Birgit HABENSTEIN Researcher CRCN (CNRS)  
 Denis MARTINEZ Postdoctoral Fellow (CNRS)  
 Ahmad SAAD PhD Student (Univ. Bordeaux)  
 Mélanie BERBON Engineer IE (CNRS)  
 Mathilde BERTONI Engineer (CNRS)  
 Jayakrishna SHENOY PhD Student (CNRS)  
 Arpita TAWANI Postdoctoral Fellow (CNRS)  
 Gaëlle LAMON PhD Student (CNRS)  
 Nadia EL MAMMERI PhD Student (Univ. Bordeaux)

The team is part of the "Institute of Chemistry and Biology of Membranes & Nanoobjects" (CBMN UMR5248), CNRS / Univ. Bordeaux / Bordeaux INP.

# NMR of Molecular Assemblies

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.

### Functional amyloids

Amyloids are proteins that can undergo a conformational change from a soluble, monomeric to an insoluble, polymeric state, defined by the formation of aggregates ranging from oligomers to protofilaments and fibrils. Several amyloid proteins have been associated with the propagation of neurodegenerative diseases. Recently, numerous amyloid proteins have been identified in mammals, fungi, bacteria or plants as crucial molecular determinants in the execution of native and beneficial biological functions, these proteins are named "functional amyloids" (in contrast to pathological amyloids). Well-known examples of functional amyloids include bacterial curli, hydrophobins or yeast prions. Recently, the formation of high-order fibrillar amyloid assemblies has been discovered in several signalling pathways controlling immunity-related cell fate. The precise role of amyloids in cell fate pathways and the structural mechanisms related to the templating and propagation of amyloid-based assemblies in signal transduction is still poorly understood. In collaboration with the group of Sven Saupe, we investigate the structure-function relationship of several functional amyloids involved in programmed cell death pathways.

We have been investigating the structural architecture of the NWD2 protein, a NOD-like receptor with a N-terminal domain showing amyloid and prion properties. The NWD2 protein is encoded in a gene adjacent to het-S, a prion inducing programmed cell death in *Podospora anserina*. Using solid-state NMR, we determined the local conformation of the amyloid core based on strategic isotope labelling at key positions. Together with *in vivo* data from the Saupe group, it reveals that the NWD2 amyloid fibrils adopt a  $\beta$ -solenoid structure with a highly similar secondary structure compared to the HET-S/s-like systems. Involvement of amyloids in programmed cell death is not limited to fungal species, as recently uncovered for the RIP1/RIP3 necrosome in humans. We engaged into the structural characterization of the protein HELLP from *C. globosum*, sharing homology to the RHIM motif found in the execution of necroptotic cell death in humans. We recombinantly produced and purified HELLP (215–278) amyloid fibrils, and first solid-state NMR data indicate a rigid amyloid core in  $\beta$ -strand conformation.

### Solid-state NMR methods

We develop solid-state NMR methods to tackle complex biomolecular assemblies, to obtain atomic information on the structural architecture, molecular interactions and assembly mechanisms. We work on the development of new solid-state NMR experiments to improve sensitivity and spectral resolution, as well as on strategic isotope labeling schemes to improve the NMR analysis process. Ultra-fast magic-angle spinning NMR techniques are also investigated to improve sensitivity on complex biomolecular systems. Recently, we developed a new solid-state NMR proton-detected three-dimensional experiment dedicated to the observation of protein proton side chain resonances in

nano-liter volumes. The experiment takes advantage of very fast magic angle spinning and double quantum  $^{13}\text{C}$ - $^{13}\text{C}$  transfer to establish efficient ( $\text{H}$ )CCH correlations detected on side chain protons. Our approach was demonstrated on the HET-s prion domain in its functional amyloid fibrillar form, fully protonated, with a sample amount of less than 500 µg using a MAS frequency of 70 kHz. The majority of aliphatic and aromatic side chain protons (70%) are observable, in addition to  $\text{H}\alpha$  resonances, in a single experiment providing a complementary approach to the established proton-detected amide-based multidimensional solid-state NMR experiments for the study and resonance assignment of biosolid samples, in particular for aromatic side chain resonances. This work was performed in collaboration with JEOL Japan (Y. Nishiyama, Riken/JEOL).

#### Remorins and nanodomain interaction (research headed by B. Habenstein)

Membrane nanodomains represent an essential tool of the versatile membrane barriers to create platforms controlling cellular functions and interactions with the cellular environment. REMORINS are nanodomain-organized proteins located in the plasma membrane and involved in cellular responses in plants. In collaboration with S. Mongrand and co-workers (LBM CNRS) we have recently visualised by solid-state NMR ( $^{13}\text{C}$ - and  $^{2}\text{H}$ -detected methods) that nanodomain localisation of REMORINS is mediated by sterols and PI4P and we could propose a model suggesting an unconventional binding mode via the C-terminal anchor domain. Using an ensemble of biophysical approaches, including solid-state NMR, cryo-EM and *in vivo* confocal imaging, we could also provide first insights into the role and the structural basis of REMORIN trimerization. REMORIN coiled-coil trimer formation regulates membrane recruitment and promotes REMORIN assembly *in vitro* into long filaments.

#### Lipid dynamics

The plasma membrane constitutes the interface between the cell and the external environment, playing a crucial role in response to external environmental factors. In order to insure essential processes such as signal transduction, membrane polarization or cellular traffic, membrane receptors adopt specific conformation, often lipid-dependent. Structural characterization of such membrane proteins is challenging due to the nature of the membrane (insoluble, heterogeneous). We use solid-state NMR to understand conformational protein changes at the membrane interface, as well as to decipher lipid dynamics, in liposomes and in nanodiscs. Nanodiscs represent a very promising technology, enabling the reconstitution of a soluble nano-object incorporated in a nanoscopic lipid bilayer. Tremendous advantages of nanodiscs (soluble, small, tunable, accessible to structural studies by high-resolution NMR and cryo-electron microscopy) make them one of the most promising tools to study membrane proteins at atomic resolution. The dynamic and structural behavior of the lipids incorporated in nanodiscs remains hardly investigated and poorly understood. For example, it remains unclear (i) if the membrane-like dynamics and thermotropism of lipids in nanodiscs are similar to the case of vesicles or cellular membranes. (ii) how the lipid-dynamics will adjust to the strictly confined membrane bilayer patch in nanodiscs upon transiting the gel-to-liquid phase transition temperature. (iii) how/if cholesterol changes the dynamics response of lipids when transiting the gel-to-liquid phase transition temperature. In collaboration with the group of Roland Riek (ETH Zurich) and Stefan Bibow (Biozentrum Basel), we have proposed a model of internal lipid dynamics inside nanodiscs and in comparison to liposomes.

#### Tannin-lipid interactions (research headed by Julie Géan)

We study tannin-lipid interactions in the field of oenology and health. In oenology, tannins are responsible for the astringency and the bitterness of red wines. The former implicates an interaction between tannins and saliva proteins during mouth lubrication, while the latter results from an interaction between tannins and taste receptors. We investigate tannin-lipid interactions and the anti-oxidant efficiency of tannins in membranes by liquid and solid-state NMR.

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**Dr. Rémi Fronzes**  
Research Director (DR2), CNRS

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

### Research team

**Dr. Esther MARZA** Lecturer MCU (Univ. Bordeaux)  
**Pr. Jean-Paul BOURDINEAUD** Prof. (Univ. Bordeaux)  
**Thibaud RENAULT** Research Associate (CNRS)  
**Dr. Chiara RAPISARDA** Postdoctoral Fellow (Univ. Bordeaux)  
**Thomas PERRY** PhD Student (Univ. Pierre & Marie Curie)  
**Pauline PONY** PhD Student (Univ. Bordeaux)  
**Leonardo TALACHIA ROSA** Postdoctoral Fellow (CNRS)  
**Pierre NOTTELET** PhD Student (Univ. Bordeaux)  
**Esther GAVELLO-FERNANDEZ** Engineer (CNRS)  
**Robin ANGER** Engineer (CNRS)

The team is part of the unit "Microbiologie Fondamentale et Pathogénicité", UMR5234 / Univ. Bordeaux / CNRS.

# Structure and Function of Bacterial Nano-Machines

Over 7 years, our research aimed at answering a simple question. How macromolecules are transferred through the bacterial cell envelope? Indeed, we study the structure and function of several bacterial secretion systems as well as of the apparatus involved in bacterial transformation (DNA uptake and recombination). These systems are essential to bacterial adaptability and virulence

We have been interested in the structure of the Type 4 and Type 6 secretion systems. These systems are involved in the transfer of proteins through the cellular envelope of Gram-negative bacteria.

The bacterial Type 6 secretion (T6S) system is one of the key players for microbial competition, as well as an important virulence determinant during bacterial infections. It assembles a nano-crossbow-like structure that propels an arrow made of Hcp tube and VgrG spike into the cytoplasm of the attacker cell and punctures the prey's cell wall. The nano-crossbow is stably anchored to the cell envelope of the attacker by a membrane core complex. In collaboration with Eric Cascales' laboratory in Marseille (France), we recently have shown that this membrane complex is assembled by the sequential addition of three proteins –TssJ, TssM and TssL– and presented a negative stain low resolution electron microscopy structure of the fully assembled complex (Nature 2015). We recently obtained the high-resolution cryoEM structure of this complex (not published).

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

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**Dr. Yaser Hashem**

Senior Research Associate (CRCN), Inserm

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

### Research team

**Dr. Marie SISSLER** Research Director DR2 (CNRS, ARNA)

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**Anthony BOCHLER** PhD Student (CNRS)

**Margarita BELINITE** PhD Student (CNRS)

**Dr. Camila PARROT ATER** Postdoctoral Fellow (Univ. Bordeaux)

**Dr. Hedy SOUFARI** Research Engineer IR (Inserm)

**Florian PIERRE** Assistant Engineer AI (CNRS)

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**Anaïs LAMOUREUX** L3 Student (Univ. Bordeaux)

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

# mRNA Translation Regulation in Pathogens and Hosts

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

mRNA translation consists on translating the genetic code carried by the mRNA into proteins by the ribosome that is universally conserved in all cells. However, its structure presents significant differences between bacteria and eukaryotes. Partly because of these differences, the bacterial ribosome can be targeted specifically by a number of antibiotics without affecting the eukaryotic host cells. However, the relative conservation of the ribosome among eukaryotes complicates substantially the search for specific drugs against eukaryotic pathogens such as certain protozoa like plasmodium and kinetoplastids.

Our work along with other studies demonstrates the existence of significant structural differences between ribosomes of protozoa and mammals. Using Cryogenic electron microscopy, we endeavor to investigate such structural differences. Because of the location of these structural differences on the ribosome, they are anticipated to affect some of the vital steps of mRNA translation, especially the initiation process.

Since the arrival of the team to the IECB, several new potential targets have been identified and are currently under investigation.

Our results will significantly advance our understanding of protein synthesis regulation in protozoa and will represent a promising step in the search for more efficient treatments against these eukaryotic pathogens.

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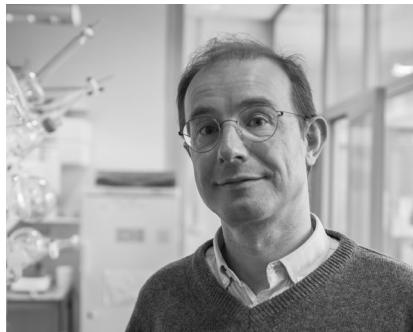
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**Dr. Gilles Guichard**  
Research Director (DR1), CNRS

Gilles Guichard graduated in chemistry from the Ecole Nationale Supérieure de Chimie in Toulouse (1991) and Univ. Montpellier (1992) in France. He received his PhD from the Univ. 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  $\beta$ -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 joined CBMN and 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, bioinspired self-assembled nanostructures and interaction with biomacromolecules.

## Research team

**Dr. Christel DOLAIN** Lecturer (MCU, Univ. Bordeaux)

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**Dr. Guillaume NAULET** ATER (Univ. Bordeaux)

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Antoine HACIHASANOGLU PhD Student (Univ. Bordeaux)

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

# Peptidomimetic Chemistry

The ability of the peptide chain to fold correctly into well-ordered tertiary structures that can further assemble into quaternary structures is a major determinant of protein function. Multiple approaches, at the interface between biology, synthetic organic and polymer chemistries are currently explored to elaborate bioinspired synthetic systems with protein-like structures and functions. By using peptidomimetic and foldamer chemistry, the general aims of our research are (i) to create folded systems mimicking protein secondary structure elements, (ii) to understand how to program folded molecules with the ability to assemble into complex nanostructures, (iii) to study their molecular recognition properties and, (iv) to design effective protein mimics for biomedical applications.

Our main line of research focuses on Peptidomimetic and Foldamer Chemistry and more specifically on aliphatic oligourea foldamers. We are now using the knowledge gained from past structural studies in the group to develop functional foldamers. Early work in this direction led to the discovery of cationic amphiphilic helices mimicking antimicrobial peptides and to sequences that interact with plasmid DNA for the delivery of nucleic acids (Bioconjug. Chem. 2019). Our recent discovery that oligourea foldamers can be interfaced with natural peptide helices and that the two helical forms do communicate within a single strand (Angew. Chem. Int Ed. 2015) is of particular significance for future applications of foldamers in biology. Applications developed in the group include the creation of composite proteins (J. Am. Chem. Soc. 2019, Highlight #1) and the recognition of protein surfaces through  $\alpha$ -helix mimicry for inhibiting protein–protein interactions (PPIs) or activating receptors (Nat. Commun. 2019, Highlight #2). Besides our work on foldamers, we are continuing the development of two structure-guided discovery programs of antibacterial peptides designed to specifically block protein synthesis and DNA replication in bacteria via inactivation of the corresponding molecular machineries: (i) the bacterial ribosome (coll. A. Innis, IECB, Pessac) and (ii) the bacterial sliding clamp (coll. D. Burnouf, IBMC, Strasbourg).

## RECENT HIGHLIGHTS:

### Highlight #1: Artificial composite proteins containing foldamer segments (J. Am. Chem. Soc. 2019 – selected for the cover ; coll. J.L. Mergny & G. Salgado)

The similarities in screw sense, pitch, and polarity between peptide  $\alpha$ -helices and oligourea helices suggest that a tertiary structure could be retained when swapping the two backbones in a protein sequence. In this work we explored the chemical synthesis, folding, and function of artificial proteins created by substituting a folded peptide segment in the target protein (e.g. a  $\alpha$ -helical region) by its non-peptide foldamer counterpart, with the expectation that the resulting molecule would maintain its ability to fold while manifesting new exploitable features. We designed a foldamer mimic of a natural zinc finger domain from the DNA-binding protein Egr1 in which the original  $\alpha$ -helix was replaced by an oligourea sequence bearing two appropriately spaced imidazole side chains for zinc coordination. We showed by spectroscopic techniques and mass spectrometry analysis under native conditions that the ability of the peptide/oligourea hybrid to coordinate the zinc ion was not affected by the foldamer replacement. Moreover, detailed NMR analysis provided evidence that the engineered zinc finger motif adopts a folded structure in which the native  $\beta$ -sheet arrangement of the peptide region and global arrangement of DNA-binding side chains are preserved.

