# Institut Européen de Chimie et Biologie

European Institute of Chemistry and Biology

I E C B

# SCIENTIFIC REPORT 2010

UNIVERSITÉ DE BORDEAUX

Inserm

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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 "Cellule Hôtels à Projets" of the CNRS, with 17 research teams accounting for more than 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 25 people.

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Michel Laguerre (structure of the auto-inhibited dimer of the human kinase PDK),
Yves Théobald (building, portraits), François Quenet (building, portraits).

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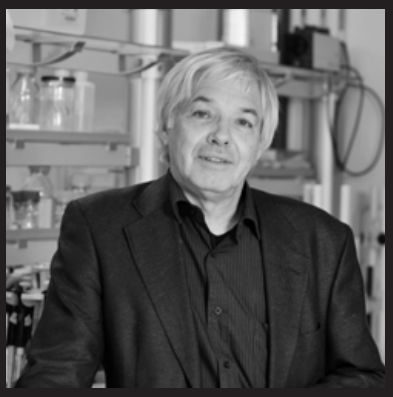
# Director's foreword

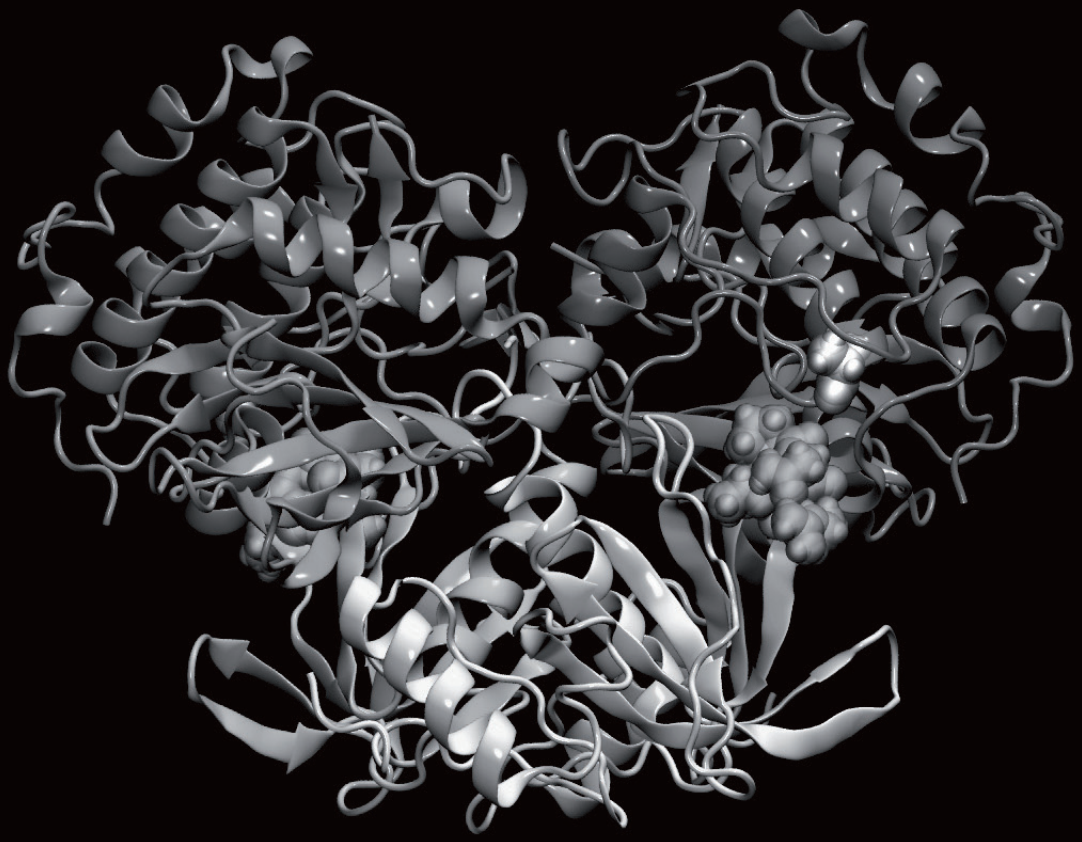


In 2010, IECB scientists were extremely productive and several seminal papers in top-notch journals were published over the year. Martin Teichmann identified a novel isoform of the human RNA polymerase III that is a signature of tumor cells. These results, published in the Proceedings of the National Academy of Sciences of the USA, were supplemented by a collaborative work with Sébastien Fribourg that describes the structure of a Pol III subunit (Nature Structural and Molecular Biology). The two teams are now taking this collaboration further, working on a subcomplex of the same enzyme. Denis Dupuy developed a very powerful tool for selecting C. elegans mutants with antibiotics, as routinely done for bacteria (Nature Methods). This opens up new avenues for unraveling regulatory networks of gene expression at the post-transcriptional level. Pier-Vincenzo Piazza contributed to two major papers showing that drug addiction is associated with impairment of synaptic plasticity (Science) and that the endocannabinoid system controls the stimulated food intake (Nature Neurosciences). Last but not least, Ivan Huc, who shares with me the IECB direction, co-authored a paper in Nature Chemistry in which a dynamic self-assembled system involving a foldamer contributes to a cascade of transformations triggered by an external signal. Other IECB teams also contributed to many high-quality publications that the reader will discover in the following pages of this report.

I would also like to highlight here some of the milestones that paved IECB's life in 2010. I was delighted to welcome a new member to the International Scientific Advisory Board (ISAB): Professor Roeland J. M. Nolte from the University of Nijmegen, Netherlands, a specialist in physical-organic and supramolecular chemistry. Upon the ISAB recommendation, a new group leader joined the institute in October 2010, Elisabeth Garanger, who brings her expertise on peptide-based polymer synthesis for the design of nanomaterials. She is affiliated to the LCPO laboratory, a new partner for institute. IECB is now hosting teams from six different biology or chemistry units of the University of Bordeaux, and is thus actively contributing to interdisciplinary networking. On the other hand, in accordance with IECB's funding principles, Pr. J. Lang and Dr. P.V. Piazza left the Institute after respectively ten and six years of hard and fruitful research. I thank them for their contribution to the spirit of IECB and wish them great success at the University of Bordeaux.

After twelve years of hard work (fight?), the IECB concept – a combination of traditional values from the French research system and of principles inspired from successful experiences in other countries (strong commitment of ISAB, autonomy of group leaders, encouraged mobility) – has demonstrated its worth for erecting an attractive and high-standard research institute. At the end of 2010, seventy per cent of IECB group leaders were trained outside Bordeaux and one third were of non-French origin. I am very proud to be at the head of this Institute, among young, energetic and talented scientists that make IECB a center of excellence for interdisciplinary research. I warmly thank all those – researchers, technicians, trustees, sponsors, with a special word for the Regional Council of Aquitaine – that make it exciting every day.

Dr. Jean-Jacques Toulmé



# Highlights


## IECB enters the TGIR-RMN network with its 800MHz NMR spectrometer

In 2009, IECB entered the TGIR-NMR (NMR Very Large Scale Facilities) with the acquisition of a high-field 800 MHz liquid/solid NMR spectrometer. The magnet itself had already provided excellent service for a decade at the ICSN in Gif-sur-Yvette. With the support of the Aquitaine Regional Council, the CNRS and the Universities Bordeaux Segalen and Bordeaux 1, the spectrometer was tuned-up and upgraded with a new console and cryoprobe before being installed at IECB in December 2009.

Being part of the TGIR-RMN network, the instrument is now made accessible to the French scientific community 30% of its operation time. Advanced technical and scientific expertise in fields such as biology, chemistry and physics is also provided through local associated research teams from IECB and CBMN (UMR 5248). Experiment proposals should be submitted online at: www.tgir-rmn.org

## Nobel Laureate 2001 Pr. Tim Hunt at IECB

In 2010, IECB group leader Derek McCusker organised a series of seminars about cell growth and cell division. The series started with Anne Royou in February (Institut Jacques Monod, Paris, at the time, group leader at IECB since March 2011) and Michel Bornens in March (Institut Curie, Paris). Derek McCusker also invited a group leader he knew during his PhD studies at Cancer Reseach UK: Tim Hunt, who was awarded the Nobel Prize in Physiology or Medicine in 2001. The conference he gave at IECB, entitled "Getting in and out of Mitosis: Setting thresholds with a protein phosphatase inhibitor", was much appreciated. "Not only has the Hunt lab contributed enormously to the cell cycle field by identifying cyclins as a key family of proteins that get cells into mitosis, but Tim then presented his new work, showing us how phosphatase activity is regulated to get cells out of mitosis. In doing so, Tim's lab has answered a major outstanding question in the field that brings our understanding of mitotic regulation full circle. This excellent work was published in December in the journal Science, so we were very lucky to hear about this work back in June at IECB" explains Derek McCusker.


## IECB "Journée Jeunes Chercheurs" approved by Interbio

In 2008, a few PhD students and post-doc researchers from IECB set up a new scientific event at the Institute: the IECB Young Scientist Symposium (Journées Jeunes Chercheurs). This event, organized by young researchers for young researchers, was aimed at promoting interdisciplinary interactions between young chemists, biologists and physicists. The Journées Jeunes Chercheurs would give them the opportunity to present their work through oral communications and posters, while 3 invited PhD graduates would speak about their career in academia, industry and the institutional sector, so as to provide information about the different career pathways available to PhD holders.
In 2010, the IECB Young Scientist Symposium, which was initially directed towards French researchers, obtained the Interbio-SUDOE label. The event, held at IECB on May 27-28th, was attended by more than 130 PhD students and post-doctoral fellows from the Interbio community (Spain, Portugal, France). Nineteen speakers contributed to the conference and 26 posters were presented. The 2011 organizing committee anticipates a similar success on May 19-20 for the 4th edition of the IECB Young Scientist Symposium.

## The Teichmann team labelised by the Ligue Contre le Cancer


Since 1999, the French charity Ligue Contre le Cancer has been awarding every year the label 'Equipe Labellisée' to about ten research teams. These teams are chosen for the quality of their research and the feasibility of their project (quality of the team and of the research facilities available on site). They receive substantial funding for at least 3 years to develop cognitive research programmes in oncology.
In December 2010, Pr. Teichmann's team (IECB– INSERM U869) was approved as 'Equipe Labellisée' by the Ligue Contre le Cancer for their project "Functional analysis of a new isoform of human RNA polymerase III with oncogenic activity". This research programme, which will provide a better understanding of tumoral transformation of human cells, will receive recurrent funding from the Ligue Contre le Cancer for the next 5 years.

## A successful first "RNAs and Cancer" seminar

80 participants attended the first seminar jointly organized by the Bordeaux RNA Club and the Cancéropôle Grand Sud-Ouest, held at IECB on December 9th 2011. This event, dedicated to RNAs and their role in cancer, was a good first step towards the development of a network of scientific and technical experts about RNAs that could create opportunities for interdisciplinary collaborative projects in cancer research. Despite unfavorable weather conditions, the event gave satisfaction to the organizers: "RNAs/Transcription is now one of the main themes within the Cancéropôle GSO's priority number 2 "Genome, structure and function". More events will be organized in the future to promote and nurture this theme" promised Karine Marendziak, from the Cancéropôle Grand Sud-Ouest.

## The Interbio network on track


In September 2009, IECB joined Interbio, a European interregional cooperation programme in the field of life sciences for health. This 3-year project, funded by European Funds for Regional Developement (FEDER), which brings together public and private institutions from the Barcelona, Bordeaux, Lisbon, Toulouse and Valencia areas, pursues three main goals: promoting interdisciplinary research, setting up a network of technology platforms and facilitating technology transfer with the view of fostering public-private partnerships in South West Europe.
IECB researchers actively contributed to the building of the network. In 2010, a delegation of 9 researchers attended the first forging partnership meeting, held in Valencia in January of that year. In April, 7 group leaders visited the ITQB, a Lisbon-based research institution with similar characteristics as the IECB. Group leaders and researchers then attended a business-to-business meeting held in Montpellier in July as well as the second forging partnership meeting, entitled "Innovation Workshop on Nanobiotechnologies and IT for health", this time held in Barcelona in October 2010. These events gave rise to two collaborative research projects between IECB and Barcelona teams and have led to the creation of an Interbio science, education and business inventory, with strong contribution from the IECB.
The IECB will continue its involvement in the Interbio network in 2011 with the organization of two major Interbio events; the IECB Young Scientist Symposium (May 19-20) and the Interbio Week at IECB (June 26-30). Finally, the institute participates in the organization of a second Interbio technology transfer meeting, to be held in Valencia, November 2011.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# Organisational structure

# BOARD MEMBERS

## International Scientific Advisory Board (ISAB)

**Pr. Iain D. CAMPBELL** Department of Biochemistry, University of Oxford, United Kingdom

**Dr. Simon CAMPBELL** Royal Society of Chemistry, London, United Kingdom

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**Pr. Bernd GIESE** Department of Chemistry, University of Basel, Switzerland

**Pr. Jean-Yves LALLEMAND** Institut de Chimie des Substances Naturelles, CNRS, Gif-sur-Yvette, France

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**Pr. Roeland NOLTE** Radboud University Nijmegen, Netherlands

**Pr. Dinshaw PATEL** Memorial Sloan-Kettering Cancer Center New York - USA

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

## Former ISAB members

**Pr. Jack BALDWIN** Department of Chemistry, University of Oxford, United Kingdom (2005-2007)

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

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

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

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

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

**Pr. Steven LEY** Department of Chemistry, University of Cambridge, United Kingdom (1999-2005)

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

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**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
- Organic & medicinal chemistry
  Pr. Léon Ghosez

### Pole 3 - Molecular Recognition

- Small RNAs & aptamers
  Dr. Jean-Jacques Toulmé
- 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

- Vesicular transport: mechanisms & regulation in pancreatic β-cells
  Pr. Jochen Lang
- Cell signalling in health & disease
  Dr. Elisabeth Génot
- Molecular basis of vulnerability to drugs
  Dr. Pier Vincenzo Piazza
- Dynamics of cell growth & cell division
  Dr. Derek McCusker
- Genome regulation & evolution
  Dr. Denis Dupuy

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## Steering Committee

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UMS 3033 / US 001

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UMS 3033 / US 001

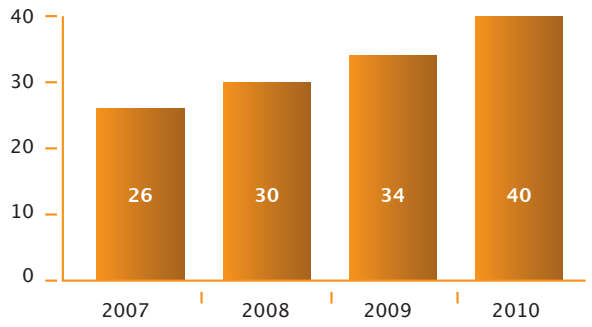
- Structural Biology
- Preparative and Analytical Techniques

## Technology Transfer & Start-Ups

- FLUOFARMA®
- NOVAPTECH

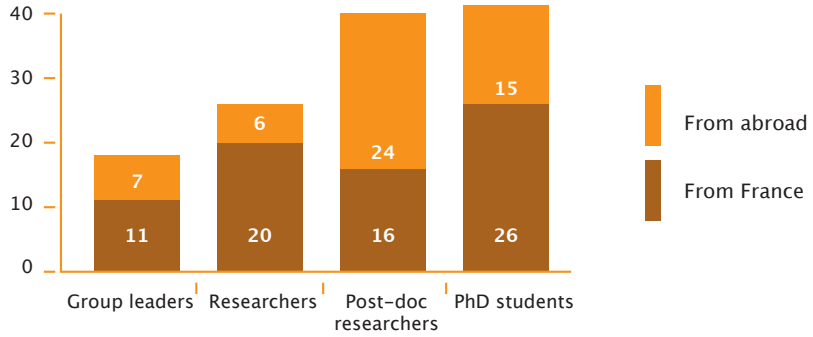
# 2010 KEY FIGURES

## Number of post-doctoral researchers over the past 4 years

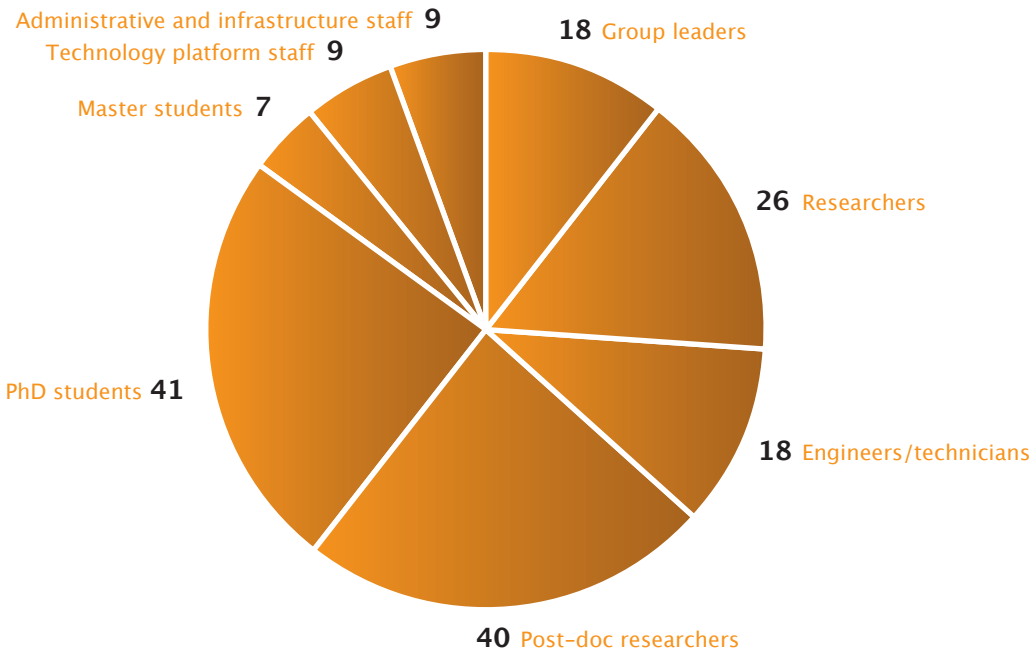



In 2010, nearly 200 people were working on the IECB site, including 168 staff and students from the institute and over 25 employees from the company Fluofarma and the technology transfer unit Novaptech. As shown on figure 1, over the past 4 years, the number of post-doctoral researchers at IECB has been appreciably growing. Young researchers (Master and Phd students, post-docs) now represent more than 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.

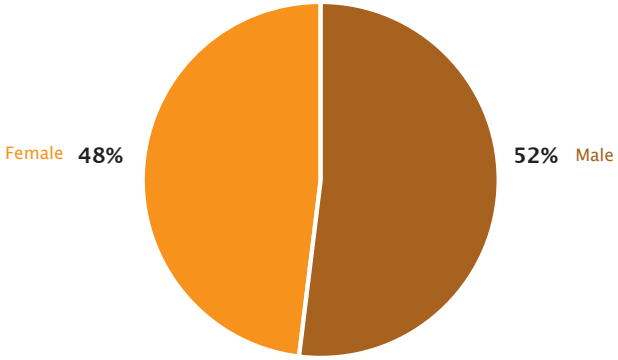
## IECB research staff by nationality and professional category



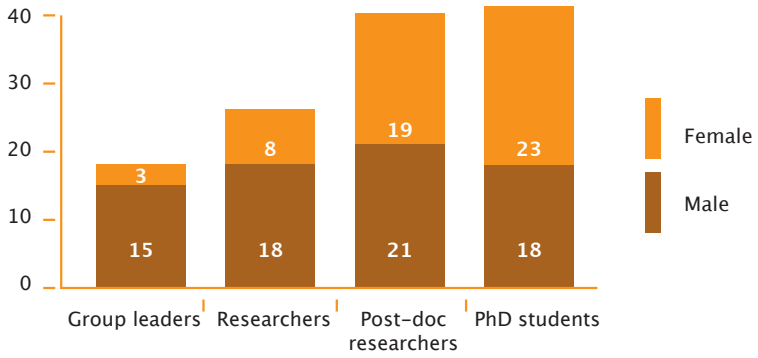

## IECB staff by professional category



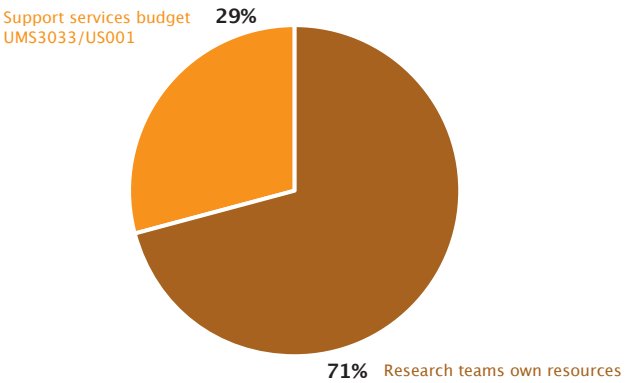
## IECB staff by gender




## IECB research staff by gender and professional category




## IECB's 2010 budget (not including permanent salaries)




IECB teams are fully independent with regards to the financial and managerial aspects of their research. As a consequence, the budget of the institute 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 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 8 permanent 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**
Annie CORREA DA COSTA, AJT, Université Bordeaux 1
**Accounting and administration officer**
Patricia MARTIN, Tech., 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
**IT technician**
Cécile RAYMOND, Tech., INSERM
**Biochemistry and molecular biology engineer**
Thierry DAKHLI, Tech INSERM
**Molecular and cell biology technician**
François PUGNAIRE, Adjt Tech., INSERM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# Research teams & output

# MOLECULAR MODELING

Dr. Michel Laguerre
Directeur de recherche (DR2), CNRS

Michel Laguerre, who graduated from the Ecole Nationale Supérieure de Chimie de 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 CNRS in 1980 and joined the Life Sciences Department at the Pharmaceutical University of 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 at the end of 1997.

## Research team

**Dr. Michel LAGUERRE** Team leader
**Dr. Juan ELEZGARAY** Senior Researcher (DR2, CNRS)
**Dr. Jean DESSOLIN** Senior Researcher (CR1, CNRS)
**Dr. Nada TAIB** Post-doc (AFM)
**Dr. Marc LAMBLIN** Post-doc (ARC)
**Dr. Chayan ACHARYA** Post-doc (E.U.)
**Dr. Pramod AKULA BALA** Post-doc (ANR)
**Jean-Michel ARBONA** PhD student (MENRT)
**Judith ELKAIM** PhD student (MENRT)
**Clément ARNAREZ** PhD student (ANR/Université Bordeaux Segalen)
**Guillaume NATURALE** PhD student (BDI co-financed CNRS/Region)
**Driss BENNANI** PhD student (Aquitaine Regional Council)
**Antoine CLEMENT** Master student

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

**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 mainly on 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 in order 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.**

Keywords / Expertise / Techniques: molecular modeling and molecular dynamics, lipidic assemblies, biomembrane models, mono- and bi-layers, micelles, membrane proteins, GPCR, building of protein models by sequence homology, apoptotic cascade, kinases and drug-design, mesoscopic or coarse-grain dynamics.

### All-atom Molecular Dynamics

The first axis encompasses mainly 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 strong 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).

