Institut Européen de Chimie et Biologie

European Institute of Chemistry and Biology

Scientific Report

2011

Director's foreword

Dr. Jean-Jacques Toulmé
Executive scientific director of the IECB
Research director (DRCE) at Inserm (U869)

The European Institute of Chemistry and Biology enters its 15th year. Created in 1998 by Prs Jean-Yves Lallemand and Léon Ghosez on the basis of an innovative concept in the French landscape of academic research, our institute proves to be more and more attractive for young talented researchers from all over the world, willing to develop interdisciplinary projects in an outstanding environment. As every year, the annual scientific report provides me with the opportunity to highlight major achievements and key events that paved the year 2011 at IECB.

First, I want to congratulate Denis Dupuy and Cameron Mackereth, two young group leaders recruited three years ago on temporary positions. Both of them were hired in June 2011 by Inserm as "Chargé de Recherche 1" following a highly competitive national process. I am particularly happy as this will allow them developing their ambitious projects under less stressing conditions. This also demonstrates that our stringent selection under the responsability of the International Scientific Advisory Board (ISAB) guarantees a high standard recruitment. Indeed, up to now, every IECB group leader got a permanent position before the end of his/her contract. I am sure this will continue and I am confidently expecting the recruitment in 2012 of our last group leader presently under contract.

This foreword also offers me the opportunity to acknowledge the wonderful job carried out by the ISAB chaired by Daniel Louvard. Simon Campbell, who used to work for Pfizer (UK) will step down after 14 years dedicated to the recruitment and the evaluation of IECB group leaders. We will miss his open mind and sharp vision. But we will keep an input from the industry thanks to Daniel Shirlin, vice-president of R&D at Sanofi-Aventis, particulaly in charge of research and translational medicine. He actually took part in the Board meeting last fall. I hope this first contact with our institute will be followed by many others. I wish to emphasize here the key role played by the Board in the scientific evolution of the institute over the years.

Several corner stone papers were published in prestigious journals by IECB group leaders and their staff in 2011. Cameron Mackereth, together with colleagues from the Helmholtz Zentrum München and the Technical University of Munich, the European Molecular Biology Laboratory in Heidelberg and the Centre for Genomic Regulation in Barcelona, has discovered how the human U2AF protein enables diverse patterns of intron elimination, and consequently increases the number of different proteins made from a single gene. The results were published online on July 13th in *Nature*. The team found that the spatial structure of the U2AF protein alternates between a closed conformation that is inactive, and an open active form that triggers intron removal. Intron sequences vary in their ability to selectively bind and stabilize the active conformation. Disruption of this key process in splicing may be involved in many diseases, including cancer.

Ivan Huc and colleagues keep going around what is now recognized as a landmark of the Institute: foldamers, i.e. synthetic biomimetic polymers adopting pre-determined and controlable three-dimensional shapes. Ivan, in collaboration with a Chinese team from the Beijing National Laboratory for Molecular Sciences, has developed the first nanopiston capable of self-assembly. A moving helix is wrapped around a rod formed of a

"Over the years, the IECB concept has demonstrated its worth for erecting an attractive and high-standard research institute."

slender molecule. The helicoidal oligomer moves along the rod depending on the acidity of the medium in which the molecular motor is immersed. By increasing the acidity, the helix is drawn towards one end of the rod; by reducing the acidity, the process is reversed and the helix goes in the other direction. This work was published in *Science*, in March 2011.

Stéphane Quideau, organic chemist and Elisabeth Génot, cell biologist, co-published on April 27th a paper in *Angewandte Chemie International Edition*. Stéphane has been investigating C-glucosidic ellagitannins, a class of natural polyphenolic products, for the past ten years. In 2007, in the frame of an IECB internal call for inter-team projects, Stéphane and Elisabeth hypothesized that vescalagin, an ellagitannin extracted from oak wood, was likely to perturb the assembly of certain proteins within the cell. Three years later, the two teams provide evidence about the ability of this polyphenol to enter the cell, to bind to fibrillar actin (F-actin) without interacting with monomeric globular actin (G-actin), and to wind F-actin filaments into aggregates without any perturbation of the microtubule network.

Alain Brisson and his team demonstrated in a paper released on April 5th in *Nature Communications* that Annexine-A5 plays a central role in cell membrane repair. Following membrane damage via laser irradiation, they observed that cells lacking Annexin-A5 presented a defect in their membrane repair machinery, and that the addition of Annexin-A5 restored their repair ability. They showed that Annexin-A5 promotes repair through the formation of 2D arrays at the sites of membrane rupture by preventing the expansion of the tear and facilitating membrane resealing. Alain will undoubtedly keep working on Annexin-A5, his favourite topic over the last twenty years, outside IECB. Indeed, he reached the end of his ten year contract. He is the seventh group leader to leave the institute, according to the IECB concept, that stipulates that teams are hosted for a limited period. I wish he will keep contacts with other IECB scientists, allowing new transdisciplinary projects to be initiated and that we will continue to benefit from his expertise in electron microscopy and membranes.

Conversely we were happy enough to attract a new group leader in molecular and cellular biology. Anne Royou joined the institute in March 2011. In 2001, she obtained a PhD thesis under the guidance of Dr. Karess, at the Centre de Génétique Moléculaire in Gif-sur-Yvette, France. Her research on non-muscle myosin II during development in drosophila led her to collaborate with Dr. William Sullivan's lab at the University of California, Santa Cruz, a team she joined in 2002 as a post-doctoral fellow. During her post-doctoral studies, Anne focused her research on the mechanism that prevents chromosomal instability. Her team at IECB, "Control and dynamics of cell division", will explore how the drosophila embryo divides when its genome is damaged. This makes available a second animal model at IECB and will extend our expertise in the mechanisms relevant to cancer development. I wish her a fruitful activity at IECB.

As every year at IECB, we are currently working hard with two new candidates strongly recommended by the ISAB after its 2011 meeting. Hopefully, with the support of our trustees and of the *Conseil régional d'Aquitaine,* two new group leaders will join us before the end of 2012, strengthening our expertise in RNA and more particularly in protein synthesis in prokaryotes on the one hand, and in mass spectrometry of non covalent macro complexes with a focus on nucleic acid complexes on the other hand.

In 2011, the many efforts made over the last two years in the frame of a European Sudoe INITERREG programme (Interbio) dedicated to biotechnology and health sciences came to fruition. We had more and more exchanges with our colleagues from Barcelona, Lisbon, Toulouse and Valencia. Several collaborative research projects were initiated over 2011. They will likely lead to exciting results and technology transfer, as this is one of the major goals of Interbio. IECB researchers took an active part in the research to business meeting organized in Valencia last Fall. I take this opportunity to acknowledge the efforts made by Alain-Michel Boudet, the Interbio coordinator, and Ijsbrand Kramer, in charge of this programme at IECB. Hopefully exchanges will continue and contacts will even be amplified in the new Transbio project that -if funded by the EU- will involve new partners; for IECB this will be of the utmost interest in the frame of the Euroregion that brings together Aquitaine in France and Euskadi in Spain.

I could conclude this 2011 foreword like the 2010 one, pinpointing that over the years *"the IECB concept has demonstrated its worth for erecting an attractive and high-standard research institute"*. Indeed, group leaders are productive; interdisciplinary projects are blossoming; transfer from research groups led to the creation of a company - Fluofarma - and of a technology transfer unit - Novaptech. IECB is more attractive than ever for young talented researchers (last year we received more than seventy applications). I could be a happy director looking for new scientific challenges. However I am afraid that the multiple labels recently distributed under the umbrella of the so-called *Investissements d'Avenir* might obscure the lanscape, lead to even more bureaucracy and encourage local feodalism without providing the necessary support. I wish that our trustees - and more particularly the University of Bordeaux - will recognize the pioneering character of IECB and the talent of the twenty-one group leaders that successively contributed to its reputation since its opening. I hope they will keep supporting and funding this institute, unique in France, which achieved international visibility through research at the frontier between chemistry and biology.

Dr. Jean-Jacques Toulmé

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

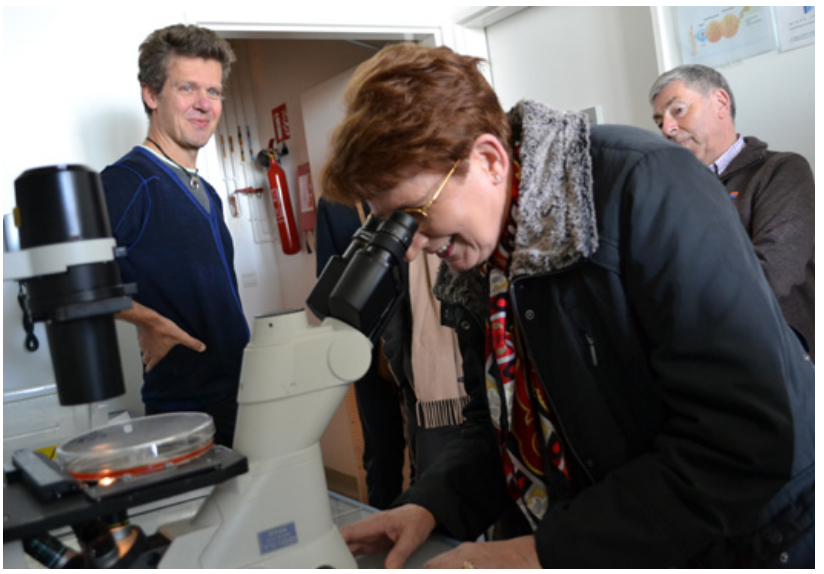
IECB's International Scientific Advisory Board guides the selection and periodic evaluation of the team leaders. After a probative period of two years, research teams are then hosted for a maximum of 8 years. During their stay at IECB, teams enjoy full financial and managerial autonomy and benefit from 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 now the largest research team incubator in France recognized by the "Mission pour l'interdisciplinarité" of the CNRS, with 15 research teams accounting for 150 researchers and expert technicians. A company – Fluofarma – and a technology transfer unit – Novaptech –, both created by former IECB team leaders, also operate on site and currently employ over 25 people.

Contents

In 2011, Neil Owens, post-doctoral fellow in the team of Gilles Guichard, was awarded the Helen Starck prize by the French Association for Cancer Research (ARC) for his research project on molecules capable of causing the death of cancer cells.

Highlights



IECB teams strengthen their ties with the French associations for cancer research

Since the Teichmann team was approved *Equipe Labellisée* by the *Ligue contre le Cancer* in 2010, the IECB teams have kept on consolidating their ties with the French associations for cancer research. In October 2011, Neil Owens, post-doctoral fellow within the Guichard team, was awarded the *Helen Starck* prize by the *ARC* for his research project on molecules capable of causing the death of cancer cells. A few weeks later, the *ARC* confirmed that the research proposal on G-quadruplexes ligands submitted by Jean-Louis Mergny was accepted in the frame of the *Programme ARC* (170 000 € over 3 years).
The IECB teams funded by the *Ligue contre le Cancer* also took action to maintain their relationships with the association. On December 1st 2011, the teams led by Sébastien Fribourg, Martin Teichmann and Jean-Jacques Toulmé, offered a guided tour of their labs to 27 donors and volunteers from the Dordorgne committee of the association (see picture above).

A rejuvenated Young Scientist Symposium

Since it was launched in 2008, the *IECB Young Scientist Symposium* has been organised *by* young researchers *for* young researchers. The 4th edition of the event, held at IECB on May 19-20, 2011, was attended by 110 young chemists, biologists and physicists from the Interbio community. Over two days, young researchers from Spain, France and Portugal had the opportunity to present their results through oral communications and posters, and discuss the various career paths available to them with professionals working in academia and technology transfer. Enthused by the success of the 2011 edition of the event, 11 PhD students and postdoctoral fellows from the IECB joined the organizing committee in October 2011! To organize the 5th *IECB Young Scientist Symposium*, they will need to raise 6000 € by May 2012.

250 researchers and entrepreneurs from South-West Europe at IECB

The first *Interbio week*, held at the IECB from the 26th to the 30th of June 2011 gathered 250 researchers and entrepreneurs from Barcelona, Bordeaux, Lisbon, Toulouse and Valencia.
This Interbio event, which was aimed at fostering interregional scientific cooperation and technology transfer in the field of life and health sciences, gave participants the opportunity to familiarize with systems biology and polypharmacology, to explore the new perspectives offered by microfluidic devices and to learn about the latest advances in RNA research.

IECB biobusinesses attend the Interbio Research-to-Business meeting

Julie Plane, sales manager at Fluofarma, Sonia Da Rocha, executive manager of Novaptech, and Andrew Goldsbrough (see p.71), CEO of Cyclops Genome Sciences, all attended the Interbio Research-to-Business meeting co-organized by FIVEC and the IECB in Valencia on November 17-18 2011. 40 companies, 2 bioregions, 6 bioclusters, 35 research centers, 26 universities and 14 technology transfer offices (including Aquitaine Valo) were represented. Almost 50 one-to-one meetings took place over the event. Julie Plane from Fluofarma, had 3 interviews and some additional contacts: *"After the conference, I contacted some of the speakers. They replied quickly and were willing to transfer my contact details to the right person in their company. The fact that people keep helping each other after the event demonstrates that there is a true network spirit within Interbio."*
According to Arturo Ortigosa, director of FIVEC, this first experience in the organization of a business-oriented Interbio event bodes well for the future: *"The event was attended by big pharmas, start-ups and technology transfer offices from all the Interbio regions. Participants provided us with very positive feedback, which is encouraging at a time when we prepare the future of Interbio, with a second INTERREG SUDOE application for the period 2012-2014 that will focus on technology transfer".*

Science Days 2011: over 200 secondary school students visited the IECB

Every year, the IECB teams open their labs to secondary school students from Aquitaine in the context of the Science Days. In 2011, at the occasion of International Year of Chemistry, two young researchers from the Stéphane Quideau team set up an activity entitled "*All the way long from plant to medicine through wine – the chemistry of polyphenols*" (see picture on the right). Participants had the opportunity to understand how chemists exctract 1 gram of vescalagin out of 1 kilogram of wood, why this molecule could be found in wine aged in oak barrels, and how this plant polyphenol could contribute to human health. The activity, led by Rémi Jacquet and Emilie Petit, was a great success: over 200 students walked in the door of their lab!

France-Japan workshop at IECB: An excellent first vintage

In October 2011, 30 senior scientists from the *Japanese Strategic Alliance Project for the Creation of Nano-Materials, Nano-devices and Nano-systems* spent a few days in Bordeaux in the context of the first France-Japan workshop held at IECB. Over two days, French and Japanese research directors working in field of bio-inspired nano-architectures, materials and imaging got to know each other better through posters sessions (see above picture), oral presentations and... Bordeaux wine tasting sessions... Following the event, further bilateral exchanges are expected to take place.

In 2011, the IECB International Scientific Advisory Board welcomed a new member: Dr Daniel Schirlin, Vice-President, Deputy Head of R&D in charge of Research and Translational Medicine at Sanofi-Aventis

Organisational structure

Board members

International scientific advisory board (ISAB)

Dr. Daniel LOUVARD President
Institut Curie, Paris, France

Pr. Iain D. CAMPBELL
Departement of Biochemistry, University of Oxford, UK

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

Dr. Witold FILIPOWICZ
Institut Friedrich Miescher, Basel, Switzerland

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

Pr. Roeland NOLTE
Radboud University Nijmegen, Netherlands

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

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

Dr. Daniel SCHIRLIN
Sanofi Aventis, Paris, France

Dr. Moshe YANIV
Institut Pasteur, Paris, France

Former ISAB members

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

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

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

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

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

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

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

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

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

Board of directors

Dr. Jean-Jacques TOULMÉ Executive Scientific Director
Research director, U869 (Inserm – Université Bordeaux Segalen)

Dr. Ivan HUC Deputy Scientific Director
Research director, UMR 5248 (CNRS – Université Bordeaux 1)

Dr. Jean-Louis MERGNY Deputy Scientific Director
Research director, U869 (Inserm – Université Bordeaux Segalen)

Mrs. Stéphanie MONTAGNER Administrative Director (CNRS)

Former directors

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

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

Steering committee

Dr. Elisabeth GÉNOT
Research director, U1053 (Inserm – Université Bordeaux Segalen)

Dr. Ivan HUC Deputy Scientific Director
Research director, UMR 5248 (CNRS – Université Bordeaux 1)

Dr. Michel LAGUERRE
Research director, UMR 5248 (CNRS – Université Bordeaux 1)

Dr. Brice KAUFFMANN Head of IECB's technology platforms
Engineer, UMR 5248 (CNRS – Université Bordeaux 1)

Dr. Jean-Jacques TOULMÉ Executive Scientific Director
Research director, U869 (Inserm – Université Bordeaux Segalen)

Dr. Jean-Louis MERGNY Deputy Scientific Director
Research director, U869 (Inserm – Université Bordeaux Segalen)

Mrs. Stéphanie MONTAGNER Administrative Director (CNRS)

Board of trustees

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

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

Université Bordeaux 1
351 cours de la Libération, 33405 Talence

Université Bordeaux Segalen
146 rue Léo Saignat, 33076 Bordeaux

Organisational chart

Research teams

- Pole 1 - Structural biology & biophysics
  - Molecular modeling — Dr. Michel Laguerre
  - Morphologies, dynamics & functions of assemblies of amphiphiles — Dr. Reiko Oda
  - Molecular imaging & nanobiotechnology — Pr. Alain Brisson
- Pole 2 - Organic & bioorganic chemistry
  - Supramolecular bioorganic & biomimetic chemistry — Dr. Ivan Huc
  - Synthesis & activity of natural substances — Pr. Stéphane Quideau
  - Peptidomimetic chemistry — Dr. Gilles Guichard
  - Peptide-based polymer assemblies — Dr. Élisabeth Garanger
- Pole 3 - Molecular recognition
  - Gene regulation & tumor research — Pr. Martin Teichmann
  - Structural biochemistry — Dr. Sébastien Fribourg
  - NMR spectroscopy of protein-nucleic acid complexes — Dr. Cameron Mackereth
  - Unusual nucleic acid structures — Dr. Jean-Louis Mergny
- Pole 4 - Molecular & cellular biology
  - Cell signalling in health & diseases — Dr. Elisabeth Génot
  - Dynamics of cell growth & cell division — Dr. Derek McCusker
  - Genome regulation & evolution — Dr. Denis Dupuy
  - Control & dynamics of cell division — Dr. Anne Royou
- Visiting scientist
  - Organic & medicinal chemistry — Pr. Léon Ghosez

Board of directors

Steering committee

Institut Européen de Chimie et Biologie

I E C B

Board of trustees

International scientific advisory board

Administrative services
UMS 3033 / US 001

Technology platforms
UMS 3033 / US 001

- Structural biology
- Preparative & analytical techniques

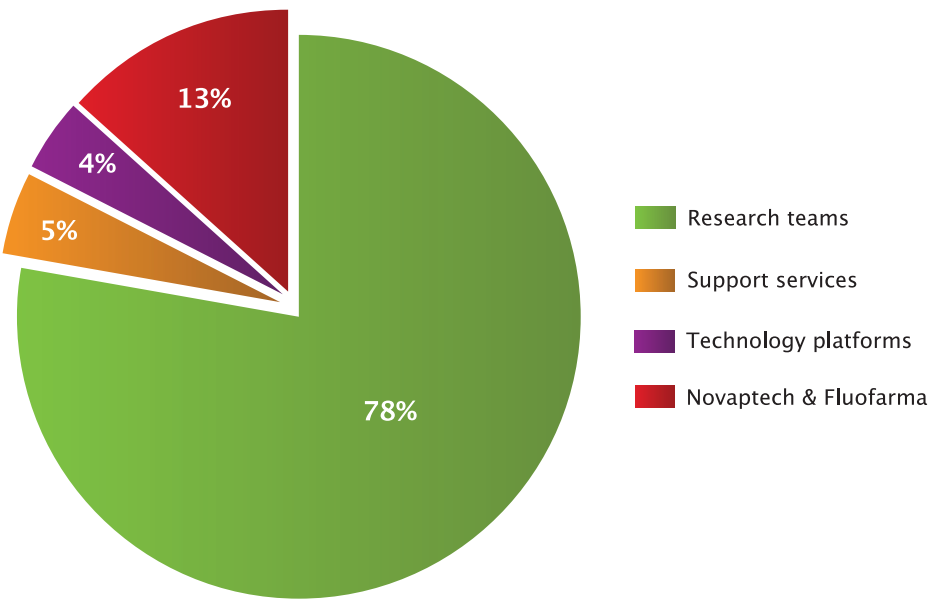
Technology transfer & start-ups

- FLUOFARMA
- NOVAPTECH

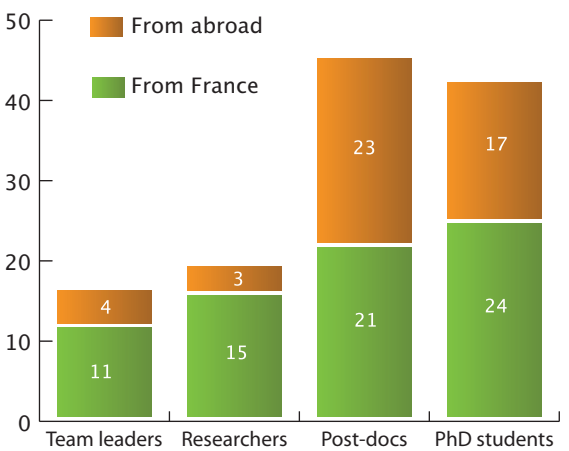
2011 key figures

In 2011, 190 people were working on the IECB site: 148 research staff, 17 employees within the IECB support services unit and 25 employees of the company Fluofarma and the technology transfer unit Novaptech. As shown in the lower right graph, over the past 5 years, the number of post-doctoral researchers at IECB has been appreciably growing, mainly due the good performance of IECB teams in national and european calls. Young researchers (Master and Phd students, postdoctoral researchers) now represent more than the half of the IECB staff. This population largely contributes to gender equality and internationalization at IECB. It also testifies to the attractiveness of the institute.

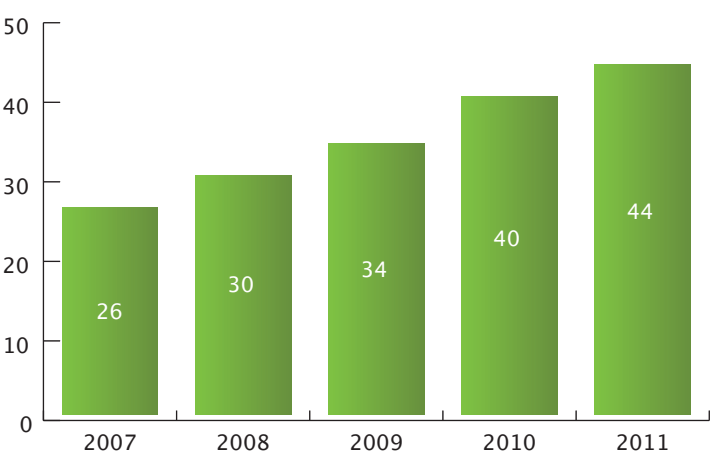
IECB staff by professional category



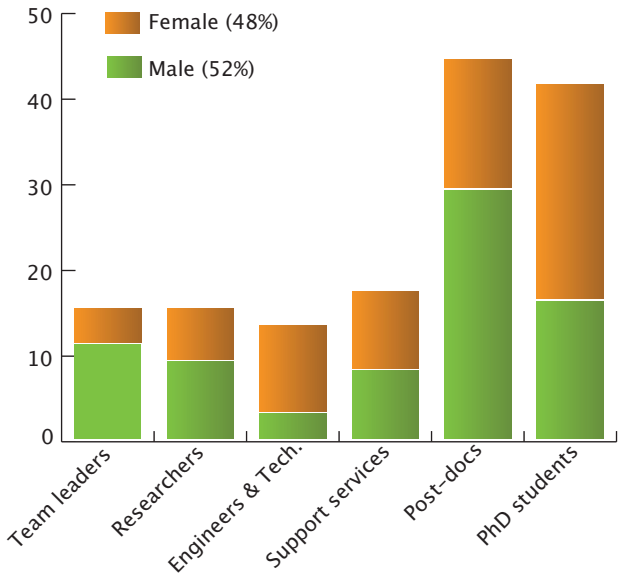
IECB researchers and students by nationality & professional category



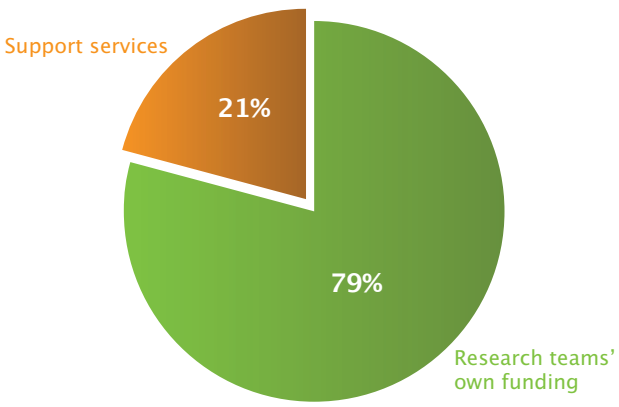
Number of post-doctoral researchers over the past 4 years



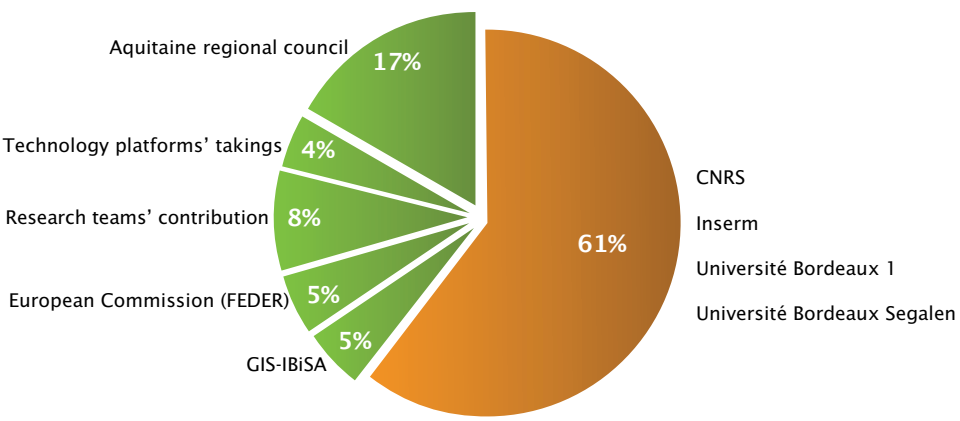
IECB research staff by gender & professional category



IECB's 2011 budget



Support services funding



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

SUPPORT SERVICES (UMS 3033 / US 001)

Support services at IECB consist of staffs in administration and finance, infrastructure and maintenance, as well as 7 engineers and technicians dedicated to IECB's technology platforms. The support services unit UMS3033/US001 is jointly funded by the CNRS, the Inserm, the Université Bordeaux 1 and the Université Bordeaux Segalen, and receives financial support from the Aquitaine Regional Council. Research teams also contribute to financing those general services.

Administration and finance

Administrative director
Stéphanie MONTAGNER, IE, CNRS
Accounting and administration officer
Sandra LAVENANT, Tech., Université Bordeaux Segalen
Accounting and administration officer
Céline DOUMEINGTS, Adj, Université Bordeaux 1
Accounting and administration officer
Patricia MARTIN, Tech., INSERM
Accounting and administration officer
Laurent KUBICKI, Tech., INSERM

Executive assistant office

Executive assistant
Elodie EMAILLE, CDD, INSERM

Communication

Communication officer
Pierre-Emmanuel GAULTIER, CDD, CNRS

Infrastructure

IT manager
Gérald CANET, IE, INSERM
Infrastructure Officer
Patrice DUBEDAT, AJT, Univ. Bordeaux 1

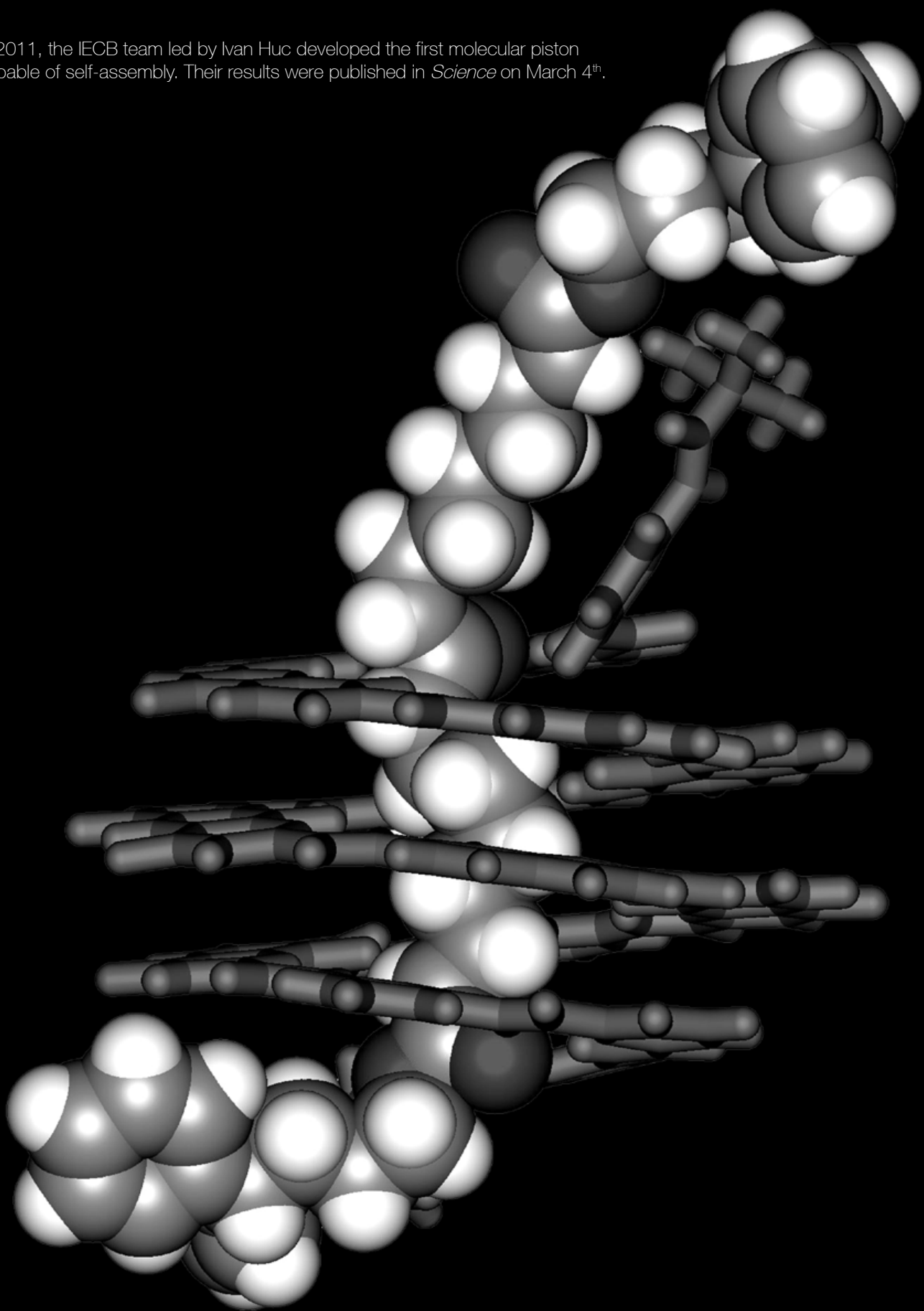
Structural biology facilities

Head of structural biology facilities and crystallography engineer
Brice KAUFFMANN, IR, CNRS
NMR engineer
Cécile COURREGES, IR, CNRS
Mass spectrometry technician
Michèle DUPIRE, Tech., Université Bordeaux 1

Analytical and preparative techniques facilities

Head of the analytical and preparative techniques facilities
Sabrina ROUSSEAU, IE, INSERM
High performance liquid chromatography assistant engineer
Yannick CHOLLET, AI, CNRS
Biochemistry and molecular biology engineer
Thierry DAKHLI, Tech., INSERM
Molecular and cell biology technician
François PUGNAIRE, Adjt Tech., INSERM

In 2011, the IECB team led by Ivan Huc developed the first molecular piston capable of self-assembly. Their results were published in *Science* on March 4th.



Research teams & output

Dr. Michel Laguerre

Research director (DR2), CNRS

Michel Laguerre, graduate from the *Ecole Nationale Supérieure de Chimie* of Toulouse, obtained his Engineering thesis in 1977 and his State Thesis (DSC) in Chemistry (Université Bordeaux I) in 1979 under the supervision of Raymond Calas (Organosilicon chemistry). He was hired by the CNRS in 1980 and joined the Life Sciences Department of the University Bordeaux Segalen, where he worked on the synthesis and design of drugs in the central nervous system area. In 1994 he moved to Centre de Recherche Paul Pascal (CRPP) in the Chemistry Department of CNRS where he reorientated his research axis toward biomembrane models and lipidic assemblies. After being promoted *Directeur de recherche*, he joined the IECB in 1998.

Research team

Dr. Juan ELEZGARAY Research director (DR2, CNRS)
Dr. Jean DESSOLIN Research officer (CR1, CNRS)
Dr. Nada TAÏB Postdoctoral fellow (AFM)
Dr. Marc LAMBLIN Postdoctoral fellow (ARC)
Dr. Pramod AKULA Postdoctoral fellow (ANR)
Dr. Vincent LEROUX Postdoctoral fellow (industrial grant, Servier)
Judith ELKAÏM PhD Student (MENRT)
Jean-Michel ARBONA PhD Student (MENRT)
Guillaume NATURALE PhD Student (CNRS/ Aquitaine Regional Council)
Driss BENNANI PhD Student (Aquitaine Regional Council)
Elodie LANDAGARAY Master Student

The team is part of the unit "Chimie et Biologie des Membranes et Nanoobjets" (CBMN), CNRS/ Université Bordeaux 1/IPB (UMR 5248)

Molecular modeling

Due to the increasing power of available computers, molecular simulation is now becoming an invaluable tool for structural biology. Using an all-atom representation, molecular dynamics allows a deep insight into the behavior of biomolecules. This approach is used in the context of three axes of research : lipidic assemblies, proteins and finally membrane proteins within biomembrane models. To overcome the limitations of the all-atom approach, mesoscopic representations of lipidic assemblies or proteins are developped, so as to gain access to simulations on long time or space scales. Finally in silico drug-design techniques allow to fulfil some gaps at the medicinal chemistry interface.

All-atom molecular dynamics

Our first research axis is devoted to molecular dynamics of complex lipidic assemblies using an all-atom representation : i.e., spherical or cylindrical micelles of various surfactants, Langmuir films and various bilayers of biologically relevant lipids. This work is performed in close collaboration with several teams involved in experimental biophysics. Very recently, we succeeded in determining at the atomic level the global structure of a nano-object containing tartrates of geminis. This is the first structure at an atomic level of such a nano object (published in JACS).

