Institut Européen de Chimie et Biologie

European Institute of Chemistry and Biology

I E C B

Scientific Report

2012

UNIVERSITÉ DE BORDEAUX

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Institut Européen de Chimie et Biologie

European Institute of Chemistry and Biology

Scientific Report

2012

Director's foreword

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

Ivan Huc is indisputedly the man of the year 2012 at IECB. Outstanding chemist, he was awarded the siver medal from the Institut de Chimie (CNRS), a deserved recognition of his past contribution on foldamers, these organized synthetic polymers mimicking structured biopolymers. Ivan also got a prestigious ERC advanced grant for supporting new exciting ideas along the same line of research from nanocapsules to molecular machines. This scientific excellence does not prevent him to serve as a deputy director at IECB, a generally non rewarding and poorly recognized task that benefits to all of us.

In parallel the title of IECB 2012 woman of the year could go to Anne Royou, a recently recruted group leader that introduced drosophila in the institute. She vas awarded a junior ERC grant for her work on mechanisms allowing accurate transmission of chromosome during cell division using live imaging techniques.

This editorial provides me also with the opportunity to congratulate Elisabeth Garanger that was hired as "Chargé de Recherche" by the CNRS following a highly competitive national process. I may therefore reitarate what I wrote last year: "this demonstrates that our stringent selection under the responsability of the International Scientic Advisory Board (ISAB) guarantees high standard recruitment. Indeed, up to now every IECB group leader got a permanent position before the end of his/her contract".

Actually the ISAB and his chairman Pr Daniel Louvard, help us year after year reaching the highest standard and contribute importantly to the international visibility of IECB. I was very pleased to welcome Dr Yves Pommmier from the National Cancer Institute (Bethesda, MD) as a new ISAB member. Dr Pommier, head of the Laboratory of Molecular Pharmacology, is a specialist of topoisomerases. His expertise in cancer research is very welcome as many teams at IECB develop projects entirely or partly related to cancer. This involvement was recently recognized through the association of both IECB teams and technical platform to the SIRIC project coordinated par Pr P. Soubeyran at the Institut Bergonié (Bordeaux).

Last year the ISAB recommanded two young scientists that joined IECB at the end of 2012. Axel Innis is a crystallographer interested in the molecular mechanisms that control the nascent polypeptide synthesis by the bacterial ribosome. Valérie Gabelica investigates structure-function relationship of nucleic acid complexes by mass spectrometry. They will nicely strengthen and complement the expertise in structural bioogy of the Institute. I wish them a very fruitful time at IECB.

I encourage the reader to discover the many other achievements of our talented young teams in this 2012 IECB report and wish you contact our scientists and engineers for more information and why not collaboration !

Dr. Jean-Jacques Toulmé

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

IECB's International Scientific Advisory Board guides the selection and periodic evaluation of the team leaders. After a probative period of two years, research teams are then hosted for a maximum of 8 years. During their stay at IECB, teams enjoy full financial and managerial autonomy and benefit from state-of-the-art facilities and dedicated technical expertise through IECB's technology platforms in structural biology and preparative and analytical techniques.

The IECB is now the largest research team incubator in France recognized by the "Mission pour l'interdisciplinarité" of the CNRS, with 15 research teams accounting for 150 researchers and expert technicians. A company – Fluofarma – and a technology transfer unit – Novaptech –, both created by former IECB team leaders, also operate on site and currently employ over 25 people.

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ERC Starting Grant for Anne Royou

1,5 million euros has been allocated by the ERC (European Research Council) to Anne Royou, group leader at IECB, head of “Control team dynamics of cell division” (IECB/IBGC, UMR 5095 CNRS-Univ. Bordeaux). ERC funding will also enable the acquisition of advanced microscopy equipment essential to the development of the project.

Highlights

Silver medal of CNRS and ERC for Ivan Huc

On September 2012, Ivan Huc, group leader at the IECB was awarded the Silver Medal of the CNRS by Prof. Régis Réau, director of the National Institute of Chemistry (INC).

This award recognizes a researcher for originality, quality and importance of his work recognized nationally and internationally.

This year Ivan Huc also received an ERC for its projects "Beyond Biopolymers : Protein-Sized Aromatic Amide Functional foldamers".

A rejuvenated Young Scientist Symposium

For the fifth consecutive year, on 21 and 22 May this year, a hundred doctoral and post-doctoral students, participated in the Young Researchers Day of IECB.

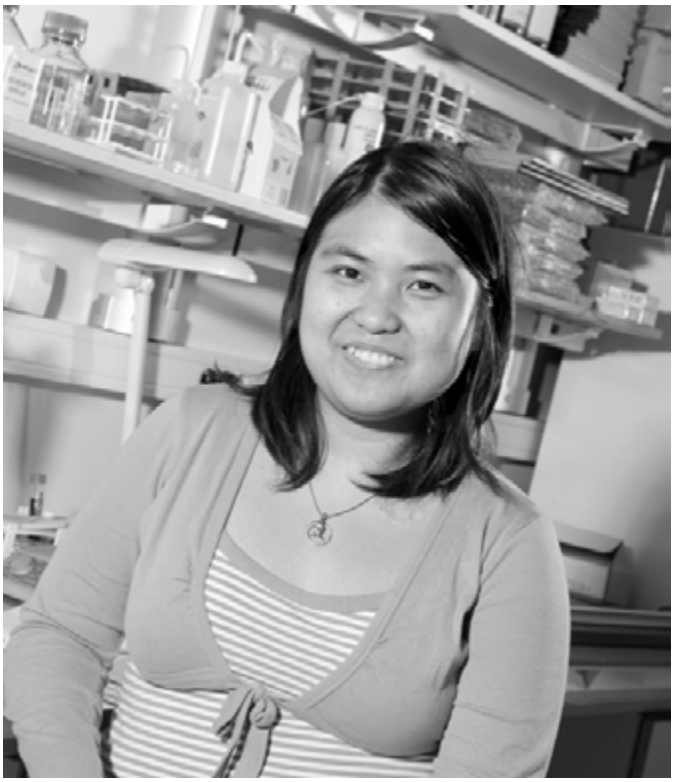
This edition has welcomed guests, including students from the Universities of Tohoku and Osaka in Japan and 21 oral presentations and 14 posters were presented. Launched in 2008 and organized by PhD students and postdocs of iecb, the JJC aim to promote interdisciplinary exchanges between young chemists and biologists.

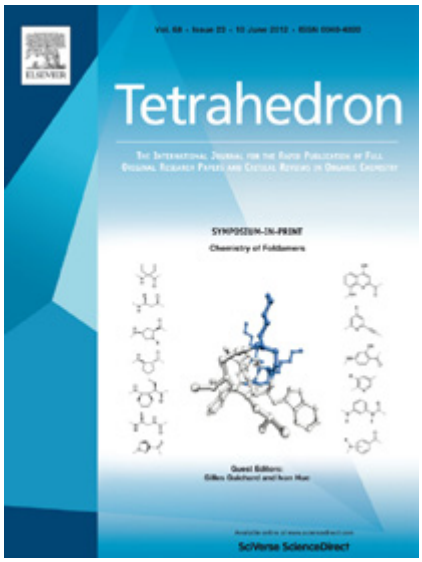
This event is an opportunity for these researchers to present their work and explore different career opportunities.

From the IECB to Princeton with a doctoral thesis prize in her bag

On March 28th, Phong Lan Thao Tran was awarded the PhD thesis prize Monique Garnier-Semancik by the doctoral school in life and health sciences of the University of Bordeaux.

After 3 years spent in the team of Jean-Louis Mergny, working on an unusual DNA structure, she will leave the IECB in summer 2012 for a post-doctoral experience at Princeton University.





A special issue of the journal Tetrahedron on the Chemistry of Foldamers edited by IECB researchers

This Tetrahedron Symposium-in-print, edited by Ivan Huc and Gilles Guichard, reflects the chemists' creativity and the breadth of research in the field of foldamers, i.e. artificial folded molecular architectures inspired by the structures of biopolymers. It contains 26 original papers authored by contributors from Australia, China, France, Hungary, India, Italy, Korea, Japan, Spain, the United Kingdom, and the USA.

Many of the results described in these papers were presented at the Bordeaux 2012 Symposium on Foldamers co-chaired by Ivan Huc and Gilles Guichard at IECB in January 2012 and organized in the frame of a COST (European Cooperation in Science and Technology) action (see http://foldamer.org/).

Bronze medal for the team iGEM

The iGEM is an international competition in the field of synthetic biology opened to undergraduate and PhD students. This year, the project of Denis Dupuy teams of a "bacterial eyespot" was to engineer a single strain of E. coli to produce different phenotypes depending on the signal sent by the neighboring cells.
This experience was a real enrichment both for intellectual and technical work and opened PhD students minds on what synthetic biology has to offer to society. Many innovative projects, which could become a reality within a few years, were presented. The iGEM is first of all a competition, but it also has for goal to develop synthetic biology through the world. All teams contribute to the enrichment of scientific culture with original ideas and DNA sequences available to all future participants.
After the end of the 2012 edition, the Bordeaux team received a Bronze medal despite not being qualified for the finals at MIT. After this first experience we are more determined than ever and will aim for a gold medal in 2013!

In 2012, the IECB International Scientific Advisory Board welcomed a new member: Dr. Yves Pommier, Chief of Laboratory of Molecular Pharmacology, Centre for Cancer Research, NIH, USA
Chaired by the Pr. Daniel Louvard the ISAB interviewed pre-selected candidates from all over the world for group leader positions.

Organisational structure

Board members

International scientific advisory board (ISAB)

Dr. Daniel LOUVARD President
Institut Curie, Paris, France

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

Dr. Witold FILIPOWICZ
Institut Friedrich Miescher, Basel, Switzerland

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

Pr. Roeland NOLTE
Radboud University Nijmegen, Netherlands

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

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

Dr. Daniel SCHIRLIN
Sanofi Aventis, Paris, France

Dr. Moshe YANIV
Institut Pasteur, Paris, France

Former ISAB members

Dr. Simon CAMPBELL
Royal Society of Chemistry, London, UK
[1]

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

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

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

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

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

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

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

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

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

Board of directors

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

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

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

Mrs. Stéphanie MONTAGNER Administrative Director (CNRS)

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

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Research director, UMR 5248 (CNRS – Université Bordeaux 1)

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

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

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

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

Mrs. Stéphanie MONTAGNER Administrative Director (CNRS)

Board of trustees

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

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

Université Bordeaux 1
351 cours de la Libération, 33405 Talence

Université Bordeaux Segalen
146 rue Léo Saignat, 33076 Bordeaux

1

Organisational chart

Research teams

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

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Steering committee

Institut Européen de Chimie et Biologie

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UMS 3033 / US 001

Technology platforms
UMS 3033 / US 001

- Structural biology
- Preparative & analytical techniques

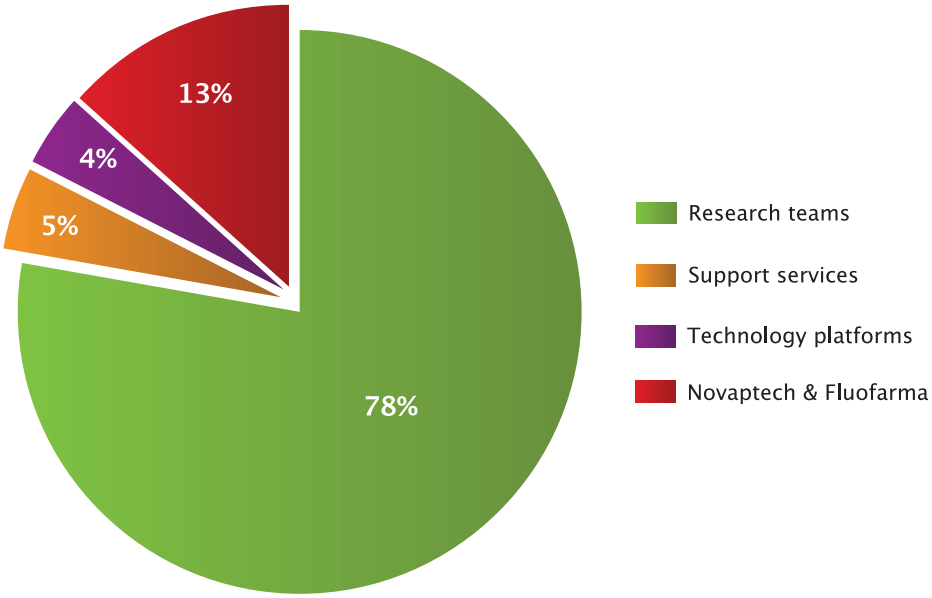
Technology transfer & start-ups

- FLUOFARMA
- NOVAPTECH

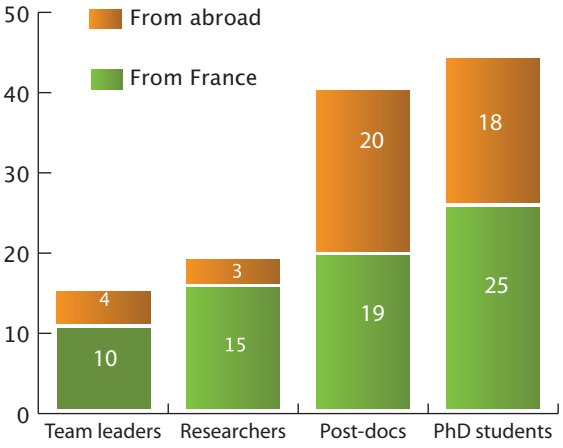
2012 key figures

In 2012, 194 people were working on the IECB site: 152 research staff, 17 employees within the IECB support services unit and 25 employees of the company Fluofarma and the technology transfer unit Novaptech. Young researchers (Master and Phd students, post-doctoral researchers) now represent more than the half of the IECB staff. This population largely contributes to gender equality and internationalization at IECB. It also testifies to the attractiveness of the institute.

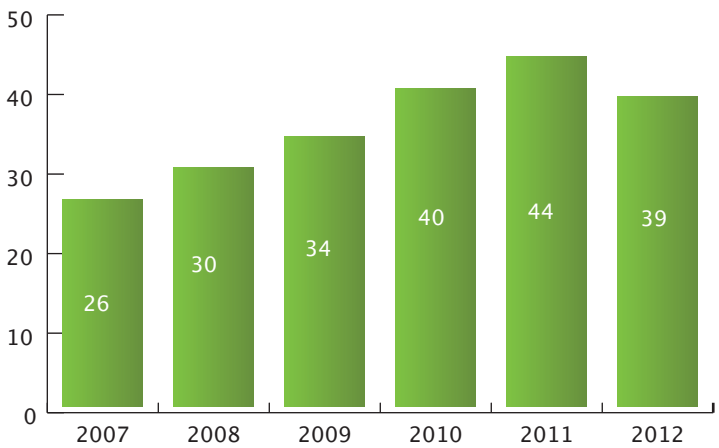
IECB staff by professional category



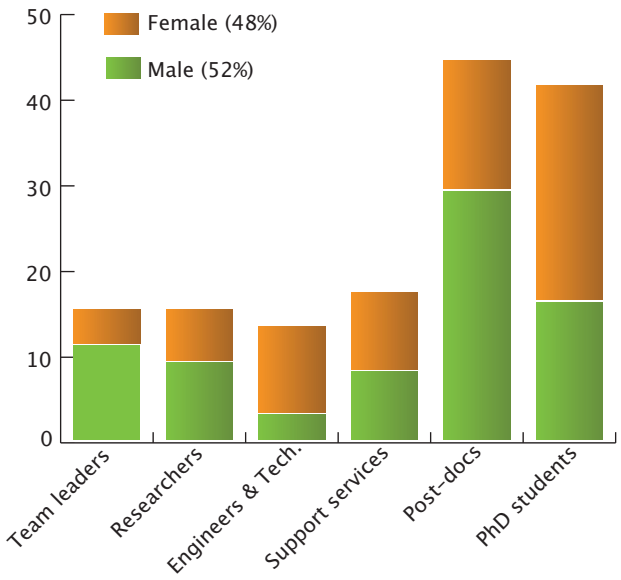
IECB researchers and students by nationality & professional category



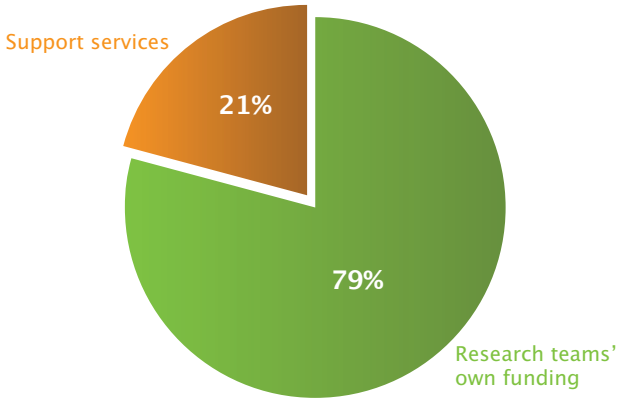
Number of post-doctoral researchers over the past 6 years



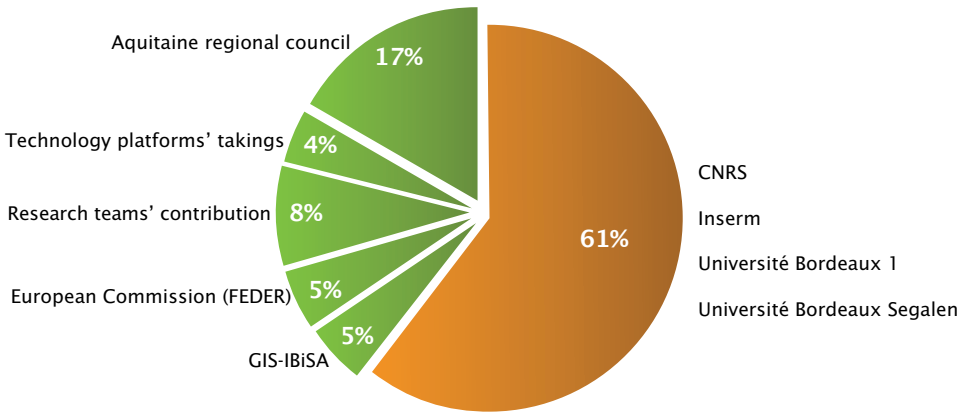
IECB research staff by gender & professional category



IECB's 2012 budget



Support services funding



The budget of the institute, which amounts to 9 millions euros including salaries, can be divided into two separate parts: the budget of the support services (UMS3033/US001) and the research teams' own resources. The first one is mainly granted by the trustees (CNRS, Inserm, Université Bordeaux 1, Université Bordeaux Segalen), while the other comes from public and private research grants and contracts.