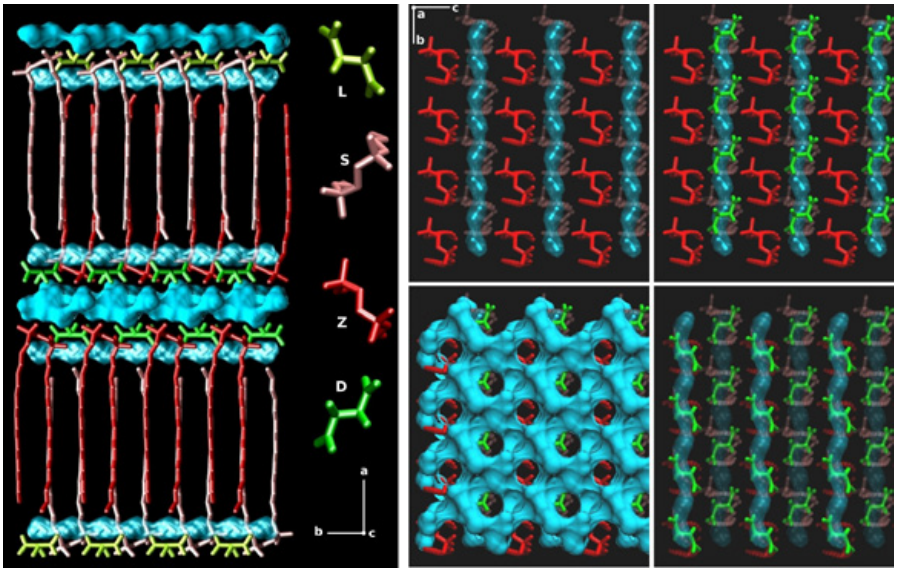


Figure 1. Final structure of the gemini tartrate film structure at an atomic level: geminis are in shade of red, tartrates in shade of green and water molecules are in blue. Tubes of aligned water molecules can be easily seen in the right panel. Between the two interdigitated layers a hexagonal lattice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

With regards to the protein axis, we have largely focused our work on kinases over-expressed in various cancers and mainly 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.
We also have considered molecular dynamics of membrane receptors in a full lipidic environment and monitoring of the drug/receptor interaction. Actually

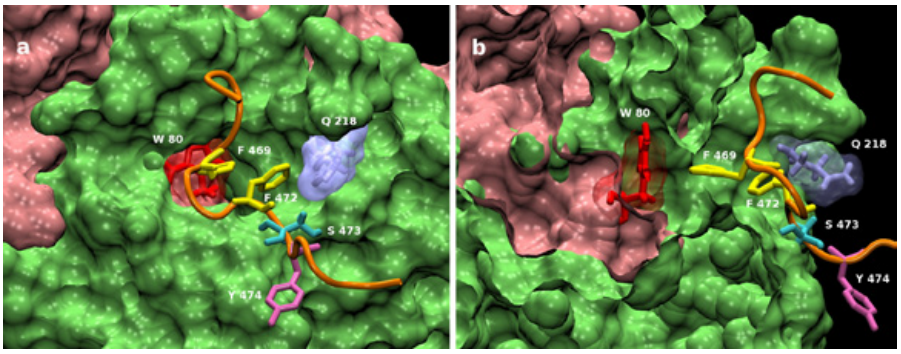


Figure 2. Complete structure of AKT-1: 2 orthogonal views of the Cterm docked on the WT PH/KIN complex : PH in pink, KIN in green, Cterm backbone in orange, W80 in red, F469 & 472 in yellow, S473 in cyan, Y474 in mauve, Q218 in aquablue. The water channel is visible in the center of the left image and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

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 has been extended now 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 search 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 and will start at fall. The subject is Helicase and this is a collaboration with Drs. P. Lestienne and J. Rosenbaum (INSERM U889).

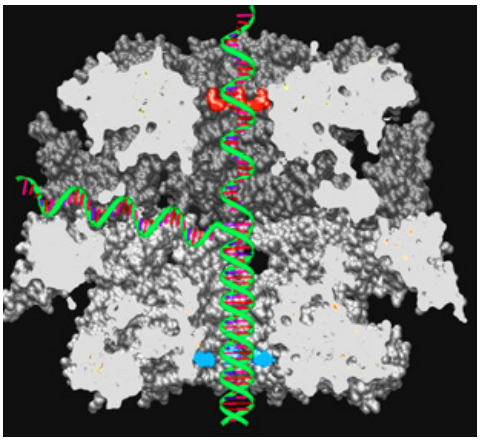

Figure 3. Complete model structure of human Helicase. Reptin is below and pontin above. A double-stranded DNA is entering the protein through a central channel. DNA is unfolded in the center of the complex and then the direct strand gets out by the top pontin pore and the indirect strand is ejected through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

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

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

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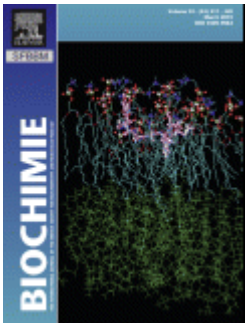
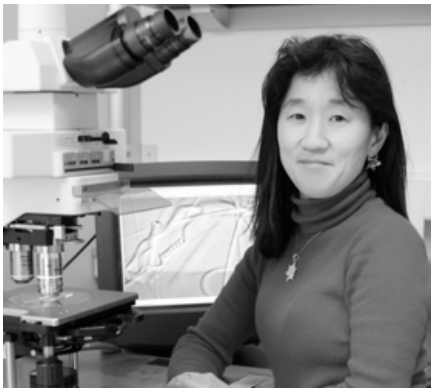


# MORPHOLOGIES, DYNAMICS & FUNCTIONS OF ASSEMBLIES OF AMPHIPHILES

**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 impact of different parameters (molecular architecture and various physico-chemical parameters) on such molecular assemblies. Once the control of the assembly formation at molecular level is achieved, their functionalisation can be envisaged. The assemblies can therefore serve as supports for the biomolecular structure formation or the induction of interactions between the aggregates via molecular recognition.**

Keywords / Expertise / Techniques: amphiphilic molecules, surfactant, lipid, gel, molecular recognition, functional molecular assemblies, self-assembled fibrillar network, micelles, vesicle / x-ray, neutron, light scattering, electron microscopy, optical microscopy, IR, CD, spectroscopy



Dr. Reiko Oda
Directeur de recherche (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 a four-year postdoctoral position in the laboratory of S. J. Candau at University Louis Pasteur (Strasbourg). She joined the IECB in 1998 as a group leader. Her research interests are the structural study and design of aggregates of amphiphilic molecules and their interactions with biological polyions, as well as the functionalization of such aggregates.

## Research team

**Dr. Reiko ODA** Team leader
**Dr. Sylvain NLATE** Teaching assistant (MC Université Bordeaux 1)
**Dr. Said HOUMADI** Post-doc (ANR-PCV)
**Rumi TAMONO** PhD student (ANR-PCV)
**Ren-Wei CHANG** PhD student (Aquitaine Regional Council)
**Dima DEDOVETS** PhD student (ANR-blanc)

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

Our activities are divided in several subjects as shown below:

### Ion specific effect

We combine experimental and computational approaches 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, aromatic carboxylates in order to elucidate the complex effects of ion properties such as 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 are coordinating a collaborative project involving 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 mechanisms of chirality transfer based on non chiral amphiphilic molecules in the presence of chiral counterions. We have shown that tartrate, when complexed with cationic surfactants, form chiral ribbons which express supramolecular chirality of the order of 10 nm to microns. The morphologies of these chiral assemblies can be controlled through 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).

### Biological anions confined at membrane surfaces

The interactions peptide-lipid and nucleic acid-lipid are the origin of a number of processes in biological systems. In order to better understand these interactions at the molecular level, it is important to understand these complexes in a simplified model system in which we can control various parameters independently. We have developed systems of lipopeptide (Figure 1) and nucleolipid by using biological polyanions such as oligopeptides or nucleotides complexed to cationic amiphiphiles (ChemCommun 2007, article submitted 2010).
Remarkably, the chirality of peptides and nucleotides led again to the expression of supramolecular chirality of the assemblies, whereas the cationic amphiphiles were achiral as in the case of tartrates. Such reciprocal and cooperative effects between membranes and counterions, seem to be general in the case of the systems studied here.

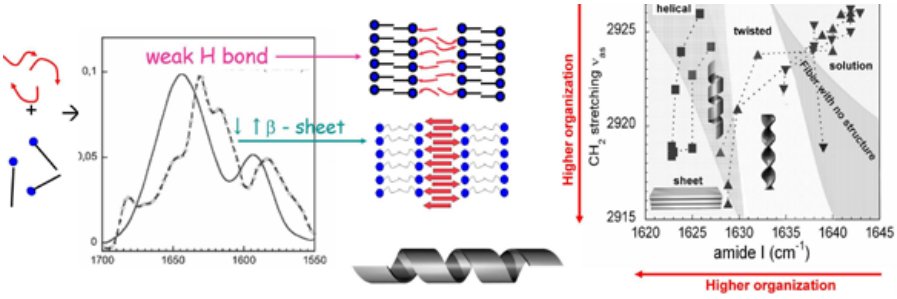



Figure 1. Chiral ribbons induced by complex cationic surfactant-anionic peptides; confined peptides form ß sheet

## Hybrid organic/inorganic nanohelices

Recently we have developed a system in which such well controlled chiral nanostructures are imprinted to inorganic structures by sol-gel transcription. These inorganic structures can then be functionalized to serve as templates for confining nanoparticles (see figure 2). (Nanoletters 2008, ANR Blanc grant 2010)

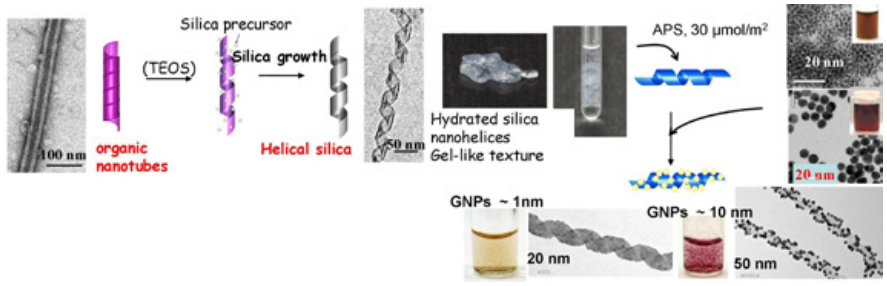



Figure 2. (left) organic nanotubules are used as template to form silica nanohelices . (right) Silica nanohelices are functionalized and gold nanoparticles with various sizes are confined at the surface.

## Memtrane protein structures and membrane fusion (coll. J.Lang, M. Laguerre, B. Desbat)

We aim at elucidating the role of the transmembrane (TM) domains of the fusogenic SNAREs proteins. We have reported that the structures of membrane domain of the SNAREs proteins are very sensitive to membrane environment undergo reversible transition between α-helix and ß-sheet, such dynamic properties of the proteins may directly be related to the stability of the lipide bilayers, and the structural transition of the proteins therefore might induce pore creation. (ANR-PCV 2007) (BBA-Biomembranes 2009, BBA-Biomembranes 2010). Our recent results with mutagenesis approach reveal the presence of crucial aminoacids which seem to have a direct link on the kinetics of the structural transformation of TM peptides and on the dynamics of exocytosis.

Starting January 2011, a new assistant professor, Sylvain Nlate, specialized in dendrimers and catalysis, joined the group. This will allow us to develop our research in the field of molecular design.

## Selected publications

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

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# MOLECULAR IMAGING & NANOBIOTECHNOLOGY

Pr. Alain Brisson
Professeur (Pr0), Université Bordeaux 1

Alain Brisson has successively led research groups at the Universities of Strasbourg as Directeur de Recherche at INSERM (87-94) and Groningen as Professor of Biochemistry (94-01), before moving to the University of Bordeaux as Professor of Biochemistry and group leader at IECB (01-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

**Pr. Alain BRISSON** Team leader
**Dr. Anthony BOUTER** Maître de Conférences (Université Bordeaux 1)
**Dr. Boris GARNIER** Post-doc (EU)
**Céline GOUNOU Assistant Engineer** (Université Bordeaux 1)
**Sisareuth TAN** Assistant engineer (CNRS)
**Nicolas ARRAUD** PhD student (MENRT)
**Yali WAN** PhD student (EU)
**Benoit FAURIE** Master student
**Fionna JASSON** Master student

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

**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.**

Keywords / Expertise / Techniques: proteins, membranes, annexins, phosphatidylserine, calcium, cryo-electron microscopy, AFM, QCM-D, flow cytometry, biosensors, protein production, protein chemistry, nanobiotechnology, surface functionalization, functionalized nanoparticles, diagnosis, drug delivery.

### 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 life (Ms submitted).

### Localization and role of Annexin-A5 in cell fusion

Cell fusion is a rare and highly regulated process that takes place in few biological tissues, namely muscle, placenta, bone and fertilization. Annexin-A5 has been proposed to participate in cell fusion events during the myoblast-myotube and cytotrophoblast-syncytiotrophoblast differenciation. We study the localization and the role of Annexin-A5 in these processes. Our methodology involves the use of imaging methods -fluorescence microscopy and electron microscopy- and biochemical methods, applied to both native tissues and model cellular systems. For the muscle system, we conclude that Annexin-A5 is not involved in the fusion process and propose that Annexin-A5 participates in the contraction or excitation function of mature muscle cells.

### 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 (Ms in preparation).

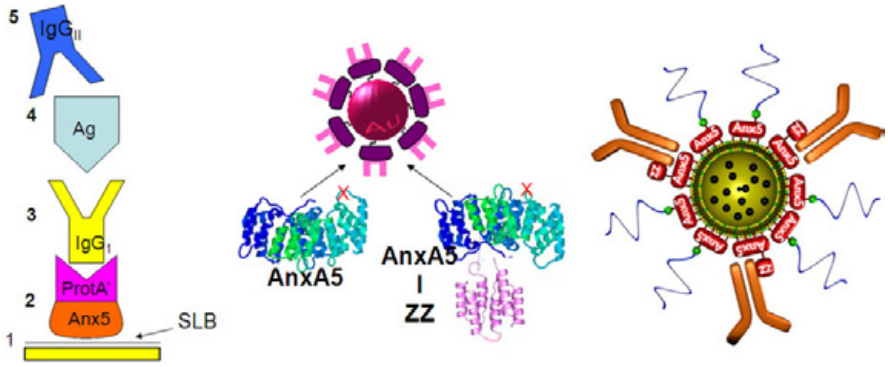


Figure 1. (top): Scheme of various AnxA5-based molecular tools. (Left): AnxA5-ZZ fusion protein for the controlled immobilization of IgGs or selected antigens; (middle): gold nanoparticle functionalized with oriented AnxA5 or AnxA5-ZZ for the specific labeling of receptors at the (sub)-cellular or tissular level; (right): liposomal nanovector functionalized with AnxA5-ZZ-IgG and encapsulating iron oxide particles for MRI.

## Development of suspended proteo-membranes

The development of lipid bilayers containing membrane proteins and suspended over nanostructured supports is carried out with the objective of creating new platforms for drug screening (EU-FP7 Asmena Project). Suspended lipid bilayers have been obtained by depositing a lipid bilayer stabilized by a 2D crystalline AnxA5 matrix on nanostructured silicon wafers by the Langmuir-Blodgett method. Surface characterization by AFM demonstrated that 2D crystals of AnxA5 bound to a lipid monolayer can be transferred onto a nanostructured support by the Langmuir-Schaefer method, providing an original approach for constructing suspended lipid bilayers (Ms in preparation). Current efforts focus on the application of such platforms to the integration of of acetylcholine receptor proteins, as a model system of membrane proteins with ion channel activity.

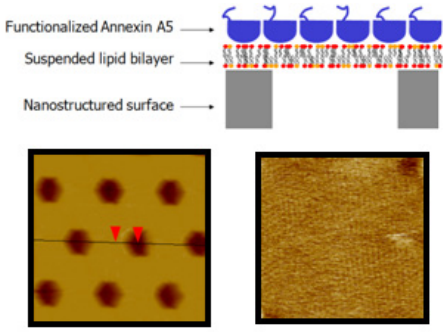


Figure 2. (top): Schematic representation of a suspended proteo-lipid bilayer. (bottom): AFM images of a proteo-lipid bilayer suspended onto a nanostructured support (left, 6x6x1 µm) and of an AnxA5 2D crystal suspended over a pore (right, 275x275x3 nm).

## Selected publications

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# SUPRAMOLECULAR BIOORGANIC & BIOMIMETIC CHEMISTRY

Dr. Ivan Huc
Directeur de recherche (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. Ivan HUC** Team leader
**Dr. Frédéric GODDE** Lecturer (MCU Université Bordeaux 1)
**Dr. Yann FERRAND** Researcher (CR2 CNRS)
**Dr. Vitor MAURIZOT** Researcher (CR1 CNRS)
**Dr. Ting QI** Post-doc (Université Bordeaux 1)
**Dr. Zehuan DONG** Post-doc (Université Bordeaux 1)
**Dr. Jone IRIONDO** Post-doc (Université Bordeaux 1)
**Dr. Chandramouli NAGULA** Post-doc (CNRS)
**Dr. Simon DAWSON** Post-doc (Université Bordeaux 1)
**Dr. Christel DOLAIN** Post-doc (Université Bordeaux 1)
**Dr. Partha BOSE** Post-doc (Université Bordeaux 1)
**Dr. Tiny DESCHRIJVER** Post-doc (CNRS)
**Marine STUPFEL** PhD student (Université Bordeaux 1)
**Quan GAN** PhD Student (CNRS)
**Hidekazu YAMADA** PhD Student (Nagoya University)

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

**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.**

Keywords / Expertise / Techniques: foldamers, peptidomimetics, helical structures, macrocycles, tertiary structures, peptide-membrane interactions, synthetic organic chemistry, structural studies, X-ray crystallography.

Our group has developed synthetic foldamers – oligomers having stable folded conformations – based on aromatic amino acids. Aromatic oligoamide foldamers possess remarkable properties: (i) They give access to an astonishing range of secondary and even tertiary-like folded structures, such as single, double, triple and quadruple helices or helix bundles (Fig. 1). (ii) They feature exceptional conformational stability in solution due to intramolecular hydrogen bonds and aromatic stacking. Some cannot be denatured at 120°C. (iii) They crystallize easily (Fig. 1); (iv) Their folded structures can, to a large extent, be reliably predicted by molecular dynamics calculations; (v) They are highly tunable: upon changing the relative orientation of the acid and amine units on each aryl group, and by varying the size of these units, the curvature of an oligomeric strand may be adjusted from strictly linear to highly bent, giving rise to helices of controllable diameter and to linear conformations; (v) They can be made soluble (>10mM) in any solvent; (vi) Being oligoamides, they are relatively easy to synthesize.

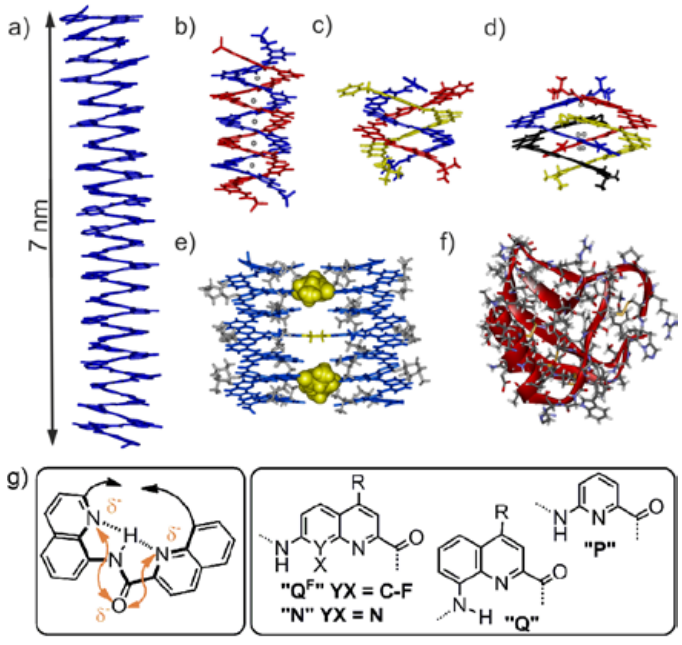


Figure 1. Crystal structures, all at the same scale, that illustrate the variety of folds accessible to aromatic oligoamides: a) single helix of Q48; b) double helix of P13; c) triple helix of N4; d) quadruple helix of (QF)4; e) bundle of two Q8PQ8 helices linked by their P units; f) a 65 amino-acid protein for size comparison. G) Structures of P, Q, N, and QF and folding mechanism of aryl-amide foldamers.

Our current research efforts aim at using these aromatic oligoamides to mimic protein tertiary structures and functions, to mimic nucleic acids hybridized architectures, and to explore how these oligomers interact with biological material in several biomedically relevant contexts as for example, amphipathic antibiotics, G-quadruplex recognition, or protein-protein interactions. Other projects focus on the use of foldamer helices as synthetic hosts that encapsulate organic guests. Below are some highlights of our recent advances:

- The **synthesis of fully water soluble helical aromatic amide foldamers** has allowed preliminary characterizations of their biological activity. 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.

- **Synthetic foldamers of unprecedented size** (> 10 kDa) have been synthesized and structurally characterized by x-ray crystallography (J. Am. Chem. Soc. 2009 and 2011). They represent the first folded abiotic architectures that compare in size to a small 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.

- **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 helical host.

- **The first artificial organic triple helices** have been evidenced (Angew. Chem. 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.

- **Helical aromatic oligoamides have been shown to transport electrons from a terminal donor group to a terminal acceptor** following a photoexcitation (JACS 2009). Electron transfer occurs at very high rates (ca 50 ps) and shows very little dependence upon the donor-acceptor distance (helix length).

- Finally, a 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 transformations** where helicates transform into other helicates following the introduction of new components in a complex mixture (Nature Chemistry 2010).

## Selected publications


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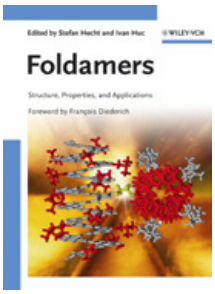



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# SYNTHESIS & ACTIVITY OF NATURAL SUBSTANCES

Pr. Stéphane Quideau
Professeur, 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 post-doctoral 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 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, and was promoted Full Professor in 2005. 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 immunotherapeutic agents.

## Research team

**Pr. Stéphane QUIDEAU** Team leader
**Dr. Denis DEFFIEUX** Lecturer (MC/HDR Université Bordeaux 1)
**Dr. Laurent POUYSÉGU** Lecturer (MC/HDR, Université Bordeaux 1)
**Dr. Céline DOUAT-CASASSUS** Researcher (CR2 CNRS)
**Rémi JACQUET** Technician (Univ. Bordeaux 1)
**Dr. Emanuela BERNI** Post-doc (ANR EllagInnov)
**Dr. Michaël JOURDES** Post-doc (CIVB - ISVV)
**Dr. Séverine GAGNÉ** Post-doc (LVMH)
**Dr. Céline FRANC** Post-doc (LVMH)
**Céline CHALUMEAU** PhD student (CIVB)
**Tony GARNIER** PhD student (Ministry of Research)
**Marion TARBE** PhD student (Servier)
**Tahiri SYLLA** PhD student (Ivory Coast Ministry of Research)
**Mélanie DELANNOY-LOPEZ** PhD student (Foundation Fundayacucho)
**Cyril BOSSET** PhD student (BDI CNRS/CRA)
**Romain COFFINIER** PhD student (ANR Iodinnov)
**Emilie PETIT** PhD student (CIVB)
**Hélène CARRIÉ** PhD student (CIVB)

This team is part of the Institut des Sciences Moléculaires (ISM), Université Bordeaux 1/ CNRS (UMR-CNRS 5255) and is associated with the Institut des Sciences de la Vigne et du Vin (ISVV).

**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 tools for the study of the biosynthesis of polyphenolic anthocyanins and flavanoids, and (4) the rational design of antigenic peptidomimetics for the development of synthetic anticancer vaccines.**

Keywords / Expertise / Techniques: hypervalent iodine chemistry, phenol oxidation chemistry, plant polyphenols chemistry and biology, synthesis of natural products, peptide and peptidomimetic synthesis, solid phase synthesis, natural products extraction and characterization, electrochemistry, NMR spectroscopy.