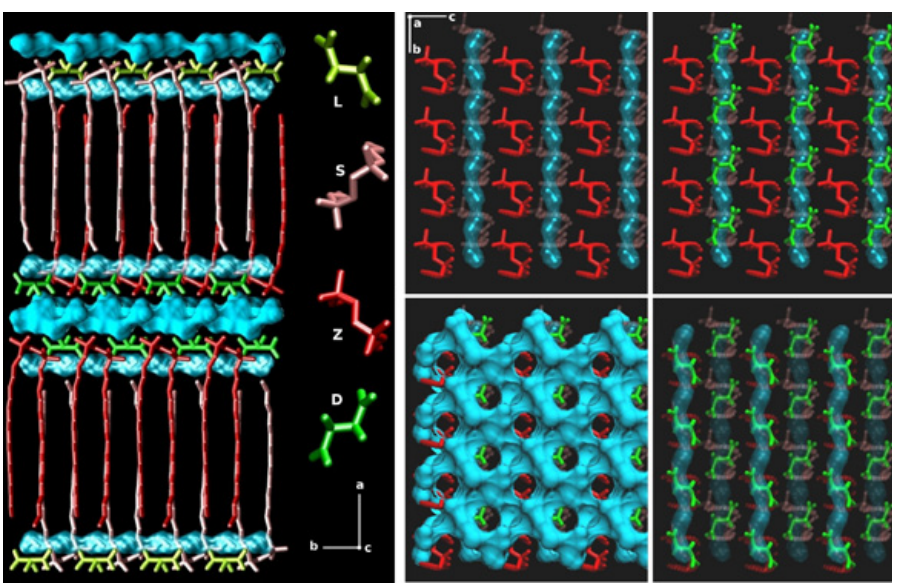


Figure 1: Final structure of the gemini tartrate film structure at an atomic level: geminis are in shade of red, tartrates in shade of green and water molecules are in blue. Tubes of aligned water molecules can be easily seen in the right panel. Between the two interdigitated layers a hexagonal lattice of water molecules insures the global cohesion of the structure.

Concerning the protein axis, we have largely focused our work on kinases over-expressed in various cancers and more particularly on the mechanism of activation of AKT-1 which is involved in numerous regulation pathways and thus in many cancers (Cancer Institute UK). Two papers have been published in PloS Biology, along with a review on the subject. The aim of the project was to unravel at an atomic level the complex activation process of this master kinase. The whole work has been highlighted in England on several internet sites like Yahoo England or Channel Four and in France in the Journal du CNRS. This work has now been extended to the kinase PDK-1, which is one of the major activating factor of the AKT cascade. A paper has been published in Science Signaling.

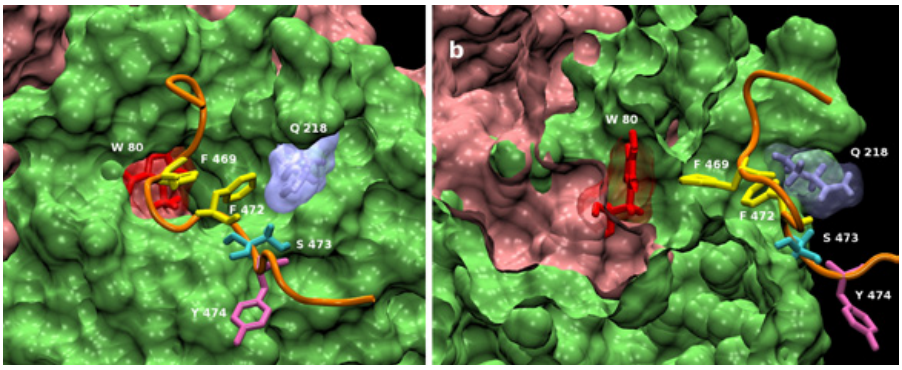


Figure 2: Complete structure of AKT-1: 2 orthogonal views of the Cterm docked on the WT PH/KIN complex : PH in pink, KIN in green, Cterm backbone in orange, W80 in red, F469 & 472 in yellow, S473 in cyan, Y474 in mauve, Q218 in aquablue. The water channel is visible in the center of the left image and on the right it is cut just at its middle by the clipping plane.

We also have considered molecular dynamics of membrane receptors in a full lipidic environment and monitored the drug/receptor interaction. Actually the main interest lies in the GPCR super-family including human dopamin D2 or leukotrien receptors and mainly the opiate receptors in collaboration with Vanderbilt University. A paper has been published in Protein Science. A second has been submitted to Mol. Pharm. This collaboration now extends to the Harvard School of Medecine.

Drug-design & high-troughput in-silico screening

The activity lies at the frontier between biology and chemistry. Starting from a biological problem, we look for small molecules able to interact with protein targets. Virtual screening is performed with pre-filtered chemical databases, or with in-house collections. This approach leads to the discrimination of the best putative ligands which are then synthesized in our group or through collaborations with other teams. A large project for 4 years has been granted by INCA. The subject is Helicase and this is a collaboration with Drs. P. Lestienne and J. Rosenbaum (INSERM U889).

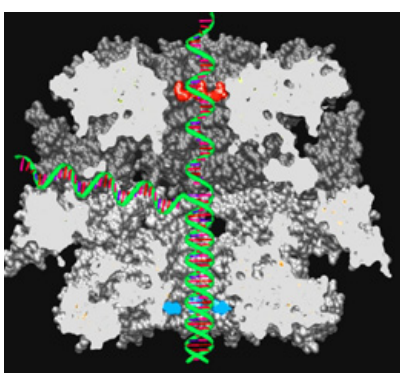


Figure 3: Complete model structure of human Helicase. Reptin is below and pontin above. A double-stranded DNA is entering the protein through a central channel. DNA is unfolded in the center of the complex and then the direct strand gets out by the top pontin pore and the indirect strand is ejected through one of the six lateral channels.

Surface plasmon microscopy

This work is the result of a close collaboration with F. Argoul's team at ENS Lyon. The goal is to develop a non intrusive tool to detect small variations of the dielectric constant in the vicinity of a metal-dielectric interface. Typical applications range from DNA microarray characterization to cell imaging. Experimentally, the Argoul's team has shown that dielectric as well as metallic nanoparticles (R > 10 nm) can be detected with this type of microscopy. The technique is based on the interferometric detection of the perturbations induced on the plasmon excitations supported by a thin gold layer (width ~ 50nm). The sample to be imaged is in the vicinity of this layer. Our contribution to this work consists in providing a model that allows a quantitative description of the measurements. The agreement between this theory and the experimental data is good excepted for particle sizes (~ 10 nm) comparable to the scale where the gold deposit cannot be considered as flat. The model also provides with a set of optimal experimental parameters, such as the gold width and the range of incident angles. Overall, the efficiency of plasmon microscopy can be traced back to the amplification by the plasmon excitations of the evanescent waves scattered by the nanoparticles.

Selected publications

Masters T.A., Calleja V., Armoogum D., Marsh R., Applebee C.J., Laguerre M., Bain A. & Larijani B. (2010). In vivo regulation of 3-phosphoinositide dependent protein kinase 1 (PDK1) activity by homodimerisation. Science Signaling, 3145, ra78.

Cala O., Pinaud N., Simon C., Fouquet E., Laguerre M., Dufourc E.J. & Pianet I. (2010). The affinity of condensed wine tannins to human saliva proteins is controlled by their conformational preference. A NMR and Molecular Modeling study. FASEB Journal, 24, 4281-4290.

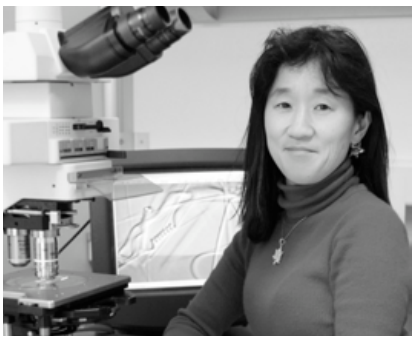
Calleja V., Laguerre M., Parker P. J. & Larijani B. (2009). Role of a Novel Phkinase Domain Interface in PKB/Akt Regulations: Structural Mechanism for Allosteric Inhibition. PLoS Biology, 7 (1): 189-200.

Oda R., Artzner F., Laguerre M. & Huc I. (2008). Structure of selfassembled chiral nanoribbons and nanotubules revealed in the hydrated state. JACS, 130(44): 14705-14712.

Moreau L., Camplo M., Wathier M., Taib N., Laguerre M., Bestel I., Grinstaff M.W. & Barthélémy P. (2008). Real Time Imaging of Supramolecular Assembly Formation via Programmed Nucleolipid Recognition. JACS, 130(44): 14454-14455.

Calléja V., Alcor D., Laguerre M., Park J., Hemmings B., Vojnovic B., Downward J., Parker P.J., Larijani B. (2007). Intra- and inter-molecular interactions of Kinase B define its activation in vivo. PLoS Biology, 5(4): 780-791.

Beaurain F., Di Primo C., Toulmé, J.J., Laguerre M. (2003). Molecular dynamics reveals the stabilizing role of loop closing residues in kissing interactions: comparison between TAR-TAR* and TAR-aptamer. NAR, 31: 4275-4284.



Dr. Reiko Oda
Research director (DR2), CNRS

Reiko Oda, after obtaining a bachelor degree in physics at the University of Tokyo in 1988, got her PhD in Physics at the Massachusetts Institute of Technology in 1994 under the supervision of Pr. D. Litster. She then had four years of postdoctoral position in the laboratory of S. J. Candau at University Louis Pasteur (Strasbourg). She joined the IECB on 1998 as a group leader. Her research deals with the structural study and design of aggregates of amphiphilic molecules and their interactions with biological polyions, as well as functionalization of such aggregates.

Research team

Dr. Sylvain NLATE Associate professor (Mdc, Université Bordeaux 1)
Dr. Emilie POUGET Research officer (CR2, CNRS)
Dr. Marie Christine DURRIEU Research officer (CR1, INSERM)
Dr. Said HOUMADI Postdoctoral fellow (Université Bordeaux 1)
Dr. Rajat DAS Postdoctoral fellow (Université Bordeaux 1)
Dr. Omar ZOUANI Postdoctoral fellow (Université Bordeaux 1)
Celine CHOLLET Postdoctoral fellow (Université Bordeaux 1)
Loic PICHAVANT Postdoctoral fellow (Université Bordeaux 1)
Yifeng Lei PhD student (Université Bordeaux 1)
Rumi TAMOTO PhD student (Université Bordeaux 1)
Alexandre CUNHA PhD student (Université de Lisbonne/Université Bordeaux 1)
Ren-Wei CHANG PhD student (Université Bordeaux 1)
Dima DEDOVETS PhD student (Université Bordeaux 1)
Alla MALINENKO PhD student (Université Bordeaux 1)
Annie Zhe CHENG PhD student (Leuven University/Université Bordeaux 1)

The team is part of the unit "Chimie et Biologie des Membranes et Nanoobjets" (CBMN), CNRS/ Université Bordeaux 1/IPB (UMR 5248)

Morphologies, dynamics & functions of assemblies of amphiphilic molecules

The team is interested in understanding the mechanism of formation of molecular assemblies in order to design and build new nanometric molecular assembly systems of amphiphilic molecules, the morphologies and functions of which can be finely tuned. This requires first of all understanding the role of different parameters (molecular architecture and various physico-chemical parameters) upon such molecular assemblies. Once the control of the assembly formation at the molecular level is achieved, their functionalization can be envisaged. The assemblies can therefore serve as the support for the biomolecular structure formation or the induction of interaction between the aggregates via molecular recognition.

Our activities are divided in several subjects as shown below:

Ion specific effect

We combine experimental and computational approach to rationalize the century old problem: ion specific effect on the balance of forces controlling aggregates structure. We investigate the aggregation behaviors of cationic amphiphilic molecules in the presence of various counterions such as Halide anions, alkyl carboxylates and aromatic carboxylates in order to elucidate the complex effects of ion properties (ionic volume, pKa, nucleophilicity, polarizability, etc.) on the properties of molecular self-assemblies from the molecular level to the bulk solution. (J. Phys. Chem. B 2008, Langmuir 2010)

We have obtained an international collaborative grant ANR-blanc International for a collaborative work between Michel Laguerre (IECB, molecular dynamics), Dario Bassani (ISM, Photochemist), and colleagues from Rutgers University : Larry Romsted (physical organic chemist: chemical trapping technique), Ronald Sauers (DFT calculation), David Case (MD/DFT approach) in order to elucidate the interface properties of amphiphilic assemblies in terms of counterion and water concentration.

Chiral assemblies

We are interested in the mechanism of formation of chiral mesoscopic molecular assemblies. We have shown that when complexed with tartrate anions, cationic surfactants form chiral ribbon which express supramolecular chirality of the order of 10 nm to microns. The morphologies of these chiral assemblies can be controlled with a number of parameters (Nature 1999, JACS 2007). The detailed study of these systems allowed us to better understand the mechanism of the chirality transfer from chiral counterions to achiral membranes from molecular level up to mesoscopic level. (JACS 2002, J. Phys. Chem. A 2004, JACS 2008, Chirality 2009). When the same cationic surfactants are complexed with peptides or nucleotides, they form simplified model systems which mimic the lipid-protein interaction, or lipid-nucleotide interaction (Figure 1). (ChemCommun 2007, Chem. Eur. J. 2011)

Remarkably, the chirality of peptides and nucleotides also lead to the expression of supramolecular chirality of the assemblies. Such reciprocal and cooperative effects between membranes and counterions, seem to be general in the case of the systems studied here.

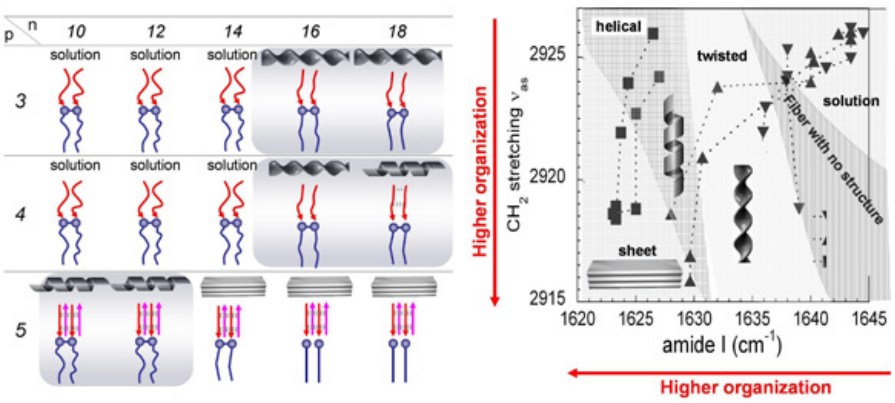


Figure 1: Chiral ribbons induced by complex cationic surfactant-anionic peptides; confined peptides form βsheet

Hybrid organic/inorganic nanohelices

We have developed a method to synthesize well controlled chiral inorganic nanostructures based on the sol-gel transcription of organic self-assemblies. These inorganic structures can then be functionalized to serve as templates for confining nanoparticles (see figure 2). (Nanoletters 2008, ANR Blanc grant 2010.)

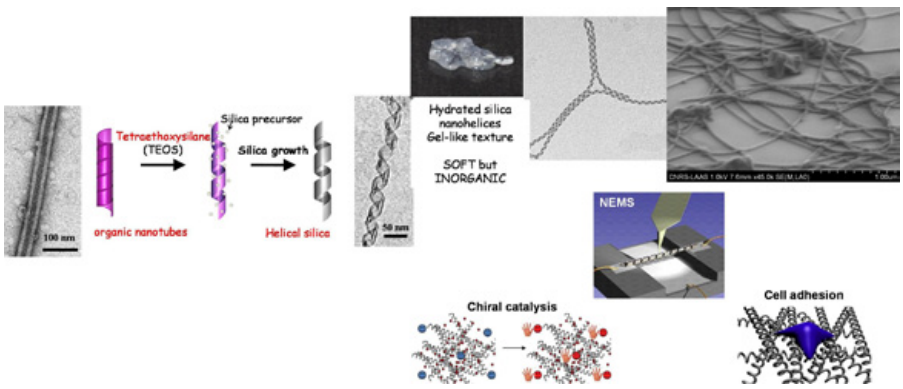


Figure 2: (left) organic nanotubules are used as template to form silica nanohelices . (right) Silica nanohelices are functionalized and their use in catalysis, cell-adhesion or NEMS are investigated.

Self assembled nanocatalysts

As of January 2011, Sylvain Nlate, an associate professor (Mdc) specialised in dendrimers and catalysis has joined the group. We started a totally new project concerning the design of new catalysis systems for asymmetric oxidation reactions using tunable nanometrical chiral molecular assemblies

The influence of nano-bio materials on stem cells differentiation

Recently, Marie-Christine Durrieu, an INSERM researcher specialized in cell adhesion on the surface joined the group. Reinforced by her expertise in tissue engineering, we are developing to a new field to investigate the effect of surface organized nanostructures on cell differentiation.

Selected publications

Kiagus-Armad R., Brizard A., Tang C., Blatchly R., Desbat B., Oda R. (2011) Cooperative and Reciprocal Chiral Structure Formation of Ala-Based Peptide Confined at the Surface of Cationic Surfactant membranes, Chem. Eur. J., 17, 9999-10009

Manet S. Karpichev Y., Bassani D, Kiagus-Ahmad R., Oda R. (2010) Counter-anion effect on micellization of cationic gemini surfactants 14-2-14 - Hofmeister and other counterions, Langmuir, 26 (13), 10645-10656

Yassine W., Milochau A., Buchoux S., Lang J., Desbat B., Oda R. (2010) Effect of monolayer lipid charges on the structure and orientation of protein VAMP1 at the air-water interface Biochimica et Biophysica Acta (BBA) - Biomembranes, 1798, 5, 928-93

Aime C., Tamoto R., Satoh T., Grelard A., Dufourc E. J., Buffeteau T., Ihara H., and Oda, R. (2009) Nucleotide-Promoted Morphogenesis in Amphiphile Assemblies: Kinetic Control of Micrometric Helix Formation. Langmuir , 25(15), 8489-8496.

Yassine W., Taib N., Federman S., Milochau A., Castano S., Sbi W., Manigand C., Laguerre M., Desbat B., Oda R., and Lang J., (2009) Reversible transition between α-helix and β-sheet conformation of a transmembrane domain Biochimica et Biophysica Acta (BBA) - Biomembranes, 1788 1722-1730

Oda R., Artzner F., Huc I., Laguerre M. (2008). Molecular structure of self-assembled chiral nano-ribbons and nano-tubules revealed in the hydrated state J. Am. Chem. Soc., 130 (44): 14705-14712

Delclos T., Aimé C., Pouget E., Brizard A. Huc I., Delville M.-H and Oda R. (2008). Individualized Silica Nanohelices and Nanotubes: Tuning Inorganic Nanostructures Using Lipidic Self-Assemblies Nanoletters, 8, (7): 1929-1935

Brizard A., Aimé C., Labrot T., Huc I., Berthier D., Artzner F., Desbat B., Oda R. (2007). Counter-ion, temperature and time modulation of nanometric chiral ribbons from gemini-tartrate amphiphiles J. Am. Chem. Soc., 129(12): 3754-3762.

Brizard A., Kiagus R.K., Ahmad R., Oda R. (2007). Control of nano-micrometric twist and helical ribbons formation with gemini-oligoalanine via interpeptidic beta-sheet structure formation Chem. Commun., 22: 2275-2277.

Aimé C., Manet S., Satoh S., Ihara H., Park K.Y., Godde F., Oda R. (2007). Self-Assembly of Nucleoamphiphiles: Investigating Nucleosides Effect and the Mechanism of Micrometric Helix Formation Langmuir, 23 (26): 12875 -12885

Pr Alain Brisson
Professor (Pr0), University Bordeaux 1

Alain Brisson has successively led research groups at the Universities of Strasbourg as Directeur de Recherche at INSERM (87-94) and in Groningen as Professor of Biochemistry (94-01), before moving to the University of Bordeaux as Professor of Biochemistry and group leader at IECB (2001-to date). His main interests are to elucidate the structure-function relationship of complexes between proteins and membranes and to understand the basic principles of their assembly, with a particular interest in annexins. His group develops original molecular tools for applications as biosensors in diagnosis and nanovectors in drug delivery.

Research team

Anthony BOUTER Associate professor (Mdc, University Bordeaux 1)
Céline GOUNOU Assistant engineer (University Bordeaux 1)
Sisareuth TAN Assistant engineer (CNRS)
Boris GARNIER Post-doctoral fellow (EU)
Nicolas ARRAUD PhD student (MENRT)
Yali WAN PhD student (EU)
Benoit FAURIE Master student
Fiona JASSON Master student
Romain LINARES Master student

The team is part of the unit "Chimie et Biologie des Membranes et Nanoobjets" (CBMN), CNRS/ Université Bordeaux 1/IPB (UMR 5248)

Molecular imaging & nanobiotechnology

The team "Molecular Imaging and NanoBioTechnology" develops its research activities along two main orientations: "structure-function studies of annexins and complexes between proteins and membranes" and "nanobiotechnological applications of annexin-based molecular tools". Basic research projects focus on the relationship between molecular structure, supramolecular organization and mechanisms of 2D assembly of proteins at membrane surfaces, with main interest in effect of annexin-A5 on processes of membrane reorganization associated with phosphatidylserine exposure, principally cell membrane repair and cell fusion processes. Nanobiotehnology-oriented projects focus on the development of molecular tools derived from annexin-A5, for applications in diagnosis and drug delivery.

Characterization of Microparticles from Blood Plasma, by Cryo-Electron Microscopy and Annexin-A5 Gold Labeling

Microparticles are membrane fragments that derive from activated or apoptotic cells and are found in plasma and other biological fluids. In plasma, a majority of microparticles originate from platelets. A fraction of plasmatic microparticles exposes at their surface the procoagulant lipid phosphatidylserine (PS) and participates in physiological processes of hemostasis or inflammation. Elevated levels of plasmatic microparticles are found in various pathological disorders, which explains efforts to use microparticles as disease biomarkers. However, the detection and quantification of microparticles is hampered by their small size, which ranges from 50 nm to 1 µm, and the limitations of current analytical methods. Here, we used cryo-Electron Microscopy and PS-specific gold labeling and provided a comprehensive structural description of the whole population of microparticles and the sub-population of PS-exposing microparticles present in plasma or derived from activated platelets. The morphology of plasmatic microparticles is described and size histograms are presented. Platelet-derived microparticles range in size from 50 nm to 3 µm, 75% of them being smaller than 500 nm. PS-exposing microparticles constitute 70% of the total population. This study provides novel structural information on platelet-derived microparticles and opens avenues for characterizing microparticles from different cell origins or associated with various physiopathological situations. (paper in revision at Blood).

Annexin-A5 function

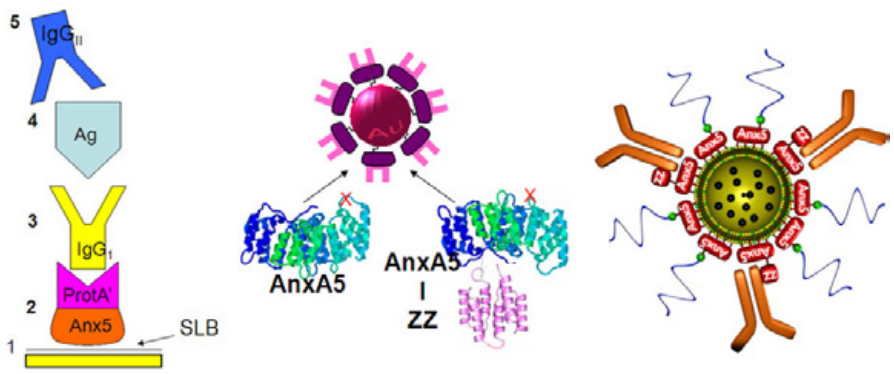
Annexins form a family of soluble proteins that share the property of binding to negatively charged phospholipid membranes in a Ca2+-dependent manner. We have previously shown that several members of the annexin family, the prototype of which is Annexin-A5, self-assemble upon membrane binding into 2D ordered arrays. Basic projects on Annexin-A5 have focused on structure-function relationship studies. The analysis of the elementary interaction between Annexin-A5 and model membranes has been achieved at unprecedented low concentrations, in the fM range. In parallel, we have ultimately discovered the function of Annexin-A5, which participates in a central function in cell's life (Paper published at Nature Communications).

Development of functionalized nanotools for applications in diagnosis or drug delivery

Nanovectors functionalized with proteins and encapsulating active principles or imaging agents are developed for drug delivery or imaging applications. On-going projects concern vectors of either polymeric or liposomal origin, for the targeting of atheroma plaque, inflammation, breast or colon cancers, and are carried out within collaborations with several Bordeaux teams and at the European level.

We have developed various types of Annexin-A5 or Annexin-A5-derived markers, including fluorescent labels, gold particles for Electron Microscopy imaging, and magnetic markers -both magneto-liposomes and polymer vesicles- for MR-imaging.

The synthesis of magneto-liposomes has been optimized and protein-functionalized magneto-liposomes have been used for imaging, ex vivo, thrombi sites in atheromatous plaques (Paper in press at Contrast Media and Molecular Imaging).



Scheme of various AnxA5-based molecular tools. (Left): AnxA5-ZZ fusion protein for the controlled immobilization of IgGs or selected antigens; (middle): gold nanoparticle functionalized with oriented AnxA5 or AnxA5-ZZ for the specific labeling of receptors at the (sub)-cellular or tissular level; (right): liposomal nanovector functionalized with AnxA5-ZZ-IgG and encapsulating iron oxide particles for MRI.

Selected publications

Bouter A., Gounou C., Bérat R., Tan S., Gallois B., Granier T., Langlois d'Estaintot B., Pöschl E., Brachvogel B., Brisson A.R. (2011) Annexin-A5 assembled into two-dimensional arrays promotes cell membrane repair. Nature Communications, DOI 10.1038/ncomms1270.

Poindron V., Berat R., Knapp A.M., Toti F., Zobairi F., Korganow A.S., Chenard M.P., Gounou C., Pasquali J.L., Brisson A.R., Martin T. (2011) Evidences for Heterogeneity of the Obstetrical Antiphospholipid Syndrome: thrombosis can be Critical for Antiphospholipid-Induced Pregnancy Loss. J Thromb Haemost. doi: 10.1111/j.1538-7836.2011.04475.x.

Sanson C., Diou O., Thévenot J., Ibarboure E., Soum A., Brûlet A., Miraux S., Thiaudière E., Tan S., Brisson A.R., Dupuis V., Sandre O. and Lecommandoux S. (2011). Doxorubicin Loaded Magnetic Polymersomes: Theranostic Nanocarriers for MR Imaging and Magneto-Chemotherapy. ACS Nano 22:1122-1140.

Garnier B., Bouter B., Gounou C., Petry K.G. and Brisson A.R. (2009). Annexin A5-functionalized liposomes for targeting phosphatidylserine-exposing membranes. Bioconjugate Chemistry, 20: 2114-2122.

Soenen S.J.H., Brisson A.R. and De Cuyper M. (2009).Addressing the problem of cationic lipid-mediated toxicity: The magnetoliposome model. Biomaterials, 30, 3691-701.

Richter R.P., Bérat R. and Brisson A.R. (2006). The formation of solid-supported lipid bilayers - an integrated view. Langmuir 22, 3497-3505.

Dr. Ivan Huc
Research director (DR1), CNRS

Ivan Huc was born in Besançon, France, in 1969. He studied chemistry at the Ecole Normale Supérieure in Paris, and received his PhD in 1994 from the Université Pierre et Marie Curie (Paris) under the guidance of Dr. C. Rolando (Ecole Normale Supérieure) and Prof. J. Rebek Jr. (Massachusetts Institute of Technology). After a one-year post-doctoral position with Dr. J.-P. Behr at Strasbourg University, he received a CNRS researcher position in the laboratory of Prof. J.-M. Lehn in Strasbourg, where he stayed from 1995 until 1998. Since 1998, he has been a group leader at the Institut Européen de Chimie et Biologie in Bordeaux where he holds a CNRS research director position. In 2008, he started to serve as co-director of the Institute. His current research interests are foldamers and the biomimetic chemistry of peptides and nucleotides.

Research team

Dr. Frédéric GODDE Associate professor (Mdc, Université Bordeaux 1)
Dr. Yann FERRAND Research officer (CR2, CNRS)
Dr. Victor MAURIZOT Research officer (CR1, CNRS)
Dr. Ting QI Postdoctoral fellow (Université Bordeaux 1)
Dr. Michael SINGLETON Postdoctoral fellow (Université Bordeaux 1)
Dr. Krzysztof ZIACH Postdoctoral fellow (Université Bordeaux 1)
Dr. Simon DAWSON Postdoctoral fellow (Université Bordeaux 1)
Dr. Tiny DESCHJRIVER Postdoctoral fellow (Université Bordeaux 1)
Dr. Christel DOLAIN Postdoctoral fellow (Université Bordeaux 1)
Dr. Chandramouli NAGULA Postdoctoral fellow (CNRS)
Dr. Bo CHI Postdoctoral Fellow (Egide)
Laure SEBAOUN PhD student (Université Bordeaux 1)
Guillaume LAUTRETTE PhD student (Université Bordeaux 1)
Christos TSIAMANTAS PhD student (Université Bordeaux 1)
Quan GAN PhD student (CNRS)
Mayumi KUDO Visiting scientist (Université Bordeaux 1)

The team is part of the unit "Chimie et Biologie des Membranes et Nanoobjets" (CBMN), CNRS/ Université Bordeaux 1/IPB (UMR 5248)

Biomimetic supramolecular chemistry

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

Highlights of important developments in the last 1 ½ year are listed below:

Solid phase synthesis

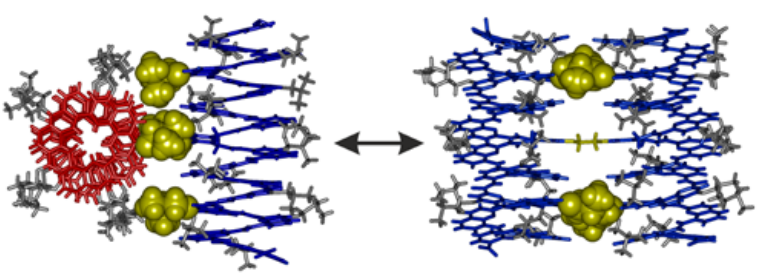
An important methodological development in aromatic amide foldamer research was published (J. Org. Chem. 2010): we have optimized protocols for synthesis helical oligomers on solid phase. This development paves the way to combinatorial approaches to prepare small libraries of these compounds and gives access to screening. In the mean time, three pharma companies have expressed their interest to collaborate with our group (one on going contract, one contract about to be signed, and preliminary contacts with the third company).

Cell penetration

The synthesis of fully water soluble helical aromatic amide foldamers has allowed preliminary characterizations of their biological activity. In particular, surprisingly efficient cell penetration was observed, considering the large size of these molecules (ChemBioChem 2010). Combined with the low toxicity and full resistance to protease degradation, this result bodes well for potential applications of aromatic amide foldamers in biology.

Proteomimetics

Synthetic foldamers of unprecedented size (> 10 kDa) have been synthesized and structurally characterized by x-ray crystallography (J. Am. Chem. Soc. 2011). They represent the first folded abiotic architectures that compare in size to a (modest-size) protein.

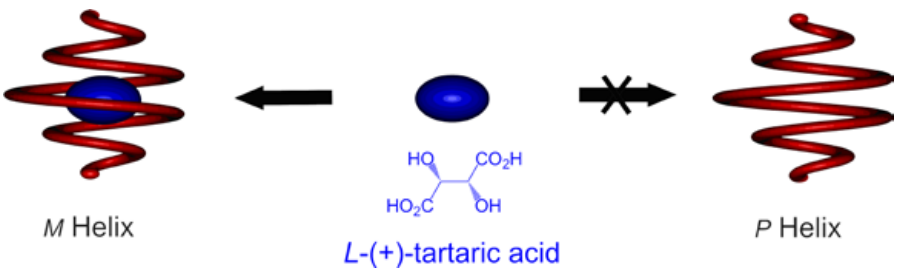


Whilst many foldamers have so far consisted of isolated helices or linear strands, future developments will likely focus on mimics of protein tertiary folds as the one we have described. The synthesis of such a large object was made possible by the incorporation of aliphatic secondary amide linkages that are compatible with the folding motifs of aromatic secondary amide linkages. The first artificial organic triple helices have been evidenced (Angew. Chem. Int Ed. 2010) among the folded structures of naphthyridine

oligoamides. This discovery follows earlier work on quadruple helices (2008) and double helices and strikingly illustrates the potential of these oligomers to form a great variety of well-defined architectures.

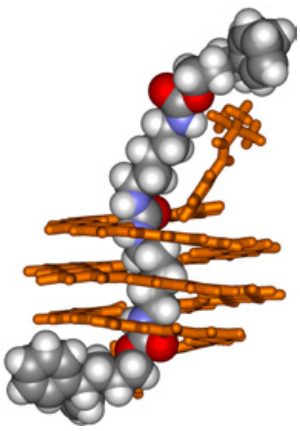
Encapsulation

Sequences of aromatic amino-acids have been designed to fold into helices having a large diameter in the center and narrow diameters at the ends, thus creating a cavity totally surrounded by the helix backbone. Encapsulation of various guests in those confined environments has been demonstrated (JACS 2010). A chiral guest such as tartaric acid is recognized with full diastereoselectivity by a helix of fixed handedness. Current unpublished developments demonstrate the capacity of these helically folded capsules to selectively bind to unsubstituted mono-saccharides.



Molecular motors

An extension of the work on foldamer capsules led to the design of helical oligomers with an open cavity that can wind around rod-like guests. Thin guests enter the helix cavities through a threading mechanism. However, when the guest possesses bulky ends, the complex can only form through an unfolding of the helix host and its refolding around the guest. This creates a considerable kinetic barrier which allows to prepare kinetically stable complexes which do not dissociate readily and allow to observe sliding motions of the helix along elongated guests, like a piston in its sheath. This development represents one of the first examples of the use of self-assembly to prepare synthetic nanomachines (Science 2011). A recent development demonstrated similar phenomena not with single helical but with double helical hosts (Angew. Chem. Int. Ed. 2011).



Cascading transformations

The collaboration with the group of Dr. Jonathan Nitschke (Cambridge) concerning the metal directed dynamic assembly of helical architectures has taken momentum with the characterization of macrocyclic helicates (Chem. Eur. J. 2009) and the design of an ensemble of cascading transformation where helicates transform into other helicates following the introduction of new components in a complex mixture (Nature Chemistry 2010).

