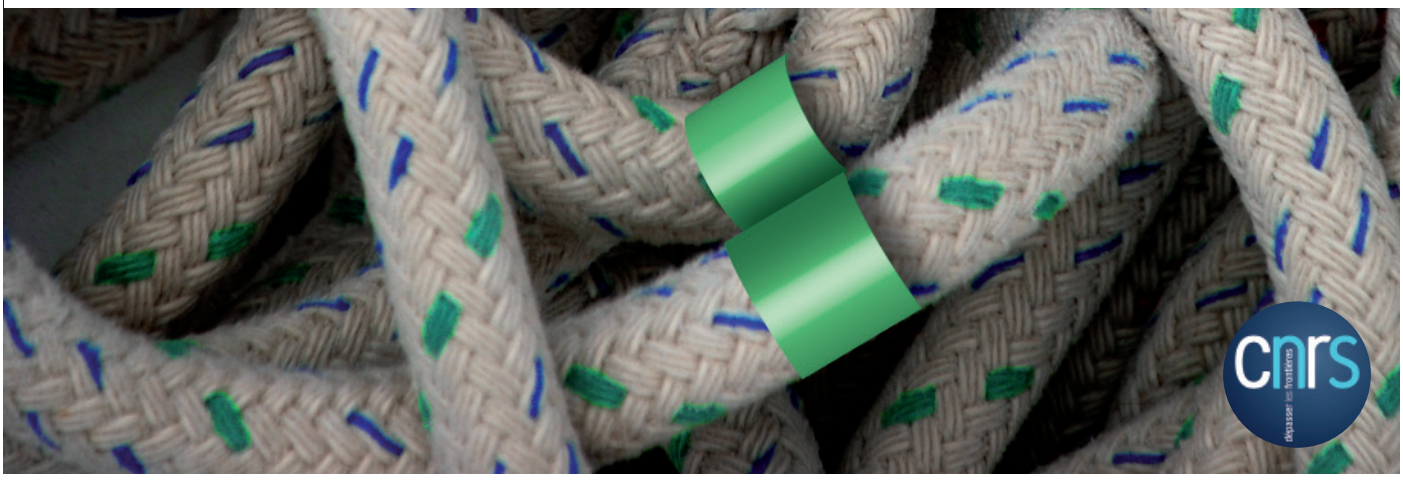
INSTITUTE OF HUMAN GENETICS

Scientific Report

CNRS UPR 1142 - MONTPELLIER - FRANCE
http://www.igh.cnrs.fr

IGH
INSTITUT DE GENETIQUE HUMAINE

October 2012



LAYOUT & DESIGN
Catherine Larose

PICTURES
Office de tourisme Montpellier
Cyril Sarrauste de Menthière, IGH Montpellier

COVER ILLUSTRATIONS
Polycomb group proteins are conserved chromatin factors critically required for the regulation of multiple target genes during cell differentiation and development. The cover picture shows a tangle of ropes on a boat, metaphorically illustrating the tangled state of chromatin in the nucleus. Green cylinders represent examples of specific 3D interactions among PcG-bound chromatin elements. Photo and Artwork credit: Cyril Sarrauste de Menthière. IGH Montpellier

http://www.igh.cnrs.fr

CONTACT / DIRECTION

Institut de Génétique Humaine

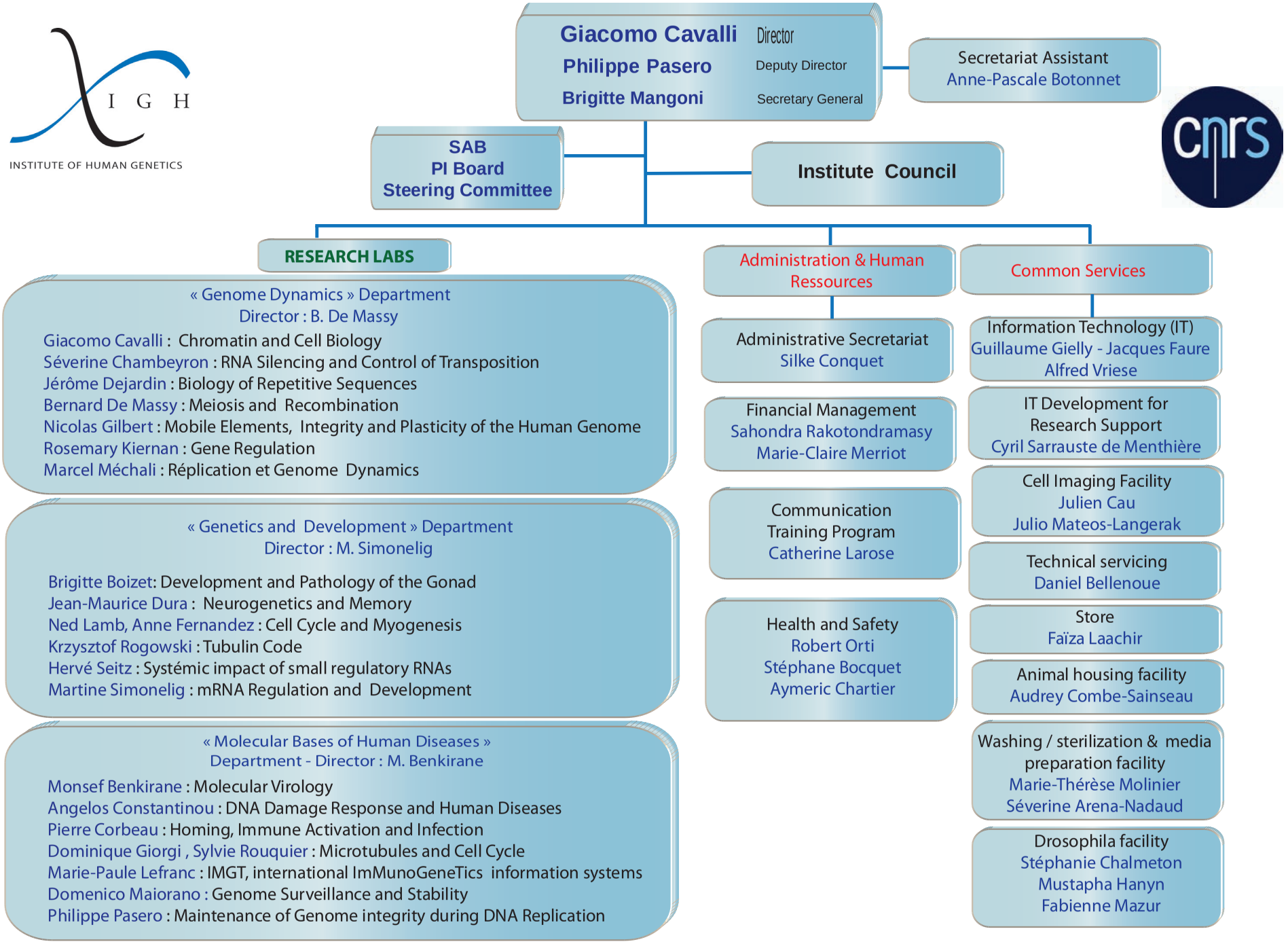
Dr. Giacomo CAVALLI

141 Rue de la Cardonille
34396 MONTPELLIER cedex 5
FRANCE

Phone : +33 (0)4 34 35 99 04 / + 33 (0)4 34 35 99 70
Fax : +33 (0)4 34 35 99 99

Giacomo.Cavalli@igh.cnrs.fr

Contents


I G H
INSTITUTE OF HUMAN GENETICS
Giacomo Cavalli Director
Philippe Pasero Deputy Director
Brigitte Mangoni Secretary General
Secretariat Assistant
Anne-Pascale Botonnet
SAB
PI Board
Steering Committee
Institute Council
cnrs
RESEARCH LABS
« Genome Dynamics » Department
Director : B. De Massy
Giacomo Cavalli : Chromatin and Cell Biology
Séverine Chambeyron : RNA Silencing and Control of Transposition
Jérôme Dejardin : Biology of Repetitive Sequences
Bernard De Massy : Meiosis and Recombination
Nicolas Gilbert : Mobile Elements, Integrity and Plasticity of the Human Genome
Rosemary Kiernan : Gene Regulation
Marcel Méchali : Réplication et Genome Dynamics
« Genetics and Development » Department
Director : M. Simonelig
Brigitte Boizet: Development and Pathology of the Gonad
Jean-Maurice Dura : Neurogenetics and Memory
Ned Lamb, Anne Fernandez : Cell Cycle and Myogenesis
Krzysztof Rogowski : Tubulin Code
Hervé Seitz : Systémic impact of small regulatory RNAs
Martine Simonelig : mRNA Regulation and Development
« Molecular Bases of Human Diseases »
Department - Director : M. Benkirane
Monsef Benkirane : Molecular Virology
Angelos Constantinou : DNA Damage Response and Human Diseases
Pierre Corbeau : Homing, Immune Activation and Infection
Dominique Giorgi , Sylvie Rouquier : Microtubules and Cell Cycle
Marie-Paule Lefranc : IMGT, international ImMunoGeneTics information systems
Domenico Maiorano : Genome Surveillance and Stability
Philippe Pasero : Maintenance of Genome integrity during DNA Replication
Administration & Human Ressources
Common Services
Administrative Secretariat
Silke Conquet
Financial Management
Sahondra Rakotondramasy
Marie-Claire Merriot
Communication
Training Program
Catherine Larose
Health and Safety
Robert Orti
Stéphane Bocquet
Aymeric Chartier
Information Technology (IT)
Guillaume Gielly - Jacques Faure
Alfred Vriese
IT Development for
Research Support
Cyril Sarrauste de Menthière
Cell Imaging Facility
Julien Cau
Julio Mateos-Langerak
Technical servicing
Daniel Bellenoue
Store
Faïza Laachir
Animal housing facility
Audrey Combe-Sainseau
Washing / sterilization & media
preparation facility
Marie-Thérèse Molinier
Séverine Arena-Nadaud
Drosophila facility
Stéphanie Chalmeton
Mustapha Hanyn
Fabienne Mazur

GIACOMO CAVALLI

Director

PHILIPPE PASERO

Deputy Director

The Institute of Human Genetics (Institut de Génétique Humaine, IGH) is a CNRS unit located in the fast growing Arnaud de Villeneuve biomedical campus of Montpellier that includes several CNRS and INSERM laboratories (Centre de Biochimie Structurale (CBS), Institut de Génomique Fonctionnelle (IGF), etc.), the future University of Montpellier School of Medicine (University of Montpellier 1) and academic hospitals. It is close to the site of the University of Montpellier 2 and the Center for Cancer Research (IRCM). The Institute occupies a surface of 3800 m^2.

It hosts more than 200 people, including scientists (36 CNRS, 11 INSERM and 9 University and Hospital researchers), engineers, technical and administrative staff (40), post-doctoral fellows (37), graduate students (33), undergraduate students and visiting scientists.

The IGH aims at providing a first class scientific environment for the development of innovative research projects. The excellence of the research carried out at the IGH is attested by the quality of the scientific production, the number of awards attributed to scientists working at the Institute as well as the prestigious grants that support their research, particularly three grants from the European Research Council (ERC).

Currently, the IGH houses 20 research groups distributed in the three scientific departments (Genome Dynamics, Genetics & Development and Molecular Bases of Human Diseases).

Director's foreword

The "Institut de Génétique Humaine" (IGH) is a high-profile institute devoted to basic biomedical research. Throughout its 13 years of life, it has provided an excellent environment in which it is possible to carry out innovative, frontier-breaking science and where the quality of the technical facilities, infrastructure and administrative department matches and supports the high scientific output of the IGH.

IGH scientific life

The IGH is characterized by a dynamic day-to-day activity that boasts both scientific and extra-scientific events which contribute to the exciting science and the pleasant daily atmosphere of the Institute. Furthermore, routine events are complemented by special meetings every year. The main activities that characterize the IGH community life are:

- weekly «external» seminars given by invited scientists. Most of these seminars are given by internationally-renowned researchers and all are held in English;

- the annual IGH Seminar Series in which leading are invited by the Institute's departments to give keynote talks on their research work;

- weekly «internal» seminars where scientists, post-doctoral fellows and PhD students expose their results and research projects. The lively informal discussions characterizing these seminars are continued in a friendly atmosphere during the Pizza time after the seminars;

- scientific retreats (every second year) organized by each Department in order to facilitate scientific interaction in beautiful places free from the everyday worries of laboratory life;

- the IGH Retreat, a meeting that brings together all the Institute staff every second year, alternating with the department retreats;

- organization of various high-level meetings like the «IGH 10th Anniversary Meeting», with lectures by outstanding scientists including the Nobel laureate David Baltimore (see http://congres.igh.cnrs.fr/IGH/IGH10ans.pdf for an overview of the program); or other prestigious international conferences (such as EMBO conference series and others). For an exhaustive list, see http://www.igh.cnrs.fr/EN/seminaire.php;

- IGH researchers are frequently involved in the organization of practical courses (Ateliers INSERM and others) to train scientists in specific approaches on which they have high-profile expertise.

Teaching activities

The IGH is strongly involved in teaching and has a close relationship with the Universities of (Universities of Montpellier 1 and 2). Several Professors and Associate Professors carry out their research activities at the IGH.

The Doctoral School «Biology and Health» (CBS2) of the Universities of Montpellier 1 and 2 is housed at the IGH and its secretary is a CNRS employee of the Institute. Every year, about thirty graduate students are pursuing their PhD program at the Institute, and 8-10 of them defend their thesis. In addition, about 20 Master students do their practical laboratory training at the IGH each year.

Technical facilities

The IGH offers an excellent technical environment and all the infrastructures needed to carry out cutting-edge molecular, cellular and developmental biology research. It also possesses two biosafety L3 laboratories. One of the main strengths of the Institute is its capacity to react rapidly to the need of updating its facilities in response to the fast technological progress of science. For the last three years we have been running an «Agence de Biomédecine»-certified laboratory devoted to the study of human embryonic stem cells. In 2009, we opened a state-of-the-art 100 m^2 imaging facility. This facility, called MRI – IGH, has imaging equipment which is worth more than 3 million Euros, including 3 confocal microscopes and more than 10 top-level epifluorescence microscopes. We have recently acquired the "OMX" super-resolution fluorescence microscope, which puts our imaging facility at the absolute forefront in fluorescence imaging acquisition/analysis in France and Europe. The IGH has also equipped the «Montpellier GenomiX» genomic facility with an Illumina HiSeq instrument, which joins the already existing Illumina Genome Analyzer IIx and microarray equipment. Together with their bioinformatic analysis pipeline, these instruments allow high throughput genomic analyses. This facility is installed in the new building of the Institute of Functional Genomics (IGF) that communicates directly with the IGH. The Institute also has rodent, Drosophila and Xenopus housing facilities.

Finally, the IGH is a member of "Biocampus", the new CNRS-funded servicing unit that provides easy access to all technical facilities available in the city to the whole Montpellier research community. The facilities located at the IGH (particularly the animal house and the imaging facility) are thus available to the whole scientific community of Montpellier.