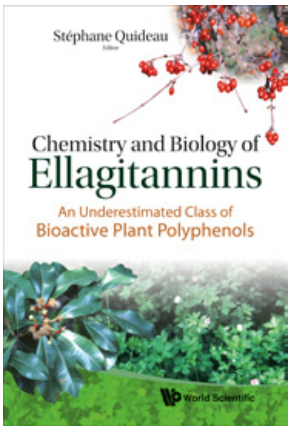
### Hypervalent Iodine-Mediated Phenol Dearomatization

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 member of the C-glucosidic class of ellagitannins, 5-O-desgalloylepipunicacortein A. This work has been accepted in October 2010 for publication in ChemComm. We have also developed, in collaboration with Carmelo 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 aim to further develop this tool to apply it to the study of the interactions between various types of polyphenolic molecules and

proteins. This tool should find useful applications in the field as it constitutes to date the best alternative to discriminate in real time specific from non-specific protein-polyphenol interactions. Moreover, our study of the in vino generation of hybrid molecules derived from "oak" C-glucosidic ellagitannins and "grape" flavanoids led us to unveil a quite fascinating example of an anthocyano-ellagitannin hybrid exhibiting a red-to-purple bathochromic shift relatively to the native grape anthocyanin pigments. This work was published in the first 2010 issue of the European Journal of Organic Chemistry and was selected for the cover of that issue. In February 2009 was released the first book ever on the chemistry and biology of ellagitannins, which I had the privilege to edit and co-author. And for those of you who want to know all about plant polyphenols, we have published a review article on the topic in Angewandte Chemie (released in January 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 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.

### 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.

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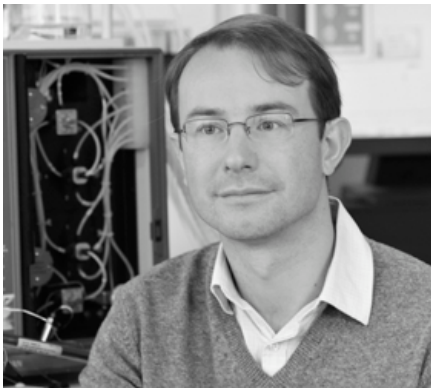
# PEPTIDOMIMETIC CHEMISTRY



Dr. Gilles Guichard
Directeur de recherche (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. Gilles GUICHARD** Team leader
**Dr. Karine GIONNET** Researcher (CR1 INSERM)
**Dr. Nagendar PENDEM** Post-doc (ANR-PCV)
**Dr. Yella-Reddy NELLI** Post-doc (Univ. Bordeaux 1)
**Dr. Lucile FISHER** Post-doc (ANR-PCV)
**Dr. Neil OWENS** Post-doc (ARC)
**Dr. Arnaud SALAÜN** Post-doc (ANR PCV)
**Thomas ARBOGAST** PhD student (Aquitaine Regional Council)
**Claire VENIN** PhD student (CIFRE Immu-Pharma)
**Juliette FRÉMAUX** PhD student (Ministry of Research)
**Marie-Charlotte LECHNER** PhD student (Ministry of Research)
**Edith CHARDON** PhD student (Ministry of Research)

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

**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.**

Keywords / Expertise / Techniques: peptide and peptidomimetic chemistry, foldamers, helices, oligoureas, solid-phase and combinatorial techniques, multimeric architectures, self-assembly, conformational studies, molecular recognition, antibacterial agents, death receptors, protein-protein interactions.

Most of our research efforts are devoted to 'Foldamer Chemistry' with the creation of urea-based foldamers and their application in (bio)molecular recognition. We are also developing multimeric peptidomimetic architectures as tools to investigate activation of receptors of the Tumour Necrosis Factor receptor (TNFR) family, including Death Receptors (DR).

### Controlling folding and self-assembly with short chain urea-based peptidomimetics

H-bonds provide a versatile way to create intrastrand connections useful to control folding in bioinspired oligomeric materials. Our research currently focuses on exploring and exploiting self-assembling and folding properties of non-oligoamide oligomers based on urea linkages (Org. Biomol. Chem, Perspective article, 2010). In previous work, we have investigated both linear and macrocyclic oligoureas of general formula [NH-CH(R)-$CH^2$-NH-CO-]n. Whereas macrocyclic oligoureas display a strong propensity to form various types of H-bonded columnar and tubular stacks, we found that linear oligomers have a remarkable propensity to fold into stable helical secondary structures reminiscent of the α-helix. 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.

Recent developments include:

- The synthesis and characterization of **hybrid urea/amide macrocycles generated by cyclooligomerization of chiral dipeptide-derived building blocks** (Fig. 1a). A high level of hierarchical and directional control can been achieved in these systems (Angew. Chem. 2009). Additionally, macrocyclic urea-amide hybrids have been reported to be functional, anion-selective membrane transporters in lipid bilayer membranes (J. Am. Chem. Soc. 2009a). Related hydrazide/amide macrocyles have also been prepared. In contrast to urea based macrocycles, these systems are folded ('Foldacycles') and feature an intramolecular H-bond network based on a recurrent C8 pseudocycle, hydrazinoturn.(J. Am. Chem. Soc. 2009b).

- **The structure determination at atomic resolution of the canonical helical structure for oligoureas** (Fig. 1b). The similarity between the structures deduced earlier from NMR studies in solution is striking and underlines the excellent complementarities of the two techniques to analyze urea-based foldamers. This study also demonstrates the robustness of the folding process, four acyclic residues being sufficient to drive complete helix formation. Overall, this crystallographic data set provides the ground for the structure-

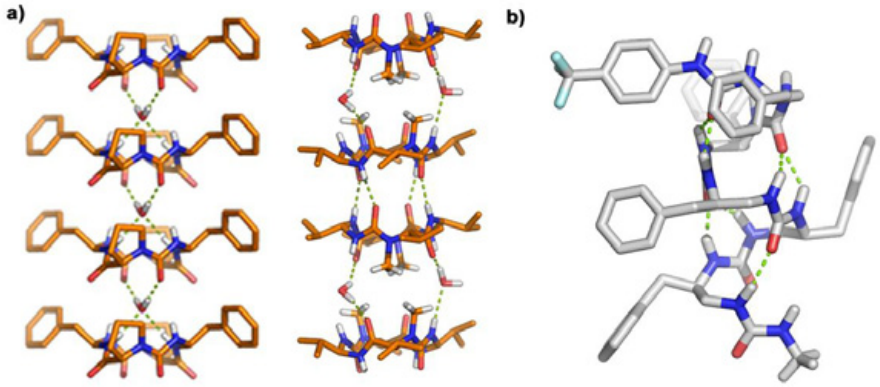



Figure 1. (a) Formation of columnar stacks by axial packing of heterogeneous amide/urea macrocycles; (b) Structure of the canonical 2.5-helical fold of oligoureas at atomic resolution.

guided development of urea foldamers with function as well as for the elaboration of new tertiary and quaternary structural motifs (Angew. Chem. 2010a)

- The finding that **oligoureas and γ-peptides although isosteric and quasi-isostructural are endowed with distinct biomolecular recognition properties** (Fig. 2). While studying the mechanisms of membrane disruption by antibacterial oligoureas mimicking host defence peptides, we found that γ-peptides are almost inactive and interact with membrane to a much lower extent compared to the corresponding oligoureas. Noteworthy, our results also pointed to heterogeneous helical urea/amide backbones which may become advantageous in the development of more potent yet less cytotoxic antimicrobial helical foldamers for in vivo applications (Angew. Chem. 2010b)

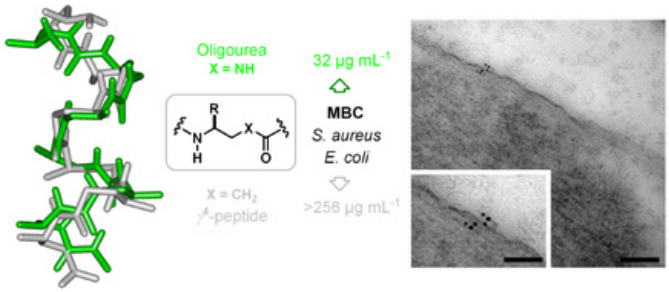



Figure 2. Antimicrobial helical urea oligomers. Differential activities of isostructural oligoureas and gamma-peptides (left). Interaction between oligoureas and bacterial membranes by immunoelectron microscopy (right).

## Multivalency as a tool to target and activate cell-surface receptors of TNFR family.

Ligand-induced oligomerization is an important process for activating cell surface receptors such as TNFR superfamilies. TNFR family members can transduce a variety of intracellular signals culminating in cell proliferation, differentiation, survival, and death. Ligands of the TNF family self-assemble around a three-fold symmetry axis to form non-covalent homotrimers that can each bind three receptor molecules. We have been interested in developing Synthetic Multivalent Ligands (SMLs) with controlled distance and topology as tuneable probes to modulate biological processes and to dissect signalling pathways associated with proapotptotic TNFRs such as DR5 (Cancer Res. 2010) We recently extended this approach to a new series of synthetic SMLs based on peptide nucleic acid (PNA) to program peptide oligomerization through hybridization (Chem Commun. 2010).

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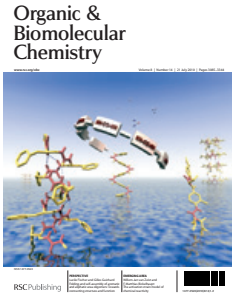


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# PEPTIDE-BASED POLYMER ASSEMBLIES

Dr. Élisabeth Garanger
Université Bordeaux 1 contract

Trained as a chemist, Elisabeth Garanger graduated in 2001 as a Chemical Engineer from 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. Elisabeth Garanger joined the IECB as team leader in October 2010.

## Research team

**Dr. Élisabeth GARANGER** Team leader
**CharlotteDRAPPIER** PhD student (LCPO, Université Bordeaux 1)

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

**The goal of the Peptide-based Polymer Assemblies team 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 hybrid materials featuring a synthetic polymer block conjugated to a peptide segment will be synthesized. After better understanding the structure and function of the peptide sequences, a recombinant approach will be used to rationally design monodisperse protein-like polymers. Recombinant DNA and protein engineering techniques will be used to produce recombinant polymers, mainly based on elastin-like motifs combined with biofunctional sequences. Self-assembly mechanisms will be 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) led by S. Lecommandoux.**

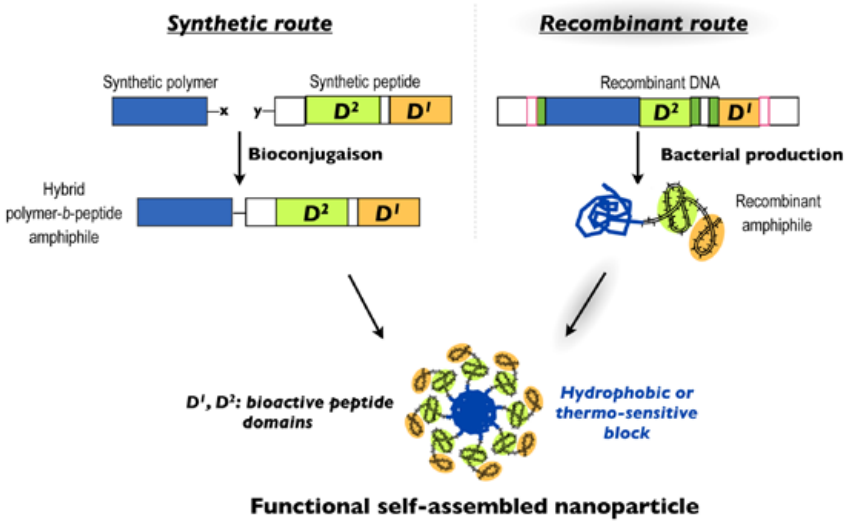
Keywords / Expertise / Techniques: self-assembly, copolymers, peptide amphiphiles, functional nanomaterials, biomaterials, solid-phase peptide synthesis, bioconjugation chemistry, chemoselective ligations, self-assembled polymer nanoparticles, manual and automated SPPS, HPLC, SEC, MS-ESI and MALDI-TOF. DLS. DSC. TEM

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 will focus on the design and synthesis of peptide-based polymer 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 will be investigated to prepare either hybrid materials from traditional peptide synthetic routes or recombinant materials from protein-engineering techniques. Self-assembly mechanisms into bio-inspired, nanoscale, and bioactive objects will be studied using techniques from physico-chemistry to cellular biology.

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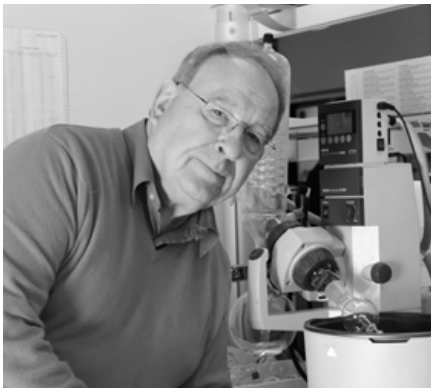
# ORGANIC & MEDICINAL CHEMISTRY



Pr. Léon Ghosez
Emeritus Professor UCL, Visiting scientist 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 the research of 125 PhD students and 135 postdoctoral associates. He also held appointments at the University of Liège (1969-1999) and the Ecole Polytechnique in Palaiseau (1993-1999). He took an active part in the creation of IECB where he established a research group in 1998 and from 2000 till the end of 2009, he shared the directorship of IECB with Dr. J.J. Toulmé. 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

**Pr. Léon GHOSEZ** Visiting scientist
**Dr. Thomasz BALAKIER** Post-doc (Université Bordeaux 1)
**Dr. Stijn CLAERHOUT** Post-doc (Université Bordeaux 1)
**Dr. Elisabeth HESS** Post-doc (Université Bordeaux 1)
**Dr. Santhosh JANGARI** Post-doc (Université Bordeaux 1)
**Dr. Oscar MENDOZA** Post-doc (Université Bordeaux 1)
**Charlotte VRANCKEN** Erasmus Master student (KUL Leuven)

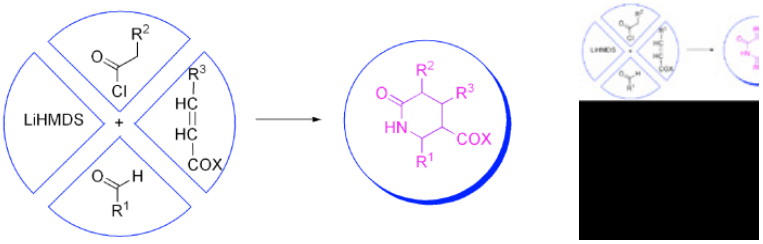
The team is part of the unit "Chimie et Biologie des Membranes et Nanoobjets" (CBMN), CNRS/ Université Bordeaux 1/ENITAB (UMR 5248)

**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.**

Keywords / Expertise / Techniques: total synthesis, diversity, synthetic methods, electrophilic catalysis, convertases ,kinases, apoptosis, tubulin, serine proteases, Blc-2, synthesis, medicinal chemistry, structural studies by spectroscopy.

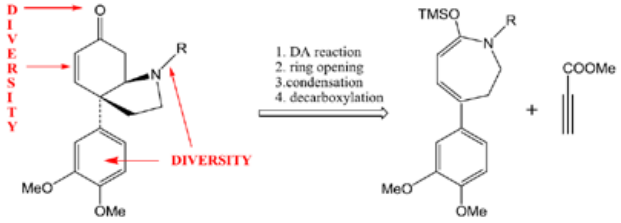
### Diverted total synthesis of natural product analogs

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. Two projects aiming at the control of apoptosis of cancer cells are now terminated but the results are still confidential.




Scheme 2 **NP analogs** **Dienes**

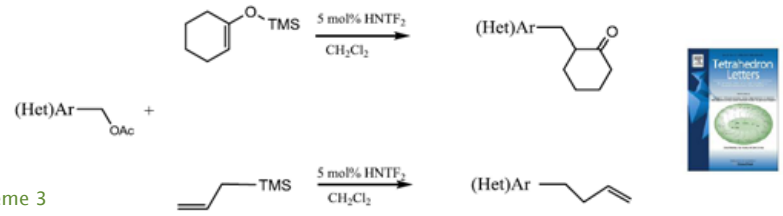
We have also developed a new class of cyclic dienes which are aimed at opening quick and efficient accesses to natural product analogs or fragments (Scheme 2).

### NP analogs for the inhibition of serine proteases, eg proprotein convertases

The most important classes of inhibitors of this family of enzymes are natural penicillins, cephalosporins and penems and their synthetic analogs. All serine proteases probably react with their substrates and inhibitors by a unified mechanism. In collaboration with the group of Dive (University of Liège), a transition statel model of the acylation reaction in the active site of a serine protease has been built which allows a prescreening of potential scaffolds. This model explaines why the most reactive γ-lactam analogs of the biologically active penicillin antibiotics were inactive. On the other hand the model predicts that the acylation of the serine residue of the protease by the corresponding 5-membered hydrazides (aza-γ-lactams) should occur much more readily (ΔΔEa~4-5 kcal/mol). More than ten scaffolds have already been prepared using a synthetic strategy based on a ring closing metathesis.

### 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.

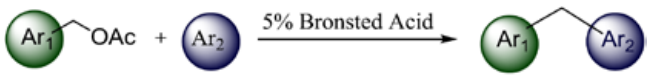



Scheme 3




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 3). 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.

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 involves stable, easily handled and non-genotoxic benzylating agents, avoids the use of metal catalysts, does not require a solvent in most cases, nor protection from air or moisture and is operationally simple and economical (Scheme 4). It leads to a wide variety of diarylmethanes which are substructures found in many pharmacologically interesting compounds.




Scheme 4

**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

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# SMALL RNAS & APTAMERS

Dr. Jean-Jacques Toulmé
Directeur de recherche (DRCE), INSERM

Jean-Jacques Toulmé got his PhD in Physical Sciences (University Paris VI) in 1982. As an Associate Professor at the Museum of Natural History (Paris) he investigated nucleic acid-protein complexes by fluorescence spectroscopy. Repeated short stays (1983-1985) at the University of Geneva and at the Cancer Institute of Amsterdam led him to develop projects on antisense oligonucleotides. He founded the Inserm Unit "Artificial Modulation of Eukaryotic Genes" at the University of Bordeaux (1994-2006) where he focused his research activity on regulatory viral RNA structures. He chaired the "Institut Fédératif de Recherches" of Infectious Diseases (1997-2000) and joined the IECB in 2000. The work of his group is devoted to the design of aptamers as diagnostic and therapeutic tools. He is presently director of the IECB and headed the Inserm Unit « ARN : Régulations Naturelle et Artficielle » until December 2010.

## Research team

**Dr. Jean-Jacques TOULMÉ** Team leader
**Dr. Carmelo DI PRIMO** Researcher (CR1, INSERM)
**Eric DAUSSE** Engineer (IE, INSERM)
**Dr. Laurence DELAURIÈRE** Post-doc (INSERM)
**Laetitia EVADÉ-FARUGGIA** Engineer (Inserm)
**Emilie DAGUERRE** Engineer (Industry)
**Dr. Sonia DA ROCHA GOMES** Researcher (Novaptech*)
**Amandine DUPHIL** Technician (Novaptech*)

This team is part of the Unit "RNA: Natural and Artificial Regulation", INSERM/Université Bordeaux Segalen (Unit 869)

* Novaptech is a technology transfer Unit connected to Inserm U869.

**Many RNA structures play a key role in the regulation of gene expression. We carry out in vitro selection (SELEX) for identifying aptamers, targeted to RNA structures of interest for viral pathologies or tumor development. RNA hairpin aptamers have been characterized – in particular by Surface Plasmon Resonance, a recognized expertise of our team – that bind to the TAR element of the Human Immunodeficiency Virus through loop-loop interaction. Nuclease-resistant derivatives of these aptamers interfere with the HIV-1 in vitro development. We also raised aptamers against the human matrix metalloproteinase-9 that were ultimately converted into a probe for imaging brain tumors ex vivo. We develop SELEX methodology and design aptamer-based tools in the frame of "Novaptech" a unit for technology transfer associated to the team.**

Keywords / Expertise / Techniques: RNA structure, RNA hairpin, mRNA, synthetic oligonucleotides, aptamer, oligonucleotide probe, HIV, HCV, cancer, matrix metalloprotease, in vitro selection (SELEX), Surface Plasmon Resonance (BIAcore), melting transition (Tm).

We are interested in modulating the function of RNA hairpins. This led us to select aptamers against such motifs and to use them as regulators of gene expression. We take advantage of our expertise for raising aptamers against a wide range of targets and converting them into biotechnological tools for sensing and probing.

### RNA ligands for modulating RNA function

Numerous RNA structures play a key role in the regulation of gene expression. These RNA motifs are targets of therapeutic interest: specific ligands binding with high affinity to these elements might interfere with their biological function. In the Human Immunodeficiency Virus type 1 (HIV-1) the synthesis of the full length retroviral mRNA requires the association of the TAR RNA hairpin, located at the very 5' end of the message, with viral and host proteins for the efficient transcription of the HIV genome.
We considered the possibility of identifying oligonucleotides specific for RNA structures through SELEX. We identified RNA hairpins recognizing TAR through loop-loop ("kissing") interactions. The structure of the aptamer/TAR loop-loop RNA/RNA complex has been solved by X-ray crystallography (collab. S. Fribourg, IECB) and by high-field NMR (collab. J. Boisbouvier, Grenoble). The formation of a G.A pair as well as a network of hydrogen bonds account for the high stability and specificity of the interaction.
The nucleolar expression of the anti-TAR RNA aptamer reduces specifically TAR-dependent transcription in cultured cells. Nuclease resistant (2'-O-Me, etc...) anti-TAR aptamers analogues retain the binding properties of the originally selected RNA molecule. They specifically inhibit TAR-dependent in vitro transcription of the HIV DNA. Chimeric anti-TAR aptamers containing as few as 1 or 2 LNA residues reduce TAR-dependent expression in cultured cells.

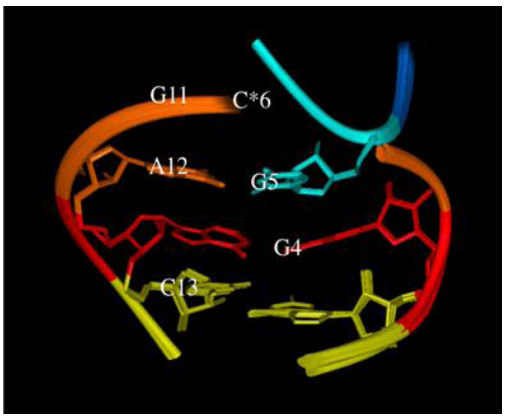


Figure 1. NMR structure of RNA aptamer-TAR RNA: detail of the aptamer stem – loop – loop helix junction (from Van Melckebecke et al. (2008).

We successfully raised kissing aptamers against pre-microRNAs and against a dual hairpin motif of the xbp1 RNA that is involved in the unconventional splicing of the pre-mRNA in response to endoplasmic reticulum stress.

### Aptamers as probes and bio-sensors

Sensors and probes can be easily enough tailored from aptamers that actually rival antibodies. We selected 2'F-pyrimidine nucleoside-containing aptamers against the human MMP-9, a matrix metalloprotease playing a crucial role in development, which is also related to cancer metastasis. Aptamers to MMP-9 bind both to the enzyme and to its precursor with a Kd of about 20 nM. A truncated oligomer 36 nt long retained the binding properties of the selected sequence. Every purine residue (RNA) of the aptamer was then substituted by a 2'-O-Me nucleoside making it fully resistant to nucleases. The resulting oligomer was conjugated to $^{99m}$Tc (collab. L. Azéma, Bordeaux, and M. Allard, Hospital Bordeaux). The molecular imaging of MMP-9 by SPECT with the Tc-labeled aptamer showed specific labelling of human brain tumor slices.