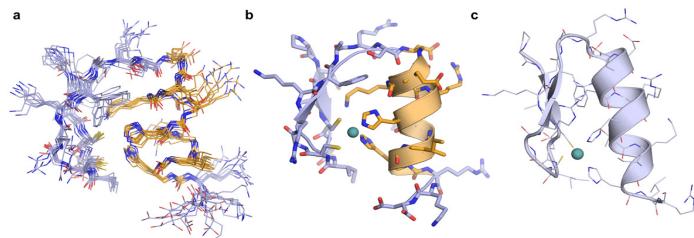


Fig. 1. (a,b) NMR-derived model of a composite zinc finger (peptide in blue and oligourea in orange) and (c) comparison with the native zinc finger

### Highlight #2: Peptide–oligourea hybrid analogues of a peptide hormone with improved action in vivo (Nat. Commun. 2019; collaborative work with UREkA)

Our ability to synthesize sequence-specific synthetic oligomers that fold into well-defined helical structures opens up enticing opportunities for mimicking peptides and addressing some of their limitations such as short in vivo half-lives. Herein, we have used peptide–oligourea hybrids to produce effective mimics of Class-B GPCR ligands with increased resistance to proteolytic degradation. In particular, we have shown that oligourea foldamers are effective tools to improve the pharmaceutical properties of GLP-1, a 31 amino acid peptide hormone involved in metabolism and glycemic control. Our strategy consists in replacing four consecutive amino acids of GLP-1 by three consecutive ureido residues by capitalizing on the structural resemblance of oligourea and  $\alpha$ -peptide helices. The efficacy of the approach was demonstrated with three GLP-1-oligourea hybrids showing prolonged activity in vivo. Our findings should enable the use of oligoureas in other peptides to improve their pharmaceutical properties. This technology named Urelax<sup>TM</sup> was patented and licensed to UREkA, a start-up company created in 2010, and located at IECB.

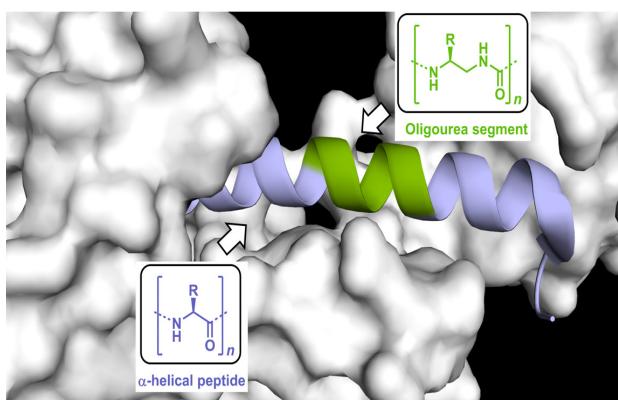
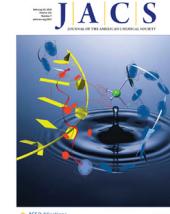


Fig. 2. Effective mimicry of GLP-1 using a foldamer-based approach that consists in replacing a  $\alpha$ -helical peptide portion by a oligourea insert (green).

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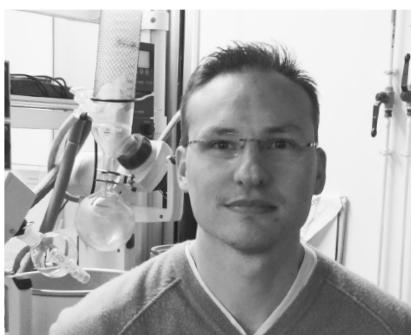
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**Dr. Frédéric Friscourt**  
ATIP-Avenir, CNRS-Univ. Bordeaux

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

## Research team

**Dr. Jürgen SCHULZ** Research Engineer IR2 (CNRS)  
**Dr. Zoeisha CHINOY** Postdoctoral Fellow (CNRS)  
**Camille FAVRE** PhD Student (Univ. Bordeaux)  
**Tarek KHALAF** Master Student (Univ. Bordeaux)  
**Magaly HARIGNORDOQUY** L3 Student (Univ. Bordeaux)  
**Dr. Danielle SKROPETA** A/P – IdEx Visiting Scholar (Univ. Wollongong)

This team is part of the “Institut de Neurosciences Cognitives et Intégratives d’Aquitaine” (INRIA), CNRS / Univ. 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.

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, thereby increasing background signal.

To address these difficulties, we are developing fluorogenic bioorthogonal systems, in which non- or weakly fluorescent reagents produce highly fluorescent products as well as more stable chemical reporters.

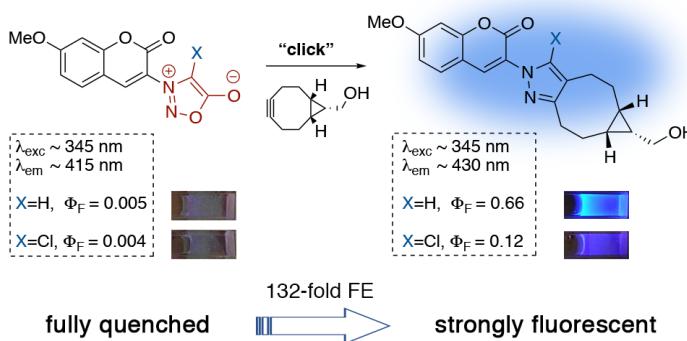
### Novel Fluorogenic Systems.

We have recently developed a fluorogenic cyclooctyne FI-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 FI-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 FI-DIBO give highly fluorescent 1H-pyrazoles (10,000 times brighter than FI-DIBO) (Chem. Eur. J 2015).

To circumvent the stability issue of diazo reagents, we turned our attention on employing sydnone, stable mesoionic 1,3-dipoles that can also generate 1H-pyrazoles upon [3 + 2] cycloadditions with alkynes. Upon copper-free click reaction with FI-DIBO, sydnone generated pyrazoles that were found to be highly fluorescent with compelling photophysical properties including excellent fluorescence enhancement (up to 240-fold) and high quantum yields (over 45%). (J. Org. Chem. 2018).



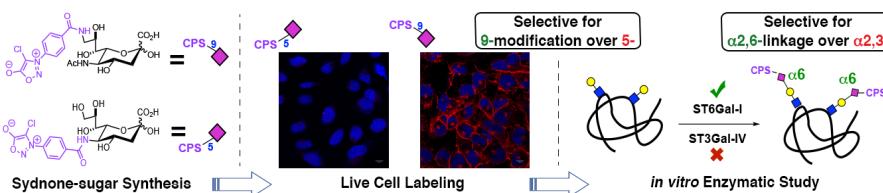
In our effort to develop novel fluorogenic reagents, we recently showed that the sydnone moiety could also efficiently quench the fluorescence of coumarin, which could be restored, with a 132-fold enhancement, upon cycloadditions with cyclooctynes and were successfully applied, in a biochemical context, for the highly specific labeling of proteins in no-wash conditions. TD-DFT calculations suggested that the fluorescence quenching of the sydnone-modified coumarins was likely due to the presence of an energetically low-lying non-emissive charge-separated state (Org. Lett. 2018).



### Sydnones as novel glyco-reporters.

Current chemical reporters are often reactive towards biological thiols, which raises concerns about their metabolic fate. To address this limitation, we recently developed modified monosaccharides with **sydnones** for the tagging of complex glycans in living mammalian cells (Angew. Chem. Int. Ed. 2019).

We showed that the positioning of the reporter on the sialic acid scaffold significantly altered its metabolic fate. While employing the 9-modified neuraminic acid led to robust cell-surface labeling, the 5-modified analog was not metabolized by cells and we identified CMP-sialic acid synthetase as the enzymatic roadblock. Further in vitro enzymatic assays also revealed that the 9-modified neuraminic acid is preferentially accepted by the sialyltransferase ST6Gal-I over ST3Gal-IV, leading to the favored incorporation of the reporter into linkage-specific  $\alpha$ 2,6-N-linked sialoproteins, making 9-sydnone modified neuraminic acid a valuable probe to selectively track and capture a subset of sialosides.



### Selected publications

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Dr. Cameron Mackereth

Research Director (DR2), 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 (chargé de recherche, CR1) within the French National Institute of Health and Medical Research (Inserm), and in 2017 became an Inserm research director (directeur de recherche, DR2).

### Research team

**Dr. Pierre BONNAFOUS** Associate Professor  
MCF (Univ. Bordeaux)

**Sabrina ROUSSEAU** Research Engineer (Inserm)

**Dr. Renata GRZYWA** Assistant Professor  
(Wroclaw University of Technology)

**Dr. Sabina KOJ** Postdoctoral Fellow (Ludwig Hirschfeld Institute of Immunology and Experimental Therapy)

**Esther MYRIAM NZE MBA EBENE M2**  
Student (Univ. Bordeaux)

This team is part of the "Acides nucléiques: régulations naturelle et artificielle" Inserm U1212, CNRS UMR 5320 / Univ. Bordeaux.

# 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. The goal is to connect protein structure and dynamics to the selective binding of RNA, and thus understand essential biomolecular interactions and to model disease mutations.

### Molecular details of RNA binding.

A major focus of the group continues to be the study of protein-RNA interactions, especially those involved in tissue-specific alternative splicing. In general, precise regulation of mRNA processing, translation, localization, and stability, relies on specific and regulated interactions with RNA-binding proteins. The biological function of these proteins, along with their target preferences, are determined by their preferred RNA motifs. This year we have published our work on the RBPMS protein family, including the MEC-8 splicing factor from the small worm *C. elegans*, as well as couch potato from the fruit fly *Drosophila melanogaster*, and human RBPMS (RNA-binding protein with multiple splicing). These proteins play important roles in tissue development in many species, and includes normal human development. To determine the molecular basis for how this protein interacts with RNA, we have collected atomic details of the RNA-binding domain common to all family members.

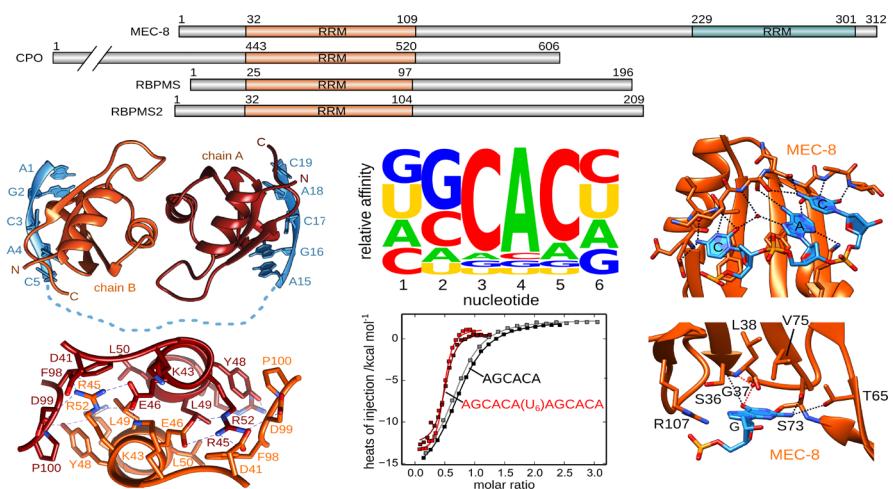


Fig. 1 : From Soufari and Mackereth, 2017, RNA, 23:308-316.

An RNA-binding domain, shown highlighted orange in the figure (RRM = RNA recognition motif), is common to all members of the RBPMS protein family. We have determined the crystal structure of the MEC-8 N-terminal RRM domain from *C. elegans* bound to a ligand containing two GCAC motif sequences. This RRM forms a tight dimer as shown by the labelled amino acids along the interface. We have used the biophysical technique of isothermal titration calorimetry (ITC) to find the optimal binding sequence with six nucleotides, and find that the middle four bases are preferred to be GCAC. In addition,

the dimer nature of the domain means that two motifs on the same ligand bind better than a single motif. Apart from the manner by which the CAC are bound by MEC-8, a key finding is that MEC-8, couch potato and RBPMS, all prefer a guanine as the first base in the RNA motif. This preference is explained by the atomic details of the complex. Using the structural and binding information will improve our understanding of how these proteins interact with their targets, and thus enable improved design of mutants to test for *in vivo* consequences of a precise lack of MEC-8, couch potato or RBPMS function in binding RNA.

Another major project in the group is the study of proline isomerases, and this year we were excited to report that the human proline isomerase FKBP25 specifically binds to RNA. In collaboration with the group of Chris Nelson at the University of Victoria (Canada) we have found that the N-terminal domain in FKBP25 represents a novel protein module that binds selectively to double-stranded RNA (dsRNA). This interaction is required to mediate the nucleolar localization of FKBP25, and also to maintain its protein–protein interaction network. The primary studies were carried out jointly by postdoc Santosh Kumar Upadhyay (IECB) and PhD Student Dave Dilworth (Univ. Victoria). Multidisciplinary approaches include the use of proximity biotin labeling (BioID), immunoprecipitation studies, immunofluorescence, NMR spectroscopy and a range of biophysical methods. Selected results are highlighted in the figure: (A) identification of cellular protein partners of FKBP25 using proximity biotin labeling (BioID) indicating a number of ribosome biogenesis factors, (B) immunofluorescence observation of RNA-dependent nucleolar localization of FKBP25, (C) FKBP25 binds to dsRNA by electrophoretic mobility shift assays, (D) a docking model of the complex between dsRNA and the N-terminal basic tilted helix bundle domain of FKBP25.

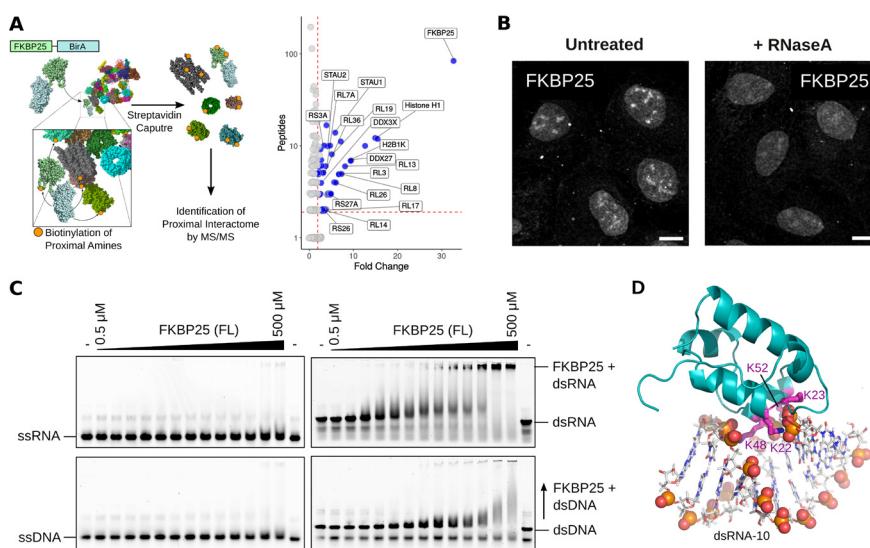


Fig. 2 : From Dilworth, Upadhyay et al, 2017, *Nucleic Acids Res.* 45:11989–12004.