Institute Governance

The acting director, Giacomo Cavalli, and the deputy director, Philippe Pasero, took up their functions in January 2011. They are assisted by a steering committee, composed by the department heads (Martine Simonelig for Genetics and Development, Bernard de Massy for Genome Dynamics, Monsef Benkirane for Molecular Bases of Human Diseases and Marcel Méchali, head of the upcoming Genopolys). Scientific issues are discussed within the group leader board and they are further examined, along with budget and other policy issues, by the 15-member Institute Council, composed by the directors and a mix of nominated and elected members from all the personnel bodies: researchers, post-doctoral fellows, PhD students, engineers, technicians and administrative managers.
Starting from 2011 the IGH Scientific Advisory Board (SAB) started its activity. The SAB includes Hervé Chneiweiss, University Paris Descartes, Paris, France; Denis Duboule, University of Geneva, Switzerland; Edith Heard, Institut Curie, Paris, France; and Stéphane Noselli, Institute of Developmental Biology and Cancer, Nice, France. A further, former SAB member, Ron Laskey stepped down this year for personal reasons. We wish to thank him for the great help he gave while in service, and wish him all the best for the continuation of his life and career. Two new SAB members, both from the Ecole Polytechnique Fédérale de Lausanne, joined the IGH in 2012; Didier Trono, expert in virology and Joachim Lingner, expert in telomere biology and replication. We wish to welcome them warmly and wish them a good collaboration with the IGH governance team, PIs, researchers and personnel. Together with the four other current SAB members, Hervé Chnieweiss, Denis Duboule, Edith Heard and Stéphane Noselli, they cover well the research fields of the three IGH departments. They will examine the overall Institute activity every two years, starting this November when they will participate in the Institute Retreat during which all groups and scientific facilities present their ongoing and past work. They will also take part in the laboratory evaluations and will give their advice on new hiring and other scientific policies.

A year of thrilling science

Last year's scientific achievements have been particularly striking. With 55 peer reviewed papers published in peer-reviewed journal under the responsibility of IGH PIs, the average impact factor is above 12, placing IGH among the very best research units in the country. It would be too long to discuss all the main discoveries published by the IGH groups but it is remarkable to see how several laboratories have published striking discoveries. We are particularly delighted to see that two junior laboratories published their research in top journals.

The laboratory of Rosemary Kiernan published in Cell (Wagschal et al, 2012) a regulatory role for microprocessor in HIV expression. Microprocessor, a complex containing RNase III endonuclease, Drosha, and a RNA binding subunit Dgcr8, was shown to act in an RNAi-independent manner to regulate transcriptional pausing at the HIV promoter and, possibly, of many other promoters. Shortly before, the laboratory of Séverine Chambeyron published in Genome Research (Grentzinger et al. 2012) their discovery that maternal inheritance of piRNAs can contribute a form of non-chromatin mediated epigenetic inheritance in Drosophila that can help controlling transposition of retroelements in changing environmental parameters (different temperatures, aging conditions, …).

It is particularly rejoicing to see young PIs succeed in their research, and we wish many more of these discoveries to come in the coming years.

New groups at IGH

Following the last IGH evaluation by the AERES agency (http://www.aeres-evaluation.fr/index.php/Etablissements/UNIVERSITE-MONTPELLIER-1, see Institut de Génétique Humaine), we have set up clear policies concerning laboratory space and the status of junior groups.

At the end of last year, the junior laboratory of Hervé Seitz "Systemic Impact of small regulatory RNAs" has joined IGH, strengthening the "Genetics and Development" Department. The junior laboratory of Reina Fernandez de Luco will join the Genome Dynamics department in 2013. We wish both of them great fun doing science at IGH, and to become world leaders in their respective fields.

Finally, the IGH has issued a junior group leader recruitment call in mid 2012. This call received about 80 applicants. 7 of them were short listed for interview and we are finalizing the interview process, hoping to finish it soon and to welcome a new junior PI in our institute by the end of 2013.

IGH and the initiative "investissements d'avenir" (investments for the future) of the French Ministry of Research

To increase French scientific competitiveness, the French Ministry of Research launched two years ago a large investment campaign in order to fund various research-related components, such as acquisition of large equipment, large facilities and infrastructures, Centers of excellence and Campuses of excellence.

The IGH PI Marcel Méchali is coordinating a Center of Excellence (Labex) called EpiGenMed: From Genome and Epigenome to Molecular Medicine. In total, 49 internationally renowned research laboratories working in different fields (mathematics, biophysics and biochemistry, molecular, cellular and developmental biology, cancer biology, infectiology and neurobiology) joined forces to address the following main questions:

- How do genome and epigenome regulations impact on cell proliferation, differentiation and development?

- What are the interactions between host and infectious pathogens, how do they induce diseases and how can we use this knowledge to cure the world's most critical infectious diseases?

- What are the molecular bases of the cell signaling processes in the central nervous system and in the sensory organs and how do signaling dysfunctions induce neurological, neurodegenerative and sensory disorders?

The next years will see these laboratories and others that may join them along the way take an innovative interdisciplinary research approach in which the knowledge from single molecule research will be followed all the way up to the development of novel diagnostic and therapeutic approaches. The project will run until 2021 thanks to massive funding that will serve to support PhD and post-doctoral fellowships, group leader hires, research, teaching and scientific communication activities as well as the clinical exploitation of the results. EpiGenMed started its activity with a first round of PhD and Postdoc programs that have been heavily subscribed by excellent applications. IGH researchers are heavily involved in the EpiGenMed research programs and they coordinate 3 of the 5 programs (biophysics and systems biology; epigenetics and genome dynamics; cell cycle, cell fate and development; infectious disease and immunology; cell signaling and neurobiology). Thus, IGH will be a major steering force of this innovative large-scale project.

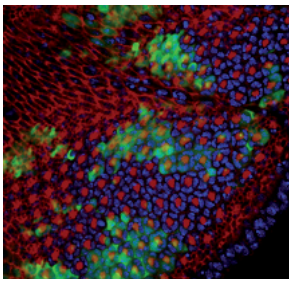
Enjoy the future!

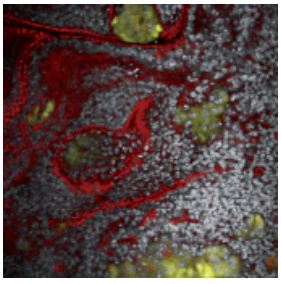
In summary, IGH has achieved strong scientific goals and has improved its organization in many ways during the last year. As always, we are committed to further enhance the quality and impact of our science, while maintaining a friendly and easy-going atmosphere. It is thus my pleasure to wish a great year to come to all IGH members.

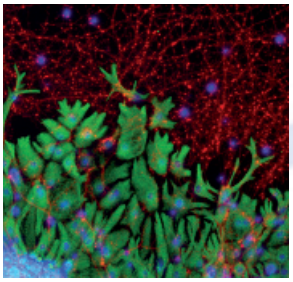
Genome Dynamics Department

Director : Bernard De Massy

General Statement about the Department





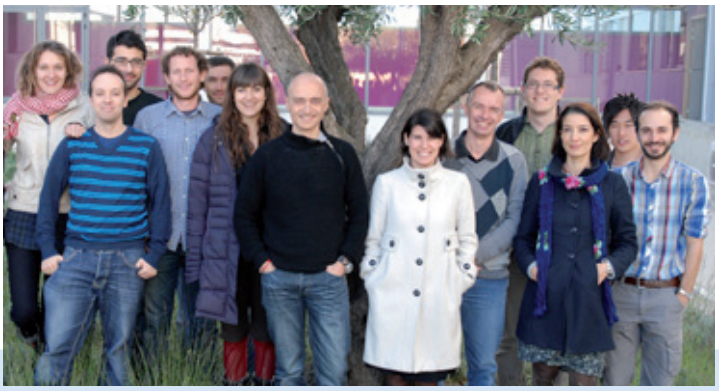


The research groups of the department of Genome Dynamics focus their research on understanding the genome functions by analyzing different aspects of its biology in various model systems (Drosophila, Xenopus, mouse, human cells). These aspects include DNA replication and recombination, chromatin structure and dynamics, mobile elements and gene expression.

Research on DNA replication aims at identifying origins of replication, understanding the molecular mechanisms of origin firing and how these events are regulated in order to take place at the right time and only once per cell cycle. A special form of the cell cycle is the meiotic division that generates gametes, and our department is exploring the processes that ensure the proper transmission of the genome by studying the mechanisms of recombination and chromosome segregation during meiosis. Specific projects are focused on understanding the mechanism of the programmed induction of DNA double strand breaks during meiosis. How genome integrity is maintained in the germline, particularly via the control of the activity of mobile elements, is also addressed through the analysis of the regulation of a small RNA family called piRNAs. Studies directly aimed at identifying the mechanism of insertion of mobile elements, such as the human L1 retrotransposons, in the genome provide a complementary approach to understand processes that could represent a threat to genome stability.

Several projects also want to determine how the organization of the genome, at the level of chromosomes and chromatin, can influence several of its activities. Specifically, we aim at understanding how the closed, compact chromatin structure called heterochromatin is regulated and its biological relevance for development and genome stability in regions of the genome, such as telomeres, pericentromeres and rDNA. How local chromatin modifications and the three-dimensional organization of chromosomes in the nucleus are integrated and how they impact on gene expression is also addressed through the study of the Polycomb and Trithorax protein families. At the gene level, factors that are involved in activation or silencing of gene expression, through direct or indirect interactions with the transcription machinery, and their links with cellular processes of RNA metabolism are investigated.

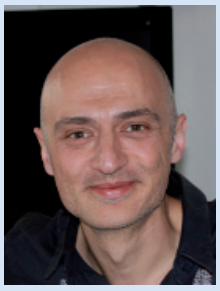
Our department has a strong expertise in a variety of approaches, particularly in biochemistry, genetics and molecular and cellular biology. State-of-the-art microscopy, imaging and bio-informatics for the analysis of next-generation sequencing data have also been recently developed by several groups. The department research groups are engaged in several collaborations that are fueled by common interests, an excellent scientific atmosphere and by formal laboratory interactions, such as the department retreats. In addition to the interactions within the department, several of our teams collaborate with laboratories in the two other departments of the Institute to understand how genome regulation drives development and its relationship with human pathologies.



Chromatin and Cell Biology

GIACOMO CAVALLI

Giacomo.Cavalli@igh.cnrs.fr



Giacomo Cavalli
Research Director CNRS

Thierry Cheutin,
Research Scientist CNRS

Anne-Marie Martinez,
Lecturer,
University Montpellier 2

Bernd Schuttengruber,
Research Scientist INSERM

Aubin Thomas,
Engineer CNRS

Inma Gonzalez,
Post-doctoral Fellow

Nicola Iovino,
Post-doctoral Fellow

Thomas Sexton,
Post-doctoral Fellow

Filippo Ciabrelli,
PhD student

Anne Delest,
PhD student

Philip Yuk Kwong Yung,
PhD student

Caroline Jacquier-Labroche
Engineer

We are more than our DNA! In the last couple of decades it has become clear that chromosomal components such as histones, regulatory proteins and noncoding RNAs contribute to regulate all aspects of DNA function and contribute to heredity. Our lab has mainly focused on the analysis of proteins of the Polycomb and Trithorax groups: key regulators of the expression of major developmental genes that coordinate the processes of cell differentiation and cell proliferation. Polycomb proteins are able to silence gene expression, while Trithorax proteins counteract gene silencing in the appropriate cells. At the molecular scale, we have studied how Polycomb and Trithorax proteins are recruited to DNA and how they may interact with other regulatory elements, such as chromatin insulators. Moreover, we published the first large-scale mapping of the distribution of Polycomb group proteins along Drosophila chromosomes at different developmental stages. We also demonstrated that polyhomeotic, a Polycomb group gene, is a tumor suppressor that controls cell proliferation by regulating Notch signaling.

A distinctive feature of these proteins is their ability to maintain the memory of gene regulatory states through successive mitotic divisions in the different cell lineages and research in our laboratory has analyzed this phenomenon. We showed that the regulation of chromosome architecture by these proteins contributes the transgenerational epigenetic inheritance of chromatin states by revealing that the transmission of this mitotic and meiotic cellular memory can bring into play long-distance chromosomal interactions in the three-dimensional space of the cell nucleus.

We recently extended the analysis of chromosome architecture by analyzing at genome-wide scale the contacts made by each locus with all other chromosome loci in the genome. From this study, we deduced the principles governing chromosome organization and the functional implications of regulation of genome architecture. We will pursue this analysis In the coming years.

- Sexton, T., Yaffe, E., Kenigsberg, E., Bantignies, F., Leblanc, B., Hoichman, M., Parrinello, H., Tanay, A., and Cavalli, G. (2012). Three-dimensional folding and functional organization principles of the Drosophila genome. **Cell,** *148*, 458-472

-Bantignies, F., Roure, V., Comet, I., Leblanc, B., Schuettengruber, B., Bonnet, J., Tixier, V., Mas, A., and Cavalli, G. (2011). Polycomb-dependent regulatory contacts between distant Hox loci in Drosophila. **Cell** , *144*, 2, 214-226.

- Martinez, A.M., Schuettengruber, B., Sakr, S., Janic, A., Gonzalez, C., and Cavalli, G. (2009). Polyhomeotic has a tumor suppressor activity mediated by repression of Notch signaling. **Nat Genet**., *41*, 10, 1076-1082.

- Grimaud, C., Bantignies, F., Pal-Bhadra, M., Ghana, P., Bhadra, U., and Cavalli, G. (2006). RNAi Components Are Required for Nuclear Clustering of Polycomb Group Response Elements. **Cell,** *124,* 957-971.

- Dejardin, J., Rappailles, A., Cuvier, O., Grimaud, C., Decoville, M., Locker, D., and Cavalli, G. (2005). Recruitment of Drosophila Polycomb group proteins to chromatin by DSP1. **Nature,** *434*, 533-538.

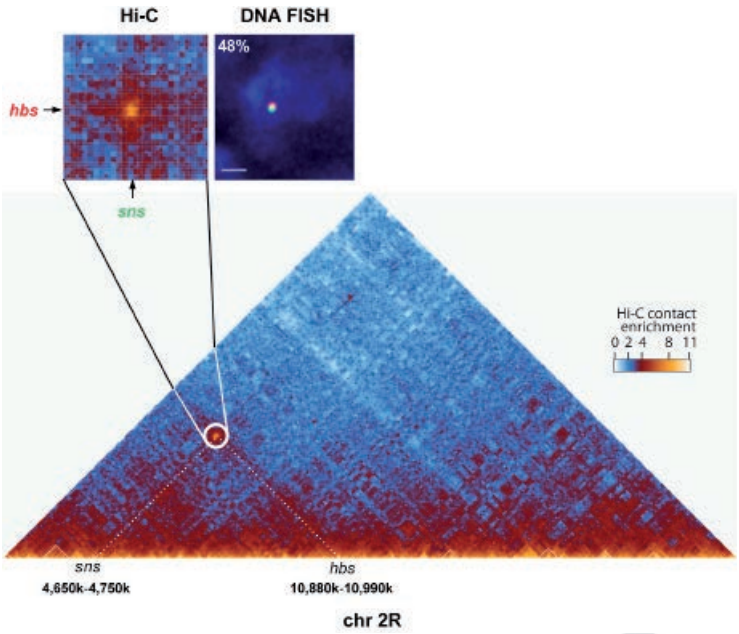


Figure 1. Hi-C, a molecular biology method to map interactions between chromatins sequences in vivo, is used to explore the spatial organization of the genome in Drosophila embryos. A cluster of strong interactions between two myoblast-specific genes, hbs and sns, located ~6 Mb apart on one chromosome arm, is highlighted. This interaction was also shown to occur at high frequency by DNA FISH (fluorescent in situ hybridization).