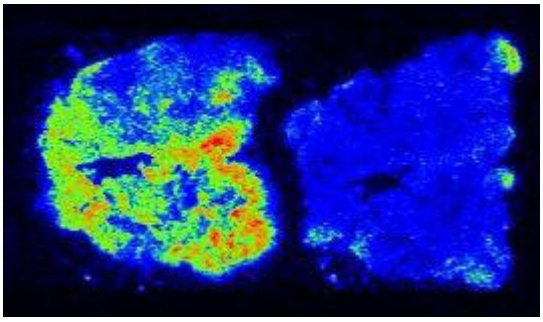

Figure 2.Labellling of human glioblastoma brain slices by Tc-conjugated anti-MMP-9 aptamer (left) or control oligonucleotide (right)

### Technology transfer: Novaptech

The production of a number of aptamers requires improved selection and identification methods. We designed a homogeneous solution-based method for screening large pools of oligonucleotide candidates generated from SELEX (collab. E. Chevet, Inserm U889, Bordeaux). This approach based on the AlphaScreen® technology allows the functional identification of high affinity aptamers. Using this HAPIscreen (High throughput APtamer Identification screen) methodology we validated the approach for aptamers targeted to RNA hairpins. HAPIscreen is faster than the current procedures that are based on sequence comparison. Moreover this methodology allows to screen larger numbers of candidates. HAPIscreen can be adapted to any type of tagged target and is fully amenable to automation.

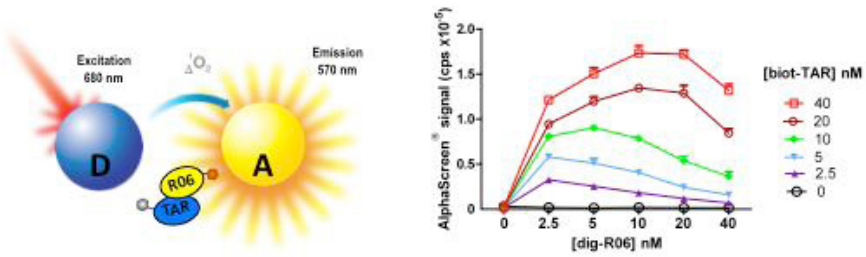


Figure 3. Left: Scheme of the assay setup using a digoxigenin-tagged aptamer (R06) and a biotinylated target RNA hairpin (TAR). Right: Results obtained when increasing concentrations of dig-R06 were added to A and D beads for different biot-TAR concentrations.

Technological developments of aptamers are now implemented in "Novaptech", a dedicated Unit for technology transfer, associated to our team, that carries out collaborative projects with academic and industrial partners.

## Selected publications

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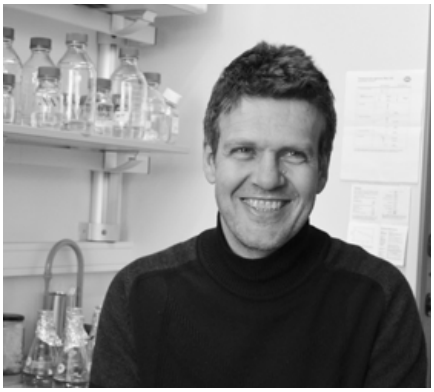
# GENE REGULATION & TUMOR RESEARCH



Pr. Martin Teichmann
Professor, 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

**Pr. Martin TEICHMANN** Team leader
**Dr. Hélène DUMAY-ODELOT** Assistant Professor (MC, Université Bordeaux Segalen)
**Stéphanie DURRIEU-GAILLARD** Technician (Université Bordeaux Segalen)
**Dr. Galina BOLDINA** Post-doc (ANR-Regpolstress)
**Daniel DA SILVA** PhD Student (Ministry for research)
**Chiara PASCALI** PhD Student (French-Italian University)
**Leyla EL AYOUBI** PhD Student (Ligue Contre le Cancer)
**Khawla SEDDIKI** Master Student (Université Bordeaux Segalen)

This team is part of the Unit "RNA: Natural and Artificial Regulation", INSERM/Université Bordeaux Segalen (Unit 869)

**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.**

Keywords / Expertise / Techniques: RNA polymerase, transcription, cellular transformation, interfering RNA, gene regulation, in vitro transcription, two-hybrid screen, generation of stable mammalian cell lines, northern-blot, protein purification (LC, FPLC), western-blot, 2D gel-electrophoresis, EMSA, DNA footprint

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 by TRF2 and interacting proteins.

In collaboration with the group of Pr Michael Kessel at the Max-Planck Institute for Biophysical Chemistry in Götingen/Germany, we were able to identify cooperative functions of TBP and TRF2 with two other transcription regulators, TIPT and geminin. We showed that the TRF2-interacting protein (TIPT) interacts with geminin. Both geminin and TIPT2 interact with several polycomb factors, with the general transcription factor TBP (TATA box binding protein), and with the related protein TRF2. TIPT2 synergizes with geminin and TBP in the activation of TATA box-containing promoters, and with TRF2 and geminin in the activation of the TATA-less NF1 promoter. We demonstrated that geminin and TIPT2 bound to chromatin near TBP- and TRF2-binding sites (Pitulescu et al., 2009).

### Complementary projects

We also performed structure/function studies of the human Pol III subunit RPC62. In collaboration with the group of Sébastien Fribourg, we have been able to obtain the structure of RPC62 by X-ray crystallography at a resolution of 2.85 Å. Furthermore, we collaborate with the group of Pr. Dieci in Parma, Italy, to study the mechanisms of termination of Pol III transcription.

## Selected publications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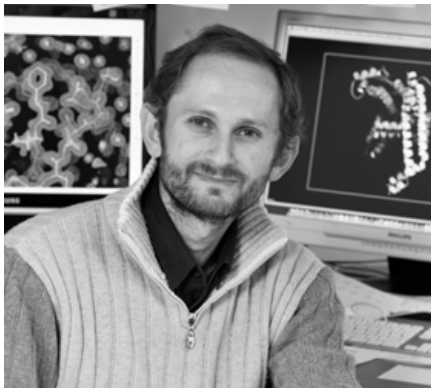
# STRUCTURAL BIOCHEMISTRY



Dr. Sébastien Fribourg
Chargé de Recherche (CR1), INSERM

Sébastien Fribourg did his Ph.D at the IGBMC 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. Sébastien FRIBOURG** Team leader
**Dr. Lionel MINVIELLE-SÉBASTIA** Senior researcher (DR2 CNRS)
**Natacha PÉRÉBASKINE** Research Technician (Université Bordeaux Segalen)
**Cécile MONFOULET** Research Technician (IE, INSERM)

This team is part of the Unit "RNA: Natural and Artificial Regulation", INSERM/Université Bordeaux Segalen (Unit 869)

**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.**

Keywords / Expertise / Techniques: structural biochemistry, X-ray crystallography, yeast genetics, multisubunit complexes, RNA processing.

### 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).

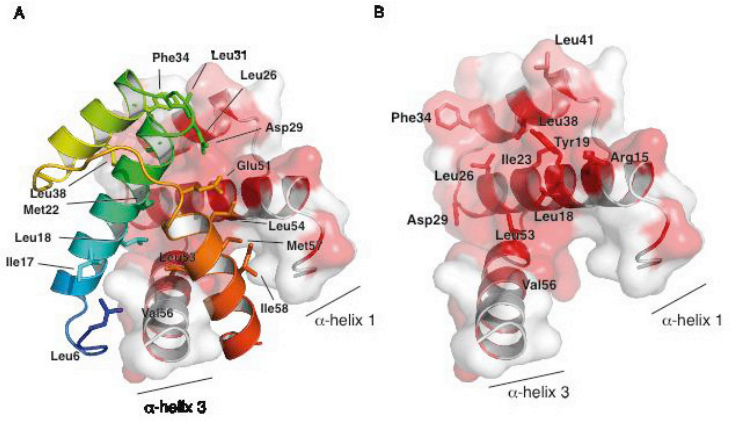



Figure 1. Overall structure of CstF-50 N-terminal domain and homodimerization determinants (Moreno-Morcillo et al., 2011).

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 et al. under revision).

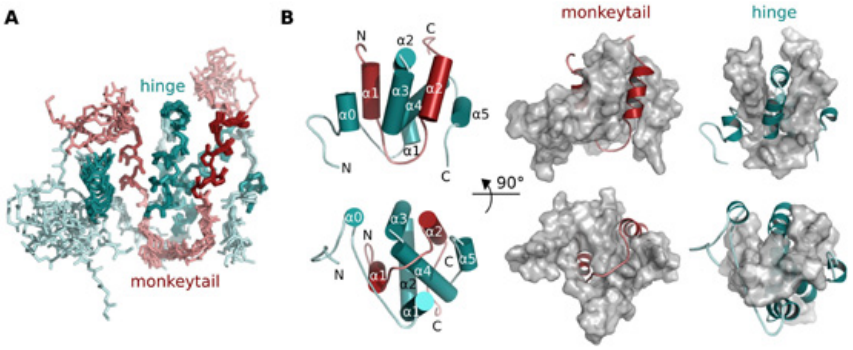
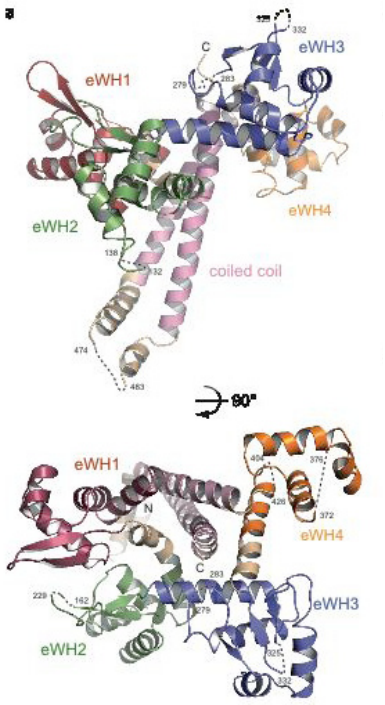



Figure 2. Solution structure of the core Rna14p-Rna15p domain. Rna14p is shown as a red ribbon whereas Rna15p is depicted in cyan.

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.

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# NMR SPECTROSCOPY OF PROTEIN-NUCLEIC ACID COMPLEXES

Dr. Cameron Mackereth
ICSN/CNRS

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.

## Research team

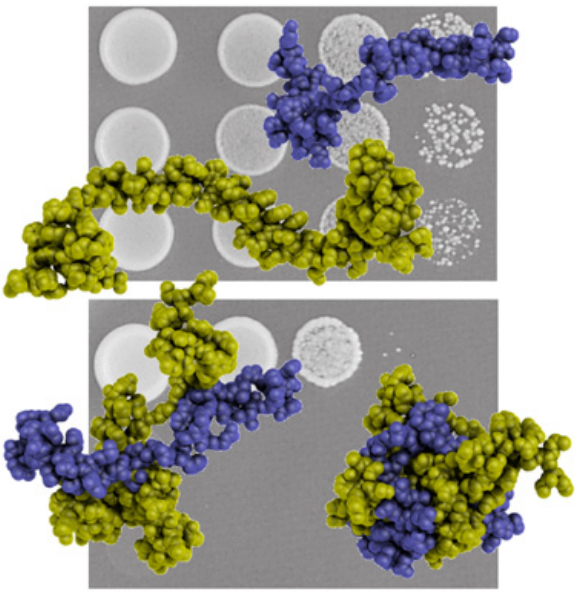
**Dr. Cameron MACKERETH** Team leader
**Dr. Samir AMRANE** Post-doc (Conseil Régional d'Aquitaine)
**Dr. Sarah BOURBIGOT** Post-doc (ICSN/CNRS)
**Yoan MONNEAU** PhD Student (ICSN/CNRS)
**Virginie JUTEAU** University Student

**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.**

Keywords / Expertise / Techniques: NMR spectroscopy, protein-RNA complexes, pre-mRNA processing, alternative splicing, protein-protein interactions, domain architecture, epigenetics, histone modification

### 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. For the four protein components of the CF IA complex (Rna14p, Rna15p, Pcf11p and Clp1p) several domain structures have been determined; significantly absent from this list is high resolution information of the complex formed between the C-terminus of Rna14p and the central region of Rna15p. To obtain the atomic details of this association, we have used NMR spectroscopy to determine the solution structure of a minimal Rna14p/Rna15p heterodimer. 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. The high degree of inter-domain contacts



In the formation of a tether between the yeast proteins Rna14p and Rna15p, the association of the monkeytail domain (blue) and hinge domain (yellow) display a coupled binding and folding mechanism to create the stable complex.

helps to explain why we have observed by NMR spectroscopy that the monkeytail or hinge domains in isolation are essentially unfolded, and require complex formation to produce a stably folded architecture. In addition, the early temperature sensitive mutants identified for Rna14p and Rna15p are located within this association complex and thus we can now explain these mutant effects at the structural level as a loss of Rna15p from the intact CF IA complex. 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.

### Tissue-specific alternative splicing in C. elegans

We have initiated a project on nematode splicing proteins with a structural investigation of the Sup-12 protein from C. elegans. In connection with the Asd-1 or Fox-1 proteins, Sup-12 is involved in the muscle-specific alternative splicing of the egl-15 mRNA. 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 trimethylated 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. 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.

## Selected publications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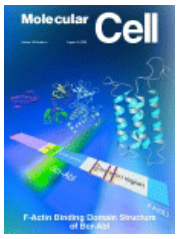



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# UNUSUAL NUCLEIC ACID STRUCTURES

Dr. Jean-Louis Mergny
Directeur de recherche (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 post-doctoral position in Basel, Switzerland with W. Gehring (Biozentrum). Afterwards he was hired by INSERM in 1993 in the Muséum National d'Histoire Naturelle, where he worked mainly on nucleic acids structures from a biophysical point of view. He was promoted Research Director in 2002, and he joined the IECB at the end of 2009.

## Research team

**Dr. Jean-Louis MERGNY** Team leader
**Dr. Anne BOURDONCLE** Lecturer (MC, Université de Poitiers)
**Dr. Gilmar SALGADO** Lecturer (MC, Université Bordeaux Segalen)
**Dr. Liliya YATSUNYK** Assistant Professor (on sabbatical leave, Swathmore College)
**Aurore GUÉDIN** Technician Assistant (A.I., INSERM)
**Lionel BEAUREPAIRE** Technician Assistant (I.E., Aquitaine Regional Council)
**Gaëlle LABRUNIE** Technician Assistant (I.E., Aquitaine Regional Council)
**Dr. NICOLE SMITH** Post-doc (ANR-PNANO QuantADN)
**Dr. SAMIR AMRANE** Post-doc (ANR-PNANO QuantADN)
**Dr. DANIEL RENCIUK** Post-doc (ANR-P3N G4Toolbox)
**Phong Lan THAO TRAN** PhD student (Ministry of research)
**Amandine RENAUD DE LA FAVERIE** PhD student (Ministry of research)

This team is part of the Unit "RNA: Natural and Artificial Regulation", INSERM/Université Bordeaux Segalen (Unit 869)

**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.**

Keywords / Expertise / Techniques: unusual nucleic acid structures, G-quadruplexes, drug-DNA interactions, telomeres and telomerase, thermodynamics, UV-absorbance, fluorescence and circular dichroism spectroscopies.

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), we investigated the role of a potential G4 in P53 alternative splicing.

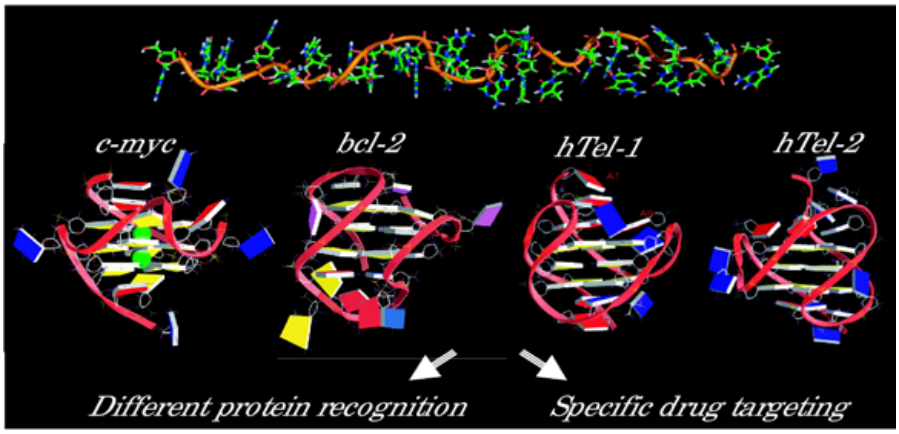


Figure 1. A G-rich single strand (top) may adopt different intramolecular G4 structures (bottom) depending on sequence and experimental conditions.

## 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.

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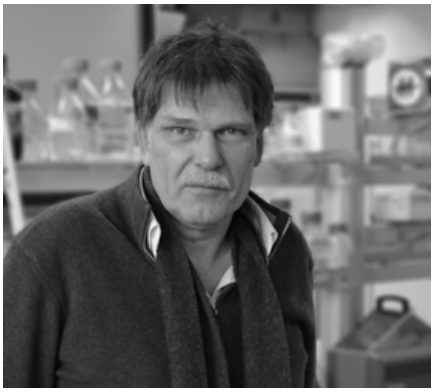
# VESICULAR TRANSPORT: MECHANISMS & REGULATION IN PANCREATIC β-CELLS



Pr. Jochen Lang
Professeur (CEI), Université Bordeaux I

Jochen Lang studied medicine as a fellow of the German University Foundation in Germany (U Wuerzburg, U Freiburg), France (Paris VI) and Switzerland (Université de Genève), with clinical clerkships in the US (Penn. State U.) and Canada (Bella Coola Indian Reserve, BC). He received his federal license and the FMGEMS in 1984. After a thesis in neuropharmacology he worked for 3 years at the Max-Planck-Institut, Martinsried. Subsequent to an internship in Medicine (Hôpital Universitaire de Genève) he joined Pr. C. B. Wollheim's Division at the Centre Medical Universitaire, Geneva, as an Assistant and later Associate Professor where he developed approaches on β-cells as a model for vesicular transport and its regulation. In 2000 he joined the IECB and created a cell biology group at the Université de Bordeaux I.

## Research team

**Dr. Jochen LANG** Team leader
**Dr. Bogdan CATARGI** Professor (PU-PH, Université Bordeaux Segalen)
**Dr. Gilles CHARPENTIER** Professor (P.U. University Bordeaux 1)
**Dr. Valérie LAGRÉE** Lecturer (MCU University Bordeaux 1)
**Dr. Pier SCOTTI** Lecturer (MCU University Bordeaux 1)
**Dr. Benoît ROGER** (Lecturer MCU University Bordeaux 1)
**Dr. Stephanie CHEVALIER** Lecturer (MCU University Bordeaux 1)
**Dr. Alexandra MILOCHAU** Assistant Engineer (IE, University Bordeaux 1)
**Julien GAITAN** Technician (University Bordeaux 1)
**Dr. Matthieu RAOUX** Post-doc (European Association for the Study of Diabetes)
**Julien PAPIN** PhD student/ATER (University Bordeaux 1)
**Benoît HASTOY** PhD student (MRT)

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

**Diabetes, a lifelong incapacitating disease, affects 5% of the population in Europe and we currently observe an epidemic increase in the two major forms of the disease, type 1 and type 2. Its complex etiology includes as an important facet deficient glucose recognition and insulin secretion from pancreatic β-cells. Insulin-secreting β-cells also provide a powerful model to dissect mechanisms and regulation of vesicular transport and fusion with the plasma membrane. Our studies on pancreatic β-cells and the islet micro-organ have three major goals: i) gaining insight in the interplay between the relevant proteins at different stages of exocytosis; ii) to investigate the regulation of protein expression and function by glucose and iii) to use islet cells as biosensors of insulin demand.**

Keywords / Expertise / Techniques: diabetes, exocytosis, vesicular transport, membrane fusion, regulation, calcium, glucotoxicity, toxin-driven permeabilisation, amperometry, patch-clamp, fluorescent videomicroscopy, microelectrode arrays, gene expression.

Pancreatic beta-cells have always been an excellent model to investigate vesicular transport. Cysteine string proteins are molecular chaperones at the synapse and in secretory cells localized attached to exocytotic vesicles. They exhibit precise domain architecture: an N-terminal J-domain that activates chaperones, the name-giving highly palmitoylated cysteine string and a variable C-terminus. We had shown that they are required for insulin secretion at a late stage of exocytosis and characterized a novel domain, the linker domain, situated between the J-domain and the cysteine string. We have now completed our study on their molecular architecture in demonstrating their functional dimerisation (Boal et al. Biochemistry, 2004), the requirements for palmitoylation (Boal et al., BBA, 2007) and more recently their interaction with synaptotagmin 9 via defined sites using biochemical approaches, modeling and FLIM (Boal et al., 2011). In summary, this work has allowed to characterize fully the role of the different domains of CSP in insulin exocytosis and to place the action of CSP clearly at the final step that is after triggering of membrane fusion by calcium influx into the cell.

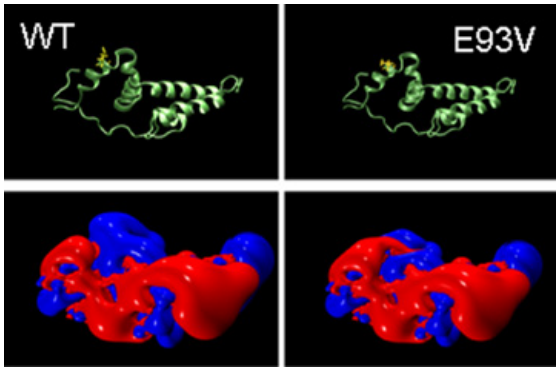



Figure 1. Folding of wt and mutant CSP

The SNARE proteins in insulin exocytosis are formed by SNAP25 and syntaxin 1 at the plasma membrane and VAMP2 on the secretory granule. The interaction and role of their cytosolic domains has been studied in detail whereas until recently only few data were available on the behavior and function of their transmembrane domains (TMDs). We jointly addressed the role of the TMD in a collaborative project (R. Oda, M. Laguerre, B. Desbats). The major observation concerns the unprecedented finding that the TMDs change drastically and reversibly their conformation, from alpha-helices to beta-sheets, solely depending on the peptide-lipid ratios. We propose that local enrichment of VAMP, as indeed seen during exocytosis, may promote membrane fusion as the bulky beta-sheets should disturb the bilayer architecture, a prerequisite to fusion. Indeed, such high local concentrations may well be attained under physiological conditions. To evaluate the potential role of these structural changes we set out to rationally design point mutants in the trans-

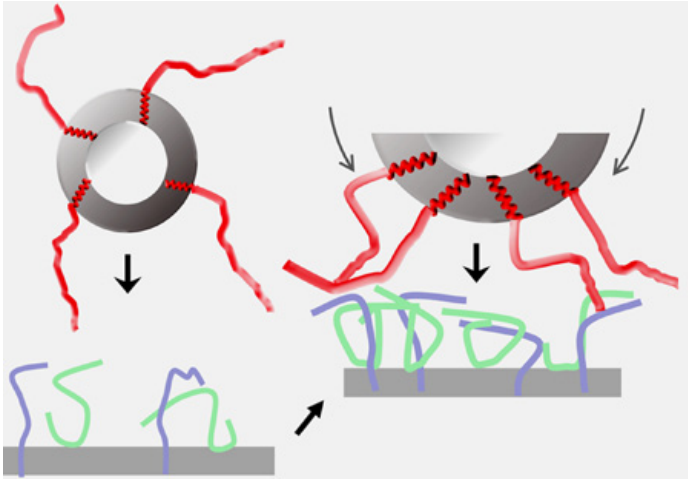


Figure 2. SNARE TMDs and membrane fusion

membrane domain that may alter the structural flexibility and henceforth induce functional consequences provided the dynamics of the TMDs play a role in membrane fusion (work in progress in collaboration with Dr D. Perrais, Institut Magendie).

We studied the effect of prolonged exposure of insulin-secreting cells to elevated glucose, also termed glucotoxicity, on the exocytotic machinery and its regulation. Glucotoxicity imitates to a certain extent the diabetic milieu. We observed a rapid loss of the secretory response with only a minor increase in apoptosis. Moreover, the secretion defect was also present upon exposure to KCl and even by direct stimulation with defined calcium-concentrations in semipermeabilized cells. As these stimuli partially or completely circumvent metabolic pathways and ion channels, a defect very distal in exocytosis must be present. Analysis of a panel some 30 exocytotic proteins revealed marked changes in the levels of several SNARE proteins and reduced amount of SNARE complexes. In a subsequent functional transcriptomics study we could identify ADCY as a major regulator whose down-regulation explains major characteristics of the phenotype in rat and human beta cells.