Selected publications

Gan Q., Ferrand Y., Bao, C. Kauffmann B., Grélard A., Jiang H., Huc I. (2011) Helix-rod host-guest complexes with shuttling rates much faster than disassembly, Science, 331, 1172

Delsuc N., Massip S., Léger J.-M., Kauffmann B., Huc I. (2011) Relative helix-helix conformations in branched aromatic oligoamide foldamers, J. Am. Chem. Soc., 133, 3165

Campbell V. E., de Hatten X., Delsuc N., Kauffmann B., Huc I., Nitschke J. R. (2010). Cascading transformations within a dynamic self-Assembled system. Nature Chem., 2, 684

Ferrand Y., Kendhale A. M., Garric J., Kauffmann B., Huc I. (2010). Parallel and antiparallel triple Helices of naphthyridine oligoamides. Angew. Chem. Int. Ed., 49, 1778.

Sánchez-García D., Kauffmann B., Kawanami T., Ihara H., Takafuji M., Delville M.H., Huc I. (2009). Nanosized hybrid oligoamide foldamers: aromatic templates for the folding of multiple aliphatic units. J. Am. Chem. Soc., 131, 8642.

Baptiste B., Godde F., Huc I. (2009). How can folded biopolymers and synthetic foldamers recognize each Other? ChemBioChem, 10, 1765.

Bao C., Kauffmann B., Gan Q., Srinivas K., Jiang H., Huc I. (2008). Converting sequences of aromatic amino acid monomers into functional three-dimensional structures: second-generation helical capsules. Angew. Chem. Int. Ed., 47, 4153.

Gan Q., Bao C. , Kauffmann B., Grélard A., Xiang J., Liu S., Huc I., Jiang H. (2008).Quadruple and double helices of 8-fluoroquinoline oligoamides. Angew. Chem. Int. Ed., 47: 1715.

Gillies E., Deiss F. Staedel C., Schmitter J.M., Huc I. (2007). Development and biological assessment of fully water-soluble helical aromatic amide foldamers. Angew. Chem. Int. Ed.,, 46, 4081.

Pr. Stéphane Quideau
Professor (CE1), Université Bordeaux 1

Stéphane Quideau received his PhD in Natural Products Chemistry at the University of Wisconsin-Madison (USA) in 1994 under the supervision of Prof. J. Ralph. After a postdoctoral stint at The Pennsylvania State University (USA) in Prof. K. S. Feldman's group, he moved to Texas Tech University (USA) as an Assistant Professor. In 1999, he moved back to France as an Associate Professor (PR2) at the University of Bordeaux. He joined the IECB as a Group Leader in 2003. He was nominated as a Junior Member of the "Institut Universitaire de France" (IUF) in 2004, was promoted Full Professor (PR1) in 2005, and Full Professor (CE1) in 2011. His current fields of interest encompass synthetic and biomechanistic studies of bioactive natural products with a focus on plant polyphenols, the development of synthetic methodologies based on hypervalent iodine chemistry, and the rational design of antigenic peptidomimetics as immuno-therapeutic agents.

Research team

Dr. Denis DEFFIEUX Associate professor (MdC, Université Bordeaux 1)
Dr. Laurent POUYSÉGU Associate professor (MdC, Université Bordeaux 1)
Rémi JACQUET Technician (Tech, Université Bordeaux 1)
Dr. Céline FRANC Postdoctoral fellow (LVMH - 5 months)
Dr. Hélène BERTRAND Postdoctoral fellow (ANR FLUNUCLEOVIR - 4 months)
Dr. Tony GARNIER Postdoctoral fellow (SASN - 4 months)
Dr. Tahiri SYLLA Postdoctoral fellow (SASN - 2 months)
Mélanie DELANNOY PhD student (Fundayacucho)
Cyril BOSSET PhD student (BDI CNRS/CRA)
Romain COFFINIER PhD student (ANR IODINNOV)
Emilie PETIT PhD student (CIVB)
Hélène CARRIÉ PhD student (CIVB)
Dong Tien TRAN PhD student (Vietnamese Government)

This team is part of the Institut des Sciences Moléculaires (UMR-CNRS 5255) at the University of Bordeaux and is associated with the Institut des Sciences de la Vigne et du Vin (ISVV).

Synthesis & activity of natural substances

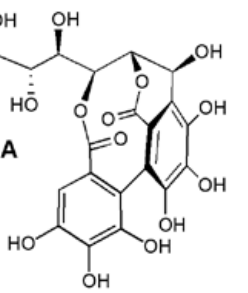
Our research activities are mainly concerned with the chemistry and biochemistry of natural products with a focus on phenolic and quinonoid compounds, and with the chemistry and biology of antigenic peptides involved in cellular immune responses. Ongoing projects are dealing with (1) the exploitation of regioselective and asymmetric oxidative dearomatization of phenols for the total synthesis of natural products, in concert with the development of chiral hypervalent iodine reagents, (2) the extraction, structural characterization and synthesis of plant (poly)phenols, in particular C-glucosidic ellagitannins, (3) the development of chemical proteomic tools for the study of protein-polyphenol interactions, and (4) the rational design of antigenic peptidomimetics for the development of synthetic anticancer vaccines.

Hypervalent Iodine-Mediated Phenol Dearomatization

Our approach to the dearomatization of phenols relies on the use of hypervalent iodine(III) and (V) reagents and is essentially aimed at producing selectively cyclohexa-2,4-dienone derivatives of the orthoquinol and orthoquinone monoketal types for the synthesis of various natural products. The most challenging aspect of the dearomatization of phenols remains its adaptation to the access of orthoquinols or orthoquinone monoketals in a non racemic format. We spent much effort in developing a substrate-controlled solution for this challenge. Some of our results on this topic were published in 2010 in a special issue of Tetrahedron (Symposium-in-Print) that was edited in tandem with Thomas Wirth from the University of Cardiff at the occasion of the 3rd International Conference of Hypervalent Iodine Chemistry, which we organized at IECB in July 2010. In this same article, we also described the use of SIBX, the stabilized IBX reagent developed in partnership with the company Simafex, for the chemoselective conversion of the natural product bergenin into its congener norbergenin and for the rapid synthesis of hydroxytyrosol, a highly potent antioxidant found in olives. We also published in 2010 a review article in Tetrahedron (Report) on hypervalent iodine-mediated phenol dearomatization in natural products synthesis. More recently, we also worked on a reagent-controlled solution to asymmetric dearomatization of phenols by relying on the use of a chiral hypervalent iodine reagent. Our first results and their unexpected mechanistic implications, which call for a possible competition between two ligand coupling-based iodine(III) and iodine(V) pathways, were published in Angewandte Chemie in 2009. Our proposal for the continuation of this work was accepted in Summer 2010 by the ANR for funding (project Iodinnov).

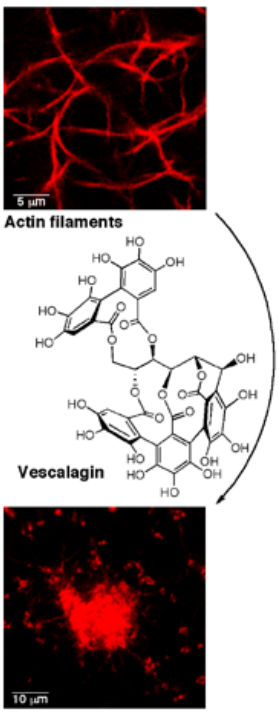
Synthesis, chemical reactivity and biological activity of polyphenolic C-glucosidic ellagitannins

Mainly funded by the Conseil Interprofessionel du Vin de Bordeaux (CIVB), the Conseil Regional d'Aquitaine and the ANR (project EllagInnov), our investigations on this topic have continued to provide us with valuable results. On the synthesis side, we recently achieved the first and biomimetic total synthesis of a first member of the C-glucosidic class of ellagitannins, 5-O-desgalloylepipunicacortein A. This work has been published in 2011 in ChemComm. We also published a review article on the chemical synthesis of ellagitannins in Natural Products Report in 2011. This article was selected for the cover. We have also developed, in collaboration with Car-



5-*O*-desgalloyl-epipunicacortein A

melo Di Primo at IECB, a new SPR-based methodology to study the interaction between C-glucosidic ellagitannnins and various proteins. This work was published in ChemBioChem in 2009. We now have extended this methodology to the study of the interactions between other types of polyphenolic molecules and various proteins. Notably, we were able to determine that the remarkable antiactin effect of the ellagitannin vescalagin, which we recently unveiled in collaboration with Elisabeth Génot's INSERM team at IECB, was due to a selective interaction of the ellagitannin molecule with the filamentous form of actin (F-actin) and not with its monomeric globular form (G-actin). These results were published in Angewandte Chemie in 2011. This SPR tool should find numerous other applications in the field as it constitutes to date the best alternative to discriminate in real time specific from non-specific protein-polyphenol interactions. In collaboration with the group of Dr Angel Galabov at the Bulgarian Academy of Sciences, we also published in 2011 an article in Antiviral Research on the combination effect of some ellagitannins and acyclovir against Herpes Simplex Viruses. And for those of you who want to know all about plant polyphenols, we have also published a review article on the topic in Angewandte Chemie in 2011 (Angewandte Chemie Top 25 most accessed articles in 2011).



Biosynthesis of Polyphenolic Anthocyanins and Flavanoids

This project is funded by the Conseil Interprofessionnel du Vin de Bordeaux (CIVB) and concerns the elucidation of the last steps of the biosynthesis of anthocyanin pigments and (oligo)flavanols (i.e., catechins and proanthocyanidins), both systems having common precursors, the leucoanthocyanidins. Several of these precursors, as well as catechin and epicatechin, have been mounted onto solid support in the aim of developing new chemical proteomic tools for the detection/purification of functional proteins in Vitis vinifera and for the study of the chemical transformations brought about by these enzymes. Initial results of the chemistry part of this project were published in Tetrahedron Letters in 2009, and were followed in 2011 by the publication of an article in ChemBioChem on the development of an affinity-based proteomic strategy for the elucidation of proanthocyanidin biosynthesis.

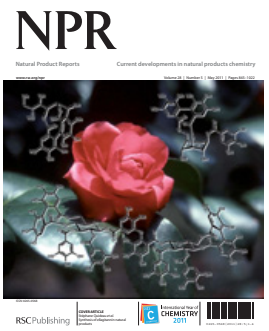
Rational design, synthesis and immunological evaluation of antigenic peptidomimetics

The major histocompatibility complex (MHC) class I-restricted recognition of tumor- and virus-derived antigenic peptides (AP) by CD8+ T-cell receptor (TCR) is a fundamental event in the development of cellular immune responses. Structural studies show that antigenic peptides could be covalently modified with small molecules to modulate the immunological outcome of these protein-peptide-protein interactions. On the basis of the results we published in 2007 in The Journal of Medicinal Chemistry a rational design approach to build bioresistant antigenic peptidomimetics tethered with various organic motifs, new series of peptidomimetics derived from ELAGIGILTV (ELA), a peptide itself derived from the Melan-A/MART-1 protein antigen expressed in 90% of primary and metastasic melanoma, were synthesized. The attachment of central organic motifs in one of these series of peptidomimetics was based on the incorporation of a central ß-lactam motif. An unusual opening of the ß-lactam ring was observed under certain conditions of cleavage from the resin support. One resulting peptidomimetic was found to stimulate T cells. This work was funded by the company Servier under the auspices of the Société de Chimie Thérapeutique (SCT) and carried out in collaboration with Prof. Aizpurua (Univ. of the Basque Country, San Sebastian, Spain), Prof. Brian Baker (University of Notre Dame, USA) and Prof. Andrew Sewell (University of Cardiff, UK). The results were published in 2010 in Organic and Biomolecular Chemistry. Also, in collaboration with Brian Baker, we published in 2010 in The Journal of Medicinal Chemistry the results of chemical and X-ray structural studies on our first generation of ELA-derived peptidomimetics bound to a class-I MHC molecule. No new result was obtained in 2011.

Selected publications

Quideau S., Douat-Casassus C., Delannoy López D. M., Di Primo C., Chassaing S., Jacquet R., Saltel F., Genot E. (2011) The C-Glucosidic Ellagitannin Vescalagin Binds Filamentous Actin and Winds it into fibrillar aggregates. Angew. Chem. Int. Ed., 50, 5099-5104.

Pouységu L., Deffieux D., Malik G., Natangelo A., Quideau S. (2011) Synthesis of Ellagitannin Natural Products. Nat. Prod. Rep. 2011, 28, 853-874 (selected for cover, most Accessed NPR article in April 2011).

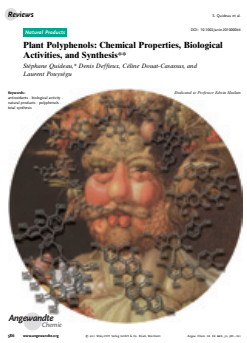


Quideau S. (2011) Triumph for Unnatural Synthesis. Nature. 474, 459-460 (News & Views).

Chalumeau C., Deffieux D., Chaignepain S., Quideau S. (2011) Development of an Affinity-Based Proteomic Strategy for the Elucidation of Proanthocyanidin Biosynthesis. ChemBioChem, 12, 1193-1197.

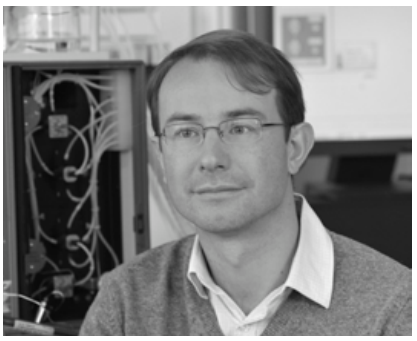
Deffieux D., Natangelo A., Malik G., Pouységu L., Charris J., Quideau, S. (2011). First and Biomimetic Total Synthesis of a Member of the C-Glucosidic Subclass of Ellagitannins, 5-O-Desgalloylepipunicacortein A. Chem. Commun., 47, 1628-1630.

Quideau S., Deffieux D., Douat-Casassus C., Pouységu L. (2011). Plant Polyphenols - Chemical Properties, Biological Activities, and Synthesis. Angew. Chem. Int. Ed., 50, 586-621.



Pouységu L., Deffieux D., Quideau S. (2010) Hypervalent Iodine-Mediated Phenol Dearomatization in Natural Products Synthesis. Tetrahedron, 66, 2235-2261 (Tetrahedron Report N° 906).

Quideau S., Lyvinec G., Marguerit M., Bathany K., Ozanne-Beaudenon A., Buffeteau T., Cavagnat D., Chénedé A., (2009). Asymmetric Hydroxylative Phenol Dearomatization Via In Situ Generation of Iodanes from Chiral Iodoarenes and m-CPBA. Angew. Chem. Int. Ed., 48, 4605-4609.



Dr. Gilles Guichard
Research director (DR2), CNRS

Gilles Guichard graduated in chemistry from the Ecole Nationale Supérieure de Chimie in Toulouse (1991) and University of Montpellier (1992) in France. He received his PhD from the University Louis Pasteur in Strasbourg (1996), working on immune recognition of pseudopeptides and synthetic vaccines. Following post-doctoral research with Prof. Dieter Seebach at the ETH in Zürich (1997) in the field of β-peptide foldamers, he joined the Institut de Biologie Moléculaire et Cellulaire (IBMC) in Strasbourg as a CNRS Chargé de Recherche (1998). Since 2006, he has been a CNRS Research Director. In 2009, he moved as a new group leader to the Institut Européen de Chimie et Biologie (IECB) in Bordeaux. His current research focuses on biomimetic chemistry of peptides, folding, self-assembly and biomolecular recognition.

Research team

Dr. Céline DOUAT-CASASSUS Research officer (CR1, CNRS)
Dr. Karine ESTIEU-GIONNET Research officer (CR1, INSERM)
Lucile FISCHER Postdoctoral fellow (CNRS)
Yella REDDY NELLI Postdoctoral fellow (Université Bordeaux I)
Neil OWENS Postdoctoral fellow (CNRS)
Karolina PULKA Postdoctoral fellow (Université Bordeaux I)
Arnaud Salaün Postdoctoral fellow (CNRS)
Juliette FREMAUX PhD student (Université Bordeaux I)
Edith CHARDON PhD student (Université de Strasbourg)
Marie-Charlotte LECHNER PhD student (Université de Strasbourg)
Claire VENIN PhD student (Université de Bordeaux I)

The team is part of the unit "Chimie et Biologie des Membranes et Nanoobjets" (CBMN), CNRS/ Université Bordeaux 1/IPB (UMR 5248)

Peptidomimetic chemistry

Functions fulfilled by proteins essentially depend on the ability of the intrinsically flexible polypeptide chain to fold correctly into well-ordered and compact tertiary structures and eventually to self-assemble. Multiple approaches, at the interface between biology, synthetic organic and polymer chemistries are currently being developed to elaborate synthetic systems with protein-like structures and functions. By using peptidomimetic chemistry, the general aims of our research are (i) to understand how to program molecules with the necessary information for self-ordering into complex and functional architectures, (ii) to create folded systems mimicking protein secondary structure elements (e.g. helices), (iii) to study interactions with biomolecules and to develop biomedical applications.

A large part of our research effort is dedicated to 'Foldamer Chemistry' (Chem Commun 2011) and peptidomimetic helices in particular. Other developments include the synthesis of multimeric peptidomimetic architectures as tools to investigate activation of cell-surface receptors (e.g. Death Receptors) as well as the use of short peptides as starting materials to elaborate heterocyclic and macrocyclic scaffolds.

A significant number of interactions mediated by proteins involve α-helical domains. Hence, synthetic α-helices and their mimetics have attracted considerable attention as scaffolds to target biomacromolecules including proteins (Expert Opin Drug Discov 2011). In this context, synthetic oligomers with predictable helical patterns (also referred to as helical foldamers) have gained interest for mimicking isolated helical peptide fragments. Advances in foldamer chemistry, together with the finding that oligomeric backbones may retain folding in water, bode well for the use of foldamers in biologically relevant context. In the past few years, we have investigated peptidomimetic oligomers consisting of urea bridging units and bearing proteinogenic side-chains. High resolution structural studies in solution by NMR spectroscopy and in the crystal state by X-ray diffraction have shown that aliphatic oligoureas of general formula [NH-CH(R)-CH2-NH-CO-]n display a remarkable propensity to fold into stable helical secondary structures reminiscent of the α-helix. Compared to peptides, helix stabilization in oligoureas is promoted by the formation of three-centred H-bonds between remote constituent units. The strong helix folding propensity, together with the diversity of available side chain appendages and resistance to protease degradation, makes the oligourea backbone a promising candidate for biomedical applications. We have reported that short sequences designed to mimic globally amphiphilic α-helical host-defense peptides display broad antibacterial activity, with some selectivity for prokaryotic over mammalian (red blood) cell membranes.

Recent developments include:

A fragment condensation approach to long aliphatic oligourea foldamers.

Although aliphatic oligoureas can be prepared by solid-phase techniques, the need for long coupling times and the limitations imposed by the choice of *N*-protecting groups have so far limited the synthesis of oligourea helices to short segments. To decrease the number of synthetic steps and thus evolve more rapidly towards longer oligomers, we have developed an iterative segment condensation strategy. The approach features insertion of *N*-pyrrolidine units (proline type) at segment junctions. Segments having up to 20-units in their sequence were readily assembled. X-ray analyses revealed that pyrrolidine units at the segment junctions do not impair 2.5-helical folding of oligoureas (Fig. 1). This modular strategy will likely facilitate the assembly of long urea helices and more complex protein-like structures (Angew Chem Int. Ed. 2011).

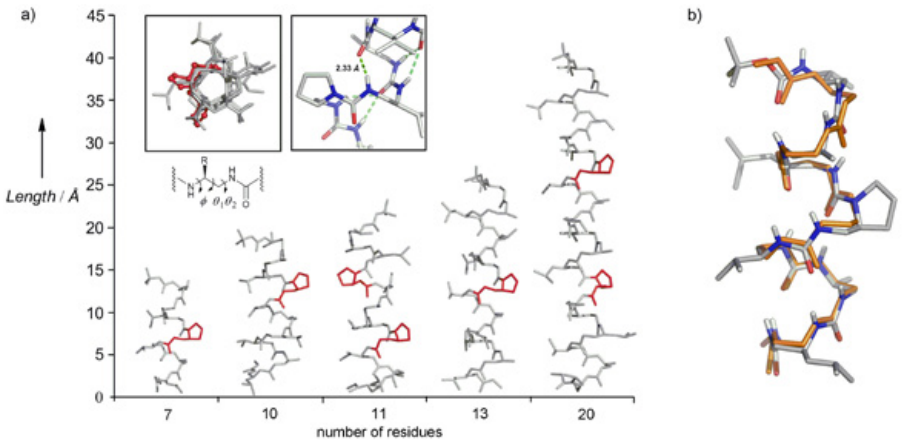


Figure 1. (a) X-ray structures of 7- to 20-residue long oligoureas obtained by fragment condensation. Pyrrolidine units at segment junctions are in red. Inset: top view of a 20-mer helix (left) and details of the noncanonical H-bond pattern at the pyrrolidine junction (right); (b) Overlay of the crystal structures of oligourea helices with and without pyrrolidine units.

Ab initio calculations of the vibrational modes of oligoureas and assignment of their experimental FT-IR spectra (collaboration with B. Desbat, CBMN and D. Cavagnat, ISM).

In contrast to α-peptides, for which the most intense vibrational mode (Amide I) is sensitive to secondary structure, the link between oligourea secondary structure (2.5 helix) and vibrational frequency modes was not yet established. The directions of the transition moments of the most intense vibrations have now been assigned for oligourea foldamers. The infrared anisotropic optical indices of the 2.5-helical secondary structure have been generated to simulate the Polarization Modulation Infrared Reflection Absorption Spectroscopy (PMIRRAS) and Attenuated Reflection Spectroscopy (ATR) spectra with respect to the orientation of the secondary structure. These theoretical and experimental data will be used to analyze PMIRRAS and ATR spectra of antibacterial oligoureas interacting with phospholipid membranes (J Phys Chem B 2011).

Selected publications

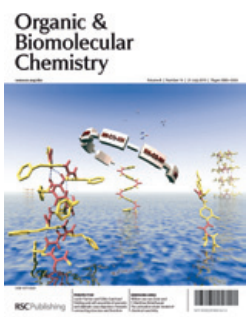
Fremaux J., Fischer L., Arbogast T., Kauffmann B., and Guichard G. (2011) Condensation Approach to Aliphatic Oligourea Foldamers: Helices with N-(pyrrolidin-2-ylmethyl) ureido Junctions, Angew. Chem. Int. Ed. 50, 11382-11385.

Guichard G., and Huc I. (2011) Synthetic foldamers, Chem Commun (Camb) 47, 5933-5941.

Estieu-Gionnet K. and Guichard G. (2011) Stabilized helical peptides: overview of the technologies and therapeutic promises, Exp. Opin. Drug Discov. 6, 937-963.

Cavagnat D., Claudon P., Fischer L., Guichard G., and Desbat B. (2011). Experimental and Theoretical Study of the Vibrational Spectra of Oligoureas: Helical versus β-Sheet-Type Secondary Structures. J Phys Chem B 115, 4446-4452.

Fischer L., Guichard G. (2010). Folding and self-assembly of aromatic and aliphatic urea oligomers: Towards connecting structure and function. Org. Biomol. Chem. 8, 3101-3117. Perspective article.



Fischer L., Claudon P., Pendem N., Miclet E., Didierjean C., Ennifar E., and Guichard G. (2010). The Canonical Helix of Urea Oligomers at Atomic Resolution. Insight Into Folding-induced Axial Organization. Angew. Chem. Int. Ed. Engl., 49 : 1067-1070.

Claudon P., Violette A., Lamour K., Decossas M., Fournel S., Heurtault B., Godet J., Mély Y., Jamart-Grégoire B., Averlant-Petit M.-C., Briand J.-P., Duportail G., Monteil H., Guichard G. (2010). Consequences of Isostructural Main-Chain Modifications for the Design of Antimicrobial Foldamers: Helical Mimics of Host-Defense Peptides Based on a Heterogeneous Amide/Urea Backbone. Angew. Chem. Int. Ed. Engl. 49: 333-336.

Pavet V., Beyrath J., Pardin C., Morizot A., Lechner M.C., Briand J.P., Wendland M., Maison W., Fournel S., Micheau O., Guichard G., Gronemeyer H. (2010). Multivalent DR5 Peptides Activate the TRAIL Death Pathway and Exert Tumoricidal Activity. Cancer Res., 70: 1101-1110.

Dr. Élisabeth Garanger

Contract researcher, GIS AMA – UB1

Trained as a chemist, Elisabeth Garanger graduated in 2001 as a Chemical Engineer from the ENSC Clermont-Ferrand with a Master's degree in Biological Organic Chemistry. She pursued her education with a PhD in chemistry and biology at the University of Grenoble. Under the supervision of Profs. P. Dumy and M.-C. Favrot, she dedicated her research to peptide-based vectors targeting tumors and their associated neo-angiogenesis. In 2006, she joined the Center for Molecular Imaging Research (Harvard Medical School, Boston) as a post-doctoral fellow and worked on contrast agents for multimodal molecular imaging. In 2009, she returned to France in the group of Prof. S. Lecommandoux (LCPO, Bordeaux) to contribute to a European project aiming at developing polymer-based nanoparticles for imaging and therapy of cancers. She joinded the IECB as group leader in 2010.

Research team

Charlotte DRAPPIER PhD student (Université Bordeaux 1)
Laure BATAILLE Engineer (Institut Polytechnique de Bordeaux)

This team is part of the unit "Laboratoire de Chimie des Polymères Organiques" (LCPO), CNRS/Université Bordeaux 1/IPB-ENSCBP (UMR 5629).

Self-assemblies from chimeric polymer-peptide materials

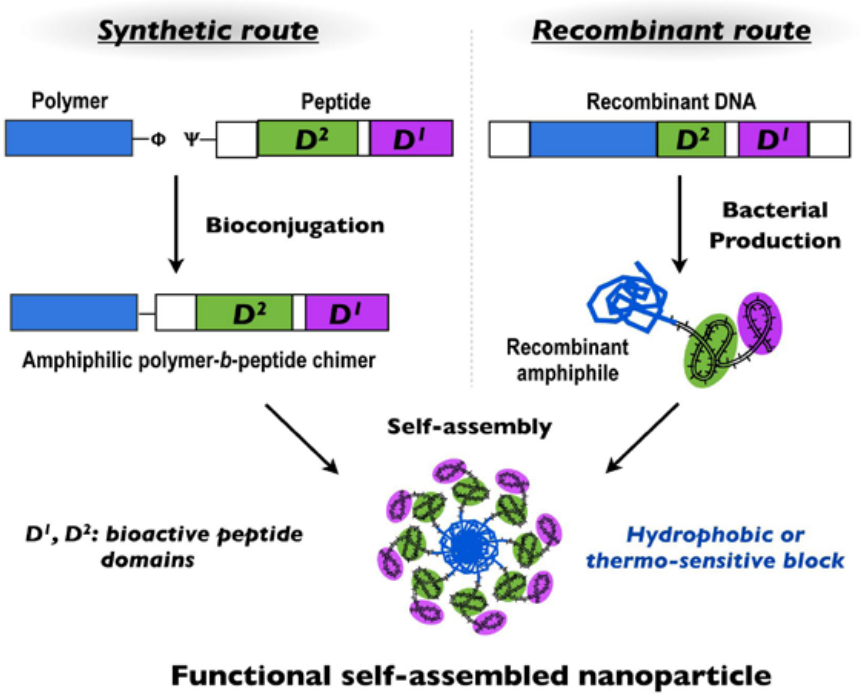
The overall goal of our research projects is to design well-defined polymer materials featuring self-assembly and biological properties encoded at the molecular level in order to access biofunctional nanomaterials. To this aim, two parallel and complementary approaches are being considered. Amphiphilic chimeric materials featuring a synthetic polymer block conjugated to a peptide segment are synthesized. Recombinant DNA and protein engineering techniques are also used to produce recombinant polymers, mainly based on elastin-like motifs combined with biofunctional peptide sequences. Self-assembly mechanisms are studied and biological activities assessed with the ultimate goal of preparing new nanodevices for imaging and therapy. This project is developed in relation with the "Polymer Nanotechnology for Life Science" team of the LCPO (UMR 5629) leaded by S. Lecommandoux.

The design of **functional self-assembled nanomaterials** is currently a major challenge of nanotechnologies and concerns domains as broad as health, communication and information, and energy.

In the specific field of **biomimetic nanotechnologies**, this goal is motivating multidisciplinary and translational research involving communities such as peptide, protein and nucleic acid specialists as well as polymer scientists. Indeed, synthetic block copolymers possess tremendous self-assembling propensities that have prompted their use for the preparation of self-assembled nano-objects. However, despite the huge number of chain lengths, sizes, architectures, and chemical characters available, most copolymers are devoid of biological information. This translates into a weak diversity of nanomaterials obtained from solely synthetic copolymers as compared to highly complex and diverse natural self-assembled structures (e.g. proteins, ribosomes, molecular motors, viruses). Conversely, **self-assembly of peptides and proteins**, that are extraordinarily rich in terms of their secondary and tertiary structures and biological functions, is extremely difficult to control and to achieve by synthetic chemists.

One of today's consensuses thus relies on the association of natural structures with polymer blocks into a single molecule in order to integrate the advantages of both materials and overcome the limitations inherent to each one separately. In particular, by **joining the self-assembly propensities of copolymers together with the richness of function-bearing peptides or protein domains**, one may ultimately be able to reproduce what nature makes and controls perfectly and be able to access biomimetic nano-assemblies able of better interacting with biological structures.

To this aim, different groups are focusing on the conjugation of functional peptides or proteins with synthetic polymer with defined self-assembly properties. In parallel, an extremely attractive and powerful approach for preparing such materials with dual self-assembly and bioactive properties consists in implementing methods from recombinant DNA and protein engineering technologies in order to have microorganisms to produce **amphiphilic biofunctional recombinant materials.**



In this context, our group is focusing on the design and synthesis of chimeric polymer-peptide materials, featuring a hydrophobic or thermo-responsive polymer block, as the driving force for self-assembly, and a peptide segment providing bioactivity to the nano-assemblies. Two parallel approaches are being investigated to prepare either chimeric materials from traditional synthetic routes, or recombinant materials from protein-engineering techniques. Self-assembly mechanisms into bio-inspired, nanoscale, and bioactive objects are studied using techniques from physico-chemistry to cellular biology.

Selected publications

Garanger E., Lecommandoux S. (2012) Towards bioactive protein polymer-based nanovehicles Angewandte Chemie Int. Edit., DOI: 10.1002/anie.201107734

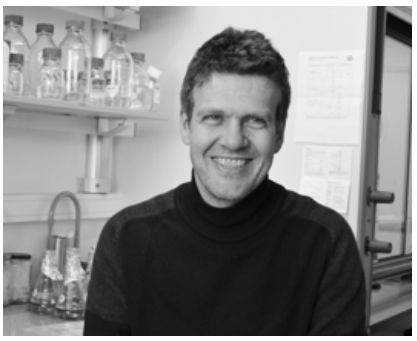
Garanger E., Hilderbrand S.A., Blois J.T., Sosnovik D.E., Weissleder R. and Josephson L. (2009) A DNA-binding Gd chelate for the detection of cell death by MRI. Chemical Communications, (29): 4444-4446

Sancey L., Garanger E., Foillard S., Schoehn G., Hurbin A., Albiges-Rizo C., Boturyn D., Souchier C., Grichine A., Dumy P. and Coll J.L. (2009) Clustering and internalization of integrin αvβ3 with a tetrameric RGD synthetic peptide. Molecular Therapy, 17 (5): 837-843

Garanger E., Aikawa E., Reynolds F., Weissleder R. and Josephson L. (2008) Simplified syntheses of complex multifunctional nanomaterials. Chemical Communications, (39): 4792-4794

Garanger E., Boturyn D., Renaudet O., Defrancq E. and Dumy P. (2006) Chemoselectively addressable template: a valuable tool for the engineering of molecular conjugates. Journal of Organic Chemistry, 71 (6): 2402-2410

Garanger E., Boturyn D., Jin Z.H., Dumy P., Favrot M.C. and Coll J.L. (2005) New multifunctional molecular conjugate vector for targeting, imaging and therapy of tumors. Molecular Therapy, 12 (6): 1168-1175



Pr Martin Teichmann

Professor (Pr1), Université Bordeaux Segalen

Born in Göttingen, Germany, Martin Teichmann studied Medicine at the Universities of Marburg and Heidelberg, Germany, where he obtained a medical degree in 1992. In 1996, he completed his doctoral work in Molecular Biology under the supervision of Prof. Klaus H. Seifart at the Institute for Molecular Biology and Tumor Research in Marburg. In 1997, he joined Prof. Robert G. Roeder's laboratory at The Rockefeller University in New York / United States as a Postdoctoral Fellow. He was promoted to Research Associate in 2000. He was appointed Group Leader at the IECB in 2002.

Research team

Dr. Hélène DUMAY-ODELOT Assistant professor (MdC, University Bordeaux Segalen)
Chiara PASCALI Postdoctoral fellow (INCa)
Galina BOLDINA Postdoctoral fellow (ANR)
Stéphanie DURRIEU-GAILLARD Technician (University Bordeaux Segalen)
Daniel DA SILVA PhD student (University Bordeaux Segalen - MRT)
Leyla EL AYOUBI PhD student (University Bordeaux Segalen)
Khawla SEDDIKI Master student (University Bordeaux Segalen)

This team is part of the unit "ARN : Régulations naturelle et artificielle" (ARNA), INSERM/ Université Bordeaux Segalen (U 869)

Gene regulation & tumor research

ÉQUIPE LABELLISÉE PAR LA LIGUE CONTRE LE CANCER

We study the regulation of human RNA polymerase III (Pol III) transcription with a focus on understanding how Pol III transcription escapes cellular control mechanisms during tumor development. Recently, we identified and characterized a novel isoform of human RNA polymerase III (Pol IIIα and Pol IIIβ). RPC32α-containing Pol IIIα is highly expressed in undifferentiated human embryonic stem cells, downregulated during differentiation and reactivated during the process of cell transformation with defined genetic elements. In contrast, the expression of RPC32β-containing Pol IIIβ is not regulated during these processes. Moreover, expression of RPC32α is important for cell transformation and anchorage-independent growth. We now try to elucidate how Pol IIIα contributes to cellular transformation.

Transcription in eukaryotic nuclei is carried out by DNA-dependent RNA polymerases I, II, and III. Human RNA polymerase III (Pol III) transcribes small untranslated RNAs that include tRNAs, 5S RNA, U6 RNA, and some microRNAs. Increased Pol III transcription has been reported to accompany or cause cell transformation. We try to shed light on mechanisms that underlie the control of Pol III transcription in normal cells and that are lost during cell transformation.

Identification and characterization of a novel isoform of human RNA polymerase III

This project concerns the identification of a novel isoform of human RNA polymerase III. It has been known for a while that Pol III transcribes small untranslated RNAs that intervene in essential cellular processes, such as transcription, splicing, regulation of mRNA-stability, translation and also protein translocation. Although being essential for homeostasis and cell survival, the importance of RNA polymerase III transcription for the regulation of cell growth and differentiation has not appropriately been appreciated for a long time. More recently, it has become clear that Pol III transcription activity is intimately linked to cellular transformation and that enhanced Pol III activity is a prerequisite for tumor cell growth. Despite this knowledge, little is known about the molecular mechanisms that may help to explain the co-regulation of Pol III transcription and tumoral growth.