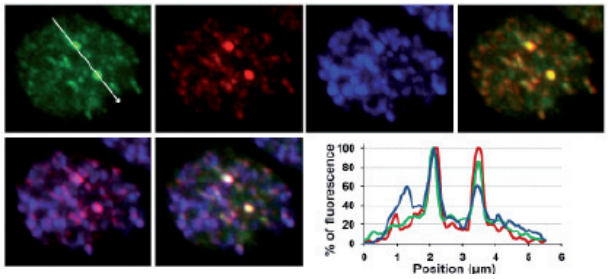


Figure 2. 3D distribution of PcG proteins (polycomb in green and polyhomeotic in red) compared to histone H3K27me3 (blue) inside the cell nucleus. They co-localize inside sub-nuclear volumes called polycomb bodies.

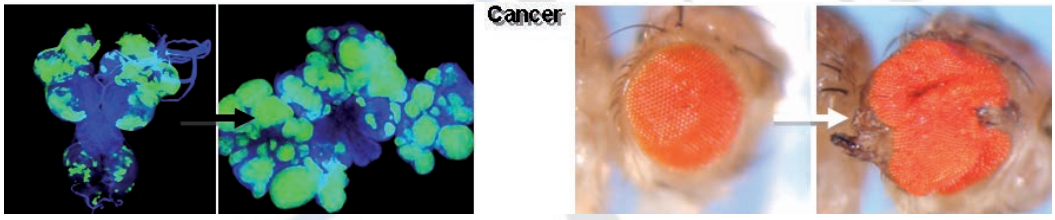
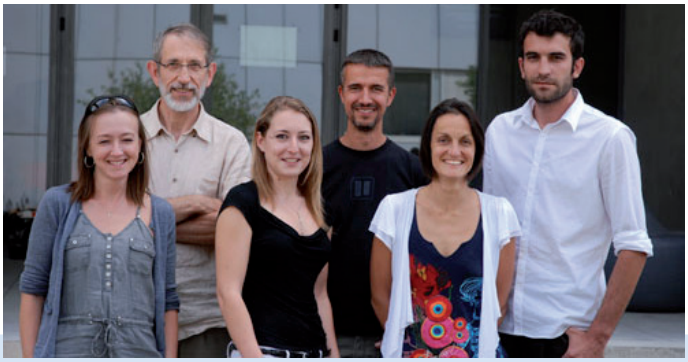


Figure 3. Mutation of the polyhomeotic locus (second panel from the left) induces over-proliferation of the mutant tissue (in green, compare to control on the left). Most larvae die but around 10% survive and, in that case, the mutant tissue over-proliferates (the mutant eye in the second panel from the right is larger than wild type eye on the left) and forms tumors.



RNA Silencing & Control of Transposition

SEVERINE CHAMBEYRON
severine.chambeyron@igh.cnrs.fr

Séverine Chambeyron
Research Scientist CNRS

Alain Pelisson,
Research Director CNRS

Christine Brun,
Technician CNRS

Bruno Mugat,
Engineer CNRS

Abdou Akkouche,
Post-doctoral fellow

Thomas Grentzinger,
PhD student

We are interested in understanding the mechanisms involved in the control of transposable elements (TEs) that are essential for the maintenance of genome integrity. They involve a class of small RNAs, the piRNAs (piwi-interacting RNAs). Since the piRNA silencing pathway is not well known, we propose to characterize in the Drosophila ovary the biogenesis and the role of this class of small non coding RNAs.

piRNAs may be considered as key elements of a sort of bipartite immune system: one genetic component is encoded by heterochromatic loci (named piRNA clusters) that contain defective copies of TEs producing antisense piRNAs; the other component is achieved by sense piRNAs produced by the functional copies of TEs located in euchromatin. In the so-called "ping-pong" biogenesis pathway, primary antisense piRNAs, produced by an unknown mechanism from piRNA clusters, target the transcripts of functional TEs that are cleaved to produce sense piRNAs. These sense piRNAs then target the transcripts of the piRNA clusters that are then cut to produce secondary antisense piRNAs.

Using two TE models, the I element in the germline and the gypsy retrotransposon in the somatic ovarian cells, we are studying the biogenesis of the piRNAs, the mechanism of the piRNA-mediated TE repression, and the epigenetic mechanisms involved in the maternal inheritance of the silencing.

Our recent results provide evidence that secondary piRNAs can repress the I element in the female germline. The I element is an excellent model because it is one of the rare transposable elements which has not yet invaded all Drosophila melanogaster strains. This invasion can therefore be reproduced at will in the lab and the establishment of the silencing followed in real time. A cryptic production of secondary piRNAs by the piRNA clusters was discovered which explains how flies submitted to various environmental treatments (aging, temperature,…) are better prepared to resist the invasion (Fig. 1). The "ping-pong" amplification loop in the ovary seems to be boosted if the egg already contained such maternally deposited cryptic piRNAs. So, secondary piRNAs are the molecular basis of the non-chromatin-mediated epigenetic memory of the environmental treatment (Fig. 2).

The "ping-pong" amplification loop does not occur in somatic ovarian cells, where TE silencing is only achieved by primary piRNAs (Fig. 3). In this tissue, we are studying the relationships between piRNA- and both the micro- and the siRNA pathways in the regulation of somatic TEs. We are also assessing to what extent the piRNA-loaded Piwi protein can affect the expression of TEs and their flanking genes by changing the chromatin landscape in and around TEs. In the germ cells, another layer of TE silencing occurs post-transcriptionally through the sequestration of TE transcripts inside the nucleus (Fig. 4).

.

- Grentzinger, T., Armenise, C., Brun, C., Mugat, B., Serrano, V., Pelisson, A., Chambeyron, S. (2012)piRNA-mediated transgenerational inheritance of an acquired trait. **Genome Res.,** *22,* 10, 1877-1888. PMID : 22555593.

- Chambeyron, S., Popkova, A., Payen-Groschêne, G., Brun, C., Laouini, D., Pelisson, A., Bucheton, A. (2008) piRNA-mediated nuclear accumulation of retrotransposon transcripts in the Drosophila female germline. **Proc. Natl. Acad. Sci. U S A**. *105*, 39, 14964-14969.

- Mevel-Ninio, MT., Pelisson, A., Kinder, J., Campos, AR., Bucheton, A.(2007) The flamenco locus controls the gypsy and ZAM retroviruses and is required for Drosophila oogenesis. **Genetics**, *175,* 4, 1615-1624.

- Pelisson, A., Payen-Groschene, G., Terzian, C., Bucheton, A. (2007) Restrictive Flamenco Alleles Are Maintained in Drosophila melanogaster Population Cages, Despite the Absence of Their Endogenous Gypsy Retroviral Targets. **Mol. Biol. Evol**., *24*, 2, 498-504.

- Pelisson, A., Sarot, E., Payen-Groschene, G., Bucheton, A. (2007) A novel rasiRNA-mediated silencing pathway downregulates sense gypsy transcripts in the somatic cells of the drosophila ovary. **J. Virol**., *81*, 4, 1951-1960.

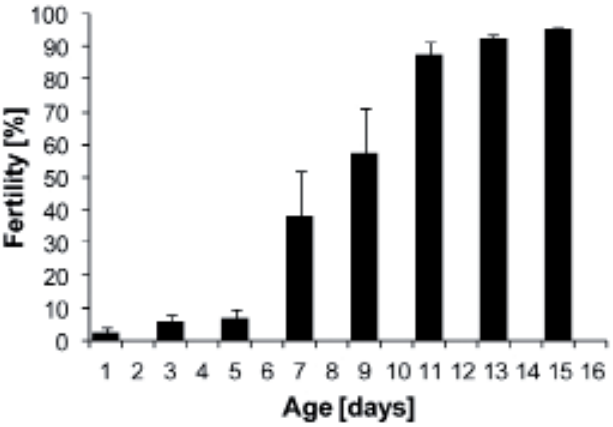


Figure 1 : Female aging rescues the sterility due to I *element* derepression in the ovaries lacking cognate piRNAs.

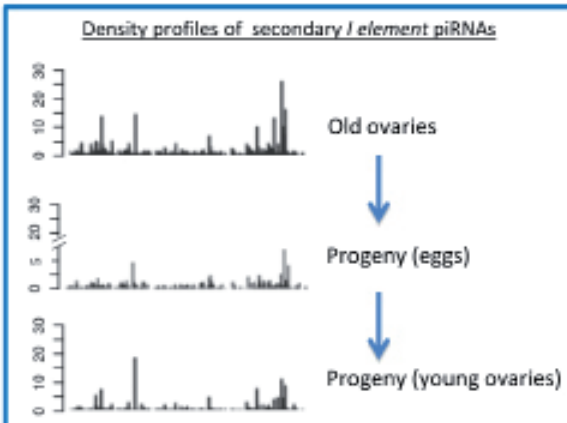


Figure 2 : Secondary piRNAs are produced in the ovary of the daughter, in response to the maternal deposition of cognate piRNAs in the eggs laid by the aged mother .

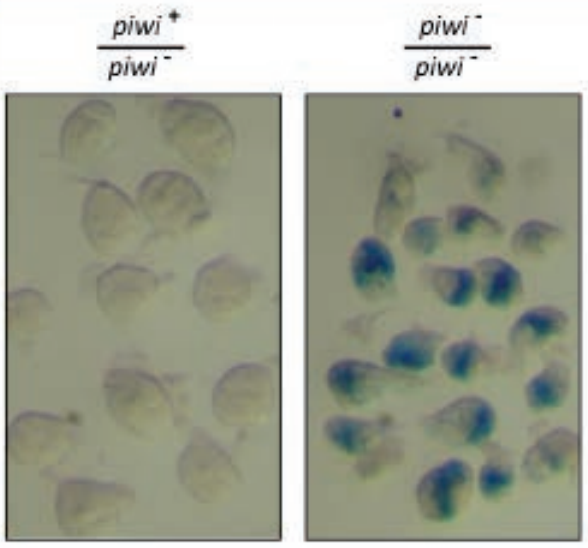


Figure 3 : Piwi-dependent repression of a *gypsy*-LacZ reporter in the somatic cells of the female gonad (X-Gal staining).

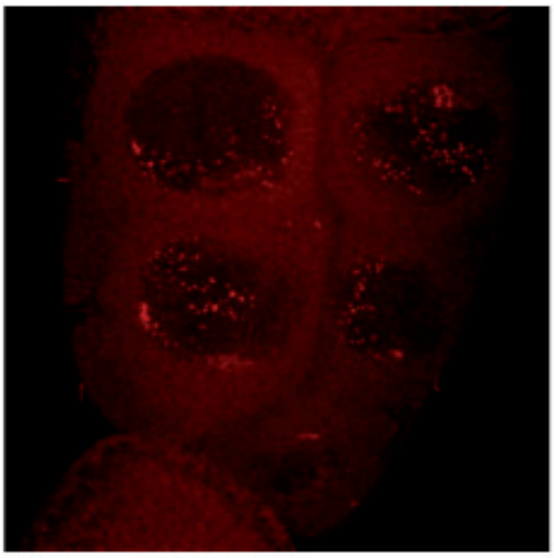
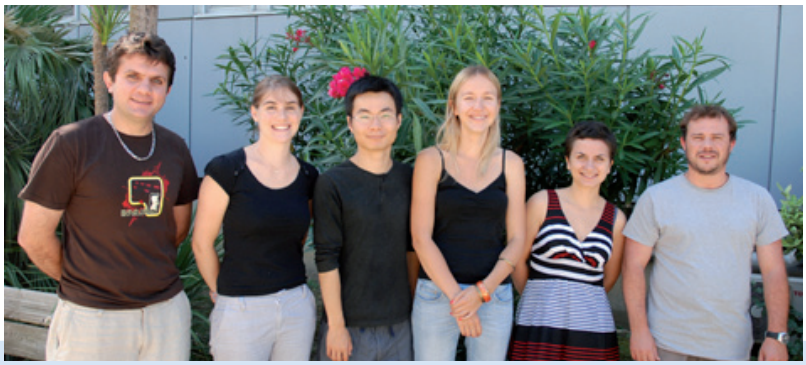


Figure 4 : Nuclear sequestration of I *element* transcripts detected by FISH



Biology of Repetitive Sequences

JEROME DEJARDIN
Jerome.Dejardin@igh.cnrs.fr

Jérôme Déjardin
Research Scientist INSERM

Satoru Ide,
Post-doctoral Fellow

Agnieszka Nowak,
Post-doctoral Fellow

Nehme Saksouk,
Post-doctoral Fellow

Alexandra Lawera,
PhD student

Paulina Marzec,
PhD student

Claudia Armenise,
Engineer

Elodie Rey-Sahinovic,
Engineer

Chromatin can be viewed as a highly complex mixture of proteins and nucleic acids that orchestrate DNA-based processes in the eukaryotic genome. Most of the mammalian genome is assembled into heterochromatin, a 'closed' structure imposed by several enzymatic activities. Such activities act on histones and the DNA itself to impinge on transcription, replication or repair.

Most of the heterochromatic fraction of the genome can be found at critical loci. These include telomeres, repetitive sequences around centromeres and a portion (about half) of the gene units encoding ribosomal RNAs. Defects in the regulation of these loci have therefore disastrous consequences on cell identity and can lead to developmental problems, cancer, premature aging or immune deficiencies. How precisely heterochromatic enzymes affect the composition of target loci has remained elusive and research in our laboratory primarily focuses on this question.

To understand how heterochromatin acts at the molecular level, we are looking at the effect of abrogating important heterochromatic activities, such as histone and/or DNA methyl-transferases, on the overall composition of key heterochromatic loci (telomeres, pericentromeres and rDNA).

In particular, we are interested in:

(i) How telomere compositional changes upon loss of heterochromatin function can explain the appearance of the ALT (Alternative Lengthening of Telomeres) pathway observed in certain cancers.

(ii) How the situation at ALT telomeres can be compared to the changes observed at human satellite 2 sequences upon loss of DNA methylation in ICF cells. Indeed, satellite 2 regions recombine aberrantly and localize to PML bodies in ICF cells, a 'behavior' also observed in the case of ALT telomeres.

(iii) How pericentric heterochromatin is regulated by such enzymatic activities during development, differentiation and why such regulation matters for genome stability.

(iv) Characterizing the new SMCHD1 chromatin protein which possibly links DNA methylation and non-coding RNAs.

(v) How is rDNA expression regulated?