SUPPORT SERVICES (UMS 3033 / US 001)

Support services at IECB consist of staffs in administration and finance, infrastructure and maintenance, as well as 6 engineers and technicians dedicated to IECB's technology platforms. The support services unit UMS3033/US001 is jointly funded by the CNRS, the Inserm, the Université Bordeaux 1 and the Université Bordeaux Segalen, and receives financial support from the Aquitaine Regional Council. Research teams also contribute to financing those general services.

Administration and finance

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

Executive assistant office

Executive assistant
Elodie EMAILLE, CDD, INSERM

Communication

Communication officer
Pierre-Emmanuel GAULTIER, CDD, CNRS

Infrastructure

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

Structural biology facilities

Head of structural biology facilities and crystallography engineer
Brice KAUFFMANN, IR, CNRS
NMR engineer
Cécile COURREGES, IR, CNRS
Mass spectrometry technician
Frédéric ROSU, CLD CNRS

Analytical and preparative techniques facilities

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

Research teams & output

Molecular modeling

Dr. Michel Laguerre

Research director (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. Juan ELEZGARAY Research director (DR2, CNRS)
Dr. Jean DESSOLIN Research officer (CR1, CNRS)
Dr. Nada TAÏB Postdoctoral fellow (AFM)
Dr. Vincent LEROUX Postdoctoral fellow (industrial grant, Servier)
Judith ELKAÏM PhD Student (MENRT)
Jean-Michel ARBONA PhD Student (MENRT)
Guillaume NATURALE PhD Student (CNRS/Aquitaine Regional Council)
Driss BENNANI PhD Student (Aquitaine Regional Council)
Marie-France Bakai, Master Student
Rémy Bailly, Master Student

The team is part of the unit "Chimie et Biologie des Membranes et Nanoobjets" (CBMN), CNRS/Université Bordeaux 1/IPB (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. The main research topics are devoted to cancers (new drugs and therapies, dissection of regulation pathways).

All-atom Molecular Dynamics

The first axis encompass 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). A new axis concerning the Hofmeister effect within the gemini surfactants series has been started following an International grant (NSF/ANR) with the Rutger's University.

Concerning 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

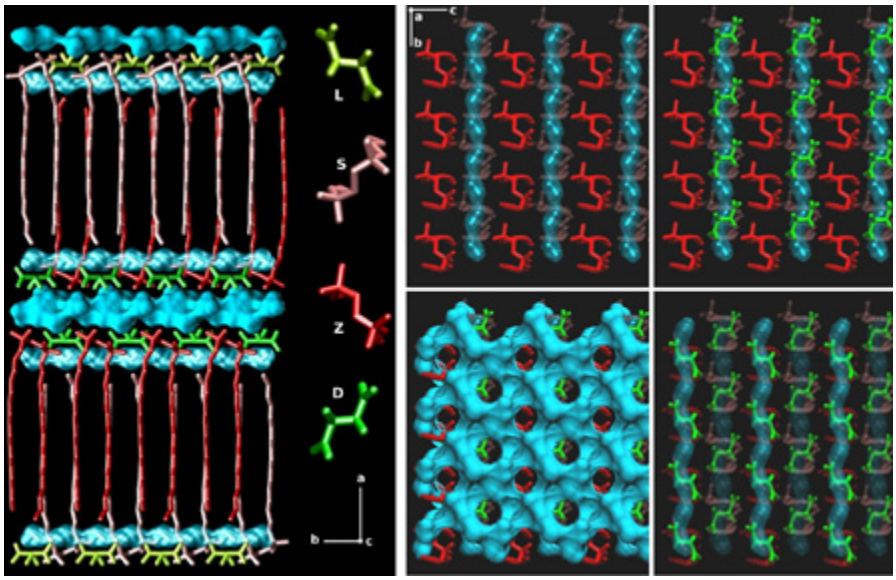


Figure 1: Final structure of the gemini tartrate film structure at an atomic level: geminis are in shade of red, tartrates in shade of green and water molecules are in blue. Tubes of aligned water molecules can be easily seen in the right panel. Between the two interdigitated layers a hexagonal lattice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

is involved in numerous regulation pathways and thus in many cancers (Cancer Institute UK). Two papers have been published in PloS Biology I alongwith 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 and the study has been extended to the kinase pKciota.

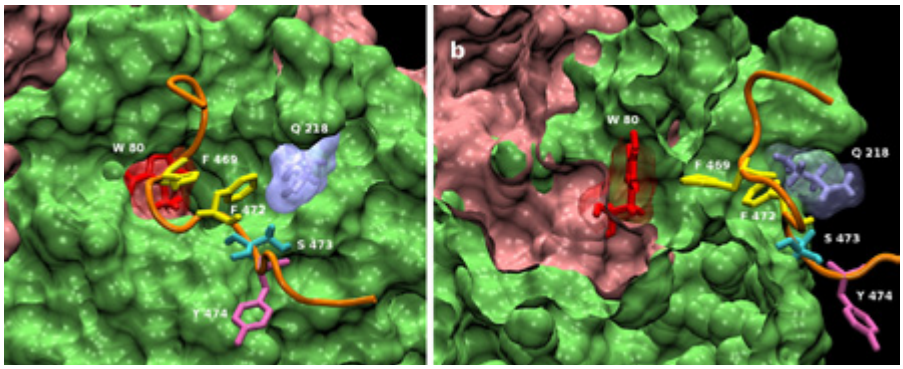


Figure 2: Complete structure of AKT-1: 2 orthogonal views of the Cterm docked on the WT PH/KIN complex : PH in pink, KIN in green, Cterm backbone in orange, W80 in red, F469 & 472 in yellow, S473 in cyan, Y474 in mauve, Q218 in aquablue. The water channel is visible in the center of the left image and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

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

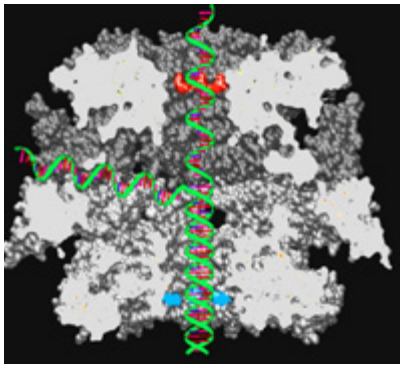


Figure 3: Complete model structure of human Helicase. Reptin is below and pontin above. A double-stranded DNA is entering the protein through a central channel. DNA is unfolded in the center of the complex and then the direct strand gets out by the top pontin pore and the indirect strand is ejected through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

DNA origami

DNA origamis are made of a 7249 bases long ssDNA scaffold (M13mp18) folded with a set of about 200 complementary short ssDNA (32 bases long) called staples. These nanostructures are at the basis of many applications. Besides immediate applications such as biosensors, many strategies take use of DNA dynamical behaviour to achieve complex functions or structure recon□guration. Prescribed tracks have been used for the development of nanomachines and nanorobots while strand displacement techniques have been employed to reorganise origami structures. However, despite these innovative realisations, the folding process of DNA origamis remains poorly understood.. Our future work will be directed to the development of DNA systems able to react in a complex way to external inputs. Basically, origamis can be seen as an adequate platform where sea-saw gates (Winfree) or other type of DNA calculators can be attached in such a way that a response can be computed as a function of the nature of external inputs. Aptamers constitute a natural candidate to play the role of input interface.

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.

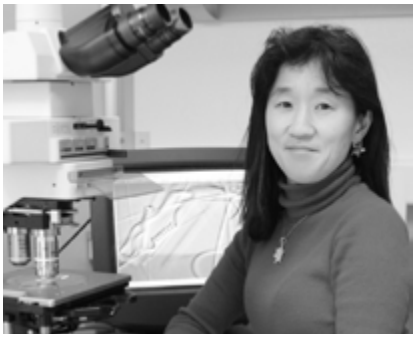
Calléja, V., Alcor, D., Laguerre, M., Park, J., Hemmings, B., Vojnovic, B., Downward, J., Parker, P.J., Larijani, B. (2007). Intra- and inter-molecular interactions of Kinase B define its activation in vivo. PLoS Biology, 5(4): 780-791.

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

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

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

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



Dr. Reiko Oda

Research director (DR2), CNRS

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

Research team

Dr. Sylvain NLATE Associate professor (Mdc, Université Bordeaux 1)
Dr. Emilie POUGET Research officer (CR2, CNRS)
Dr. Marie Christine DURRIEU Research officer (CR1, INSERM)
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Dr. Omar Zouani Postdoctoral fellow (Université Bordeaux 1)
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Xi-Shiang Huang PhD student (Leuven University/Université Bordeaux 1)
Annie Zhe CHENG PhD student (Leuven University/Université Bordeaux 1)

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

Morphologies, dynamics & functions of assemblies of amphiphilic molecules

The team is interested in understanding the mechanism of formation of molecular assemblies in order to design and build new nanometric molecular assembly systems of amphiphilic molecules, the morphologies and functions of which can be finely tuned. This requires first of all understanding the role of different parameters (molecular architecture and various physico-chemical parameters) on the molecular assemblies. Once the control of the assembly formation at molecular level is achieved, their functionalisation can be envisaged. The assemblies can serve as the support for the bio-inspired complex structures or hybrid materials

Our activities are divided in several subjects as shown below:

Ion specific effect

We combine experimental and computational approach to rationalize the century old problem: ion specific effect on the balance of forces controlling aggregates structure. We investigate the aggregation behaviors of cationic amphiphilic molecules in the presence of various counterions such as Halide anions, alkyl carboxylates, 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, Langmuir Feature invited article 2013 Cover image March 2013)
We perform a collaborative work between Michel Laguerre (IECB, molecular dynamics), Dario Bassani (ISM, Photochemist), and colleagues from Rutgers University, Larry Romsted (Physical organic chemist: chemical trapping technique), Ronald Sauers (DFT calculation), David Case (MD/ DFT approach) in order to elucidate the interface properties of amphiphilic assemblies in terms of counterion and water concentration. (PhD Thesis, Alla Malinenko, Postdoc, Max Porrini (Laguerre))

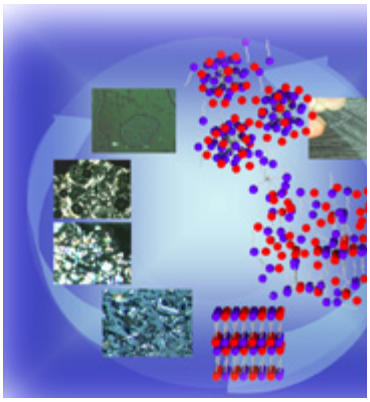

Figure 1 : solubilisation mechanisme of surfactants and the role of counterions (Langmuir Cover image March 2013)

Chiral assemblies

We are interested in the mechanisms of chirality transfer based on non chiral amphiphilic molecules in the presene of chiral counterions. We have shown that tartrate, when complexed with cationic surfactants, form chiral ribbon which express supramolecular chirality of the order of 10 nm to microns. The morphologies of these chiral assemblies can be controlled with a number of parameters (Nature 1999, JACS 2007). The detailed study of these systems allowed us to better understand the mechanism of the chirality transfer from chiral counterions to achiral membranes from molecular level up to mesoscopic level. (JACS 2002, J. Phys. Chem. A 2004, JACS 2008, Chirality 2009).

Biological anions confined at membrane surfaces

The interaction 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 molecu-

lar level, it is important to understand these complex in the simplified model system for which we can control various parameters in independent manners. We have developed the systems of lipopeptide (Figure 1) and nucleolipid by using biological polyanions such as oligopeptides or nucleotides complexed to cationic amiphiphiles. (ChemCommun 2007, Chem. Eur. J., 2011,)
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 it was the case with tartrates. Such reciprocal and cooperative effects between membranes and counterions, seem to be general in the case of the systems studied here.

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 (Nanoletters 2008). These inorganic structures can then be functionalized to serve as templates for confining nanoparticles for optical application (SERS, metamaterials) (LabEx-Metamaterials), or coating with piezoelectric layer for nanoelectromechanical systems (NEMS), (ANR Blanc grant 2010.). (PhD student, D. Dedovets, J. Cheng)

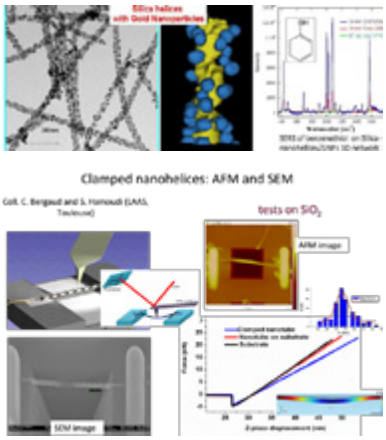

Figure 2 (top) (left) silica nanohelices coated with gold nanoparticles, (center) Reconstructed TEM tomography image. (right) SERS of benzenthiol on Silica nanohelices/GNPs 3D network. (bottom)(Left) schematic and SEM image of a silica nanotube suspended above the microcavity of a Si substrate and clamped at its extremity. (Right) Histogram showing elastic modulus distribution after repetitive force curve measurements

With Sylvain Nlate, a Maître de Conference specialised in dendrimers and catalysis who recently has joined the group. We started a new project concerning the design of new catalysis systems for asymmetric oxidation reactions using tunable nanometrical chiral molecular assemblies. We have recently awarded a new collaborative projects (JSPS-CNRS PRC) with the laboratory of Prof. Sagawa, Kyushu Univ. and Prof. Ihara, Kumamoto Univ. Japan to develop a new type of supramolecular chiral catalyst.
From October 2011, Marie-Christine Durrieu, an INSERM researcher specialized in cell adhesion on the surface joined the group. Reinforced by her expertise in tissue engineering, we are developing a totally new field to investigate the effect of surface organized nanostructures on the cell differentiation. We designed a surface functionalized with the silica nanohelices functionalized with bioactive peptides which mimic ExtraCellular-Matrix (ECM) in order to investigate the effect of these surfaces on the adhesion, growth, and differenciation of stem celles. A postdoctoral fellow has been hired for the project, and we demonstrated the covalent grafting of these silica nanoribbons onto activated glass substrates can direct the commitment of human mesenchymal stem cells (hMSCs) into osteoblast lineage in vitro, free of osteogenic inducing media. (a manuscript has been just accepted in ACS Nano)

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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Tamoto, R; Lecomte, S; Si, S; Moldovan, S; Ersen, O; Delville, MH; Oda, R Gold Nanoparticle Deposition on Silica Nanohelices: A New Controllable 3D Substrate in Aqueous Suspension for Optical Sensing, JOURNAL OF PHYS. CHEM. C 116 43 23143-23152

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

Dr. Ivan Huc
Research director (DR1), CNRS

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

Research team

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Dr. Krzysztof ZIACH Postdoctoral fellow (Université Bordeaux 1)
Dr. Simon DAWSON Postdoctoral fellow (Université Bordeaux 1)
Dr. Tiny DESCHJRIVER Postdoctoral fellow (Université Bordeaux 1)
Dr. Chandramouli NAGULA Postdoctoral fellow (CNRS)
Dr. Bo CHI Postdoctoral Fellow (Egide)
Laure SEBAOUN PhD student (Université Bordeaux 1)
Guillaume LAUTRETTE PhD student (Université Bordeaux 1)
Christos TSIAMANTAS PhD student (Université Bordeaux 1)
Quan GAN PhD student (CNRS)
Xuesong LI PhD Student (Université Bordeaux 1)
Xiang WANG PhD Student (China Scholarship Council)
Misae Kanai Visiting Scientist (Université Bordeaux 1)

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

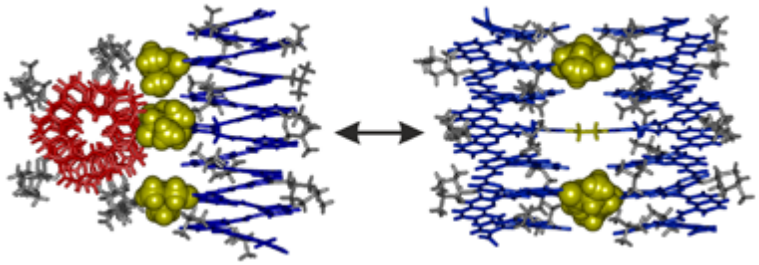
Biomimetic Supramolecular Chemistry

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

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

Proteomimetics

Synthetic foldamers of unprecedented size (> 10 kDa) have been synthesized and structurally characterized by x-ray crystallography (J. Am. Chem. Soc. 2011). They represent the first folded abiotic architectures that compare in size to a (modest-size) protein. Whilst many foldamers have so far consisted of isolated helices or linear strands, future developments will likely focus on mimics of protein tertiary folds as the one we have described. The synthesis of such a large object was made possible by the incorporation of aliphatic secondary amide linkages that are compatible with the folding motifs of aromatic secondary amide linkages. The first artificial organic triple helices have been evidenced (Angew. Chem. Int Ed. 2010) among the folded structures of naphthyridine oligoamides. This discovery follows earlier work on quadruple helices (2008) and double helices and strikingly illustrate the potential of these oligomers to form a great variety of well-defined architectures.