In a biotechnology project we used extracellular recordings from microelectrode arrays as noninvasive, long-term and repetitive approach to exploit the properties of islet cells as biosensor. The set-up is currently used not only for the development as biosensor, but also as an analytical tool for our research addressing issues of long-term regulation. We have already published two specialized reviews on the topic and deposited a patent.

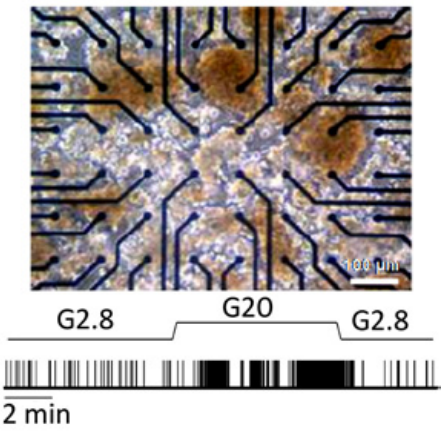



Figure 3. Glucose induced firing of islet cells

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# CELL SIGNALLING IN HEALTH & DISEASE

**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. Analysing 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.**

Dr. Elisabeth Génot
Directeur de recherche (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

**Dr. Elisabeth GÉNOT** Team leader
**Dr. IJsbrand KRAMER** Professor (PR1 Univ. Bordeaux 1)
**Dr. Frédéric SALTEL** Researcher (CR1 INSERM)
**Edith REUZEAU** Technician (TCE Univ. Bordeaux 1)
**Dr. Thomas DAUBON** Post-doc (ARC)
**Dr. Véronique VEILLAT** Post-doc (ANR)
**Dr. Anne LECLERCQ** Post-doc (FRM)
**Amélie JUIN** PhD student (Ministry of research)
**Isabel EGANA** PhD student (EU)
**Filipa CURADO** PhD student (EU)
**Audrey BERTHOU** Master student

This team is part of the unit "Fibrose Hépatique et Cancer du Foie", Université Bordeaux Segalen/INSERM (U889)

Keywords / Expertise / Techniques: GTPase, endothelial cells, adhesion, survival, cytoskeleton, podosomes, cell dynamics, Video-/confocal microscopy, transient and stable transfection, protein kinase activity assays, selective precipitation and in situ examination of active GTPases

Our aim is to understand some of the mechanisms by which endothelial cells (ECs) contribute to the pathophysiology of vascular diseases. We are studying how environmental cues impact on ECs 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 ECs represent a major target of its action. We focus our analysis on EC 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 to manipulate 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. How-

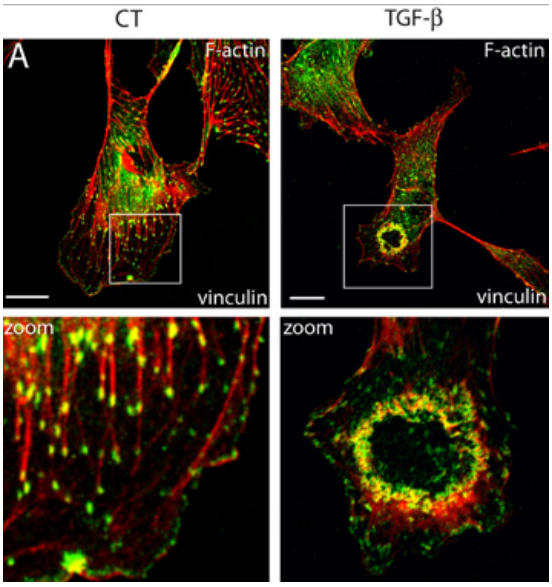


Figure 1. Endothelial podosome rosettes in cultured endothelial cells.
(A) Representative immunoconfocal images of F-actin (red) and vinculin (green) organisation in control (left panel) and TGFβ-treated (right panel) cultured aortic endothelial cells. In untreated cells, vinculin is localised at the tips of stress fibers. TGFβ-treated cells exhibit ring-like structures (podosome rosettes, right panel), where vinculin surrounds F-actin cores (tbottom panel: higher magnification of the boxed areasl). Bar, 10 µm.

ever, 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.

We have undertaken an extensive characterization of podosomes in different types of ECs. These analyses have brought to light novel components not described previously, which could be involved in specific EC functions of ECs. 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 ECs 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.

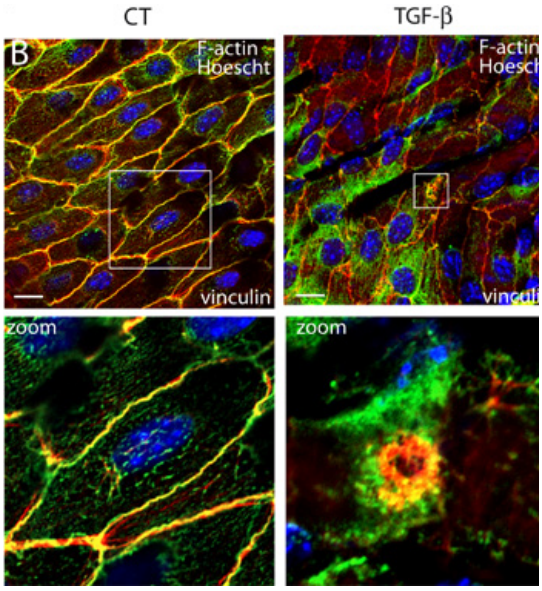


Figure 2: Endothelial podosome rosettes in the endothelium of an aortic vessel segment (B) Aortic vessel segments were prepared for immunofluorescence, labelled with phalloidin (red), vinculin (green) and Hoechst (blue) and mounted en face for confocal observation. Viewed face on, vinculin/F-actin staining 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 ECs 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).

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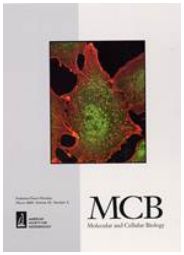


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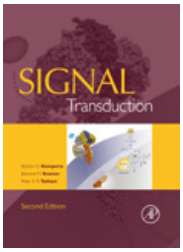


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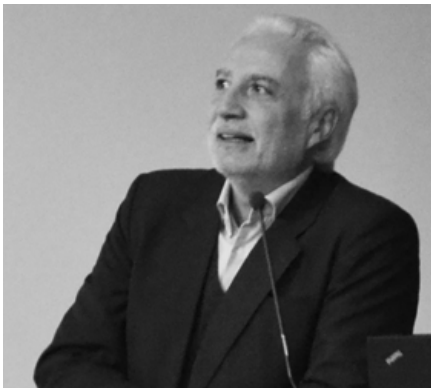
# MOLECULAR BASIS OF VULNERABILITY TO DRUGS



Dr. Pier Vincenzo Piazza
Directeur de recherche (DR1), INSERM

Pier Vincenzo Piazza was trained as an MD and a psychiatrist at the university of Palermo, Italy. During his psychiatry residency he entered a PhD program and devoted his career to basic research in the field of the pathophysiological basis of behavioral pathologies. He arrived in France as a post-doctoral fellow in 1988 and was hired by INSERM (chargé de recherche) in 1990. He developed his own group in 1995 in the INSERM unit 259 and was named director of the INSERM unit 588 in 2003. Since his arrival in Bordeaux, Dr. Piazza has principally studied the biological basis of the propensity to develop addiction shown by certain vulnerable individuals. This research has been developed over the years using a multitude of approaches including behavioral, system and molecular neurosciences.

## Research team

**Dr. Pier Vincenzo PIAZZA** Team leader
**Dr. Guillaume DRUTEL** Lecturer (MCU Université Bordeaux Segalen)
**Dr. Thierry LESTE-LASSERRE** Engineer (IE, INSERM)

The team is part of the laboratory "Physio-pathologie de la plasticité Neuronale", INSERM/Université Bordeaux Segalen (U862)

**An essential step for developing appropriate therapies for addiction is the identification of those factors that underlie the vulnerability of certain individuals to make the transition, first, from a sporadic drug use to a regular intensified drug intake, and then, to the compulsive drug-taking that characterizes true addiction. A decisive step in the understanding of the respective role of drugs and individuals in the transition to addiction was taken five years ago when it was demonstrated that in the rodent, after prolonged drug use, behaviors similar to the ones considered the landmark of addiction in humans appear (Deroche Gamonet et al., 2004). Addiction seems to result from an interaction between the degree of drug exposure and the degree of vulnerability in the exposed individual. Thus, addiction-like behavior appears only after extended access to the drug. However, despite similar drug intake in all subjects, addiction-like behaviors appear only in a few. Two different vulnerable phenotypes were leading to addiction in a two-step process. The first, the "drug prone" phenotype facilitated the development of sustained drug use setting the conditions for true addiction. However the shift to true addiction after sustained drug use was determine by a second "addiction prone" phenotype that determined the loss of control on drug intake observed only in reduced proportion of users.**

Keywords / Expertise / Techniques: dopamine, glucocorticoids, neurosteroids, addiction, gene profiling, behaviour, neurochemistry, transgenesis.

Over the last years, the general aim of our research project was the identification of the psychobiological basis of transition to addiction and in particular the one of the addiction prone phenotype. To tackle this issue we developed two complementary strategies: 1. the comparison of addict and non addict rats; 2. the transfer of the addiction model from rat to mice.

### Comparison of addicts and non addict rats

Our model presents a unique advantage for uncovering the biological basis of the addiction prone phenotype. Thus, with the exception of the very few challenges that evaluate addiction-like behaviors (a total of 3-4 sessions), addict and non addict rats do not differ for drug intake over the rest of the experiment (60 to 80 days). Since addict and non addict animals have equal drug intake, the comparison of the two groups should allow singling out changes specifically related to addiction from drug-induced, but addiction unrelated, modifications.
Addict and non addict animals were principally compared at two levels: a) gene expression, studied using Affymetrix microarrays and real time qPCR; b) synaptic plasticity, studied by analyzing LTP and LTD.

### Transfer to mice of the addiction model that was initially developed in rat

This research line was developed in order to enable the use of conditional transgenic animals to investigate causal relationships between specific biological factor and vulnerability to develop addiction. Therefore, two years ago, based on our rat model (Deroche Gamonet et al., 2004) and on one of the longest expertise in intravenous self-administration in mice, we started investigating addiction-like behavior in C57BL/6J mice, the most common genetic background of transgenic mice.

### Major results

Addict and not addict animals adapt very differently to cocaine. After a short period of self-administration, before addiction-like behavior appears, synaptic plasticity (LTD) was completely suppressed by cocaine in all individuals. However after three months, when addiction develops in certain subjects, non-addict animals recovered this crucial function whilst addict did not. These results indicate that transition to addiction is associated with the incapacity to adapt to drug-induced loss in synaptic plasticity, whilst the

ability to maintain a controlled drug intake is associated with the recovery of this crucial function. The recovery of LTD in non-addict animals was associated with changes in the expression of neuronal genes relevant to the control of synaptic plasticity. In contrast, in addicts, the lack of recovery in LTD was associated with changes in the expression of genes extrinsic to neurons and involved in innate and acquired immunity.

More and more evidence indicate that activation of the immune response can modify synaptic plasticity (Di Filippo et al., Trends in Pharmacological Sciences, 2008, 29(8):402-412). A shift from an intrinsic neuronal adaptation to an immune-driven neuronal desadaptation could be the pathophysiological mechanism mediating the shift from drug use to addiction and may be more generally from normal to pathological behavior? It is certain that a lot remains to be done to prove this concept. Unfortunately, this is the case each time a discovery opens a completely unforeseen avenue of investigation. The model of addiction that we have now successfully developed in mice will be extremely helpful to establish causal relationships of identified key genes for most of which specific mutants are available.

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# DYNAMICS OF CELL GROWTH & CELL DIVISION


## Dr. Derek McCusker
Chargé de Recherche (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. Derek MCCUSKER** Team leader
**Dr. Mini Jose DEEPAK** Post-doc (Université Bordeaux Segalen)
**Mr. Romain MITTEAU** PhD Student (Université Bordeaux Segalen)

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

**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.**

Keywords / Expertise / Techniques: cell growth, cell cycle, cell polarity, Rho GTPase, endocytosis, exocytosis, cyclin-dependent kinase, phosphorylation, cell biology, TIRF-microscopy, membrane dynamics, biochemistry, mathematical modeling.

Recently, I identified a key role for cyclin dependent kinase 1 (Cdk1) in the initiation and maintenance of polarized growth in the model eukaryote Saccharomyces cerecisiae. I found that 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 fluorescence 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). 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,

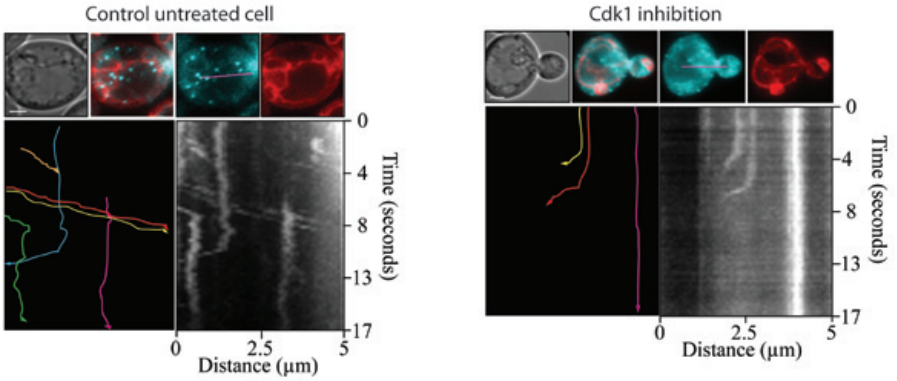


Figure 1. Chemical genetic inhibition of Cdk1 results in aberrant post-Golgi vesicle targeting. 80-100 images were then acquired at 220 ms intervals and stacked vertically to generate kymographs. In each set, the top 4 panels show a DIC image, merged images of post-Golgi vesicles (cyan) and FM4-64 (red), 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 colored line represents the trajectory of a different post-Golgi vesicle, with the arrowhead showing the direction of movement Scale bar is 2 µm.

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.

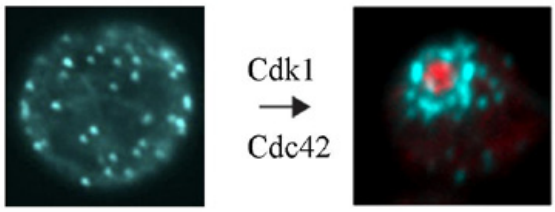


Figure 2. Early in the cell cycle (left image), endocytosis-associated actin patches (cyan) are distributed randomly throughout the cytoplasm. During the initiation of polarized growth, endocytic vesicles (cyan) corral a central zone of exocytic post-Golgi vesicles (red) that are targeted to a tight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

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# GENOME REGULATION & EVOLUTION

Dr. Denis Dupuy
Avenir – Inserm/ Fondation Bettencourt-Schueller

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. Denis DUPUY** Team leader
**Dr. Karine REBORA** Post-doc (Inserm/ Fondation Bettencourt-Schueller)
**Ilyass ZNIBER** PhD student (Aquitaine Regional Council)
**Rosina GIORDANO** PhD student (MNRT)
**Léo GUIGNARD** Software specialist (Inserm/ Fondation Bettencourt-Schueller)

This team is part of the Unit "RNA: Natural and Artificial Regulation", INSERM/Université Bordeaux Segalen (Unit 869)

**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.**

Keys words / Expertise / Techniques: C. elegans, development, GFP, systems biology, bioinformatics, high throughput RNAi, in vivo, miRNA, splicing, post transcriptional regulation, evolution

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

We 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

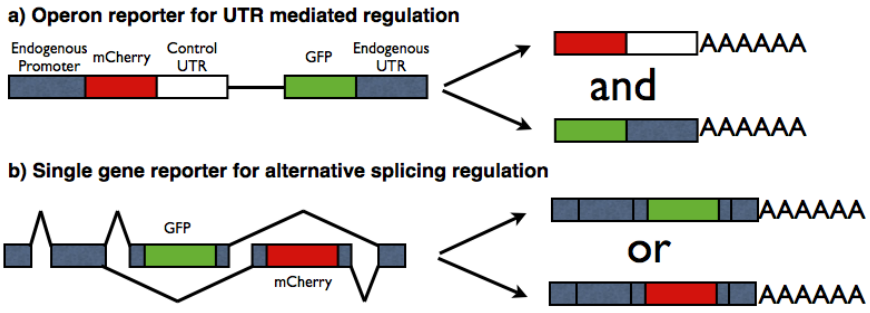


Figure 1. Two-color reporters for in vivo post-transcriptional regulation studies. a) The function of endogenous UTR sequences will be tested by direct comparison of expression levels with the unc-54 control expressed from the same double-reporters operon. b): Tissue and temporal specificity of alternate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

using a custom-made microarray, only ~20% of the tested genes showed a significant change in isoform ratio in the course of development27. 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.

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# 2009-2010 PUBLICATIONS & PATENTS

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## 2009-2010 patents


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4. Raoux M., Charpentier G., Catargi B., Renaud S., Lang J. Patent "Capteur pour la mesure des besoins d'insuline d'un patient et procédé de fabrication de celui-ci" (2010) Patent No FR 10/20502

# 2009-2010 RESEARCH CONTRACTS

## European contracts

Coordinated by IECB researchers/IECB researchers as participants

| IECB Researcher | Funding body | Research project | Period |
|---|---|---|---|
| J.J. TOULMÉ | FP6 – NoE | Special non invasive Advances in Foetal and neo-natal Evaluation network | 2004-2009 |
| I. HUC | FP6 – Marie Curie RTN | Dynamic combinatorial chemistry | 2006-2009 |
| A. BRISSON | FP7 – NMP | Functional assays for membrane protein on nanostructured supports (AS-MENA) | 2008-2010 |
| P.V. PIAZZA | DG RTD | Phenotypical characterisation of animal models for neuropsychiatric disorders (#LHSM-CT-2007-037669) | 2007-2009 |
| I. HUC | FP7 Marie Curie IIF | Helical transporters: aromatic foldamers as drug delivery carriers | 2009-2010 |
| I. HUC | FP7 Marie Curie IEF | Helical transporters: aromatic foldamers as drug delivery carriers | 2009-2010 |
| E. GÉNOT | FP7 Marie Curie ITN | Tissue Transmigration Training Network (T3Net) | 2009-2012 |
| I. HUC | FP7 Marie Curie IAPP | Foldamers against protein-protein interactions (FOLDAPPI) | 2009-2012 |
| M. LAGUERRE | FP7 Marie Curie IAPP | Foldamers against protein-protein interactions (FOLDAPPI) | 2009-2012 |
| D. MCCUSKER | FP7 Marie Curie IRG | GROWTHANDDIVISION | 2009-2012 |
| I. HUC | FP7 Marie Curie IIF | Aromatic foldamers for single molecule electronics | 2010-2011 |

## National contracts

Coordinated by IECB researchers/IECB researchers as participants

| IECB Researcher | Funding body | Research project | Period |
|---|---|---|---|
| G. GUICHARD | ANR Blanc | SYNTHEFOLD | 2005-2009 |
| E. GÉNOT | ANR Blanc | PODOSOMES | 2006-2009 |
| J.L. MERGNY | ANR PNANO | QUANTADN | 2006-2011 |
| A. BRISSON | ANR EMPB | MPAuA5 | 2007-2009 |
| S. FRIBOURG | ANR | MRARE RIBODBA | 2007-2009 |
| J. LANG | ANR PCV | Exodynamics | 2007-2010 |
| P.V. PIAZZA | ANR Blanc | NEUROLAPS – Identification and selective manipuylation of neuronal micro-circuits implicated in relapse of fear and addiction behaviors | 2007-2010 |
| P.V. PIAZZA | ANR RIB | High Content Methods for Drug Discovery» « HICOMET» | 2007-2010 |
| S. QUIDEAU | ANR Blanc | ELLAG'INNOV – Synthèse et évaluation antitumorale d'ellagitannins C-aryl glycosidiques et d'analogues de ces polyphénols naturels. | 2007-2010 |
| J.J. TOULMÉ | ANR SEST | Integration of aptamer-based devices into microchip : direct analysis of algal toxins in environmental samples | 2007-2010 |
| G. GUICHARD | ANR PCV | TRANSPEP | 2007-2011 |
| I. HUC | ANR-PCV | Directed evolution of oligonucleotides/synthetic oligomers complexes for the recognition of Hepatitis C Virus proteins | 2007-2011 |
| M. TEICHMANN | ANR Blanc | RegPolStress | 2007-2011 |
| J.J. TOULMÉ | ANR PCV | Directed evolution of oligonucleotide/synthetic oligomer complexes for specific recognition of HCV proteins | 2007-2011 |
| M. LAGUERRE | ANR MitoScop | Multi-level modelling of mitochondrial energy metabolism | 2008-2010 |
| R. ODA | ANR-PCV | Dynamic structures of SNARE transmembrane domains and lipids in membrane organization and their function in exocytosis | 2008-2011 |
| J.J. TOULMÉ | ANR BiotecSan | Nanohybrids grafted to aptamers targeting tumoral tissue for multimodal detection and therapy | 2008-2011 |
| M. LAGUERRE | ANR PIR | Biocapteur Origami ADN : un dynamomètre moléculaire | 2009 |
| J.J. TOULMÉ | ANR Blanc | G4 toolbox | 2009-2011 |

| IECB Researcher | Funding body | Research project | Period |
|---|---|---|---|
| G. GUICHARD | ANR PiriBio | SYMULI | 2009-2012 |
| I. HUC | ANR Blanc | Foldamer sequences as self-organized molecular capsules | 2009-2012 |
| J.L. MERGNY | ANR-Blanc | G4-ToolBox | 2009-2012 |
| J.L. MERGNY | ANR-P3N | F-DNA | 2009-2013 |
| E. GÉNOT | ANR | VASCULOSOMES | 2010-2012 |
| G. GUICHARD | ANR RPD | UREKAT | 2010-2012 |
| S. FRIBOURG | ANR | RIBOPRE40S | 2010-2013 |
| R.ODA | ANR-Blanc | Functional hybrid organic-inorganic nanohelices: studies of the exalted phonomena at nanometric scales | 2010-2013 |
| S. QUIDEAU | ANR Blanc | IODINNOV | 2010-2013 |
| C. DI PRIMO | ANR Blanc | ECSTASE : Développement d'un aptacapteur avec amplification électrocatalytique pour la détection sensible et éniantosélective de drogues amphétaminiques | 2010-2013 |
| C. DI PRIMO | ANRS | Etude des régions de l'ARN viral impliquées dans la réplication de l'ARN du VHC | 2008-2010 |
| J. LANG | CNRS | Programme « Longévité » | 2009 |
| G. GUICHARD | CNRS | ATIP Program | 2009-2011 |
| J.L. MERGNY | CNRS-Interdisciplinary Program | Screening | 2010-2011 |
| M. LAGUERRE | INCa | Rôles de la Reptine et de la Pontine dans la carcinogénèse hépatique | 2010-2013 |
| P.V. PIAZZA | MILDT/INCa | De l'usage de la cocaine à l'addiction: étude de bases biologiques et comportementales au moyen d'un modèle animal pertinent de la pathologie. | 2009-2011 |
| J.L. MERGNY | INCa | P53 gene and quadruplexes | 2010-2012 |
| E. GÉNOT | INSERM | Post-Doctoral Fellowship | 2006-2009 |
| S. FRIBOURG | Inserm | Avenir award | 2007-2009 |
| G. GUICHARD | Ministry of Research | Pre-doctoral Fellowship | 2007-2010 |
| G. GUICHARD | Ministry of Research | Pre-doctoral Fellowship | 2008-2011 |
| E. GÉNOT | Ministry of Research | Pre-doctoral Fellowship | 2009-2011 |
| I. HUC | Ministry of Research | Pre-doctoral Fellowship | 2010-2013 |
| J.L. MERGNY | Ministry of Research | Chaire Université-Organisme | 2010-2014 |