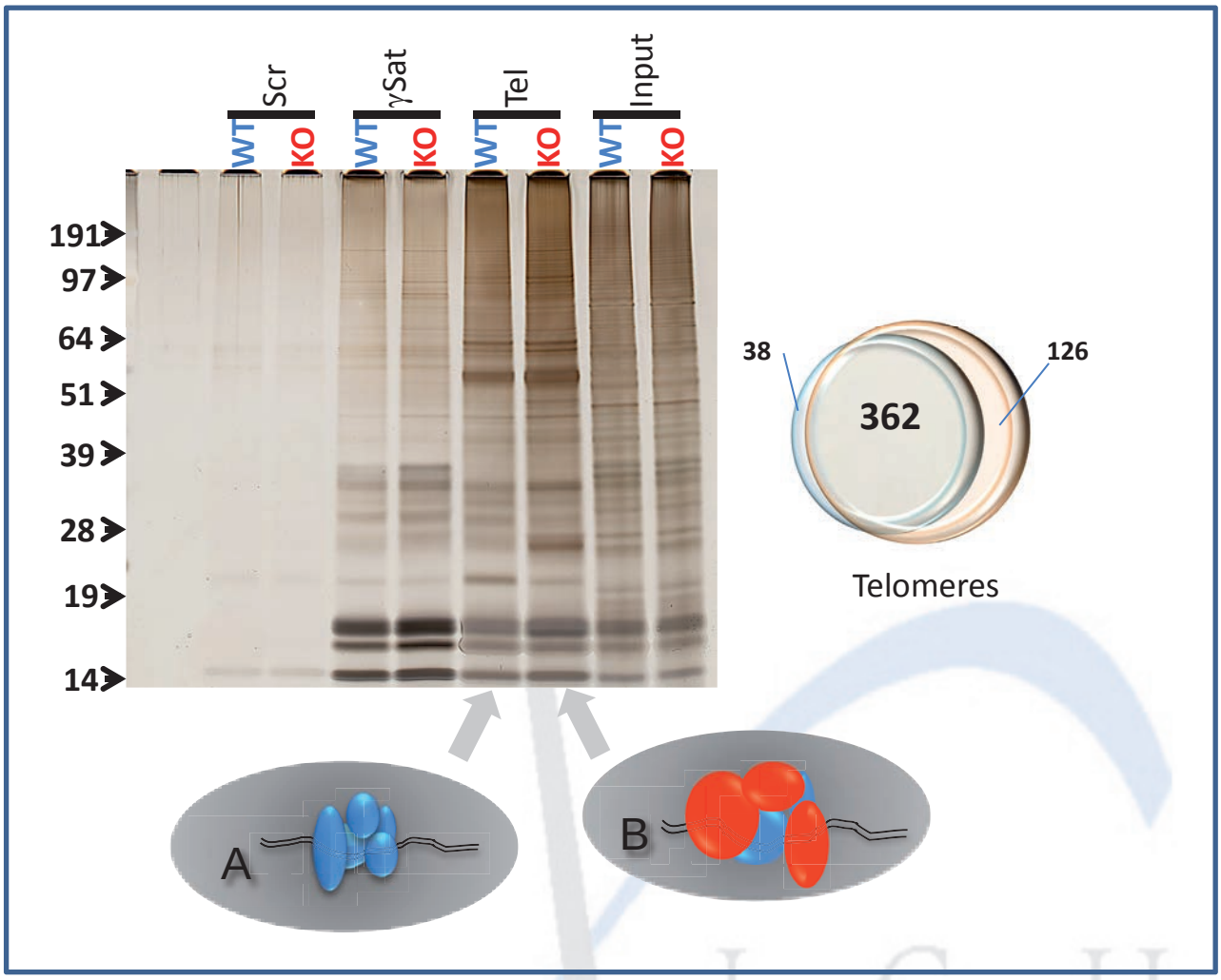
We have initiated these studies using a quantitative version of the PICh technology, qPICh, which couples SILAC with PICh. This approach allows the unbiased characterization of proteins bound to a specific locus in vivo (see figure). By correlating compositional and phenotypic changes at distinct loci, we hope our research will uncover important determinants of gene expression and genome stability. Importantly, because PICh has been adapted to quantitative approaches, we are now able to precisely monitor the dynamics of heterochromatin in vivo.

For more information, please, see:

Déjardin J and Kingston R (2009). Locus specific chromatin proteomics. Cell 136(1):175-86.

- Déjardin, J., Kingston, R.E. (2009) Purification of proteins associated with specific genomic Loci. **Cell**, *139*, 1, 175-186

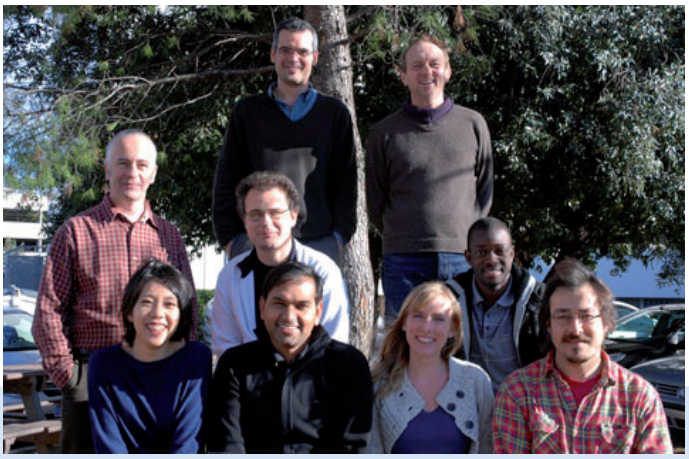
- Dejardin, J. (2012) How chromatin prevents genomic rearrangements: Locus colocalization induced by transcription factor binding. **Bioessays,** *34*, 2, 90-93. doi: 10.1002/bies.201100122



Purification of major satellites (γ Sat) and telomeres from mouses embryonic stem cells in WT or Suv39h1+h2 K.O. backgrounds. Composition of both loci is established in the two backgrounds, allowing to determine:

- the signature of constitutive heterochromatin in mammals, i.e. proteins found enriched in common at both loci (e.g. HP1 isoforms, etc ...)

- the role of Suv39h in the biology of these targets : specific proteins are lost or gained at telomeres or pericentric chromatin in the absence of this important heterochromatin enzyme.



Meiosis and Recombination

BERNARD DE MASSY
Bernard.de-Massy@igh.cnrs.fr

Bernard de Massy
Research Director CNRS

Frédéric Baudat,
Research Scientist CNRS

Jérôme Buard,
Research Scientist CNRS

Corinne Grey,
Research Scientist CNRS

Thomas Robert,
Research Scientist CNRS

Rajeev Kumar,
Post-doctoral Fellow

Boubou Diagouraga,
PhD student

Denis Dunoyer de Segonzac
PhD student

Yukiko Imai,
PhD student

In sexually reproducing species, meiosis allows the formation of haploid gametes from diploid cells. The halving of the DNA content results from a specialized cell cycle, where a single phase of DNA replication is followed by two divisions. In most species, the proper segregation of chromosomes at the first meiotic division requires connections between homologous chromosomes that result from reciprocal homologous recombination events or crossovers. Crossovers also generate new allele combinations and thus increase genetic diversity. The absence of crossover leads to segregation defects and sterility, and alteration of the meiotic recombination pathway can lead to genome rearrangements and aneuploidy.

Our group is investigating several aspects of the mechanism and regulation of meiotic recombination using the mouse as a model system. Meiotic recombination events are initiated by the formation of DNA double-strand breaks (DSBs), the repair of which leads to both crossovers and non-crossovers (gene conversion without crossover) (Fig. 1). Several hundreds DSBs, catalyzed by the SPO11 protein, are formed at the beginning of the first meiotic prophase in mouse meiotic cells. SPO11 is homologous to the catalytic subunit of the Topo VI family of type II DNA topoisomerases, and is conserved among eukaryotes.

We are interested in understanding how the frequency and distribution of these DSBs are regulated, and how DSB formation and repair are coordinated. We have recently discovered a major component that determines the sites where DSBs are formed in mammals: the Prdm9 gene. This gene encodes a protein with a methyl-transferase activity and a tandem array of C2H2 zinc fingers. PRDM9 recognizes specific DNA motifs in the genome and is thought to promote trimethylation of lysine 4 of Histone H3 at these sites (Fig. 2). How does this protein actually function in vivo and how its activity allows the recruitment of the recombination machinery remains to be determined. In addition, a remarkable property of PRDM9 is its rapid evolution and diversity. We are currently investigating both its molecular and evolutionary features.

DSB formation is expected to be a highly coordinated process given the potential threat to genome integrity, and studies in yeast have shown that, in addition to SPO11, several other proteins are necessary for DSB formation. We have recently identified two mouse proteins that are orthologs of the yeast Rec114 and Mei4 proteins and shown that Mei4 is required for DSB formation in mice (Fig. 3). We are currently investigating the activities and functions of these proteins using biochemical, molecular, cytological and genetic approaches.

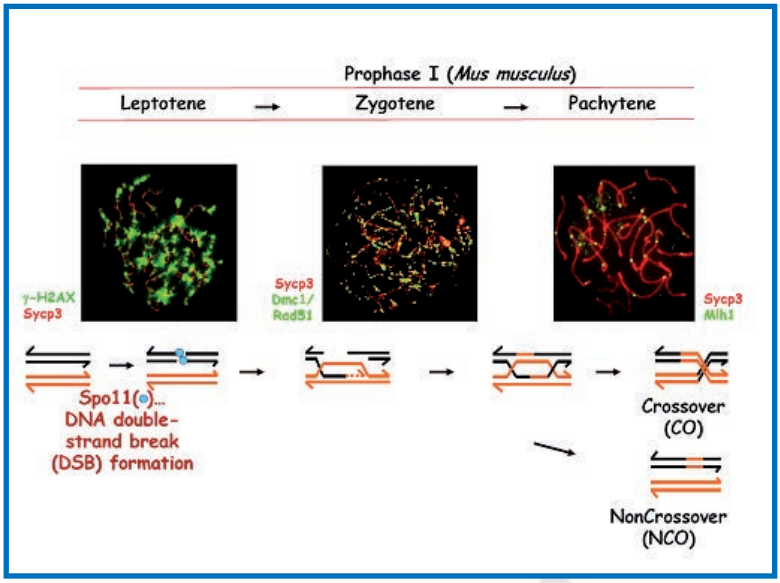
- Grey C, Barthès P, Chauveau-Le Friec G, Langa F, Baudat F and de Massy B. (2011) Mouse PRDM9 DNA-Binding Specificity Determines Sites of Histone H3 Lysine 4 Trimethylation for Initiation of Meiotic Recombination. **PLoS Biol.,** *9,* 10, e1001176.

- Lichten, M., de Massy, B. (2011) The impressionistic landscape of meiotic recombination. **Cell,** *147,* 267-270.

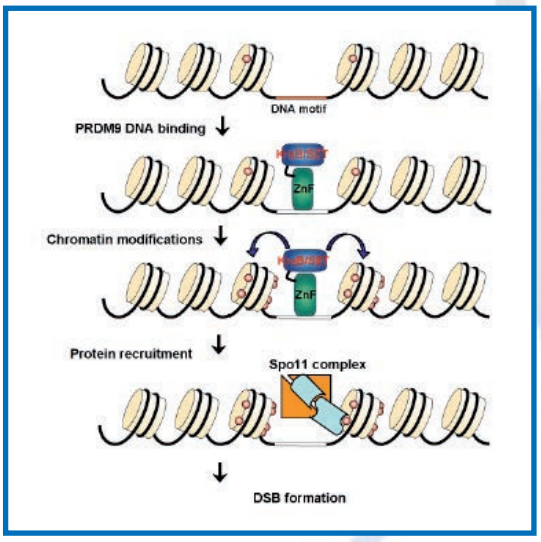
- Baudat, F. *, Buard, J. *, Grey, C. *, Fledel-Alon, A., Ober, C., Przeworski, M., Coop, G., and de Massy, B. (2010) PRDM9 is a Major Determinant of Meiotic Recombination Hotspots in humans and mice. **Science,** *327*, 836-840.

- Kumar, R., Bourbon, HM., and de Massy, B. (2010) Functional conservation of Mei4 for meiotic DNA double-strand break formation from yeasts to mice. **Genes Dev.,** *24,* 1266-1280.

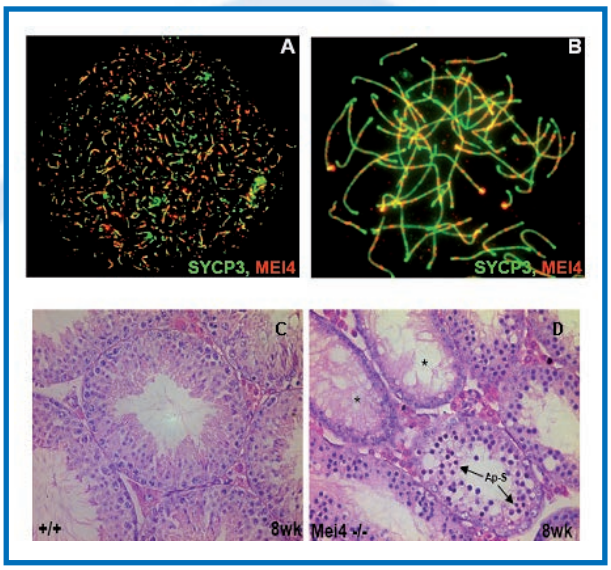
- Grey, C., Baudat, F. and de Massy, B. (2009) Genome wide regulation of meiotic recombination, **PLoS Biol.**, *7,* 2, e35.



- **Fig.1**. DNA and cytological events during meiotic prophase.
Meiotic recombination is initiated by DSBs, which are catalyzed by SPO11 and visualized by the appearance of γH2AX (the phosphorylated form of H2AX). DSB repair, with the strand exchange activity of RAD51 and DMC1, leads to crossover (CO) and non- crossover (NCO) events. CO sites are visualized by the presence of MLH1 on chromosome axes (SYCP3) at the pachytene stage.



- **Fig.2**. Model of PRDM9 specification of meiotic recombination initiation sites in mammals.
PRDM9 binds to a DNA motif through its zinc finger domain and induces H3K4Me3 on adjacent nucleosomes (beige cylinder and histone post-translational modifications as red balls). Additional chromatin modifications and/or remodeling may take place and other proteins may be recruited. SPO11 is then recruited, binds to DNA and promotes DSB formation.



- Fig.3. *Mei4 is* essential for male and female fertility.
MEI4 (red) localizes as discrete foci along unsynapsed chromosome axes (labeled with SYCP3, green) at leptotene (A) and zygotene-like stages (B) in Spo11-/- and wild type (not shown) spermatocytes. Spermatogenesis in wild type (C) and Mei4 -/- (D) mice: meiotic arrest and apotosis are observed in Mei4 -/- mice. *, empty tubules; Ap-S, Apoptotic spermatocytes.

GENOME DYNAMICS

JUNIOR LABORATORY

Mobile elements, Integrity and Plasticity of the Human Genome

NICOLAS GILBERT

Nicolas.Gilbert@igh.cnrs.fr

Nicolas Gilbert
Research Scientist INSERM

Oliver Siol,
Post-doctoral Fellow

Interspersed repeat sequences are present in almost all eukaryotic genomes. The LINE-1 (Long Interspersed Element-1, or L1) retrotransposon is the most abundant mobile element of the human genome.