We initially identified a novel protein that we designated as RPC32β because it exhibited high amino acid homology to the well known Pol III subunit RPC32 (hereafter referred to as RPC32α). The identification of RPC32β led to the demonstration of two human Pol III isoforms (Pol IIIα and Pol IIIβ). RPC32β-containing Pol IIIβ is ubiquitously expressed and essential for growth of human cells. Suppression of RPC32β by siRNAs is lethal in HeLa cells, suggesting that RPC32α-containing Pol IIIα cannot replace all functions of RPC32β-containing Pol IIIβ. In contrast, Pol IIIα is dispensable for cell survival and its expression is restricted to undifferentiated human embryonic stem cells and to tumor cells. In this regard, and most importantly, suppression of RPC32α expression impedes anchorage-independent growth of HeLa cells whereas overexpression of RPC32α in a well defined cellular model system enhances colony formation in soft-agar assays. RPC32α-induced cell transformation is accompanied by dramatic changes in the expression of several tumor-related mRNAs and proteins, including the repression of p53, increased expression of Aurora A, cyclin E or also the metastasis-associated protein S100 A4. Moreover, overexpression of RPC32α induces strongly enhanced expression of a subset of Pol III RNAs, including 7SK RNA, U6 RNA or 5S RNA, whilst the expression of other Pol III genes, notably of many tRNAs remains unchanged. These results suggest that RPC32α-containing Pol IIIα exerts important functions in the establishment and the

maintenance of cells in an undifferentiated state. Taken together, our results identify a novel human Pol III isoform and isoform-specific functions in the regulation of cell growth and transformation (Haurie et al., 2010; Dumay-Odelot et al., 2010; Teichmann et al., 2010).

Regulation of RNA polymerase II transcription termination

In collaboration with the group of Pr Giorgio Dieci at the University of Parma, Italy, we analyzed the constraints in DNA sequences that are required for efficient transcription termination by human RNA polymerase III. We were able to show that many Pol III genes possess imperfect transcription termination sequences. These sequences allow transcription to proceed beyond the terminators, giving rise to RNA sequences that may be processed from the primary transcript and that may act as regulatory RNAs (Orioli et al., 2011a; Orioli et al., 2011b).

Structure-function studies of human RNA polymerase III subunit RPC62

In collaboration with the group of Sébastien Fribourg, we have been able to determine the structure of RPC62 by X-ray crystallography at a resolution of 2.85 Å. We analyzed the DNA-binding properties of RPC62 and of its protein interaction partner RPC39. We could show that RPC39 binds to double-stranded DNA, whereas RPC62 binds to single-stranded DNA. These data indicate that RPC39 and RPC62 may contribute to promoter melting and to the maintenance of the transcription bubble (Lefèvre et al., 2011).

Identification of mutations in the largest subunits of RNA polymerase III that may cause a recessive hypomyelinating Leukodystrophy

In collaboration with the laboratory of Dr. Bernard Brais (Departments of Pediatrics, Neurology and Neurosurgery, Montreal Children's Hospital, McGill University Health Center, Montreal, Quebec, Canada), we identified and characterized mutations in the two largest subunits of human RNA polymerase III (POLR3A; POLR3B) that cause the onset of a recessive hypomyelinating leukodystrophy (tremor-ataxia with central hypomyelination [TACH]). TACH has been characterized as a childhood-onset hypomyelinating leukodystrophiy with prominent cerebellar dysfunction, oligodontia and hypogonadotropic hypogonadism. The protein levels of the POLR3A (RPC160) subunit were markedly reduced in affected individuals (Tétreault et al., 2011; Bernard et al., 2011).

Selected publications

Tétreault M., Choquet K., Orcesi S., Tonduti D., Balottin U., Teichmann M., Fribourg S., Schiffmann R., Brais B., Vanderver A. and Bernard G. (2011). Recessive Mutations in POLR3B, Encoding the Second Largest Subunit of Pol III, Cause a Rare Hypomyelinating Leukodystrophy. Am. J. Hum. Genet. 89(5), 652-655.

Bernard G., Chouery E., Putorti M.L., Tétreault M., Takanohashi A., Carosso G., Clément I., Boespflug-Tanguy O., Rodriguez D., Delague V., Abou Ghoch J., Jalkh N., Dorboz I., Fribourg S., Teichmann M., Megarbane A., Schiffmann R., Vanderver A. and Brais B. (2011). Mutations of POLR3A Encoding a Catalytic Subunit of RNA Polymerase Pol III Cause a Recessive Hypomyelinating Leukodystrophy. Am. J. Hum. Genet. 89(3), 415-423.

Orioli A., Pascali C., Pagano A., Teichmann M. and Dieci G. (2011). RNA polymerase III transcription control elements: themes and variations. Gene Jun 25. [Epub ahead of print].

Orioli A., Pascali C., Quartararo J., Diebel K.W., Praz V., Romascano D., Percudani R., van Dyk L.F., Hernandez N., Teichmann M. and Dieci G. (2011). Widespread occurrence of non-canonical transcription termination by human RNA polymerase III. Nucleic Acids Res. 39, 5499-5512.

Lefèvre S., Dumay-Odelot H., Budd A., Legran P., Pinaud N., Teichmann M. and Fribourg S. (2011). Structure - function analysis of hRPC62 provides insights into RNA polymerase III transcription initiation. Nature Structural & Molecular Biology, Mar;18(3):352-8.

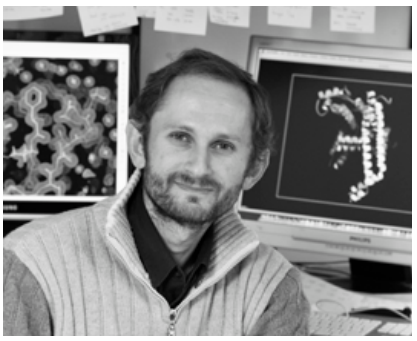
Teichmann M., Dieci G., Pascali C. and Boldina G (2010). General transcription factors and subunits of RNA polymerase III: Paralogues for promoter- and cell type-specific transcription in multicellular eukaryotes. Transcription, 1 (3), 130-135.

Dumay-Odelot H., Durrieu-Gaillard S., Da Silva D., Roeder R.G., Teichmann M. (2010). Cell growth- and differentiation-dependent regulation of RNA polymerase III transcription. Cell Cycle. 9 (18), 3687-3699.

Haurie V., Durrieu-Gaillard S., Dumay-Odelot H., Da Silva D., Rey C., Prochazkova M., Roeder R.G., Besser D. and Teichmann M. (2010). Two isoforms of human RNA polymerase III with specific functions in cell growth and transformation. Proc. Natl. Acad. Sci. USA., 107, 4176-4181.

Dieci G., Fiorino G., Castelnuovo M., Teichmann M. and Pagano A. (2007) The expanding RNA polymerase III transcriptome. Trends Genet. 23 (12), 614-622.

Dumay-Odelot H., Marck C., Durrieu-Gaillard S., Lefebvre O., Jourdain S., Prochazkova M., Pflieger A. and Teichmann M. (2007). Identification, molecular cloning, and characterization of the sixth subunit of human transcription factor TFIIIC. J. Biol. Chem. 282 (23): 17179-17189.



Dr. Sébastien Fribourg

Research officer (CR1), Inserm

Sébastien Fribourg did his PhD at the IGBMC, in Strasbourg, under the supervision of Dino Moras (1996-2000) working on the Pol II basal transcription factor TFIIH in collaboration with Jean-Marc Egly. He then joined the group of Elena Conti at the EMBL in Heidelberg, for a post-doctoral training (2001-2004) working on nuclear export transport factors and NMD in collaboration with Elisa Izaurralde. He joined IECB in Nov. 2004. Since then, he has developed a research activity based on the structural study of proteins and factors involved in RNA processing mechanisms (Pol III transcription initiation, mRNA and rRNA maturation).

Research team

Dr. Lionel MINVIELLE-SÉBASTIA Research director (CNRS)
Natacha PÉRÉBASKINE Technical assistant (University Bordeaux Ségalen)
Cécile MONFOULET Technical assistant (Inserm)
Adrien DUPIN PhD student (University Bordeaux Ségalen)

This team is part of the unit "ARN : Régulations naturelle et artificielle" (ARNA), INSERM/ Université Bordeaux Segalen (U 869)

Structural biochemistry

The scientific activity of the X-ray crystallography group at IECB is focused on the structural and functional aspects of various RNA metabolism processes including RNA polymerase III transcription initiation (in collaboration with Pr. Teichmann, IECB), 3' end pre-mRNA maturation and small subunit ribosomal RNA maturation (with Pr Gleizes & Yves Henry, LBME Toulouse, France and Pr. U. Kutay, ETH Zurich). The aim of these structural studies is to get insights into the basic mechanisms underlying those processes and their relationship with associated human diseases when appropriate.

mRNA polyadenylation factors

Poly(A) tail addition to the pre-mRNA at the 3' end protects mRNAs from degradation by 3'- 5' exonucleases. As other mRNA maturation steps, poly(A) addition is necessary for mRNA export from the cytoplasm to the nucleus and for translation efficiency.
3' end mRNA processing is a two-step mechanism comprising an initial endonucleolytic cleavage followed by a polymerization step. In higher eukaryotes, more than a dozen of proteins are necessary. Most of those factors assemble in two major complexes called CPSF (Cleavage and Polyadenylation Stimulation Factor) and CstF (Cleavage stimulation Factor), or respectively CPF and CF I in yeast. These factors assemble onto the pre-mRNA according to the localization of conserved sequence signals in cis on the RNA.
Little is known about the self-assembly of those factors and about the recognition of sequence signals on the pre-mRNA. Our goal is to gain insights into these various mechanisms.
The CstF complex is a ternary entity built up around CstF-77 that bridges CstF-50 and CstF-64. This complex recognizes sequence elements downstream of the polyadenylation site. CstF links 3' end mRNA maturation to RNA pol II transcription through interaction with the CTD of RNA pol II and PC4, a transcription co-activator and to DNA repair mechanism. CF IA is a quaternary complex composed of Rna14p and Rna15p, altogether interacting with the heterodimer of Clp1p-Pcf11p.
After solving the crystal structure of CstF-77 and providing evidence for homodimerization of this subunit, we analyzed the N-terminal domain of CstF-50. The overall structure reveals that this domain is the homodimerization domain of CstF-50 and strongly suggests that CstF is rather a heterohexamer than a trimer, as previously described. It also reveals the presence of a number of highly conserved residues at its surface suggesting a second role of this domain in the process (Figure 1).

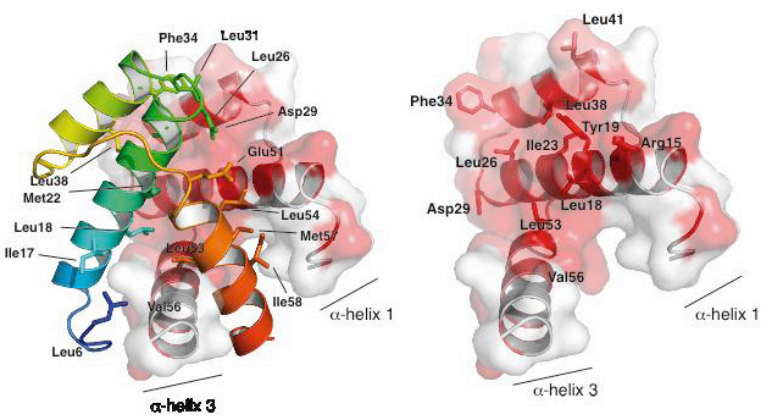
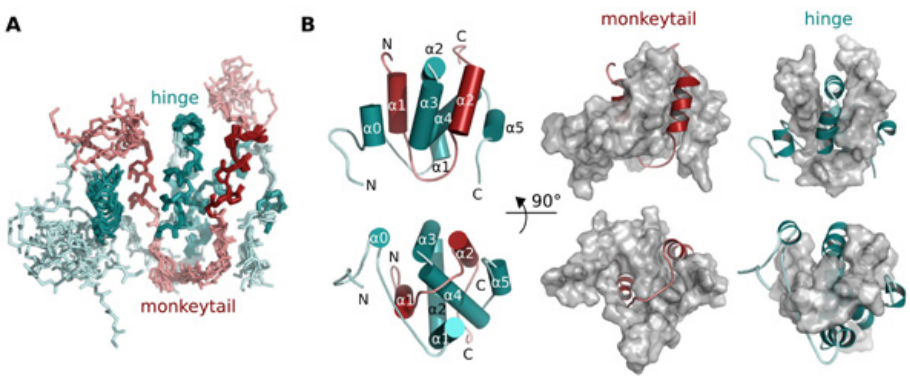


Figure 1: Overall structure of CstF-50 N-terminal domain and homodimerization determinants (Moreno-Morcillo et al., 2011).

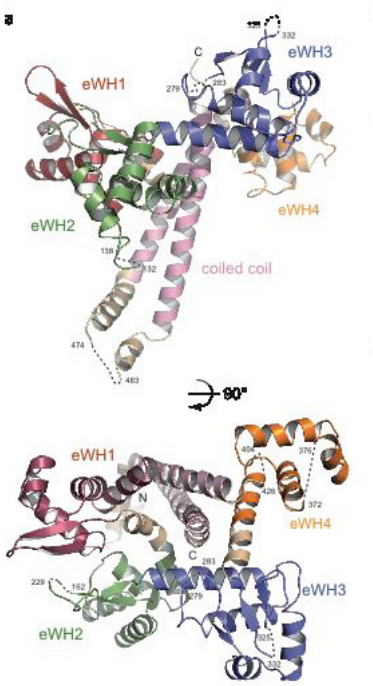
From the structure of CstF-77, we identify the C-terminus of this protein and its yeast counterpart Rna14p, as the domain involved in CstF-64/Rna15p recognition (Legrand et al. 2007). In collaboration with Dr C. Mackereth at the IECB, we managed to solve the solution structure of this complex (Figure 2)(Moreno-Morcillo et al. 2011).



Upon binding, the short C-terminal region from Rna14p (named the monkeytail domain) wraps intimately within the hinge region from Rna15p. Mutants with destabilized monkeytail/hinge interactions prevent association of Rna15p within CF IA. Conservation of buried interdomain residues reveals that the structural tethering is preserved in the homologous mammalian CstF-77 and CstF-64 proteins of the related Cleavage stimulation Factor (CstF) complex.

RNA Polymerase III transcription initiation (in collaboration with Pr M. Teichmann, IECB)

Eukaryotic cells use three different forms of RNA polymerase for the transcription of their genome. These RNA polymerases are structurally conserved and ten subunits define the core of the enzyme. RNA polymerase III (Pol III), the largest of the eukaryotic RNA polymerases, transcribes short untranslated RNA genes, which include tRNA, 5S rRNA and U6 snRNA, as well as the 7SL RNA component of the signal recognition particle.



Among the five Pol III specific subunits, hRPC62, hRPC39 and hRPC32 in human, associate into a stable subcomplex. This salt labile complex is crucial for specific transcription initiation at Pol III promoters.
We reported the crystal structure of hRPC62 and its functional analysis. This subunit folds around a central coiled coil motif surrounded by four consecutive extended-winged helix domains (eWH). Through a structure-function analysis of hRPC62 and its complex with hRPC39 and hRPC32 two isoforms, we provide a detailed map of the protein-protein interaction. We also investigated the nucleic acid binding properties of hRPC62 and hRPC39 demonstrating a specific recognition of single versus double stranded DNA for hRPC62 and reverse for hRPC39. Altogether, we propose that the ternary complex could help binding of duplex DNA to Pol III-TFIIIB-TFIIIC pre-initiation complex and then stabilize melted DNA during transcription initiation. We also suggest a role in Pol III transcription elongation.

Selected publications

Lefevre S., Dumay-Odelot H., El Ayoubi L., Budd A., Legrand P., Pinaud N., Teichmann M., Fribourg S. (2011). Structure-function analysis of hRPC62 provides insights into RNA polymerase III transcription initiation. Nat. Struct. Mol. Biol., 18(3): 352-358.

Moreno-Morcillo M., Mackereth C.D., Minvielle-Sébastia L., Fribourg S. (2011). Hexameric architecture of CstF supported by CstF-50 homodimerization domain structure. RNA,17 : 412-418.

Haddad R., Maurice F., Viphakone N., Voisinet-Hakil F., Fribourg S, Minvielle-Sebastia L. (2011). An essential role for Clp1 in assembly of polyadenylation complex CF IA and Pol II transcription termination. Nucleic Acids Res., in press.

Moreno-Morcillo M., Minvielle-Sebastia L., Fribourg S., Mackereth C.D. (2011). Locked tether formation by cooperative folding of Rna14p monkeytail and Rna15p hinge domains in the yeast CF IA complex. Structure, 19 : 534-545.

Lebars I., Legrand P., Aimé A., Pinaud N., Fribourg S., Di Primo C. (2008). Exploring TAR-RNA aptamer loop-loop interaction by X-ray crystallography, UV spectroscopy and surface plasmon resonance. Nucleic Acids Res., 36 : 7146-7156.

Legrand P., Pinaud N., Minvielle-Sebastia L. & Fribourg S. (2007). The structure of CstF-77 provides insights into CstF assembly. Nucleic Acids Res., 35 : 4515-4522.

Gregory L.A., Aguissa-Touré A.H., Pinaud N., Legrand P., Gleizes P.E. & Fribourg S. (2007). Molecular basis of Diamond-Blackfan anemia: structure of RPS19. Nucleic Acids Res., 35, 5913-5921

Fribourg S., Gatfield D., Izaurralde E. & Conti E. (2003) A novel mode of RBD-protein recognition in the Y14-Mago complex. Nat. Struct. Biol.,10, 433-439.

Fribourg S., Braun I., Izaurralde E. & Conti E. (2001) Structural basis for the recognition of a nucleoporin FG repeat by the NTF2-like domain of TAP/p15 mRNA nuclear export factor. Mol. Cell, 8, 645-655.

Fribourg S., Kellenberger E., Rogniaux H., Poterszman A., Van Dorsselaer A., Thierry J.C., Egly J.M., Moras D. & Kieffer B. (2000). Schultz P., Fribourg S., Poterszman A., Mallouh V., Moras D. & Egly J.M. (2000). Molecular structure of human TFIIH. Cell, 102, 599-607.

Dr. Cameron Mackereth

Research officer (CR1), Inserm

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

Research team

Yoan MONNEAU PhD student (CNRS/ICSN)

Following successful recruitment within Inserm in 2011, this team is now part of the unit "ARN : Régulations naturelle et artificielle" (ARNA), INSERM/Université Bordeaux Segalen (U 869)

NMR spectroscopy of protein-nucleic acid complexes

The lab studies molecular details of large protein-nucleic acid macromolecules 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 labelling to acquire information on long-range contacts, as well as in vitro mutational analysis and other binding assays. For smaller proteins and domains, standard NMR-based approaches are used, but with additional insight gained from complementary techniques. 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.

Complexes involved in pre-mRNA 3' processing

In collaboration with the lab of S. Fribourg at IECB, we are investigating the structure and dynamics of the yeast cleavage/polyadenylation factor IA (CF IA) and metazoan cleavage stimulation factor (CstF) complexes, both involved in the removal of the terminal sequence of the pre-mRNA prior to the addition of multiple adenosine to form the poly(A) tail. The current research in the laboratory deals with the structural characterization of the complete set of folded domains involved in protein-protein and protein-RNA interactions within CstF and CF IA, as a step toward looking at the architecture of the larger assembled complexes. As one example, we have used NMR spectroscopy to determine the solution structure of the minimal Rna14p/Rna15p heterodimer of CF IA. Our studies reveal an intimate architecture of the interacting peptides, such that the peptide from Rna14p (which we name the monkeytail domain) wraps around a core set of helices from the Rnap15p hinge domain, which is in turn further embraced by adjacent N- and C-terminal regions in Rna15p (Figure 1). We have also used NMR spectroscopy to provide details of the N-terminal homodimerzation domain from the CstF-50 protein to complement the crystallographic structure from the Fribourg laboratory.

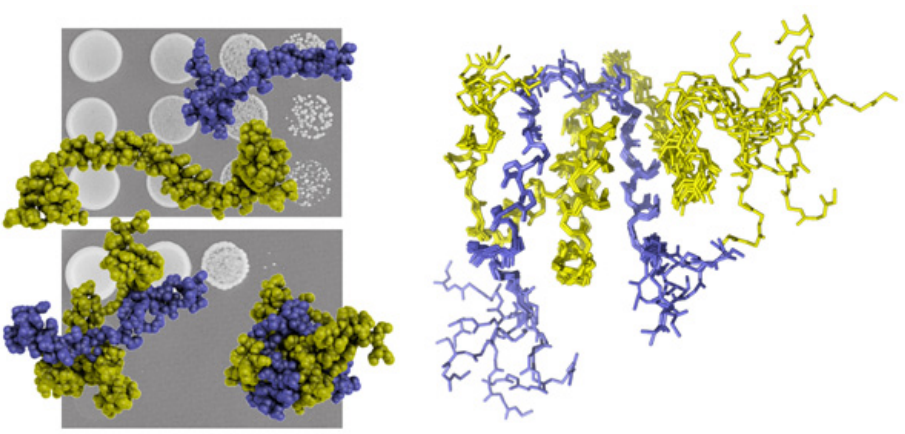


Figure1. Using yeast genetics it was found that mutations in either the Rna14 or Rna15 proteins prevents growth at high temperatures (last two lines in grey). Using NMR spectroscopy to deduce the atomic details, we found that these two proteins form a complex that brings together the Rna14 monkeytail domain (blue) with the Rna15 hinge domain (yellow). These peptides are initially disordered, but form a defined tight assembly upon binding to each other.

Tissue-specific alternative splicing in C. elegans

In 2011 we reported the molecular basis by which the efficiency of mRNA splicing is transmitted from the RNA sequence to the spliceosome, and found this to be in the selective binding of one of two confomations of the essential splicing factor U2AF65 (Figure 2). In contrast to this basal splicing mechanism, we have recently investigated the manner by which alternative splicing is regulated in multi-cellular organisms, in particular to understand the role of this important process in the development of specific tissues. In particular, we have initiated a project on nematode splicing proteins with a structural investigation of the Sup-12 protein from C. elegans. Combined with the Asd-1 or Fox-1 proteins, Sup-12 is involved in the muscle-specific alternative splicing of the egl-15 mRNA, which is required to generate a specific form of egl-15 that is required for proper muscle development. Using NMR spectroscopy we have determined a preliminary solution structure of the RNA recognition mofit (RRM) domain of Sup-12 bound to an RNA ligand. The structure and mode of RNA-binding is similar to the Asd-1 RRM domain, a splicing protein that also regulates alternative splicing of egl-15 and other genes in C. elegans. We are therefore investigating the atomic basis for the difference in ligand preference for the Fox-1 family and Sup-12 RRM domains, and studying how these two classes of splicing factors interact with one another as they bind adjacent RNA motifs in the egl-15 mRNA. Using an optimal Sup-12 RNA motif, we have initiated a bioinformatic approach to identify additional mRNA targets of the Sup-12 protein.

Structural and dynamic consequences of histone modification

Using an established methylation protocol coupled with a new scheme to encode the site of modification, we have created a set of mono-, di- and tri-methylated peptides for use in a mass spectrometry analysis to provide binding preferences for proteins that recognize modified lysines. In addition, we are currently optimizing a method to insert specific lysine acetylation analogs into proteins with the specific intent of allowing incorporation of NMR stable isotopic labelling. In addition to covalent modification, it has been shown that the cis-trans conformation of key proline residues in histone H3 can be converted by the enzyme Fpr4, leading to increased levels of subsequent methylation. Following NMR characterization of the catalytic domain from Fpr4, we are looking at the dynamics and association properties of the histone H3 N-terminal tail in the presence and absence of yeast Fpr4, as well as the human orthologue FKBP25.

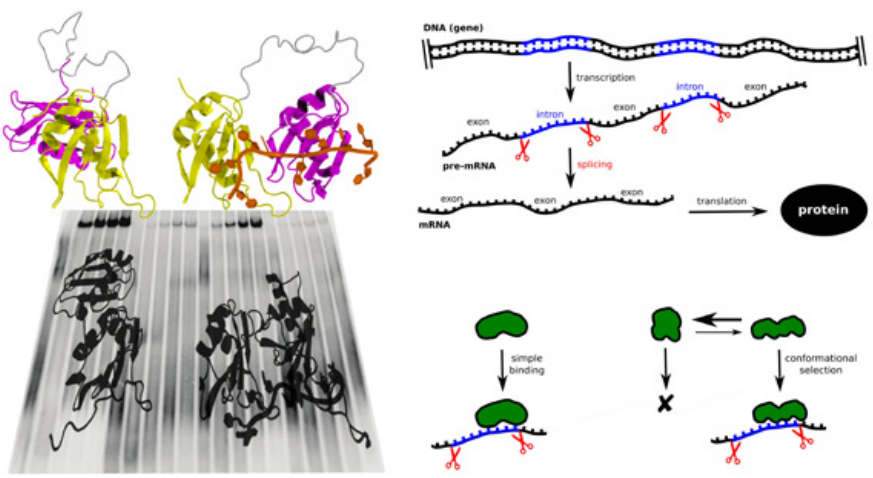


Figure 2. The genetic information to make proteins comes from the genome DNA via an intermediate mRNA molecule. During splicing, elements that do not encode the protein (introns) must be removed and the remaining protein coding segments (exons) joined together. The accurate definition of the intron boundary is helped in part by the the essential splicing factor U2AF65. Using a combination of NMR spectroscopy, biophysical binding measurements and in vitro assays, we have determined that the RNA-binding domains from U2AF65 (yellow and magenta) exist in two arrangements. Only one conformation binds with high affinity to the intron RNA (orange) and is able to promote the splicing process. Sequences within highly spliced introns can selectively bind the active conformation from the mix of the two that both exist within the cell.

Selected publications

Mackereth C.D., Madl T., Bonnal S., Simon B., Zanier K., Gasch A., Rybin V., Valcárcel J., Sattler M. (2011) Multi-domain conformational selection underlies pre-mRNA splicing regulation by U2AF. Nature, 475:408-411

Moreno-Morcillo M., Minvielle-Sébastia L., Fribourg S., Mackereth C.D. (2011) Locked tether formation by cooperative folding of Rna14p monkeytail and Rna15p hinge domains in the yeast CF IA complex, Structure, 19, 534-545

Monneau Y.R, Nelson C.J., Mackereth C.D. (2011) Chemical shift assignments of the catalytic domain from the yeast proline isomerase Fpr4p. Biomol. NMR Assign. DOI: 10.1007/s12104-011-9338-x

Moreno-Morcillo M., Minvielle-Sébastia L., Mackereth C., Fribourg S. (2011) Hexameric architecture of CstF-50 supported by homodimerization domain structure, RNA, 17, 412-418

Mackereth C.D. (2011) Chemical shift assignments of a minimal Rna14p/Rna15p heterodimer from the yeast cleavage factor IA complex, Biomol NMR Assign, 5, 93-95

Mourão A., Varrot A., Mackereth C.D., Cusack S., Sattler M. (2010). Structure and RNA recognition by the snRNA and snoRNA transport factor PHAX. RNA, 16: 1205-1216.

Simon B., Madl T., Mackereth C.D., Nilges M., Sattler M. (2010). An Efficient Protocol for NMR-Spectroscopy-Based Structure Determination of Protein Complexes in Solution. Angew. Chem. Int. Ed. Engl. 49: 1967-1970.

Soares L.M., Zanier K., Mackereth C.D., Sattler M., Valcárcel J. (2006). Intron removal requires proofreading of U2AF/3' splice site recognition by DEK. Science, 312: 1961-1965.

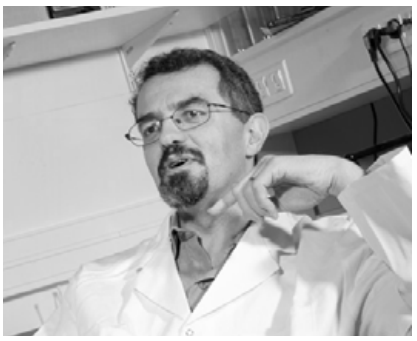
Mackereth C.D., Simon B, Sattler M. (2005). Extending the size of protein-RNA complexes studied by nuclear magnetic resonance spectroscopy. ChemBioChem, 6: 1578-1584.

Hantschel O., Wiesner S., Güttler T., Mackereth C.D., Remsing Rix L.L., Mikes Z., Dehne J., Görlich D., Sattler M., Superti-Furga G. (2005). Structural basis for the cytoskeletal association of Bcr-Abl/c-Abl. Mol. Cell, 19: 461-473.

Mackereth C.D., Schärpf M., Gentile L.N., Macintosh S.E., Slupsky C.M., McIntosh L.P. (2004). Diversity in structure and function of the Ets family PNT domains. J. Mol. Biol., 342: 1249-1264.

Tognon C.E., Mackereth C.D., Somarsini A., McIntosh L.P, Sorensen P.H. (2004). Mutations in the SAM domain of the ETV6-NTRK3 chimeric tyrosine kinase block polymerization and transformation activity. Mol. Cell. Biol., 24: 4636-4650.

Christendat et al. Structural proteomics of an archeon. (2000). Nature Struct. Biol., 7: 903-909.



Dr. Jean-Louis Mergny

Research director (DR1), INSERM

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

Research team

Dr. Anne BOURDONCLE Associate professor (MdC, Université Poitiers)
Dr. Gilmar SALGADO Associate professor (MdC, Université Bordeaux Segalen)
Pr. Liliya YATSUNYK Visiting scientist (sabbatical leave, Swarthmore College, USA)
Aurore GUÉDIN Tech. assistant (AI, INSERM)
Gaëlle LABRUNIE Tech. assistant (CDD-IE, Région Aquitaine)
Lionel BEAUREPAIRE Tech. assistant (CDD-IE, Aquitaine Regional Council)
Dr. Nicole SMITH Postdoctoral fellow (ANR-F-DNA)
Dr. Daniel RENCIUK Postdoctoral fellow (ANR-G4Toolbox)
Dr. Rui MORIYAMA Postdoctoral fellow (JSPS/ANR-F-DNA)
Dr. Jun ZHOU Postdoctoral fellow (Région Aquitaine)
Phong Lan THAO TRAN PhD student (MENRT)
Amandine RENAUD DE LA FAVERIE PhD student (MENRT)
Emilien DUBUC M2 student (Université Bordeaux Segalen)

This team is part of the unit "ARN : Régulations naturelle et artificielle" (ARNA), INSERM/Université Bordeaux Segalen (U 869)

Unusual nucleic acid structures

Appel à Projets "Programme ARC" 2012

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 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 compelling. Our goals are to conceive new biochemical, bioformatic, and physico-chemical tools to be used to demonstrate that G4 DNA or RNA is involved in particular biological functions.

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. Our first objective will be to experimentally obtain a better understanding of DNA and RNA G4 stability. The ultimate goal will be to build thermodynamic stability tables for quadruplexes as has been done by Santa Lucia and collaborators for duplex/hairpin DNA and to incorporate these data into MFOLD.

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.

G4 regulation at the RNA level. The UTRs of a number of mRNA molecules harbor G-rich sequences that may form quadruplexes. This is true both in eukaryotes and prokaryotes. G4-prone sequences are not only present in mRNA but may also be found in short and long non-coding RNAs such as TERRA and hTR. These results prompted us to study in more detail the biological functions of these G4-prone RNAs. In collaboration with P. Hainaut (IARC, Lyon, France) and J. Hall (Curie, Orsay, France), we investigated the role of a potential G4 in P53 alternative splicing.

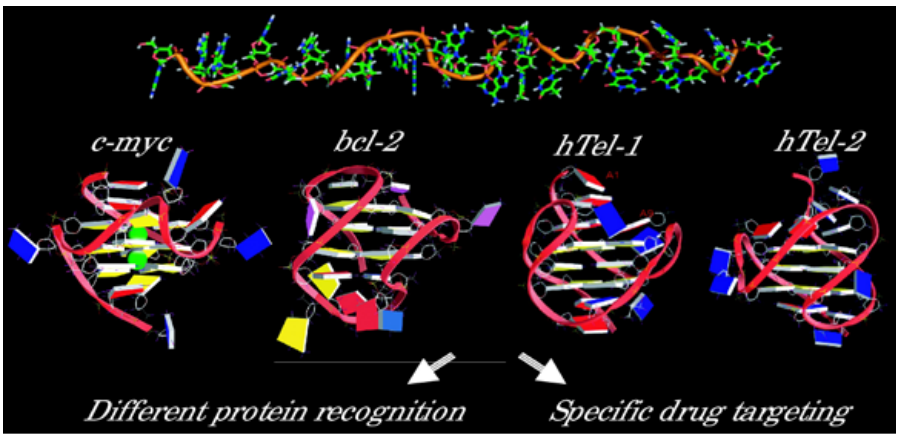


Figure 1. A G-rich single strand (top) may adopt different intramolecular G4 structures (bottom) depending on sequence and experimental conditions.

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 from the Institut Curie (M.P. Teulade-Fichou) we successfully identified a variety of G4 ligands and we wish to improve and functionalize these compounds, analyse their biological effects, and ultimately find new classes of anti-proliferative agents with anticancer properties.

Beyond biology

Quadruplexes may well be biologically relevant, but they could also be used for various applications that are disconnected from cells. DNA is an attractive material for nanotechnologies because of its self-assembly properties. The ability of nucleic acids to self-assemble into a variety of nanostructures and nanomachines is being exploited by a growing number of researchers. Extremely sophisticated structures and nanodevices may be constructed with DNA. We believe that quadruplex structures offer interesting new possibilities and we have demonstrated that quadruplexes can be incorporated into nanodevices. An independent topic relates to the use of quadruplex DNAs as molecular beacons (MB). We previously demonstrated that a G4-based MB outperforms a regular MB thanks to its differential ionic sensitivity.

Selected publications

Lacroix L., Séosse A. & Mergny, J.L. (2011) Fluorescence based duplex-quadruplex competition screen for telomerase RNA quadruplex ligands. Nucleic Acids Res. 39: e21.

Marcel V., Tran P.L.T., Sagne C., Martel-Planche G., Vaslin L., Teulade-Fichou M.P., Hall J., Mergny J.L., Hainaut P. & Van Dyck E. (2011). G-quadruplex structures in TP53 intron 3: role in alternative splicing and in production of p53 mRNA isoforms. Carcinogenesis 32: 271-8.

Struts A.V., Salgado G.F., Martinez-Mayorga K., Job C., Tanaka K., Krane S., Nakanishi K., and F. Brown. M. (2011) Deuterium Spin-Lattice Relaxation Reveals Functional Dynamics of Retinal Chromophore of Rhodopsin. Nature Struct. & Mol. Biol., 18: 392-4.