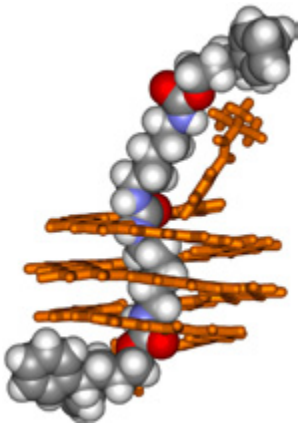


Encapsulation

Sequences of aromatic amino-acids have been designed to fold into helices having a large diameter in the center and narrow diameters at the ends, thus creating a cavity totally surrounded by the helix backbone. Encapsulation of various guests in those confined environments has been demonstrated. A chiral guest such as tartaric acid is recognized with full diastereoselectivity by a helix of fixed handedness. A recent extension of this work allowed to characterize the mechanism by which the guest goes in and out of the capsule (J. Am. Chem. Soc. 2012), and how the binding and release rates can be tuned upon increasing the overall stability of the helical structure. Current unpublished developments demonstrate the capacity of these helically folded capsules to selectively bind to unsubstituted mono-saccharides. This work offers a new design strategy for synthetic receptors targeted to polar and chiral guests, and also to control over the

timeframe of their capture and release.acid is recognized with full diastereoselectivity by a helix of fixed handedness. Current unpublished developments demonstrate the capacity of these helically folded capsules to selectively bind to unsubstituted monosaccharides.

Molecular motors



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

Foldamer-DNA recognition

In a joint effort with the group of J-J Toulmé, directed DNA evolution (SELEX) was used to decipher DNA-foldamer interactions. These experiments revealed highly selective interactions between some foldamers and G-quadruplex DNA: some foldamers were identified that recognize a quadruplex and not another, that recognize a DNA quadruplex and not the corresponding RNA sequence, or that recognize a DNA quadruplex and not its enantiomer comprised of L-nucleobases (Angew. Chem. Int. Ed. 2012). This work emerged as an original approach to learn about DNA recognition: while it is difficult to design a foldamer that binds to a given DNA, it is easier to identify DNA sequences that bind to a given foldamer and learn about its DNA binding ability.

Selected publications

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

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

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

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

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

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

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

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

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

Research team

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Dr. Laurent POUYSÉGU Associate professor (MdC, Université Bordeaux 1)
Rémi JACQUET Technician (Tech, Université Bordeaux 1)
Dr. Amir AHMED Postdoctoral fellow (HEC Pakistan Gov)
Dr. Gloria Zedda Postdoctoral fellow (ANR Flunucleovir)
Mélanie DELANNOY PhD student (Fundayacucho)
Cyril BOSSET PhD student (BDI CNRS/CRA)
Romain COFFINIER PhD student (ANR IODINNOV)
Emilie PETIT PhD student (CIVB)
Hélène CARRIÉ PhD student (CIVB)
Dong Tien TRAN PhD student (Vietnamese Government)
Mourad EL ASSAL Doctoral Student (French Gov)
Aude WATRELOT Doctoral Student (INRA Avignon)

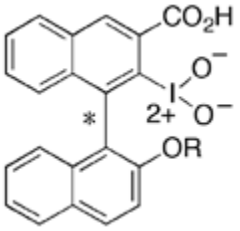
This team is part of the Institut des Sciences Moléculaires (UMR-CNRS 5255) at the University of Bordeaux and is associated with the Institut des Sciences de la Vigne et du Vin (ISVV).

Synthesis & activity of natural substances

Our research activities are today mainly concerned with the chemistry and biochemistry of natural products with a focus on (poly)phenolic and quinonoid compounds, and with the chemistry of hypervalent iodine compounds as novel reagents for modern organic synthesis. 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, and (3) the development of chemical proteomic tools for the study of protein-polyphenol interactions.

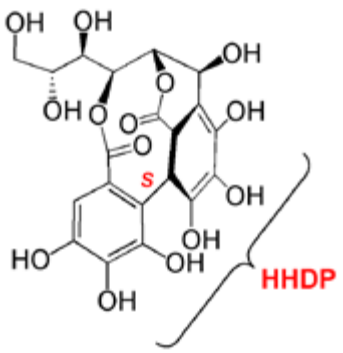
Hypervalent Iodine-Mediated Phenol Dearomatization

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. After having developed a substrate-controlled solution for this challenge, we explored a reagent-controlled solution to asymmetric dearomatization of phenols by relying on the use of a chiral binaphthylic hypervalent iodine reagents. We have been pursuing this effort over the last two years with the financial support of the ANR (project Iodinnov), the CNRS and the Conseil Regional d'Aquitaine. Our results will soon be published. The utility of our stabilized version of the hypervalent iodine(V) 2-iodoxybenzoic acid (SIBX) in regioselective phenol oxygenation and dearomatisation has been further demonstrated and reviewed in an article on the synthesis of biologically active catechols in Current Organic Synthesis in 2012. SIBX is also now referenced in Wiley's Encyclopedia of Reagents for Organic Synthesis (since March 2012).



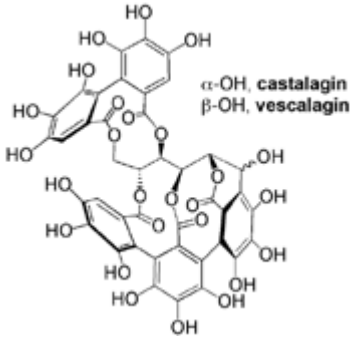
Synthesis, chemical reactivity and biological activity of polyphenolic C-glucosidic ellagitannins

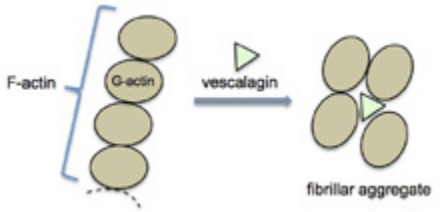
Mainly funded by the Conseil Interprofessionel du Vin de Bordeaux (CIVB), the Conseil Our investigations on this multiple topic, which were in part funded by the ANR (project Ellaginnov), the Conseil Regional d'Aquitaine and still today by Conseil Interprofessionel du Vin de Bordeaux (CIVB), continue to provide us with valuable results. On the synthesis side, we recently achieved the first and biomimetic total synthesis of a first member of the C-glucosidic class of ellagitannins, 5-O-desgalloylepipunicacortein A. A preliminary version of this work was published in 2011 in ChemComm. In 2012, we published in Chemistry - A European Journal a full paper article describing two alternative synthetic routes, including a diastereoselective construction of the (S)-HHDP unit, to access this ellagitannin and others. On the chemical reactivity side, new results on a series of oxidation of the ellagitannin castalagin in the presence of wine olfacto-



5-O-desgalloylepipunicacortein A

ry thiols will soon be published, as well as results on a remarkable chemoselective oxidation of the flavano-ellagitannin acutissimin A into mongolicaine A. On the biological activity side, we were able to determine, by a surface plasmon resonance technique we developed with our INSERM colleague Carmelo Di Primo at IECB, that the anti-actin activity of vescalagin is due to its selective interaction with the filamentous form of actin (F-actin) and not with its monomeric globular form (G-actin). This anti-actin effect of vescalagin was discovered in collaboration with our INSERM colleague Elisabeth Génot at IECB. These results were published in Angewandte Chemie in 2011, and we since filed a patent request on the possible application of vescalagin as a drug against osteoporosis (PCT/EP2012/053017). In collaboration with our INSERM colleague Philippe Pourquier and our colleagues at Fluofarma, we also published in 2012 a report in Molecular Pharmacology on the preferential catalytic inhibition of the alpha-isoform of human DNA topoisomerase II by certain C-glucosidic ellagitannins.





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). Catechin and epicatechin, among other polyphenolics, have been mounted onto polyfunctional chemical probes in the aim of developing new chemical proteomic tools for the detection/purification/identification of known (and yet unknown) functional proteins in Vitis vinifera. New results will soon be published.

The third volume of the book series Recent Advances in Polyphenol Research, edited by S. Quideau and colleagues from the Groupe Polyphénols society, was released in Spring 2012. And finally, for those of you interested in plant polyphenols, our new definition of plant polyphenols, which we proposed in a review article in Angewandte Chemie in 2011, will soon appear in Wiley's eLS.

Selected publications

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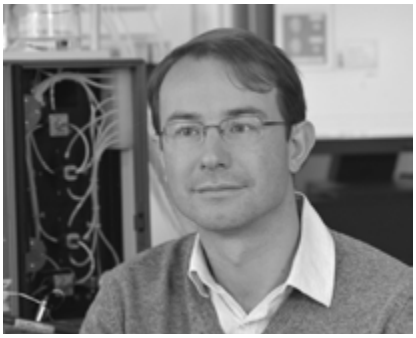

Dr. Gilles Guichard
Research director (DR2), CNRS

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

Research team

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

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

Peptidomimetic chemistry

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

"Foldamer Chemistry" is the main focus of our recent work. Our project capitalizes on previous findings from our group showing that aliphatic urea oligomers form well defined and remarkably stable helical secondary structures reminiscent of peptide helices. Compared to other foldamer backbones reported in the literature, aliphatic urea-based foldamers possess several features that make them well suited for biological applications: (1) the canonical 2.5-helix of oligoureas and the α-helix superimpose quite well; (2) helical folding is maintained in aqueous environment, though helix stability is diminished compared to organic solvents and (3) Urea oligomers are highly resistant to the action of proteases. Our present work in the foldamer area essentially follows 5 main directions: (i) synthetic developments and exploration of requirements for helix formation by urea-based oligomers; (ii) the analysis of their folding propensity in various environments, (iii) the construction of folded objects of increasing complexity, (v) the investigation of their interactions with biomacromolecules and exploration of their biomedical potential. Significant achievements in 2011-2012 include:

An efficient microwave-assisted solid-phase method for the synthesis of oligoureas (Org. Lett. 2012).

Several solid phase synthesis (SPS) methodologies to access aliphatic oligoureas have been described. All are based on a sequential coupling of activated monomers derived from monoprotected ethylenediamine derivatives such as succinimyl carbamates developed by our laboratory. Although these monomers have proven useful to access short oligoureas in reasonable yields and purities, they still suffer some drawbacks: long coupling times (2 × 120 min) and a large excess of monomers (at least double couplings of 3 equiv) are typically needed. We have now developed a practical and efficient microwave-assisted solid-phase method for the synthesis of N,N□-linked oligoureas and related amide/urea hybrid oligomers, featuring the use of succinimidyl (2-azido-2-substituted ethyl) carbamate monomers (Fig. 1). The rate enhancement of urea formation under microwave irradiation combined with the mild conditions of the phosphine-based azide reduction makes this approach very effective for routine access to oligoureas and possibly for library production.

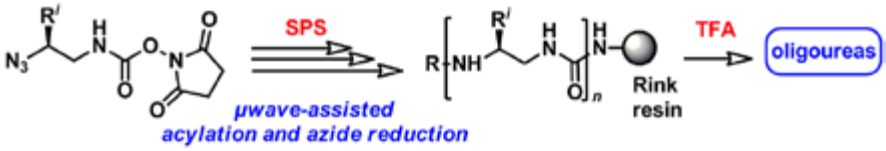

Figure 1. New activated monomers for the microwave-assisted SPS of oligoureas and related amide/urea heterogeneous backbones

An efficient synthetic approach to monomeric units with imidazolyl (histidine-like) side chain (Tetrahedron 2012).

Histidine is a remarkable amino acid in which the basic 1H-imidazolyl side-chain plays a pivotal role for the biological activity of many peptides and proteins. We recently became interested in appending histidine-type side chains on the helical oligourea scaffold. A robust synthesis of a suitably protected N-Boc-protected monomer for the synthesis of oligourea foldamers containing the (1H-imidazolyl-4yl)methyl side chain of histidine, has been developed starting from Trt-His(τ-Trt)-OMe (Fig. 2). This protecting group combination on histidine was found to be critical to ensure efficient access to the requisite activated building block. This new derivative, suitable for solid phase synthesis, expands the current arsenal of building blocks with proteinogenic side chains useful for the design of peptidomimetic oligourea foldamers.

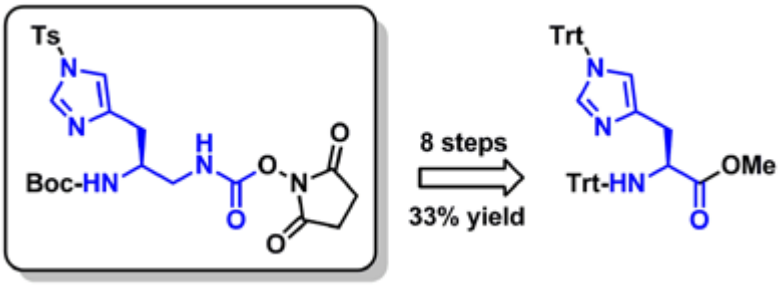

Figure . 2. Synthesis of an activated building block for insertion of His side chain into oligoureas.

Interaction of ^{15}N-labelled antimicrobial helical oligoureas with oriented lipid membranes by solid state NMR (Org. Biomol. Chem. 2012)

We have reported previously that oligoureas designed to mimic globally amphiphilic α-helical host-defense peptides display broad antibacterial activity. We have now used solid state NMR spectroscopy to study the three-dimensional structure, dynamics and topology of these antibacterial amphiphilic oligoureas in lipid bilayers (collaboration with B. Bechinger, Univ. de Strasbourg). The ^{15}N chemical shift tensor of a model ^{15}N-labelled diurea was determined for the first time and found to exhibit properties related to that of the amide tensor of the peptide bond. Using this information the association of an antimicrobial amphipathic oligourea (specifically ^{15}N-labelled) with oriented lipid membranes was studied successfully and a surface alignment was obtained analogous to observations made for amphipathic antibacterial helical polypeptides. Topologies that agree with the experimental constraints (Fig. 3) correspond to (approximately) inplanar orientations of the oligourea helix.

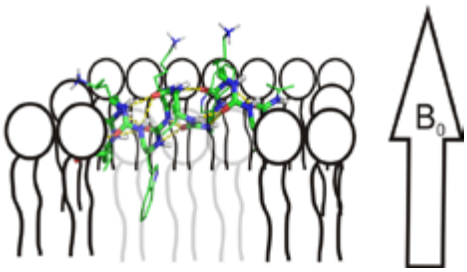

Figure 3. Molecular alignments of antimicrobial amphipatic oligoureas consistent with 15N chemical shift and ^{15}N-1H dipolar coupling.

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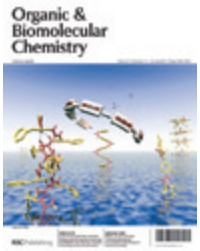

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Dr. Élisabeth Garanger

Research Officer (CR2) CNRS

Trained as a chemist, E. Garanger graduated in 2001 as a Chemical Engineer from ENSC Clermont-Ferrand and with a Master's degree in Biological Organic Chemistry. She pursued her education with a PhD in Chemistry and Biology at the Univ. 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 neoangiogenesis. In 2006, she was appointed as a post-doctoral fellow at the Center for Molecular Imaging Research (Harvard Med. School, Boston) to design contrast agents for multimodal molecular imaging. In 2009, she joined the group of Prof. S. Lecommandoux (LCPO) to work on the design, synthesis/production and self-assembly of chimeric polymer-peptide materials for biomimetic/biological/biomedical applications..

Research team

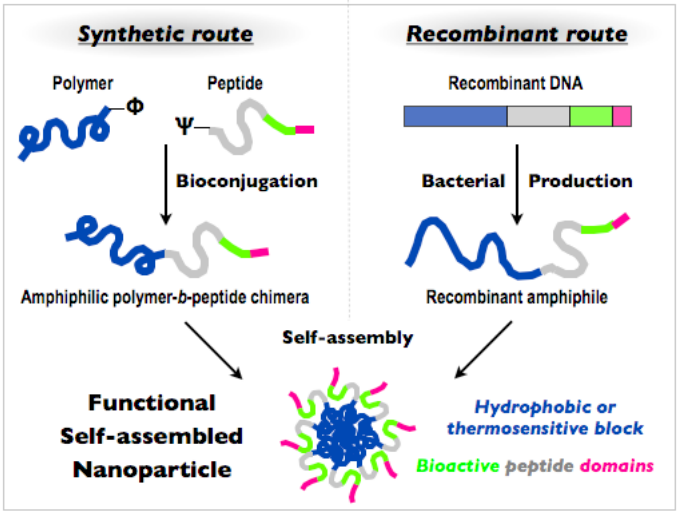
Charlotte DRAPPIER PhD student (Université Bordeaux 1)
Laure BATAILLE Engineer (Institut Polytechnique de Bordeaux)
Olivia CONDASSAMY Master Student (University Bordeaux 1)

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

Self-assemblies from chimeric polymer-peptide materials

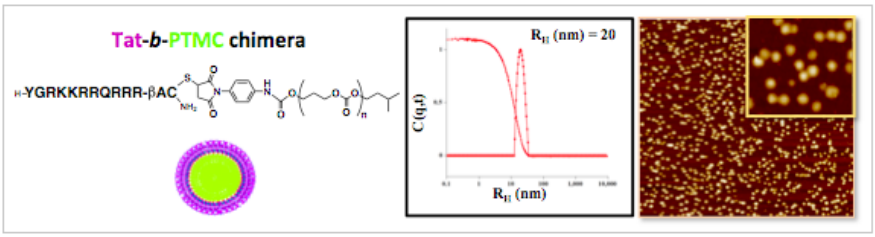
Our main objective is the production of innovative polymer-based materials fulfilling prerequisites of precision, functionality and sustainability. We particularly focus on well-defined polymer materials featuring self-assembly and biological properties encoded at the molecular level obtained from two parallel complementary approaches. Amphiphilic chimeric materials featuring a synthetic polymer block conjugated to a peptide segment are synthesized, while recombinant DNA and protein engineering techniques are used to produce recombinant polymers based on elastin motifs. Self-assembly mechanisms are studied and biological activities assessed with the ultimate goal of preparing biofunctional nanomaterials. This project is developed in relation with the LCPO theme "Polymers and Life Sciences".

The design of functional self-assembled nanomaterials is currently a major challenge of nanotechnologies and concerns domains as broad as health, communication, 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 secondary/tertiary structures and biological functions, is sometimes difficult to control by synthetic chemists. One of today's consensuses thus relies on the association of natural 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. Towards this goal, our group is investigating two different approaches to access biofunctional precision block copolymers: i) either a synthetic approach involving the conjugation of functional peptides with synthetic polymers, ii) or a recombinant approach based on protein engineering technologies to have microorganisms (e.g. bacteria) produce amphiphilic biofunctional recombinant protein-like polymers.