Approximately 500,000 copies of L1 are present in the human genome and represent ~17% of human DNA. The vast majority of these copies are considered as molecular fossils. However, ~100 elements remain potentially active (RC-L1). Because of its activity, L1 can induce genetic diseases by insertional mutation in either coding or regulatory regions. Moreover, due to its high representation in the genome, L1 can generate deleterious genomic rearrangements induced by non-allelic homologous recombination.

Although L1 mobility can induce genetic instability, the mechanism of L1 retrotransposition is still poorly understood. Our group focuses on understanding the molecular mechanisms of L1 transposition and its impact on the genome. We are particularly interested in the L1 ribonucleoprotein complex formation, an intermediate of retrotransposition.

We also would like to understand the interplay between DNA repair mechanisms and the resolution of L1 insertion. We use two complementary approaches. First, we utilize a cell culture assay that allows us to control L1 retrotransposition. It will help us to decorticate the different steps of L1 retrotransposition. Second, we perform in silico analyses to support our molecular approach and to determine L1 implication in genomic variability and evolution of mammalian genomes.

.

- Doucet, A., Hulme A., Sahinovic, E., Kulpa, D., Moldovan, J., Kopera, H., Athanikar, J., Hasnaoui, M., Bucheton, A., Moran, J., Gilbert, N. (2010) Characterization of LINE-1 Ribonucleoprotein Particles, **PLoS Genetics** : *6*, 10, pii: e1001150.

- Hasnaoui, M., Doucet, a.J., Meziane, O., Gilbert, N. (2009) Ancient repeat sequence derived from U6 snRNA in primate genomes **GENE**, *448*, 2, 139-144.

- Garcia-Perez, JL., Doucet, AJ., Bucheton, A., Moran, JV., Gilbert, N. (2007) Distinct mechanisms for trans-mediated mobilization of cellular RNAs by the LINE-1 reverse transcriptase. **Genome Res.**, *17*, 5, 602-611.

- Gasior, SL., Preston, G., Hedges, DJ., Gilbert, N., Moran, JV., Deininger, PL. (2007) Characterization of pre-insertion loci of de novo L1 insertions. **Gene,** *390*, 1-2, 190-198.

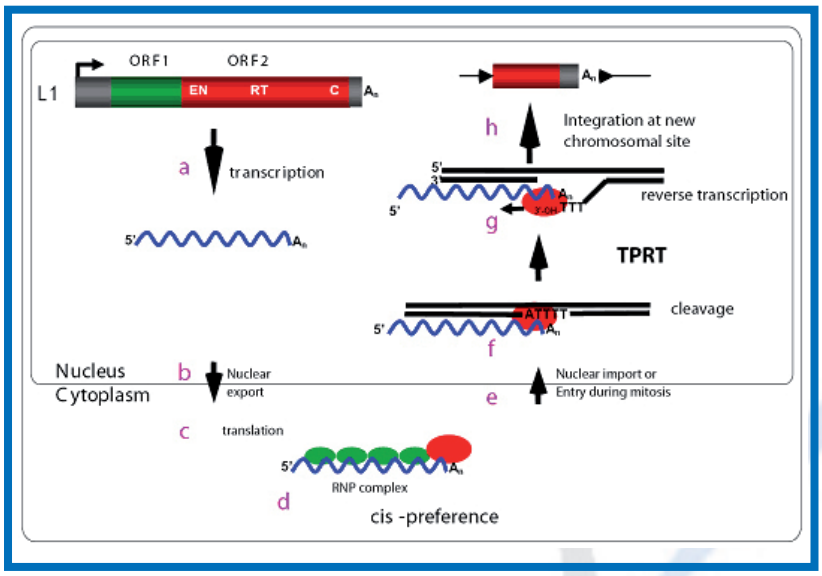


Figure 1: Structure of an L1 and model of retrotransposition.
ORF2 encodes enzymatic activities essential for L1 mobility, EN for endonuclease and RT for reverse transcriptase. ORF2 presents also a cysteine-rich domain important for L1 retrotransposition in its carboxyl end, but of unknown function (C). The essential steps (a to h) of the mechanism are shown. TPRT stands for Target-site Primed Reverse Transcription, i.e. the endonuclease domain of ORF2p cleaves the DNA target site (step f) and reverse transcription is initiated at this site by the RT domain (step g).

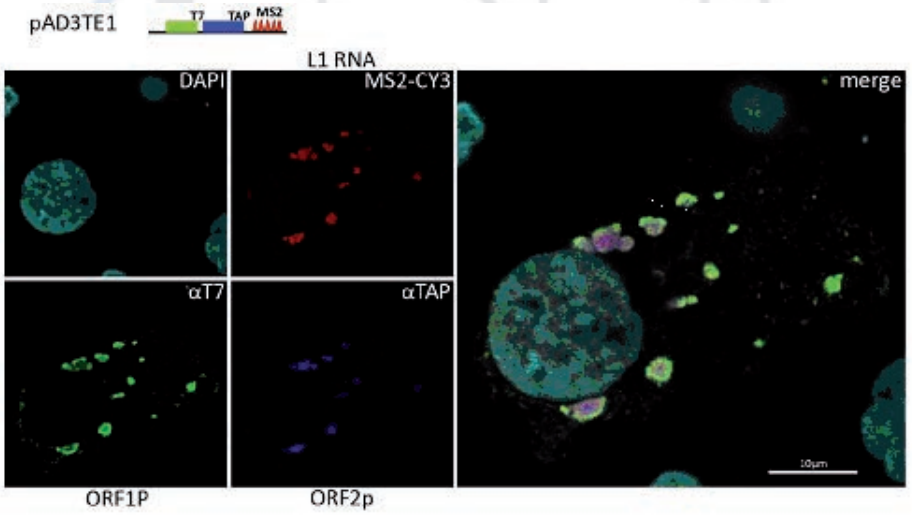
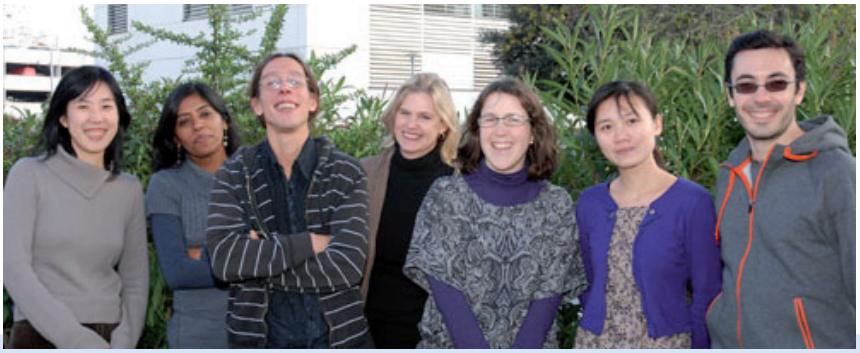


Figure 2: Cell localization of L1-encoded proteins and RNA.
Immunofluorescence/RNA FISH was carried out using pAD3TE1-transfected U-2 OS cells 48 hours post-transfection. T7-tagged ORF1p (green), TAP-tagged ORF2p (blue), L1 RNA (red) and DAPI (turquoise) staining are shown in the four micrographs on the left. A merged image is shown in the rightmost panel. The schematic of pAD3TE1, our engineered active L1 element, is shown above the micrographs.



GENOME DYNAMICS

JUNIOR LABORATORY

Gene Regulation

ROSEMARY KIERNAN
Rosemary.Kiernan@igh.cnrs.fr

Rosemary Kiernan
Research Scientist CNRS

Xavier Contreras,
Research Scientist INSERM

Poornima Basavarajaiah,
Post-doctoral Fellow

Daniel Latreille,
PhD student

Lisa Bluy,
Engineer

All organisms must regulate gene expression to achieve the silencing of certain genes and the activation of others during development and homeostasis.

Deregulation of gene expression frequently has dire consequences, and can lead to pathologies such as cancer. The regulation of gene expression occurs at different levels, all of which depend on a multitude of factors.

Chromatin is a primary regulator of gene expression. Physical compaction of the genome into chromatin controls accessibility to the transcription machinery.

Studies performed over recent years have revealed the enormous complexity involved in modifying chromatin to regulate gene expression.

Once the genome becomes accessible, the engagement of the transcription machinery is a highly orchestrated process involving the recruitment of hundreds of factors that co-operate to achieve gene expression.

Finally, transcription of a gene is linked to cellular processes required for the maturation and export of the mRNA in order to achieve gene expression.

The Gene Regulation Laboratory is interested in understanding the mechanisms that contribute to the silencing or activation of mammalian genes. We use the promoter of the human immunodeficiency virus (HIV-1) as a model to study gene regulation in mammalian cells.

Using this model, we have shown that the ubiquitin-proteasome system (UPS) strongly regulates HIV-1 transcription through recruitment of the 19S subunit to HIV-1 chromatin. We determined that a proteasome-associated protein, PAAF1, is a potent co-activator of transcription from the HIV-1 promoter. Ongoing studies are aimed at further characterizing the role of 19S and PAAF1 in transcription from HIV-1 and cellular promoters.

We have also recently shown that HIV-1 transcription is controlled by premature termination induced by the co-operative activities of microprocessor, Setx, Xrn2 and Rrp6. A subset of cellular genes and an endogenous retrovirus were also found to be regulated by this pathway.

- Wagschal, A., Rousset, E., Basavarajaiah, P., Contreras, X. , Harwig, A., Laurent-Chabalier, S. , Nakamura, M., Chen, X., Zhang, K., Meziane, O., Boyer, F., Parrinello, H., Berkhout, B., Terzian, C., Benkirane, M., Kiernan, R. (2012) Microprocessor, Setx, Xrn2 and Rrp6 Co-Operate to Induce Premature Termination of Transcription by RNAPII. 2012. **Cell,** *150,* 6, 1147-1157. doi: 10.1016/j.cell.2012.08.004. PMID: 22980978

- Nakamura, M., Basavarajaiah, P., Rousset, E., Beraud, C., Latreille, D., Henaoui, I.S., Lassot, I., Mari, B., Kiernan, R. (2012) Spt6 levels are modulated by PAAF1 and proteasome to regulate the HIV-1 LTR. **Retrovirology**, *9*, 13.

- Sobhian, B., Laguette, N., Yatim, A., Nakamura, M., Levy, Y., Kiernan, R., Benkirane, M. (2010) HIV-1 Tat assembles a multifunctional transcription elongation complex and stably associates with the 7SK snRNP. **Molecular Cell**, *38*, 439-451.

- Lassot, L., Latreille, D., Rousset, E., Sourisseau, M., Linares, L.K., Chable-Bessia, C., Coux, O., Benkirane, M., Kiernan, R. (2007) The Proteasome Regulates HIV-1 Transcription by Both Proteolytic and Non-Proteolytic Mechanisms. **Molecular Cell,** *25,* 369-383.

Replication & Genome Dynamics

MARCEL MECHALI - Marcel.Mechali@igh.cnrs.fr

Marcel Méchali
Research Director CNRS

Christelle Cayrou,
Research Scientist CNRS

James Hutchins,
Research Scientist CNRS

Magali Kitzmann,
Research Scientist CNRS

Malik Lutzmann,
Research Scientist CNRS

Stéphane Bocquet,
Research Assistant CNRS
Isabelle Peiffer,
Engineer CNRS

Post-doctoral Fellows :
Hanane Agherbi,
Philippe Coulombe,
Michail Fragkos,
Olivier Ganier,
Sabine Traver

PhD students :
Marta Rodriguez-Martinez,
Fabien Velilla,

Emmanuelle Beyne,
Engineer

Silke Conquet,
Secrétary

Paradoxically, a major cell function such as the faithful duplication of the genome remains poorly understood in metazoans. During embryonic development chromosomes should be duplicated while maintaining memory of the specific on-going transcription programs, because, in multicellular organisms, cell proliferation must not only deal with cell growth, but also with cell differentiation. In mammals, DNA replication starts at around 30 000-50 000 sites along chromosomes. These sites are called DNA replication origins. As they do not share any detectable consensus sequence, unveiling their common features remains an ambitious challenge. We wish to decipher the code of DNA replication origins in metazoans and unravel its involvement in cell identity. We also aim at dissecting the molecular mechanisms used to build a chromosomal DNA replication origin and wish to analyze how epigenetic mechanisms control the organization of chromatin domains for replication.

We have used different approaches to identify replication origins (Figure 1) including a genome-wide analysis of mouse pluripotent stem cells and differentiating cells as well as of Drosophila cells. To this aim, we purified nascent DNA strands synthesized at replication origins and identified their distribution along chromosomes by micro-array analysis and high-throughput sequencing. We could characterize several new features of replication origins and we found that they are conserved, including a new genetic element that we called Origin G-rich Repeated Element (OGRE) and can forms G-quadruplexes. We also analyzed the global organization of origins by DNA combing (Figure 1). Bioinformatic simulations using the data obtained suggest a flexible replicon model in which origins are organized in groups of adjacent potential origins that define a replicon. Moreover, a single origin is activated in each replicon and the chosen one can vary from cell to cell. Other studies mimicking the nuclear transfer experiments used for animal cloning allowed us to observe a dramatic reorganization of chromosomes and replication origins when differentiated nuclei are exposed to a mitotic embryonic context. We further showed that Xenopus egg extracts can efficiently reprogram differentiated mouse cells to become pluripotent cells, in a reaction that also requires mitotic events (Figure 2).

In the second axis of our project, we exploit in vitro systems derived from Xenopus eggs (Figure 3) as well as mammalian cells to identify and characterize new replication proteins. During the past decade, we have characterized several replication factors, including Cdt1, MCM8, MCM9 and MCM-BP. We found that Cdt1 and geminin form a complex that acts as an ON/OFF switch at replication origins. We also reported two new members of the MCM helicase family, MCM8 and MCM9, and found that they play distinct roles during DNA replication. We also discovered that MCM8 and MCM9 form a new complex involved in the control of recombination, DNA repair and animal fertility.