Guédin A., Gros J. & Mergny J.L. (2010). How long is too long ? Effect of loop size on G-quadruplex stability. Nucleic Acids Res. Vol. 38, 7858-7868.

Guédin A., Lacroix L. & Mergny J.L. (2010), Thermal melting studies of ligand DNA interactions, Methods Mol. Biol. 613: 25-35.

Reinhold W.C., Mergny J.L., Liu H., Ryan M., Pfister T.D., Kinders R., Parchment R., Doroshow J., Weinstein J.N., & Pommier Y. (2010). Exon Array Analyses across the NCI-60 Reveal Potential Regulation of TOP1 by Transcription Pausing at Guanosine Quartets in the First Intron. Cancer Res. 70: 2191-2203.

Mergny J.L. & Lacroix L. (2009). UV melting of G-quadruplexes, Current Protocols in Nucleic Acids Chemistry. 17.1.1-17.1.15.

Stegle O., Payet L., Mergny J.L, MacKay D.J.C. & Huppert J.L. (2009). Predicting and understanding the stability of G-quadruplexes. Bioinformatics, 25: pp374-382.

Guédin A., Alberti P. & Mergny J.L. (2009). Stability of intramolecular quadruplexes: sequence effects in the central loop. Nucleic Acids Res. 37: 5559-5567.

Mendez-Bermudez A., Hills M., Pickett H., Mergny J.L., Riou J.F. & Royle N. (2009).Human telomeres that contain (CTAGGG)n repeats show replication dependent instability in somatic cells and the male germline. Nucleic Acids Res. 37: 6225-6238.

Lim K.W. Alberti P., Guédin A., Lacroix L., Riou J.F., Royle N., Mergny J.L. & Phan A.T. (2009). Sequence variant (CTAGGG)n in the human telomere favors a G-quadruplex structure containing a G•C•G•C tetrad. Nucleic Acids Res. 37: 6239-6248.

Dr. Elisabeth Génot

Research director (DR2), INSERM

Elisabeth Génot, trained in both biology and biochemistry at the University Pierre & Marie Curie in Paris, got her PhD in 1988 at the Curie Institute (Paris). Starting her career in immunology, she worked on the regulation of B lymphocyte expansion during the immune response and the molecular mechanisms underlying hairy cell leukemia oncogenicity. She trained in signal transduction at the University of Washington in Seattle (USA) under the guidance of Ed. Clark and Ed. Krebs and thereafter focused her work on intracellular signalling involving the RhoGTPase family of proteins at the LRI (London, UK). She started her own group at Imperial College in 1997, arrived at the University of Bordeaux in 2000 and joined IECB in 2002. Her current research focuses on endothelial cell biology in health and diseases.

Research team

Pr. IJsbrand KRAMER Professor (Université Bordeaux 1)
Edith REUZEAU Technician (Université Bordeaux 1)
Dr. Pirjo SPUUL Visiting Scientist (Finish fund)
Dr. Anne LECLERCQ Postdoctoral fellow (FRM)
Dr. Thomas DAUBON Postdoctoral fellow (ARC)
Dr. Véronique VEILLAT Postdoctoral fellow (ANR-blanc VASCULOSOMES)
Isabel EGANA PhD student (ITN-FP7-T3net)
Filipa CURADO PhD student (ITN-FP7-T3net)

This team is part of the unit "Liver Fibrosis and Liver Cancer", INSERM U1053 /Université Bordeaux Segalen

Signal transduction in health & diseases

Transforming growth factor-β plays an important role in the development and maintenance of homeostasis of the vascular systems by regulating functions of endothelial cells and smooth muscle cells. Analyzing the effects of TGFβ on cytoskeleton organisation led us to discover actin-rich structures named podosomes in aortic endothelial cells. Ongoing projects aim at demonstrating the existence of podosomes in vivo and determine their role in endothelial cell (patho) physiology. In vitro work aims at a full characterization of the molecular composition of podosomes and elucidation of the molecular mechanisms involved in their assembly and disassembly in both microvascular and macrovascular endothelial cells.

Our aim is to understand some of the mechanisms by which endothelial cells contribute to the pathophysiology of vascular diseases. We are studying how environmental cues impact on endothelial cells and translate into functional alterations focusing on changes in ECM composition/rigidity and cytokine contexts. TGFß plays a key role in cancer, fibrosis and inflammatory processes and endothelial cells represent a major target of its action. We focus our analysis on endothelial cells' cytoskeleton remodeling and differentiation in response to TGFß and accumulation of pathological matrix. Our studies aim at a better understanding of the signaling cascades underlying endothelial cell behaviour in human diseases such as tumoral angiogenesis and metastasis, inflammation or atherosclerosis, with the long term goal of manipulating these cascades for therapeutical intervention.

Our work has established that TGFß causes the repolymerisation of actin into punctate structures named podosomes. A podosome is made of a columnar actin-rich core standing perpendicular to the plane of the ventral plasma membrane and embedded in a ring structure of integrins and integrin-associated proteins. Other components include signalling molecules such as tyrosine-kinases, GTPases and effectors proteins as in focal adhesion. However, unlike focal adhesions, gelsolin, dynamin, cortactin and WASp/N-WASp are also detected. Another peculiarity of podosomes is that they are enriched in matrix metalloproteases, bestowing them with the capacity to degrade the ECM. Podosomes are found in a restricted number of cell types (macrophages, immature dendritic cells and osteoclasts) where they seem to be involved in adhesion and invasion. These cells share in common the ability to cross anatomical boundaries.

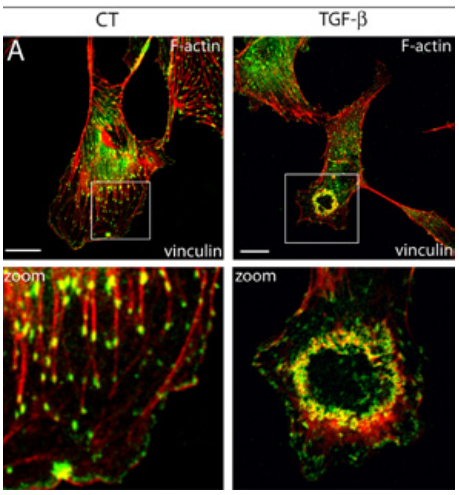


Figure A: Endothelial podosome rosettes in cultured endothelial cells.

Representative immunoconfocal images of F-actin (red) and vinculin (green) organisation in control (left panel) and TGFß-treated (right panel) cultured aortic endothelial cells. In untreated cells, vinculin is localised at the tips of stress fibers. TGFß-treated cells exhibit ring-like structures (podosomes rosettes, right panel), where vinculin surrounds F-actin cores (tbottom panel: higher magnification of the boxed areasl). Bar, 10 µm.

We have undertaken an extensive characterization of podosomes in different types of endothelial cells. These analyses have brought to light novel components not described previously, which could be involved in specific functions of endothelial cells. We are presently exploring the contribution of these molecules to podosome formation and functioning.

The question arises whether podosomes are also formed in physiological contexts. We therefore set up an “en face” viewing system to visualise the endothelium in its native environment. This system enabled us to visualise the cytoskeleton of endothelial cells in murine aortic vessel segments and establish that the normal endothelium is devoid of podosomes. However, upon exposure to physiological concentrations of TGFß, the formation of podosome rosettes was induced. The detection of podosomes in living tissues opens the way to investigate in which cellular process podosome forming cells are engaged.

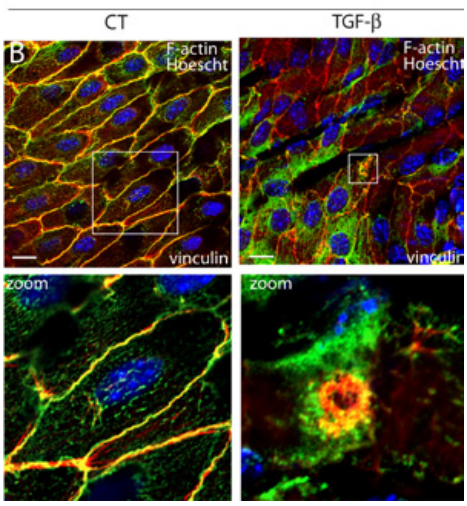


Figure B: Endothelial podosome rosettes in the endothelium of an aortic vessel segment

(B) Aortic vessel segments were prepared for immunofluorescence, labelled with phalloidin (red), vinculin (green) and Hoechst (blue) and mounted en face for confocal observation. Viewed face on, vinculin/F-actin staining of the endothelium delineates individual cells in control condition (left panel). TGFβ-treated aortic vessel segments (right panel) show the relocalisation of vinculin at the podosome rosette (bottom panel: higher magnification of the boxed areas). Bar, 10 µm. Comparison of (A) and (B) reveals that podosome rosettes formed in their native environment are more compact than those assembled in the tissue culture conditions.

We have now provided evidence for the existence of podosomes in living endothelia ex vivo in aortic endothelial cells obtained from inflamed endothelia, potentially under pro-angiogenic conditions, suggesting that podosomes are associated with a pathological state. We are particularly interested in the role of podosomes in vascular disorders involving hyperactivation of TGFß signalling pathways such as Marfan syndrome or those involving defective TGFß signalling such as Hereditary Hemorrhagic Teleangiectasia (HHT).

Selected publications

Le Roux-Goglin E., Varon C., Spuul P., Asencio C., Mégraud F., Génot E. (2012) Helicobacter infection induces podosome assembly in primary hepatocytes in vitro. Eur J Cell Biol. 91(3) p 161-170

Saltel F., Daubon T., Juin A., Ganuza I.E., Veillat V., Génot E. (2011) Invadosomes: intriguing structures with promise., Eur J Cell Biol. Feb-Mar;90(2-3):100-7. Review.

Daubon T., Buccione R., Génot E. (2011). The Aarskog-Scott syndrome protein Fgd1 regulates podosome formation and extracellular matrix remodeling in TGFb-stimulated aortic endothelial cells. Mol. Cell. Biol.,31(22): 4430-41

Quideau S., Douat-Casassus C., Delannoy López D.M., Di Primo C., Chassaing S., Jacquet R., Saltel F., Génot E. (2011) Binding of filamentous actin and winding into fibrillar aggregates by the polyphenolic C-glucosidic ellagitannin vescalagin. Angew Chem Int Ed Engl. 23;50(22):5099-104.

Rottiers P., Saltel F., Daubon T., Chaigne-Delalande B., Tridon V., Billottet C., Reuzeau E., and Genot E. (2009). TGFbeta-induced endothelial podosomes mediate basement membrane collagen degradation in arterial vessels. J Cell Sci, 122(Pt 23):4311-8.

Varon C., Tatin F., Moreau V., Van Obberghen-Schilling E., Fernandez-Sauze S., Reuzeau E., Kramer I., Genot E. (2006). Transforming Growth Factor {beta} Induces Rosettes of Podosomes in Primary Aortic Endothelial Cells. Mol Cell Biol., 26(9):3582-94.

Moreau V., Tatin F., Varon C., Génot E. (2003). Actin can reorganise in podosomes in porcine aortic endothelial cells, a process controled by Cdc42 and RhoA. Mol. Cell. Biol., 23: 6809-6822.

Signal Transduction. Gomperts B.D., Kramer I.M., Tatham P.E.R., authors (2009). 2nd edition. Academic Press/Elsevier (ISBN-10: 0-12-369441-8), 576 pages. Foreign editions: China, Japan, Korea

Dr. Derek McCusker

Research officer (CR1), CNRS

Derek McCusker graduated from Glasgow University. His PhD focused on the role of the proteasome in antigen presentation in Prof John Trowsdale's lab at Cancer Research UK. 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 lab 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

Dr. Mini Jose DEEPAK Postdoctoral fellow (FRM)
Dr. Christophe VELOURS Postdoctoral fellow (ANR)
Dr. Sylvain TOLLIS Postdoctoral fellow (Aquitaine Regional Council)
Mr. Romain MITTEAU PhD student (Université Bordeaux Segalen)
Ms Manon BONNET-SAVE BTS undergraduate student (Lycée Technologique St. Louis, Bdx)
Ms Xiaoli Yang Undergraduate student (University of California Berkeley)

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

Dynamics of cell growth & cell division

During the cell cycle, major structural rearrangements in cellular architecture ensue as duplicated chromosomes are split asunder and segregated to opposite poles, while cleavage of the intervening cytoplasm generates two appropriately sized cells. Coordination between the cell cycle machinery and proteins that regulate cell polarity ensure the fidelity of cell division; however the underlying mechanisms are unclear. Failure of these control mechanisms can result in aneuploidy or the loss of cell polarity, both of which are associated with malignant tumour formation. The goal of the Cell Growth and Division Laboratory is to understand how changes in cell polarity are orchestrated with cell cycle progression.

The lab has identified a key role for cyclin dependent kinase 1 (Cdk1) in the initiation and maintenance of polarized growth in the model eukaryote Saccharomyces cerevisiae. Cdk1 phosphorylates regulators of the GTPase Cdc42, including the GEF, GAP and adaptors. Cdk1-dependent regulation of the Cdc42 GTPase module serves to activate this master regulator of cell polarity, thus establishing a polarity axis along which cell division occurs. Using interdisciplinary state-of-the-art approaches including chemical genetics, high-speed in vivo imaging, and mass spectrometry my group is exploring the molecular mechanisms by which Cdk1 activity triggers these events. The mammalian homologues of the Cdc42 GEF and GAPs are oncogenes and tumour suppressors respectively. Moreover, recent work indicates that they too are regulated by cell cycle kinases including Cdk1, demonstrating that communication between the cell cycle and cell polarity machinery is a conserved feature of eukaryotic cell biology that may be critical for normal proliferation.

What are the molecular mechanisms by which Cdk1 activates Cdc42 to establish cell polarity?

High-speed flourescence microscopy of post-Golgi vesicle dynamics indicates that Cdk1 plays a critical role in trafficking of post-Golgi vesicles to the plasma membrane (Figure 1).

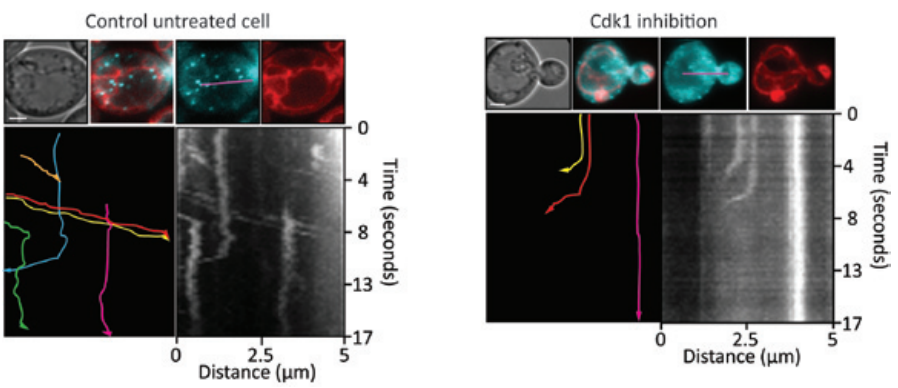


Figure 1: Chemical genetic inhibition of Cdk1 results in aberrant post-Golgi vesicle targeting. 80-100 images were then acquired at 220 ms intervals and stacked vertically to generate kymographs. In each set, the top 4 panels show a DIC image, merged images of post-Golgi vesicles (cyan) and FM4-64 (red), and the individual images used to generate the merge. The longitudinal line used to generate kymographs is shown in purple. The lower right panel is the resulting kymograph, and the lower left panel is a tracing of the kymograph in which each coloured line represents the trajectory of a different post-Golgi vesicle, with the arrowhead showing the direction of movement Scale bar is 2 µm.

Recently, we showed that Cdk1 phosphorylates regulators of the Cdc42 GTPaes module that control post-Golgi vesicle targeting. In collaboration with Dr. S.P. Gygi (Harvard Medical School, Boston, MA), we have now mapped the Cdk1-dependent phosphorylation sites on the Cdc42 GTPase module (GEF, GAP and adaptors) by mass spectrometry. Our objective is to identify the function that phosphorylation plays in regulating Cdc42 activity. Specifically, we are investigating whether phosphorylation of the GTPase module influences the affinity of the GEF, GAP and adaptors for each other, for membranes or for downstream effectors. These studies are providing insight into the mechanisms by which multi-site phosphorylation regulates the switch-like activation of a GTPase module.

How do rearrangements in the actin cytoskeleton, which controls membrane trafficking dynamics, establish a polarity axis during the cell cycle?

Cdk1-dependent activation of Cdc42 induces polarization of the actin cytoskeleton towards the site at which a new cell, or bud, will grow. Post-Golgi exocytic vesicles are targeted to the bud via filamentous actin cables. Filamentous actin generated by the Arp2/3 nucleation machinery is also utilized for endocytic internalization of vesicles at sites of polarized growth. Thus actin polymerization is utilized for endocytosis and exocytosis, raising the question of how these competing activities are coordinated, and how these trafficking domains are organized. We have discovered that trafficking domains at the plasma membrane undergo extensive reorganization early in the cell cycle as growth becomes polarized (Figure 2). A screen is underway to isolate mutants that perturb this process and identify the mechanisms underlying the generation of cell polarity.

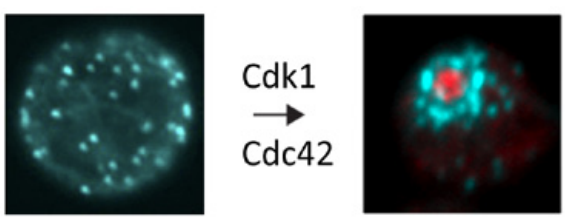


Figure 2: Early in the cell cycle (left image), endocytosis-associated actin patches (cyan) are distributed randomly throughout the cytoplasm. During the initiation of polarized growth, endocytic vesicles (cyan) corral a central zone of exocytic post-Golgi vesicles (red) that are targeted to a tight patch on the plasma membrane.

Selected publications

Artiles K., Anastasia S., McCusker D. and Kellogg D. (2009). The Rts1 regulatory subunit of protein phosphatase 2A (PP2A) is required for G1 cyclin transcription and nutrient modulation of cell size. PLoS Genetics. 5: e1000727.

Egelhofer T.A., Villen J., McCusker D., Gygi S.P. and Kellogg D.R. (2008). The septins function in G1 pathways that influence the pattern of cell growth in budding yeast. PLoS ONE. 3: e2022.

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

McCusker D., Denison C,. Anderson S., Egelfofer T., Shokat K., Yates J. and Kellogg D. (2007). Cdk1 Coordinates cell surface growth with the cell cycle. Nature Cell Biol. 9: 506-515.

McCusker D., Barale S. and Arkowitz R. (2006). Cdc42p GDP/GTP cycling is necessary for cell fusion during yeast mating. Mol. Biol. Cell. 17: 2824-38.

Barale S., McCusker D., and Arkowitz R. (2004). The exchange factor Cdc24 is required for cell fusion during yeast mating. Eukaryotic Cell 4 :1049-1061.

McCusker D., Wilson M., and Trowsdale J. (1999). Organisation of the genes encoding the human proteasome activators PA28 alpha and beta. Immunogenetics. 49: 438-45.

McCusker D., Jones T., Sheer D., Trowsdale J. (1997). Genetic relationships of the genes encoding the human proteasome b subunits and the proteasome PA28 complex. Genomics 45: 362-367.

Dr. Denis Dupuy

Research officer (CR1), Inserm

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

Research team

Dr Karine REBORA Postdoctoral fellow (Inserm)
Ilyass ZNIBER PhD student (Inserm-Aquitaine Regional Council)
Rosina GIORDANO PhD student (Inserm-MENRT)
Léo GUIGNARD Software specialist (Fondation Bettencourt-Shueller)
Cécile QUÉRÉ PhD student (Aquitaine Regional Council)

Following successful recruitment within Inserm in 2011, this team is now part of the unit "ARN : Régulations naturelle et artificielle" (ARNA), INSERM/Université Bordeaux Segalen (U 869)

Genome regulation & evolution

Our goal is to perform a systematic and quantitative analysis of post-transcriptional regulation in vivo in C. elegans. More specifically, we combine quantitative analysis methods with genome wide RNAi screens to systematically identify all the genetic components involved in post-transcriptional regulation and characterize their functional interactions.
We use transgenic animals carrying two fluorescent markers to visualize the respective contribution of transcriptional and post-transcriptional regulation events for every gene considered. The data collected in the course of this project will constitute the first high-throughput in vivo quantitative analysis of post-transcriptional regulation in a metazoan organism.

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

We will focus our effort on two major aspects of post-transcriptional regulation:

Quantitative analysis of UTR-mediated regulation

Small non-coding RNAs such as microRNAs (miRNAs) and small interfering RNA (siRNAs) have recently emerged as a novel class of post-transcriptional gene expression regulators that interact with 3' untranslated regions (UTR) and interfere with the translation of the mRNAs, or cause their degradation, thus altering the amount of the corresponding protein in the cell2-13. The 115 miRNAs identified to date in C. elegans have been predicted to regulate about 10% of the protein coding genes but only a few of these predicted miRNA/UTRs interactions have been experimentally validated and functionally characterized in C. elegans.
More than one miRNA is generally predicted to interact with a given UTR, providing the opportunity to study combinatorial regulation. We will select 200 genes displaying an UTR predicted to interact with a variety of combinations of miRNAs to produce the first genome-scale quantitative survey of the function of these interactions in vivo. For each selected gene, we will generate transgenic animals carrying a polycistronic construct in which the corresponding endogenous promoter will be driving the expression of two reporters19: a red fluorescent protein (mCherry) with the permissive unc-54 UTR to monitor the transcriptional activity of the promoter and a green transcriptional fusion (GFP) associated to the cognate UTR to measure the contribution of post-transcriptional regulation (Figure 1a).

Quantitative analysis of alternative splicing

Alternative splicing of pre-mRNAs is a widespread mechanism that contributes to the spatiotemporal diversity of gene expression in metazoans. In Caenorhabditis elegans, it has been estimated that ~10% of genes are subjected to alternative splicing. To date, there is no information about global regulation of alternative splicing during worm development. In a recent study using a custom-made microarray, only ~20% of the tested genes showed a significant change in isoform ratio in the course of development27.

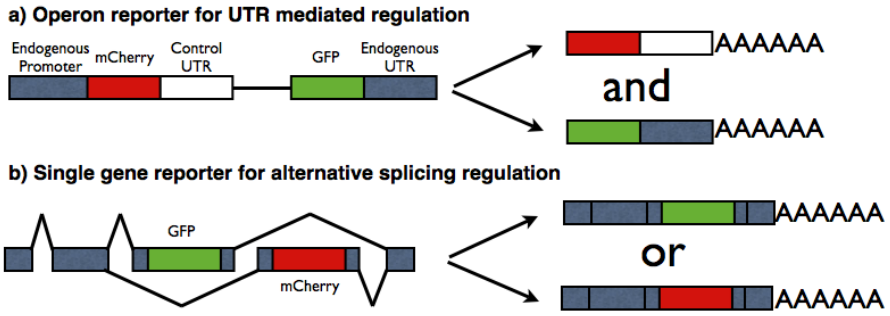


Figure 1: Two-color reporters for in vivo post-transcriptional regulation studies. a) The function of endogenous UTR sequences will be tested by direct comparison of expression levels with the unc-54 control expressed from the same double-reporters operon. b): Tissue and temporal specificity of alternate isoforms will be investigated by generating reporter constructs expressing distinct fluorescent markers

For the majority of the genes, for which EST data indicates alternative splicing events, no variation has been observed. This might indicate that most alternative isoforms are regulated in a tissue-specific rather than stage-specific manner. Such tissue- or cell-specific events are notoriously difficult to follow using microarray analyses. We will use a variation of the two-color reporter system pioneered by our collaborator H. Kuroyanagi (Tokyo) in which two fluorescent reporters are respectively fused to mutually exclusive alternatively spliced exons (Figure 1b), to characterize the alternative splicing patterns of 200 genes. This will provide the first large-scale overview of alternative splicing regulation in vivo in a metazoan organism.

In summary

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

Selected publications

Giordano R., Milstein S., Svrzikapa N., Vidal M., Dupuy D. (2010) A novel antibiotic selection system for nematode transgenesis. Nature Methods 7(9) 721-723

Reece-Hoyes J.S., Shingles J., Dupuy D., Grove C.A., Walhout A.J.M., Vidal M., Hope I.A. (2007). Insight into transcription factor gene duplication from Caenorhabditis elegans. Promoterome-driven expression patterns. BMC Genomics 8(1):27.

Bertin N., Simonis N., Dupuy D., Cusick M.E., Han J-D.J., Le Peuch C., Fraser H.B., Roth F.P. and Vidal M. (2007). Confirmation of Organized Modularity in the Yeast Interactome. PLoS Biology, 5(6): e153.

Ceron J., Rual J.F., Chandra A., Dupuy D., Vidal M., van den Heuvel S. (2007). Large-scale RNAi screens identify novel genes that interact with the C. elegans retinoblastoma pathway as well as splicing-related components with synMuv B activity. BMC Developmental Biology, 7:30.

Dupuy D., Bertin N., Hidalgo C.A., Venkatesan K., Tu D., Lee D., Rosenberg J., Svrzikapa N., Blanc A., Carnec A., Carvunis A.R., Pulak R., Shingles J., Reece-Hoyes J., Hunt-Newbury R., Viveiros R., Mohler W.A., Tasan M., Roth F.P., Le Peuch C., Hope I.A., Johnsen R., Moerman D.G., Barabási A.L., Baillie D., Vidal M. (2007). Genome-scale analysis of in vivo spatiotemporal promoter activity in Caenorhabditis elegans. Nature Biotechnology, 25(6): 663-668.

Han J.D., Dupuy D., Bertin N., Cusick M.E., Vidal M. (2005). Effect of sampling on topology predictions of protein-protein interaction networks Nature, 23(7): 839-844.

Dupuy D.., Li Q.R., Deplancke B., Boxem M., Hao T., Lamesch P., Sequerra R., Bosak S., Doucette-Stamm L., Hope I.A, Hill D.E., Walhout A.J. Vidal, M. (2004). A first version of the Caenorhabditis elegans Promoterome. Genome Res., (10B):2169-75.

Dr. Anne Royou

Research officer (CR1), 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. 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.

Research team

Marie-Charlotte CLAVERIE Technician (IBGC)
Emilie MONTEMBAULT Postdoctoral fellow (IBGC)
Nicolas DERIVE PhD student (IBGC)

This team is part of the "Institut de Biochimie et Génétique Cellulaire" (IBGC), CNRS/Université Bordeaux Segalen (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 of Drosophila neuronal stem cells. The first mechanism involves the faithful segregation of damaged chromosomes. We monitor cells entering mitosis with broken chromosomes. Our studies reveal that chromosome fragments segregate properly to opposite poles. This poleward motion is mediated through DNA tethers that connect the chromosome fragments. The second mechanism involves the coordination of chromosome segregation with cell cleavage. We found that cells can adapt to a four-fold increase in chromatid length by elongating transiently during anaphase. This mechanism ensures the clearance of chromosomes from the cleavage plane prior to completion of cell division.

Mitosis is the final stage of the cell cycle where a copy of the duplicated genome is transmitted to each daughter cell. Failure to do so produces daughter cells with an inappropriate genome content also called aneuploidy. Aneuploidy can have deleterious consequences for the cell and the organism as the cell looses the integrity of its genome. Aneuploidy is a hallmark of cancerous cells and there is growing evidence that it contributes to tumorigenesis. Aneuploidy can arise from aberrant cell division due to failure in DNA repair or defects in chromosome segregation. To protect its genome content, the cell relies on checkpoints. The DNA damage checkpoint acts in interphase to prevent the cell from entering mitosis in the presence of altered DNA. This provides time for repair. The spindle assembly checkpoint acts in mitosis to delay anaphase onset until all chromosomes are properly attached to the spindle via their centromere/kinetochore. It ensures that chromatids are faithfully segregated to the poles so that each daughter cell inherits the correct number of chromosomes. However, cells can adapt to checkpoints and resume the cell cycle. For instance, adaptation to the DNA damage checkpoint results in a situation in which the cell enters mitosis with damaged DNA. Entering mitosis with unrepaired DNA double strand break results in the production of chromosome fragments lacking centromeres (acentric fragments). Since the centromere is required for kinetochore function and thus chromatid segregation, these acentric chromosome fragments would be incapable of moving poleward during anaphase. If unchecked, this situation might lead to the production of aneuploid daughter cells.

Is there a mechanism that processes broken chromosomes in mitosis and thus prevents the production of aneuploid daughter cells?

We investigated the fate of cells going through mitosis with broken chromosomes. We used the I-CreI endonuclease to make site-specific DSB in the Drosophila sex chromosomes (Figure 1A). While I-CreI expression produces acentric chromatids in the vast majority of dividing cells, remarkably, it had no effect on adult survival. By monitoring chromosome segregation in live neuroblasts by time-lapse microscopy, we discovered that acentric fragments lagged during anaphase but eventually segregated toward the poles (Figure 1B). The poleward movement of the acentric fragment is mediated through DNA tethers connecting the acentric fragments to their centric partners. These tethers are decorated with Polo kinase, a key mitotic regulator, the spindle checkpoint component BubR1 and two chromosomal passenger complex (CPC) proteins, INCENP and Aurora-B (Figure 1C). Reduced BubR1 or Polo function results in abnormal segregation of acentric chromatids, a decrease in acentric chromosome tethering and a great reduction in adult survival. This led to the proposal that BubR1 and Polo facilitate the accurate segregation of acentric chromatids by maintaining the integrity of the tethers that connect acentric and centric fragments. My group is currently defining the nature

and property of the DNA tether and the molecular pathway that regulate its formation and maintenance. In particular, we are focusing on deciphering the role and regulation of BubR1 localization on the tether.

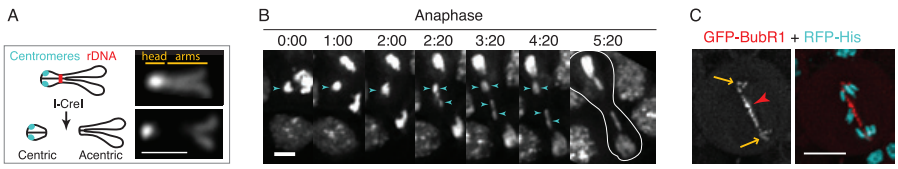


Figure 1: BubR1-coated DNA tethers facilitate the poloward segregation of acentric chromatids. (A) Schematic illustration (left) and DAPI straining (right) of the Drosophila mitotic X chromosome. The centromere (cyan circles) are near the telomere in the heterochromatin "head" brightly stained with DAPI. The endonuclease I-CreI cuts at the rDNA locus located in the pericentromeric heterochromatin. I-CreI generates two distinct chromosome fragments, a small heterochromatic fragment containing the centromeres (centric) and a long fragment containing the sister chromatid arms (acentric). Scale Bar=2µm. (B) Time lapse images of mitotic GFP-H2Av-labeled neuroblasts from heat shocked larvae expressing I-CreI. The acentrics (cyan arrowheads) are aligned at the metaphase plate . At anaphase, they lag behind the main chromatids but eventually move toward the poles. Two acentric fragments are seen moving toward each pole (cyan arrowheads. The white lines in the last column highlight the contour of the dividing cells. Time: min:sec. Scale Bar: 5µm. (C) Neuroblasts from I-CreI heat shocked larvae double labeled with GFP-BubR1 (red, top row) and RFP-Histone (cyan). The yellow arrows highlight BubR1 signal at the kinetochore. The red arrow points to BubR1 localization on the tether. Scale Bar: 10µm.

How does the cell senses that the sister chromatids have cleared the cleavage plane before the completion of cell division?

My group is equally interested in addressing the fundamental, yet largely uncovered issue of how chromosome segregation is coordinated with cell division. This coordination is essential for proper transmission of the genetic material into daughter cells. We monitored Drosophila neuroblasts going through mitosis with abnormally long chromosomes induced by the expression of the endonuclease I-CreI. Our study revealed a novel mechanism by which cells coordinate chromosome segregation with cell division. Cells can adapt to a four-fold increase in chromatid length by elongating transiently during anaphase/telophase (Figure 2). This increase in cell length is concomitant with the spreading of cortical myosin rings without compromising cytokinesis. This response is mediated by the Rho Guanine-nucleotide exchange factor. This novel signaling between chromatid arm and cortical myosin ensures the coordination between the clearance of chromatid arms from the cleavage site and completion of cytokinesis. We are currently trying to elucidate the mechanism by which the trailing chromatid arm triggers cell elongation.

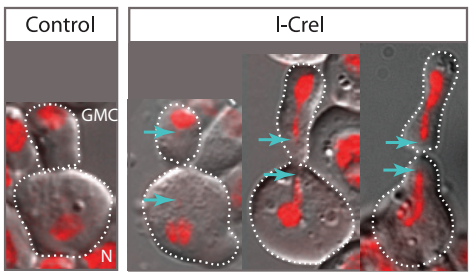


Figure 2. Increase in chromatid length is associated with cell elongation during cytokinesis. Images of live neuroblasts expressing the RFP::H2Av (red) at a single time points during late cytokinesis. Neuroblasts divide asymmetrically to give rise to a large neuroblast (N) and a small Ganglion Mother Cell (GMC). Cells from I-CreI larvae exhibit chromatid arms of various length compared with control cells. The blue arrows indicate the position of the tip of the longest chromatid. The Increase in chromatid length is associated with cell shape changes from a sphere to a tubule for the GMC or a pear-like shape for the neuroblast. The white dashed traits outline the cells.