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**Dr. Jean-Louis Mergny**  
Research Director (DR1), Inserm

Jean-Louis Mergny graduated from Ecole Normale Supérieure, 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, Univ. Bordeaux)

**Dr. Gilmar SALGADO** Assistant Professor (MdC, Univ. Bordeaux)

**Dr. Samir AMRANE** Researcher (CRCN, Inserm)

**Dr. Carmelo DI PRIMO** Researcher (CRHC, Inserm)

**Aurore GUÉDIN** Tech. Assistant AI (Inserm)

**MINGPAN CHENG** Postdoctoral Fellow (Idex - Bordeaux)

**Mona SAAD** PhD Student (Univ. Bordeaux - U. Liban)

**Julien MARQUEVIELLE** PhD Student (Univ. Bordeaux)

**Jielin CHEN** PhD Student (Univ. Nanjing)

**Pierre NOTTELET** M2 Student (Univ. Bordeaux)

**Mona WAHIB** M2 Student (Univ. Bordeaux)

**Almamy DIALLO** M2 Student (Univ. Bordeaux)

**Coralie ROBERT** M1 Student (Univ. Bordeaux)

**Harry KASKI** L3 Student (Univ. Bordeaux)

**Malick DIALLO** L3 Student (Univ. Bordeaux)

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

# 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. In addition, we are also interested in the unusual structures formed by C-rich DNA sequences, called the i-motif.

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 tested first on DNA and now on RNA. 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; Gueddouda, BBA, 2017).

### 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 anticancer, antiviral or antiparasitic 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 and i-motifs can be incorporated into nanodevices.

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**Dr. Derek McCusker**

Research Director (DR2), CNRS

Derek McCusker studied Immunology at Glasgow University and focused on the role of the proteasome in immunity 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 (CNRS)

**Julien MECA** PhD Student (Univ. Bordeaux)

**Dr. Elodie SARTOREL** Postdoctoral Fellow (CNRS)

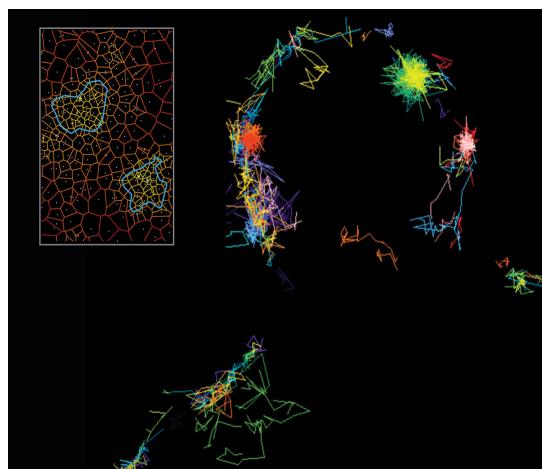
This team is part of the unit "Institut de Biochimie et Génétique Cellulaire" (IBGC), CNRS UMR 5095 / Univ. Bordeaux.

# Dynamics of Cell Growth & 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. In humans, 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 in the model eukaryote *Saccharomyces cerevisiae*. We address these fundamental questions using cutting-edge interdisciplinary approaches.

### Phosphatidylserine and GTPase activation control Cdc42 nanoclustering to counter dissipative diffusion.

All cells establish a single polarity axis that enables chromosomes to be equally partitioned into the mother and daughter cell at the end of each cell cycle. Defects in the establishment of a single polarity axis are directly linked to tumourogenesis. Cdc42 is an essential, conserved polarity regulator in all eukaryotic species. In budding yeast, Cdc42 localization defines where the cell will grow and divide during the cell cycle. The mechanisms ensuring that Cdc42 concentrates at a single site are incompletely understood. Here, we used high-density single protein tracking combined with photoactivation localization microscopy (sptPALM) to monitor Cdc42 dynamics and organization at single molecule resolution in budding yeast (Figure 1). We found that the mobility of Cdc42 was reduced at the pole of the cell compared with other regions of the membrane. This is important, since reduced mobility would stabilize the protein at the pole, helping to concentrate it there and establish a robust polarity axis. We found that Cdc42 is organized in very small "nanoclusters" and that these clusters are larger at the cell pole than elsewhere on the plasma membrane (Figure 1, inset). Two factors were identified that reduce Cdc42 mobility and promote its nanoclustering: the activation of the GTPase and a specific lipid called phosphatidylserine that is enriched at the cell pole. Phosphatidylserine appears to promote Cdc42 nanoclustering via a scaffold protein called Bem1 that interacts with Cdc42, and that we previously demonstrated boosts the activation of Cdc42. These studies reveal how the mobility of a Rho GTPase is controlled to counter the depletive effects of diffusion, thus stabilizing Cdc42 on the plasma membrane and sustaining cell polarity. This work was published in MBoC in 2018.



*Figure 1. Single molecule imaging of Cdc42 in budding yeast. On the right, each track displays a single molecule localization. Note how some Cdc42 molecules are highly confined (green, pink and orange) while others are free to diffuse. Inset displays single molecule localizations in white and Cdc42 nanoclusters in blue.*

### Avidity-driven polarity axis establishment via multivalent lipid-GTPase module interactions.

While Rho GTPases are indispensable regulators of cellular polarity, the mechanisms underlying their anisotropic activation at membranes have been elusive. Using the budding yeast Cdc42 GTPase module, which includes a Guanine nucleotide Exchange Factor (GEF) Cdc24 and the scaffold Bem1, we found that avidity generated via multivalent anionic lipid interactions is a critical mechanistic constituent of polarity establishment. We identified basic cluster (BC) motifs in Bem1 that drive the interaction of the scaffold-GEF complex with anionic lipids including phosphatidylserine at the cell pole. This interaction appears to influence lipid acyl chain ordering, thus regulating membrane rigidity and feedback between Cdc42 and the local membrane environment. Sequential mutation of the Bem1 BC motifs, PX domain and the PH domain of Cdc24 led to a progressive loss of cellular polarity stemming from defective Cdc42 nanoclustering on the plasma membrane and perturbed GTPase signaling (Figure 2). Our work demonstrates the importance of avidity via multivalent anionic lipid interactions in the spatial control of GTPase activation.

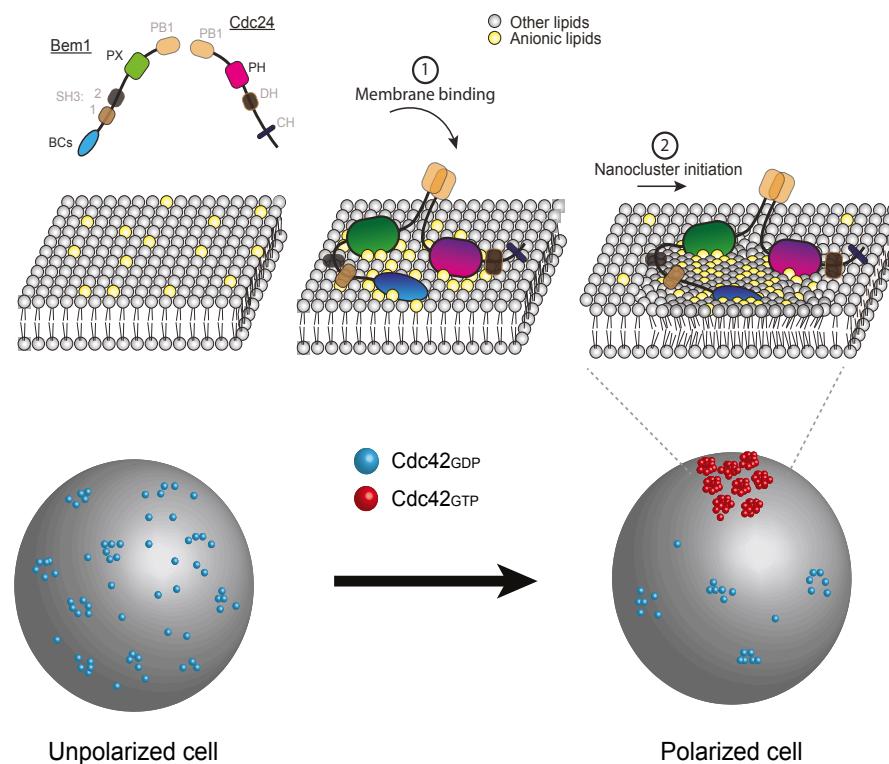


Figure 2. Schematic illustrating the relationship between Cdc42 regulators and the membrane environment during the establishment of a polarity axis. 1) The Bem1-Cdc24 complex is recruited to the plasma membrane via multivalent interactions with anionic lipids such as phosphatidylserine. The BC motifs in Bem1 provide the strongest affinity for anionic lipids at this step. 2) Upon their recruitment to anionic lipids, the Bem1 BC motifs may influence the local membrane environment, contributing to local Cdc42 activation by Cdc24 and Cdc42 nanoclustering.

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• See highlights on CNRS INSB website: <http://www.insb.cnrs.fr/fr/cnrsinfo/le-reglage-de-la-boussole-cellulaire>

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**Dr. Anne Royou**  
Research Director (DR2), CNRS

Following a bachelor degree in physiology and cell biology, Anne Royou did a postgraduate 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. In 2016 she was promoted DR2 by the CNRS.

### Research team

**Dr. Anne ROYOU** Team Leader (CNRS)  
**Marie-Charlotte CLAVERIE** Assistant Engineer (Univ. Bordeaux)  
**Dr. Emilie MONTEBAULT** Researcher (CNRS)  
**Priscillia PIERRE-ELIES** Assistant Engineer (CNRS)  
**Lou BOUIT** Assistant Engineer (ERC-STG NoAneuploidy)  
**Dr. Jérôme TOUTAIN** Hospital practitioner (CHU Bordeaux/CNRS)  
**Dr. James JENKINS** Postdoctoral Fellow (Région Aquitaine)

This team is part of the "Institut de Biochimie et Génétique Cellulaire" (IBGC), CNRS / Univ. 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 trailing chromatids 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

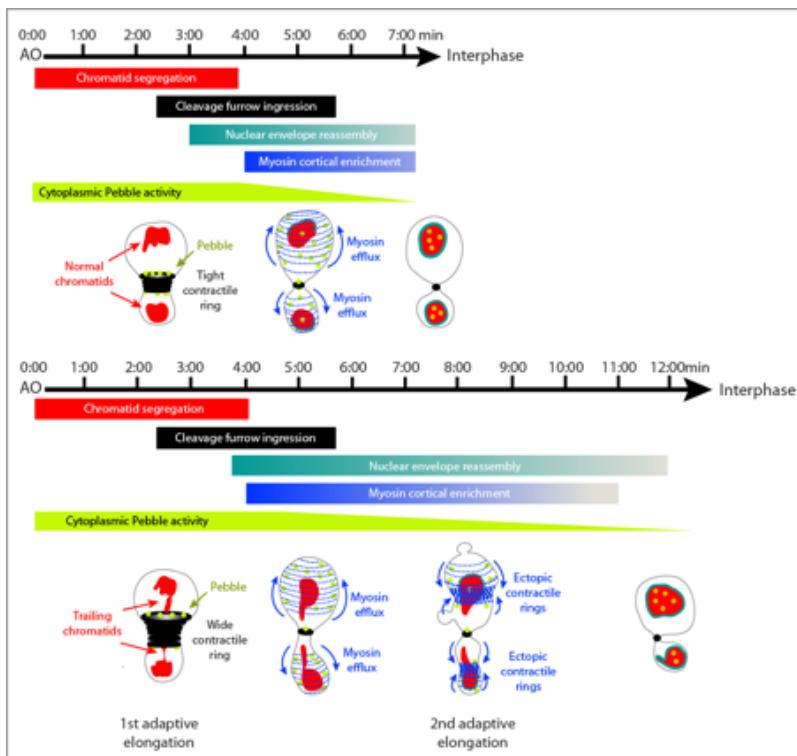
The presence of DNA damage, such as DNA double-strand breaks (DSB), triggers the activation of the DNA Damage Response (DDR), which delays the cell cycle and promotes DNA repair. While the DNA damage response is well documented in interphase, less is known about the response to DSB during mitosis. The presence of DSB 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. Our team has uncovered a process by which broken chromosomes are faithfully transmitted, via the tethering of the two broken chromosome ends. We demonstrate that the mitotic proteins Polo, BubR1 and Bub3 accumulate on DSB during mitosis and facilitate the proper segregation of the broken chromosome fragment. This requires the BubR1-mediated sequestration FizzyCdc20 (Fzy) and subsequent local inhibition of the E3 ubiquitin ligase Anaphase-promoting-complex/cyclosome (APC/C) at the site of damage.

Using a pulsed UV laser to create DNA breaks in a precise spatiotemporal manner, we monitor the dynamics of Polo, BubR1, Bub3 and Fzy at DNA lesions. Our data reveal that Polo is promptly recruited to DNA damage and precedes BubR1, Bub3 and Fzy. All proteins reach their maximum level on DNA lesions just after anaphase onset, which coincides with the sharp decline of CDK1 activity. While BubR1, Bub3 and Fzy completely disassemble from DSB at the end of mitosis, a pool of Polo remains on the lesions well into the next interphase. Attenuation of Polo kinase activity severely alters the kinetics of Polo, BubR1 and Bub3 at DNA lesions indicating that Polo acts to promote the robust recruitment of BubR1 and Bub3 to DNA breaks. Finally we demonstrate that the DNA damage sensor complex Mre11-Rad50-Nbs1 (MRN) is necessary and sufficient for the localization of Polo, and, hence, BubR1 and Bub3, to DNA lesions. Our data support a model in which, DNA damage in mitosis are rapidly marked by the MRN complex, which, in turn, promotes the recruitment of Polo and the subsequent accumulation of BubR1 and Bub3. The BubR1/Bub3-mediated APC/C inhibition at damage sites prevents the

degradation of key components involved in tethering the broken fragments throughout mitosis.

#### 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 trailing chromatids at the site of division by transiently, but dramatically, elongating during anaphase, thus facilitating the clearance of the trailing chromatids from the cleavage plane. This adaptive elongation depends on myosin activity and the Rho Guanine-nucleotide exchange factor, Pebble. Cells promote the clearance of trailing chromatids from the cleavage site by undergoing two phases of adaptive elongation. The first phase relies on assembly of a wide contractile ring at the onset of cytokinesis. The second phase requires outward flux of myosin from the ring toward the polar cortex during ring constriction. Myosin efflux is a novel feature of cytokinesis and its duration is coupled to nuclear envelope reassembly (NER) and the ensuing nuclear sequestration of Pebble. Trailing chromatids induce a delay in NER concomitant with a prolonged period of cortical myosin activity, thus providing forces for the second adaptive elongation. The cytoplasmic retention of Pebble is sufficient to prolong myosin efflux and promote elongation in the absence of trailing chromatids. We propose that the modulation of cortical myosin dynamics is part of the cellular response triggered by an anaphase checkpoint that delays NER when trailing chromatids are present at the midzone (Figure 1).