The dissociation of replication complexes at the end of S phase is crucial to avoid mitotic defects. We found that Topoisomerase II couples termination of DNA replication with the clearing of the replication complexes at the end of S phase. The ORC complex, in addition to its known role in the assembly of the replication initiation complex in G1, is also required for its disassembly at mitotic entry. Specifically, MCM-BP, a protein that interacts with the MCM2-7 helicase, contributes to MCM complex dissociation from DNA at the end of DNA synthesis. Further information is available at: http://www.igh.cnrs.fr/equip/mechali/

- Lutzmann, M., Grey, C., Traver, S., Ganier, O., Maya-Mendoza, A., Ranisavljevic, N., Bernex, F., Nishiyama, A., Montel, N., Gavois, E., Forichon, L., de Massy, B., and Méchali, M. (2012) MCM8- and MCM9-Deficient Mice Reveal Gametogenesis Defects and Genome Instability Due to Impaired Homologous Recombination. **Mol Cell**. *47,* 523-534
- Cayrou C., Coulombe P, Vigneron A., Stanojcic S., Ganier O., Peiffer I., Rivals E., Puy A., Laurent-Chabalier S., Desprat R., and Méchali M. (2011) Genome-scale analysis of metazoan replication origins reveals their organization in specific but flexible sites defined by conserved features. **Genome Res.**, *9*, 1438-1449.
- Ganier O., Bocquet, S., Peiffer, I., Brochard, V., Arnaud, P., Puy, A., Jouneau, A., Feil, R., Renard, J.P., and Méchali M. (2011) Synergic reprogramming of mammalian cells by combined exposure to mitotic Xenopus egg extracts and transcription factors. **Proc Natl Acad Sci U S A.,** *108,* 17331-17336.
- Méchali, M, (2010), DNA replication origins: many choices for appropriate answers. **Nature Rev Mol Cell Biol**, *11*, 728-738.
- Lutzmann, M., and Mechali, M. (2008) MCM9 binds Cdt1 and is required for the assembly of prereplication complexes. **Mol Cell**, *31*, 190-200.
- Lemaitre, JM., Danis, E., Y Vassetzky, Y., Pasero. P., and Méchali., M. (2005) Mitotic remodeling of the replicon and chromatin structure, **Cell,** *123*, 787-801.
- Maiorano, D., Cuvier, O., Danis, E., and Méchali, M. (2005) MCM8 is an MCM2-7 related protein that functions as a DNA helicase during replication elongation and not initiation. **Cell,** *120*, 315-28.

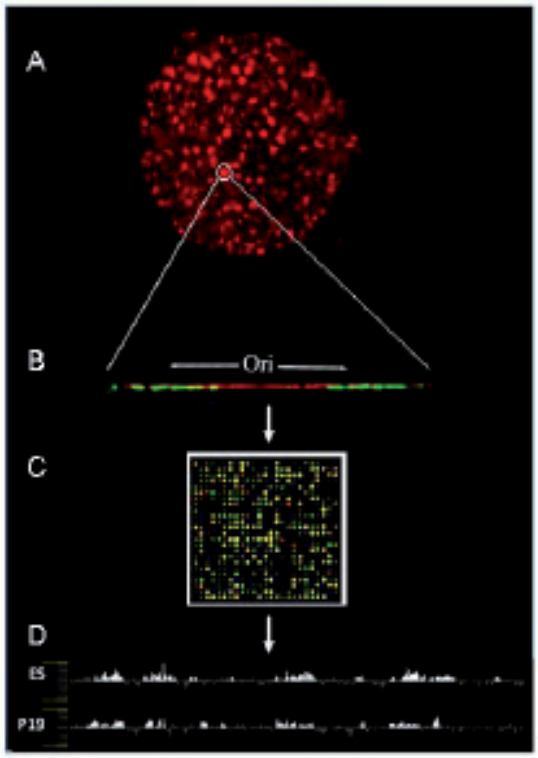


Fig.1. From replication foci to the replication origin code.
A) A nucleus, in which replication foci are labeled with BrdUTP, followed by fluorescence imaging; (B) when two consecutive pulses of labeling (red and then green) are performed and the DNA combed on silanized glass, replication origins can be visualized, with the red labeling the origin and the green highlighting the progressing replication forks; (C) nascent strand isolation and microarrray analysis allow genome-wide identification of replication origin sequences, the positions of which (D) in the chromosomes can then be visualized (shown for two cell lines: E5 and P19).

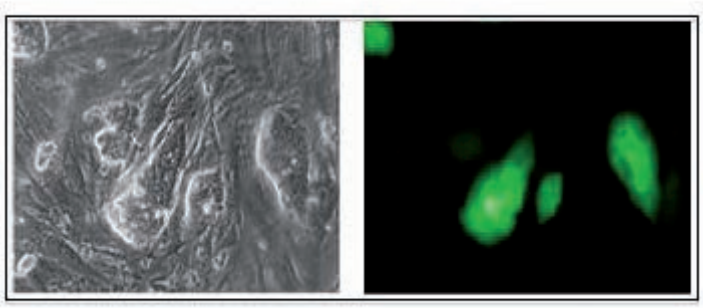


Fig.2. Mouse embryonic fibroblasts reprogrammed by Xenopus egg extracts express OCT4, a marker of pluripotency. Left, phase-contrast image. Right, fluorescence image showing cell clones expressing GFP under the control of the Oct4 promoter.

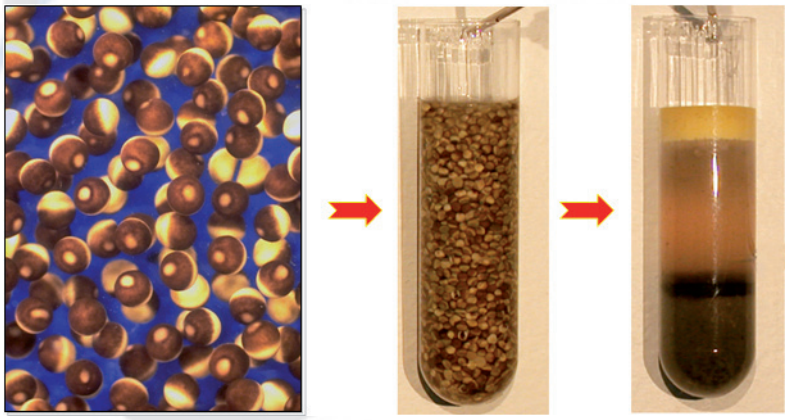
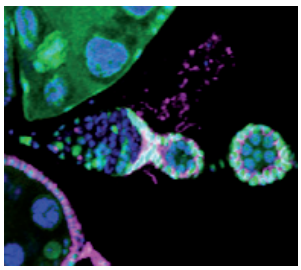


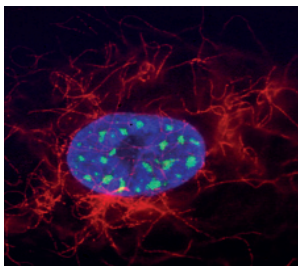
Fig.3. *From Xenopus eggs to DNA replication extracts*

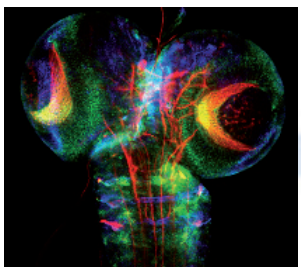
Genetics and Development Department

Director : Martine Simonelig

General Statement about the Department







Developmental Genetics aims at understanding how the genetic information is translated into the production of many different cell types that are coherently organized in a complete organism. Groups in the Department of **Genetics and Development** are interested in various aspects of developmental genetics, from the establishment of cell polarity in the egg, to muscle differentiation, or the formation of an extremely complex structure such as the adult brain. Research topics in the Department include the identification of the molecular and signaling pathways that control the cell cycle as well as those involved in stem cell biology, in the development of the gonads and of the germ line and in muscle differentiation. Another topic concerns the ligand/receptor interactions in axonal guidance during the development and function of the central nervous system. Several groups are interested in deciphering specific molecular regulations that control developmental processes, such as RNA silencing by small non-coding RNAs (microRNAs and piRNAs) and post-translational regulations.

These fundamental biological questions are addressed using model organisms (*Drosophila* and the mouse) and a variety of approaches. Groups in the Department have strong expertise in classical and cutting-edge genetic techniques, biochemistry, molecular and cell biology, advanced light microscopy and bioinformatics.

All the groups in the Department of **Genetics and Development** work towards understanding the molecular mechanisms of human diseases. Tumorigenesis is an important question addressed in the Department, through the utilization of cell and mouse models. Several groups have also developed *Drosophila* models of human diseases (e.g. muscular dystrophy, motoneural dysfunction, sterility), in which sophisticated genetic approaches can be applied to gain insights into the molecular pathways involved in these diseases. The analysis of multipotent stem cells showing regenerative potential is another important topic of research in the Department.

The Department of **Genetics and Development** has strong transversal interactions with other groups at the IGH and groups located in the close-by Institute of Functional Genomics that are also interested in some aspects of embryonic and germ line development, neurogenesis or muscle differentiation. The Department organizes each year the IGH Seminar Series on Genetics and Development.

Development and Pathology of the Gonad

BRIGITTE BOIZET
Brigitte.Boizet@igh.cnrs.fr

Brigitte Boizet
Research Director CNRS

Françoise Paris,
Lecturer, Hospital Practitioner,
University Montpellier 1

Pascal Philibert,
Hospital Assistant,
University Montpellier 1

Francis Poulat,
Research Scientist INSERM

Charles Sultan,
Professor, Hospital Practitioner,
University Montpellier 1

Massilva Rahmoun,
Post-doctoral Fellow

Safdar Ujjan,
PhD student

The correct development of the reproductive organs, testis and ovary, requires the highly coordinated and regulated determination/differentiation of the embryonic gonads, and the maturation of the reproductive organs. Any abnormality in these processes during early embryo development, due to intrinsic genetic factors but also due to environmental factors, will result in diseases. In the male, testicular dysgenesis syndromes (TDS) lead to sexual differentiation disorders (gonad dysgenesis, including sex-reversal), undescended testes (cryptorchidism, hypospadias), reduced sperm quantity and quality, semen abnormalities (male infertility) and testicular cancer. In the female, the gynecological implications of ovarian dysfunctions include cycle disturbances, anovulation, cyst formation and untreatable infertility and can favor ovarian cancer development.

In mammals, testicular differentiation is controlled by the gene Sry located on the Y-chromosome. This gene, which encodes a HMG (High Mobility Group) domain-containing transcription factor of the SOX family, induces a variety of morphogenetic events, including cell proliferation, cell migration and Sertoli cell determination. At the molecular level, SRY directly activates Sox9 expression; SOX9 acts as the effector gene for Sertoli cell differentiation, which then induces the differentiation of the other gonadal cell lineages and subsequently testis cord formation. Our current research focuses on the cellular and molecular mechanisms involved in the formation of the embryonic gonad, particularly on the implication of the prostaglandin D2 (PGD2) signaling pathway in this process and in the regulation of the expression and function of SOX9.

In the mouse, we have demonstrated the regulation of the L-Pgds (Lipocalin-prostaglandin D synthase gene by SOX9; L-Pgds gene encoding a PGD2-producing enzyme, belong to a regulatory loop that is independent of the FGF9/SOX9 loop and both contribute to maintaining Sox9 expression and induce testis formation. Recently, we observed that the H-Pgds (hematopoietic-prostaglandin D synthase) enzyme, the second source of PGD2 is expressed in the fetal gonads in both somatic and germ cell lineages and is involved in the onset of SOX9 nuclear translocation. Analysis of E17.5 male gonads fully depleted of PGD2 (i.e., male fetuses null for both L- and H-Pgds : double L/H-Pgds KO) reveals an abnormal proliferation of male germ cells at this late embryonic stage and an expression of pluripotent germ cell markers (Oct4, Sox2…), exhibiting a carcinoma in situ like phenotype, a precursor of tumour germ cells of the testis in adult. These data suggest that besides being essential for the early somatic differentiation, the PGD2 signalling pathway is a key regulator of the male germ cells differentiation; the primordial germ cells being the precursors of the gametes, spermatozoa and oocytes that will be produced in the adult life through the gametogenesis process.
We also recently identified that both heterozygous and homozygous mice deficient for L-Pgds presented unilateral cryptorchidism affecting the second phase of testicular descent,. Moreover, we also showed that PGD2, through H-PGDS expression, is a positive effector of the activity of the FSH and LH hormones in the normal adult ovary.
Finally, to understand the early events induced by SOX9 and leading to differentiation of Sertoli cells and formation of the embryonic testis at 13.5 dpc (days post coitum), SOX9 chromatin immunoprecipitation coupled to high-throughput sequencing (ChIP-seq) was performed to identify genes regulated, directly or undirectly, by this transcription factor. We established a large set of genes controlled by SOX9 and genes coding for microRNAs (miRs), as potential targets of SOX9 during testicular differentiation. These new factors might be involved in sex reversal and infertility disorders in human.

- P. Philibert, B. Boizet-Bonhoure, A. Bashamboo, F. Paris, K. Aritake, Y. Urade, J. Leger, C. Sultan and F. Poulat. (2012). Unilateral cryptorchidism in mice mutant for Ptgds. **Human Mutation,** *in press*. doi: 10.1002/humu.22231. PMID: 23076868

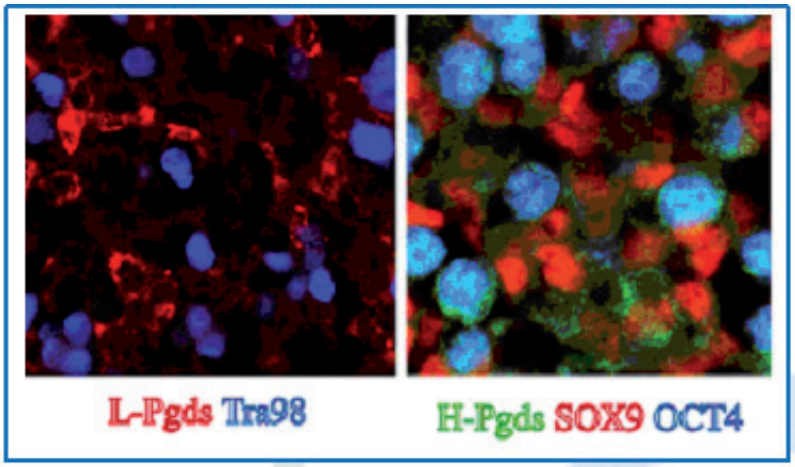
- B. Moniot, A. Farhat, K. Aritake, F. Declosmenil, S. Nef, N. Eguchi, Y. Urade, F. Poulat and B. Boizet-Bonhoure. (2011). Hematopoietic Prostaglandin D synthase (H-Pgds) participates to the initial nuclear translocation of the SOX9 protein during mouse testicular determination. **Dev. Dyn**. *240*, 2335-2343.

- A. Farhat, P. Philibert, C. Sultan, F. Poulat and B. Boizet-Bonhoure. (2011). Hematopoietic Prostaglandin D2 synthase is required for normal differentiation of granulosa cells and steroidogenesis in adult ovary. **J. Ovarian Res.** *4,* 3-8.

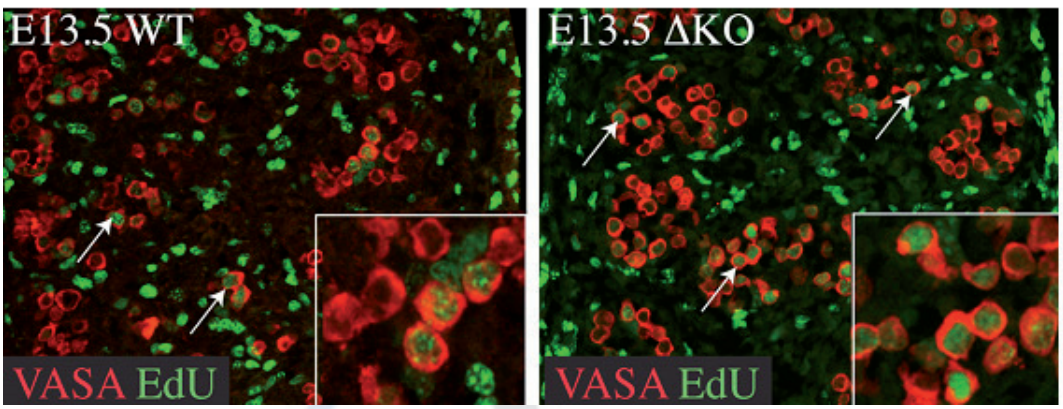
- Sim H, Argentaro A, Czech DP, Bagheri-Fam S, Sinclair AH, Koopman P, Boizet-Bonhoure B, Poulat F, Harley VR. (2011). Inhibition of SRY-Calmodulin Complex Formation Induces Ectopic Expression of Ovarian Cell Markers in Developing XY Gonads. **Endocrinology**,*152*, 2883-2893.