Selected publications

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

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

Riggs B., Fasulo B., Royou A., Mische S., Cao J., Hays TS., Sullivan W. (2007) The concentration of Nuf, a Rab11 effector, at the microtubule-organizing center is cell cycle regulated, dynein-dependent, and coincides with furrow formation. Mol. Biol. Cell. 18(9) : 3313-22

Chodagam S., Royou A., Whitfield W., Karess R., Raff JW. (2005) The centrosomal protein CP190 regulates myosin function during early Drosophila development. Curr. Biol. 15 (14) : 1308-13

Royou A., Macias H., Sullivan W. (2005) The Drosophila Grp/Chk1 DNA damage checkpoint controls entry into anaphase. Curr. Biol. 15(4) :334-9

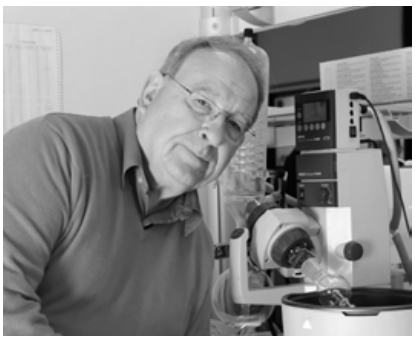
Silva E., Tiong S., Pedersen M., Homola E., Royou A., Fasulo B., Siriaco G., Campbell S.D. (2004) ATM is required for telomere maintenance and chromosome stability during Drosophila development. Curr. Biol. 14(15) :1341-7

Royou A., Field C., Sisson J. Sullivan W., Karess R. (2004) Reassessing the role and dynamics of nonmuscle myosin II during furrow formation and cellularization in the early Drosophila embryo. Mol. Biol. Cell. 15: 838-50

Royou A., Sullivan W., Karess R. (2002) Cortical recruitment of non muscle myosin II in early syncytial Drosophila embryos: its role in nuclear axial expansion and its regulation by Cdc2 activity. J. Cell. Biol. 158(1):127-37

Winter C.G., Wang B., Ballew A., Royou A., Karess R., Axelrod J.D., Luo L.. (2001) Drosophila Rho-associated Kinase (Drok) Links Frizzled-mediated Planar Cell Polarity Signaling to the Actin Cytoskeleton. Cell. 105:81-91

Sisson J.C., Field C., Ventura R., Royou A., Sullivan W. (2000) Lava Lamp, a Novel Peripheral Golgi Protein, is Required for Drosophila Cellularization. J. Cell. Biol. 151(4):905-18



Pr. Léon Ghosez

Emeritus Professor at the UCL
Visiting scientist at IECB

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). He also collaborated for a few months with Prof. R. Huisgen at the University of Munich. He got his "Habilitation" in 1969 at the age of 32 and became Professor at the University of Louvain. During his career in Louvain (1963-1999) he supervised 125 PhD students and 135 postdoctoral associates. He also held appointments at the University of Liège (1969-1999) and the Ecole Polytechnique in Palaiseau (1993-1999). He took an active part in the creation of the IECB, where he established a research group in 1998. From 2000 till the end of 2009, he shared the directorship of the IECB with Dr. J.J. Toulmé. Presently he is a visting scientist at IECB and Prof. Emeritus at UCL. Léon Ghosez is an Emeritus Member of the Royal Academy of Sciences, Literature & Fine Arts of Belgium. He recently received the Medal of the French Chemical Society.

Research team

Dr. Stijn CLAERHOUT Postdoctoral fellow (Université Bordeaux 1)
Dr Charles SIMON Postdoctoral fellow (Université Bordeaux 1)
Charlotte VRANCKEN Erasmus Master student (KUL Leuven)

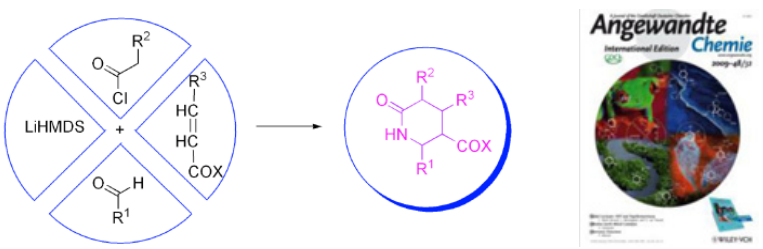
The team is part of the unit "Chimie et Biologie des Membranes et Nanoobjets" (CBMN), CNRS/ Université Bordeaux 1/IPB (UMR 5248)

Organic & medicinal chemistry

Small natural molecules have been shaped and optimized by evolution and are therefore perfectly tailored to interact with natural macromolecules and induce a biological response. Our first research project consists in producing by short sequences of reactions a set of structurally complex scaffolds which can be transformed into a wide diversity of natural product analogs of therapeutic interest. This should provide an entry into the drug discovery process at a much more advanced stage that does the screening of standard diversity libraries.
A second field of research deals with the development of new synthetic methods most often inspired by problems encountered in natural product syntheses. The group mainly focuses on the development of asymmetric catalytic reactions using non-genotoxic reagents.

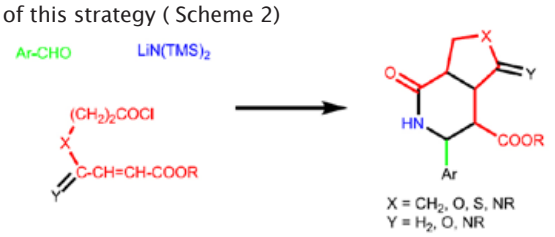
Diverted total synthesis of natural product analogs

Synthesis of « small » molecules will be needed as long as they will be used for the discovery of biological macromolecules, the study of their biological function and their potential for the development of new therapeutic agents. This approach requires the development of synthetic methods which provide a quick access to complex and diverse molecular structures exhibiting properties never seen before. However biological molecules populate only a very small fraction of the multidimensional chemical descriptor space available by synthesis. The synthetic chemist will therefore need guidelines to prepare molecules with a chemical descriptor allowing them to interact with biological macromolecules. Analogs of natural products which have been shaped by evolution should allow for entry into the discovery process of bioactive molecules at a much more advanced stage that does the screening of standard diversity libraries. One of our major endeavour at IECB has been the development of efficient synthetic processes for the production of new natural product analogs. We have developed unique 3-6 component reactions which enable to create a variety of heterocyclic scaffolds which can then be transformed in a few steps in a wide variety of complex heterocycles that could modulate biomacromolecular functions in a useful way (Scheme 1).



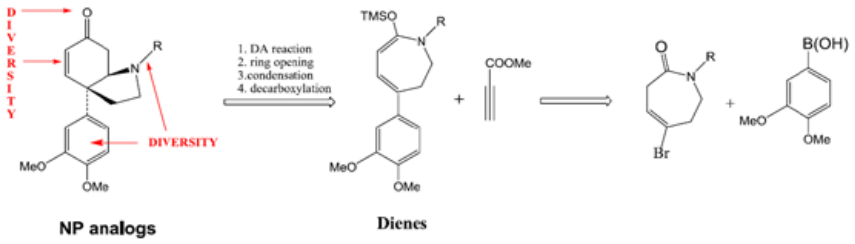
Scheme 1

This approach is now being applied to the synthesis of "fragments" inspired by pharmacologically interesting natural products or by known pharmacophores. A wide variety of new natural product-like scaffolds have been efficiently synthesized by an intramolecular version of this strategy (Scheme 2)



Scheme 2

We have also developed a new class of cyclic dienes which are aimed at opening quick and efficient accesses to natural product analogs or fragments as illustrated in Scheme 3.

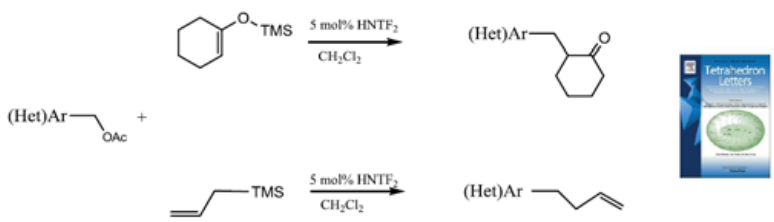


Scheme 3

Design and evaluation of non-metallic catalysts for alkylation under non-genotoxic conditions

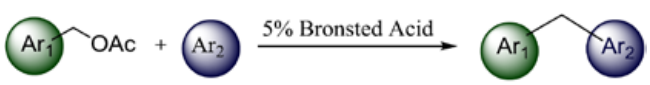
Previous research in our group had led to the seminal discovery of silicon-derived Lewis superacids derived from perfluorinated triflimides. These Lewis-acid catalysts are "green" catalysts which have been used by us and later by other groups around the world for the activation of carbonyl compounds. These catalysts tolerate many functional groups and are not toxic.

More recently we have performed studies of a reaction protocol allowing the benzylation and allylation of nucleophilic substrates like enol ethers, allyl silanes or aromatic and heteroaromatic compounds using non-genotoxic benzylating or allylating reagents in the presence of trialkylsilyl triflimides catalysts. Interestingly the catalytic activity could be tuned up by choosing the most appropriate alkyl substituent on silicon. Yields were high and work-up was easy (Scheme 4). In most cases the reactions could be performed without solvent. We believe that this procedure should appeal to the synthetic chemists looking for practical, safe and environmentally acceptable synthetic methods.



Scheme 4

In the course of these studies we discovered that benzylic acetates could be used in Friedel-Crafts benzylation reactions of aromatics and heteroaromatics catalyzed by Brönstedt acids such triflic acid or triflimides. This new procedure (Scheme 5) leads to a wide variety of diarylmethanes which are substructures found in many pharmacologically interesting compounds.



Scheme 5

However most of recent studies have been devoted to the search of chiral versions of our new silicon-derived catalysts. Challenges are : (1) to find chiral silylated triflimides which Lewis superacids as the parent scalemic derivatives, (2) obtain high enantiomeric excesses in a serie of model reactions. A wide variety of silylated triflimides carrying RO-, R2N-, F, and diaminocarbene groups have been prepared and evaluated as potential catalysts for model reactions such as Diels-Alder of dienes with methyl acrylate or crotonate, or the benzylation of silylenol ethers with benzylacetate. We also have examined various derivatives of myrtenal as potential catalysts.

Future

Priority will be given to the development of the above projects. We have successfully applied for a Marie Curie fellowship on the development of new silicon-based catalysts. The project on natural product analogs is supported by industry and we will look for further support from industry for the fragment approach.

Selected publications

Mendoza O., Rossey G., Ghosez L. (2011). Brönstedt acid-catalyzed synthesis of diarylmethanes under non-genotoxic conditions. Tetrahedron Lett. 2011, 52(17), 2235-2239

Mendoza O., Rossey G., Ghosez L . (2010). Trialkylsilyltriflimides as easily tunable organocatalysts for allylation and benzylation of silyl carbon nucleophiles with non-genotoxic reagents. Tetrahedron Lett. 2010, 51, 2571-2575 (cover)

Zhu W., Mena M., Jnoff E., Sun N., Pasau P., Ghosez L. (2009). Multicomponent reactions for the synthesis of complex piperidine scaffolds. Angew. Chem. Int. Ed., 48, 5880-5883 (cover)

Yang G., Ghosez L. (2009). Synthesis of enantiopure α-chlorocyclobutanones as scaffolds for the diverted total synthesis of serine protease inhibitors. Eur. J. Org. Chem., 111738-1748 (special issue, invited paper)

Commandeur M., Commandeur C., De Paolis M., Edmunds A.J., Maienfisch P., Ghosez L. (2009). Studies related to the total synthesis of the sesquiterpene core of the pyrrolobenzoxazine natural product CJ-12662. Tetrahedron lett., 50, 3359-3362 (special issue, invited paper)

Champeil E., Crean C., Larraya C., Pescitelli G., Proni G., Ghosez L. (2008). Functionalization of [60] fullerene via organometallic reagents. Tetrahedron, 64: 10319-10330.

Commandeur C., Commandeur M., Bathany K., Kauffmann B., Edmunds A.J.F., Maienfisch P., Ghosez L. (2008) Study of the oxidation of 3-hydroxypyrroloindoles to pyrrolobenzoxazine alkaloids Tetrahedron, 2011, 67(51), 9899-9908

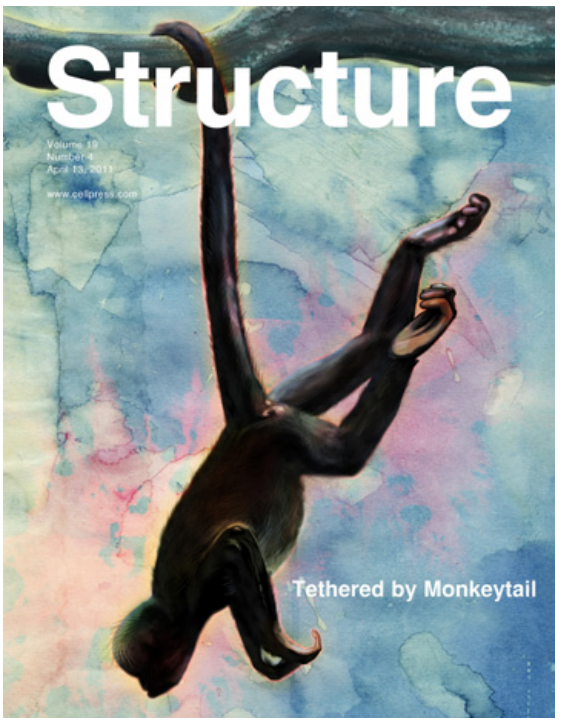
Srinivas K., Kauffmann B., Dolain C., Léger J.M., Ghosez L., Huc. I. (2008). Remote substituent effects and regioselective enhancement of electrophilic substitutions in helical aromatic oligoamides. J. Am. Chem. Soc, 130: 13210-13211.

Akhatou A., Rahini M. Cheboub K., Ghosez L., Hanquet G. (2007). Acid-promoted enan-tioselective oxygen-atom transfer from N-alkyl binaphtyl-derived oxaziridines onto sulfides. Tetrahedron, 63, 8449-8462 (invited paper, Tetrahedron 50th anniversary issue).

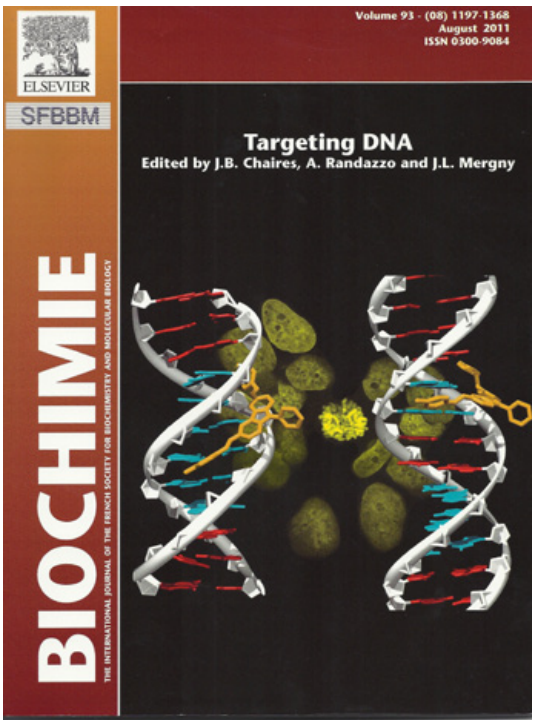
Depré D., Chen L.-Y., Ghosez L. (2003). A short multigram asymmetric synthesis of prostanoid scaffolds. Tetrahedron, 59, 6797-6812

Peer-reviewed articles

1. Alves I., Staneva G., Tessier C., Salgado G.F. & Nuss P. (2011) The interaction of antipsychotic drugs with lipids and subsequent lipid reorganization investigated using biophysical methods. Biochim Biophys Acta. Vol. 1808, 2009-18.
2. Andreoli F., Doukara A.L., Mehdid A.M., Vanthuyne N., Roussel C., Dessolin J., Kraus J.L. (2011) Novel phenyl(thio)ureas bearing (thio) oxothiazoline groupas potential BACE-1 inhibitors: synthesis and biological evaluation. J. Enzym. Inhib. Med. Ch., doi:10.3109/14756366.2011.642375
3. Berguiga L., Roland T, Monier K., Elezgaray J. & Argoul F. (2011) Amplitude and phase images of cellular structures with a scanning surface plasmon microscope. Optics Express, 19, 7, 6571-6586.
4. Bernard G., Chouery E., Putorti M.L., Tétreault M., Takanohashi A., Carosso G., Clément I., Boespflug-Tanguy O., Rodriguez D., Delague V., Abou Ghoch J., Jalkh N., Dorboz I., Fribourg S., Teichmann M., Megarbane A., Schiffmann R., Vanderver A. and Brais B. (2011). Mutations of POLR3A Encoding a Catalytic Subunit of RNA Polymerase Pol III Cause a Recessive Hypomyelinating Leukodystrophy. Am J Hum Genet. Aug 17.
5. Bertrand H., Granzhan A. Monchaud D., Saettel N., Guillot R., Clifford S., Guédin A., Mergny J.L. & Teulade-Fichou M.P. (2011) Recognition of G-Quadruplex DNA by Triangular Star-Shaped Compounds: With or Without Side Chains? Chem. Eur. J. Vol. 4529-4539.
6. Boal F., Laguerre M., Milochau A., Lang J. & Scotti P.A.(2011) A Charged Prominence in the Linker Domain of the Cysteine String Protein Cs Mediates the Interaction with the Calcium Sensor Synaptotagmin 9 during Exocytosis. FASEB Journal, 25, 132-143.
7. Bouchecareilh M., Higa A., Fribourg S., Moenner M., Chevet E. (2011). Peptides dervied from the bifunctional kinase/RNase enzyme IRE1a modulate IRE1a activity and protect cells from endoplasmic reticulum stress. FASEB J, 25 : 3115-3129.
8. Bouter A., Gounou C., Bérat R., Tan S., Gallois B., Granier T., Langlois d'Estaintot B., Pöschl E., Brachvogel B., Brisson A.R. (2011) Annexin-A5 assembled into two-dimensional arrays promotes cell membrane repair. Nature Communication, DOI 10.1038/ncomms1270.
9. Bruyère C., Madonna S., Lamoral-Theys D., Van Goietsenoven G., Mathieu M., Dessolin J., Kraus J.L., Lefranc F., Kiss R. (2011) JLK1486, a bis 8-hydroxyquinoline substituted benzylamine, display cytostatic effects in experimental gliomas through MyT1 and STAT1 activation, and to a lesser extent PPARg activation. Translational Oncology, 4, 3, 126-137.
10. Cala O., Fabre S., Pinaud N., Dufourc E. J., Fouquet E., Laguerre M. & Pianet I. (2011) Towards a Molecular Interpretation of Astringency: Synthesis, 3D Structure, Colloidal State, and Human Saliva Protein Recognition of Procyanidins. Planta Med., 77, 11, 1116-1122.
11. Calleja V., Laguerre M. & Larijani B. (2011) Role of the C-terminal regulatory domain in the allosteric inhibition of PKB/Akt . Advances in Enzyme Regulation, Available online 12 September 2011, in press
12. Calligari P.A.,* Salgado G.F.,* Pelupessy P., Lopes P., Ouazzani J., Bodenhausen G., and Abergel D. (2011) Insights into internal dynamics of 6-Phosphogluconolactonase from Trypanosoma brucei studied by NMR and Molecular Dynamics. Proteins: Structure, Function and Bioinformatics. *Both authors contributed equally to this work. DOI: 10.1002/prot.24019.
13. Cavagnat D., Claudon P., Fischer L., Guichard G. and Desbat B. (2011). Experimental and Theoretical Study of the Vibrational Spectra of Oligoureas: Helical versus β-Sheet-Type Secondary Structures. J Phys Chem B 115: 4446-4452.
14. Chalumeau C., Deffieux D., Chaignepain S., Quideau, S. (2011) Development of an Affinity-Based Proteomic Strategy for the Elucidation of Proanthocyanidin Biosynthesis. ChemBioChem, 12, 1193-1197.
15. Chardon E., Puleo G.L., Dahm G., Guichard G., and Bellemin-Laponnaz S. (2011). Direct functionalisation of group 10 N-heterocyclic carbene complexes for diversity enhancement. Chem Commun 47: 5864-5866.
16. Commandeur C., Commandeur M., Bathany K., Kauffmann B., Edmunds A., Maienfisch P., Ghosez L. (2011) Studies of the oxidation of 3-hydroxypyrroloindoles to pyrrolobenzoxazines. Tetrahedron, special issue, 52(17), 2235-2239



17. Courreges C., Nallet F., Dufourc E., Oda R. (2011) Unprecedented observation of days-long remnant orientation of phospholipid Bicelles: A Small Angle X-Ray Scattering and theoretical study" Langmuir 27: 9122-9130
18. Daubon T., Buccione R., Génot, E. (2011). The Aarskog-Scott syndrome protein Fgd1 regulates podosome formation and extracellular matrix remodeling in TGFb-stimulated aortic endothelial cells. Mol. Cell. Biol. 31(22): 4430-41
19. Deffieux D., Natangelo A., Malik G., Pouységu L., Charris J., Quideau S. (2011) First and Biomimetic Total Synthesis of a Member of the C-Glucosidic Subclass of Ellagitannins, 5-O-Desgalloylepipunicacortein A. Chem. Commun. 47, 1628-1630.
20. Delsuc N., Massip S., Léger J.-M., Kauffmann B., Huc I. (2011) Relative helix-helix conformations in branched aromatic oligoamide foldamers, J. Am. Chem. Soc., 133, 3165
21. Diebold M.L.*, Fribourg S.*, Koch M., Metzger T., Romier C. (2011) Deciphering correct strategies for multiprotein complexe assembly by co-expression: Applications to complexes as large as the histone octamer. J Struct Biol. 175(2):178-88 *equal first
22. Estieu-Gionnet K., Guichard G. (2011) Stabilized helical peptides: overview of the technologies and therapeutic promises. Expert Opin. Drug Discov. 6 (9): 937-963.
23. Fezoua-Boubegtiten Z., Brisson A.R., Gounou C., Desbat B., Laguerre M. & Lecomte S. (2011) Effect of Mg2+ versus Ca2+ on behavior of Annexin A5 in a membrane-bound state. Eur. Biophys. J., 40, 5, 641-649.
24. Fremaux J., Fischer L., Arbogast T., Kauffmann B., and Guichard G. (2011) Condensation Approach to Aliphatic Oligourea Foldamers: Helices with N-(pyrrolidin-2-ylmethyl)ureido Junctions, Angew. Chem. Int. Ed. 50, 11382-11385.A43
25. Galarraga M.E., Mitaine-Offer A.-C., Amaro-Luis J.M., Miyamoto C., Tanaka C., Pouységu L., Quideau S., Rojas L. B., Lacaille-Dubois M.-A (2011) Steroidal Saponins from the Fruits of Cestrum ruizteranianum. Nat. Prod. Commun. 6, 1825-1826.
26. Gan Q., Ferrand Y., Bao C., Kauffmann B., Grélard A., Jiang H., Huc I. (2011) Helix-rod host-guest complexes with shuttling rates much faster than disassembly, Science, 331, 1172
27. Gan Q., Shang J., Kauffmann B., Wang Y., Bie F., Jiang H. (2011) A highly stable double helix of aromatic oligoamide comprised of fused ring aromatic units, Tetrahedron. Available online 1 December 2011.



28. Giordano-Santini R. and Dupuy D. (2011) Selectable genetic markers for nematode transgenesis. Cell Mol Life Sci. 68(11):1917-27.
29. Gopal Bag B., Garai C., Majumdar R. & Laguerre M. (2011) Natural Triterpenoids as Renewable Nanos. Structural Chemistry, doi: 10.1007/s11224-011-9881-1.
30. Grosjean A., Daro N., Kauffmann B., Kaiba A., Létard J.F., Guionneau P. (2011) The 1-D polymeric structure of the [Fe(NH2trz)3](NO3)2•nH2O (with n = 2) spin crossover compound proven by single crystal investigations. Chem Commun (Camb). 7;47(45):12382-4.
31. Guichard G., Huc I. (2011). Synthetic Foldamers. Chem. Commun., 47, 5933-5941.
32. Haddad R., Maurice F., Viphakone N., Voisinet-Hakil F., Fribourg S, Minvielle-Sebastia L. (2012). An essential role for Clp1 in assembly of polyadenylation complex CF IA and Pol II transcription termination. Nucl. Acids Res. 40 (3): 1226-1239. First published online: October 12, 2011
33. Hamon F., Largy E., Guédin A., Rouchon-Dagois M., Sidibe A., Monchaud D., Mergny J.L., Riou J.F., Nguyen C.H. & Teulade-Fichou M.P. (2011) A new acyclic oligoheteroaryle that discriminates strongly between diverse G-quadruplex topologies. Angew Chem. 50: 8747-9.
34. Jahier C., Coustou M-F., Cantuel M., McClenaghan N. D., Buffeteau T., Cavagnat D., Carraro M., Nlate S. (2011) Optically Active Tripodal Dendritic Polyoxometalates: Synthesis, Characterization and Their Use in Asymmetric Sulfide Oxidation with Hydrogen Peroxyde. Eur. J. Inorg. Chem, 727-738.
35. Jourdes M., Michel J., Saucier C., Quideau S., Teissedre P.-L. (2011) Identification, Amounts and Kinetics of Extraction of C-Glucosidic Ellagitannins During Wine Aging in Oak Barrels or in Stainless Steel Tanks with Oak Chips. Anal. Bioanal. Chem. 401, 1531-1539.
36. Juin A., Billottet C., Moreau V., Destaing O., Albiges-Rizo C., Rosenbaum J., Saltel F., Génot E. (2011) Physiological type I collagen organisation induces the formation of a novel class of linear invadosomes. Mol Biol Cell. Epub Nov 23.
37. Kendhale A. M., Poniman L., Dong Z., Laxmi-Reddy K., Kauffmann B., Ferrand Y., Huc I. (2011) Absolute control of helical handedness in quinoline oligoamides, J. Org. Chem., 76, 195
38. Kiagus-Armad R., Brizard A., Tang C., Blatchly R., Desbat B., Oda, R. (2011) Cooperative and Reciprocal Chiral Structure Formation of Ala-Based Peptide Confined at the Surface of Cationic Surfactant membranes. Chem. Eur. J., 17, 9999-10009 .
39. Kremerskothen J., Stölting M., Wiesner C., Korb-Pap A., Van Vliet V., Linder S., Huber T.B., Rottiers P., Reuzeau E., Génot E., Pavenstädt H. (2011) Zona occludens proteins modulate podosome formation and function. FASEB J. Feb;25(2):505-14.
40. Lacroix L., Séosse A. & Mergny J.L. (2011) Fluorescence based duplex-quadruplex competition screen for telomerase RNA quadruplex ligands. Nucleic Acids Res. Vol. 39, e21.
41. Lefèvre S., Dumay-Odelot H., El-Ayoubi E., Budd A., Legrand P., Pinaud N., Teichmann M., Fribourg S. (2011) Structure-function analysis of hRPC62 provides insights into RNA polymerase III transcription initiation. Nature Structural and Molecular Biology, 18(3), 352-358
42. Mackereth C.D. (2011). Book review: Protein NMR Spectroscopy Principal Techniques and Applications, Ed. Lu-Yun Lian and Gordon Roberts. ChemBioChem doi: 10.1002/cbic.201100703
43. Mackereth C.D. (2011). Chemical shift assignments of a minimal Rna14p/Rna15p heterodimer from the yeast cleavage factor IA complex. Biomol. NMR Assign., 5:93-95
44. Mackereth C.D., Madl T., Bonnal S., Simon B., Zanier K., Gasch A., Rybin V., Valcárcel J., Sattler M. (2011). Multi-domain conformational selection underlies pre-mRNA splicing regulation by U2AF. Nature, 475:408-411
45. Marcel V., Tran P.L.T., Sagne C., Martel-Planche G., Vaslin L., Teulade-Fichou M.P., Hall J., Mergny J.L., Hainaut P. & Van Dyck E. (2011) G-quadruplex structures in TP53 intron 3: role in alternative splicing and in production of p53 mRNA isoforms. Carcinogenesis Vol. 32, 271-278.
46. Mendoza O., Rossey G., Ghosez, L. (2011) Brönstedt acid-catalyzed synthesis of diarylmethanes under non-genotoxic conditions, Tetrahedron Lett. 52, 2235-2239
47. Merle P., Evrard B., Petitjean A., Lehn J.M., Teulade-Fichou M.P., Chautard E., De Cian A., Guittat L., Tran P.L.T., Mergny J.L., Verrelle P. & Tchirkov A. (2011) Targeting telomeres with a new G4 ligand enhances radiation-induced killing of human glioblastoma cells. Mol. Cancer. Ther. Vol. 10, (10) 1784-95.
48. Monneau Y.R, Nelson C.J., Mackereth C.D. (2011). Chemical shift assignments of the catalytic domain from the yeast proline isomerase Fpr4p. Biomol. NMR Assign., doi: 10.1007/s12104-011-9338-x
49. Moreno-Morcillo M., Minvielle-Sébastia L., Fribourg S., Mackereth C.D. (2011). Locked tether formation by cooperative folding of Rna14p monkeytail and Rna15p hinge domains in the yeast CF IA complex. Structure, 19:534-545
50. Moreno-Morcillo M., Minvielle-Sébastia L., Mackereth C., Fribourg S. (2011). Hexameric architecture of CstF-50 supported by homodimerization domain structure. RNA, 17:412-418

51. Mueller-Dieckmann C., Kauffmann B. & Weiss M. S. (2011). Trimethylamine N-oxide as a versatile cryoprotective agent in macromolecular crystallography. J. Appl. Cryst. 44, 433-436.
52. Orioli A., Pascali C., Pagano A., Teichmann M., Dieci G. (2011) RNA polymerase III transcription control elements: Themes and variations. Gene. Epub 2011 Jun 25.
53. Orioli A., Pascali C., Quartararo J., Diebel K.W., Praz V., Romascano D., Percudani R., van Dyk L.F., Hernandez N., Teichmann M., Dieci G. (2011) Widespread occurrence of non-canonical transcription termination by human RNA polymerase III. Nucleic Acids Res. doi: 10.1093/nar/gkr074
54. Permpoonpattana P., Tolls E.H., Nadem R., Tan S., Brisson A. & Cutting S.M. (2011) Surface Layers of Clostridium difficile Endospores. Journal of Bacteriology, 193(23):6461-70.
55. Pichavant L., Bourget C., Durrieu M.C., Héroguez V. (2011) Synthesis of pH-Sensitive Particles for Local Delivery of an Antibiotic via Dispersion ROMP. Macromolecules, 44(20): 7879-87.
56. Poindron V., Berat R., Knapp A.M., Toti F., Zobairi F., Korganow A.S., Chenard M.P., Gounou C., Pasquali J.L., Brisson A., Martin T. (2011) Evidences for Heterogeneity of the Obstetrical Antiphospholipid Syndrome: thrombosis can be Critical for Antiphospholipid-Induced Pregnancy Loss. J Thromb Haemost. Aug 17. doi: 10.1111/j.1538-7836.2011.04475.x.
57. Pouységu L., Deffieux D., Malik G., Natangelo A., Quideau S. (2011) Synthesis of Ellagitannin Natural Products. Nat. Prod. Rep., 28, 853-874 (selected for the cover of the issue)
58. Quideau S. (2011) Triumph for Unnatural Synthesis. Nature. 474, 459-460 (News & Views).
59. Quideau S., Deffieux D., Douat-Casassus C., Pouységu L. (2011) Plant Polyphenols - Chemical Properties, Biological Activities, and Synthesis. Angew. Chem. Int. Ed., 50, 586-621
60. Quideau S., Douat-Casassus C., Delannoy López D. M., Di Primo C., Chassaing S., Jacquet, R., Saltel F., Genot E. (2011) The C-Glucosidic Ellagitannin Vescalagin Binds Filamentous Actin and Winds it into fibrillar aggregates. Angew. Chem. Int. Ed. 50, 5099-5104.
61. Quideau S., Douat-Casassus C., Delannoy López D.M., Di Primo C., Chassaing S., Jacquet R., Saltel F., Génot E. (2011) Binding of filamentous actin and winding into fibrillar aggregates by the polyphenolic C-glucosidic ellagitannin vescalagin. Angew Chem Int Ed Engl. 23;50(22):5099-104.
62. Reigadas S., Masquelier B., Calmels C., Laguerre M., Lazaro E., Vandenhende M., Neau D., Fleury H. & Andréola M. L.(2011) Structure analysis of HIV-1 IN Y143C/R Raltegravir resistance mutation in association with the secondary mutation T97A. Antimicrobial Agents and Chemotherapy, 55, 7, 3187-3194.
63. Renaud de la Faverie A., Hamon F., Di Primo C., Largy E., Dausse E., Delaurière L., Guetta C., Toulmé J.J., Teulade-Fichou M.P. & Mergny J.L. (2011) Nucleic acids targeted to drugs: SELEX against a quadruplex ligand. Biochimie. Vol. 93, 1357-67.
64. Rosario-Amorin D., Gaboyard M., Clérac R., Nlate S., Heuzé K. (2011) Enhanced catalytic recovery in an aqueous copper-free Sonogashira cross-coupling reaction. Dalton trans. 40, 44-46.
65. Saltel F., Daubon T., Juin A., Egana-Ganuza I., Veillat V., Génot E. (2011) Invadosomes: intriguing structures with promise. Eur J Cell Biol. 90(2-3):100-7.
66. Sanson C., Diou O., Thévenot J., Ibarboure E., Soum A., Brûlet A., Miraux S., Thiaudière E., Tan S., Brisson A., Dupuis V., Sandre O. and Lecommandoux S. (2011) Doxorubicin Loaded Magnetic Polymersomes: Theranostic Nanocarriers for MR Imaging and Magneto-Chemotherapy.ACS Nano, Feb 22; 5(2):1122-1140
67. Smith N.M., Labrunie G., Corry B., Tran P.L.T., Norret M., Djavaheri-Mergny M., Raston C.L. & Mergny, J.L. (2011) Unraveling the relationship between structure and stabilization of triarylpyridines as G-quadruplex binding ligands. Org. Biomol. Chem., 9: 6154-62.
68. Soenen S.J.H., Brisson A.R., Tan S., Nuytten N., Himmelreich U. and De Cuyper M. (2011) The labeling of cationic iron oxide nanoparticle-resistant hepatocellular carcinoma cells using targeted magnetoliposomes. Biomaterials. Feb;32(6):1748-58. Epub 2010 Nov 26.
69. Sosa A., Rosquete C., Bruno J., Rojas L., Pouységu L., Quideau S., Léger J.-M., Massip S., Lacaille-Dubois M.-A., Mitaine-Offer A.-C. (2011) Crystal Structure Analysis of 6,7-Di-O-Methyl-Quercetagetin-3-O-b-D-Glucopyranoside Dihydrate Isolated from Urena sinuata L. Avances en Química. 6, 55-59.
70. Sosa A., Rosquete C., Rojas L., Pouységu L., Quideau S., Paululat T., Mitaine-Offer A.-C., Lacaille-Dubois M.-A. (2011) New Triterpenoid and Ergostane Glycosides from the Leaves of Hydrocotyle umbellata L. Helv. Chim. Acta, 94, 1850-1859.
71. Stefan L., Guédin A., Amrane S., Smith N., Denat F., Mergny J.L., & Monchaud D. (2011) DOTASQ as a prototype of nature-inspired G-quadruplex ligand . Chem. Comm. Vol. 47, 4992-4994.
72. Stern E., Goossens L., Retailleau P., Kauffmann B., Bonte J.P., Depreux P., Goossens J.F. (2011) Preparative enantiomeric separation of new selective CB2 receptor agonists by liquid chromatography on polysaccharide-based chiral stationary phases:determination of enantiomeric purity and assignment of absolute stereochemistry by X-ray structure analysis. Chirality. 23(5):389-96.
73. Struts A.V., Salgado G.F. & Brown M.F. (2011) Solid-state 2H NMR relaxation illuminates functional dynamics of retinal cofactor in membrane activation of rhodopsin. Proc Natl Acad Sci USA. Vol. 108, 8263-8.
74. Struts A.V., Salgado G.F., Martínez-Mayorga K. & Brown M.F. (2011) Retinal dynamics underlie its switch from inverse agonist to agonist during rhodopsin activation. Nat Struct Mol Biol. Vol. 18, 392-4.
75. Tetreault M., Choquet K., Orcesi S., Tonduti D., Balotin U., Teichmann M., Fribourg S, Schiffmann R., Brais B., Vanderver A., Bernard G. (2011). Recessive mutations in POLR3B, encoding the second largest subunit of Pol III, cause hypomyelinating leukodystrohpy. Am. J. Hum. Genet., 89 : 652-655.
76. Tran P.L.T., Largy E., Hamon F., Teulade-Fichou M.P. & Mergny J.L. (2011) Fluorescence intercalator assay for screening G4 ligands towards a variety of G-quadruplex structures. Biochimie. Vol. 93, 1288-96.
77. Tran P.L.T., Mergny J.L. & Alberti P. (2011) Stability of telomeric quadruplexes. Nucleic Acids Res. Vol. 39, 3282-3291.
78. Tran P.L.T., Moriyama R., Maruyama A., Rayner B. & Mergny J.L.(2011) A mirror image tetramolecular DNA quadruplex. Chem. Comm. Vol. 47, 5437-5439.
79. Tran P.L.T., Virgilio A. & Esposito V., Citarella G., Mergny J.L. & Galeone A. (2011) Effects of 8-methylguanine on structure, stability and kinetics of formation of tetramolecular quadruplexes. Biochimie Vol. 93, 399-408.
80. Vidal G., Delord B., Neri W., Gounel S., Roubeau O., Bartholome C., Ly I., Poulin P., Salvetat J.P., Labrugère C., Sellier E., Durrieu MC., Amédée J. (2011) The effect of surface energy, adsorbed RGD peptides and fibronectin on the attachment and spreading of cells on multi-walled carbon nanotube papers, Carbon, 49(7), 2011, 2318-2333
81. Vilhelmova N., Jacquet R., Quideau S., Stoyanova A., Galabov A.S. (2011) Three-Dimensional Analysis of Combination Effect of Ellagitannins and Acyclovir on Herpes Simplex Virus Types 1 and 2. Antiviral Res. 89, 174-181.
82. Vives G, Giansante C, Bofinger R, Raffy G, Del Guerzo A, Kauffmann B, Batat P, Jonusauskas G, McClenaghan ND. Facile functionalization of a fully fluorescent perfluorophenyl BODIPY: photostable thiol and amine conjugates. Chem Commun(Camb). 2011 Oct 7;47(37):10425-7.
83. Wolff P., Oliéric V., Briand J.P., Chaloin O., Dejaegere A., Dumas P., Ennifar E., Guichard G., Wagner J.r.m. and Burnouf D.Y. (2011). Structure-Based Design of Short Peptide Ligands Binding onto the E. coli Processivity Ring. J Med Chem 54: 4627-4637.