**Figure 1 | Model for adaptive cell elongation in the presence of trailing chromatids**

The top and bottom panels illustrate key mitotic exit events in cells with normal (NC) and trailing chromatids (TC) respectively, from anaphase onset (AO). The red, black, cyan and blue rectangles represent the average duration of chromatids poleward movement, cleavage furrow ingression, nuclear envelope reassembly (NER) and myosin cortical enrichment respectively. The rectangles are timely positioned with respect to AO. The variability in the duration of NER and myosin efflux is symbolized by color fading at the extremities. The green shape symbolizes putative Pebble cytoplasmic activity throughout mitotic exit. The schemes illustrate the state of the four events listed above at key moments during mitotic exit. Three minutes after AO, Pebble (green dots) concentrates at the midzone where a tight contractile ring (black circles) assembles when chromatids (red) have segregated to the poles. The presence of trailing chromatids at the midzone favors the assembly of a wide ring, whose contraction generates the first cell elongation. Next, myosin initiates Pebble-mediated efflux and invades the polar cortex (blue dashed thin curves) while nuclear envelope starts reassembling on the chromosome mass at the poles (cyan dashed lines). In control cells, myosin disassembles from the polar cortex upon completion of NER (cyan lines), 7 minutes, on average, after AO. The presence of TC near the midzone induces a severe delay in NER completion. Consequently, the delay in Pebble nuclear import prolongs active cortical myosin, which reorganizes into ectopic lateral rings (blue dashed thick curves). The partial contraction of the rings promotes the second phase of elongation, allowing the clearance of the trailing chromatids from the cleavage plane. Myosin dissociates from the cortex upon completion of NER 12 minutes, on average, after AO.

#### Selected publications

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Malmanche N., Dourlen P., Gistelinck M., Demiautte F., Link N., Dupont C., Vanden Broeck L., Werkmeister E., Amouyel P., Bongiovanni A., Bauderlique H., Moehars D., Royou A., Bellen HJ., Lafont F., Callaerts P., Lambert JC., Dermaut B. (2017) Sci Rep. 23;7:40764



**Dr. David Santamaría**

Group leader (DR2), Inserm

David Santamaría received his PhD from University Autónoma of Madrid (Spain) in 1999, under the guidance of Prof. Jorge B. Schwartzman, studying replication fork barriers. He then joined the laboratory of Prof. Ronald A. Laskey, (1999–2003) at the Wellcome/CRC Institute (Cambridge, UK) where he dealt with the initiation of DNA replication and its connection with cell cycle control. He returned to Spain (2003–2016) as a staff scientist in Prof. Mariano Barbacid group (CNIO, Madrid) where he used mouse genetics to conduct a comprehensive analysis of the Cyclin Dependent Kinase family and to identify therapeutic targets in lung adenocarcinoma. He joined the IECB in 2016 and obtained a DR2 Inserm position starting January 2018. He will continue his research on novel oncogenic pathways and signalling mediators in lung adenocarcinoma.

### Research team

**Dr. Marie-Julie Nokin** Postdoctoral Fellow (Univ. Bordeaux)  
**Sonia SAN JOSÉ** Assistant Ingénierie (Univ. Bordeaux)  
**Oriane GALMAR** PhD Student (Univ. Bordeaux)  
**Aurélie LACOUTURE** M2 Student (Univ. Bordeaux)

The team is part of the unit ACTION U1218 Inserm / Univ. Bordeaux.

# Novel Mediators in Lung Oncogenesis

We use mouse models to characterize new signalling pathways and oncogenic functions that govern the onset of lung adenocarcinoma (LUAD). We have a particular interest in the mechanisms that regulate the initiation, intensity and duration of the RAS-ERK signalling. The regulation of this pathway is an essential feature controlling tumour initiation, disease progression and drug resistance to several targeted agents. Our recent work identified a key role of KRAS membrane dimerization/clusterization in this process. The characterization of the molecular basis underlying this feature may identify novel therapeutic targets with low toxicity and potential clinical applicability.

Lung cancer is the leading cause of cancer deaths worldwide (<http://www.who.int/cancer/en/>) causing more casualties than breast, pancreas, prostate and colon cancers combined. The discovery of driver oncogenic mutations has revolutionized lung adenocarcinoma (LUAD) treatment as it allowed the development of rationally targeted therapies. In some LUAD patients the use of targeted drugs led to unprecedented results inducing response rates greater than 60% and a remarkable improvement in progression-free survival. Ironically, the development of precision therapies has not been possible for the most abundant LUAD patient group: those harbouring KRAS mutations.

Our aim is to better understand KRAS biology to identify potential tumour-specific vulnerabilities. We have recently participated in the validation of KRAS dimerization/clusterization as an essential oncogenic function. KRAS dimerization in the membrane is required for the activation of downstream signalling and the establishment of an oncogenic output (Ambrogio et al, 2018). This finding suggests that there are considerable gaps in our knowledge of KRAS function and that new discoveries might have potential therapeutic application. We are currently developing a genetic approach *in vivo* to better understand KRAS dimerization and how it can be exploited as a therapeutic strategy, using lung adenocarcinoma as a working model. We aim to identify and characterize structural co-factors that are required for the formation and/or stabilization of KRAS-clusters and the downstream signalling pathways that depend on them. To this end we will combine biochemical and imaging approaches including protein-specific localized crosslinking combined with proteomics and single-molecule localization microscopy. Finally, we will develop a flexible cellular system compatible with high-throughput screening for the identification of compounds preventing KRAS dimerization. In summary, our current efforts aim to elucidate whether targeting KRAS *in vivo* by interfering with its dimerization/clusterization capacity could provide therapeutic benefit with low systemic toxicity, the ideal combination for any anti-cancer treatment.

In addition, we have a special interest in understanding the biological basis of drug resistance to targeted agents. In LUAD, most drugs currently undergoing clinical evaluation target the RAS-ERK pathway. In this context, disease relapse is often associated with RAS-ERK reactivation. Indeed, recent evidences suggest that RAS-ERK regulators implicated in signal reactivation can be targeted to restore drug sensitivity (Dardaei et al, 2018). Yet, we still have incomplete understanding of the regulation of this network. Using a combination of inducible oncogenes we have demonstrated that the intensity of the RAS-ERK signal *in vivo* is critical in dictating the nature of the cancer-initiating cell and the resulting tumour phenotype (Nieto et al, 2017). We are currently using cell lines derived from these mouse models to induce quantitative differences in the RAS-ERK pathway including a toxic condition. This provides selective pressure to perform unbiased screens to identify novel positive and negative regulators of the RAS-ERK cascade.

Finally, recent studies in BRAFV600E mutant melanoma patients have identified that drug resistance occurs at the expense of new vulnerabilities that can be exploited in the clinic to efficiently fight disease relapse (Wang et al, 2018). Using cell lines and patient derived xenografts we are currently investigating whether similar acquired vulnerabilities occur in BRAFV600E mutant LUAD.

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Ambrogio C., Darbo E., Lee S.W., Santamaría D. (2018) A putative role for Discoidin Domain Receptor 1 in cancer chemoresistance. *Cell Adh Migr.* 3, 1–4. doi: 10.1080/19336918.2018.1445954.

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**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 a permanent position as FNRS research associate 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. She obtained an ERC Consolidator grant in 2014. 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.

V. Gabelica has been validated as group leader by the IECB International Advisory Board in October 2018.

### Research team

Dr. Eric LARGY Maître de Conférences (Univ. Bordeaux)  
Dr. Steven DALY Postdoctoral Fellow (Inserm)  
Dr. Anirban GHOSH Postdoctoral Fellow (Inserm)  
Dr. Nina KHRISTENKO Postdoctoral Fellow (Inserm)  
Dr. Jorge GONZALEZ IdEX Postdoctoral Fellow (Univ. Bordeaux)  
Stefano PICCOLO PhD Student (Inserm)

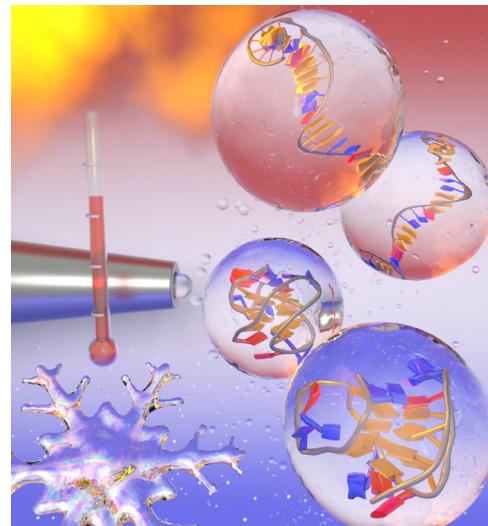
This team is part of the unit "RNA: Natural and Artificial Regulation" (ARNA), Inserm U1212 / CNRS UMR5320 / Univ. Bordeaux.

# Mass Spectrometry of Nucleic Acids & Supramolecular Complexes

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

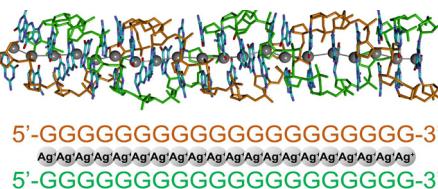
### G-quadruplex interactions with cations and ligands

In the past years, we intensively studied G-quadruplex interactions with cations and ligands. By integrating mass spectrometry in the panel of biophysical methods, we have the advantage of a direct readout of the stoichiometry of the complexes, and thus the ability to reveal unexpected ones. The main highlight of the last year was the first MS monitoring of thermal denaturation of ligand-nucleic acid complexes (*J. Am. Chem. Soc.* 2018). Designing ligands targeting G-quadruplex nucleic acid structures and affect cellular processes is complicated because there are multiple target sequences and some are polymorphic. Further, structure alone does not reveal the driving forces for ligand binding. To know why a ligand binds, the thermodynamics of binding must be characterized. Electrospray mass spectrometry enables one to detect and quantify each specific stoichiometry (number of strands, cations and ligands) and thus to simultaneously determine the equilibrium formation constants for each complex. Using a temperature-controlled nano-electrospray source, we determined the temperature dependence of the equilibrium constants, and thus the enthalpic and entropic contributions to the formation of each stoichiometric state. Enthalpy drives the formation of each quartet-K<sup>+</sup>-quartet unit, whereas entropy drives the formation of quartet-K<sup>+</sup>-triplet units. Consequently, slip-stranded structures can become more abundant as the temperature increases. In most cases, ligand-G4 binding is entropically driven, and we discuss that this may have resulted from biases when ranking ligand potency using melting experiments. Other thermodynamic profiles could be linked to topology changes in terms of number of G-quartets, which is reflected in the number of specific K<sup>+</sup> ions in the complex. The thermodynamics of ligand binding to each form, one ligand at a time, provides unprecedented detail on the interplay between ligand binding and topology changes in terms of number of G-quartets. Our results revisit years of biophysical research based on thermal denaturation.



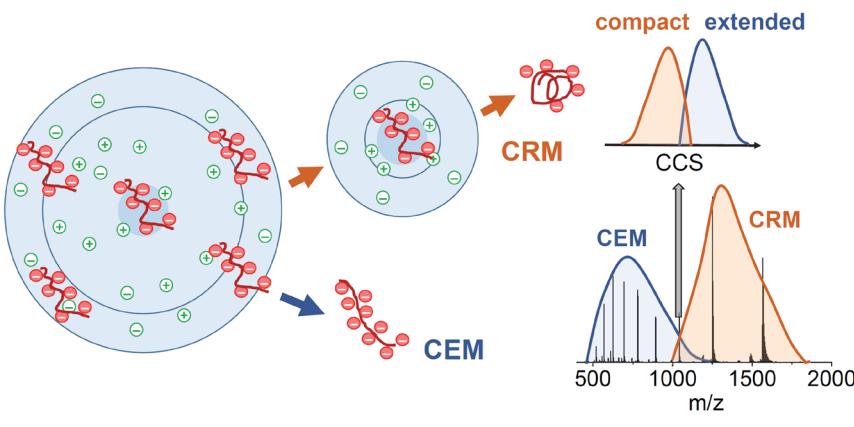
### Adding a structural dimension to mass spectrometry

The biggest challenge in mass spectrometry of intact folds and intact complexes lies in the characterization of the different states. We focused on deepening the fundamental understanding of how to ion mobility spectrometry data to molecular models, the aim being to characterize each ensemble after separation by mass and shape. This led to a community paper for international recommending on reporting ion mobility measurements (Mass Spectrom. Rev. 2019). We also unveiled limitations of gas-phase force field molecular dynamics to model structures relevant to ion mobility MS (ACS Cent. Sci. 2017) and recently turned towards ab initio DFT or semi-empirical methods to model gas-phase structures. These higher-level approaches were used to deduce the structure of novel parallel guanine duplexes bound to a nanowire of Ag(I) ions (J. Phys. Chem. Lett. 2018). Finally, thanks to ERC funding, we continue our development of gas-phase circular dichroism spectroscopy, to record the CD signal of ions trapped in a mass spectrometer. This year we obtained the first full CD spectra.



### Understanding what happens during electrospray ionization

We also focus on a very fundamental question in native mass spectrometry: before it can be applied in a more routine manner to study solution conformations, it is essential to understand to what extent the different types of secondary or tertiary structures are preserved, or affected, by the transition from the solution to the gas phase. For example, we found that nucleic acid double helix structures are not necessarily preserved in the gas phase, but undergo compaction due to extra phosphate-phosphate contacts formed during gradual desolvation (ACS Cent. Sci. 2017). We recently highlighted, in the case of i-motif DNA, the interplay between the analyte partitioning in the electrospray droplets, the charging mechanism, and the ion mobility results (J. Am. Soc. Mass Spectrom. 2019). These fundamental studies are important to pave the way to wiser applications of mass spectrometry, for nucleic acids and for other biomolecular or synthetic systems.



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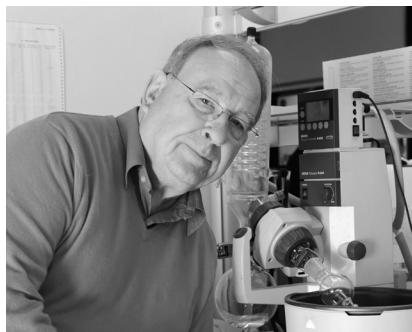
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### Pr. Léon Ghosez

Professor Emeritus UCL, Associate Member  
IECB, Univ. Bordeaux

Léon Ghosez was born in Aalst, Belgium, in 1934. He studied at the University of Louvain where he got a PhD in 1958 under the supervision of Prof. G. Smets,. He then spent 2 years as postdoctoral researcher at Harvard University (Prof. R.B. Woodward) and also collaborated for a few months with Prof. R. Huisgen in the Department of chemistry of the University of München He got his "Habilitation" at the age of 32 for his independent work on the stereochemistry of synthesis and stereochemistry of the rearrangement of halocyclopropanes. In 1969 he became "Professeur Ordinaire" at the University of Louvain where he created the laboratory of organic synthesis. During his career in Louvain (1963-1999) he supervised the research of 297 PhD Students and postdoctoral associates. He also held appointments as professor 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. From 2000 to 2010, he was deputy director of IECB. Since 2011 he is an invited scientist in the same Institute. His current research interests include the design and total synthesis of biologically active molecules, the search of mild, efficient and "green" Lewis acid catalysts and the design of eco-friendly reaction of deoysubstitution of hydroxyl-containing compounds. In 2007, he received the medal of the Société Française de Chimie as a recognition of his support to the development of organic chemistry in France. Léon Ghosez is an emeritus member of the Royal Academy of Sciences of Belgium and a fellow of the Royal Society of Chemistry. He has been recently promoted to the rank of "Chevalier de la Légion d'Honneur".