Peptide-b-polymer molecular chimeras

We have recently reported the precision synthesis and characterization of amphiphilic peptide-b-polymer molecular chimeras encoding, at the molecular level, self-assembly properties and biological functions, presently cell membrane penetrating motifs. The Tat47-57 sequence from the transactivator of transcription protein of HIV-1 (TAT) is a hydrophilic peptide presenting cell penetrating ability as well as blood-brain barrier crossing capabilities. Poly(trimethylene carbonate) (PTMC) is a biodegradable and biocompatible hydrophobic polymer segment with compelling self-assembly properties. A series of amphiphilic Tat-b-PTMC molecular chimeras were thus synthesized and characterized using different techniques (e.g. DOSY NMR, MALDI-MS). By direct dissolution in aqueous buffer, Tat-b-PTMC diblocks self-assembled into size-tunable, highly monodisperse core-shell nanometer-sized particles with hydrodynamic diameters ranging from 22 to 40 nm. Their transduction properties, cellular toxicity and interaction mode with phospholipid membrane models is currently investigated.



Recombinant protein-like polymers

Elastin-like polypeptides (ELPs), as initially pioneered by Dan W. Urry at the University of Birmingham (Alabama, USA), are repetitive sequences of (Val-Pro-Gly-Xaa-Gly) pentapeptides derived from the hydrophobic domain of mammalian elastin containing (Val-Pro-Gly-Val-Gly) repeats. In ELPs, the guest residue at the fourth position (Xaa) can be any amino acid other than proline. A major characteristic of ELPs is their temperature-sensitive behavior: above a minimal length, ELPs present a transition temperature (Tt), similar to a lower critical solubility temperature (LCST), below which they are fully soluble and above which they aggregate. The Tt value of an ELP chain can be tuned by modifying different parameters such as the length and molecular weight of the ELP, the nature of the guest residue within the pentapeptide motifs, or the ionic strength of the solution. The latter constitutes a wonderful means to control the ELP self-assembly process, as well as a useful trick to isolate and purify ELPs from the production media (bacterial lysates). Using well-established biotechnological methods, we currently work on the design and production of precision ELP homopolymers, copolymers and block copolymers for specific post-polymerization modifications.

Projects conducted in our team are at the crossroads between the fields of synthetic biology, bioconjugation chemistry and physical chemistry.

Selected publications

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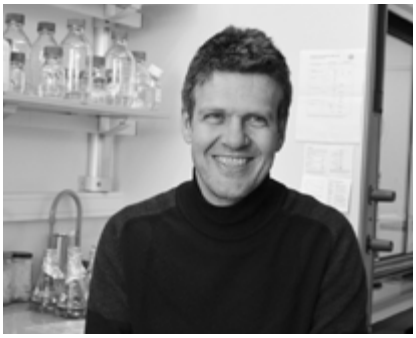

Pr Martin Teichmann

Professor (Pr1), Université Bordeaux Segalen

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

Research team

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

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

Transcription - Maturation & Structures

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 III□ and Pol III□). RPC32□-containing Pol III□ 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 RPC32□-containing Pol III□ is not regulated during these processes. Moreover, expression of RPC32□ is important for cell transformation and anchorage-independent growth. We now try to elucidate how Pol III□ contributes to cellular transformation.

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

Identification and Characterization of a novel Isoform of human RNA polymerase III

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

We initially identified a novel protein that we designated as RPC32τ because it exhibited high amino acid homology to the well known Pol III subunit RPC32 (hereafter referred to as RPC32β). The identification of RPC32τ led to the demonstration of two human Pol III isoforms (Pol IIIτ and Pol IIIβ). RPC32τ-containing Pol IIIτ is ubiquitously expressed and essential for growth of human cells. Suppression of RPC32τ by siRNAs is lethal in HeLa cells, suggesting that RPC32τ-containing Pol IIIτ cannot replace all functions of RPC32β-containing Pol IIIβ. In contrast, Pol IIIτ 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 RPC32τ expression impedes anchorage-independent growth of HeLa cells whereas overexpression of RPC32τ in a well defined cellular model system enhances colony formation in soft-agar assays. RPC32τ-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 RPC32τ 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 RPC32τ-containing Pol IIIτ 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 III transcription termination

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

Structure-function studies of human RNA polymerase III subunit RPC62

In collaboration with the group of Sébastien Fribourg, we have been able to determine the structure of RPC62 by X-ray crystallography at a resolution of 2.85 Å. We analyzed the DNA-binding properties of RPC62 and of its protein interaction partner RPC39. We could show that RPC39 binds to double-stranded DNA, whereas RPC62 binds to single-stranded DNA. These data indicate that RPC39 and RPC62 may contribute to promoter melting and to the maintenance of the transcription bubble (Lefèvre et al., 2011; Teichmann et al., 2012).

Identification of mutations in the largest subunits of RNA polymerase III causing recessive hypomyelinating Leukodystrophy

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

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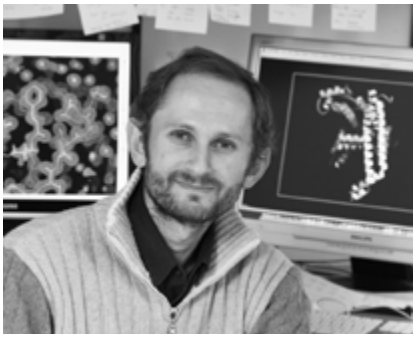

Dr. Sébastien Fribourg

Research officer (CR1), Inserm

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

Research team

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Natacha PÉRÉBASKINE Technical assistant (University Bordeaux Ségalen)
Cécile MONFOULET Technical assistant (Inserm)
Adrien DUPIN PhD student (University Bordeaux Ségalen)
Julia GUEGUENIAT PhD student University Bordeaux Ségalen

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

Structural biochemistry

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

mRNA polyadenylation factors

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

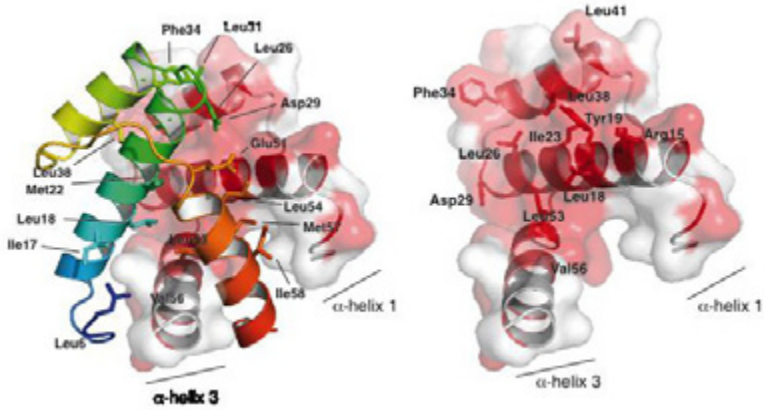


Figure 1: Overall structure of CstF-50 N-terminal domain and homodimerization determinants (Moreno-Morcillo et al., 2011).

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

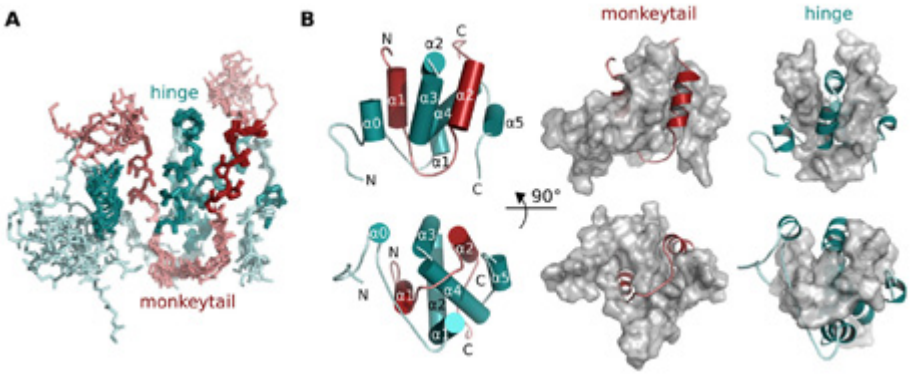
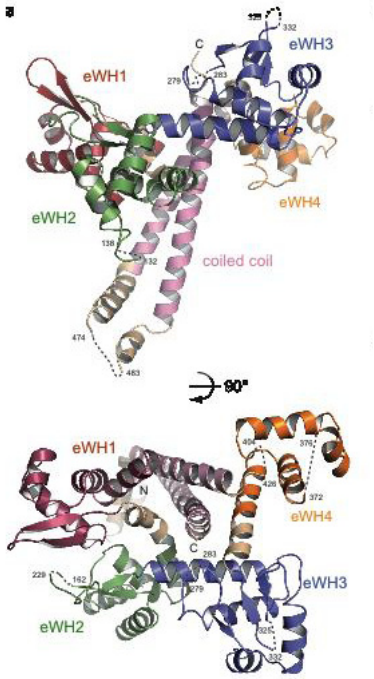


Figure 2: Solution structure of the core Rna14p-Rna15p domain. Rna14p is shown as a red ribbon whereas Rna15p is depicted in cyan.

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. Further work is still under process in order to obtain structural data on the overall CF IA complex either by X-ray crystallography or alternative low-resolution lethods such as SAXS and Electron Microscopy. In parallel to these structural studies we pursue the associated functional analysis of these factors (Haddad et al., 2012)

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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Dr. Cameron Mackereth

Research officer (CR1), Inserm

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

Research team

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Heddy SOUFARI PhD student Inserm/ Aquitaine Region

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

NMR spectroscopy of protein-nucleic acid complexes

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

Tissue-specific alternative splicing in C. elegans

Previous work has reported on the molecular basis by which the efficiency of mRNA splicing is transmitted from the RNA sequence to the spliceosome, and found this to be in the selective binding of one of two conformations of the essential splicing factor U2AF65. In contrast to this basal splicing mechanism, we have recently investigated the manner by which alternative splicing is regulated in multi-cellular organisms, in particular to understand the role of this important process in the development of specific tissues. Combined with the ASD-1 or FOX-1 proteins, SUP-12 is involved in the muscle-specific alternative splicing of the egl-15 mRNA, which is required to generate a specific form of egl-15 that is required for proper muscle development. Using NMR spectroscopy we have determined a solution structure of the RNA recognition motif (RRM) domain of SUP-12 bound to RNA and DNA ligands. In collaboration with the group of D. Dupuy at IECB, we have used a series of fluorescent report to study this alternative splicing regulation in live C. elegans.

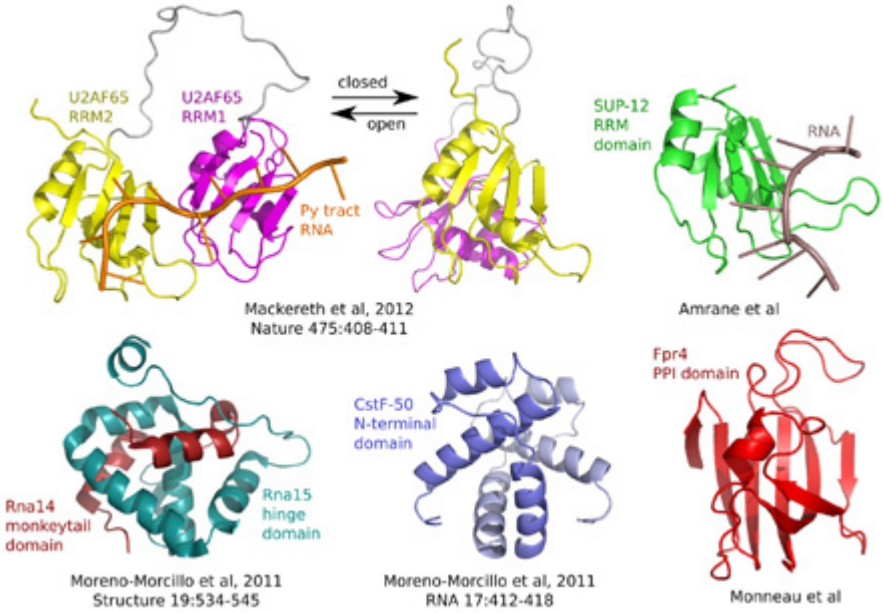
Complexes involved in pre-mRNA 3' processing

In collaboration with the lab of S. Fribourg at IECB, we are investigating the structure and dynamics of the yeast cleavage/polyadenylation factor IA (CF IA) and metazoan cleavage stimulation factor (CstF) complexes, both involved in the removal of the terminal sequence of the pre-mRNA prior to the addition of multiple adenosine to form the poly(A) tail. The current research in the laboratory deals with the structural characterization of the complete set of folded domains involved in protein-protein and protein-RNA interactions within CstF and CF IA, as a step toward looking at the architecture of the larger assembled complexes. We have 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. We are continuing our investigations with additional and previously uncharacterized domains from with the CF IA complex.

Proline isomerases and histone chaperones

In the field of epigenetics and histone regulation, we are also looking at the role of proline isomerization of the histone N-terminal tails by two members of the FKBP family. We are collaborating with Dr. Chris Nelson who uses yeast genetics and biochemistry to study this topic at the University of Victoria in Canada. We have character-

ized a specific yeast peptidyl-prolyl isomerase, Fpr4p, by NMR spectroscopy and have determined that the relative affinity of the various decapeptide substrates appear to correlate well with the classical chymotrypsin-based proline isomerase activity assay. However, the actual increase in isomerization due to Fpr4p is highly dependent on the nature of residues C-terminal to the peptidyl-prolyl bond and which are absent in the classical assay. In addition, NMR spectroscopy titration studies and the use of strategic attachment of paramagnetic spin labels to look at transient association, has allowed us to provide a model for peptide recognition by FKBP domains which has so far been significantly absent in the literature. Current work focusses on details of the inter- and intra-molecular regulation for both Fpr4 and the human orthologue FKBP25. This latter protein appears to be implicated in specific functions within the cell and is aberrant expressed in cancer.



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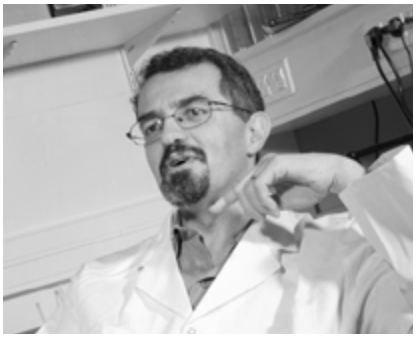

Dr. Jean-Louis Mergny

Research director (DR1), INSERM

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

Research team

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Aurore GUÉDIN Tech. assistant (AI, INSERM)
Dr. Samir AMRANE Postdoctoral fellow ANRS
Dr. Daniel RENCIUK Postdoctoral fellow (ANR-G4Toolbox)
Dr. Rui MORIYAMA Postdoctoral fellow (JSPS/ANR-F-DNA)
Dr. Jun ZHOU Postdoctoral fellow (Région Aquitaine)
Dr. Souheila AMOR Postdoctoral fellow (Fondation ARC)
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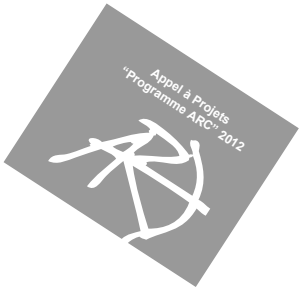
Amina BEDRAT PhD student (Ministère)
Dursun NIZAM KORKUT M2 student Université Bordeaux Segalen
Amandine RENAUD DE LA FAVERIE PhD student (MENRT)
Daimel CASTILLO Visitor (U. Las Villas)
Ha-Ho LEUNG Visitor (Hong-Kong Baptist U.)
Beata KLEJESKAJA Visitor (Imperial college London)
Sofie Louise KRAIGH Visitor (Nano Aarhus)

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

Unusual nucleic acid structures



Nucleic acids are prone to structural polymorphism: in addition to the well-known double helix, a number of alternative structures may be formed. However, most non-canonical conformations are stable only under non-physiological conditions and have been considered 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, bioinformatic, and physico-chemical tools to be used to demonstrate that G4 DNA or RNA is involved in particular biological functions.

Our objectives are to answer the following questions:

Where and when ?

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

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. We recently demonstrated that one can build a trimolecular G-quadruplex (Zhou, Angewandte, 2012) An independent topic relates to the use of quadruplex DNAs as molecular beacons (MB). We previously demonstrated that a G4-based MB outperforms a regular MB thanks to its differential ionic sensitivity.

Selected publications

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Dr. Elisabeth Génot

Research director (DR2), INSERM

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

Research team

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Dr. Anne LECLERCQ Postdoctoral fellow (FRM)
Dr. Thomas DAUBON Postdoctoral fellow (ARC)
Dr. Véronique VEILLAT Postdoctoral fellow (ANR-blanc VASCULOSOMES)
Isabel EGANA PhD student (ITN-FP7-T3net)
Filipa CURADO PhD student (ITN-FP7-T3net)
Paola CIUFICI PhD student (ITN-FP7 (T3net)

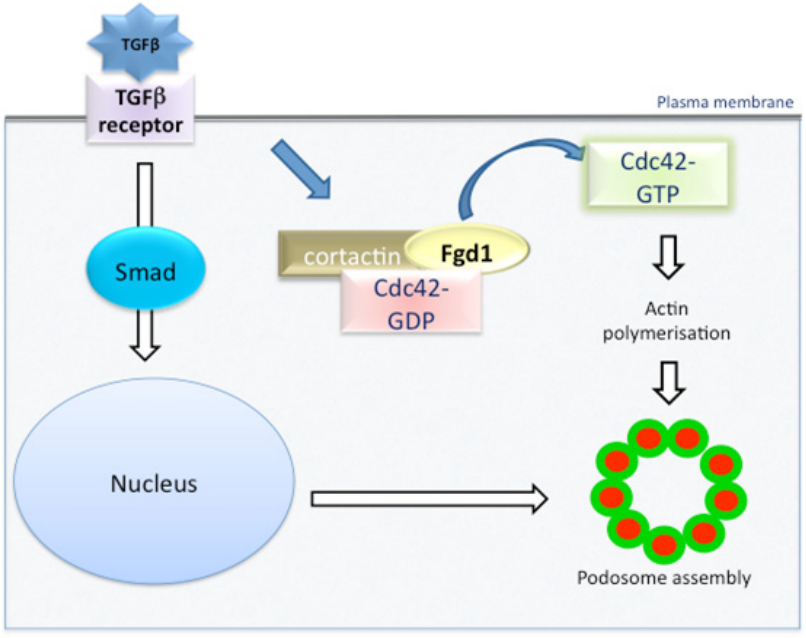
This team is part of the unit "Liver Fibrosis and Liver Cancer", INSERM U1053 /Université Bordeaux Segalen

Signal transduction in health & diseases

Transforming growth factor-ß 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 TGFß 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 endothelial podosomes and elucidation of the molecular mechanisms involved in their assembly and disassembly in both microvascular and macrovascular endothelial cells.