# Regional contracts

Coordinated by IECB researchers

| IECB Researcher | Funding body | Contract | Period |
|---|---|---|---|
| D. DUPUY | Aquitaine Regional Council | Starting grant | 2008-2010 |
| E. GARANGER | Aquitaine Regional Council | Starting grant | 2010-2013 |
| E. GÉNOT | Aquitaine Regional Council - INSERM | Pre-doctoral Fellowship | 2007-2009 |
| G. GUICHARD | Aquitaine Regional Council | Pre-doctoral Fellowship | 2009-2011 |
| I. HUC | Aquitaine Regional Council - CNRS | Pre-doctoral Fellowship | 2010-2013 |
| J. LANG | Aquitaine Regional Council -FEDER | DELIVRER | 2008-2010 |
| C. MACKERETH | Aquitaine Regional Council | Starting grant | 2008-2010 |
| D. MCCUSKER | Aquitaine Regional Council | Molecular mechanisms that coordinate cell growth and cell division | 2009-2011 |
| JL MERGNY | Aquitaine Regional Council | Starting grant | 2009-2012 |
| PV PIAZZA | Aquitaine Regional Council | Etude de la physiopathologie de la plasticité neuronale | 2009 |

| IECB Researcher | Funding body | Contract | Period |
|---|---|---|---|
| S. QUIDEAU | Aquitaine Regional Council | Research programme funding | 2009-2010 |
| E. GARANGER | GIS AMA | Conception et synthèse de matériaux hybrides polymère/peptide par voies « classique et recombinante » : nano-objets auto-assemblés multifonctionnels d'intérêt biologique. | 2010-2013 |
| J. LANG | Université Bordeaux 1 | BQR | 2009 |
| G. GUICHARD | Université Bordeaux 1 | Post-doctoral fellowship | 2009-2010 |
| G. GUICHARD | Université Bordeaux 1 | Starting grant | 2009-2010 |
| E. GARANGER | Université Bordeaux 1 | Starting grant | 2010-2013 |
| G. GUICHARD | Université de Strasbourg | Post-doctoral Fellowship | 2008-2009 |

# Charity-funded research projects

Coordinated by IECB researchers/IECB researchers as participants

| IECB Researcher | Funding body | Research project | Period |
|---|---|---|---|
| J.L. MERGNY | Association Fr. Ataxie de Friedreich | Screening | 2010-2011 |
| E. GÉNOT | ARC-INCa "Tumoral Micro-environnement" grant | Cell migration in the tumor microenvironment : dynamics and function of podosomes/invadopodia. | 2007-2009 |
| E. GÉNOT | Association pour la Recherche sur le Cancer (A.R.C.) | Recherche du rôle de la protéine adaptatrice Tks5 dans l'invasiveté des cellules endothéliales | 2009-2010 |
| E. GÉNOT | Association pour la Recherche sur le Cancer (A.R.C.) | Post-Doctoral Fellowship | 2009-2011 |
| G. GUICHARD | Association pour la Recherche sur le Cancer (A.R.C.) | Post-doctoral Fellowship | 2010-2013 |
| I. HUC | Association pour la Recherche sur le Cancer (A.R.C.) | Pancreas cancer: towards a new therapeutic approach | 2010-2012 |
| M. LAGUERRE | Association pour la Recherche sur le Cancer (A.R.C.) | Post-doctoral grant "PhD return" | 2009- 2011 |
| M. LAGUERRE | Association pour la Recherche sur le Cancer (A.R.C.) | La Reptine, une nouvelle cible thérapeutique en cancérologie. Rôle de l'activité ATPase et fonctions cytoplasmiques | 2009- 2011 |
| D. DUPUY | Bettencourt-Schueller Fondation | Avenir Award | 2008-2010 |
| J. LANG | European Foundation for the Study of Diabetes | MSD Research Grant | 2010-2011 |
| E. GÉNOT | Fondation de France, Recherche Cardiovasculaire (F.D.F.) | Rôle des podosomes dans le remodelage vasculaire | 2007-2009 |
| D. DUPUY | Fondation pour la Recherche Medicale (FRM) | Prix Spécial Aquitaine | 2008-2010 |
| D. MCCUSKER | Fondation pour la Recherche Medicale (FRM) | Installation grant | 2010 |
| J.L. MERGNY | Fondation pour la Recherche Médicale | Installation grant | 2010 |
| E. GÉNOT | Ligue Nationale française contre le Cancer (L.N.F.C.C.) | Interaction cellules cancéreuses – cellules endothéliales sinusoïdales : implication des invadopodes dans la formation des métastases hépatiques. | 2009 |
| E. GÉNOT | Ligue Nationale française contre le Cancer (L.N.F.C.C.) | Etude du rôle de la protéine Tks5 dans l'assemblage des podosomes et des invadopodes | 2010 |
| J. LANG | European Foundation for the Study of Diabetes | MSD Research Grant | 2010-2011 |
| J. LANG | Société française du Diabète | Post-doctoral fellowship | 2009-2010 |

# Contracts with the industry

Coordinated by IECB researchers

| IECB Researcher | Funding body | Research project | Period |
|---|---|---|---|
| L. GHOSEZ | Confidential | Undisclosed | 2009-2010 |
| G. GUICHARD | ImmuPharma & ANRT | Pre-doctoral Fellowship | 2010-2012 |
| G. GUICHARD | ImmuPharma & ANRT | 2 Pre-doctoral Fellowships | 2006-2009 |
| G. GUICHARD | ImmuPharma | CIFRE research contract | 2006-2009 |
| I. HUC | CIVB | Development of fluorescent probes for the detection of wine acids | 2010-2013 |
| J.L. MERGNY | Sanofi | KRas oncogene | 2009-2010 |
| S. QUIDEAU | CIVB | Undisclosed | 2008-2010 |
| S. QUIDEAU | CIVB | Undisclosed | 2007-2010 |
| S. QUIDEAU | CIVB | Undisclosed | 2010-2013 |
| S. QUIDEAU | CIVB | Undisclosed | 2010-2013 |
| S. QUIDEAU | Servier | Undisclosed | 2007-2010 |
| S. QUIDEAU | LVMH | Undisclosed | 2008-2011 |
| J.J. TOULMÉ | LVMH - DIOR | Selection and design of aptamers against two targets for potential application in cosmetology | 2007-2010 |

# Other contracts

Coordinated by IECB researchers/IECB researchers as participants

| IECB Researcher | Funding body | Research project | Period |
|---|---|---|---|
| D. DUPUY | Egide (Franco-Japanese collaboration) | Sakura programme | 2009-2010 |
| S. FRIBOURG | IECB | Internal IECB call | 2008-2009 |
| G. GUICHARD | IECB | Starting grant | 2010 |
| J. LANG | IECB internal grant | Exodynamics | 2008 |
| G. GUICHARD | International Center for Frontier Research in Chemistry (FRC) Strasbourg | Multivalent ligands | 2009 |
| E. GÉNOT | National Science Foundation of America (NSF) (USA) | In search of best methods to illustrate complex information | 2009-2011 |

# 2009-2010 COLLABORATIONS

## Pole 1 - Structural Biology & Biophysics

### Molecular modeling
Dr. Michel Laguerre

1. Dr. B. Larijani, Cell Biophysics Laboratory, Cancer Research UK (London, UK)
2. Dr. J. Parello, Department of Pharmacology, Vanderbilt University School of Medicine (Nashville, USA)
3. Pr. S. Wettig, School of Pharmacy, University of Waterloo (Ontario, Canada)
4. Pr. L. Romsted, Rutgers Laboratories, State University of New Jersey (Pistacataway, USA)
5. Pr. B. Gopal Bag, Department of Chemistry and Chemical Technology, Vidyasagar University Midnapore (India)
6. Dr. Elisabeth Davioud-Charvet, Biochemie-Zentrum Heidelberg (Germany)
7. Pr. J.-L. Kraus, IBDML UMR CNRS 6216, Laboratoire de Chimie Biomoléculaire, Université Aix-Marseille II (France)
8. Dr. F. Argoul Laboratoire de Physique de L'ENS Lyon (France)
9. Société FLUOFARMA (Pessac, France)
10. Pr. P. Barthélémy, Unité Inserm U869, ARNA, Université Bordeaux Segalen (Bordeaux, France)
11. Pr. J. Rosenbaum & P. Lestienne, Unité Inserm U889, Université Bordeaux Segalen (Bordeaux, France)
12. Pr. C. Cullin, IBGC, UMR CNRS 5095, Université Bordeaux Segalen (Bordeaux, France)
13. Dr. I. Pianet, CESAMO, Université Bordeaux I (Bordeaux, France)
14. Pr. A. Brisson, IECB, UMR 5248 (Bordeaux, France)
15. Dr. B. Desbat, CBMN, UMR 5248 (Bordeaux, France)
16. Pr. J.M. Schmitter, CBMN, UMR 5248 (Bordeaux, France)
17. Dr. E.J. Dufourc CBMN, UMR 5248 (Bordeaux France)
18. Dr. R. Oda, IECB, Pole 1, UMR 5248 (Pessac, France)
19. Dr. I. Huc, IECB, Pole 2, UMR 5248 (Pessac, France)
20. Pr. L. Ghosez, IECB, Pole 2, UMR 5248 (Pessac, France)
21. Pr. J. Lang, IECB, Pole 4, UMR 5248 (Pessac, France)
22. Dr. J.J. Toulmé, IECB, Pole 3, INSERM U 869 (Pessac, France)
23. Pr. J.A. Veenstra, Université de Bordeaux, CNRS CNIC UMR 5228 (Talence, France)
24. Pr. C. Arpin, Université Bordeaux Segalen, CNRS - UMR 5234 (Bordeaux, France)

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

1. Dr. Yevgen Karpichev, Ukraine Academy of Science (Donetsk, Ukraine)
2. Pr. Gianfranco Savelli, Perugia University (Perugia, Italy)
3. Pr. Hirotaka Ihara, Kumamoto University (Kumamoto, Japan)
4. Pr. Larry Romsted, Rutgers University (Piscataway, USA)
5. Pr. Ronald Sauers, Rutgers University (Piscataway, USA)
6. Dr. Michel Laguerre, IECB, Pole 1, CNRS UMR 5248 (Pessac, France)
7. Dr. Erick Dufourc, CMBN, CNRS UMR 5248 (Pessac, France)
8. Dr. Ivan Huc, IECB, Pole 2, CNRS UMR 5248 (Pessac, France)
9. Pr. Jochen Lang, IECB, Pole 4, CNRS UMR 5248 (Pessac, France)
10. Dr. Bernard Desbat, CMBN, CNRS UMR 5248 (Bordeaux, France)
11. Dr. Dario Bassani, ISM (Bordeaux, France)
12. Dr. Thierry Buffeteau, ISM (Bordeaux, France)
13. Dr. Christophe Cullin, IBGC (Bordeaux, France)
14. Dr. Marie-Hélène Delville, ICMCB (Bordeaux, France)

### Molecular imaging & nanobiotechnology
Pr. Alain Brisson

1. Pr. S. Cutting, Royal Holloway (London, UK)
2. Pr. S. Pikula, Nencki Institute (Warsaw, Poland)
3. M. De Cuyper, University of Leuven (Belgium)
4. R. Richter, CICBiomagune (San Sebastian, Spain)

## Pole 2 - Organic & Bioorganic Chemistry

### Supramolecular bioorganic & biomimetic chemistry
Dr. Ivan Huc

1. Pr. S. Balasubramanian, Cambridge University, Department of Chemistry (Cambridge, UK)
2. Dr. H. Jiang, Chinese Academy of Science, Institute of Chemistry (Beijing, China)
3. Dr. J. Nitschke, Cambridge University, Department of Chemistry (Cambridge, UK)
4. Dr. M. Takafuji, Department of Applied Chemistry, Univ. Kumamoto (Kumamoto, Japan)
5. Pr. T. Ha, Department of Chemistry, Univ. Illinois (Urbana, USA)
6. Dr. A. Schening Technical Univ. Eindhoven (Eindhoven, Netherlands)
7. Pr. D. Dubreuil, Univ. Nantes (Nantes, France)
8. Dr. M.-H. Delville, ICMCB (Bordeaux, France)
9. Dr. C. Staedel, INSERM U869 (Bordeaux, France)
10. Dr. R. Oda, CNRS-U.Bx1, UMR 5248 (Bordeaux, France)
11. Pr. J.M. Léger, Université Bordeaux Segalen, Laboratoire de Pharmacochimie (Bordeaux, France)
12. Dr. T. Buffeteau, CNRS-U.Bx1, UMR 5255 (Bordeaux, France)

### Synthesis & activity of natural substances
Pr. Stéphane Quideau

1. Pr. J. M. Aizpurua, University of the Basque Country (San Sebastian, Spain)
2. Pr. B. Baker, University of Notre Dame (Notre Dame, USA)
3. Pr. A. Sewell, University of Cardiff, School of Medicine (Cardiff, UK)
4. Pr. J. Charris, University Central of Venezuela (Caracas, Venezuela)
5. Pr. L. Rojas, University of the Andes (Merida, Venezuela)
6. Pr. O. Dangles, Université d'Avignon (Avignon, France)
7. Pr. M.-A. Lacaille-Dubois, Université de Dijon (Dijon, France)
8. Prs. P.-L. Teissedre & C. Saucier, ISVV (Bordeaux, France)
9. Dr. L. Ducasse, ISM, Université de Bordeaux (Bordeaux, France)
10. Dr. T. Buffeteau and D. Cavagnat, ISM, Université de Bordeaux (Bordeaux, France)
11. Dr. C. Di Primo, INSERM/IECB (Bordeaux, France)

### Peptidomimetic chemistry
Dr. Gilles Guichard

1. Pr. Wolfgang Maison, Univ. Giessen (Giessen, Germany)
2. Pr. Stefan Matile, Univ. Geneva (Geneva, Switzerland)
3. Dr. Claude Didierjean, Univ H. Poincaré (Vandoeuvre lès Nancy, France)
4. Dr. Eric Ennifar, IBMC (Strasbourg, France)
5. Pr. Sylvie Fournel, IBMC (Strasbourg, France)
6. Pr. Brigitte Jamart-Grégoire, ENSIC (Nancy, France)
7. Dr. Philippe Le Grel, Univ. Rennes (Rennes, France)
8. Pr. Yves Mely, Univ. Strasbourg (Strasbourg, France)
9. Dr. Olivier Micheau, INSERM (Dijon, France)
10. Dr. Emeric Miclet, UPMC (Paris, France)
11. Pr. Nicolas Winssinger, ISIS (Strasbourg, France)

### Organic & medicinal chemistry
Pr. Léon Ghosez

1. G. Rossey, Sanofi-Aventis (Montpellier, France)

## Pole 3 - Molecular Recognition

### Small RNAs & aptamers
Dr. Jean-Jacques Toulmé

1. Dr. Gait Michael, MRC (Cambridge, UK)
2. Pr. Desmecht Daniel, Faculté de Médecine Vétérinaire (Liège, Belgium)
3. Pr. Schroeder Renée, University of Vienna (Vienna, Austria)
4. Dr. Gorka Basañes Asua, Universidad del Pais Vasco (Bilbao, Spain)
5. Dr. Fribourg Sébastien, Inserm, IECB (Pessac, France)
6. Dr. Huc Ivan, CNRS, IECB (Pessac, France)
7. Pr. Barthélémy Philippe, Inserm, University of Bordeaux (Bordeaux, France)
8. Dr. Allard Michèle, University of Bordeaux, CHU Bordeaux (Bordeaux, France)
9. Pr. Peyrin Eric, CNRS, University of Grenoble (Grenoble, France)
10. Dr. Michel Ventura, CNRS, University of Bordeaux (Bordeaux, France)
11. Dr. Eric Chevet, Inserm, University of Bordeaux (Bordeaux, France)
12. Pr. Stéphane Quideau, CNRS, University of Bordeaux (Bordeaux, France)
13. Pr. Moenner Michel, INSERM, University of Bordeaux (Pessac, France)
14. Dr. Génot Elisabeth, INSERM, University of Bordeaux (Pessac, France)
15. Dr. Slama-Schwok, INRA (Jouy-en-Josas, France)

### Gene regulation & tumor research
Pr. Martin Teichmann

1. Dr. Daniel Besser, Max-Dellbrück Center (Berlin, Germany)
2. Pr. Robert G Roeder, The Rockefeller University (New York, USA)
3. Pr. Giorgio Dieci, Universita' di Parma (Parma, Italy)
4. Pr. Michael Kessel, Max-Planck Institute for Biophysical Chemistry (Göttingen, Germany)

### Structural biochemistry
Dr. Sébastien Fribourg

1. Dr. U. Kutay, ETH Zurich (Zurich, Switzerland)
2. Pr. M. Teichmann, IECB (Bordeaux, France)
3. Pr. P.E. Gleizes, LBME (Toulouse, France)
4. Dr. Y. Henry, LBME (Toulouse, France)
5. Dr. P. Legrand, Synchrotron SOLEIL (Paris, France)
6. Dr. P. Legrand, Synchrotron SOLEIL (Paris, France)
7. Dr. C. Mackereth, IECB (Bordeaux, France)

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

1. Dr. Bernd Simon, European Molecular Biology Laboratory (Heidelberg, Germany)
2. Dr. Michael Sattler, Helmholtz Zentrum, Technische Universität München (Munich, Germany)
3. Dr. Sébastien Fribourg, IECB, Inserm U869 (Pessac, France)
4. Dr. Lionel Minvielle-Sébastia, IECB, Inserm U869 (Pessac, France)
5. Dr. Michael Nilges, Institut Pasteur (Paris, France)

### Unusual nucleic acid structures
Dr. Jean-Louis Mergny

1. Dr. R. Eritja, IRB (Barcelona, Spain)
2. Pr. A.T. Phan, NTU (Singapore)
3. Pr. N. Royle, U. Leicester (Leicester, UK)
4. Pr. J. L. Huppert, Cavendish Lab (Cambridge, UK)
5. Dr. Y. Pommier, NIH (Bethesda, USA)
6. Dr. M.P. Teulade-Fichou, Institut Curie (Orsay, France)
7. Dr. D. Monchaud, U. Bourgogne (Dijon, France)
8. Dr. A. Nicolas, Institut Curie (Paris, France)
9. Pr. J.F. Riou, MNHN (Paris, France)
10. Dr. D. Gomez & P. Calsou, IPBS (Toulouse, France)
11. Dr. J.J. Toulmé, IECB (Pessac, France)
12. Dr. B. Rayner, U869 (Bordeaux, France)

## POLE 4 - Molecular & Cellular Biology

### Vesicular transport: mechanisms & regulation in pancreatic β-cells
Pr. Jochen Lang

1. Dr. N. Moustaïd Moussa, University of Tennessee, Department of Nutrition (Knoxville, USA)
2. Dr. J.C. Jonas, ULB, Dept. Endocrinology (Louvain La Neuve, Belgium)
3. Dr. F. Pattou, INSERM ERIT-M 0106, Cellular Therapy of Diabetes, CHU Lille (Lille, France)
4. Dr. P. Vacher, Institut Bergonié, Université Bordeaux Segalen (Bordeaux, France)
5. Dr. S. Renaud, CNRS, ENSEIRB (Bordeaux, France)
6. Dr. M. Laguerre, IECB, CNRS-UMR 5248 - Université Bordeaux 1 (Pessac, France)
7. Dr. R. Oda, IECB, CNRS-UMR 5248 - University Bordeaux-1 (Pessac, France)

### Cell signalling in health & disease
Dr. Elisabeth Génot

1. Dr. J. Kremerskothen, Department for Molecular Nephrology, Internal Medicine Dep., University Clinic Münster (Münster, Germany)
2. Dr. S. Linder, Institut für Kreislaufkrankheiten, Virology and Hygiene (Hamburg, Germany)
3. Dr. H-R Dahmani, Laboratoire de Recherches en didactique des Sciences, ENS Kouba (Algers, Algeria)
4. Pr. P. Schneeberger, Laboratoire Cultures Education Sociétés, Université Bordeaux Segalen (Bordeaux, France)
5. Dr. R. Rossignol, INSERM U688, Université Bordeaux Segalen (Bordeaux, France)

### Molecular basis of vulnerability to drugs
Dr. Pier Vincenzo Piazza

1. S. Cabib, Institut de Psychologie (Roma, Italy)
2. E.R. De Kloet, Division de sciences Biopharmaceutiques - centre de recherche pharmaceutique (Leiden, Netherlands)
3. Spanagel, Institut Max Planck (Munich, Allemagne)
4. R. Maldonado, Department of experimental and health sciences - Neuropharmacology Unit (Barcelona, Spain)
5. F. Tronche, Collège de France (Paris, France)

# 2009-2010 CONFERENCES & SEMINARS

Invited participation in international meetings / Participation in national meetings, invited seminars and courses and non-invited contribution to international meetings

## Pole 1 - Structural Biology & Biophysics

### Molecular modeling

- Rutgers University, N.J., USA, October 26 2010 (M. Laguerre)
- 4èmes Journées de l'Association Bordelaise de Cristallographie, Bordeaux, France, June 22-23 2010 (M. Laguerre, J. Dessolin)
- Centre de Recherche de la Société Servier (IDRS), Croissy s/Seine, France, May 26th 2010 (M. Laguerre)
- Interbio Seminar at ITQB, Lisbon, Portugal, April 12 2010 (M. Laguerre)
- INTERBIO Meeting "Forging Partnerships", Valencia, Spain, January 18-21 2010 (J. Dessolin)
- Groupe thématique de recherche sur la vectorisation, Paris, France, December 2009 (N. Taïb)
- "Physics of complexity", Lyon, France, June 2-6 2009 (J. Elezgaray)
- Groupe thématique de recherche sur la vectorisation, Paris, France, December 2009 (N. Taïb)

### Morphologies, dynamics & functions of assemblies of amphiphiles

- Suprabio, Bordeaux, France, October 2010 (R. Oda)
- Interbio, Barcelona, October 2010 (R. Oda)
- MRS-Asia, Qindao, China, September 2010 (R. Oda)
- Interbio, Lisbon, May 2010 (R. Oda)
- Symposium on Ordered Structure and Dynamic Behavior of Soft and Wet Matter, Sapporo, Japan, January 2010 (R. Oda)
- RIKEN, Harima, Japan, January 2010 (R. Oda)
- NanoSWEC, Bordeaux, October 2009 (R. Oda)
- Biologie et Physique de Grand Ouest 4, Ile de Berder, France, June 2009 (R. Oda)
- Surfactant in Solution Conference, Melbourne, Australia, December, 2010 (R. Oda)
- Paris Univ. Marie Paule Pileni, Paris, November 2010, Controllable Size of Gold Nanoparticles on Surface of Silica Nano-Helices (R. Oda)
- Kumamoto University, Kumamoto, Japan, October 2010 (R. Oda)
- Tokyo University, Kashiwa, Japan, October 2010 (R. Oda)
- NIMS Tsukuba, Japan, October 2010 (R. Oda)
- Yokohama National University, Yokohama, Japan, October, 2010 (R. Oda)
- ECIS Prague, September 2010 (R. Tamoto)
- Georgetown University, Washington DC, USA, September, 2009 (R. Oda)
- ECIS Antalya, September, 2009 (R. Tamoto)
- RIKEN, Molecular & Informative Life Science Unit, Wako, Japan, April 2009 (R. Oda)