### Research team

**Wafa GATI** Postdoctoral Fellow (Univ. Bordeaux)  
**Harsha REDDY VARDHAN** Postdoctoral Fellow (Univ. Bordeaux)  
**Camille TISNANT** Trainee (Univ. Bordeaux)

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

# Organic & Medicinal Chemistry

### 1. Synthesis of privileged scaffolds designed after natural products

Natural products are unique templates for the design of privileged scaffolds (PS) for the construction of libraries of biologically relevant natural products analogs. These PS have to be accessible in multigram amounts by efficient synthetic routes. The group has designed and synthesized PS derived from Lycorine alkaloids and Ottelione-A by short and stereoselective syntheses based on the use of novel reagents.

### 2. New reagents for the selective deoxy-fluorination of hydroxyl-containing compounds

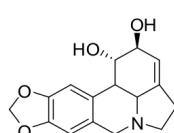
The replacement of an OH group by a nucleophile is an extremely important reaction. The group has initiated an original approach to effect this transformation with cheap, mild, non-toxic and sustainable reagents. Proof of principle has been obtained for deoxyamination and deoxyfluorination reactions. Both transformations are important for the synthesis of bioactive molecules. The fluorination is particularly interesting since the introduction of fluorine or fluorinated group in bioactive molecules often imparts interesting physiological properties. Compounds containing radioactive fluorine atom are also extensively used in PET scan.

### 3. Synthetic and biological studies of highly potent spirocyclic ligands of glucocorticoid receptors

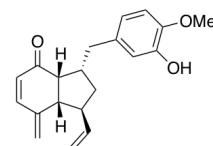
A short and efficient synthetic sequence of pure diastereomeric spirocyclic analogs of fluorocortivazol was developed. This led to the identification of several subnanomolar agonists which are selective for the GR's receptors. This project will be pursued in collaboration with Prof. E. Badarau from CBNM.

### Synthesis of privileged scaffolds designed after lycorine and ottelione A.

Small Natural Products (SNMPs) are the results of long-term co-evolution within biological communities: interacting organisms generated compounds which could act on biological processes of other organisms. SNMPs should thus offer an entry into the discovery process at a more advanced stage than does the screening of standard diversity libraries. Also the pharmacoviability of SNMPs should be better than that of compounds arising from random libraries : Lipinski's rules do not apply to SNMPs. A few years ago, we have initiated a programme aiming at the design, synthesis and biological evaluation of natural-products inspired scaffolds as an efficient source of molecules of therapeutic interest. This project is a collaborative effort with the pharmaceutical industry which is responsible for the production of small libraries derived from our privileged scaffolds and for the biological evaluation.



**Lycorine**



**Ottelione A**

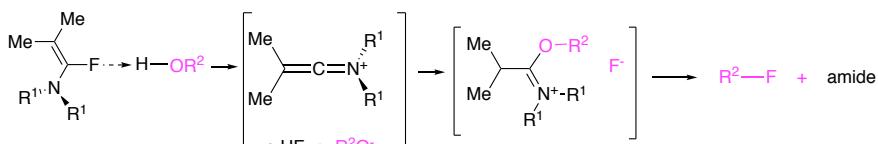
*Scheme 1: Natural products as templates*

The privileged scaffolds should retain some structural features of the NP which are thought to be important for the biological activity (help of molecular modelling). The design of the scaffold also uses pattern recognition in substructures of these NPs. In Lycorine the recognized pattern was a Diels–Alder pattern involving a new

class of nitrogen-containing cyclic dienes, in ottelione the pattern was that of a cyclopentannulation reactions discovered in our laboratory. This project is almost finished and has generated new chemistry of general interest.

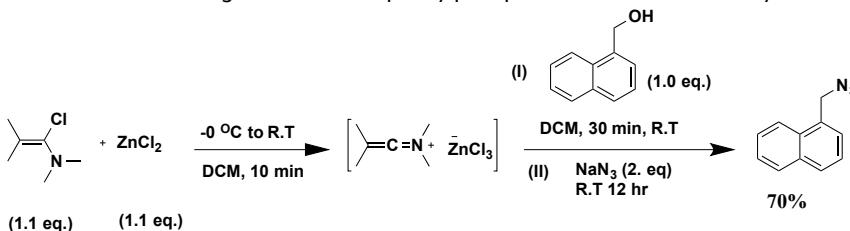
#### New reagents for the selective deoxy-fluorination of hydroxyl-containing compounds

Tetramethylchloroenamine (TMCE, Ghosez' reagent) and the corresponding tetramethyl bromo- and iodoenamine generated *in situ* from TMCE have been shown to be mild, selective and efficient reagents for the deoxyhalogenation of hydroxyl-containing compound such as hydroxyacids, alcohols, activated phenols....). The key properties of these reagents are their ability to generate keteniminium salts which reacted with hydroxylated molecules. We have unexpectedly found that tetramethylfluoroenamine (TMFE) and other fluorenamines were also able to generate keteniminium salts in the presence of hydroxylated molecules (Scheme 2).



Scheme 2. A mild method for the deoxyfluorination of hydroxyl-containing molecules

We found that they reacted with alcohols, acids and activated aromatic alcohols to give the corresponding fluorides under very mild conditions. The most efficient reagent was the enamine carrying two isopropyl groups. These results have been disclosed in a plenary lecture at the International Symposium on Fluorine Chemistry in Oxford in July 2018. More recently we found that deoxyamination reactions could also be performed using a similar strategy (Scheme 3). The method could become a very attractive substitute for the classical Mitsunobu reaction which is widely used in spite of many drawbacks such as the generation of triphenylphosphine oxide and a toxic hydrazide.



Scheme 3. A new mild method for the deoxyamination reaction of an alcohol

#### Synthetic and biological studies of highly potent spirocyclic ligands of glucocorticoid receptors

We have designed spirocyclic analogs of fluorocortivazol as potential ligands for hGR. An efficient synthesis of the target compounds was developed which eventually yielded the desired spirocyclic analogs. We have now completed the biological studies with the help of our industrial partner. This led to the identification of novel highly active glucocorticoid ligands. The best ligand identified so far in this series, had an excellent IC<sub>50</sub> of 0.4 nM, 30-fold more potent than prednisolone, the classical reference GR ligand used in the same experiment (IC<sub>50</sub> = 13 nM). Preliminary results also showed that this new class of hGR binders were selective over the PR. The study also revealed some interesting structure-activity relationships. The results have been published.

#### Selected publications

Ghosez L. Synthesis: Science or Technology? A few comments from an Old-timer. *Isr. J. Chem.* 2018, 58, 1–5 (Special issue: Rosarium Philosophorum on Organic Synthesis).

Badarau E., Robert F., Massip S., Jakob F., Lucas S., Fornmann S., Ghosez L. Design and synthesis of spirocyclic ligands of glucocorticoid receptors. *Tetrahedron* 2018, 74, 5119–5128 (Special issue dedicated to Prof. D. Barton Centenary).

Badarau E., Robert F., Massip S., Jakob F., Lucas S., Friebe D., Hennen S., Fornmann S., Ghosez L. Discovery of a subnanomolar and selective spirocyclic ligand of the glucocorticoid receptor. *Eur. J. Med. Chem.* 2019, 161, 354–363.

Ghosez L. A Lifetime Journey into the World of Chemistry. *Tetrahedron* 2019 (Special issue dedicated to LG), ASAP.

# Peer-reviewed Articles

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2. Badarau E., Robert F., Massip S., Jakob F., Lucas S., Frommann S., Ghosez L. Design and synthesis of spirocyclic ligands of glucocorticoid receptors. *Tetrahedron* 2018; 74, 5119–5128 (Special issue dedicated to Prof. D. Barton Centenary).
3. Baudin A., Guichard A., Collie GW., Rousseau S., Chaignepain S., Hocquellet A., Berbon M., Loquet A., Mackereth C., Guichard G., Odaert B. 1H, 13C, 15N NMR resonance assignments and secondary structure determination of the extra-cellular domain from the human proapoptotic TRAIL-R2 death receptor 5 (DR5-ECD). *Biomol. NMR Assign.* 2018; 12 (2), 309–314.
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## Other Publications

1. Charon J., Manteca A., Innis CA. (2019). Using the Bacterial Ribosome as a Discovery Platform for Peptide-Based Antibiotics. *Biochemistry*, 58, 75.
2. Gabelica V., Marklund E. Fundamentals of ion mobility spectrometry. *Curr. Opin. Chem. Biol.* 2018, 42:51–59.
3. Graf M., Mardirossian M., Nguyen F., Seefeldt AC., Guichard G., Scocchi M., Innis CA., Wilson D.N. (2017). Proline-rich antimicrobial peptides targeting protein synthesis. *Nat Prod Rep.* 34, 702.
4. Ghosez L. A Lifetime Journey into the World of Chemistry. *Tetrahedron* 2019 (Special issue dedicated to LG), ASAP.
5. Guca E., Hashem Y. Major structural rearrangements of the canonical eukaryotic translation initiation complex. *Curr Opin Struct Biol.* 2018. doi: 10.1016/j.sbi.2018.08.006.
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7. Loquet A., El Mammeri N., Stanek J., Berbon M., Bardiaux B., Pintacuda G., Habenstein B. 3D structure determination of amyloid fibrils using solid-state NMR spectroscopy. *Methods*. 2018 Apr 1;138–139:26–38. doi: 10.1016/j.ymeth.2018.03.014.
8. Rapisarda C., Tassinari M., Gubellini F., Fronzes R. Using Cryo-EM to Investigate Bacterial Secretion Systems. *Annu Rev Microbiol.* 2018 Sep 8;72:231–254. doi: 10.1146/annurev-micro-090817-062702. Epub 2018 Jul 13. PubMed PMID: 30004822.

## Patents

- Miron C., Petitjean A., Mergny JL. Platinum complexes for binding Guanine quadruplexes. US62/581,964, filed November 6, 2017; PCT/CA2018/05399 filed November 6, 2018.

## Prizes, Awards

- Best Presentation award – Ruffec Rotary Club prize, Bordeaux Neurocampus Day, Bordeaux, France, [F. Friscourt](#).
- Prix du Dr et de Mme Henri Labb  , Acad  mie des Sciences, [V. Gabelica](#).
- Prix Monique Garnier Prize for the best thesis, U. of Bordeaux, [C. Seefeldt](#).

## Journal & Scientific Society Boards

- Associate Editor, Biochemistry and Cell Biology, [C. Mackereth](#).
- Editor, Biochimie, [JL. Mergny](#).
- Editorial Advisory Board, Journal of Mass Spectrometry, [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](#).
- Member, Publications committee of the American Society for Mass Spectrometry, [V. Gabelica](#).
- Reviewer, eLife, [D. McCusker](#).
- Reviewer, Molecular Biology of the Cell, [D. McCusker](#).
- Scientific Advisor, Soci  t   de Chimie Th  rapeutique (SCT), [G. Guichard](#).
- Vice President, Soci  t   Chimique de France – Section Aquitaine, [G. Guichard](#).

## Evaluation Boards

- ETH Zurich Research Commission – Expertise, ETH, [A. Loquet](#).
- Grant Reviewer, Strasbourg IdEx Program, [D. McCusker](#).
- Grant Reviewer, Wellcome Trust India Alliance Grant, [D. McCusker](#).
- Major Research Instrumentation Program – Expertise, NSF, [A. Loquet](#).
- Membre de Section, Comit   National de la Recherche scientifique, [G. Guichard](#).
- Netherlands Organisation for Scientific Research – Expertise, NWO, [A. Loquet](#).
- Panel Member, PRC5 Committee, SOLEIL Synchrotron, [A. Innis](#).
- Panel Member , Scientific council – NIC – Slovenia, [G. Salgado](#).
- Rapporteur, Thesis committee, [A. Royou](#).

# Teaching

- Bioinformatics – 50h, First year Masters (M1), [P. Bonnafous](#).
- Bioinformatics – 40h, Third year undergraduate (L3), [P. Bonnafous](#).
- Biophysics, Physical Chemistry, Scientific English, Biochemistry, Chemistry, methods in biophysics 1st, 2d and 3d year undergraduates, Master 1 and Master 2 (198 h per year), [G. Salgado](#).
- Biophysics (16h/year), thermodynamic, kinetics and physical chemistry (56h), enzymology (24h), physics for biologist (27h), methodology in sciences (35h), coordination of teaching duties (5h), student orientation (20h) Total: 183h, 1st, 2d and 3d year undergraduates, [A. Bourdoncle](#).
- Biophysics-Surface Plasmon Resonance (35.5 h), Licence 3, Master 1, ENSTBB (school of engineers in biotechnologies), [C. Di Primo](#).
- Chimie générale, Chimie organique, Biomolécules du vivant, Biologie Chimique : 192 HETD, BSc Level (L1 SVSTC Chimie, L2 SVSTC Chimie), MSc Level (M1 MMF/COSV Chimie du vivant, M2 COSV biologie chimique, [C. Dolain](#).
- Chimie générale, chimie organique, vectorisation, peptides bioactifs, sondes en imagerie, chimie thérapeutique : 192 HETD, PACES (Première Année Commune aux Etudes de Santé), cursus pharmacie 2ème année et 3ème année, module chimie du double cursus "Ecole Santé Sciences" (2ème année de pharmacie, odontologie et médecine), Master 2 TECSAN. Coresponsabilité du module de chimie du double cursus "Ecole Santé Sciences", [G. Compain](#).
- Drosophila as a model organism, Master 1 program, [E. Montembault](#).
- Master M2 – 2h First year Masters (M1), [C. Mackereth](#).
- Methodology – 40h, Second year undergraduate (L2), [P. Bonnafous](#).
- Module 4TBG405U – Génétique 2 (32 hours of TP), L2 students ("Génétique"), [A. Herrero del Valle](#).
- Nucleic acids (6h), Master 1 & 2, [JL. Mergny](#).
- Spectroscopy – 12h, Third year undergraduate (L3), [P. Bonnafous](#).
- Structural biochemistry – 43h, First year undergraduate (L1), [P. Bonnafous](#).
- Structural biology (6 hours of lectures + 4 hours of TD), Master 1 students ("Biologie, Santé"), University of Bordeaux, [A. Innis](#), [J. Charon](#).
- UE unité et diversité du vivant (20h of microbiology TD + 4h of TP) d'observation (microbio), L1 sciences de la vie, [E. Leroy](#).
- UE Microbiologie: 8h of TD, L2 sciences de la vie, [E. Leroy](#).