Endothelial cells contribute to the pathophysiology of most diseases. We are studying how environmental cues impact on these cells and translate into alterations of their functions, focusing on changes in extracellular matrix composition/rigidity and cytokine contexts. Our studies aim at a better understanding the cellular and molecular processes affecting endothelial cell behavior in human diseases such as tumor angiogenesis and pathological vessel remodeling, with the long term goal to identify molecular targets for therapeutic intervention.

Our studies have established that TGFß causes the reorganization of the actin cytoskeleton 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 signaling molecules such as tyrosine-kinases, GTPases and effectors proteins as in focal adhesion. However, unlike focal adhesions, gelsolin, dynamin, cortactin and WASp/N-WASp are also detected. Another peculiarity of podosomes is that they are enriched in matrix metalloproteases, bestowing them with the capacity to degrade the extracellular matrix. Podosomes are usually found in cells of the myelomonocytic lineage where they seem to be involved in adhesion and invasion. These cells share in common the ability to cross anatomical boundaries. However, the role played by endothelial podosomes is still unknown and there is yet no direct evidence proving the occurrence of podosomes in vivo.

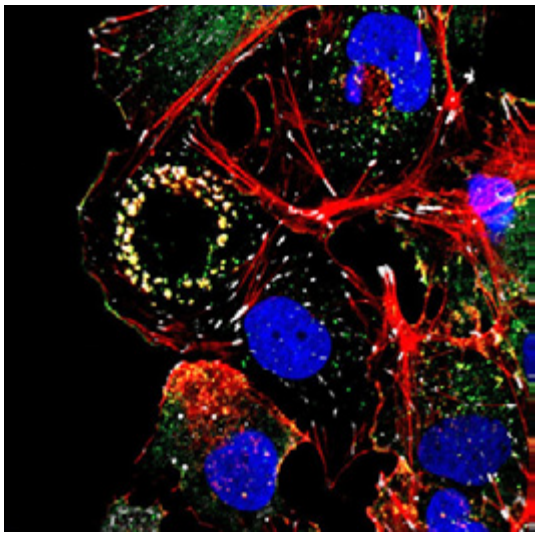


To establish physiological relevance of endothelial podosomes, we set up an “en face” viewing system to visualise the endothelium in murine aortic vessel segments. This model enables us to visualise the cytoskeleton of endothelial cells in its native environment. Whereas the normal endothelium is devoid of podosomes, exposure of the tissue to physiological concentrations of TGFß induces the formation of the structures in situ. The detection of podosomes in living tissues opens the way to investigate in which cellular processes podosome forming cells are engaged. Our hypothesis is that podosomes are cellular devices devoted to vessel remodeling. The next aim is to demonstrate the occurrence of endothelial podosomes in vivo.

We also find podosomes in endothelial cells isolated from diseased human aortic vessel segments, suggesting that podosomes are associated with a pathological state. We are particularly interested in the role of podosomes in vascular genetic disorders involving hyperactivation of TGFß signaling pathways such as Marfan syndrome or those involving defective TGFß signaling such as Hereditary Hemorrhagic Teleangiectasia (HHT).

In terms of signal transduction, canonical Smad pathways activated downstream of TGFß receptors play a central role. For the non-canonical pathways, Cdc42 is a master regulator of podosome formation. We have now established that Fgd1 is the guanine exchange factor regulating Cdc42 in this programme. Fgd1 undergoes Src-dependent tyrosine phosphorylation, translocates to the membrane and works in a complex with cortactin to activate Cdc42 and induce actin polymerization for podosome formation (Fig.1). These findings reveal the involvement of Fgd1 in endothelial cell biology and open up new avenues to study its role in vascular pathophysiology. Because Fgd1 appears as a central regulator of extracellular matrix remodeling, we are focusing our work on Fgd1 regulation by TGFß signals.

We also demonstrated that TGFß induces podosome formation in other cells. Helicobacter pylori promotes podosome formation in murine primary hepatocytes in vitro, and this occurs through the release of TGFß (Fig. 2). Liver cells with podosomes have reduced self-healing capacities. Helicobacter pylori which colonizes the stomach in about 50% of all humans is well known as a key risk factor in gastric diseases, it may also damage liver, causing cirrhosis and liver cancer. Although it is not yet clear which role podosomes play in the response to bacterial infection, one may expect that in vivo, podosomes in liver cells infected with Helicobacter pylori contribute to the pathological state.



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Dr. Derek McCusker

Research officer (CR1), CNRS

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

Research team

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

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

Dynamics of cell growth & cell division

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

Cdk1-dependent membrane trafficking dynamics

Cyclin-dependent kinase 1 (Cdk1) is required for polarization of the actin cytoskeleton and phosphorylates key Rho-GTPase regulators that direct actin polarization and growth. Attention has therefore focused on a role for Cdk1 in initiating growth via polarization of actin. However, Rho-family GTPases also control membrane trafficking. We therefore tested whether the role of Cdk1 in polarized cell growth extends beyond its role in controlling the actin cytoskeleton. To do so, we investigated the dynamics of membrane trafficking pathways after Cdk1 inhibition using "chemical genetics", biochemistry and high speed evanescent-field imaging in live cells.
We made the following observations that were published in Molecular Biology of the Cell in 2012:

- Inhibition of Cdk1 attenuates cell surface growth to a similar extent as actin depolymerization.
- Cdk1 activity is required for normal trafficking of post-Golgi secretory vesicles (Figure 1).
- Whereas actin depolymerization results in the accumulation of post-Golgi vesicles in the cytoplasm, vesicles do not accumulate after inhibition of Cdk1 activity.

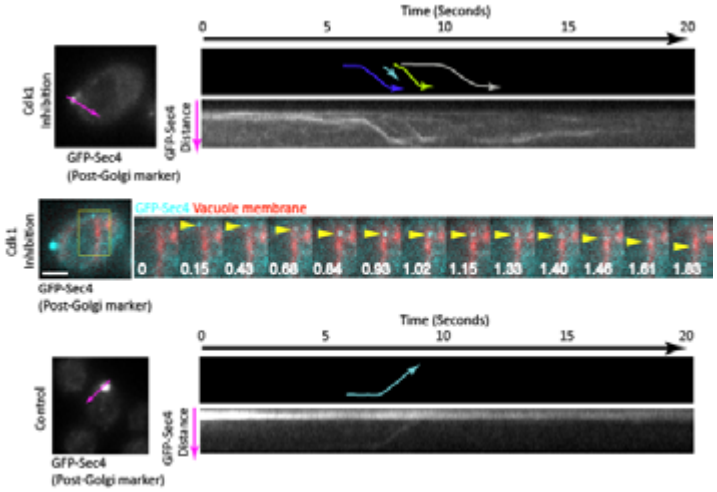

Figure 1. Retrograde streaming of post-Golgi vesicles from the sites of polarized growth into the mother cell after Cdk1 inhibition. The top panel shows a schematic kymograph where the coloured lines indicate a vesicle trajectory and the arrow indicates the direction of movement. (Top) After Cdk1 inhibition: the movement of vesicles is away from the plasma membrane. (Middle) After Cdk1 inhibition a vesicle (yellow arrow head) moves to the vacuolar membrane (red), then disappears. (Bottom) Control cells where vesicles move normally from the mother cell to the bud.

Cdk1, a core cell cycle regulator, thus plays a novel role in regulating cell surface growth that extends beyond its role in organizing the actin cytoskeleton. This may involve the regulation of membrane trafficking events that have to be coordinated with cell cycle progression in order to maintain cell size and shape. This work is part of an ongoing collaboration between my group and Prof. Douglas Kellogg, University of California, Santa Cruz, USA.

Robust polarity establishment via an endocytosis-based cortical corralling mechanism.

The final size and shape that cells adopt is governed in part by the rate and location of plasma membrane growth. This growth is largely driven by exocytic vesicle fusion, while endocytosis removes membrane. The relative rates of these two processes therefore contributes to cell size. In budding yeast, endocytic and exocytic vesicles localize to growth sites in the bud. Given the antagonistic relationship of these processes, this arrangement could be incompatible with the membrane efflux required for polarized growth of the bud. Our previous work demonstrated that endocytic vesicles form a ring around exocytic sites at the cortex. To address whether this might facilitate the formation of a stable polarity axis that contributes to polarized growth, we studied the dynamics of endo- and exocytic vesicles using high resolution in vivo imaging and in silico mathematical modeling (Figure 2).

We made the following observations that will be published in the Journal of Cell Biology in 2013:

- Robust polarity establishment involves dynamic changes in exocytic and endocytic trafficking systems (Figure 2).
- Robust polarity establishment involves the generation of a specific endocytic signature.
- Endocytic cortical corralling is required for robust polarity establishment.

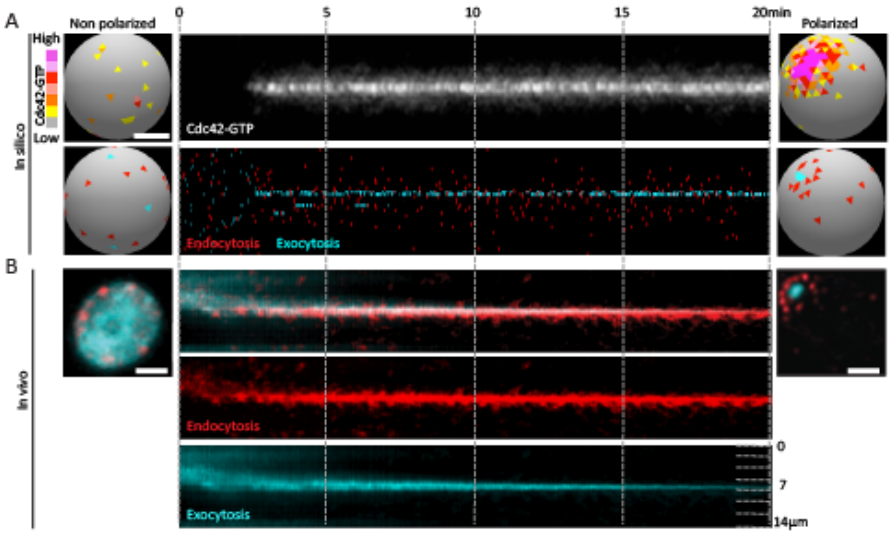

Figure 2. Robust polarity establishment involves dynamic changes in exocytic and endocytic trafficking systems. (A) Transition of an "in silico" cell from a non-polarized (left) to a polarized state. Membrane-bound active Cdc42 depolarized over the plasma membrane (top left) polarizes to a unique cluster of active Cdc42 over time (top right). The Cdc42 kymograph (upper panel) shows active Cdc42 during polarization. The kymograph in the lower panel shows individual endocytic and exocytic events over time (x-axis) along the cortex (y-axis). A tight pole of exocytosis develops (cyan) overlapping with the active Cdc42, and is corralled by a ring of endocytosis (red, bottom right). (B) Random endocytic and exocytic distributions in vivo in a non-polarized cell (left) change to an organized 'bull's-eye-pattern' in a polarized cell (right) with a tight exocytic zone surrounded by endocytic vesicles.

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Dr. Denis Dupuy

Research officer (CR1), Inserm

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

Research team

Dr Karine REBORA Postdoctoral fellow (Inserm)
Dr Esther MARZA Postdoctoral fellow (Inserm)
Ilyass ZNIBER PhD student (Inserm-Aquitaine Regional Council)
Cécile QUÉRÉ PhD student (Aquitaine Regional Council)
Jonathan MILLET PhD student (Inserm-MNRT)

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

Genome regulation & evolution

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

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

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

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 cell. 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 reporters: a red fluorescent protein (mCherry) with the permissive unc-54 UTR to monitor the transcriptional activity of the promoter and a green transcriptional fusion (GFP) associated to the cognate UTR to measure the contribution of post-transcriptional regulation (Figure 1a).

Quantitative analysis of alternative splicing

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

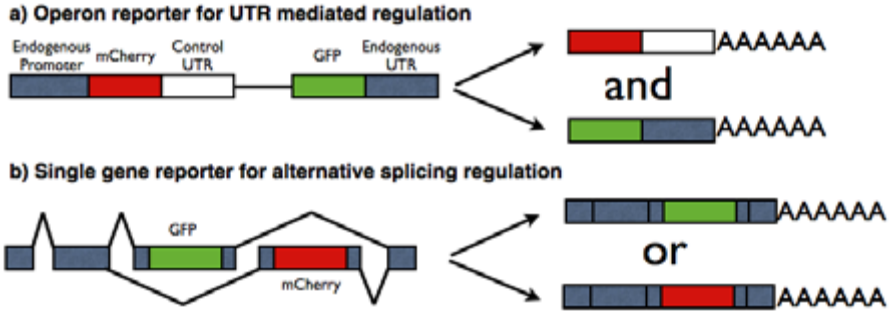

Figure 1: Two-color reporters for in vivo post-transcriptional regulation studies. a) The function of endogenous UTR sequences will be tested by direct comparison of expression levels with the unc-54 control expressed from the same double-reporters operon. b): Tissue and temporal specificity of alternate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

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

In summary

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

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Dr. Anne Royou

Research officer (CR1), CNRS

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

Research team

Marie-Charlotte CLAVERIE Technician (IBGC)
Dr Emilie MONTEMBAULT Postdoctoral fellow (IBGC)
Dr Cédric SOLER PhD student (University de Bordeaux Segalen)
Nicolas DERIVE PhD student (IBGC)

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

Control & dynamics of cell division

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

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

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

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

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

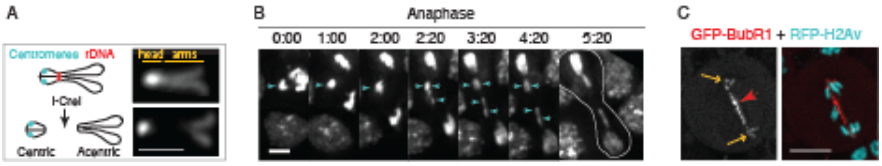

Figure 1: BubR1-coated DNA tethers facilitate the poleward segregation of acentric chromatids. (A) Schematic illustration (left) and DAPI staining (right) of the Drosophila mitotic X chromosome. The centromeres (cyan circles) are near the telomeres in the heterochromatin "head" brightly stained with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

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

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

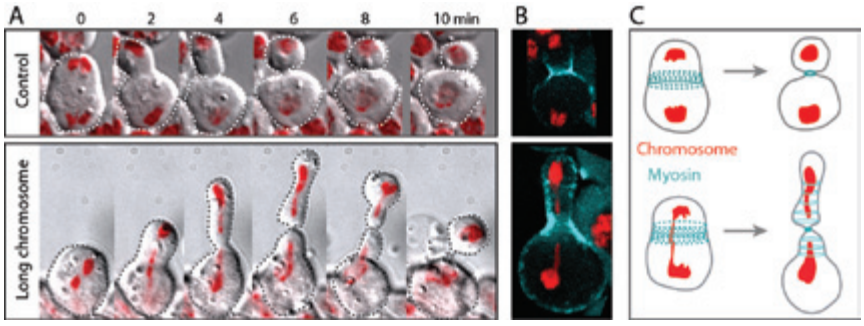

Figure 2: Cell elongation is an adaptive response for clearing long chromatid arms from the cleavage plane. (A) Time-lapse images of control cells (top row) and cells carrying an abnormally long chromosome (Bottom row). The chromosomes are marked with H2Av::RFP. The cell carrying a long chromosome transiently elongates during anaphase and rounds up once the chromatids have cleared the cleavage plane. (B) Still images of control cell (top row) and cell with long chromosome (bottom row) expressing H2Av::RFP (Red) and Myosin::GFP (Cyan). In control cells, Myosin forms a tight ring that cleaves the cell during a process called cytokinesis. In cells with long chromosomes, cortical myosin forms a main contractile ring plus additional rings that facilitate cell deformation. (C) Model for coordinating chromosome segregation and cell division. In anaphase, the presence of long chromatids at the cleavage site triggers the formation of extra myosin rings beyond the main contractile ring. These extra myosin rings deform the cortex provoking the elongation of the cell.

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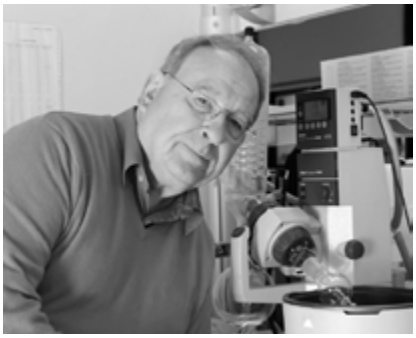


Pr. Léon Ghosez

Emeritus Professor at the UCL
Visiting scientist at IECB

Léon Ghosez was born in Aalst, Belgium, in 1934. He studied at the University of Louvain where he got a PhD in 1958 under the supervision of Prof. G. Smets. He then spent 2 years as postdoctoral researcher at Harvard University (Prof. R.B. Woodward). He also collaborated for a few months with Prof. R. Huisgen at the University of Munich. He got his "Habilitation" in 1969 at the age of 32 and became Professor at the University of Louvain. During his career in Louvain (1963-1999) he supervised 125 PhD students and 135 postdoctoral associates. He also held appointments at the University of Liège (1969-1999) and the Ecole Polytechnique in Palaiseau (1993-1999). He took an active part in the creation of the IECB, where he established a research group in 1998. From 2000 till the end of 2009, he shared the directorship of the IECB with Dr. J.J. Toulmé. Presently he is a visting scientist at IECB and Prof. Emeritus at UCL. Léon Ghosez is an Emeritus Member of the Royal Academy of Sciences, Literature & Fine Arts of Belgium. He recently received the Medal of the French Chemical Society.