- Malki S, Boizet-Bonhoure B, Poulat F. (2010). Shuttling of SOX proteins. **Int J Biochem Cell Biol.,** *42*, 411-416 Review.

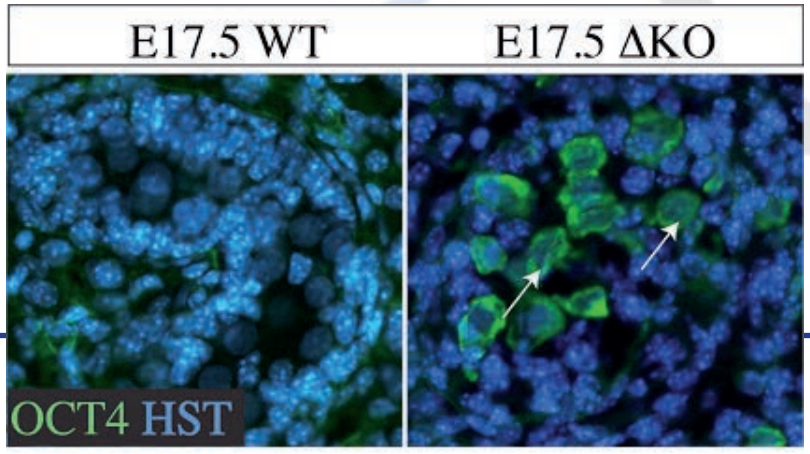
- Moniot B*, Declosmenil F*, Barrionuevo F, Scherer G, Aritake K, Malki S, Cohen-Solal A, Klattig J, Englert C, Kim Y, Capel B, Eguchi N, Urade Y, Boizet-Bonhoure B§ and Poulat F§. (2009). PGD2 pathway, independently of Fgf9, amplifies the Sox9 activity in Sertoli cells during male sexual differentiation. **Development,** *136,* 1813-1821. (* et §: co-auteurs).



Expression of L-PGDS (red) and H-PGDS (green) in embryonic male gonads (E11.5) by immunofluorescence. SOX9, marker of Sertoli cells (red), and TRA98 and OCT4, germ cell markers (blue).



PGD2 controls germ cells proliferation in the E13.5 male gonad: in PGD2-depleted gonads (Δ KO), proliferation (EdU positive cells in green) of the germ line (VASA positive cells in red) increases by two fold compared to that in WT gonads.



PGD2 controls the expression of pluripotency markers such as OCT4 (in green): in PGD2-depleted gonads (ΔKO), germ cells still expressed OCT4 whereas wild type gonads (WT) do not expressed it. (HST : Hoescht dye labelling nuclei)

Neurogenetics and Memory

JEAN-MAURICE DURA
Jean-Maurice.Dura@igh.cnrs.fr

Jean-Maurice Dura
Research Director CNRS

Ana Boulanger,
Research Engineer CNRS

Elodie Reynaud,
PhD student

Developmental molecular genetics of Drosophila adult brain.

Developmental molecular genetics of Drosophila adult brain is a young science that is gaining momentum. We can reasonably foresee that the gene cascades at work during Drosophila brain development are conserved in mammals as well. In Drosophila, novel techniques are now available and allow working efficiently on this topic. Mushroom bodies (MB) may be considered as the analog of the mammalian hippocampus and are an excellent model for studying brain development. Each of the 4 MB neuroblasts generates, in a sequential fashion, three distinct classes of neurons. First the γ then the α'β' and finally the αβ neurons appear during development. MBs are essential for several forms of learning and memory. We have introduced in the laboratory a memory paradigm based on male courtship behavior (in collaboration with M.L. Parmentier and Y. Grau, IGF). Therefore we are able to correlate the developing brain structure with its function.

I) Genetic control of neuronal remodeling during brain and neuro-muscular junction (NMJ) development. Neuronal remodeling occurs widely during the construction of both invertebrate and vertebrate nervous systems. Alteration of neuronal remodeling is also a key aspect of neurodegenerative diseases, such Alzheimer's. MB γ neurons arise during early larval stage and undergo pruning at metamorphosis. We have recently shown that ectopic expression of the HR39 nuclear hormone receptor blocks γ axon pruning and impairs short-term, but not long term, memory. Pruning is also present at NMJ during metamorphosis. This mechanism is still poorly understood and hardly studied. We have described in detail this pruning and showed that some of the molecular actors are conserved between these two pruning systems.

II) Genetic control of axonal growth and guidance during brain development. One MB neuron typically sends an axon, which at a precise location of its trajectory splits in two processes (branched axon). Moreover, these branched axons consist of an orthogonal system. Therefore, a very precise axonal guidance mechanism is at work. We have already identified three relevant genes for axonal guidance: the linotte/derailed receptor type tyrosine kinase (orthologue of the oncogene H-Ryk), its ligand Wnt5 (orthologue of the oncogene/tumor suppressor Wnt5a) and Drl-2 one of the two drl paralogue. The axons integrate molecular information provided by the ligand and the two receptors (intrinsic and extrinsic) for their guidance.

- Boulanger A., Farge M., Ramanoudjame C., Wharton K. and Dura J.-M. (2012) Drosophila motor neuron retraction during metamorphosis is mediated by inputs from TGF-β/BMP signaling and orphan nuclear receptors. **PLoS One,** *7*, 7, e40255. doi:10.1371/journal.pone.0040255.

- Redt-Clouet C., Trannoy S., Boulanger A., Tokmatcheva E., Savvateeva-Popova, Parmentier M.-L., Preat T. and Dura J.-M. (2012) Mushroom body neuronal remodeling is necessary for short-term but not for long-term courtship memory in Drosophila. **European Journal of Neuroscience,** *35*, 1684-1691.

- Trannoy S., Redt-Clouet C., **Dura* J.-M** and **Preat* T.** (2011) Parallel processing of appetitive short-and long-term memories in Drosophila. **Current Biology,** *21*, 1647-1653 . *** Co-corresponding authors**.

- Boulanger A., Clouet-Redt C., Farge M., Flandre A., Guignard T., Fernando C., Juge F. and Dura J.M. (2011) ftz-f1 and Hr39 opposing roles on EcR expression during Drosophila mushroom body neuron remodeling. **Nature Neuroscience**, *14*, 1 , 37-44

- Fradkin L.G., Dura J.M. and Noordermeer J.N. (2010) Wnt/Ryk interactions during neurogenesis, axon guidance, synaptogenesis and axon regeneration. **Trends in Neurosciences,** *33*, 2, 84-92.

- Grillenzoni N., Flandre A., Lasbleiz C. and Dura J.M. (2007) Respective roles of the DRL receptor and its ligand WNT5 in Drosophila mushroom body development. **Development ,** *134*, 3089-3097.

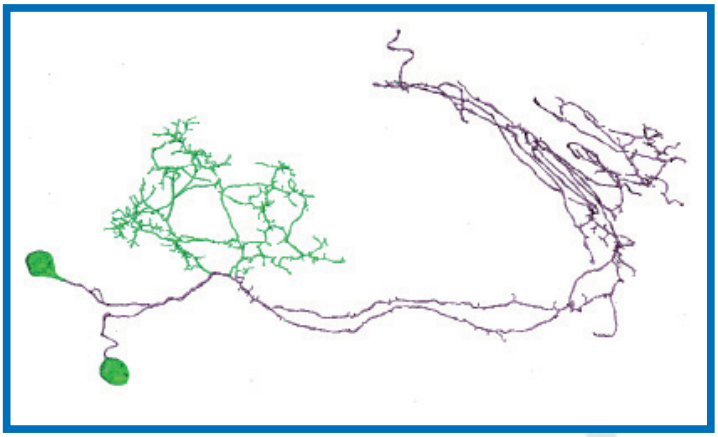


Fig 1 : 2 γ neuron clone in a larval brain (in green the cell bodies and the dendrites).

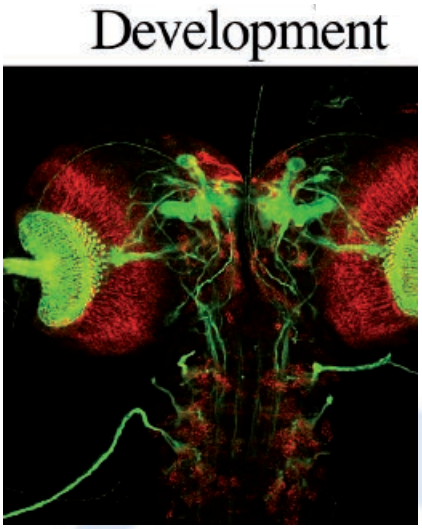


Fig 2 : Larval brain with DRL receptor in red and FASII in green (after the cover of September 2007 issue of Development)

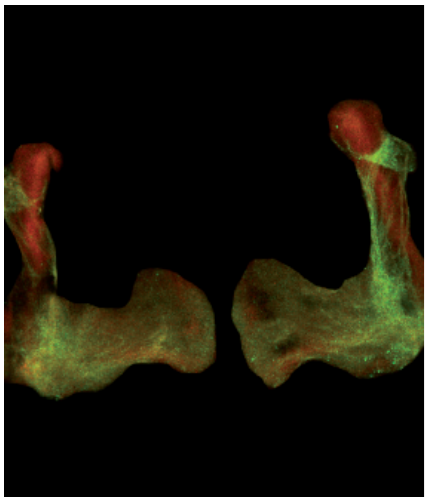


Fig 3 : Adult MB with un-remodelled γ axons (green) and normal αβ axons (red).

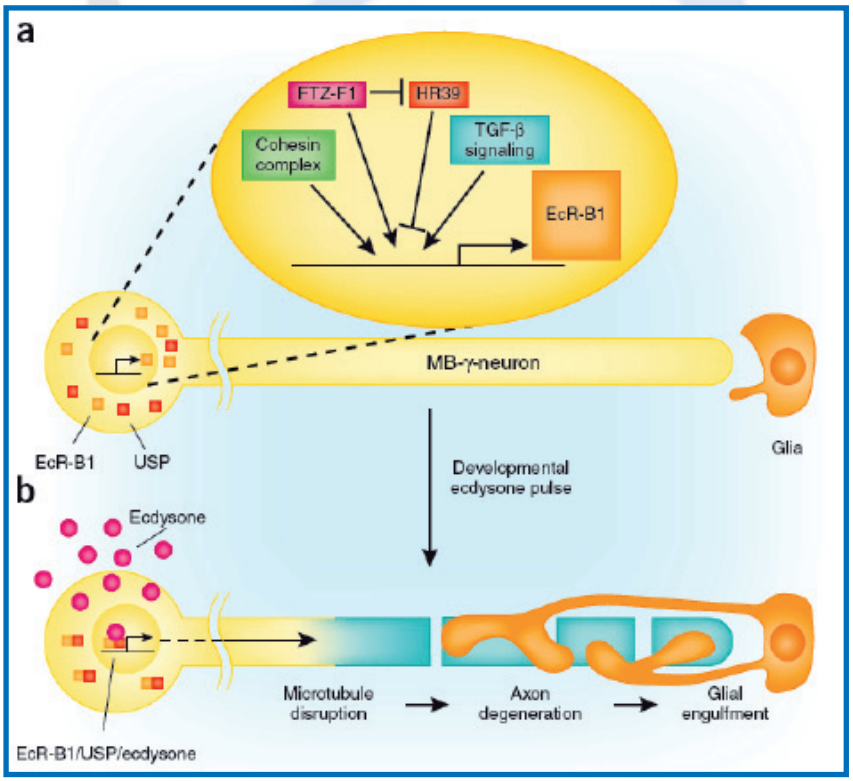
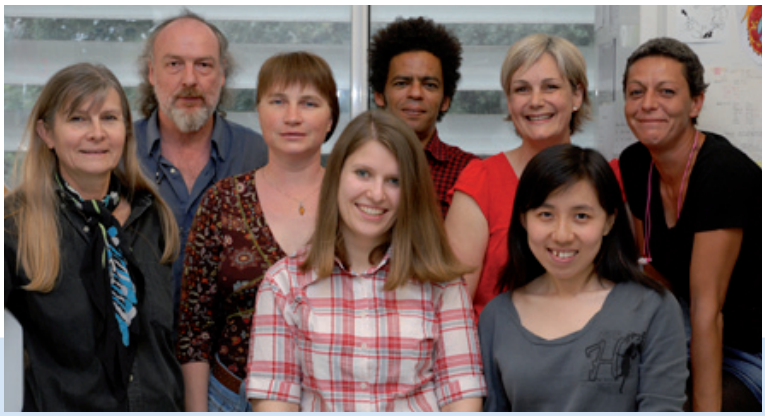
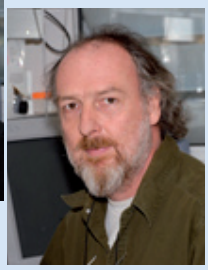


Fig 4 : Model for EcR-B1 activation in MB neuron remodeling. After a News and Views by Awasaki and Lee introducing Boulanger *et al.*, 2011.



Cell cycle, differentiation and metabolism



ANNE FERNANDEZ & NED LAMB

Anne-Fernandez@igh.cnrs.fr - Ned.Lamb@igh.cnrs.fr

Anne Fernandez
Ned Lamb
Research Directors CNRS

El-Habib Hani,
Research Scientist CNRS

Lisa Héron-Milhavet,
Research Scientist CNRS

Céline Franckhauser,
Engineer CNRS

Mattia Lorenzo Di Francesco,
Post-doctoral Fellow

Daria Mamaeva,
Post-doctoral Fellow

Romain Davaze,
PhD student

Violeta Mitutsova,
PhD student

Wendy Yeo,
PhD student

Our research themes are focused on the study of mammalian cell differentiation and cell transformation in cancer using primary and established human and rodent cultured cells and adult stem cell isolated from skeletal muscle. Using cell biological and biochemical approaches to the study of signalling pathways, we investigate their impact on transcriptional and post-translational regulation of the cell division cycle and the transition from cell proliferation into terminal differentiation, in particular muscle cell differentiation.

We have identified key points in the crosstalk of major multi-tasking enzymes, such as cAMP-dependent Protein Kinase (PKA), Akt/PKB family kinases and phosphatase 2A (PP2A) in the modulation Cyclin-Dependent Kinases (CDK) during cell cycle progression. This crosstalk is the target of specific checkpoints which are bypassed in transformed cells and we are specifically investigating these bypass mechanisms in normal and tumor-derived human cells.