# PhD Theses

- Johanne Mbianda, "Protein Surface Recognition with Urea-based foldamers: Application to the design of ligands targeting histone chaperone proteins", [G. Guichard](#), [C. Douat](#), Univ Bordeaux, Ligue contre le Cancer, 2018.
- Julien Marqueville "Biophysics characterization of G-quadruplexes from KRAS by NMR", [G. Salgado](#), Ecole doctorale science de la vie Bordeaux, Ministère de l'Education, 2016-2019.
- Léonie Cussol "Inhibition d'interactions protéine-protéine par Des foldamères mixtes oligoamide/oligoueree", [G. Guichard](#), [C. Dolain](#), Univ Bordeaux, Ministry of Research, 2018.
- Mona Saad "Dictyostelium comme modèle pour l'analyse des G-quadruplexes", [JL. Mergny](#), Ecole doctorale science de la vie Bordeaux, Lebanon, 2016-2018.

# Science & Society

- Fête de la Science, Bordeaux, France, [A. Innis](#), [A. Herrero del Valle](#), [E. Leroy](#), [MC. Claverie](#).
- Fête de la Science ; Atelier «De l'autre côté du miroir : l'asymétrie dans la vie», Pessac, France, [M. Pasco](#).
- Société Française de Biophysique, France 2018, [C. Di Primo](#).

# Team Funding

## European funding

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher(s)	Funding body	Research project	Period
S. Koj	Wroclaw Centre of Biotechnology KNOW programme	Internship	2018
R. Grzywa	Wroclaw Centre of Biotechnology KNOW programme	Internship	2018
V. Gabelica	H2020-MSCA-ITN-2014	MetaRNA : RNA-based technologies for single-cell metabolite analysis	2015-2018
E. Sartorel	Marie-Curie	Lipids & Polarity : The diffusion and nanoclustering of a polarity module in the lipid environment	2016-2018
G. Salgado	Action intégrée France-Portugal	Paulif : K-ras G-Quadruplexes as an innovative theragnostic strategy for cervicel cancer	2018-2019
V. Gabelica	ERC-2013-CoG	DNAFOLDIMS : Advanced mass spectrometry approaches to reveal nucleic acid folding energy landscapes	2014-2020
A. Loquet	ERC	Weakinteract	2015-2020
A. Innis	EMBO	EMBO Young Investigator Award	2018-2020
A. Manteca	EMBO	EMBO Long Term Fellowship	2018-2020
V. Gabelica	H2020-MSCA-IF-2017	CROWDASSAY : Folding Pathways of DNA G-quadruplexes in Crowding Conditions, and Implications for Mass Spectrometrybased Ligand Screening Assays	2018-2020
A. Innis	ERC Consolidator Grant	NascentTomiX : Ribosome inhibition by nascent or antimicrobial peptides	2017-2022
R. Fronzes	ERC	PneumoTransfo : Structure and Function of the Bacterial Transformasome	2017-2022
C. Di Primo	Euronanomed III	ABISens : Monitoring of acquired brain injury and recovery biomarkers by the combined label-free nanosensing of multiple circulating molecules	2019-2022
Y. Hashem	ERC Starting Grant 2017	Undisclosed	2018-2023

## International funding

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher(s)	Funding body	Research project	Period
C. Mackereth	France-Canada Research Fund	Structure and binding kinetics of the cocaine-binding aptamer	2018-2020

## National funding

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Funding body	Research project	Period
D. McCusker	ANR	Polarflux : Regulation and dynamics of a Rho-GTPase signalling module	2013-2017
D. McCusker	CNRS	Activepole : Testing the role of cooperative lipid interactions as a source of non-linearity in polarity establishment	2018
Y. Hashem	ANR @RAction	Undisclosed	2014-2018
G. Guichard / C. Dolain	Ministry of Research	PPI Inhibitors	2015-2018
Y. Hashem	ANRS	Research on AIDS and viral Hepatitis	2016-2018
D. Santamaria	Fondation ARC	Development of a targeted therapy for the treatment of chemoresistant lung adenocarcinoma	2017-2018
G. Guichard	ANR Generic Call 2015	CHIMPP2I : PPI inhibitors	2015-2019
B. Habenstein	idEx	Chaire d'Installation	2017-2019
R. Fronzes	ANR	DacSyMy : Dissection moléculaire du système de clivage d'anticorps des mycoplasmes	2017-2019
A. Loquet	ANR	FUNHYDRO : Fungal Hydrophobins	2016-2020
Y. Hashem	ANR grant, Partner	Program MITRA	2016-2020
A. Loquet	Ministry of research	Structures of amyloid fibrils	2017-2020
A. Loquet	ANR	SFAS : Structure and function in amyloid signaling	2017-2020
F. Friscourt	CNRS ATIP-Avenir	Making the invisible, visible, detecting traumatic brain injury	2017-2020
B. Habenstein	CNRS MOMENTUM	Mécanisme moléculaires de la génération de force lors de la division bactérienne à l'échelle atomique	2018-2020
M. Pasco	ANR JCJC	FOLDINGUE : Mimétisme et ingénierie d'enzymes artificielles à l'aide de foldamères	2017-2021
G. Salgado	ANR	DEMENTIA : Exploiting genetic biomarkers of neurodegenerative diseases for developing early diagnostic tests and possible treatments	2018-2021
Y. Hashem	ATIP-Avenir	(not funded consequently to obtaining the ERC StG)	2018-2021
G. Guichard	ANR Generic Call 2018	HCO_for_LLAC : Systèmes hélicoïdaux à base d'urées : catalyse asymétrique à faible charge de catalyseur	2018-2022
Y. Hashem	ANR grant, Partner	Program ABC-F	2018-2022
V. Gabelica	ANR	POLYnESI : Understanding Native Electrospray of Artificial and Natural Polymers	2019-2022

## Regional funding

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Funding body	Type of funding	Period
G. Guichard	Siric BRIO	Development of foldamer-based inhibitors of p53/MDM2 interaction with improved properties	2018
F. Friscourt	IDEX Bordeaux	BSSPROBE : Bioorthogonal Probes for Chemical Glycobiology	2014-2018
A. Royou	Conseil Régional d'Aquitaine	Mechanisms that control chromosome transmission	2014-2018
S. Amrane	Conseil Régional d'Aquitaine	TETRAVIR : Les G-quadruplexes dans les virus : fonctions et applications thérapeutiques	2015-2018
J. Meca	University of Bordeaux	Interaction of a Rho GTPase module with its lipid environment	2016-2018
D. McCusker / R. Fronzes	University of Bordeaux	Activepole : Reconstitution of Rho GTPase regulation in controlled lipid environments	2017-2018
A. Innis	Conseil Régional d'Aquitaine (CRA)	The exit tunnel of the ribosome as a high-throughput selection platform for the development of novel antibiotics	2015-2019
F. Friscourt	LabEx TRAIL	FITTING : Traumatic Brain Injury Glycobiomarker	2016-2019
G. Guichard	IDEX Bordeaux	MR-AFP : Foldamer Self-assemblies and Molecular Recognition	2017-2019
J. Gonzalez Garcia	IDEX Bordeaux	LIG4 : Fluorescent ligands to probe G-quadruplex structures: how to bridge the gap between in vitro quantitative studies and fluorescence life imaging in cells	2017-2019
Y. Hashem	Junior Excellence chair, Université de Bordeaux	Implantation of the team including salaries and operations	2017-2021
G. Guichard / C. Palomo	IDEX Bordeaux	Bioinspired Foldamer-based Asymmetric Catalysis at low catalyst loading	2018-2021
G. Guichard	Regional Council/DGA	Nouveaux Peptides Antibiotiques	2018-2021

## Charity-funded research projects

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Charity	Research project	Period
G. Guichard / C. Douat	Ligue contre le cancer	Protein Surface Recognition with Urea-based foldamers: Application to the design of ligands targeting histone chaperone proteins	2015-2018
D. Santamaria	Fondation ARC	Development of a targeted therapy for the treatment of chemoresistant lung adenocarcinoma.	2017-2018
A. Innis	Fondation Bettencourt Schueller	Bacterial translation inhibition by nascent or antimicrobial peptides	2017-2019
A. Royou	Ligue contre le cancer	Etude de FANCD2 au niveau des ponts ultrafins d'ADN en anaphase	2018-2019
J.L. Mergny	La Ligue contre le cancer	Antiproliferative effects of G4 ligands	2018-2019
G. Guichard	Fondation ARC	Optimisation et proof of concept in vivo d'inhibiteurs du chaperon d'histones ASF1 pour le traitement des cancers	2017-2020

## Contracts with the industry

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Company	Research contract	Period
H. Vardhan Reddy	Servier	Undisclosed	2018
W. Gati	DART Neurosciences	Undisclosed	2018
G. Guichard	UreKa	Convention Générale de Collaboration	2017-2021

# Collaborations

## Pole 1 – Structural biology & biophysics

### Translation regulation of gene expression

Dr. Axel Innis

1. Prof. Daniel Wilson, Gene Center, LMU (U. of Hamburg), Hamburg, Germany

### Solid-state NMR of molecular assemblies

Dr. Antoine Loquet

1. Dr. Job, CEA, Grenoble, France
2. Prof. Galan, Yale University, New Haven, USA
3. Prof. Santosh, Jain University, Jain, India
4. Dr. Mongrand, LBM CNRS, Villenave d'Ornon, France
5. Dr. Seuring, Center for Free-Electron Laser Science, Hamburg, Germany
6. Dr. Pintacuda, ISA CNRS, Lyon, France
7. Dr. Nishiyama, JEOL / Riken, Akishima, Japan
8. Prof. Riek, ETH Zurich, Switzerland
9. Dr. Saupe, IBGC CNRS, Bordeaux, France

### Structure and function of bacterial nano-machines

Dr. Rémi Fronzes

1. Dr. Eric Cascales, CNRS, Marseille, France
2. Dr. Patrice Polard, CNRS, Toulouse, France
3. Dr. Terradot Laurent, CNRS, Lyon, France

### mRNA Translation Regulation in Pathogens and Hosts

Dr. Yaser Hashem

1. Dr. Marat Yusupov, Inserm, Strasbourg, France
2. Dr. Gulnara Yusupova, Inserm, Strasbourg, France
3. Dr. Pascale Romby, CNRS, Strasbourg, France
4. Dr. Stefano Marzi, CNRS, Strasbourg, France

## Pole 2 – Organic & bioorganic chemistry

### Peptidomimetic chemistry

Dr. Gilles Guichard

1. Prof. Sylvie Fournel, Faculté de Pharmacie, Univ. Strasbourg, Illkirch, France
2. Dr. Antoine Kichler, Faculté de Pharmacie, Univ. Strasbourg, Illkirch, France
3. Dr. Gilmar Salgado, ARNA, Pessac, France
4. Dr. Jean-Louis Mergny, ARNA, Pessac, France
5. Dr. Olivier Micheau, Université de Bourgogne, Dijon, France
6. Dr. Benoit Odaert, CBMN, Pessac, France
7. Dr. Dominique Burnouf, Institut de Biologie Moléculaire et Cellulaire, Strasbourg, France
8. Dr. Jérôme Wagner, ESBS – Univ. Strasbourg, Illkirch, France
9. Dr. Vincent Oliéric, Swiss Light Source (SLS), Villigen, Switzerland
10. Dr. Céline Douat, Department of Pharmacy, Ludwig-Maximilians-Universität, Munich, Germany
11. Dr. Sébastien Goudreau, UREkA Sarl, France

### Chemical neuroglycobiology

Dr. Frédéric Friscourt

1. Dr. Jerome Badaut, CNRS UMR5287, Bordeaux, France
2. Dr. Raul Duran, Inserm U1218, Bordeaux, France
3. Prof. Kelley Moremen, University of Georgia, CCRC, Athens, GA, USA

## Pole 3 – Molecular recognition

### NMR spectroscopy of protein–nucleic acid complexes

Dr. Cameron Mackereth

1. Dr. Ivan Huc, Ludwig Maximilian University, Munich, Germany
2. Dr. Michal Jewginski, Wrocław University of Science and Technology, Wrocław, Poland
3. Dr. Gilles Guichard, CNRS UMR 5248 (CBMN), Pessac, France

### 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. Mirek Fojta, Dr. Lukas Trantirek, Dr. Michaela Vorlickova, Dr. Jiri Sponer, Dr. Jiri Fajkus, Institute of Biophysics Czech Academy of Sciences, Brno, Czech Republic
3. Dr. Jean-Baptiste Boulé, Dr. Patrizia Alberti, Prof. Jean-Francois Riou, MNHN – CNRS UMR 7196 / Inserm U1154 – Sorbonne Universités, Paris, France
4. Prof. Jun Zhou, Nanjing University, Nanjing, Chine
5. Prof. Carla Cruz, Uni. Beira Interior, Covilhá, Portugal
6. Dr. Isabel Alves, CNRS – CBMN, 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. Marie-Line Andreola, CNRS UMR5234, Bordeaux, France
10. Dr. Gilles Guichard, IECB – CBMN, Pessac, France
11. Dr. Valérie Gabelica, IECB – ARNA, Pessac, France
12. Dr. Geneviève Pratviel, Université de Toulouse, Toulouse, France
13. Dr. Delphine Pannetier, Laboratoire P4 Inserm Jean Mérieux, Lyon, France
14. Dr. Raul Duran, IECB now CAMIBER, Sevilla, Spain

## Pole 4 – Molecular & cellular biology

### Dynamics of cell growth & cell division

Dr. Derek McCusker

1. Prof. Steven Gygi, Harvard Medical School, Boston, USA
2. Dr. Antoine Loquet, IECB/CBMN/CNRS, Pessac, France
3. Dr. Birgit Habenstein, IECB/CBMN/CNRS, Pessac, France
4. Dr. Jean-Baptiste Sibarita, IINS, Bordeaux, France

### Novel Mediators in Lung Oncongenesis

Dr. David Santamaria

1. Dr. Chiara Ambrogio, Dana Farber Cancer Institute, Boston, USA

## Associate members

### Mass spectrometry of nucleic acids and supramolecular complexes

Dr. Valérie Gabelica

1. Prof. Stephen J. Valentine, West Virginia University, Morgantown, USA
2. Prof. Kazuo Nagasawa, Tokyo University of Agriculture and Technology, Tokyo, Japan
3. Prof. Modesto Orozco, Institute for Research in Biomedicine (IRB Barcelona), Barcelona, Spain
4. Dr. Marie-Paule Teulade-Fichou, Institut Curie, CNRS UMR176, Centre Universitaire Paris XI, Orsay, France
5. Dr. Jean-Louis Mergny, IECB, U1212 ARNA, Pessac, France
6. Dr. Gilles Guichard, IECB, UMR 5248 CBMN, Pessac, France
7. Pr. Elisabeth Gwinn, University of California Santa Barbara, Santa Barbara, USA
8. Dr. Daiki Asakawa, National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Japan
9. Prof. Renato Zenobi, ETH, Zurich, Switzerland
10. Dr. Yann Ferrand, UMR 5248 CBMN, Pessac, France
11. Dr. Jos Oomens, Radboud University, Nijmegen, The Netherlands

### Organic & medicinal chemistry

Pr. Léon Ghosez

1. Corticoids, S. Frorrmann, Grünenthal, Aachen, Germany
2. Corticoids, R. Frédéric, Univ. Bordeaux, ISM, CNRS UMR 5255 Talence, France