Research team

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

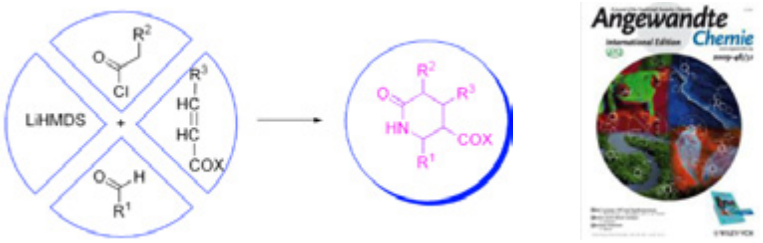
The team is part of the unit "Chimie et Biologie des Membranes et Nanoobjets" (CBMN), CNRS/ Université Bordeaux 1/IPB (UMR 5248)

Organic & medicinal chemistry

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

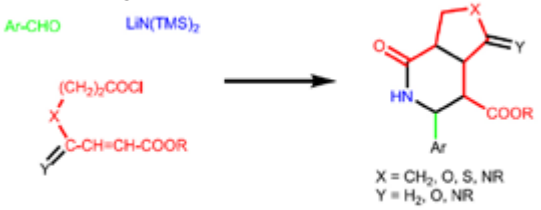
Diverted total synthesis of natural product analogs

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



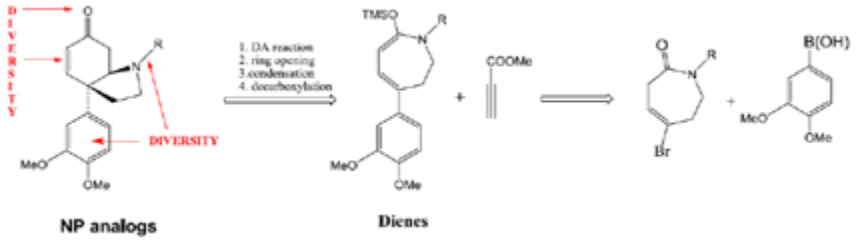
Scheme 1

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



Scheme 2

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

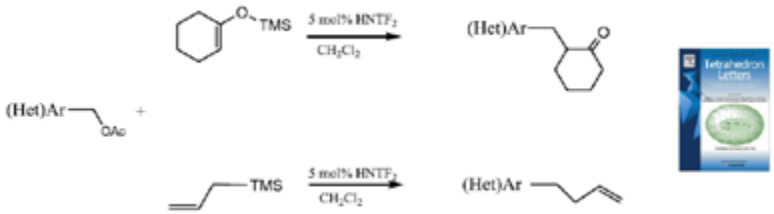


Scheme 3

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

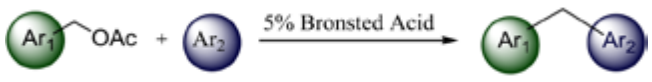
Previous research in our group had led to the seminal discovery of silicon-derived Lewis superacids derived from perfluorinated triflimides. These Lewis-acid catalysts are "green" catalysts which have been used by us and later by other groups around the world for the activation of carbonyl compounds.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

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



Scheme 4

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



Scheme 5

The search for new "green" silicon catalysts has been pursued in 2012 in the framework of a Marie Curie fellowship. We have succeeded in establishing a "structure-catalytic" relationship for catalysts of general structure R^1R^2XSi-LG where R^1, R^2 are alkyl groups of various sizes, X= F, Cl and LG = TfO^-, Tf_2N^-, $ArSO_2(Tf_2)N^-$.... From these informations, new chiral catalysts have been designed.

Future

Priority will be given to the above projects. A joint programme on the new catalysts with the group of J. Cossy in Paris will be implemented. A new programme on the design and synthesis of inhibitors of proprotein convertases will start in a few months. It will involve a tight collaboration with Dr. Majid Khatib of Inserm U1029. Dr. Majid Khatib has done seminal contributions showing the key role of convertases on invasion, carcinogenesis and angiogenesis.

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Other publications

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2. Huc I., Jiang H. (2011) Organic Foldamers and helices, book chapter in "Supramolecular chemistry: from molecules to nanomaterials. Steed, J. W., Gale, P. A. Eds, Wyley.
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5. Mergny J.L., Yatsunyk L., Guédin A., Gros J., Renaud de la Faverie A., Smith N., Renciuk D., Tran P.L.T. & Bourdoncle A. (2011) DNA quadruplexes for bio- and nano-technologies. Chemistry of Nucleic Acid Components - Collection symposium series. Vol. 12, 218-221.
6. Oda R. (2011) chapter in "The next generation Cutting edge research on Biomimetics" (in Japanese), CMC edition, Japan
7. Rajpar S., Guittat L. & Mergny J.L. (2011) Télomères : un nobel pour le début de la fin. Bull. Cancer, 98: 999-1009.

Patents

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2. Deffieux, D.; Quideau, S. Method of Preparation of Hydroxytyrosol. European Patent N° EP12305091.6.
3. Quideau, S.; Génot, E.; Saltel, F.; Douat-Casassus, C.; Delannoy López M. D. C-Glucosidic Ellagitannin Compounds for Use for Altering the Supramolecular Arrangement of Actin. European Patent N° EP11305186.6, N° PCT/EP2012/053017.

Team funding

International funding

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher(s)	Funding body	Research project	Period
R. Oda (M. Laguerre)	ANR – NSF		2011–2014
R. Oda	ANR–Blanc	A Comprehensive Computational/Experimental Analysis of the Hofmeister Effect	2011–2014
E. Génot	Call: FP7–PEOPLE–ITN–2008	Marie Curie Initial Training Networks (ITN), "Tissue Transmigration Training Network (T3Net)" (including salaries for 2 PhD)	2009–2013
I. Huc	China Scholarship Council	Foldamer based molecular motors	2012–2015
A. Royou	ERC	Mecanisms that prevent aneuploidy	2013–2018
D. McCusker	EU	Molecular mechanisms coordinating cell growth and cell division.	2010–2013
J. Zhou	EU	Single unusual DNA	2012–2014
J.Elezgaray	FP7 – COST		2010–2012
I.Huc	FP7 – Ideas – ERC advanced	Functional Aromatic Amide Foldamers: Beyond Biolpolymers	2013–2018
G. Guichard	FP7 – IEF	An integrated peptide and Foldamer chemistry approach towards pro–apoptotic TRAIL mimetics	2011–2013
I. Huc	FP7 – People – IAPP	Foldamers against protein–protein interactions	2009–2013
I. Huc	FP7 – People – IIF	Foldamers for single molecule electronics	2010–2012
I. Huc	FP7 – People – IIF	Catalytic Foldamers: Engineering a Second Coordination Sphere Around a Hydrogenase Mimic	2011–2013
I. Huc	FP7 – People – ITN	Dynamic Molecular Nanostructures	2010–2014
C. Mackereth	French Embassy in Canada	Structural and biological studies of histone proline isomerases	2011–2013
Durrieu/R Vilar	Fundação para a Ciencia e Tecnologia (FCT),	Bio–inspired multiscale interfaces dental and skeletal reconstruction biomaterials	2010–2014
R. Oda	JSPS–CNRS	Development of light–management–materials for highly efficient conversion of solar energy	2013–2014
G.Laroche/ Durrieu	NSERC CREATE program for regenerative medicine (NCPRM)	Surface pattrening for cell growth	2012–14
S. Quideau	Pakistan Higher Education Commission and French Embassy	Synthesis of flavanoids	2012
Durrieu/Gillet	Région Wallone University of Liege	Fonctionnalisation de lentilles intraoculaires acryliques par greffage de biomolécules limitant la cataracte secondaire	2011–14
Oda/Karpichev	Ukrainian Academy of Science–CNRS	DESIGN OF TUNABLE NANOMETRICAL CATALYTIC SURFACTANT ASSEMBLIES FOR NUCLEOPHILIC REACTIONS	2012–2013

National funding

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Funding body	Research project	Period
D. MCCusker	ANR	Coordination of Cell Growth and Cell Division.	2011–2014

IECB Researcher	Funding body	Research project	Period
C. Mackereth	ANR	Structural and functional analysis of yeast cleavage and polyadenylation factors	2012-2016
D. Dupuy	ANR	Titaniums	2011-2014
F. Godde (M. Laguerre)	ANR	Mimes oligoamides aromatiques de l'ADN double brin	2011-2015
I. Huc	ANR - blanc	Foldamer capsules for saccharide recognition	2009-2013
I. Huc	ANR - blanc	Foldamers Scaffolds for Electron Transport	2012-2011
I. Huc	ANR - blanc	Aromatic Amide Nucleic Acid Mimics	2012-2016
Durrieu	ANR Emergence -Tec	Biomatériau, vecteur de gentamicine - Etude in vivo chez le lapin	2009-2012
G. Guichard	ANR Piribio	Probing molecular dynamics of TNFR family members upon stimulation in the membrane of live cells	2009-2013
L. Fischer	ANR RPD	Molecular recognition with urea-based foldamers : From anion receptors to bioinspired organocatalysts	2010-2013
E. Génot	ANR-Blanc	VASCULOSOMES(including salary for one post-doc salary)	2009-2012
JL. Mergny	ANR-Blanc	G4 Toolbox	2009-2012
R. Oda	ANR-Blanc	Functional hybrid organic-inorganic nanohelices: studies of the exalted phonomena at nanometric scales	2010-2013
L. Pouységu	ANR-Blanc	IODINNOV	2010-2013
S. Quideau	ANR-Blanc	FLUNUCLEOVIR	2010-2013
S. Fribourg	ANR-Blanc	Late pre-40S maturation step	2010-2013
S. Fribourg	ANR-Blanc	SAFAPOLYA	2012-2016
JL. Mergny	ANR-P3N	Fullere-DNA	2009-2013
R. Oda (M. Laguerre)	ANR-PCV	Dynamic structures of SNARE transmembrane domains and lipids in membrane organization and their function in exocytosis	2008-2011
J.-P. Aimé (J. Elezgaray, J.-M. Arbona)	ANR-PIR	Biocapteur Origami ADN	2009-2011
S. Amrane	ANRS	Quadruplexes dans le genome HIV	2012-2014
A. Royou	ATIP/AVENIR/INCa	Mechanisms that prevent chromosomal instability in mitotic cells	2011-2014
E. Pouget	BQR (U. Bordeaux)	Synthèse de Nano-Bio Matériaux hybride et leurs influences sur la différenciation de cellules souches	2012
JL. Mergny	INCa	Quadruplexes & P53	2009-2012
M. Teichmann	INCa	TRANSLA-tRNA	2010-2013
J. Rosenbaum (M. Laguerre, J. Dessolin, J. Elkaïm)	INCA	Rôles de la Reptine et de la Pontine dans la carcinogénèse hépatique	2010-2013
JL. Mergny	Initiative Excel	Nanobiotech call	2011-2015
D. Dupuis	Inserm-Avenir	In vivo analysis of pos transcriptional regulation in C. elegans	2011-2012
J. Elezgaray	Investissement d'Avenir	Imaging of Biological and Bioinspired Nanosystems	2011-2014
I. Huc	Ministry of research	Pre-doctoral Fellowship	2010-2013

IECB Researcher	Funding body	Research project	Period
M. Laguerre	SIRIC (INCa)	Bordeaux Recherche Intégrée Oncologie	2012-2015
JL. Mergny	Travel Grant	G4 ligands (with Hong Kong / Prof. E. Ma)	2011-2012
S. Fribourg	Inserm	3' end mRNA processing	2011-2013

Regional funding

Coordinated by IECB researchers

IECB Researcher	Funding body	Type of funding	Period
H. Soufari	Aquitaine Regional Council & INSERM	PhD Fellowship	2012-2015
G. Guichard	Aquitaine Regional Council	Instrumentation and post-doctoral fellowship	2009-2012
G. Guichard	Aquitaine Regional Council & DGA	Pre-doctoral fellowship	2012-2015
I. Huc	Aquitaine Regional Council & CNRS		2010-2012
A. Royou	Aquitaine Regional Council	Post-doc Equipement research	2011-2013
E. Garanger	Aquitaine Regional Council	Equipment	2010-2013
M. Teichmann	Aquitaine Regional Council	Cooperation Aquitaine-Emilie-Romaigne	2010-2012
JL. Mergny	Aquitaine Regional Council	Chaire d'accueil	2009-2012
JL. MERGNY	Aquitaine Regional Council	Inter-region	2012-13
D. McCusker	Aquitaine Regional Council	Postdoc, equipmentresearch	2009-2012
D. McCusker	Aquitaine Regional Council	Postdoc equipment	2012-2014
S. Fribourg	Aquitaine Regional Council	PhD fellowship (co-funded with Inserm) Equipment (MALLS, Tetrad dissector)	2011-2013
M. Laguerre	Aquitaine Regional Council	Thesis	2010-2012
J. DESSOLIN	Aquitaine Regional Council & CNRS	Cofinanced BDI grant	2009-2012
E. Garanger	GIS-AMA	Salary	2010-2012
L. Bataille	GIS-AMA	Salary	2012-2013
G Salgado	Inserm & University Bordeaux Segalen	Chaire mixte	2010-2015
L. Bataille	Institut Carnot	Salary	2011-2012
E. Garanger	Institut Polytechnique de Bordeaux	Research	2011
A. Royou	University Bordeaux Segalen	Thesis	2011-2014
D. McCusker	University Bordeaux Segalen	Thesis	2010-2013
C. Mackereth	Univ. Bordeaux/CNRS	Research	2012
G. Guichard	University of Bordeaux I	Pre-doctoral fellowship	2010-2013

Charity-funded research projects

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Charity	Research project	Period
D. McCusker	ARC	Modeling a cell polarity switch: new insight into cell cycle deregulation during carcinogenesis.	2012-2014
S. Upadhyay	ARC	Molecular details of p21 mRNA stabilization by the RNA-binding protein RNPC1	2012-2014
I. Huc	ARC	Pancreas cancer: towards a new therapeutic approach	2010-2013
JL. Mergny	ARC	Programme ARC : Effets biologiques ligands	2011-2014
E. Génot	Charity National	Specific features of the aortic endothelium in a murine model of Marfan Syndrome	2013
E. Génot	Charity National	Etude du rôle des cellules endothéliales dans les lésions anévrismales de l'aorte thoracique	2012-2013
E. Génot	Charity National	Etude du rôle de la protéine Tks5 dans l'assemblage des podosomes et des invadopodes	2012-2014
E. Génot	Charity National	Caractérisation des podosomes des cellules endothéliales microvasculaires et recherche du rôle de ces structures dans l'étape d'invasion de l'angiogénèse tumorale	2010-2012
G. GUICHARD	Fondation ARC	Criblage de Chimiothèques de foldamères oligoamides pour l'identification de ligands des récepteurs de mort ; vers de nouvelles molecules pro-apoptotiques	2010-2013
D. McCusker	FRM	Investigation of the molecular mechanisms underlying the establishment and maintenance of cell polarization.	2011-2012
M. Teichmann	Ligue Nationale contre le Cancer	Equipe Labellisée: Analyse fonctionnelle d'une nouvelle isoforme d'ARN polymérase III humaine avec une activité oncogénique.	2011-2015
G. Guichard	Ligue contre le cancer	Conception et synthèse de ligands proapoptotiques, agonistes du récepteur à domaine de mort DR5	2012
I. Huc	Simone & Cino del Duca Foundation	Foldamers beyond biopolymers	2013

Contracts with the industry

Coordinated by IECB researchers/IECB researchers as participants

IECB Researcher	Company	Research contract	Period
I. Huc	Undisclosed	Molecular recognition of protein surfaces by aromatic amide foldamers	2011-2013
I. Huc	CIVB	New fluorescent probes for the simultaneous analysis of wine acids	2010-2013
G. Salgado	Biocodex	Les effets de l'etifoxine sur le récepteur GABA-A	2012-2013
M.C Durrieu	Teknimed	L'induction Osseuse induite par des Matériaux fonctionnalisés avec un Peptide Mimétique de la BMP-2.	2012-2013
I. Huc (M. Laguerre, V. Leroux)	SERVIER	Undisclosed	2011-2012
S. Quideau	CIVB	Chimie des ellagitannins	2010-2013
D. Deffieux	CIVB	Biochimie des flavanoïdes	2010-2013
G. Guichard	ImmuPharma	Undisclosed	2010-2013
G. Guichard	ImmuPharma & ANRT	Undisclosed	2010-2012

Collaborations

Pole 1 – Structural biology & biophysics

Molecular modeling
Dr. Michel Laguerre

1. Dr. Reiko Oda, IECB, Pole 1, CNRS UMR 5248, Pessac, France
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22. Pr. Ronald Sauers, Rutgers University, Piscataway, USA
23. Dr. Banafshe Larijani, Cancer Research UK, London, UK
24. Pr. Shawn Wettig, School of Pharmacy, Waterloo, Canada
25. Pr. Braja Gopal Bag, Vidyasagar University, Midnapore, India
26. Dr. Kazushi Kinbara, Tohoku University, Sendaï, Japan

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

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11. Dr. Marie-Hélène DelvilleI, CMCB, Bordeaux, France
12. Dr. Bertrand Audoin, I2M, Bordeaux, France
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14. Dr. Yevgen Karpichev, Ukraine Academy of Science, Donetsk, Ukraine
15. Prof. Gaetan Laroche, Laval University, Quebec, Canada
16. Prof. Ruis VilarInstituto, Superior Tecnico, Lisbonne, Portugal
17. Prof. Gianfranco Savelli, Perugia University, Perugia, Italy
18. Prof. Hirotaka Ihara, Kumamoto University, Kumamoto, Japan
19. Prof.Larry Romsted, Rutgers University, Piscataway, USA
20. Prof. Ronald Sauers, Rutgers University Piscataway, USA
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24. Pr. T. Colin, IMB, Talence, France
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26. Dr. C. Ayela, IMS, Talence, France
27. Dr. A. Guignandon, INSERM U 890 "Contraintes Mécaniques et Tissu Osseux", Saint Etienne, France
28. Dr. G. Amador, Laboratoire EA 3826, Nantes, France