Other publications

1. Chaires J.B., Randazzo A. & Mergny J.L. (2011) Targeting DNA. Editorial. Biochimie. Vol. 93 (8) v-vi
2. Huc I., Jiang H. (2011) Organic Foldamers and helices, book chapter in "Supramolecular chemistry: from molecules to nanomaterials. Steed, J. W., Gale, P. A. Eds, Wyley.
3. Mergny J.L. (2011) The fake meeting society (Editorial) . Biochimie Vol. 93, (4) v.
4. Mergny J.L., Bourdoncle A., Spindler L. (2011) Meeting report: Guanosines and Quadruplexes (London, Sept 15-17 2010) Biochimie Vol. 93, 121-126.
5. Mergny J.L., Yatsunyk L., Guédin A., Gros J., Renaud de la Faverie A., Smith N., Renciuk D., Tran P.L.T. & Bourdoncle A. (2011) DNA quadruplexes for bio- and nano-technologies. Chemistry of Nucleic Acid Components - Collection symposium series. Vol. 12, 218-221.
6. Oda R. (2011) chapter in "The next generation Cutting edge research on Biomimetics" (in Japanese), CMC edition, Japan
7. Rajpar S., Guittat L. & Mergny J.L. (2011) Télomères : un nobel pour le début de la fin. Bull. Cancer, 98: 999-1009.

Patents

1. Burnouf D., Stote A., Guichard G., Wagner, J. Olieric, V. (2011) Compounds binding to the bacterial beta ring. EP11162733, April 15, 2011; Applicant CNRS
2. Nguyen C.H., Rouchon-Dagois M., Guédin-Beaurepaire A., Monchaud D., Teulade-Fichou M.P., Riou J.F., Mergny J.L., Grierson D. (2011) Poly-heteroaryl derivatives for the treatment of cancer. US Patent 13/124,136
3. Quideau S., Génot E., Saltel F., Douat-Casassus C., Delannoy Lopez M.D. (2011) C-Glucosidic Ellagitannin Compounds for Use for Altering the Supramolecular Arrangement of Actin. European Patent N° EP11305186.6.

Team funding

International funding

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher(s)	Funding body	Research project	Period
Huc I.	FP7 – People – IIF	FARQUAD: Foldamers: a new family of G-quadruplex ligands	2009-2011
Huc I.	FP7 – People – IEF	HELICAL TRANSPORTERS Aromatic foldamers as drug delivery carriers	2009-2011
Huc I. Laguerre M.	FP7 – Marie Curie IAPP	FOLDAPPI	2009-2012
Génot E.	FP7 – People – ITN	Tissue Transmigration Training Network (T3Net) (including salaries for 2 PhD)	2009-2012
McCusker D.	FP7 – Marie Curie – IRG	Dynamics of Cell Growth and Cell Division	2009-2012
Elezgaray J.	FP7 – COST	BioInspired COST Action TD1003	2010-2012
Huc I.	FP7 – People – IIF	FOSIMEL Foldamers for single molecule electronics	2010-2012
Huc I.	FP7 – People – ITN	DYNAMOL Dynamic Molecular Nanostructures	2010-2014
Claerhoudt S.	EU, Marie Curie	New silicon-derived environmentally-benign Lewis-acid catalysts for asymmetric synthesis	2011-2012
Guichard G.	FP7 Marie Curie IEF	FOLDAPOP An Integrated Peptide and Foldamer Chemistry Approach Towards Pro-apoptotic TRAIL mimetics	2011-2013
Huc I.	FP7 – People – IIF	CATAMERS Catalytic Foldamers: Engineering a Second Coordination Sphere Around a Hydrogenase Mimic	2011-2013
Oda R. Laguerre M.	ANR-Blanc International-NSF	Hofmeistgemini: A Comprehensive Computational/Experimental Analysis of the Hofmeister Effect	2011-2014
Royou A.	Marie Curie IRG	BroChroMito Mecanisms that prevent aneuploidy	2011-2015
Quideau S.	FACCTS	Development of Asymmetric Diels-Alder Catalysts for Synthesis of Densely Functionalized Molecules	2009-2011
Kramer I.	Natl Science Foundation (NSF)	In Search of Best Methods to Illustrate Complex Information	2009-2011
Durrieu M.C. Vilar R.	Fundação para a Ciencia e Tecnologia (FCT)	Bio-inspired multiscale interfaces dental and skeletal reconstruction biomaterials	2010-2013
Mackereth C.	French Embassy in Canada	Structural and biological studies of histone proline isomerases	2011-2013

National funding

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Funding body	Research project	Period
Huc I.	ANR – PCV	FOLDAPTAMER Directed evolution of synthetic oligomers/oligonucleotide complexes targeted against HCV proteins	2007-2011
Teichmann M.	ANR	Regpolstress	2007-2011
Guichard G.	ANR PCV	TRANSPEP Pseudo-peptides for transfection : Chemical synthesis, biophysical analysis of supramolecular complexes and biological assays	2008-2011
Oda R. Laguerre M.	ANR-PCV	Exodynamics : Dynamic structures of SNARE transmembrane domains and lipids in membrane organization and their function in exocytosis	2008-2011
Elezgaray J.	ANR-PIR	Biocapteur Origami ADN	2009-2011

IECB Researcher	Funding body	Research project	Period
Durrieu M.C.	ANR Emergence -Tec	Bioimplant: Biomatériau, vecteur de gentamicine - Etude in vivo chez le lapin	2009-2012
Guichard G.	ANR Piribio	SYMULI Probing molecular dynamics of TNFR family members upon stimulation, in the membrane of live cells.	2009-2012
Mergny J.L.	ANR-Blanc	G4 Toolbox	2009-2012
Huc I.	ANR - blanc	FOLDAPSULE Foldamer capsules for saccharide recognition	2009-2013
Mergny J.L.	ANR	F-DNA	2009-2013
Génot E.	ANR-Blanc	VASCULOSOMES (including salary for one post-doc salary)	2010-2012
Fribourg S.	ANR-Blanc	RIBOPRE40S Late pre-40S maturation step	2010-2013
Guichard G.	ANR RPD	UREKAT Molecular Recognition with Urea-based Foldamers: From Anion Receptors to Bioinspired Organocatalysts	2010-2013
Oda R.	ANR-Blanc	Nanosprings: Functional hybrid organic-inorganic nanohelices: studies of the exalted phonomena at nanometric scales	2010-2013
Pouységu L.	ANR-Blanc	IODINNOV	2010-2013
Quideau S.	ANR-Blanc	FLUNUCLEOVIR	2010-2013
McCusker D.	ANR-JCJC	Dynamics of Cell Growth and Cell Division	2011-2013
Godde F. Laguerre M.	ANR	ARYNAMICS :Mimes oligoamides aromatiques de l'ADN double brin	2011-2015
Dupuy D.	ANR	Titaniums	2011-2014
Mergny J.L.	INCa	Quadruplexes & P53	2009-2012
Laguerre M. Dessolin J. , Elkaïm J.	INCA	Rôles de la Reptine et de la Pontine dans la carcinogénèse hépatique	2010-2013
Teichmann M.	INCa	TRANSLA-tRNA	2010-2013
Guichard G.	CNRS ATIP Program	Artificial Oligomers with Protein-like Structures and Functions	2009-2011
Dupuy D.	Inserm-Avenir	In vivo analysis of pos transcriptional regulation in C. elegans	2011-2012
Mergny J.L.	CNRS-PIR IT	Criblage de la chimiothèque essentielle Nat	2010-2011
Huc I.	Ministry of research	Pre-doctoral Fellowship	2010-2013
Mergny J.L. Elezgaray J.	Initiative Excel	VIBBNANO Imaging of Biological and Bioinspired Nanosystems	2011-2015
Mergny J.L.	Travel Grant	G4 ligands (with Hong Kong / Prof. E. Ma)	2011-2012

Regional funding

Coordinated by IECB researchers

IECB Researcher	Funding body	Type of funding	Period
Oda R.	Aquitaine Regional Council	Predoctoral fellowship	2008-2011
McCusker D.	Aquitaine Regional Council	Post-doctoral fellowship	2009-2011
Dessolin J.	Aquitaine Regional Council & CNRS	Cofinanced BDI grant	2009-2012

IECB Researcher	Funding body	Type of funding	Period
Guichard G.	Aquitaine Regional Council	Chaire d'Accueil	2009-2012
Mergny J.L.	Aquitaine Regional Council	Chaire d'accueil	2009-2012
Guichard G.	Aquitaine Regional Council	Post-doctoral fellowship	2010-2011
Teichmann M.	Aquitaine Regional Council	Cooperation Aquitaine-Emilie-Romaigne	2010-2011
Laguerre M.	Aquitaine Regional Council	Predoctoral fellowship	2010-2012
Garanger E.	Aquitaine Regional Council	Instrumentation	2010-2013
Guichard G.	Aquitaine Regional Council	Predoctoral fellowship	2010-2013
Huc I.	Aquitaine Regional Council & CNRS	Pre-doctoral Fellowship	2010-2013
Fribourg S.	Aquitaine Regional Council & Inserm	PhD fellowship	2011-2013
Fribourg S.	Aquitaine Regional Council	Instrumentation	2011-2013
Royou A.	Aquitaine Regional Council	Mecanisms that control chromosome transmission	2011-2013
Garanger E.	GIS-AMA	Salary	2010-2013
Garanger E.	Univ. Bordeaux 1	Pre-doctoral fellowship	2010-2013
Garanger E.	Institut Polytechnique de Bordeaux	Iron oxide nanoparticles functionalization with elastin-based recombinant polymers and study of their aggregation properties	2011
Salgado G.	Inserm/UBS	Chaire mixte	2010-2015
McCusker D.	Univ. Bordeaux Segalen	Post-doctoral fellowship	2009-2011
McCusker D.	Univ. Bordeaux Segalen	Pre-doctoral fellowship	2010-2012

Charity-funded research projects

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Charity	Research project	Period
Dessolin J.	ARC	Post-Doctoral "return grant"	2009-2011
Genot E.	ARC	Caractérisation des podosomes des cellules endothéliales microvasculaires et recherche du rôle de ces structures dans l'étape d'invasion de l'angiogenèse	2010-2011
Laguerre M. Dessolin J.	ARC	La reptine, une nouvelle cible thérapeutique en cancérologie. Rôle de l'activité ATPase et fonctions cytoplasmiques	2010-2011
Guichard G.	ARC	Criblage de Chimiothèques de Foldamères Oligoamide pour l'Identification de Ligands des Récepteurs de Morts: Vers de Nouvelles Molécules Pro-Apoptotiques	2010-2013
Huc I.	ARC	Pancreas cancer: towards a new therapeutic approach	2010-2013
Guichard G.	ARC	Pre-doctoral fellowship	2011
Mergny J.L.	ARC	Programme ARC : Effets biologiques des ligands de G-quadruplexes	2011-2014
Jose-Deepak M. McCusker D.	ARC	Mechanisms underlying the establishment of cellular polarity.	Awarded but declined
Mergny J.L.	AFAF	Screening / Friereich's ataxia	2010-2011

IECB Researcher	Charity	Research project	Period
Jose-Deepak M. McCusker D.	FRM	Mechanisms underlying the establishment of cellular polarity.	2011-2012
Fribourg S.	Ligue Contre le Cancer	Pol III transcription initiation	2011
Genot E.	Ligue contre le cancer	Etude du role de la protéine Tks5 dans l'assemblage des pdosomes et des invadopdodes	2011
Teichmann M.	Ligue contre le Cancer	Equipe Labellisée: Analyse fonctionnelle d'une nouvelle isoforme d'ARN polymérase III humaine avec une activité oncogénique.	2011-2015

Contracts with the industry

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Company	Research contract	Period
Quideau S. Deffieux D.	LVMH	Chemistry of vine polyphenols	2008-2011
Guichard G.	ImmuPharma	Undisclosed	2010-2011
Guichard G.	ImmuPharma	CIFRE research contract	2010-2012
Guichard G.	ImmuPharma, ANRT	CIFRE Pre-doctoral fellowship	2010-2012
Deffieux D.	CIVB	Biochemistry of flavonoid	2010-2013
Huc I.	CIVB	New fluorescent probes for the simultaneous analysis of wine acids	2010-2013
Quideau S.	CIVB	Chemistry of ellagitannins	2010-2013
Ghosez L.	undisclosed	Synthesis of polycyclic scaffolds mimicking steroids	2011
Oda R.	Living Proof (Cambridge, USA)	Consulting	2011
Huc I., Laguerre M. Leroux V.	Servier	Undisclosed - Post-doctoral fellowship	2011-2012
Huc I.	Undisclosed	Molecular recognition of protein surfaces by aromatic amide foldamers	2011-2013

IECB funding

Coordinated by IECB researchers

IECB Researcher	Funding body	Research project	Period
Guichard G. Mergny J.L.	IECB 2011 call for internal projects	Towards identification of new molecular scaffolds interacting with nucleic acids by a medium throughput screening approach	2011
A. Royou	IECB/CNRS	Instrumentation	2011
Mackereth C. McCusker D.	IECB 2011 call for internal projects	MuiltiPhos: Multi-site phosphosphorylation	2011-2012

Collaborations

Pole 1 – Structural biology & biophysics

Molecular modeling
Dr. Michel Laguerre

1. Dr Reiko Oda, IECB, Pole 1, CNRS UMR 5248, Pessac, France
2. Dr. Erick Dufourc, CBMN, CNRS UMR 5248, Pessac, France
3. Dr. Ivan Huc, IECB, Pole 2, CNRS UMR 5248, Pessac, France
4. Dr. Bernard Desbat, CBMN, CNRS UMR 5248, Bordeaux, France
5. Dr. J. Rosenbaum, INSERM, U1053, Bordeaux, France
6. Prof. Philippe Barthélémy, INSERM, U869, Bordeaux, France
7. Dr. Françoise Argoul, Laboratoire Joliot Curie – ENS, Lyon, France
8. Pr. Robert Kiss, Institut de Pharmacie, Brussels, Belgique
9. Dr. Joseph Parello, Vandelbilt University, Nashville, USA
10. Prof. Larry Romsted, Rutgers University, Piscataway, USA
11. Prof. Ronald Sauers, Rutgers University, Piscataway, USA
12. Dr. Banafshe Larijani, Cancer Research UK, London, UK
13. Prof. Shawn Wettig, School of Pharmacy, Waterloo, Canada
14. Prof. Braja Gopal Bag, Vidyasagar University, Midnapore, India

Morphologies, dynamics & functions of assemblies of amphiphiles
Dr. Reiko Oda

1. Dr. Michel Laguerre, IECB, Pole 1, CNRS UMR 5248, Pessac, France
2. Dr. Erick Dufourc, CMBN, CNRS UMR 5248, Pessac, France
3. Dr. Ivan Huc, IECB, Pole 2, CNRS UMR 5248, Pessac, France
4. Dr. Bernard Desbat, CMBN, CNRS UMR 5248, Bordeaux, France
5. Dr. Dario Bassani, ISM, Bordeaux, France
6. Dr. Thierry Buffeteau, ISM, Bordeaux, France
7. Dr. Valérie Héroguez, LCPO, Bordeaux, France
8. Dr. Bertrand Audoin, I2M, Bordeaux, France
9. Dr. Yevgen Karpichev, Ukraine Academy of Science, Donetsk, Ukraine
10. Prof. Ruis Vilar, Instituto Superior Tecnico, Lisbon, Portugal
11. Prof. Gianfranco Savelli, Perugia University, Perugia, Italy
12. Prof. Hirotaka Ihara, Kumamoto University, Kumamoto, Japan

Molecular imaging & nanobiotechnology
Pr. Alain Brisson

1. Prof. Thierry Martin, Inst. Hématologie et Immunologie, Strasbourg, France
2. Prof. Jean-Louis Pasquali, Inst. Hématologie et Immunologie, Strasbourg, France
3. Dr. Sébastien Lecommandoux, LCPO, Bordeaux, France
4. Dr. Sylvain Miraux, RMSB, Bordeaux, France
5. Dr. Bernard Desbat, CBMN, Bordeaux, France
6. Dr. Bernard Gallois, CBMN, Bordeaux, France
7. Prof. Simon Cutting, Royal Holloway, UK
8. Dr. Marcel De Cuyper, Leuven, Belgium
9. Dr. Ralf Richter, CIC Biomagune, San Sebastian, Spain
10. Prof. Ernst Pöschl, Norwich, UK
11. Dr. Bent Brachvogel, Cologne, Germany

Pole 2 – Organic & bioorganic chemistry

Supramolecular bioorganic & biomimetic chemistry
Dr. Ivan Huc

1. Dr. Jean-Jacques Toulmé, INSERM, U869 ARNA, Pessac, France
2. Prof. Jean-Michel Léger, Univ. Bordeaux Segalen, Laboratoire de Pharmacochimie, Bordeaux, France
3. Prof. Hua Jiang, Chinese Academy of Science, Institute of Chemistry, Beijing, China

Synthesis & activity of natural substances
Pr. Stéphane Quideau

1. Dr. Elisabeth Génot, IECB, INSERM U1053, Pessac, France
2. Dr. Carmelo Di Primo, INSERM U869, Pessac, France
3. Prof. Pierre-Louis Tesseidre, ISVV, Bordeaux, France
4. Prof. Marie-Aleth Lacaille-Dubois, Université de Dijon, France
5. Prof. Angel Galabov, University of Sofia, Bulgaria
6. Prof. Luis Rojas ULA, Mérida, Venezuela
7. Prof. Carmelo Rosquette, ULA, Mérida, Venezuela
8. Prof. Jaime Charris,UCV, Caracas, Venezuela
9. Prof. Stefano Manfredini, University of Ferrara, Italy

Peptidomimetic chemistry
Dr. Gilles Guichard

1. Dr. Stéphane Bellemin-Laponnaz, IPCMS, UMR 7504, Strasbourg, France
2. Dr. Dominique Burnouf, IBMC, UPR 9002, Strasbourg, France
3. Dr Dominique Cavagnat, ISM, UMR CNRS 5255, Bordeaux, France
4. Dr. Claude Didierjean Université Henri Poincaré, Nancy, France
5. Dr. Bernard Desbat, CMBN, CNRS UMR 5248, Talence, France
6. Dr. Eric Ennifar, IBMC, UPR 9002, Strasbourg, France

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

1. Prof. Sébastien Lecommandoux, LCPO, CNRS UMR 5629, Pessac France
2. Dr. Olivier Sandre, LCPO, CNRS UMR 5629, Pessac, France
3. Prof. Bertrand Garbay, EA 4135, Univ. Bordeaux Segalen, France
4. Dr. Pierre Voisin, RMSB, Univ. Bordeaux Segalen, France
5. Prof. Ashutosh Chilkoti, Duke University, Durham, USA (NC)

Pole 3 – Molecular recognition

Gene regulation & tumor research
Pr. Martin Teichmann

1. Dr. Sébastien Fribourg, IECB, Pessac, France
2. Prof. Robert G. Roeder, The Rockefeller University, New York, USA
3. Prof. Giorgio Dieci, University of Parma, Italy
4. Pr. Bernhard Brais, Université de Montréal, Canada

Structural biochemistry
Dr. Sébastien Fribourg

1. Prof. Martin Teichmann, IECB, U869, Pessac, France
2. Dr. Cameron Mackereth, IECB, 869, Pessac, France

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

1. Dr. Sébastien Fribourg, IECB/Inserm U869, Pessac, France
2. Dr. Michael Sattler, Helmholtz/TUM, Munich, Germany

3. Dr. Juan Valcárcel, Centre for Genomic Regulation Barcelona, Spain
4. Dr. Chris Nelson, Univeristy of Victoria Victoria, Canada

Unusual nucleic acid structures
Dr. Jean-Louis Mergny

1. Dr. Jean-Jacques Toulmé, INSERM U869, Pessac, France
2. Dr. Jean-Pierre Aimé, CMBN, CNRS UMR 5248 Pessac, France
3. Dr. Isabel Alves, CMBN, CNRS UMR 5248, Pessac, France
4. Dr. Gilles Guichard, IECB, Pole 2, CNRS UMR 5248, Pessac France
5. Dr. Mojgan Djavaheri-Mergny, Institut Bergonié, Inserm U869, Bordeaux, France
6. Dr. Christian Cazenave, CNRS, Univ. Bordeaux Ségalen, Bordeaux, France
7. Dr. Geneviève Pratviel, LCC, Toulouse, France
8. Dr. Marie Paule Teulade-Fichou, Institut Curie, Orsay, France
9. Dr. Alain Nicolas, Institut Curie, Paris, France
10. Dr. Jean-Francois Riou, MNHN, Paris, France
11. Dr. Ludovic Jullien, Université Paris VI, Paris, France
12. Dr. Eric Le Cam, Institut Gustave Roussy, Villejuif, France
13. Dr. David Monchaud, Université de Bourgogne, Dijon, France
14. Dr. Pierre Hainaut - Janet Hall, iARC - Institut Curie, Lyon, Orsay, France
15. Dr. Dennis Gomes, IPBS, Toulouse, France
16. Dr. Pierre Verrelle / A. Tchirkov, Centre Jean Perrin, Clermont-Ferrand, France
17. Dr. Valérie Gabélica, Université de Liège, Liège, Belgium
18. Prof. Aldo Galeone, Université de Naples, Naples, Italy
19. Dr. Yves Pommier, NIH, Bethesda, USA
20. Dr. Atsushi Maruyama, Kyushu University, Fukuoka, Japan
21. Dr. Anh Tuan Phan, NTU, Singapore
22. Prof. Edmund Ma, Hong-Kong Baptist University, China

Pole 4 - Molecular & cellular biology

Cell signalling in health & disease
Dr. Elisabeth Génot

1. Prof Stéphane Quideau, IECB, ISM, UMR 5255, Pessac, France
2. Dr Carmelo Di Primo, INSERM 869, Pessac, France
3. Dr Joachim Kremerskothen, Department for Molecular Nephrology, Internal Medicine D, University Clinic, Münster Germany
4. Prof Stefan Linder, Universitätsklinikum Eppendorf, Institut für medizinische Mikrobiologie, Virologie und Hygiene, Hamburg, Germany
5. Dr Roberto Buccione, Consorzio Mario Negri Sud, Santa Maria Imbaro, Chiety, Italy

Dynamics of cell growth & cell division
Dr. Derek McCusker

1. Dr. Jean-Baptiste Sibarita, Institut Francois Magendie, CNRS UMR5091, Bordeaux, France
2. Dr. Cameron Mackereth, IECB, ARNA Lab INSERM U869, Pessac, France
3. Dr. Gavin Fox, SOLEIL Synchrotron, St. Aubin, France
4. Dr. Anne Royou, IECB, IBGC, CNRS UMR5095, Pessac, France
5. Dr. Steven P. Gygi, Harvard Medical School,Boston, USA
6. Dr. John Yates3rd, SCRIPPS Institute, La Jolla, USA

Genome regulation & evolution
Dr. Denis Dupuy

1. Dr. Cameron McKereth, IECB, Inserm U869, Pessac, France
2. Dr. Marie-Hélène Delville, ICMCB, Bordeaux, France
3. Dr. Hervé Seznec, CENBG, Bordeaux, France
4. Dr. David Baillie, Simon Fraser University, Vancouver, Canada
5. Dr. Jenny Bryan, University of British Colombia, Vancouver, Canada
6. Dr. Hidehito Kuroyanagi, Graduate School of Biomedical Science, Tokyo, Japan

Organic & medicinal chemistry
Pr. Léon Ghosez

1. Dr. Michel Laguerre, IECB, Pole 1, CNRS UMR 5248, Pessac, France
2. Dr. Erick Dufourc, CMBN, CNRS UMR 5248, Pessac, France
3. Dr. Ivan Huc, IECB, Pole 2, CNRS UMR 5248, Pessac, France
4. Prof. Jochen Lang, CNRS UMR 5248, Pessac, France
5. Dr. Serge Mignani, Private Consultant, Paris, France
6. Dr. Daniel Michelet, Private Consultant, Nice, France
7. Dr. Georges Dive, University of Leuven, Belgium
8. Prof. Ken Houk, UCLA, Los Angeles, Cal., USA
9. Prof. Svetlana Tsogoeva, University Erlangen, Germany
10. Chemists and biologists from three industrial labs, France, Germany

Invited conferences

Pole 1 – Structural biology & biophysics

Molecular modeling

- Nanobiomed, Bilbao, Spain, April 2011, J. Elezgaray, J.-M. Arbona
- Interbio, Lisbon, Portugal, May 2011 J. Dessolin
- Servier Laboratory, Croissy, France, May 2011, M. Laguerre
- 4th European Conference on Chemistry for Life Sciences, Budapest, Hungary, August 2011, J. Elkaïm

Morphologies, dynamics & functions of assemblies of amphiphiles

- Neo-Biomimetic Symposium, Tsukuba, Japan, February 2011, R. Oda
- 8th French Colloquium on Organic Fluorine Chemistry, Obernai, France, March 2011, R. Oda
- ACS Colloid and Interface Science, Montreal, Canada, June 2011, R. Oda
- Telluride Science Research Center, The Physics, Chemistry, and Biology of Ions and Osmolytes in Solution, Telluride, Colorado, July 2011, R. Oda
- COST-D40 Action, Innovative Catalysis: New Processes and Selectivities, Malta, June 2011, S. Nlate
- 9ème Journées des phénomènes ultrarapides, Rouen, France October 2011, B. Audouin, Y. Guillet, T. Dehoux, O. Zouani, M.C. Durrieu

Molecular imaging & nanobiotechnology

- University of Bern, Dept. of Anatomy, Pr. A. Draeger, Bern, Switzerland, May 2011, A. Brisson
- 11ème Congrès de la Société Française des Microscopies, Strasbourg, France, June 2011, A. Brisson
- Université Laval, Dr. E. Boilard, Québec, Canada, July 2011, A. Brisson
- Fifth Annual Dysferlin Conference, Jain Foundation, Chicago, USA, July 2011, A. Brisson
- 6th International Meeting on Annexins, Barcelona, Spain, Aug. 2011, A. Brisson
- Institut de Myologie, Paris, Oct. 2011, A. Brisson
- Microvesicles and Exosomes, Orlando, USA, Oct. 2011, A. Brisson

Pole 2 – Organic & Bioorganic Chemistry

Supramolecular bioorganic & biomimetic chemistry

- Minisymposium, University Pierre et Marie Curie, Paris, France, January 2011, I. Huc
- 10th German Peptide Symposium, Berlin, Germany, March 2011, I. Huc
- Korean Society Meeting, Jeju Island, Korea, April 2011, I. Huc
- 46th Bürgenstock Conference, Brunnen, Switzerland, May 2011, I. Huc
- Tetrahedron Symposium, "Frontiers in Organic and Bioorganic Chemistry", Sitges, Spain, June 2011, I. Huc
- RICT (International Meeting of Therapeutic Chemistry), Lyon, France, July 2011, I. Huc
- COST Action CM0803 Workshop "Foldamers: From Synthesis and Folding, to Function", Leeds, UK, September 2011, I. Huc

Synthesis & activity of natural substances

- 1er Symposium Francophone de Synthèse Totale, Marseille, France, May 2011, L. Pouységu
- JFECO XVI Journées Franco-Espagnoles de Chimie Organique, Burgos, Spain, June 2011, S. Quideau (Plenary), M. Delannoy, L. Pouységu, D. Deffieux
- 17th European Symposium on Organic Chemistry (ESOC 2011), Hersonissos, Crete July 2011, S. Quideau

Peptidomimetic chemistry

- Invited lecture, Université Pierre et marie Curie Paris, France, February 2011, G. Guichard
- 17th GFPP meeting, Aussois, France, February 2011, L. Fischer
- Foldamers: Synthesis and Structure of Functional Materials, Barcelona, Spain, April 2011, Y.R. Nelli
- Invited lecture at ICSN, Gif sur Yvette, France, April 2011, G. Guichard
- 47th International Conference on Medicinal Chemistry, Lyon, France, July 2011, C. Venin
- 31st REGIO-Symposium, Sornetan, Switzerland, September 2011, G. Guichard
- COST Action CM0803 Workshop "Foldamers: From Synthesis and Folding, to Function", Leeds, UK, September 2011, J. Fremaux
- Bioinspired nanosystems and nanomaterials, NanoSWEC Workshop Bordeaux, France, November 2011, G. Guichard

Pole 3 – Molecular Recognition

Gene regulation & tumor research

- 2ème workshop de l'axe Génome, Structure et Fonctions, Toulouse, France, March 2011, M. Teichmann
- Mechanisms of Eukaryotic Transcription, Cold Spring Harbor, Etats-Unis, August 2011, M. Teichmann

Structural biochemistry

- EMBLHeidelberg, GermanyJanuary 2011, S. Fribourg
- MPI Martinsried Munich, Germany, March 2011, S. Fribourg
- Interbio Symposium Lisbon, Portugal, May 2011, S. Fribourg

NMR spectroscopy of protein-nucleic acid complexes

- Frontiers in Protein Research, Lisbon, Portugal, May 2011, C. Mackereth
- RNA Club Bordeaux, France June 2011, C. Mackereth
- 7th Figeac Meeting, Figeac, France, Sept 2011, C. Mackereth
- Guelph-Bordeaux-Columbia Workshop, Bordeaux, France, Sept 2011, C. Mackereth Y. Monneau
- Users Meeting: National NRM Large Scale Research Infrastructure, Orléans, France, Nov2011, C. Mackereth

Unusual nucleic acid structures

- GDR Quadruplexes, Paris, France, March 2011, JL Mergny, P.L.T. Tran
- Young scientist symposium, Pessac, France, May 2011, P.L.T. Tran
- Société Fr. Physique, Bordeaux, France, June 2011, L. Yatsunyk
- SFR Transbiomed meeting Pessac, France, June 2011, J.L. Mergny
- CNRS-Innovations Ther., Paris, France, June 2011, J.L. Mergny
- International G4 meeting, Sorrento, Italy, June 2011, J.L. Mergny, L. Yatsunyk
- SCNAC, Cesky Krumlov, Cz, June 2011, J.L. Mergny
- G4 school, Spa, Belgium, Sep 2011, J.L. Mergny
- FIBER symposium, Kobe, Japan, Nov 2011, J.L. Mergny
- ISNAC #38, Sapporo, Japan, Nov 2011, J.L. Mergny

Pole 4 – Molecular & Cellular Biology

Cell signalling in health & disease

- GRRC, Printemps de Cardiologie, Lyon, France, May 2011, E. Génot
- 5eme journée de Biologie Cellulaire du Grand Campus, Orsay, France, May 2011, I. Kramer
- Cell adhesion and migration in inflammation and Cancer, 5th Zoo meeting, Amsterdam, The Nederlands, May 2011, T. Daubon, A. Juin

- 4th International meeting on Podosomes, Invadopodia and Focal Adhesions in Physiology and Pathology, Madrid, Spain, September 2011, E. Génot
- VII colloque francophone des petites protéines G, Poitiers, France, October 2011, E. Génot
- 14th Imperial College London symposium: Vascular endothelium: Role in disease pathogenesis & as a therapeutic target, London, UK December 2011, A. Leclercq

Dynamics of cell growth & cell division

- Institut Curie, Dept. Cell Biology, Invited seminar, Paris, France, April 2011, D. McCusker
- CRBM, Invited seminar, Montpellier, France, May 2011, D. McCusker
- Small G-proteins meeting Poitiers, France, September 2011, D. McCusker
- EMBO Cell Cycle meeting Montpellier, France, September 2011, D. McCusker

Control and dynamics of cell division

- 10th International Conference on Drosophila Heterochromatin, Gubbio, Italy, June 2011, A. Royou
- 15th European Cell Cycle Conference – EMBO Workshop on "exploring the logic of the cell cycle", Montpellier, France, Sept. 2011, A. Royou
- 7ème Rencontres de Figeac, France, Sept. 2011, A. Royou

Organic & medicinal chemistry

- Sanofi-Aventis, Frankfurt, Germany, October 2011, L. Ghosez

Conference organisation

- 17th GFPP meeting, Aussois, France, February 2011, G. Guichard
- Doc'66 meeting (IFR66, University Victor Segalen), Pessac, France, April 2011, F. Saltel, T. Daubon, C. Billottet
- Young scientists meeting, Pessac, France, May 2011, PLT Tran, A. Renaud de la Faverie, T. Daubon, F. Curado, I. Egaña
- Rethinking Targets for Therapeutic Intervention (Interbio Scientific Conference), IECB, Bordeaux-Pessac, France, June 2011, S. Quideau, C. Mackereth, I. Kramer, J.L. Mergny, D. McCusker
- Microfluidics MiniSymposium, IECB, Pessac, France, July 2011, B. Kauffmann, D. McCusker
- 11th Tetrahedron Symposium, Sitges, Spain, June, 2011, L. Ghosez, Chairman
- French-Japanese symposium in Supramolecular chemistry, biomimetics, bioimaging, and biomaterials, Pessac, France, Oct. 2011 R. Oda
- 3rd Aquitaine conference on Polymers, Arcachon, France, October 2011, I. Huc
- VII colloque francophone des petites protéines G, co-organizer, Poitiers, France, October 2011, E. Génot
- 5èmes recontres Figeac, Figeac, France, October 2011, J.L Mergny
- Interbio research to business tech transfer, co-organizer, Valencia, Spain, November 2011, I. Kramer

Thesises

- Rosina GIORDANO-SANTINI "Development of a new transgenesis marker for nematode transformation" (D. Dupuy) Université Bordeaux Segalen, MENRT-FRM grant
- Omar F. ZOUANI "Étude de l'Ostéogénèse par la Conception de Biomatériaux Intelligents" (M.C. Durrieu) Université Bordeaux 1, MNERT grant
- Phong Lan Thao TRAN "Guanine Quadruplexes: formation, stability and interactions" (J.L. Mergny) Inserm U869-IECB, MNERT grant
- Yoan MONNEAU "Etude des modifications post-traductionnelles des histones : La production semi-synthétique d'une protéine acétylée et l'analyse structurofonctionnelle d'une peptidyl-prolyl isomérase" (C. Mackereth) Univ. Bordeaux Segalen, ICSN/CNRS grant
- Daniel DA SILVA "Caractérisation des deux isoformes de l'ARN Polymérase III Humaine" (M. Teichmann), Inserm U869-IECB, MNERT grant
- Rumi TAMOTO "Chiral Nano/Micro Self-assemblies of cationic surfactants: from dynamic behavior of supramolecular architectures towards hybrid nanomaterials" (R. Oda) CBMN UMR 5248, Université Bordeaux 1
- Nicolas ARRAUD "Etude cinétique de la liaison élémentaire entre Annexine-A5 et membranes et mise au point d'un test de quantification des microparticules plasmatiques pro-coagulantes, par cytométrie en flux" (A. Brisson) CBMN UMR 5248, Université Bordeaux 1
- Judith ELKAIM "Drug design in silico : Criblage virtuel de protéines à visée thérapeutique" (J. Dessolin) CBMN UMR 5248, Université Bordeaux 1
- Renwei CHANG "Processus photoioniques au sein des architectures amphiphiles" (R. Oda) CBMN UMR 5248, Université Bordeaux 1 - Aquitaine Regional Council
- Adakarleny SOSA MORENO "Etude Phytochimique Bioguidée de Plantes Médicinales des Andes Vénézuéliennes: Bauhinia cumanensis et Urena sinuata" (S. Quideau) PCP, cosupervised with the University of the Andes, Mérida, Venezuela
- Laura Vanessa SANTIAGO BRUGNOLI "Etude Phytochimique Bioguidée de Plantes Médicinales des Andes Vénézuéliennes: Zanthoxylum rhoifolium et Trattinickia rhoifolia" (S. Quideau) PCP, cosupervised with the University of the Andes, Mérida, Venezuela
- Marie-Charlotte LECHNER "Synthèse et utilisation d'architectures multimériques peptidiques comme outils d'étude des mécanismes d'activation du récepteur à domaine de mort DR5" (G. Guichard) Strasbourg University, MNERT grant
- Edith CHARDON "N-Heterocyclic Carbene Complexes : Toward Innovative Anticancer Agents" (G. Guichard/S. Bellemin-Lapponaz) Strasbourg University, MNERT grant
- Chiara PASCALI "Identification à l'échelle génomique de génes transcrits par deux isoformes de l'ARN polymérase III humaine" (M. Teichmann/ G. Dieci) University Bordeaux Segalen, French-Italian University grant

Besides training PhD students in the labs, IECB researchers contribute to various bachelor and master's courses of the Université Bordeaux 1 and the Université Bordeaux Segalen. In 2011, they provided over 1600 hours of teaching.