# Invited Conferences

## Pole 1 – Structural biology & biophysics

### Translational Regulation of Gene Expression

- EMBO Meeting, Vienna, Austria, May 2018, [A. Innis](#)

### NMR of Molecular Assemblies

- Translational Biophysics, Bilbao, Spain, 2018, [A. Loquet](#)
- TGIR User meeting, Orléans, France, 2018, [A. Loquet](#)
- FEBS Prague, Czech Republic, 2018, [A. Loquet](#)
- PRION, Santiago della Compostela, 2018, [A. Loquet](#)

### mRNA Translation Regulation in Pathogens and Hosts

- High-Resolution Protein Structures: Understanding Human Diseases, Symposium, Beer Shiva, Israel, March 2018, [Y. Hashem](#)
- The 27<sup>th</sup> tRNA meeting, Strasbourg, France, September 2018, [Y. Hashem](#)

## Pole 2 – Organic & Bioorganic Chemistry

### Peptidomimetic Chemistry

- 10<sup>th</sup> International Peptide Symposium, Kyoto, Japan, December 2018, [G. Guichard](#)
- 4<sup>th</sup> Annual Meeting of LIA-CNPA, Pessac, France, September 2018, [G. Guichard](#)
- 16<sup>th</sup> Naples Workshop on Bioactive Peptides, Naples, Italy, June 2018, [G. Guichard](#)
- PEPTFE : Peptide Meeting in Tenerife, Tenerife, Spain, March 2018, [G. Guichard](#)

### Chemical Neuroglycobiology

- Research Centre for Natural Sciences, Institute of Organic Chemistry, Hungarian Academy of Sciences, Department Seminar Budapest, Hungary, April 2018, [F. Friscourt](#)
- 27ème Journées du Groupe Français des Glycosciences (GFG2018) Nouan le Fuzelier, France, May 2018, [F. Friscourt](#)
- 27ème Journées du Groupe Français des Glycosciences (GFG2018) Nouan le Fuzelier, France, May 2018, [Z. Chinoy](#)
- Neurocampus Day, Bordeaux, France, May 2018, [F. Friscourt](#)
- Young Scientist Symposium 2018, Bordeaux, France, May 2018, [C. Favre](#)
- 7th International Chemical Biology Symposium (ICBS2018) Vancouver, Canada, September 2018, [F. Friscourt](#)
- Simon Fraser University, Department of Chemistry, Department Seminar, Vancouver, Canada, September 2018, [F. Friscourt](#)

## Pole 3 – Molecular Recognition

### NMR Spectroscopy of Protein–Nucleic Acid Complexes

- 12<sup>th</sup> NMR Winter Retreat of Protein–RNA Interactions, Parpan, Switzerland, January 2018, [C. Mackereth](#)
- 9<sup>th</sup> Bordeaux RNA Club Symposium Pessac, France, June 2018, [C. Mackereth](#)
- 2nd International Caparica Conference in Splicing, Lisbon, Portugal, July 2018, [C. Mackereth](#)

### Unusual Nucleic Acid Structures

- FEBS Meeting Prague, Czech Republic, July 2018, [JL. Mergny](#)
- Biol. of non-canonical nucleic acids: from humans to pathogens Padua, Italy, Sept 2018, [JL. Mergny](#)
- ANNA: Advances in noncanonical nucleic acids, Portoroz, Slovenia Oct 2018, [JL. Mergny](#)
- Interdisciplinary Approaches to Complex Biological Systems Poznam, Poland, Nov 2018, [JL. Mergny](#)
- Annual Dictyostelium conference, Egmond aan Zee, Holland Aug 2018, [M. Saad](#)
- Biacore User days, Paris, France, Nov 2018, [C. Di Primo](#)
- Société Française de Biophysique, Carry-le-Rouet, Bouches-du-Rhône, France, Nov 2018, [GF. Salgado](#)

## Pole 4 – Molecular & Cellular Biology

### Dynamics of Cell Growth & Cell Division

- Yeast Imaging Meeting, Toulouse, France, May 2018, [D. McCusker](#)

### Control and Dynamics of Cell Division

- Schlumberger Conference Les Treilles, France, April 2018, [A. Royou](#)
- IRB Cell Biology seminars Barcelona, Spain, February 2018, [A. Royou](#)
- I2BC Cell Biology seminars, Gif-sur-Yvette, France, February 2018, [A. Royou](#)

## Associate members

### Mass Spectrometry of Nucleic Acids and Supramolecular Complexes

- ASMS Sanibel Conference 2018: Molecular Modeling and Quantum Mechanical Calculations in Mass Spectrometry: From Small Molecules to Large Multimeric Protein Complexes, St. Petersburg, FL, USA, January 2018, [V. Gabelica](#)
- Agilent Ion Mobility User Meeting, Utrecht, The Netherlands January 2018, [V. Gabelica](#)
- G-quadruplexes: Benchmarking from Structures to Functions Paris, France, February 2018, [V. Gabelica](#)
- COST BM1403 MC meeting & annual research conference Vienna, Austria, February 2018, [E. Largy](#)
- European Mass Spectrometry Conference, Saarbrücken, Germany, March 2018, [S. Daly](#)
- Annual Meeting of the Belgian Society for Mass Spectrometry (plenary lecture), Liège, Belgium, March 2018, [V. Gabelica](#)
- 66<sup>th</sup> ASMS Conference on Mass Spectrometry and Allied Topics San Diego, CA, USA, June 2018, [V. Gabelica](#)
- 66<sup>th</sup> ASMS Conference on Mass Spectrometry and Allied Topics San Diego, CA, USA, June 2018, [F. Rosu](#)
- 66<sup>th</sup> ASMS Conference on Mass Spectrometry and Allied Topics San Diego, CA, USA, June 2018, [E. Largy](#)
- Michael T. Bowers 50th Year at UCSB Celebration, Santa Barbara, CA, USA, June 2018, [V. Gabelica](#)
- International Symposium "BIONIC 2018 Biology of non-canonical nucleic acids: from humans to pathogens", Padova, Italy, September 2018, [E. Largy](#)
- COST BM1403 workshop, Berlin, Germany, October 2018, [V. Gabelica](#)
- 4<sup>th</sup> International Conference on Physics & Biological Systems, Gif-sur-Yvette, France, October 2018, [V. Gabelica](#)
- Symposium Advances in Noncanonical Nucleic Acids (ANNA 2018) Portorož, Slovenia, October 2018, [V. Gabelica](#)
- Invited seminar Université de Montpellier, France, October 2018, [V. Gabelica](#)

### Organic & Medicinal Chemistry

- Oxford International Fluorine Symposium (PL) Oxford, UK, July 2018, [L. Ghosez](#)
- NOST Conference (PL), Goa, India, September 2018 [L. Ghosez](#)
- IISER (5 lectures), Bhopal, India, August 2018, [L. Ghosez](#)
- CDRI, Lucknow, India, August 2018, [L. Ghosez](#)
- CBMR, Lucknow, India, August 2018, [L. Ghosez](#)
- IIIM, Jammu, India, August 2018, [L. Ghosez](#)
- IICT, Hyderabad, India, September 2018, [L. Ghosez](#)
- UOH, Hyderabad, India, September 2018, [L. Ghosez](#)
- ICT, Mumbai, India, September 2018, [L. Ghosez](#)
- LIMA, Strasbourg, France, October 2018, [L. Ghosez](#)
- BOSS, Brussels, Belgique, July 2018, [L. Ghosez](#)

# Conference Organisation

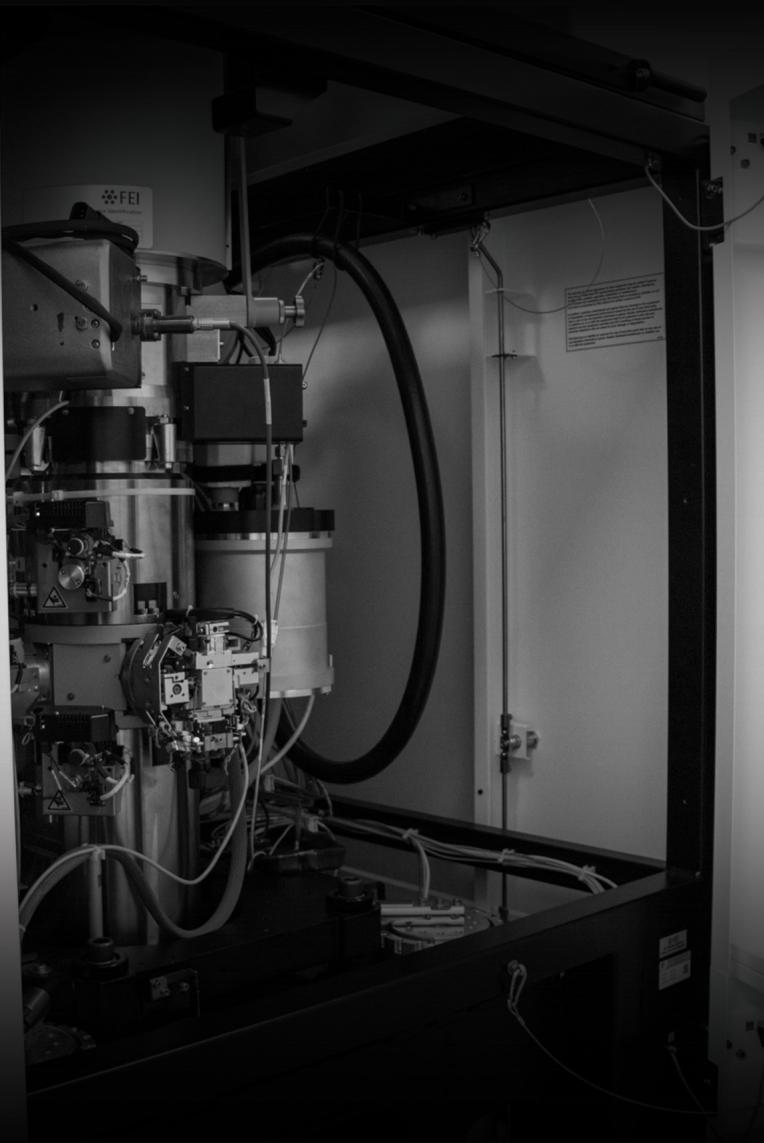
- 10<sup>th</sup> Bordeaux RNA Club Symposium Bordeaux, France, June 2018, [A. Innis](#)
- 11<sup>th</sup> IECB Young Scientist Symposium (JJC), Bordeaux, France, May 2018, [A. Herrero del Valle](#)
- RMN à Hauts Champs et problématiques industrielles Bordeaux, June 2018, [A. Loquet](#)
- Ecole thématique en biophysique structurale, Bordeaux, October 2018, [B. Habenstein](#)
- 2018 Bordeaux Symposium on Foldamers, Pessac, France, September 2018, [G. Guichard](#), [C. Dolain](#)
- 10<sup>th</sup> Bordeaux RNA Club Symposium Pessac, France, June 2018, [C. Mackereth](#)
- RNA Club Symposium, Pessac, France, June 2018, [C. Di Primo](#)
- Ion Mobility interest group meeting at the 66<sup>th</sup> ASMS conference: "Ion mobility spectrometer: how to build your own" San Diego (CA), USA, June 2018, [V. Gabelica](#)

## **Access to the platform's services : A new method of structural characterization of amyloid proteins by proton NMR with rotation at the magic angle :**

An IECB team (Antoine Loquet group – CBMN UMR5248 laboratory) in collaboration with Yusuke Nishiyama of the Japanese company JEOL Resonance Co. and Sven Saupe of the IBGC, published in 2018 a new solid state NMR method allowing the detection of proton nuclei (<sup>1</sup>H) of macromolecular assemblies at very low concentration (500 µg of sample) and rotated at very high frequency (70 kHz). This collaboration with JEOL has thus enabled the development of a new 3-dimensional NMR experiment for the detection of aliphatic and aromatic side chains protons.

Tolchard, J., et al., Detection of side-chain proton resonances of fully protonated biosolids in nano-litre volumes by magic angle spinning solid-state NMR. *J Biomol NMR*, 2018. 70(3): p. 177–185.

People from the BPCS involved: Axelle Grelard and Estelle Morvan.



## **Optimizing Native Ion Mobility Q-TOF in Helium and Nitrogen for Very Fragile Noncovalent Structures.**

Although how to carry out ion mobility measurements is well established, how to interpret the ion mobility experiments in terms of structure is an active matter of research, to which our platform contributes in synergy with the mass spectrometry group at IECB (Valérie Gabelica). In 2018, a joint article described the various trade-offs between ion activation, ion transmission, and ion mobility performance for native MS of very fragile structures. The amount of internal energy imparted to the ions prior to the ion mobility cell influences the ion structure and thus the collision cross section.

Gabelica, V., et al., Optimizing Native Ion Mobility Q-TOF in Helium and Nitrogen for Very Fragile Noncovalent Structures. *J Am Soc Mass Spectrom*. 2018 Nov;29(11):2189–2198.

People from the BPCS involved: Frédéric Rosu.

# 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

Marchand A., Rosu F., Zenobi R., Gabelica V. Thermal Denaturation of DNA G-Quadruplexes and their Complexes with Ligands: Thermodynamic Analysis of the Multiple States Revealed by Mass Spectrometry. *J. Am. Chem. Soc.* (2018)

Muraoka, Takahiro, Tatsuya Shima, Takashi Kajitani, Norihisa Hoshino, Estelle Morvan, Axelle Grelard, Erick J. Dufourc, Takanori Fukushima, Tomoyuki Akutagawa, Kota Nabeya, and Kazushi Kinbara. 'Heat-Triggered Crystallization of Liquid Crystalline Macrocycles Allowing for Conductance Switching through Hysteretic Thermal Phase Transitions', *Chemistry, an Asian journal*. (2018)

Martinez D, Legrand A, Gronnier J, Decossas M, Gouguet P, Lambert O, Berbon M, Verron L, Gréard A, Germain V, Loquet A, Mongrand S, Habenstein B. Coiled-coil oligomerization controls localization of the plasma membrane REMORINs. *J Struct Biol.* (2018).

Badarau, Eduard, Frédéric Robert, Stéphane Massip, Florian Jakob, Simon Lucas, Sven Frermann, and Léon Ghosez. 'Design and synthesis of spirocyclic ligands of glucocorticoid receptors', *Tetrahedron*, 74: 5119–28. (2018)

Nguyen TL, Nokin MJ, Egorov M, Tomé M, Bodineau C, Di Primo C, Minder L, Wdzieczak-Bakala J, Garcia-Alvarez MC, Bignon J, Thoison O, Delpech B, Surpateanu G, Frapart YM, Peyrot F, Abbas K, Terés S, Evrard S, Khatib AM, Soubeiran P, Iorga BI, Durán RV, Collin P. mTOR Inhibition via Displacement of Phosphatidic Acid Induces Enhanced Cytotoxicity Specifically in Cancer Cells. *Cancer Res.* (2018).

Saha, S., B. Kauffmann, Y. Ferrand, and I. Huc. 2018. 'Selective Encapsulation of Disaccharide Xylobiose by an Aromatic Foldamer Helical Capsule', *Angewandte Chemie-International Edition* (2018).