Pole 2 – Organic & bioorganic chemistry

Biomimetic Supramolecular Chemistry
Dr. Ivan Huc

1. Prof. Didier Dubreuil Univ. Nantes, Nantes, France
2. Dr. Guy Lauquin IBGC, CNRS Univ Bordeaux, Bordeaux, France
3. Dr. Jean-Jacques Toulmé IECB, INSERM, U869 ARNA, Pessac, France
4. Prof. Jean-Michel Léger Univ. Bordeaux Segalen, Laboratoire de Pharmacochimie, Bordeaux, France
5. Prof. Hua Jiang Chinese Academy of Science, Institute of Chemistry Beijing, China
6. Prof. Makoto Takafuji Kumamoto University Kumamoto, Japan
7. Dr. Kolupula Srinivas NIPER Hyderabad, Hyderabad, India

Synthesis & activity of natural substances
Pr. Stéphane Quideau

1. Dr. Elisabeth Génot IECB, INSERM U1053, Pessac, France
2. Prof. Pierre-Louis Tesseidre ISVV, Bordeaux, France
3. Prof. Marie-Aleth Lacaille-Dubois Université de Dijon, Dijon, France
4. Prof. Luis Rojas ULA, Mérida, Venezuela
5. Prof. Carmelo Rosquette ULA, Mérida, Venezuela
6. Prof. Stefano Manfredini University of Ferrara, Ferrara, Italy
7. Prof. Roberta Bernini Viterbo, Italy

Peptidomimetic chemistry
Dr. Gilles Guichard

1. Dr. Stéphane Bellemin-Laponnaz IPCMS, UMR 7504, Strasbourg, France
2. Dr. Claude Didierjean Université Henri Poincaré, Nancy, France
3. Dr. Burkhard Bechinger Université de Strasbourg, Strasbourg, France

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

1. Prof. Lecommandoux Sébastien LCPO, CNRS UMR 5629, Pessac, France
2. Dr. Sandre Olivier LCPO, CNRS UMR 5629, Pessac, France
3. Prof. Garbay Bertrand EA 4135, Université Bordeaux Segalen, Bordeaux, France
4. Dr. Bathany Katell CBMN, CNRS UMR 5248, Pessac, France
5. Dr. Alves Isabel CBMN, CNRS UMR 5248, Pessac, France
6. Prof. Chilkoti Ashutosh Duke University Durham (NC), USA

Pole 3 – Molecular recognition

Gene regulation & tumor research
Pr. Martin Teichmann

1. Pr. Roeder, Robert G. The Rockefeller University, New York, USA
2. Pr. Dieci, Giorgio University of Parma, Parma, Italy
3. Dr. Fribourg, Sébastien IECB, Pessac, France

4. Pr. Brais, Bernhard Université de Montréal, Montréal, Canada

Structural biochemistry
Dr. Sébastien Fribourg

1. Prof. Martin Teichmann, IECB, U869, Pessac, France

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

1. Dr. Sébastien Fribourg, IECB/Inserm U869, Pessac, France
2. Dr. Denis Dupuy, IECB/Inserm U869, Pessac, France
3. Dr. Michael, Sattler Helmholtz/TUM, Munich, Germany
4. Dr. Chris Nelson, University of Victoria, Victoria, Canada

Unusual nucleic acid structures
Dr. Jean-Louis Mergny

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

Pole 4 - Molecular & cellular biology

Cell signalling in health & disease
Dr. Elisabeth Génot

1. Dr. Hassen-Reda Dahmani, Pedagogical department, ENS Kouba Alger, Algeria
2. Pr. Patricia Schneeberger, Laboratoire Cultures Education Sociétés, EA 4140, University of Bordeaux, Bordeaux, France
3. Dr. Roberto Buccione Consorzio, Mario Negri Sud Santa Maria Imbaro, Chiety, Italy
4. Dr. Emmanuelle Planus, Corinne Albiges-Rizo, Olivier Destaing Institut Albert Bonniot - inserm 823, Grenoble, France
5. Dr. Vincenzo Sorrentino, Department of Neuroscience University of Siena, Siena, Italy
6. Dr. Chritine Varon, Francis Megraud, Corinne Ascenso, Emilie Lereoux-Goglin INSERM 853, Bordeaux, France
7. Dr. Fabien Guillemot, INSERM 1026, Bordeaux, France
8. Dr. Nicolas Bourmeyster, Tristan Rochelle CNRS FRE 3511, Poitiers, France

Dynamics of cell growth & cell division
Dr. Derek McCusker

1. Dr. Jean-Baptiste Sibarita, Institut of Interdisciplinary Neuroscience, CNRS UMR5091, France, Bordeaux
2. Prof. Douglas Kellogg, University of California, Santa Cruz, USA
3. Dr. Anne Royou IECB, IBGC, CNRS UMR5095, France, Pessac
4. Dr. Steven P. Gygi, Harvard Medical School, Boston, USA

Control & dynamics of cell division
Dr. Anne Royou

1. Prof. William Sullivan, University of California, Santa Cruz, USA
2. Dr. Derek McCusker, IECB, IBGC, CNRS UMR5095, France Pessac

Organic & medicinal chemistry
Pr. Léon Ghosez

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

Invited conferences

Pole 1 – Structural biology & biophysics

Molecular modeling

- Engineering Neo-Biomimetics Tsukuba, Japan, February 2012, M. Laguerre
- E-MRS Spring 2012 Croissy, France, May 2012, J. Elezgaray
- DNA-18 Symposium Aarhus, Danemark August 2012, J. Elezgaray

Morphologies, dynamics & functions of assemblies of amphiphiles

- The 3rd PHOENICS International Symposium Kumamoto, March, 2013, R. Oda
- Journées André Collet de la Chiralité, Dinar Sept. 2012, R. Oda
- Univ. Bordeaux 1 / Waterloo Institute for Nanotechnology 2nd Strategic research workshop, Bordeaux, June. 2012, R. Oda
- RIKEN-Max Planck Symposium Dortmund, March, 2012, R. Oda
- Beyond Self-assembly Bad Gastein Bad Gastein, January 2012, R. Oda

Pole 2 – Organic & Bioorganic Chemistry

Biomimetic Supramolecular Chemistry

- Ischia Advanced School of Organic Chemistry, Ischia, Italy, September 2012, I. Huc
- Cost meeting on Foldamers Regensburg, Germany, September 2012, I. Huc
- 4th EuchMS Chemistry Congres Prague, Czech Republic, August 2012, I. Huc
- 26th French-Belgian meeting on Pharmacochemistry Orléans, France, May 2012, I. Huc
- Symposium: "Molecular Chirality Asia 2012 Fukuoka, Japan, May 2012, I. Huc
- Department Seminar, Rennes University Rennes, France December 2012, I. Huc
- Department Seminar, Centre de Recherche Paul Pascal, Bordeaux, France, July 2012, I. Huc
- Department Seminar, Technical Univ. Eindhoven Eindhoven, The Netherlands, June 2012, I. Huc
- Department Seminar, Univ. Poitiers, Poitiers, France May, 2012, I. Huc

Synthesis & activity of natural substances

- 6th International Meeting on Halogen Chemistry (HALCHEM-VI) Bangalore, India December 2012, S. Quideau
- 2012 International Congress on Natural Products Research (8th Joint Meeting of AFERP, ASP, GA, PSE & SIF) New York, USA July 2012, S. Quideau
- 6th International Society of Antioxidants in Nutrition and Health Congress - Paris Polyphenols 2012, Paris, France, June 2012, S. Quideau

Peptidomimetic chemistry

- PEM6-The Sixth Peptide Engineering Meeting Atlanta, USAO c t o - ber/2012, G. Guichard
- Journée Rhône-Alpes des Biomolécules 2012 Grenoble, France June/2012, G. Guichard
- 6th NanoDay Copenhagen, Denmark April/2012, G. Guichard
- Journée ED Chimie Lyon 2011-2012 Lyon, France-April 2012, G. Guichard
- Bordeaux 2012 Symposium on Foldamers Bordeaux, France January-February/2012, G. Guichard

Self-assemblies from chimeric polymer-peptide materials

- NanoSpain conference, Santander, Spain, February 2012, E. Garanger
- SFR TecSan: bioengineering and nanotechnology, Bordeaux, France, May 2012, E. Garanger

Pole 3 – Molecular Recognition

Gene regulation & tumor research

- Keystone Symposia conference on Chromatin Dynamics Keystone, Colorado, USA January 2012, M. Teichmann
- 8th International Biennial Conference on RNA Polymerases I and III Arlie, Virginia, USA June 2012, H. Dumay-Odelot
- 8th International Biennial Conference on RNA Polymerases I and III Arlie, Virginia, USA June 2012, C. Pascali
- 8th International Biennial Conference on RNA Polymerases I and III Arlie, Virginia, USA June 2012, S. Durrieu-Gaillard
- Transcription and Chromatin EMBL, Germany August 2012, M. Teichmann

Structural biochemistry

- Odd Pols meeting Warrenton, V, USA June, 2012, S. Fribourg
- ESRF user's meeting Grenoble, France February, 2012, S. Fribourg

NMR spectroscopy of protein-nucleic acid complexes

- Victoria-Bordeaux workshop on histone proline isomerases Victoria, Canada July/2012, C. Mackereth, H. Soufari

Unusual nucleic acid structures

- International G4 meeting Sitges, Spain October 2012, A. Renaud de la Faverie, Jun Zhou
- TNT meeting Madrid, Spain September 2012, J.L. Mergny
- FASEB meeting Saxtons River, VT, USA June 2012, J.L. Mergny
- SFB/SFBBM meeting Grenoble, France November 2012, J.L. Mergny
- 4ème réunion des Utilisateurs RMN TGIR Lille, France Novemeber 2012, S. Amrane
- Réunion microcalorimétrie SUD-France Lyon, France, June 2012, S. Amrane

Pole 4 – Molecular & Cellular Biology

Cell signalling in health & disease

- Printemps de la cardiologie, Recherche Fondamentale et Clinique, Bordeaux, France April 2012, A. Leclercq
- 4eme Colloque du club adhérence cellulaire, Bordeaux, France May 2012, F. Saltel
- Journée Jeunes Chercheurs Transbiomed, Bordeaux, France June 2012, A. Juin
- Vascular meeting London, UK december 2012, A. Leclercq
- College de France Paris, France july 2012, I. Egana

Dynamics of cell growth & cell division

- Endo- Exocytosis meeting Isle-Sur-Sorgue, France May, 2012, D. McCusker
- American Society for Cell Biology San Francisco, USA December, 2012, D. McCusker
- Modelling oscillations in biological systems symposium Orsay, France May, 2012, S. Tollis
- Endo- Exocytosis meeting Isle-Sur-Sorgue, France May, 2012, M. Jose

Control and dynamics of cell division

- French Drosophila Conference Clermont-Ferrand, France, September 2012, Anne Royou
- American Society for Cell Biology San Francisco, USA, December, 2012, Anne Royou

Genome regulation & evolution

- Ver-Midi Paris, France, January, Denis Dupuy
- IGEM European Jamboree Amsterdam, Netherland, October, Denis Dupuy, Cécile Quéré, Jonathan Millet

Conference organisation

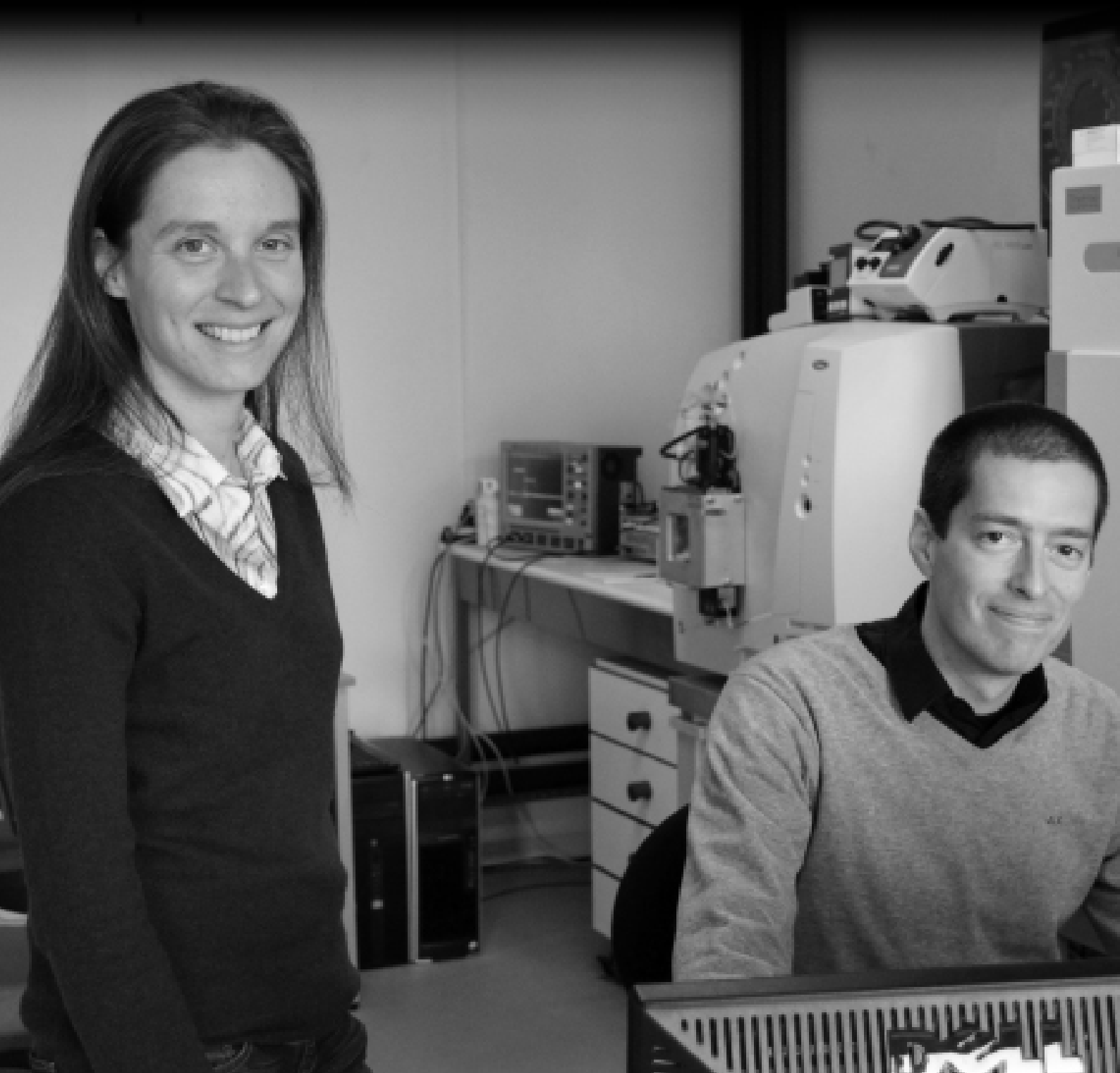
- IECB Young Scientist Symposium Pessac, France, May 2012, T. Daubon, F. Curado, I. Egaña, A. Renaud de la Faverie, C. Drappier
- G-quadruplex National Day, Pessac, France January 2012, J.L Mergny
- Bordeaux 2012 Symposium on Foldamers, Bordeaux, France, January 2012, I. Huc, G. Guichard
- IDS-FunMat Training School 2012, Anglet, France, March 2012, MC. Durrieu
- Co-Chair of XXVI International Conference on Polyphenols, Florence, Italy, July 2012, S. Quideau

Thesises

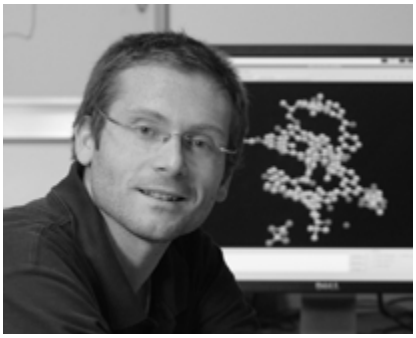
- Tracey Marshall "Dynamic chemistry : nucleobase recognition by synthetic receptors and cis-trans isomerism of acylhydrazones" (I. Huc) IECB, CBMN
- Yao Seydou "Imagerie IRTF de haute résolution des interactions cellules-fibres pour létude des effets pathogènes des amiantes" (Cyril Petibois),CBMN
- Guillaume Naturale "Approches Radicalaires pour la Fonctionnalisation Directe de Quinones à Visée Anticancéreuse" (Michel Laguerre)
- Quan Gan "Foldaxanes : foldamer-based self-assembled pseudorotaxanes. Structures and molecular motions" (I. Huc) IECB, CBMN

Besides training PhD students in the labs, IECB researchers contribute to various bachelor and master's courses of the Université Bordeaux 1 and the Université Bordeaux Segalen. In 2012, they provided over 1600 hours of teaching.

Since fall, IECB welcomes a new visiting scientifst : Dr. Valérie Gabelica and a new inglineer in mass spectrometry : Frédéric Rosu.



Technology platforms



Dr. Brice Kauffmann
Head of IECB's technology platform in structural biology (IR), CNRS

Head of IECB's Structural Biology technology platform, IR, CNRS After a PhD in protein crystallography (2003, University of Nancy I), Brice Kauffmann spent three years at the European Molecular Biology Laboratory (EMBL) in Hamburg (Germany) working on the evelopment 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

Batat P, Vives G, Bofinger R, Chang RW, Kauffmann B, Oda R, Jonusauskas G, McClenaghan ND. Dynamics of ion-regulated photoinduced electron transfer in BODIPY-BAPTA conjugates. Photochem Photobiol Sci. 2012 Nov;11(11):1666-74.

Beniazza R, Desvergnes V, Girard E, Kauffmann B, Berlande M, Landais Y. Development of domino processes by using 7-silylcycloheptatrienes and its analogues. Chemistry. 2012 Sep 17;18(38):11976-86.