### Molecular imaging & nanobiotechnology

- 5th International Conference on Annexins "Annexin2009" Lacanau, France, Sept. 20-24 2009 (A. Brisson)
- Workshop on Diagnosis of infectious diseases, HoChiMinh City, Vietnam, August 17-18 2009 (A. Brisson)
- Workshop on infectious diseases, Hanoi, Vietnam, August 8-14 2009 (A. Brisson)
- 11ème Congrès de la Société Française des Microscopies, Paris, France, 22-26 June 2009 (S.C. Gounou, S. Mornet, A.. Brisson)
- Soc. Guerbet, Paris, France, Nov. 9 2010 (A. Brisson)
- 9th France-Japan DDS Symposium "Recent Trends in Gene and Drug Delivery", Kumamoto, Japan, Sept. 26-29 2010 (A. Brisson)
- BioNanoSciences Workshop BOKU-AIT, Vienna, Austria, Sept. 13-15 2010 (A. Brisson)
- Colorobbia, Florence, Italy, June 10 2010 (A. Brisson)
- 8ème Colloque Francophone Thématique de Biologie Cutanée Humaine, CoBiP, Lyon, France, March 24 2010 (A. Brisson)

## Pole 2 - Organic & Bioorganic Chemistry

### Supramolecular bioorganic & biomimetic chemistry

- Pacifichem, Symposium #98 "The New Age of Advanced Materials: Supramolecular Architectures and Smart Materials ", Honolulu, USA December 2010 (I. Huc)
- Pacifichem, Symposium #168 "Supramolecular Nanoarchitectures and Extended Frameworks", Honolulu, USA, December 2010 (I. Huc)
- 31st European Peptide Symposium Copenhagen, Denmark September 2010 (I. Huc)
- Chirality 2010, ISCD-22, Sapporo, Japan, July 2010 (I. Huc)
- First Symposium "Supramolecular Chemistry for Materials and Life Sciences", Akademgorodok, Russia, June 2010 (I. Huc)
- 21st French-Japanese Symposium on Medicinal & Fine Chemistry, Kyoto, Japan, April 2010 (I. Huc)
- International conference "Foldamers: from design to protein recognition", Bordeaux, France, January 2010 (I. Huc)
- Riken 2010 conference on Soft matter and interfaces, Harima, Japan, January 2010 (I. Huc)
- International symposium on medicinal chemistry, Brussels, Belgium, November 2009 (I. Huc)
- International symposium on novel aromatic compounds, Luxemburg, July 2009 (I. Huc)
- French-Japanese workshop on Nanomaterials, Tsukuba, Japan, June 2009 (I. Huc)
- NIH-INRIA workshop modeling in structural biology, Rocquencourt, France, June 2009 (Huc, I.)
- Journée de bilan ANR blanc 2005, Paris, France,, March 2009 (I. Huc)
- Symposium on Magnetic Resonance & Biomolecular Mimetics, Hyderabad, India February 2009 (I. Huc)
- The Scripps Research Institute, La Jolla, USA, December 2010 (I. Huc)
- Ochanomizu University, Tokyo, Japan, October 2010 (I. Huc)
- Chiba University, Tokyo, Japan, October 2010 (I. Huc)
- Tokyo University, Faculty of Engineering, Tokyo, Japan, October 2010 (I. Huc)
- Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France, October 2010 (I. Huc)
- Université d'Orsay, Paris, France, September 2010 (I. Huc)
- Ecole Doctorale de Chimie, Université Claude Bernard, Lyon, France, September 2010 (I. Huc)
- Tohoku University, Sendai, Japan, July 2010 (I. Huc)
- Laboratoires Servier, Croissy-sur-Seine, France, May 2010 (I. Huc)
- Kyoto University, Kyoto, Japan, May 2010 (I. Huc)
- Julius-Maximilians Universität Würzburg, Würzburg, Germany April 2010 (I. Huc)
- Department of Chemistry, National University of Singapore, Singapore,March 2010 (I. Huc)
- Bochum University, Bochum , Germany, January 2010 (I. Huc)
- Ecole Normale Supérieure de Lyon, Lyon, France, December 2009 (I. Huc)
- Fudan University, Shanghai, China, December 2009 (I. Huc)
- East Chinese University of Science and Technology, Shanghai, China, December 2009 (I. Huc)
- Institute of Chemistry, Chineses Academy of Science, Beijing, China, December 2009 (I. Huc)
- LMU Münich, Germany, January 2009 (I. Huc)
- Indian Institute of Science Bangalore, India, February 2009 (I. Huc)
- Nagoya Institute of Technology, Nagoya, Japan, April 2009 (I. Huc)
- Kumamoto University, Kumamoto, Japan, April 2009 (I. Huc)
- Tokyo University, Faculty of Engineering, Tokyo, Japan, April 2009 (I. Huc)
- Nagoya University, Nagoya, Japan, April 2009 (I. Huc)
- Kanagawa University, Kanagawa, Japan, June 2009 (I. Huc)
- Novosibirsk Institute of Chemical Kinetics and Combustion RAS, Russia, March 2009 (I. Huc)
- Institut de Chimie et des Matériaux Paris-Est, Thiais, France, September 2009 (I. Huc)

### Synthesis & activity of natural substances

- 6th Annual Symposium of the Indo-French Center in Organic Synthesis (CEFISO-IFCOS), Villard de Lans, France, September 14-17 2010 (S. Quideau)
- 4ème Journées Internationales de l'AFERP - Biodiversité, Chimie des Substances Naturelles et Médicaments, Besançon, France, July 16-18 2010 (S. Quideau)
- 22 Irseer Naturstofftage der DECHEMA - « Aktuelle Entwicklungen in der Naturstoff-Forschung », Irsee, Germany, February 24-26 2010 (S. Quideau,)
- 5th International Workshop on Anthocyanins - « Expanding World of Anthocyanins », Nagoya, Japan, September 15-18 2009 (S. Quideau)
- XIIème Symposium de l'Institut de Chimie des Substances Naturelles (ICSN, 50ème Anniversaire) - « De la Synthèse Organique à la Chimie Biologique », Gif-sur-Yvette, France, June 11-12 2009 (S. Quideau)
- Université Paul Sabatier, Toulouse, France, Toulouse, France, November 19 2010 (S. Quideau)
- Institut Universitaire de la Vigne et du Vin, Jules Guyot, Université de

Bourgogne, Dijon, France, July 16 2010 (S. Quideau)
- Journée de l'Ecole Doctorale Normande de Chimie, Caen, France, June 3 2010 (S. Quideau)
- Institut de Recherche en Chimie Organique Fine (IRCOF) de Rouen, Mont Saint Aignan, France, June 4 2010 (S. Quideau)
- Rencontre Inaugurale du Club MECCAiNO – Mécanismes Moléculaires et Innovations en Cancérologie, IECB, Pessac, France, May 13 2010) (S. Quideau)
- 6ème Rencontres de Chimie Organique de Marseille – « De la Chimie Organique Physique à la Synthèse Organique Totale », Campus Saint Charles, Marseille, France, May 6-7 2010 (S. Quideau)
- Université de Nantes, Nantes, France, March 3 2010 (S. Quideau)
- Consejo Superior de Investigaciones Científicas (CSIC), Centro de Edafología y Biología Aplicada del Segura (CEBAS), Murcia, Spain, July 10 2009 (S. Quideau)
- XXVème Journée d'Etude « Chimie-Biologie », Université Paul Sabatier, Toulouse, France, June 2 2009 (S. Quideau)
- Sanofi-Aventis, Recherche & Développement, Vitry-sur-Seine, France, May 26 2009 (S. Quideau)
- Boehringer Ingelheim Ltd, Research & Development, Laval (Québec), Canada, May 12 2009 (S. Quideau)
- Département de Chimie, Université du Québec à Montréal, Montréal (Québec), Canada, May 11 2009 (S. Quideau)
- Annual "Steinheimer Gespräche » Meeting of the German Chemical Industry Fund Rödermark, Germany, April 23 2009 (S. Quideau)
- Bonn University Bonn, Germany, February 03 2009 (S. Quideau)
- Journée "Polyphénols et Santé", Institut de Recherche en Nutrition Humaine d'Aquitaine (IRNHA), ISTAB, Université de Bordeaux, Pessac, France, January 29 2009 (S. Quideau)

## Peptidomimetic chemistry

- 5th International Peptide Symposium Kyoto, Japan, December 2010 (G. Guichard)
- 7th ERA-Flash Conference: Bioinspired Chemistry, Santiago de Compostela, Spain, October 2010 (G. Guichard)
- 46th International Conference on Medicinal Chemistry RICT, Reims, France, June-July 2010 (G. Guichard)
- EMRS Spring Meeting, Peptide-Based Materials : From Nanostructures to applications, Strasbourg, France, June 2010 (G. Guichard)
- 12th Naples Workshop on Bioactive Peptides, Naples, Italy, June 2010 (G. Guichard)
- 47ème Semaine d'Etude de Chimie Organique (SECO), Seignosse, France, May 2010 (G. Guichard)
- FOLDAMERS: from design to protein recognition, COST Action CM0803 – Marie Curie IAPP FOLDAPPI joint Symposium, Bordeaux-Pessac, France, January 2010 (G. Guichard)
- InterBio Meeting Forging Partnerships, Valencia, Spain, January 2010
- COST meeting : Foldamers: building blocks, structure and function", Szeged, Hungary, September 2009 (G. Guichard)
- Ochanomizu University, Tokyo, Japan, December 2010 (G. Guichard)
- Kyoto University, Kyoto, Japan, December 2010 (G. Guichard)
- Nagasaki University, Nagasaki, Japan, December 2010 (G. Guichard)
- Symposium on collaborative research, InterBio Meeting¸ ITQB Lisbon, Portugal, April 2010 (G. Guichard)
- Sphaera Pharma, New Delhi, India, October 2009 (G. Guichard)
- Strasbourg University, Strasbourg, France, June 2009 (G. Guichard)
- FOLDAMERS: Design, Synthesis and Applications, COST Meeting Bologna, Italy, October 2010 (L. Fischer)
- Journée de la Société de Chimie Thérapeutique, Paris, France, February 2010 (M.C. Lechner)
- Journée de la Société de Chimie Thérapeutique, Paris, France, February 2009 (P. Claudon)

## Peptide-based polymer assemblies

- Gordon Research Conferences – Drug Carriers In Medicine & Biology, Waterville Valley, USA, August, 15-20th 2010 (E. Garanger)
- Probes for peptide science: design and methodological development , Paris, France, April 8-9 2010 (E. Garanger)

## Organic & medicinal chemistry

- Colorado State University, Fort Collins, Col. and University of Colorado Boulder, Col., US, September 2010 (L. Ghosez)
- Chinese University of Hong Kong, Hong Kong, China, July 2010 (L. Ghosez)
- University of Beijing, Beijing, China, June 2010 (L. Ghosez)
- Institute for Materia Medica, Chinese Academy of Sciences Shanghai, China, June 2010 (L. Ghosez)
- University of Namur, Namur, Belgium, May, 2010 (L. Ghosez)
- Universities of Caen, Le Havre and Rouen, France, May 2010 (L. Ghosez)
- Grünenthal Group, Aachen, Germany, February 2010 (L. Ghosez)
- Interbio conference, Valencia, Spain, January 2010 (L. Ghosez)
- Symposium in honour of Professor R. Jacquier, Montpellier, France, November 2009 (L. Ghosez)
- "Bellus" Symposium, Basel, Switzerland, February 2009 (L. Ghosez)
- University of York, York, UK, January 2009 (L. Ghosez)

# Pole 3 - Molecular Recognition

## Small RNAs & aptamers

Dr. Jean-Jacques Toulmé

- Eurotides, Barcelona, Spain, November 2010 (J.J. Toulmé)
- Current Trends in ITC and SPR symposium, Baltimore, USA, October 2009 (J.J. Toulmé)
- International conference on RNA nanotechnology and therapeutics, Cleveland, USA, October 2010 (J.J. Toulmé)
- Nanotechnology and IT foir Health, Barcelona, Spain, September 2010 (J.J. Toulmé)
- XIX International round table on nucleosids, nucleotides and oligonucleotides, Lyon, France, August, 2010 (J.J. Toulmé)
- Smart chemistry in drug discovery, Beijing, China, May 2010 (J.J. Toulmé)
- Valencia, Spain Interbio-SUDOE, January, 2010 (J.J. Toulmé)
- Annual meeting of Medicinal Chemistry, Brussels, Belgium, November 2009 (J.J. Toulmé)
- 7th Congress "Drug discovery, Science and Technology", Shangaï, China, October 2009 (J.J. Toulmé)
- 45th RICT Drug discovery and selection, Orléans, France, July 2009 (J.J. Toulmé)
- Workshop ARN & Cancer, Pessac, France, December 2010 (J.J. Toulmé)
- Conferencia Bioforo, Universidad del Pais Vasco, Bilbao, Spain, October 2010 (J.J. Toulmé)
- Journées de la chimiothèque nationale, Caen, France, June 2010 (J.J. Toulmé)
- 10ème réunion du réseau national hépatites de l'ANRS, Paris, France january 2010 (J.J. Toulmé)
- NanoSwec, Pessac, France, November 2009 (J.J. Toulmé)
- Journée Biomolécules, Lyon, France, June 2009 (J.J. Toulmé)
- Journée DNA and technology, Toulouse, France, June 2009 (J.J. Toulmé)

## Gene regulation & tumor research

- World Congress Gene 2010, Foshan, China, December 2010 (M. Teichmann)
- Odd Pols' meeting, Airlie, Virginia, USA, June 2010 (M. Teichmann)
- World Congress Gene 2009, Foshan, China, December 2009 (M. Teichmann)
- Université de Ulm, Ulm, Germany, March 2010 (M. Teichmann)

## Structural biochemistry

- Bordeaux RNA Club, Bordeaux, France, September 30 (F. Maurice)
- RNA Meeting Seattle, Seattle, USA, June 22-26 2010 (M. Moreno-Morcillo)
- JABC4, Bordeaux, France, June 22-23 2010 (S. Fribourg)
- Grenoble EMBO Course, Grenoble, France, May 31-June 3 2010 (F. Maurice)
- IBMC Strasbourg, Strasbourg, France, February 25 2009 (S. Fribourg)
- Bordeaux RNA Club, Bordeaux, France, June 18 2009 (S. Lefèvre)
- JABC2, Bordeaux, France, 2009 (S. Lefèvre)
- IFR 66, Bordeaux, France, 2009 (S. Lefèvre)

## NMR spectroscopy of protein-nucleic acid complexes

- Murnau Conference on Structural Biology: The Modern RNA World, Murnau, Germany, October 14 2010 (C. Mackereth)
- Aquitaine NMR Network, Pessac, France, June 21 2010 (S. Amrane)
- University of British Columbia, Vancouver, Canada, June 21 2010 (C. Mackereth)
- University of Victoria, Victoria, Canada, June 18 2010 (C. Mackereth)
- Bordeaux RNA Club, Pessac, France, March 18 2010 (C. Mackereth)
- Université Henri Poincaré, Nancy, France, February 18 2010 (C. Mackereth)
- Institut de Génétique et de Biologie Moléculaire et Cellulaire, Strasbourg, France, November 22 2009 (C. Mackereth)
- 14th Annual Meeting of the RNA Society, Madison, USA, May 26 2009 (C. Mackereth)

# CONFERENCE ORGANISATION & AWARDS

Invited participation in international meetings / Participation in national meetings, invited seminars and courses and non-invited contribution to international meetings

## Unusual nucleic acid structures

- Pacifichem Meeting, Hawaii, USA, December 2010 (G. Salgado)
- Pacifichem Meeting, Hawaii, USA, December 2010 (J.L. Mergny)
- InterBio Meeting, Barcelona, Spain, October 2010 (J.L. Mergny)
- COST Quadruplex meeting, London (UK), September 2010 (J.L. Mergny)
- IRT N3A, Lyon, France, September 2010 (J.L. Mergny)
- Medicinal Chemistry Meeting, Beijing, China, May 2010 (J.L. Mergny)
- French Quadruplex Meeting, Pessac, France, January 2010 (J.L. Mergny)
- COST Training School, Naples, Italy, October 2009 (J.L. Mergny)
- European Science Foundation Research Conference, Innsbruck, Austria, June 2009 (J.L. Mergny)
- Second International Quadruplex meeting, Louisville, USA, April 2009 (J.L. Mergny)
- French Quadruplex Meeting, Institut Curie, Paris, France, January 2009 (J.L. Mergny)
- Université de Sherbrooke Sherbrooke, Canada, December 13 2010 (J.L. Mergny)
- Chinese Academy of Sciences, Changchun, China, May 20 2010 (J.L. Mergny)
- Hong Kong Baptist University, Hong Kong, China, May 17 2010 (J.L. Mergny)
- Bordeaux RNA Club, Pessac, France, December 10 2009 (J.L. Mergny)
- ENS-Cours National d'Oncologie, Paris, France, October 9 2009 (J.L. Mergny)
- NIH, Bethesda, US, April 17 2009 (J.L. Mergny)

# Pole 4 - Molecular & Cellular Biology

## Vesicular transport: mechanisms & regulation in pancreatic β-cells

- Islet study group, EASD satellite meeting "Pancreatic b-Cells as biosensors", Tällberg, Sweden, September 2010 (M. Raoux)
- European Club for the study of GLP-1, "GLP-1, What is known, new, and controversial?", Marseille, France, June 2010 (J. Lang)
- 2emes Rencontres Euro-régionales, Montpellier, France, July 2010 (J. Lang, S. Renaud)
- Frontiers in cell signalling and diabetes, Geneva, Switzerland, April 2010 (J. Lang)
- Concertation and Consultation Workshop on Micro-Nano-Bio Convergence Systems (MNBS), Neuchatel, Switzerland, February 2010 (J. Lang)
- EASD, Stockholm, Sweden, Sept. 2010 (M. Raoux)
- Club Exo-Endocytose, Paris, France, June, 2010 (B. Hastoy)
- EASD, Vienna, Autria, Sept. 2009 (J. Papin)
- 8th EMBO/Annaberg Workshop: Protein & Lipid function in secretion and endocytosis, Annaberg, Austria, Jan. 2010 (J. Lang)
- 9e Colloque Société des Neurosciences, Bordeaux, France, Nov. 2009 (M. Raoux, J. Lang)
- MCS Symposium, Reuttlingen, Germany, Nov. 2009 (M. Raoux)
- Congrès Société française de Diabétologie, Lille, France, Fev. 2009 (M. Raoux)

## Cell signalling in health & disease

- 4th International meeting on "Adhesion meeting: Podosomes, Invadopodia, & focal adhesion", Hyères, France, September 26- October 1 2009 (F. Saltel)
- Gordon Conferences, Visualization in Science and Education, Magdalen College, Oxford, UK, July 26-31 2009 (I. Kramer)
- Université Paul Sabatier, UFR Sciences de la vie et de la terre, Institut de Pharmacologie et de Biologie Structurale, Toulouse, France, June 28 2010 (I. Kramer)
- BioCell Grand Campus, Université Paris-Sud11, Institut Curie-Orsay, Orsay, France, May 11 2010 (I. Kramer)
- GIS Matériaux en Aquitaine "Multi-fonctionnalisation de biomatériaux et assemblage 3D pour l'ingénierie tissulaire", Bordeaux, France, December 14 2009 (F. Saltel)

## Molecular basis of vulnerability to drugs

- 7th International Summer School of Neuroscience, Catania, Italy, July 11-17 2009 (P.V. Piazza)
- "Biotechnologie : Bientôt des médicaments sur mesure ?", Bordeaux, December 14, 2010 (P.V. Piazza)
- Premier colloque aquitain de la plasticité cérébrale, Bordeaux, September 30- October 2010 (P.V. Piazza)
- Groupe d'Animation et de Communication Externe Inserm U.836, Grenoble, October 21 octobre 2010 (P.V. Piazza)
- Collège Régional des Alcoologues Aquitains Cité Mondiale, Bordeaux, October 7 2010 (P.V. Piazza)
- 7th FENS Forum of European Neuroscience, Amsterdam, The Netherlands, July 3-7 2010 (P.V. Piazza)
- 41th European Brain and Behaviour Society Meeting (EBBS), Rhodes Island, Greece, September 14-18 2009 (P.V. Piazza)
- 9ème Colloque de la Société des Neurosciences, Bordeaux, France, May 26-29 2009 (P.V. Piazza)
- ECNP Workshop on Neuropsychopharmacology for Young Scientists in Europe, Nice, France, March 5-8 2009 (P.V. Piazza)
- 5th International Meeting Steroids and Nervous System, Turin, Italy February 14-18 2009 (P.V. Piazza)

## Dynamics of cell growth & cell division

- Synchrotron, SOLEIL, Gif-Sur-Yvette, France, December 2010 (D. McCusker)
- 6th SALK Institute Cell Cycle Meeting, La Jolla, USA, July 2009 (D. McCusker)
- University of California at Berkeley, Berkeley, USA, August 2009 (D. McCusker)

## Genome régulation & evolution

- RNAi & miRNA Europe, Dublin, Ireland, September 2010 (D. Dupuy)
- 5th Microsymposium on Small RNAs, Vienna, Austria, May 2010 (D. Dupuy)
- 5th Predictive Human Toxicity and ADMET, Brussels, Belgium, January 2010 (D. Dupuy)
- Lausanne Life Sciences Festival, Lausanne, Switzerland, May 2009 (D. Dupuy)
- 3rd East Asia Worm Meeting, Tokyo, Japan, July 2010 (K. Rebora, I. Zniber, R. Giordano)
- University of British Columbia, Vancouver, Canada, January 2010 (D. Dupuy)
- Simon Fraser University, Vancouver, Canada, January 2010 (D. Dupuy)
- Centre de Biologie du Développement, Toulouse, France, October 2009 (D. Dupuy)
- Tokyo School of Biomedical Science, Tokyo, Japan, September 2009 (D. Dupuy)
- 17th International C. elegans Meeting, Los Angeles, USA, June 2009 (K. Rebora)
- Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, May 2009 (D. Dupuy)
- 2nd Spanish Worm Meeting, Barcelona, Spain, March 2009 (D. Dupuy)
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# Conference organization

- Joint Symposium COST/FOLDAPPI, IECB, Pessac, January 25-28 2010 (M. Laguerre, co-organiser)
- 5th International Conference on Annexins "Annexin2009" Lacanau, France (A. Brisson, chairman of the organization committee)
- Foldamer Symposium "From design to protein recognition", Bordeaux, France, January 25-28 2010 (I. Huc, chairman of the organization committee)
- 2nd Aquitaine conference on Polymers, Arcachon, France, October 13-16 2009 (I. Huc, member of the organization committee)
- 25th International Conference on Polyphenols, ICP2010, Montpellier, France, August 24-27 2010 (S. Quideau, Co-Chair)
- 3rd International Conference on Hypervalent Iodine Chemistry, ICHIC2010, Bordeaux-Pessac, France, July 4-7 2010 (S. Quideau, chairman)
- 11th International Conference on the Chemistry of Antibiotics and Other Bioactive Compounds, ICCA-11, San Sebastian, Spain, September 29-October 2 2009 (S. Quideau, member of the international scientific committee)
- Boss meeting, Namur, Belgium, 2010 (L. Ghosez, member of the Advisory Board)
- Tetrahedron Symposium Beijing, China, 2010 (L. Ghosez, member of the scientific committee)
- Tetrahedron Symposium, Barcelona, Spain, 2011 (L. Ghosez, chairman)
- Workshop RNA club Bordeaux, Pessac, France, June 2009 (J.J.Toulmé, chairman of the organization committee)
- Journée Aptamères, Pessac, France, December 2009 (J.J. Toulmé, chairman of the organization committee)
- Workshop RNA club Bordeaux, Pessac, France, June 20010 (J.J. Toulmé, chairman of the organization committee)
- Annual French Quadruplex Meeting Pessac, France, January 2010 (J.L. Mergny, organiser)
- "VIII rencontres de Figeac" Figeac, France, September 2011 (J.L. Mergny, member of scientific committee)
- 4th International meeting on "Adhesion meeting: Podosomes, Invadopodia, & focal adhesion", Hyères, France, September 26-October 2009 (E. Génot, co-organizer)
- Interbio ; macromolecules and chemical design to drug discovery, regenerative medicine and stem cells, Institut Principe Felipe, FIVEC, Valencia, Spain, January 18-21 2010 (I. Kramer, co-organizer)
- Interbio: nanobiotechnology & IT for life sciences and medicine, Autonomous University of Barcelona, Cerdanyola del Vallès, Spain, October 4-6 october 2010 (I. Kramer, co-organizer)
- 2nd City University Systems Biology Workshop, Hong-Kong, China, August 2009 (D. Dupuy, organizer)