The IECB technology platform in structural biology acquired in 2011 a last generation surface plasmon resonance (SPR) instrument : the Biacore T200.

Technology platforms

Dr. Brice Kauffmann
Head of IECB's technology platform in structural biology (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

Gan Q., Shang J., Kauffmann B., Wang Y., Bie F., Jiang H. (2011) A highly stable double helix of aromatic oligoamide comprised of fused ring aromatic units, Tetrahedron, Available online 1 December 2011.

Nelli Y.R., Douat-Casassus C., Claudon P., Kauffmann B., Didierjean C., Guichard G. (2011) An activated building block for the introduction of the histidine side chain in aliphatic oligourea foldamers, Tetrahedron, Available online 29 November 2011.

Commandeur C., Commandeur M., Bathany K., Kauffmann B., Edmunds A.J.F., Maienfisch P., Ghosez L. (2011) Study of the oxidation of 3-hydroxypyrroloindoles to pyrrolobenzoxazine alkaloids, Tetrahedron, Volume 67, Issue 51, 23, pp 9899-9908.

Grosjean A., Daro N., Kauffmann B., Kaiba A., Létard J.F., Guionneau P. (2011) The 1-D polymeric structure of the [Fe(NH2trz)3](NO3)2•nH2O (with n = 2) spin crossover compound proven by single crystal investigations. Chem Commun (Camb). 7;47(45):12382-4.

Vives G., Giansante C., Bofinger R., Raffy G., Del Guerzo A., Kauffmann B., Batat P., Jonusauskas G., McClenaghan N.D. (2011) Facile functionalization of a fully fluorescent perfluorophenyl BODIPY: photostable thiol and amine conjugates. Chem Commun(Camb). 2011 Oct 7;47(37):10425-7.

Stern E., Goossens L., Retailleau P., Kauffmann B., Bonte J.P., Depreux P., Goossens J.F. (2011) Preparative enantiomeric separation of new selective CB2 receptor agonists by liquid chromatography on polysaccharide-based chiral stationary phases:determination of enantiomeric purity and assignment of absolute stereochemistry by X-ray structure analysis. Chirality. 23(5):389-96.

Structural biology

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

Services and expertise of IECB's structural biology Platform

cgfb BIOLOGIE STRUCTURALE

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

I E C B

cgfb BORDEAUX FUNCTIONAL GENOMIC CENTER

Liquid/solid NMR

Services and expertise

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

Equipment

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

Technical contacts

Axelle Grélard, a.grelard@iecb.u-bordeaux.fr
Cécile Courrèges, c.courreges@iecb.u-bordeaux.fr

Scientific expertise

Erick Dufourc, e.dufourc@iecb.u-bordeaux.fr
Cameron Mackereth, c.mackereth@iecb.u-bordeaux.fr
Gilmar Salgado, g.salgado@iecb.u-bordeaux.fr

Electron microscopy

Services and expertise

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

Equipment

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

Main contact

Alain Brisson, a.brisson@iecb.u-bordeaux.fr

Surface plasmon resonance (SPR)

Services and expertise

- Informations: interactions (yes or no answer), affinity, binding kinetics, thermodynamics (5°C to 40°C), stoichiometry and active concentrations.
- Samples: proteins, nucleic acids, small molecules (not limit for organic molecules), liposomes, bacteria, extracts.
- Recovery function: the instrument can recover compounds bound to the functionalized surface.
- Sensorchips are available for the immobilisation of compounds via thiol, amines, aldehyde functions, for streptavidin/biotin coupling, Tag-HIS and liposomes capturing.
- Measured parameters: association rate constants 10^3 to $3x10^9$ $M^{-1}s^{-1}$ for proteins, 10^3 to $5x10^7M^{-1}s^{-1}$ for LMW molecules; dissociation rate constant 10^{-5} to 1 s^{-1}; sample concentration ≥ 10 pM.
- Baseline noise: typically < 0.03 RU (RMS)
- Baseline drift: typically < 0.3 RU/min
- Immobilized interactant consumption: typically 0.03 to 3 µg/flow cell.

Equipment

Biacore 3000 and Biacore T200

Main contact

Carmelo Di Primo, carmelo.diprimo@inserm.fr

Mass spectrometry

Services and expertise

- Small molecules (exact mass)
- Small molecules (low resolution)
- Polyphenols
- Peptids
- Lipids
- Antimicrobial substances
- Nucleic acids
- Compounds of organic synthesis

Equipment

- LCT Premier
- LCQ Advantage: available for external user 50% of its operation time
- Reflex Bruker

Scientific expertise

Schmitter Jean-Marie, jm.schmitter@cbmn.u-bordeaux.fr

Molecular modeling

Services and expertise

- Molecular Dynamics of supra- molecular assemblies
- Drug design of bio-active molecules (agonists or antagonists) within biologic complex process.

Equipment

Cluster IBM with 66 processors Intel Xeon 2.8Ghz and 17 Go RAM

- 1 Transtec blade with 32-core AMD Opteron Processor 6136 2.4Ghz and 256 Go RAM
- 1 Transtec blade with 24-core AMD Opteron Processor 6168 1.9 Ghz and 32 Go RAM
- 2 Advanced Capacities blades with 48-core AMD Opteron Processor 6172 2.1 Ghz and 64 Go RAM
- 3 Transtec blades with 48-core AMD Opteron Processor 6168 1.9Ghz and 64 Go RAM

Other :

- Storage Serveur Facility DAS raid 6 with 162 To raw (140 To real) - to securely store simulations and experimental results during 3 to 5 years max.

Softwares :

- Installed Molecular Dynamics Softwares : GROMACS, NAMD, AMBER, CHARMM and DESMOND from Schrödinger Inc.
- Installed Molecular Mechanics and Drug-Design Softwares : DOCK, AUTODOCK, VINA + group-licence for MACROMODEL from Schrödinger Inc.
- several licences and modules of DISCOVERY STUDIO 2.1 from Accelrys Inc.
- In-house Softwares (Molecular Lipophilicity, sdorted or selected protein or molecule data bases, ...)

Main contact

Michel Laguerre, m.laguerre@iecb.u-bordeaux.fr

Crystallogenesis

Services and expertise

- Robotised crystallogenesis (screening and optimization of crystallization conditions)
- Crystallogenesis of membrane proteins in mesophase
- Crystallogenesis of supramolecular self-assemblies

Equipment

- Robot Cartesian Honeybee 961 Genomic solutions
- Robot Mosquito TTP Labtech
- Robot Beckman Coulter Biomek NX
- Robot Beckman Coulter Biomek 3000 equiped with a micro-seringe for pipeting small volumes of viscous solutions (crystallization in mesophase...)

Technical contact

Brice Kauffmann, b.kauffmann@iecb.u-bordeaux.fr

Scientific expertise

- Supramolecular assemblies/foldamers - Ivan Huc, i.huc@iecb.u-bordeaux.fr
- Macromolecules - Sébastien Fribourg, sebastien.fribourg@inserm.fr

X-ray diffraction and diffusion

Services and expertise

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

Equipment

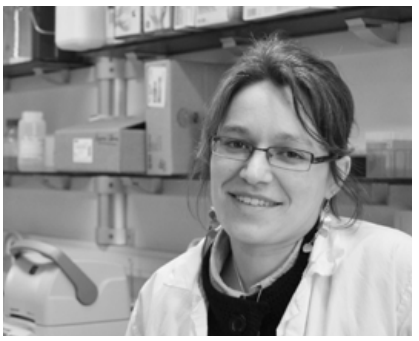
- Microfocus rotating anode Rigaku MM07 800W
- Microfocus rotating anode Bruker Microstar 2.7kW (macromolecules)

Technical contact

Brice Kauffmann, b.kauffmann@iecb.u-bordeaux.fr

Scientific expertise

- Small organic molecules/foldamers - Ivan Huc, i.huc@iecb.u-bordeaux.fr
- Small organic molecules - Jean-Michel Léger, jean-michel.leger@u-bordeaux2.fr
- SAXS/WAXS - Reiko Oda, r.oda@iecb.u-bordeaux.fr
- Macromolecules - Sébastien Fribourg, sebastien.fribourg@inserm.fr



Sabrina Rousseau
Head of IECB's technology platform in preparative and analytical techniques (IE), Inserm, UMS 3033/US001

Sabrina Rousseau graduated from the University of Brest (UBO) with a Master of Cell Biology and Physiology in 2004. She joined the European Institute of Chemistry and Biology in November 2007 as manager of the preparative and analytical facility in biology.

Contact
s.rousseau@iecb.u-bordeaux.fr

Preparative & analytical techniques

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

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

Cell biology	Flow cytometry Confocal microscopy
Molecular biology	Cloning Genotyping Site directed mutagenesis
Preparative biochemistry	Protein expression assay Protein production and purification
Other services	Generation of cDNA libraries Purification of oligonucleotides

cgfb BIOLOGIE STRUCTURALE

Flow cytometry

Service / expertise
The flow cytometer is equipped with 3 lasers and allows counting, examining and sorting microscopic particles or suspended cells in a fluid stream. Two types of services can be performed by flow cytometry: analysis or sorting of cells.

Equipment
High-speed sorter: FACSAria (Becton Dickinson)
Specifications: High speed sorting
- 3 solid lasers: 488nm, 633nm et 407nm
- High-speed digital acquisition : 70,000 evt/s
- Multicolor analysis of up to 15 parameters
- Sorting up to 4 simultaneous populations
- Sorting in tubes, plates or slide through the ACDU system

Technical contact
Sabrina Rousseau, s.rousseau@iecb.u-bordeaux.fr

Confocal microscopy

Equipment
Confocal microscope Carl Zeiss: LSM 510 equipped with the Imaris software.
Description:
- Confocal videomicroscopy
- FRAP (Fluorescence Resonance Energy Transfert)
- FRET (Fluorescence Recovery after photobleaching)
- IRM (Interference Reflection Microscopy)

Technical contact
Sabrina Rousseau, s.rousseau@iecb.u-bordeaux.fr

Scientific expertise
Elisabeth Génot, e.genot@iecb.u-bordeaux.fr

Molecular biology

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

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

Technical contact
Sabrina Rousseau s.rousseau@iecb.u-bordeaux.fr

Scientific expertise
Sébastien Fribourg, sebastien.fribourg@inserm.fr

Preparative biochemistry

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

Equipment
- Centrifuges:
  - AVANTI J26XP (Beckman coulter) equipped with rotors JLA 8.1000, JA25.50.
  - 5804R (Eppendorf) equipped with: swinging bucket rotor for plates A-2-DWP, Standard rotor for 1,5/2ml tubes FA-45-30-11, Rotor F-34-6-38 (Adaptator for 15ml, 15-18ml or 50ml tubes).
  - 5418 (Eppendorf) equipped with Rotor for 1,5/2ml tubes FA-45-18-11
- Ultracentrifuges:
  - OPTIMA-L80XP (Beckman coulter) equipped with rotors SW40Ti, 50.2 Ti.
  - OPTIMA MAX (Beckman coulter) equipped with rotors: TLA 120, MLS 80, MLA 80.
- Bacterial refrigerated incubator: MaxQ 6000 (Thermofisher).
- Bacterial incubator: StabiliTherm (Thermofisher).

Technical contact
Sabrina Rousseau, s.rousseau@iecb.u-bordeaux.fr

Scientific expertise
Sébastien Fribourg, sebastien.fribourg@inserm.fr

Other services

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

Technical contact
Sabrina Rousseau, s.rousseau@iecb.u-bordeaux.fr

Scientific expertise
Sébastien Fribourg, sebastien.fribourg@inserm.fr

In November 2011, a new visiting scientist joined the IECB: Dr. Andrew Goldsborough. Within the past 15 years, this British biologist submitted over 30 patent applications and created 3 biotech companies. Specialized in RNA stabilization techniques, he intends to start a new company by 2013.

Technology transfer & start-ups

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

Collaborative research

Servier, Sanofi-Aventis, LVMH, EDF, Conseil Interprofessionnel du Vin de Bordeaux, ... Several key industry players work with IECB teams. In 2011, the institut totalized more than 10 ongoing projects with industrial partners.

Contract services and consulting

The IECB brings together a wide range of scientific equipments and expertise in chemistry and biology. Such resources are made available to public and private research centers through IECB's technology platform in stuctural biology and the preparative and analytical techniques facilities.

Technology transfer

IECB researchers are strongly encouraged to patent their discoveries. In 2011, 3 additional patents were submitted by team leader Gilles Guichard, Jean-Louis Mergny, Elisabeth Génot and Stéphane Quideau. A technology transfer unit, Novaptech, was also created in 2008 by an IECB team leader (see on the right).

Incubating start-ups

IECB has a 300m2 work space dedicated to start-ups. This area is presently occupied by Fluofarma. This company, which was created in 2003 by two team leaders from the IECB, has seen its turnover grow by 412% over the past 5 years and has now a staff of 23 people.

FLUOFARMA

Created in 2003 by former IECB team leaders, Fluofarma is a start-up company specialized in High Content Screening (HCS), a powerful drug discovery method that combines the highest level of information from cell biology experiments with industrial throughput and standards. The company, which has now a customer portfolio including more than 40 clients worldwide, increased its turnover by 30% in 2010 and was awarded 2 regional prizes from Ernst&Young and Oséo. This knowledge-based company also maintains collaborations with IECB teams to improve its technology.

What is Fluofarma's High Content Screening (HCS)?

Fluofarma's HCS technology is based on modern cell biology methods; it allows the simultaneous detection of multiple precise molecular and phenotypic cellular events. Fluofarma HCS technology is optimized for a wide range of substrates. Numerous cell lines are available along primary cell cultures and 3D microtissues in order to increase the relevance of the experiments, and thus providing the most predictive results possible. The automation process allows a high throughput analysis of a whole population at the single cell level, exceeding the industrial requirements.

Fluofarma divisions:

Bioengineering	Development of new cell-based assay / Customization of cell-based assay / Miniaturization of cell-based assay / Mechanism Of Action studies
Bioscreening	Off-the-shelf cellular assays (over 500 entries) / Disease-oriented screening / Predictive toxicology
Biocomputing	Custom-tailored data analysis / Development of new image analysis software

Jean-Baptiste Pin
Fluofarma CEO

Year of creation 2003

Staff 23

2011 turnover 2.2 M euros

Collaborative projects with IECB teams in 2011 3

Website www.fluofarma.com

NOVAPTECH

Aptamers are relevant biotechnological tools in many fields : health, cosmetics, environmental sciences (enzyme inhibitor, label, probe, biosensor...). In 2005, the IECB team "Small RNA & Aptamers" (INSERM U869) assembled the first automated platform for aptamer selection in France, an equipement that speeds up the selection from 3 months to 2 weeks. In order to develop biotechnological applications of aptamers, the team created Novaptech, a technology transfer unit associated to the lab. Since, Novaptech's has been collaborating with academic and private labs, using aptamer-based tools against proteins, peptides, small molecules, toxins or nucleic acids :

Service agreements

- Identification of aptamers (RNA, DNA, chemically modified oligonucleotides) through an automated in vitro process)
- Optimization of selected aptamers by minimizing their size and improving nuclease resistance,
- Conjugation of aptamers to biotin, fluorophore, amine, thiol groups.

Biotechnological development of aptamers

- Development of new tools in analytical, diagnostic (sensoring. imaging) or therapeutic fields.

Collaborative research projects

- Implementation of new strategies to promote and develop the use of aptamers
- Improvement of the automated platform by developing new procedures and components.

Dr. Sonia Da Rocha Gomes
Novaptech Executive Manager

Year of creation 2008

Staff 4 (3 cdi, 1 cdd)

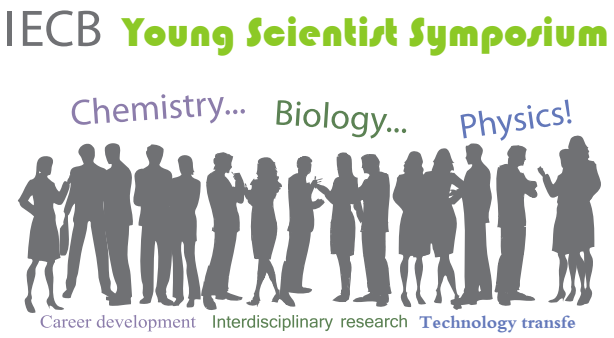
Collaborative projects with IECB teams in 2010 2

Contact sonia.darocha@novaptech.com

On October 6th 2011, the IECB organized its 4th *Looking to the Future* workshop. The 10 preselected candidates for group leader positions at IECB who participated in the workshop were coming from the most prestigious international institutions: the ETH in Switzerland, the MRC and the Universities of Oxford and Cambridge in the UK, and the Yale University and the MIT in the US.

Scientific events

IECB workshops & symposia



IECB Young Scientist Symposium, May 19-20

International and interdisciplinary events for young research organized by the PhD students and post-doctoral fellow of the IECB with the support of the Interbio project.

110 young biologists, chemists and physicists from Barcelona, Bordeaux, Toulouse, Lisbon and Valencia attended this event. They presented 15 short talks and 26 posters over 2 days.

3 keynote speakers working in the academia and in technology transfer were invited to discuss the various career paths avaible after a PhD.

Interbio week at IECB, June 26-30

3 Interbio events organized by the IECB within a week:

- *Symposium Interbio Rethinking targets for therapeutic intervention* on June 26th-28th

- *Workshop Interbio Microfluidics, from single molecule to cell biology* on June 29th

- *3rd Bordeaux RNA Club Annual Workshop* on June 30th

The Interbio week was attended by more than 250 researchers and entrepreneurs from South-West Europe. 38 international speakers participated in the event. Learn more at www.iecb.u-bordeaux.fr/interbioweek/

IECB: Looking to the Future, October 6

Speakers:

- Dr. Vass Bavro, Dept. of Physics, University of Oxford, UK
- Dr. Axel Innis, Yale University, Center for Structural Biology, USA
- Dr. Valérie Gabelica, Physical Chemistry and Mass Spectrometry Laboratory, University of Liège, Belgium
- Dr. Franck Artzner, Institut de Physique de Rennes, Université Rennes 1, France
- Dr. Zbigniew Lech Pianowski, Laboratory of Organic Chemistry, ETH Zurich, Switzerland
- Dr. Anthony Bugaut, University of Cambridge, Department of Chemistry, UK
- Dr. Razvan Nutiu, Massachusetts Institute of Technology, USA
- Dr. Maria Antonietta Cerone, Breakthrough Breast Cancer Research Centre, The Institute of Cancer Research, UK
- Dr. Ana O'Loghlen, MRC Clinical Sciences Centre,Imperial College Faculty of Medicine, UK
- Dr. Giovanni Stefani, Yale University, Department of Molecular, Cellular and Developmental Biology, USA

IECB group leaders'seminar, October 7

Term of tenure seminar:

- Alain Brisson (CNRS/UB1 UMR5248) 'Highlights and vicissitudes of 10 years of research"

Laureates of IECB's 2008 internal call for proposals:

- Dr. Sébastien Fribourg (Inserm/UBS U869) "Functional and structural study of RNA Polyme¬rase III specific subunits"
- Pr. Jochen Lang (CNRS/UB1 UMR5248) "Dynamics of SNARE transmembrane domains and exocytosis"

Other scientific events at IECB

France-Japan Workshop

Bio-inspired approaches: Micro- & Nano-Architectures, Materials & Imaging

France-Japan Workshop on Bio-inspired approaches: Micro- and Nano- Architectures, Materials & Imaging, October 11-12

30 senior scientists from the *Japanese Strategic Alliance Project for the Creation of Nano-Materials, Nano-devices and Nano-systems* were invited at IECB over two days to meet their French counterparts in Bordeaux. The meeting was attended by 80 participants. z55 posters were presented.

Workshop on Dynamic Molecular Nanostructures (Marie Curie ITN DYNAMOL), November 8-9

60 attendees. Invited speakers:

- Luisa De Cola, Univ. Munster, Germany
- Sijbren Otto, ,Univ. Groningen, The Netherlands
- Milko van Derboom, Weinzman Inst., Israel
- Stefan Kubik, Univ. Kaizerslautern, Germany
- Elwin Vrouwe, Micronit, The Netherlands
- Aldrik Velders, Univ. Twente, The Netherlands
- Olof Ramstrom, KTH, Sweden
- Ivan Huc, Univ. Bordeaux, France
- Gérard Bricogne, Global Phasing, UK
- Ulrich Lüning, Univ. Kiel, Germany
- Jonathan Nitschke, Univ. Cambridge, UK
- Kay Severin, EPFL, Switzerland

RNA CLUB Bordeaux

RNA Club, March 17

60 participants. Invited speakers:

- Ciarán Condon, CNRS UPR9073 Institut de Biologie Physico-Chimique (IBPC), Paris, France
- Bernard Rayner, INSERM U869, Université Bordeaux Segalen, France
- Vincent Parissi, Laboratoire MCMP, UMR 5234 CNRS-Université Bordeaux Segalen, France
- Galina Boldina, IECB/INSERM U869/Univ. Bordeaux Segalen, France
- Anne-Lise PEILLE, INSERM U916 VINCO, Bergonié Institute, Bordeaux, France

Club Meccainno, March 11

NanoSWEC Workshop "Bioinspired nanosystems and nanomaterias!", November 14-17

Journée SFR Tecsan, November 2011

Attended by 70 scientists from Bordeaux.

RNA Club, RNA & Development, December 8

60 participants. Invited speakers:

- Dr. Denis Dupuy, Inserm U869/IECB, France
- Dr. Shona Murphy, Oxford University, England
- Dr. Pierre Thiebaud, UMR5164 CNRS, Bordeaux, France
- Dr. Jérôme Cavaillé, LBME, Toulouse, France

Seminars

1. Prof. Martin Teichmann (ARNA & IECB) "Regulation of RNA polymerase III transcription during differentiation and transformation of human cells"
2. Prof. Andrew Sewell (Cardiff University School of Medicine) "Four different clinical applications of enhanced T-cell receptor/antigen interactions"
3. Dr. Christophe Demaille (UMR LEM, Université Paris-Diderot) "Probing the Distribution and Conformational Dynamics of Surface-Immobilized Redox-Tagged Macromolecules using Electrochemical-Atomic Force Microscopy (AFM-SECM)"
4. Dr/ Cameron Mackereth (ARNA & IECB) "Using NMR spectroscopy to discover how proteins stick together, move around, and target mRNA"
5. Dr. Didier Auboeuf (Inserm U590, Centre Léon Bérard, Lyon, France) "Alternative splicing and tumor growth"
6. Dr. Anne-Ruxandra Carvunis (CCSB/ Dana-Farber Cancer Institute, Harvard Medical School, Boston) "From proteins and their interactions to evolutionary principles of biological systems"
7. Prof. Marcel Hibert (Université de Strasbourg) "The screening strategy in an academic environment : scientific and therapeutic outcome"
8. Dr. Edouardo Angles-Cano (INSERM U-919, Serine Proteases in Neurovascular Pathology, Caen) "Cellular microvesicles, new proteolytic messengers, effectors and potential biomarkers"
9. Dr. Redouane Borsali (CERMAV-UPR5301, Université Joseph Fourier) ""Sweet" nanoparticles and nano-structured thin glycofilms"
10. Dr. Atsushi Hozumi (National Institute of Advanced Industrial Science and Technology, Tsukuba, Japan) "Designing surface molecular architecture for control of motion of liquids"
11. Dr. Satoshi Nishimura (National Institute of Advanced Industrial Science and Technology, Tsukuba, Japan) "Electrokinetic Coupling in Alignements of Colloidal particles under AC Electric Field"
12. Prof. David Vocadlo (Department of Chemistry, Simon Fraser University, Vancouver, Canada) "Controlling O-GlcNAc processing enzymes in cells and tissues using chemical biology"
13. Dr. Peter Hamley (Sanofi-Aventis Deutschland GmbH) "Accelerating Drug Discovery through High Throughput Chemistry"
14. Prof. Masatsugu Shimomura (Advanced Institute for Materials Research, Tohoku University, Japan) "New Trends in Biomimetics: Mariage of Self-organization Nanotechnology and Biological Diversity"
15. Prof. Takehiko Wada (Advanced Institute for Materials Research, Tohoku University, Japan) "Novel strategy for cancer cell specific oligonucleotide therapeutics using Peptide Ribonucleic Acids (PRNA)"
16. Prof. Chris Meier (University of Hamburg) "Chemistry meets Biology – Nucleoside analogs, prodrugs of phosphorylated nucleosides and chemically damaged oligonucleotides"
17. Prof. Wim DeHaen (K. U. Leuven, Belgique) "Helicenes based on heterocyclic building blocks"
18. Prof. Olivier Baudoin (Université Lyon 1 – CPE Lyon) "Pallado-catalyzed functionalization of unactivated C(sp3)-H bonds"
19. Dr. Moganty R. Rajeswari (All India Institute of Medical Sciences, New Delhi) "Triplex DNA in pathogenesis and therapy"
20. Dr. Stefan Bellevik (Société Quiagen) "PCR Array SABiosciences: Une solution complète et validée pour l'étude de voies de signalisation et la recherche de biomarquers"
21. Dr. William McKenna (Department of Molecular, Cell & Developmental Biology, University California, Santa Cruz) "Tbr1 and Fefzf2 regulate alternate neuronal identities during early cortical development"
22. Dr. Franck Artzner (UMR CNRS 6626, Université Rennes 1, France) "Biomimetic assemblies: mechanisms, morphological control and applications"
23. Prof. Herbert Waldmann (MPI of Molecular Physology, Dortmund) "Biology Oriented Synthesis (BIOS)"
24. Dr. Vincent Postis (Univ. Leeds, UK) "Membrane biology in the genomics era: Class 2A transporter from gene to structure"
25. Prof. Evan A. Evans (Boston University, USA) "Using tension to probe free energy landscapes governing symmetry breaks and nucleation of nanopores in fluid-lipid membranes"
26. Prof. Claudio Toniolo (University of Padova, Italy) "The 3-10 helix, an old but re-emerging polypeptide conformation: 3D-structural and spectroscopic characterizations, and recent applications"
27. Prof. David Perrin (UBC, Vancouver) "DNAzymes with an Expanded Catalytic Repertoire: Cleaving RNA with Imidazoles, Amines and Guanidines in the absence of Mg2+"
28. Prof. Victoria Birkedal (Interdisciplinary Nanoscience Center, Aarhus University, Denmark) "Insights into the conformations of DNA and RNA nanostructures from single molecule fluorescence studies"
29. Dr. Martine Simonelig (Institut de Génétique Humaine de Montpellier) "mRNA regulation by deadenylation and small non-coding RNA during Drosophila early development"
30. Prof. V. Tsuruk (School of Materials Science and Engineering, Georgia Institute of technology, Atlanta) "Learning from Nature for better sensing"
31. Dr. Cedric Soler (Institut de Génétique Humaine, CNRS UPR 1142, Montpellier, France) "Ubiquitin Proteasome pathway implication in a Drosophila model of muscular dystrophy (OPMD)"
32. Dr. Juan Cortés (LAAS-CNRS, Toulouse) "Simulating molecular motions with robotics-inspired algorithms. Control of enzyme selectivity by engineering the substrate binding site and access channel"
33. Prof. Dr. Thomas Wirth (School of Chemistry, Cardiff University) "Advanced Concepts for Catalysis in Microreactors and Synthesis"
34. Prof. Jochen Lang (CBMN & IECB) "The sweets of cell biology: From regulated membrane fusion to biosensors"
35. Dr. Claudio Gomes (Instituto Tecnologia Quimica e Biologica (ITQB/UNL), Universidade Nova de Lisboa, Portugal) "Protein deposition pathways in the unique chemical biology of the synaptic milieu"
36. Prof. Jonathan Hall (ETH – Zürich) "RNA Drugs and Targets"
37. Dr. Andrew Goldsborough (Cyclops Genome Sciences, Ltd.

Cambridge, UK) "Customizing the biophysical properties of RNA using chemical modification of the 2'-OH"

38. Dr. Valérie Marchi-Artzner (CNRS – Université de Rennes) "Surface chemistry and Nanochemistry applied to biology and nanostructured materials"
39. Prof. Hirotaka Ihara (Kumamoto Univ., Japon) "Profile of Glutamide Unit as Versatile Self-assembling Tool"
40. Dr. Anne Laurencon (CNRS- Univ. Lyon) "DNA damage checkpoints and genome stability in Drosophila melanogaster"
41. Dr. Rémi Fronzes (Institur Pasteur) "DNA transfer across the bacterial cellular envelope"
42. Dr. Naohiro Kameta (National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Japan) "Construction of Self-Assembled Organic Nanotubes and Exploitation of Their Liquid-Phase Nanospaces"
43. Prof. Donal O'Shea (University College Dublin, Ireland) "BF2-Tetraarylazadipyrromethenes as Near Infrared Fluorescence Imaging and Photodynamic Therapeutic Platforms"
44. Prof. Julian Eastoe (Bristol University, UK) "New surfactants to turn carbon dioxide into a working 'green' solvent"
45. Prof. Ilhyong Ryu (Osaka University, Japan) "Some Unique Radical and Organometallic Reactions Using Metal Hydrides"
46. Prof. Jean-Louis Reymond (Univ. Bern, Switzerland) "Chemical Space as a Source for New Drugs"
47. Dr. Emilie Montembault (IECB) "Nessun Dorma, a pectate lyase-like protein, is required for the stability of Drosophila male and female ring canals"
48. Prof. Janez Plavec (NMR centre, National Institute of Chemistry, Ljubljana, Slovenia) "NMR studies of cation localization and movement within G- quadruplexes of different topologies"
49. Prof. Erik Goormaghtigh (Université Libre de Bruxelles, Center for Structural Biology and Bioinformatics) "Protein structural changes monitored by ATR-FTIR"
50. Dr. Eric Freyssingeas (Laboratoire de Physique de l'ENS de Lyon) "Evolution of the Global Internal Dynamics of a Living Cell Nucleus during Interphase"
51. Prof. B. Deplancke (Institute of Bio-engineering and School of Life Sciences, EPFL, Switzerland) "Deciphering the metazoan regulatory code"
52. Dr. Marc Boudvillain (Centre de Biophysique Moléculaire, Orléans) "Mechanism and regulation of transcription termination factor Rho, an atypical RNA helicase from bacteria"
53. Dr. Hervé Moine (IGBMC, Strasbourg) "Functions of the FMRP protein in the regulation of neuronal mRNA metabolism"
54. Dr. Bruno Kieffer (IGBMC, Strasbourg) "Subtle regulation mechanisms of Nuclear Receptors function : an NMR view"
55. Prof. Romano Regazzi (Université de Lausanne) "Emerging roles of microRNAs in the control of pancreatic beta cell functions"
56. Dr. Gilles LABESSE (Centre de Biochimie Structurale, Montpellier) "Using comparative docking for drug design"