Harmand L, Cadet S, Kauffmann B, Scarpantonio L, Batat P, Jonusauskas G, McClenaghan ND, Lastécouères D, Vincent JM. Copper catalyst activation driven by photoinduced electron transfer: a prototype photolatent click catalyst. Angew Chem Int Ed Engl. 2012 Jul 16;51(29):7137-41.

Sanchez JF, Kauffmann B, Grélard A, Sanchez C, Trézéguet V, Huc I, Lauquin GJ. Unambiguous structure of atractyloside and carboxyatractyloside. Bioorg Med Chem Lett. 2012 Apr 15;22(8):2973-5.

Kjaergaard CH, Durand F, Tasca F, Qayyum MF, Kauffmann B, Gounel S, Suraniti E, Hodgson KO, Hedman B, Mano N, Solomon EI. Spectroscopic and crystallographic characterization of "alternative resting" and "resting oxidized" enzyme forms of bilirubin oxidase: implications for activity and electrochemical behavior of multicopper oxidases. J Am Chem Soc. 2012 Mar 28;134(12):5548-51.

Structural biology

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

Services and expertise of IECB's Structural Biology Platform

cgfb BIOLOGIE STRUCTURALE

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

I E C B

cgfb BORDEAUX FUNCTIONAL GENOMIC CENTER

Liquid/solid NMR

Services and expertise

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

Equipment

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

Technical contacts

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

Scientific expertise

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

Electron microscopy

Services and expertise

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

Equipment

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

Main contact

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

Surface plasmon resonance (SPR)

Services and expertise

- Informations : interactions (yes or no answer), affinity, binding kinetics, thermodynamics (5°C to 40°C), stoichiometry and active concentrations.
- Samples : proteins, nucleic acids, small molecules (>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 103 to 107 M-1s-1, dissociation rates : 5 10-6 to 10-1s-1, equilibrium constant 104 to 2.1010 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

Mass spectrometry

Services and expertise

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

Equipment

- LCT Premier (Waters): optimized for large masses
- LCQ Advantage (Thermo): available for external users 50% of its operation time
- Reflex III (Bruker)
- Orbitrap Exactive (Thermo)

Technical contact

Frédéric Rosu, f.rosu@iecb.u-bordeaux.fr

Scientific expertise

Proteomic and lipidomic - Jean-Marie Schmitter, jm.schmitter@cbmn.u-bordeaux.fr
Nucleic acids and supramolecular assemblies - Valérie Gabelica, v.gabelica@iecb.u-bordeaux.fr

Molecular modeling

Services and expertise

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

Equipment

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

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

Other :

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

Softwares :

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

Main contact

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

Crystallogenesis

Services and expertise

- Robotised 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 expertise

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

X-ray diffraction and diffusion

Services and expertise

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

Equipment

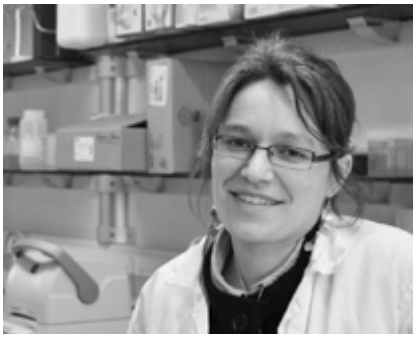
- Microfocus rotating anode Rigaku MM07 800W
- Microfocus rotating anode Bruker Microstar 2.7kW (macromolecules)

Technical contact

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

Scientific expertise

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



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

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

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

Preparative & analytical techniques

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

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

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

cgfb BIOLOGIE STRUCTURALE

Flow cytometry

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

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

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

Confocal microscopy

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

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

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

Molecular biology

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

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

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

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

Preparative biochemistry

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

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

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

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

Collaborative research

Servier, Sanofi-Aventis, LVMH, EDF, Conseil Interprofessionnel du Vin de Bordeaux, ... Several key industry players work with IECB teams. In 2012, the institut totalized 9 on-going projects with industrial partners.

Contract services and consulting

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

Technology transfer

IECB researchers are strongly encouraged to patent their discoveries. In 2012, 3 additional patents were submitted by team leader, Elisabeth Génot and Stéphane Quideau. A technology transfer unit, Novaptech, was also created in 2008 by an IECB team leader (see on the right).

Incubating start-ups

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

FLUOFARMA

Created in 2003 by former IECB team leaders, Fluofarma is a preclinical contract research organization dedicated to the discovery of new therapeutic targets, compounds & biomarkers. Specialized in the development of cell-based & biomarker assays, the company utilizes high-content analysis technologies to report phenotypic & molecular events at the single cell level in complex in vitro cellular models, blood and tissues.

Fluofarma now delivers drug discovery & proof-of-concept services to over 70 clients worldwide, including big pharmas, biotech companies & academic researchers. The company maintains on-going collaborations with IECB group leaders, either to test potential drug candidates or to develop new high-content screening methods.

Fluofarma services & capacities in drug discovery:

Development of complex in vitro models & cell-based assays

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

Cell-based high-content screening (over 100 validated cellular assays)

- High-throughput functional target validation : SiRNA screening
- Phenotypic & molecular screening of compound libraries, lead optimization services
- Preclinical proof-of-concept services : drug efficacy, predictive toxicology, mechanism of action studies

Quantitative biomarker analysis in blood & tissues

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

Jean-Baptiste Pin
Fluofarma CEO

Year of creation 2003

Staff 25

2011 turnover 2.2 M euros

Collaborative projects with IECB teams in 2012 2

Website www.fluofarma.com

NOVAPTECH

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

Service agreements

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

Biotechnological development of aptamers

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

Collaborative research projects

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

Dr. Sonia Da Rocha Gomes
Novaptech Executive Manager

Year of creation 2008

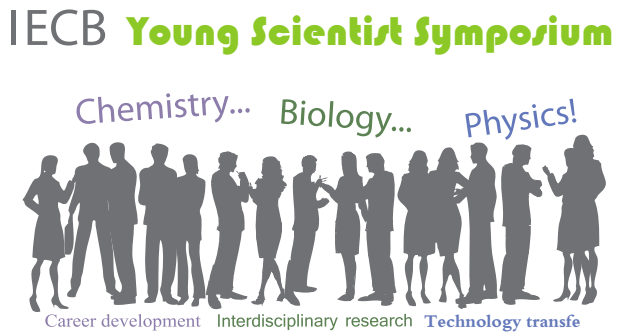
Staff 4 (3 cdi, 1 cdd)

Collaborative projects with IECB teams in 2011 2

Contact sonia.darocha@novaptech.com

Scientific events

IECB workshops & symposia



IECB Young Scientist Symposium, May 21-22

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

Young biologists, chemists and physicists from all over the world attended this event. They presented 14 short talks and 21 posters over 2 days.

IECB: Looking to the Future, October 11

Speakers:

- Dr. Christian Klammt, the Salk Institute for Biological Studies, USA
- Dr. Peter Crowley, National University of Ireland, School of Chemistry, Ireland
- Dr. Mireya McKee, Biological Physics, Clarendon Labs, University of Oxford, UK
- Dr. Raul Duran Diaz, Biozentrum, University of Basel, Switzerland
- Dr. Kerstin Gari, London Research Institute, UK
- Dr. Roberto Ferrari, University of California Los Angelas, USA

IECB group leaders'seminar, October 12

Term of tenure seminar:

- Dr. Reiko Oda (CNRS/ Bordeaux 1)

4th annual workshop of the Bordeaux RNA Club, RNA & nothing else ! June 29

60 participants. Invited speakers :

- Dr. Alejendro Toledo-Arana, Instituto de Agrobiotechnologia, Universidad Publica de Navarra, CSIC, Pamplona, Spain
- Dr. Marie Bouvier, Université Paul Sabatier, CNRS, Toulouse
- Dr. Yulia Redko, Institut Pasteur, Paris, France
- Dr. P. Cramer, Gene Center, Ludwig Maximilians, Universität München, Munich, Germany
- Marion Maurel, Inserm U1053, Université Bordeaux Segalen, Bordeaux, France
- Dr. Jesper Wengel, Nucleic Acid Center, Dep. Physics and Chemistry, University of Southern Denmark, Denmark
- Dr. Amit Patwa, ARNA, Inserm U869, Bordeaux, France
- Dr. Thao Tran, ARNA, Inserm U869, Bordeaux, France
- Dr. Ulrike Kutay, Institute of Biochemistry, ETH, Zurich, Switzerland
- Dr. Isabelle Iost, ARNA, Inserm U869, Université Bordeaux Segalen, Bordeaux, France

Bordeaux 2012 Symposium on Foldamers, January 30 - February 2, 2012

110 participants. Invited speakers :

- Pr. Padmanabhan Balaram, Indian Institute of Science, Bangalore, India
- Pr. William DeGrado, Univ. California, San Fransisco, USA
- Pr. Donald Hilvert, ETH Zürich, Switzerland
- Pr. Stefan Matile, Univ. Geneva, Switzerland
- Pr. Eiji Yashima, Nagoya Univ., Japan
- Pr. Paramjit Arora, New York Univ. USA
- Pr. Beate Koksch, Freie Univ. Berlin, Germany
- Pr. Hee-Seung Lee, KAIST, Daejon, Korea
- Dr. Gilles Guichard, CNRS, Univ. Bordeaux, France
- Pr. Masahiko Yamaguchi, Tohoku Univ. Sendai, Japan
- Dr. Jean-Marc Escudier, CNRS, Univ. Toulouse, France
- Pr. Luc Brunsveld, Technical Univ. Eindhoven, The Netherlands
- Pr. Jean-François Lutz, CNRS, Strasbourg, France
- Pr. Gerard Roefles; Univ. Groningen, The Netherlands
- Pr. Annelise Barron, Stanford University, USA

Other scientific events at IECB

France-Venezula PCP Program, March 2

Invited speaker :

- Pr. Marie-Aleth Lacaille-Dubois Lab. Pharmacognosie, UMIB, Univ. de Bourgogne, Dijon, Search for bioactive saponins in the field of cancerology and immunology
- Pr. Juan Manuel Amaro-Luis Lab. de Productos Naturales, Univ. de Los Andes, Mérida, Venezula

Journée SFR Tecsan, March 23

"Molecules and targets of therapeutic or diagnostic interest"

Attended by 60 scientists from Bordeaux.

RNA Club, March 29

60 participants. Invited speakers:

- Dr. Eric Ennifar, IBMC Strasbourg, France
- Dr. Andrew Goldsborough, Cyclops Genome Sciences, Cambridge, UK
- Ahissan Aime, INSERM U869 Bordeaux, France
- Dr. Bruno Cardinaud, INSERM U1035, ESNTBB, Bordeaux, France
- Anne-Lise PEILLE, INSERM U916 VINCO, Bergonié Institute, Bordeaux, France

Journée SFR Tecsan, May 10

Axe 2 : Bioingénierie et Nanotechnologies

RNA Club, September 21

50 participants. Invited speakers:

- Dr. Joost Zomerdijk,Centre for Gene Regulation and Expression, College of Life Sciences, University of Dundee, Dundee, UK
- Ahissan Aimé, Université Bordeaux Segalen, Inserm U869
- Pr. Anne Bourdoncle, Inserm U869, IECB, Bordeaux
- Pr. Cathy Staedel, Inserm U869, Bordeaux Segalen, Bordeaux

Science Day, October 9

Pr. Denis Dupuy, IECB, Inserm U869, Qu'est-ce qu'un OGM.

Attended by secondary school students from Aquitaine.

MSIB2012, November 5, 6

"Morpho-Spectral Imaging in Bioscience"

RNA Club, December 6

60 participants. Invited speakers:

- Dr. Monsef Benkirane, IGH, CNRS UPR 1142, Montpellier
- Dr. Cyril Masante, CNRS UMR 5234, Univ. Bordeaux, Bordeaux
- Dr. Leyla El Ayoubi, Inserm U869, Univ. Bordeaux, Bordeaux

Seminars

1. Eric Freyssingeas, Laboratoire de Physique de l'ENS de Lyon Evolution of the Global Internal Dynamics of a Living Cell Nucleus during Interphase
2. Dr. Irwin Davidson, IGBMC – Strasbourg-Illkirch Molecular aspects of retinoic acid receptor function in mouse ES cell differentiation
3. Prof. Marie-Aleth Lacaille-Dubois, Lab. de Pharmacognosie, UMIB, Univ. de Bourgogne, Dijon Search for bioactive saponins in the field of cancerology and immunology
4. Prof. Juan Manuel Amaro-Luis, Lab. de Productos Naturales, Univ. de Los Andes, Mérida, Venezuela Potentiality of the Venezuelan Andean Flora as Natural Product Source
5. Prof. Takehiko Wada, Tohoku University, Japon Time-Resolved CD Apparatus with Ellipticity-Change-Detection System: Toward the Application to High Sensitive Detection for the DNA/RNA Structural and Conformational Change
6. Dr Pierre Roblin, Synchrotron SOLEIL, France Presentation of the SWING beamlime and description of the HPLC environment used for biological research on SWING
7. Xavier Périole, Univ. Groningen, Pays-Bas Exploring protein/lipid interplay: Structural determinants of the supramolecular organization of G protein-coupled receptors in bilayers and respiratory chain supercomplexes
8. Aris Xenakis, Institute of Biological Research & Biotechnology, Nat. Hellenic Research Foundation, Athène, Grèce Nano-biotechnology: Enzymique bioconversions in nanodispersions
9. Dr. Robert Arkowitz, Institut de Biologie Valrose (iBV), Univ. Nice A steep phosphoinositide phosphate gradient critical for fungal filamentous growth
10. Dr. Gaétan Laroche, Univ. Laval, Canada Surface plasma modification to improve materials biocompatibility: on the importance of characterizing the plasma process and the surface chemistry
11. Prof. Fulvio Reggiori, Department of Cell Biology, University Medical Centre Utrecht, Pays-Bas Autophagy in Health and Disease
12. Jean-Marc Lancelin (institut des Sciences Analytiques, Université de Lyon, France) Fragment--Based Engineering of Protein-Ligand Interactions Using NMR and Other Biophysical Methods: TowardsTailor--made Drugs
13. Dr. Charles White, Univ. Blaise Pascal, Clermont-Ferrand, France Recombinaison et stabilité du génome chez Arabidopsis
14. Prof. Ashutosh Chilkoti, Duke University, Caroline du Nord, USA Genetically Engineered Polypeptides for Drug Delivery
15. Dr. Christian Richter, Univ. Johann Wolfgang Goethe, Francfort, Allemagne Advanced NMR experiments for oligonucleotides applied to RNA hairpins, and riboswitch-models
16. Leif Lundin, CSIRO Food and Nutritional Sciences, Australie Structure design for temporal release and perception of taste and aroma
17. Dr. Olivier Sordet, Institut Claudius Regaud, Toulouse, France Transcriptional responses to topoisomerase I-targeting drugs
18. Prof. Anh Tuan Phan, NTU, Singapour Structure and recognition of DNA and RNA G-quadruplexes
19. Prof. Takuzo Aida, Department of Chemistry and Biotechnology,Tokyo University Advanced molecular design of functional materials
20. Prof. Marc Fontecave, Collège de France, Paris Lessons from nature: highly selective radical-based chemistry in metabolic and biosynthetic pathways
21. Prof. Shigeki Sasaki, Kyushu University, Japon An efficient method for site-specific chemical modification of RNA triggered by in situ hybridization
22. Dr. Patrick Chène, Novartis Oncology Research, Basel, Suisse New targets for new drug discovery opportunities
23. Dr. Thomas Landrain, Institut de Biologie Systémique et Synthétique, Evry, France De novo automated design of RNA logic circuits
24. Prof. Olivia Reinaud, Université Paris Descartes Metals in Biomimetic Cavities
25. Prof. Kay Severin, Ecole Polytechnique Fédérale de Lausanne, Suisse Molecular Nanostructures and Sensors by Self-Assembly
26. Dr. Vincent Croquette, LPS, Ecole Normale Supérieure, Paris, France Single-molecule study of helicases and polymerases using a hairpin substrate, possible application to single molecule sequencing
27. Prof. Seung-Wuk Lee, University of California, Berkeley, USA Virotronics: Making Virus Work For Us!
28. "Antoine Loquet, Max Planck Institute, Göttingen, Allemagne Structures of Supramolecular Assemblies Revealed by Solid-State NMR
29. Dr. Edurne Berra, CICbioGUNE, Bilbao, Espagne HIF and PHDs-mediated hypoxia tolerance
30. Center for Structural Biology and Bioinformatics) "Protein structural changes monitored by ATR-FTIR"
31. Dr. Eric Freyssingeas (Laboratoire de Physique de l'ENS de Lyon) "Evolution of the Global Internal Dynamics of a Living Cell Nucleus during Interphase"
32. Prof. B. Deplancke (Institute of Bio-engineering and School of Life Sciences, EPFL, Switzerland) "Deciphering the metazoan regulatory code"
33. Dr. Marc Boudvillain (Centre de Biophysique Moléculaire, Orléans) "Mechanism and regulation of transcription termination factor Rho, an atypical RNA helicase from bacteria"
34. Dr. Hervé Moine (IGBMC, Strasbourg) "Functions of the FMRP protein in the regulation of neuronal mRNA metabolism"
35. Dr. Bruno Kieffer (IGBMC, Strasbourg) "Subtle regulation mechanisms of Nuclear Receptors function : an NMR view"
36. Prof. Romano Regazzi (Université de Lausanne) "Emerging roles of microRNAs in the control of pancreatic beta cell functions"
37. Prof. Takuzo Aida, Department of Chemistry and Biotechnology, Tokyo University "Advanced molecular design of functional materials"
38. Prof. Marc Fontecave, Collège de France, Paris "Lessons from nature : highly selective radical-based chemistry in metabolic and biosynthetic pathways"
39. Prof. Stefan Matile, Univ. Geneva, Switzerland "Synthetic supramolecular systems (th)at work"
40. Dr. Gilles LABESSE (Centre de Biochimie Structurale, Montpellier) "Using comparative docking for drug design"

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