# Thesis

## 2009

- Driss BENNANI «Inhibition d'interactions protéine-protéinepar des foldamères fonctionnalisés - Design et modélisation» (M. Laguerre) Université Bordeaux-I, Bourse Région Aquitaine
- Guillaume NATURALE «Synthèse de nouveaux hétérocycles à visées anticancéreuses» (J. Dessolin) Université Bordeaux-I, BDI Cofinancée CNRS
- Judith ELKAIM «Criblage virtuel: méthodologies et applications» (J. Dessolin) Université Bordeaux-I, MENRT
- Jean-Michel ARBONA «Origami d'ADN» (J. Elezgaray ) Université Bordeaux-I, MENRT
- Clément ARNAREZ «Modélisation par dynamique moléculaire des complexes de la chaîne respiratoire mitochondriale» (J. Elezgaray ) Université Bordeaux-I, ANR
- Boris GARNIER "Développement de vecteurs liposomaux fonctionnalisés par des protéines dérivées de l'Annexine 5 et encapsulant des marqueurs pour l'imagerie" (A. Brisson et K. Petry) Université Bordeaux-2
- Mélanie MARGUERIT « Désaromatisation Hydroxylante de Phénols par des Réactifs Iodés Hypervalents - Application à la Synthèse de Substances Naturelles » (S. Quideau) Université Bordeaux-1, BDI CNRS, Sélection Glaxo-SmithKline/SFC
- Gaëlle MALIK «Vers la Synthèse Totale d'Ellagitannins CArylglucosidiques - Une Approche Biomimétique Visant la Vescaline» (S. Quideau) Université Bordeaux-1, Ministère-Thèse à la Mobilité
- Pauline PERREAU-MORILLON «Identification et caractérisation d'un inhibiteur général de la transcription réalisée par l'ARN polymérase III humaine» (M. Teichmann) Université Bordeaux-2
- S. LEFÈVRE «Etude structurale de hRCP62, une sous-unité de l'ARN polymérase III humaine» (S. Fribourg) Université Bordeaux-I, Bourse Région Aquitaine
- Julien PAPIN "Bases moléculaires des défauts sécrétoires des cellules b-pancréatiques lors de la glucotoxicité" (J. Lang, Université de Bordeaux-1)
- Patricia ROTTIERS "Rôle essentiel du récepteur de type I, ALK1 et de la fibronectine dans un contexte d'activation de la cellule endothéliale" (Elisabeth Génot) Université Bordeaux-1

## 2010

- Marine STUPFEL "Reconnaissance de surface de protéine par des foldamères" (I. Huc), Université Bordeaux 1
- Anna NATANGELO "Vers la Première Synthèse Totale d'Ellagitannins C-Arylglucosidiques - Une Approche Biomimétique" (S. Quideau, D. Deffieux) Università Italo-Francese, University of Ferrara, Italy
- Marion TARBE "Conception, Etude Structurale et Propriétés Fonctionnelles de Nouveaux Peptidomimes Antigéniques pour une Immunothérapie Antitumorale" (S. Quideau), Société de Chimie Thérapeutique, Servier
- Tony GARNIER "Déaromatisation et Couplage Phénoliques par Oxydation Chimique et Electrochimique - Application à la Synthèse Totale de Substances Naturelles Bioactives" (S. Quideau, D. Deffieux, L. Pouységu) EDSC Bordeaux 1, Thèse à la Mobilité, French Ministry of Research
- Céline CHALUMEAU "Développement d'Outils Chimiques pour l'Elucidation de la Biogenèse des Flavanoïdes du Raisin - Anthocyanes versus Proanthocyanidines" (S. Quideau, D. Deffieux), CIVB
- Tahiri SYLLA "Substances (Poly)phénoliques Bioactives: Synthèse Totale de Gallotannins Depsidiques et Hémisynthèse de la Norbergénine C-Arylglucosidique" (S. Quideau, L. Pouységu), Ivory Coast Ministry of Research
- Maria Moreno MORCILLO "Étude structural du complexe CstF et de son homologue chez la levure CF IA, deux facteurs indispensables pour la maturation 3' des pré-ARN messagers" (S. Fribourg) Université Bordeaux Segalen, Caixa fundacion, ARC


Rigaku
MERCURY

# Technology platforms

# STRUCTURAL BIOLOGY

Dr. Brice Kauffmann
Head of IECB's Structural Biology technology platform, (IR) CNRS, Unité de Soutien UMS3033/US001

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

Tabatchnik-Rebillon A., Aubé C., Bakkali H., Delaunay T., Manh G.T., Blot V., Thobie-Gautier C., Renault E., Soulard M., Planchat A., Le Questel J.Y., Le Guével R., Guguen-Guillouzo C., Kauffmann B., Ferrand Y., Huc I., Urgin K., Condon S., Léonel E., Evain M., Lebreton J., Jacquemin D., Pipelier M., Dubreuil D. (2010). Electrochemicalsynthesis and characterisation of alternating tripyridyl-dipyrrole molecular strands with multiple nitrogen-based donor-acceptor binding sites. Chemistry, 18;16(39):11876-89.

Chu C.C., Raffy G., Ray D., Del Guerzo A., Kauffmann B., Wantz G., Hirsch L., Bassani D.M. (2010). Self-assembly of supramolecular fullerene ribbons via hydrogen-bonding interactions and their impact on fullerene electronic interactions and charge-carrier mobility. J Am Chem Soc., 15;132(36):12717-23.

Campbell V.E., de Hatten X., Delsuc N., Kauffmann B., Huc I., Nitschke J.R. (2010). Cascading transformations within a dynamic self-assembled system. Nat. Chem., 2(8):684-7.

Ferrand Y., Kendhale A.M., Kauffmann B., Grélard A., Marie C., Blot V., Pipelier M., Dubreuil D., Huc I. (2010). Diastereoselective encapsulation of tartaric acid by a helical aromatic oligoamide. J Am Chem Soc. 16;132(23):7858-9.

Baptiste B., Zhu J., Haldar D., Kauffmann B., Léger J.M., Huc I. (2010). Hybridization of long pyridine-dicarboxamide oligomers into multi-turn double helices: slow strand association and dissociation, solvent dependence, and solid state structures. Chem Asian J., 1;5(6):1364-75.

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:**

- Liquid/Solid NMR
- Electronic Microscopy
- Mass spectrometry
- Surface Plasmon Resonance (SPR)
- Molecular modeling
- Crystallogenesis
- X-ray diffraction and diffusion

# Liquid/solid NMR

### Services and expertise

- NMR of membrane lipids in the context of bicelles and membrane domains (rafts), atherosclerosis, and cellular signalling (e.g. nano-objects oriented by magnetic fields, sterols and phosphoinositids)
- NMR of peptides and membrane proteins involved in cancer, apoptosis or featuring particular antibiotic and 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 contacts

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

# Electronic 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

# 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

### Technical contact

Michelle Dupire, m.dupire@iecb.u-bordeaux.fr

### Scientific expertise

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

# Surface Plasmon Resonance (SPR)

### Services and expertise

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

### Equipment

Biacore 3000TM (www.biacore.com).
A new instrument will be available soon.

### Main contact

Carmelo Di Primo, carmelo.diprimo@inserm.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 Cristallogenesis (screening and opitmization of cristallization conditions)
- Cristallogenesis of membrane proteins in mesophase
- Cristallogenesis of supramolecular self-assemblies

### Equipment

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

### Technical contact

Brice Kauffmann ( b.kauffmann@iecb.u-bordeaux.fr )

### Scientific contacts

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

# X-ray diffraction and diffusion

### Services and expertise

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

### Equipment

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

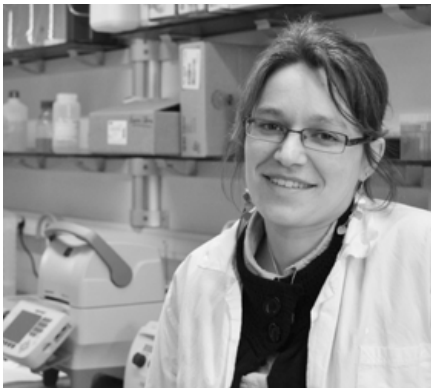
### Technical contact

Brice Kauffmann ( b.kauffmann@iecb.u-bordeaux.fr )

### Scientific contacts

- 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, s.fribourg@iecb.u-bordeaux.fr

# PREPARATIVE AND ANALYTICAL TECHNIQUES



Sabrina Rousseau
Head of IECB's technology platform in preparative and analytical techniques (IE), INSERM, Unité de Soutien 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

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<br>Confocal Microscopy |
| Molecular Biology | Cloning<br>Genotyping<br>Directed site Mutagenesis |
| Preparative Biochemistry | Tests of protein expression<br>Protein production and purification |
| Other Services | Generation of CDNA libraries<br>Purification of Oligonucleotides |

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# 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
- DIRECTED SITE MUTAGENESIS - It consists in introducing a specific mutation or deletion in a target gene. Two different PCR methods are used : high fidelity Taq polymerase or Lightning Quick Change mutagenesis kit from Stratagene.

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

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

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

# Preparative Biochemistry

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

**Equipment**
- Centrifuges:
  - AVANTI J26XP (Beckman coulter) equipped with rotors JLA 8.1000, JA25.50.
  - 5804R (Eppendorf) equipped with: Swing-bucker rotor for plates A-2-DWP, Standard rotor for 1,5/2ml tubes FA-45-30-11, Rotor F-34-6-38 (Adaptator for 15ml, 15-18ml or 50ml tubes).
  - 5418 (Eppendorf) equipped with Rotor for 1,5/2ml tubes FA-45-18-11
- Ultracentrifuges:
  - OPTIMA-L80XP (Beckman coulter) equipped with rotors 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

# Technology transfer & start-ups

# 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. Over the 2009-2010 period, the institute totalized more than 13 projects with industrial partners.

## Contract services and consulting

The IECB brings together a wide range of scientific equipments and expertises 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. Over 2009-2010, 4 additional patents were submitted by team leaders Dr. Jean-Jacques Toulmé and Pr. Jochen Lang. 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-Baptsite Pin
Fluofarma CEO

**Year of creation** 2003

**Staff** 23

**2010 turnover** 2.2 M euros

**Collaborative projects with IECB teams in 2010** 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** 2

**2010 turnover** 66 000 euros
(+ 44 000 euros of public funding from the Aquitaine Regional Council)

**Collaborative projects with IECB teams in 2010** 2

**Contact** sonia.darocha@inserm.fr

# Scientific events

# IECB conferences and workshops

### Journée U869-IECB sur l'ADN Quadruplexe
January 12 2010
Organized by Jean-Louis Mergny

### Symposium "FOLDAMERS, from design to protein recognition"
January 26-28 2010
Organized by Ivan Huc, Gilles Guichard and Michel Laguerre

### Conference IECB: Tim Hunt - Nobel Laureate 2001 (Cancer Research UK)
June 4 2010, "Getting in and out of Mitosis: Setting thresholds with a protein phosphatase inhibitor", organized by Derek McCusker

### Journées Jeunes Chercheurs IECB
May 27-28 2010
Oganized by IECB Phd students and postdoctoral researchers


### International symposium on hypervalent iodine chemistry
July 4-7 2010, organized by Stéphane Quideau's team

### Fête de la Science
October 19 2010
On the 19th of October, 3 research teams from IECB participated to the CNRS Science Days. The activities proposed to secondary school students were :
- Lab visit : "Oak and vine : two natural inexhaustible sources of polyphenols" (Quideau team)
- Lab visit "Discovering the internal world of the cell" (McCusker team)
- Conference "What is a genetically modified organism ?" (Denis Dupuy)


### IECB's workshop "Looking to the future", 3rd Workshop of candidates for group-leader positions at IECB
November 25 2010
- Candidates in Structural Biology: Ansgar Siemer (Columbia University, New York, NY, USA), Maria Mapelli (IFOM-IEO Campus, Milano, Italy), Frans Mulder (University of Groningen, Groningen, The Netherlands)
- Candidate in Cell Biology: Anne Royou (University Paris Diderot, Paris, France)
- Candiates in Bio-inspired Materials, Molecular Modelling and Biological chemistry: Andrew Miller (Kings College, London, UK), Agnezska Bronowska (Institute for Theoretical Studies, Heidelberg, Germany), Anne Petitjean (Queen's University, Kingston, ON, Canada)

### IECB Term of tenure seminars
November 26 2010
- Dr. Piervi Piazza - IECB (Inserm U862, Univ. Bordeaux Segalen)
- Pr. Jochen Lang - IECB (CNRS UMR 5248, Univ Bordeaux 1, U5248)
- Dr. Jean-Jacques Toulmé - IECB (Inserm U869, Univ. Bordeaux Segalen)

# Other scientific events organized at IECB

### Bordeaux RNA Club seminars
March 18 2010
Invited speakers : Lionello Bossi (Centre de Génétique Moléculaire, Gif-sur-Yvette), Jessica Baud (INSERM U869 Bordeaux), Laurent Azéma (INSERM U869 Bordeaux), Cameron Mackereth, (IECB)

June 11 2010
Invited speakers: Edouard Bertrand (Montpellier, France), Elmar Whale (Halle, Germany), Mary O'Connell (Edinburgh, Ireland), Javier Martinez (Vienna, Austria), Karin Moelling (Zurich, Switzerland)

September 30 2010
Invited speakers: Thierry Lagrange (Université de Perpignan), Laurent Bui (LCPO-ENSCPB), Patricia Thebault (CBiB Bordeaux 2), Frédérique Maurice (IECB-U869)

### JOURNEE "ARNs ET CANCER"
December 9 2010
Jointly organised by the Bordeaux RNA Club and the Canceropôle Grand Sud-Ouest (see scientific highlights).

### France-Taiwan seminar on X-Ray nano-tomography of angiogenesis
March 29 2010

### Club MECCAiNO (Mécanismes moléculaires et innovations en cancérologie)
April 13 2010

### NMR symposium
June 21-22 2010

# 2010 SEMINARS AT IECB

1. Prof. Samuel Gellman (Univ. Wisconsin) "Foldamers: Accomplishments and Goals"
2. Nicolas Wissinger (ISIS, Strasbourg) "Translating instructions into function through nucleic acid encoding"
3. Dr Michel Werner (CEA, iBiTec-S, Gif/yvette) "Genome-wide mechanisms of transcription in eukaryotes"
4. Prof. Ilane Marek (Technion – Israel Institute of Technology, Haïfa) "When simplicity leads to complexity"
5. Christophe Thibaudeau (Université de Nantes) "Etudes RMN de la structure et la stabilité de complexes du microARN let-7 avec ces cibles LCS-1 et LCS-2 au sein de la région 3'-UTR de l'ARNm lin-41"
6. Dr. Anne Royou (Institut Jacques Monod, Université Paris Diderot P7) "Hanging by a thread: segregation of broken chromosomes in mitosis"
7. Dr. José Cancela (NBCM, Gif/Yvette) "Involvement of NAADP, a new calcium releasing messenger, in the calcium-dependent secretion; a multidisciplinary approach"
8. Brian Baker (Univ. of Notre-Dame, USA) "Flexibility and conformational changes in T cell receptor recognition "
9. Prof. S. Chandrasekhar (Indian Institute of Chemical Technology, Hyderabad, India) "Amino acids as building blocks in natural product synthesis and peptidomimetics"
10. Friedrich Simmel (Technical University Munich) "DNA nanotechnology: supramolecular structures and nanodevices"
11. Prof. David Sanchez-Garcia (IIQS, Universitat Ramon Llull, Barcelona) "Aryl Porphycenes: Applications in Photodynamic Therapy"
12. Hinrich Gronemeyer (IGBMC Strasbourg) "Tumor-selective apoptosis: Epigenetic silencing of TRAIL during tumorigenesis"
13. Michel Bornens (Institut Curie, Paris) "Control of the division axis in proliferating cells and of ciliogenesis in cell-cycle arrested cells"
14. Prof. Jan van Esch (Techn. Univ. Delft, Pays-Bas) "Orthogonal self-assembly of surfactants and hydrogelators: towards new multi-compartment nanostructures"
15. Prof. Anthony Davis (Univ. Bristol, UK) "Synthetic Lectins: Biomimetic Carbohydrate Recognition in Aqueous Solution"
16. Frank Lafont (Institut Pasteur Lille) "Atomic force microscopy with living cells to study cellular interaction"
17. Prof. G. V. M. Sharma (Indian Institute of Chemical Technology, Hyderabad, India) "Synthesis of Peptides with Mixed Helices and their use in the Design of 'Hybrid Helices' as New Motifs"
18. Dr Yoshihiro Ito (RIKEN Advanced Science Institute, Nano Medical Engineering Laboratory) "Molecular Evolutionary Engineering to Create New Functions"
19. Prof. Karl Gademan (Univ. Bâle) "Controlling Biological Processes by Synthetic Natural Products"
20. Prof. M. Sherburn (Australian National University, Canberra, Australia) "The Dendralenes: Syntheses, Properties and Applications"
21. Céline Bottier (EPFL, Lausanne, Switzerland) "Interactions protéine/membrane: du système modèle à la cellule vivante"
22. Dr Yogesh Sanghvi (Rasayan Inc, Encinitas, CA, USA) "Gram to Kilogram-scale Synthesis of Therapeutic Oligonucleotides Using Green Chemistry"
23. Prof. T. Yokosawa (Kanagawa University, Japon) "Precision synthesis of condensation polymers and pi-conjugated polymers"
24. Prof. Naoki Sugimoto (Frontier Institute for Biomolecular Engineering Research and Konan university) "Molecular Crowding Effect on Functional Nucleic Acids"
25. Prof. Larry Romsted (Rutgers University, USA) "If there is Magic on the planet, it is contained in water. A new view on the balance of forces controlling micellar morphologies of ionic surfactants"
26. Dr. Shinji Ogasawara (Riken Institute, Japon) "Reversible photoregulation of nucleic acid function by photochromic nucleobases"
27. Prof. Sylvain Rault (Centre d'Etudes et de Recherche sur le Médicament de Normandie) "Les activités de Chimie Thérapeutique du CERMN. A propos de la création, de l'enrichissement, du criblage et de l'exploitation des résultats de sa chimiothèque. Raison et Hasard"
28. Prof. Dongsheng Liu (Department of Chemistry, Tsinghua University, Beijing) "Nanodevices and smart materials based on DNA i-motif structures"
29. Vitaly V. Kuryavyi, PhD (Memorial Sloan-Kettering Cancer Center, New York) "Recombinogenic potential of G-quadruplex structures"
30. Prof. Alex Heckel (Goethe Universität, Frankfurt) "Triggers and Glue for Nucleic Acids"
31. Prof. M. P. Sibi (North Dakota State University, USA) "Cooperative catalysis: a novel method for constructing quaternary centers "
32. Denis Lucquin (Sofinnova Partners) "Venture capital and start-ups creation, how does it works ?"
33. Anthony Bugaud (Department of Chemistry, University of Cambridge, UK) "Translation regulation by G-quadruplex-forming sequences within the 5' UTRs of mRNAs"
34. Sylvain Tollis (Biological Physics Group, Imperial College London, UK) "How one cell eats another: experiments and modelling elucidate biophysical requirements for uptake"
35. Elisabeth Garanger (LCPO & IECB) "Toward Functional Polymer-Peptide Self-Assembled Nanomaterials "
36. Dr Dominique Housset (Institut de Biologie Structurale J.-P. Ebel, Grenoble) "Alloreactivity, public response, peptide immunogenicity: what did we learn from TCR-peptide-MHC complex structures?"
37. Jochen Lang (CBMN & IECB) "The sweets of cell biology: From regulated membrane fusion to biosensors"
38. Pr. Olivier Dangles (Université D'Avignon) "Modélisation chimique de la réactivité des polyphénols et des caroténoïdes dans le tractus digestif"

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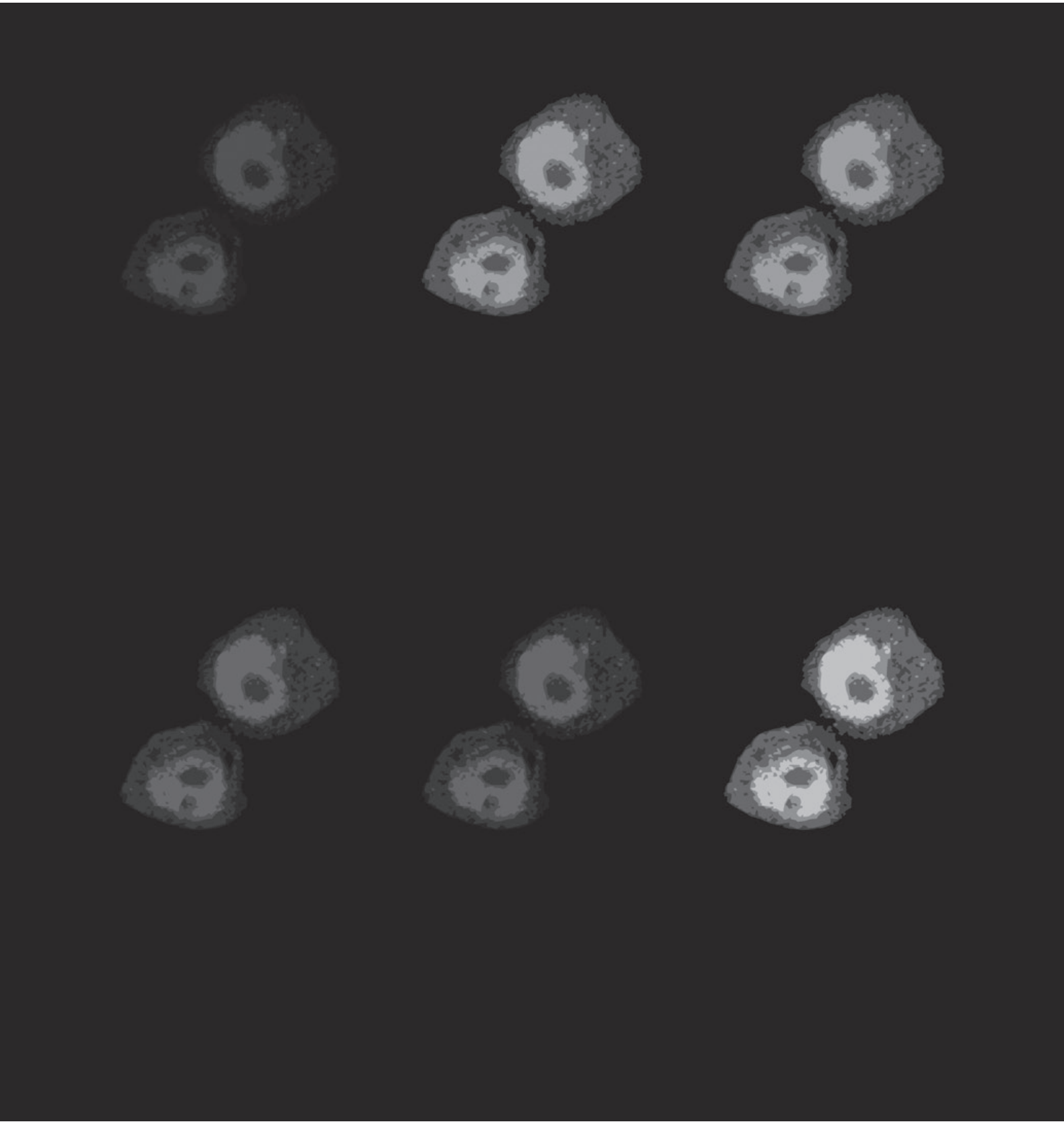

Institut Européen de Chimie et Biologie
2, rue Robert Escarpit
33607 Pessac FRANCE

Tél. : +33(0)5 40 00 26 24
Fax. : +33(0)5 40 00 22 15
www.iecb.u-bordeaux.fr