# Biophysical & Structural Chemistry platform (BPCS)

The role of the BPCS is to be at the forefront of methodological developments in Structural Biochemistry and Biophysics, by gathering at IECB a coherent set of techniques and expertise. This expertise is nurtured by the synergies between the technical staff of the platform and research teams. At the BPCS-IECB, molecular recognition and supramolecular assemblies are investigated from a structural and biophysical perspective, by regrouping expertise in NMR spectroscopy (liquid and state of the art solid state on supramolecular assemblies), electron microscopy and cryo-microscopy at near atomic resolution, X-ray crystallography (including SAXS/WAXS), mass spectrometry (including a strong specificity in the study of non covalent complexes using native mass spectrometry hyphenated to ion mobility (IM-MS)), surface plasmon resonance and spectroscopies (absorption and circular dichroism spectroscopy). Importantly, the platform is positioned at the frontiers between chemistry and biology, by focusing both on biological and on synthetic molecules (foldamers) conceived to fold and self-assemble like biological molecules, and/or interact with biological systems.

The BPCS-IECB is a member of the CGFB (Center for Functional Genomics in Bordeaux), a larger network of platforms which all have the IBISA (infrastructures en biologie santé et agronomie) national label. BPCS-IECB is also identified as a technical support facility in different networks :

At a local level : Labex AMADEUS, IDEX Université de Bordeaux, SFR Tecsan, SIRIC BRIO (Bordeaux Recherche Oncologie).

At the national level : CNRS THC-NMR IR, CNRS GDR EMIE, CNRS INC Recipros network.

At the european level : EU COST action ARBRE MOBIEU (between atom and cell, CA15126) and EU COST action (BMS COST BM1403 Native Mass Spectrometry).

### Access to the platform's services :

The platform is accessible to researchers from the public and from the private sector. All informations on available equipment and process to request services or contact experts can be found on the BPCS web page:

<http://www.iecb.u-bordeaux.fr/index.php/en/structural-biophysico-chemistry>

Three types of services are offered:

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

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

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



## Organisation

### Biophysical and Structural Chemistry platform (BPCS)



Scientific director : Mergny Jean-Louis  
Technical coordination : Kauffmann Brice



#### NMR



#### CryoEM



#### X-ray



#### Mass Spec



#### Biochem



#### SPR-ITC-CD



##### STAFF

E. Morvan (IE)  
**A. Gréland** (IR)  
UMR5348 – IRTMC

##### EXPERTS

A. Loquet  
C. Mackereth  
G. Salgado

##### STAFF

A. Bezault (IE)  
**M. Decossas** (IR)  
S. Tan (AI)  
UMR5248

##### EXPERTS

A. Loquet  
C. Mackereth  
G. Salgado

##### STAFF

B. Kauffmann (IR)  
S. Massip (IE)

##### EXPERTS

R. Fronzes  
A. Innis  
G. Guichard

##### STAFF

F. Rosu (IR)  
L. Klinger (AI)

##### EXPERTS

V. Gabelica

##### STAFF

JM. Blanc (IE)  
T. Dakhli (Tech)  
M. Mederic (AJT)

##### EXPERTS

A. Loquet  
A. Innis  
C. Mackereth

##### STAFF

L. Minder (AI)

##### EXPERTS

C. Di Primo  
A. Bourdoncle  
F. Rossu



**Certification ISO9001 – NFX50-900**  
Loïc Klinger (AI) RMQ – Julie Kowalski (Master Tecsan)



## Figures for 2018

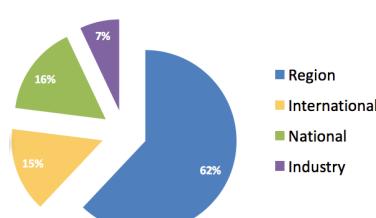
### Users of the platform

In 2018, the platform contributed to 156 projects for more than 50 different public or private laboratories or companies.

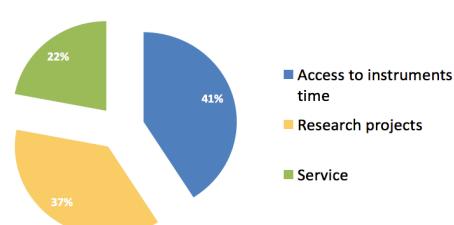
### Key numbers

- More than 70 people trained per year (students, technicians, researchers)
- 44 publications with staff members as co-author or with acknowledgments for the BPCS.

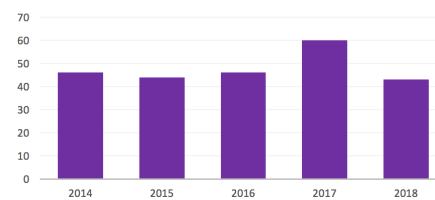
BPCS users in 2018



BPCS activities in 2018



Peer reviewed publications @BPCS





# 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 transferred to economic players via different routes:

## Collaborative research

Servier, UreKa, DART Neurosciences... Several key industry players work with IECB teams. In 2018, the institut totalized 3 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 Biophysical and Structural Chemistry platform.

IECB researchers are strongly encouraged to patent their discoveries. In 2018, 1 additional patent was submitted by team leaders C. Miron, A. Petitjean and J.L Mergny.

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

## Incubating start-ups

IECB has a 300m<sup>2</sup> 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.

## Technology transfer





Fluofarma, a Porsolt company, is a preclinical contract research organization which provides 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 includes *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.

Fluofarma's parent company – Porsolt SAS – is a long established preclinical CRO with an international reputation for expertise in physio-pathological models. Porsolt holds an extensive portfolio of services in drug discovery.

#### **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 micrarrays (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

**2018 turnover** Not disclosed

**Website** [www.fluofarma.com](http://www.fluofarma.com)



Established in the region of Bordeaux since 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 in the field of foldamer research, conducted within the laboratory of Gilles Guichard. UREkA is now performing research programs to apply its Urelix™ technology for the discovery of innovative therapeutics in close collaboration with IECB group leader Gilles Guichard.



Dr. Sébastien Goudreau  
Ureka Research Director

**Year of creation** 2010

**Staff** 5

**Collaborative projects with IECB teams in 2018:** 2

**Website** [www.urekapharma.com](http://www.urekapharma.com)

**Contact**

[sebastien.goudreau@immupharma.com](mailto:sebastien.goudreau@immupharma.com)

#### **Medicinal chemistry – diseases of interest**

- Diabetes
- Hypoglycemia
- Obesity
- Non-alcoholic steatohepatitis (NASH)
- Cancer

#### **Collaborative research projects**

- Implementation of Urelix™ technologies in partners projects.
- Design and synthesis of bioactive foldamers.
- Hit to lead
- SAR
- Development

IECB welcomed children and students for the Science Fair in October 8<sup>th</sup>-9<sup>th</sup> 2018.  
IECB researchers, engineers and students held a series of workshops about chemistry  
(focused on chirality) and biology.



# Scientific Events

# Workshops & symposia held at IECB

*A l'occasion du 20<sup>e</sup> anniversaire de l'Institut Européen de Chimie et Biologie et de l'attribution du grade de Chevalier de la Légion d'Honneur au Professeur L. Ghosez*

## Symposium "Science, Culture et Société"

Lundi 9 avril 2018 à l'IECB 2 Rue Robert Escarpit à Pessac
10:00–10:15 Dr Jean-Louis Merugy (INSERM), directeur de l'IECB Accueil des participants
10:15–11:15 Prof. Axel Marchal (ISVV, Bordeaux) « De la terre à la tête, voyage dans un verre de vin ? »
11:15–12:15 Prof. Jean-Marie André (Univ. Namur) « Quelques relations entre Sciences et Art : impostures ou inspiration mutuelle »
12:15–14:00 Lunch break. Exposition d'oeuvres de Isabelle Rico-Lattes, Dr. Sc. de Guy Rossey, Dr.Sc. et du Dr. Jean-Jacques Toulmé.
14:00–15:00 Dr. Philippe Walter (UPMC, Paris) « Quand les peintres rencontrent les chimistes »
15:00–16:00 Prof. Armand Lattes (Univ. Toulouse) « Je suis chimiste et je vous veux du bien »
16:00–17:00 Pause café
17:00–18:00 Mise académique : Prof. Jean-Marie Lehn (DSULP Strasbourg) « Etapes de la Matière vers la Vie - Chimie ! »
18:00–19:30 Dr. Jean-Louis Merugy « On n'a pas tous les jours 20 ans ! » Prof. Léon Chosson « La recherche de Rouquerol à l'IECB : remerciements d'un Belge à ses amis français » Conclusion : M. Alain Rousset (Président du Conseil Régional de Nouvelle-Aquitaine)
19:30 Réception dans le hall de l'IECB



## Symposium "Science, Culture et Société", April 9

20th anniversary of the European Institute of Chemistry and Biology (IECB) – Awarding the rank of knight of the legion of honor to Professor L. Ghosez.

### Speakers:

- Prof. Jean-Marie André
- Prof. Armand Lattes
- Prof. Jean-Marie Lehn
- Prof. Axel Marchal
- Dr. Philippe Walter

### Exhibitors of watercolors:

- Dr. Isabelle Rico-Lattes
- Dr. Guy Rossey
- Dr. Jean-Jacques Toulmé

**A great opportunity**  
to exchange knowledge on an interdisciplinary level!



## 11<sup>th</sup> Young Scientist Symposium

24<sup>th</sup> - 25<sup>th</sup> MAY 2018

at the IECB (Pessac, France)

Come to meet young scientists in Chemistry & Biology

### Registration is now open

Deadline for abstract submission

20<sup>th</sup> April 2018

Round table Career Session and

2 Keynote Lectures:

#### Pr. Martin Karplus

Prof. at Harvard University

Nobel prize in Chemistry 2013

#### Dr. Luisa Gronenberg

Researcher at Biosyntia, Denmark



## 11<sup>th</sup> IECB Young Scientist Symposium, May 24–25

### Keynote speakers:

- Pr. Martin Karplus
- Dr. Luisa Gronenberg

### Career session:

- Antoine Amestoy
- Antoine Scalabre
- Nathalie Caplet
- Sonia Ciudad
- Léonie Cussol
- Thomas Perry



## Bordeaux Symposium on Foldamers, September 24-25-26

### Plenary Speakers:

- Prof. Jonathan Clayden
- Dr. David Liu
- Prof. Scott Miller
- Prof. Jonathan Nitschke
- Prof. Hanodi Sleiman

## 10th Bordeaux RNA Club Symposium, June 14–15

### Speakers:

- Prof. Gerald Joyce
- Dr. Lori Passmore
- Prof. Scott Blanchard
- Dr. Julian König
- Dr. Kathi Zarnack
- Dr. Florence Besse

# External workshops organized by IECB group leaders



RMN Meeting, June 14

# Seminars

1. Kevin Alessandri, Maxime Feyeux, Max-Planck Institute for Biophysical Chemistry, Göttingen, Germany: Encapsulation of cells as a tool to get beyond 2D biology: from cancer to pluripotent stem cells.
2. Alexandre David, Institut de Génomique Fonctionnelle, CNRS, Inserm, Univ. Montpellier, Montpellier, France : Nuclear and Cytoplasmic TRM61 Activities-Converge to Fine-tune Translation.
3. Nico Reyes, Institut Pasteur, Paris, France: Structure and dynamics of a human excitatory Neurotransmitter transporter.
4. Antonio Maraver, Institut de Recherche en Cancérologie de Montpellier, Inserm U1194–Université Montpellier – ICM, Montpellier, France: Role of the Notch pathway in lung adenocarcinoma: beyond the KrasG12V mouse model.
5. Yann Fichou, Department of chemistry, University of California Santa Barbara, USA: From solution tau to amyloid aggregates: pathway matters a great deal.
6. Gert Bange, Center for Synthetic Microbiology & Dept. of Chemistry, Philipps-University Marburg, Marburg, Germany.
7. Prof. Hiroshi Yabu, AIMR, Tohoku University, Japan: Nature-inspired polymer materials; honeycomb films and biomimetic functional polymers.
8. Petya Krasteva, Institute for Integrative Biology of the Cell (I2BC), CNRS UMR9198, Université Paris Sud, Gif-sur-Yvette, France.
9. André Estevez-Torres, Laboratoire Jean Perrin, CNRS UMR8237, Paris, France: Synthesis of spatio-temporal structures with DNA molecular programs.
10. Prof. Pierre Strazewski, ICBMS, CNRS UMR5246, CO20Glyco, Université de Lyon, France: Ex inanimo: How to Animate a Chemical System?
11. Prof. Ramon Vilar, Department of Chemistry, Imperial College London, London, UK: Targeting and imaging G-quadruplex DNA with metal complexes.
12. Sébastien Benizri, ChemBioPharm, Inserm U1212 UMR 5320 CNRS, ARNA (Team P. Barthélémy), Bordeaux, France: Synthesis and characterization of amphiphilic oligonucleotides for therapeutic application.
13. Mitsugu Shimobayashi, Biozentrum, University of Basel, Switzerland: Adipose tissue mTORC2 signaling in physiology and disease.
14. Dr Kiyohiko Kawai, Osaka University, Japan: Structural analysis of nucleic acids by controlling the fluorescence blinking.
15. Barry M.Trost, Department of Chemistry, Stanford University, CA, USA: Self Assembly of Dinuclear Main Group Complexes for Asymmetric Catalysis.
16. Jérôme Gouge, Institute of Cancer Research, London, UK.
17. Petya V. Krasteva, Institute for Integrative Biology of the Cell, Gif-sur Yvette, France.
18. Gabriele Sulli, Salk Institute for Biological Studies, La Jolla, CA, USA.
19. Julian Valero Moreno, Center of Advanced European Studies and Research (CAESAR), University of Bonn, Germany.
20. Alexander Buell, Institute of Physical Biology of the Heinrich-Heine-University Dusseldorf, Germany.
21. Emmanuelle Thimon, The Francis Crick Institute London, UK.
22. Dorit Hanein, Institut Pasteur, Paris, France.
23. Marc Bramkamp, Ludwig-Maximilians-University Munich, Faculty of Biology, Planegg-Martinsried, Germany: The mysterious role of flotillins in bacterial plasma membranes: Scaffold for lipid rafts or rather signaling hubs for stress response?
24. Nitin T.Patil, Department of Chemistry, Indian Institute of Science Education and Research, Bhopal, India: New Reactivities through Gold and Chiral Brønsted Acid Catalysis.
25. Takehiko Wada, Institute of Multidisciplinary Research for Advanced Materials (IMRAM), Tohoku University, Sendai, Japan : Utilizing a Dynamics of Photoexcited Molecule for New Type of Asymmetric Photoreaction.
26. Marisela Vélez, Instituto de Catálisis y Petroleoquímica, CSIS, Madrid, Spain : Functional anchoring of proteins on modified surfaces : from bacterial cytoskeleton to redox proteins.
27. Jean-François Paquin, Département de chimie, Université Laval, Québec, Canada: Exploration et quelques découvertes en chimie des composés organofluorés.
28. Olivier Micheau, Inserm U866, Faculty of Medicine, Dijon, France : Exploiting TRAIL for cancer treatment.



# Institut Européen de Chimie et Biologie

European Institute of Chemistry and Biology