In the process of myogenic differentiation we are examining the role of the insulin/IGF pathway and the downstream activator PKB/Akt protein kinase family. Our studies are focusing on differentiating the interacting partners, such as p21 and CTMP, and the specific action of Akt1 and Akt2 isoforms in proliferating normal or transformed cells and in determining the specific nuclear events involved in the myogenic transition to post-mitotic muscle cells.

Another recent connection in our study of signaling pathways in cell function, involves analyzing the role of PKA regulatory and anchoring proteins in the intracellular localization and trafficking of insulin secretory granules in beta islet cells.

Our second major research theme involves the isolation and characterization of a new population of skeletal muscle-derived stem cells, skMDSC, capable of multipotent differentiation particularly into spontaneously beating cardiac muscle cells and neuronal lineages. In collaboration with IGF teams, we are analyzing the in vivo multi-lineage differentiation and physiological repair potential of skMDSC using mouse models of targeted diseases and lineage-specific tracking of skMDSC differentiation. In particular, we have undertaken with the team of Dr. Mangoni, a detailed characterization of the in vitro differentiated beating myocytes to demonstrate that these cells are fully functional pacemaker cells such as those found in the sino-atrial node of the heart. Transplantation experiments in mutant mice show that multipotent skMDSC possess a very promising repair and regeneration potential without any development of teratoma nor tumors and thus represent a valuable source of autologous stem cells for cell therapy approaches in the treatment of numerous degenerative and traumatic diseases.

- Heron-Milhavet L, Khouya N, Fernandez A, Lamb NJ. (2011), Akt1 and Akt2: differentiating the aktion. **Histol Histopathol.** *26*, 651-62. Review.

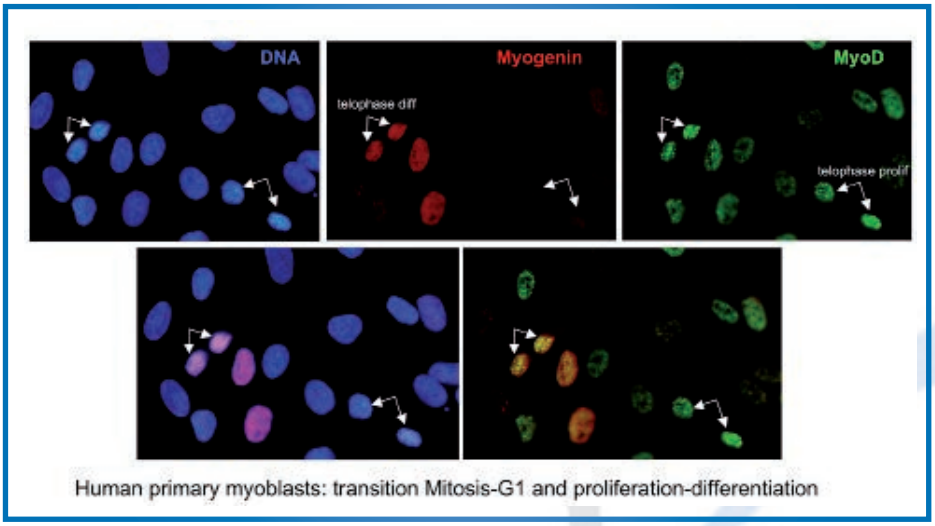
- Heron-Milhavet, L., Mamaeva , D., LeRoith, D., Lamb, N., and Fernandez, A. (2010) Impaired muscle regeneration and myoblast differentiation in mice with a muscle-specific KO of IGF-1R. **J. Cell. Physiol.**, *225* , 1, 1-6.

- Franckhauser, C., Mamaeva, D., Heron-Milhavet, L., Fernandez, A., Lamb, NJ. (2010). Distinct pools of cdc25C are phosphorylated on specific TP sites and differentially localized in human mitotic cells. **PLoS One**. , *5,* 7, e11798.

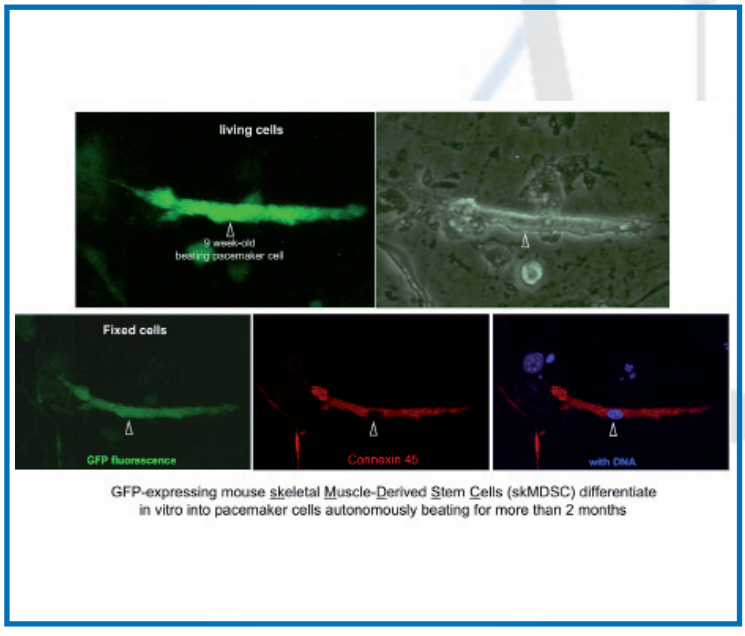
- Arsic, N., Mamaeva, D., Lamb, NJ., Fernandez, A. (2008) Muscle-derived stem cells isolated as non-adherent population give rise to cardiac, skeletal muscle and neural lineages. **Exp. Cell Res.** , *314*, 6, 1266-1280

- L'honore, A., Rana ,V., Arsic, N., Franckhauser, C., Lamb, NJ., and Fernandez, A. (2007) Identification of a New Hybrid SRF and MEF2-binding Element in MyoD Enhancer Required for MyoD Expression during Myogenesis. **Mol. Biol. Cell.** *18*, 6, 1992-2001.

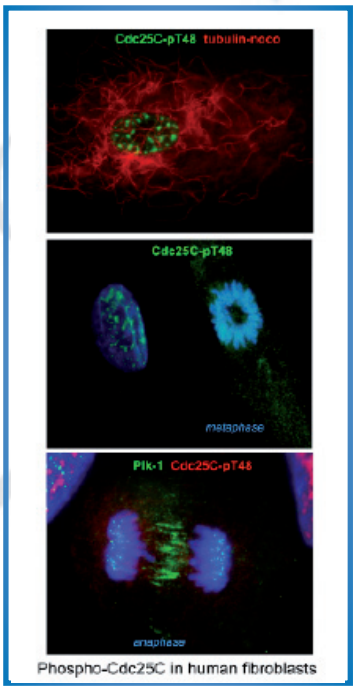
- Heron-Milhavet, L., Franckhauser, C., Rana, V., Berthenet, C., Fisher, D., Hemmings, BA., Fernandez, A. and Lamb, NJC. (2006). Only Akt1 is required for proliferation while Akt2 promotes cell cycle exit through p21 binding. **Mol. Cell. Biol.**, *26,* 22, 8267-8280.



Human primary myoblasts: transition Mitosis-G1 and proliferation-differentiation



GFP-expressing mouse skeletal Muscle-Derived Stem Cells (skMDSC) differentiate in vitro into pacemaker cells autonomously beating for more than 2 months



Phospho-Cdc25C in human fibroblasts


Tubulin Code

KRZYSZTOF ROGOWSKI

Krzysztof.Rogowski@igh.cnrs.fr

Krzysztof Rogowski
Research Scientist CNRS

Juliette Van Dijk,
Research Scientist CNRS

Olivier Blard,
Post-doctoral Fellow

Guillaume Bompard,
Post-doctoral Fellow

Microtubules (MTs) are essential cytoskeletal elements composed of alpha- and beta-Tubulin heterodimers. They are involved in a range of cellular functions including cell division, maintenance of cell shape, intracellular transport as well as cell motility. The mechanisms that allow MTs to perform such a diverse range of functions are poorly understood, but it is clear that each specific MT function requires the recruitment of a particular set of MT-associated proteins (MAPs). Strikingly, many MAPs interact with the C-terminal tails of Tubulins, which are known to protrude from the MT surface and to undergo several unusual post-translational modifications (Westermann and Weber, 2003). Such Tubulin C-terminal modifications include the removal of the very C-terminal tyrosine from alpha-Tubulin and two so-called poly-modifications, namely poly-glutamylation and poly-glycylation, which consist in the addition of side chains of either glutamate or glycine residues to the C-terminal tails of both alpha- and beta-Tubulin. The combination of the different Tubulin C-terminal modifications together with the fact that the side chains generated by the poly-modifications vary in length provides a high potential for encoding patterns on the MT surface that might recruit specific MAPs and allow the functional adaptation of MTs. In addition, since all these modifications have been shown to be reversible, they permit rapid changes in the MT properties.

Given the range of signals that the Tubulin C-terminal modifications can generate, it is not surprising that particularly high levels of these post-translational marks are present in complex and sophisticated MT-based structures, such as the ones found in neurons or in cilia and flagella. However, until recently, very little was known about their functions, mainly due to the lack of knowledge about the modifying and demodifying enzymes involved. For a long time, the only known enzyme involved in Tubulin modifications was Tubulin Tyrosine Ligase (TTL) (Ersfeld et al., 1993), which re-attaches the C-terminal tyrosine to detyrosinated alpha-Tubulin. During the last few years, we have identified the enzymes involved in Tubulin poly-glutamylation and poly-glycylation and shown that they belong to the TTL-like (TTLL) protein family (Janke et al., 2005; Rogowski et al., 2009; van Dijk et al., 2007). Recently, we have also discovered several deglutamylases, the enzymes catalyzing the removal of poly-glutamylation, as members of the cytosolic carboxypeptidase (CCP) family (Rogowski et al., 2010).

The main goal of our research is to understand how the three Tubulin C-terminal tail modifications (detyrosination, poly-glutamylation and poly-glycylation) regulate MT functions. The only cell types where all these modifications coexist are ciliated and flagellated cells. Cilia and flagella are involved in a number of cellular processes that range from motility, development, fluid movement to signal transduction. Recently, cilia moved into the spotlight due to the growing number of diseases associated with their defects. Defective cilia lead to a wide variety of disorders, including hydrocephalus, primary ciliary diskinesia, polycystic kidney disease, situs inversus, retinal degeneration, obesity, hypergenitalism and polydactyly as well as cancer (Sharma et al., 2008).

- Rogowski, K., Van Dijk, J., Magiera, M.M., Bosc, C., Deloulme, J.C., Bosson, A., Peris, L., Gold, N., Lacroix, B., Bosch-Grau, M., et al. (2010). A family of protein deglutamylating enzymes associated with neurodegeneration. **Cell,** *143*, 564-578.

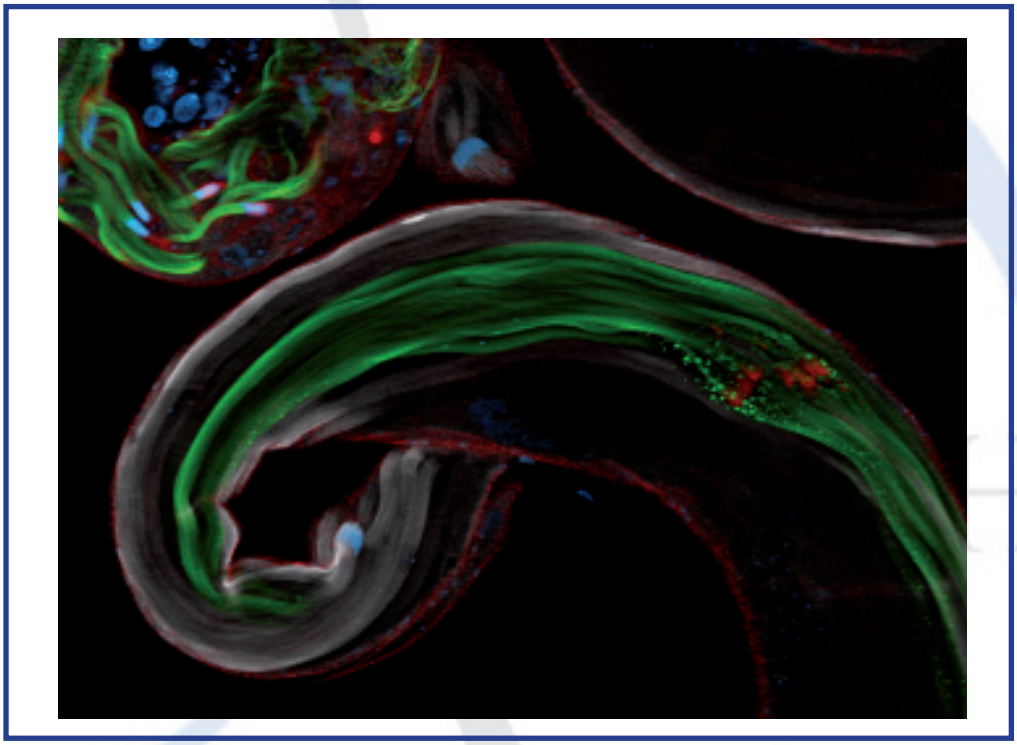
- Rogowski, K., Juge, F., van Dijk, J., Wloga, D., Strub, J.M., Levilliers, N., Thomas, D., Bre, M.H., Van Dorsselaer, A., Gaertig, J., et al. (2009). Evolutionary divergence of enzymatic mechanisms for posttranslational polyglycylation. **Cell,** *137*, 1076-1087.

-van Dijk, J., Rogowski, K., Miro, J., Lacroix, B., Edde, B., and Janke, C. (2007). A targeted multienzyme mechanism for selective microtubule polyglutamylation. **Mol Cell**, *26*, 437-448.

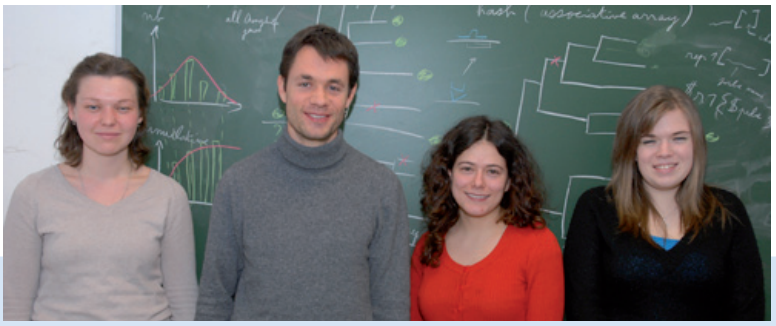
-Janke, C., Rogowski, K., Wloga, D., Regnard, C., Kajava, A.V., Strub, J.M., Temurak, N., van Dijk, J., Boucher, D., van Dorsselaer, A., et al. (2005). Tubulin polyglutamylase enzymes are members of the TTL domain protein family. **Science,** *308*, 1758-1762.

Quite often, cilia-related diseases occur in combination with male sterility, thus underlying the functional and structural similarities between cilia and flagella. Hence, we are using sperm development in Drosophila and mice as a model system to study the roles of Tubulin modifications in the assembly and functions of cilia and flagella.

- Ersfeld, K., Wehland, J., Plessmann, U., Dodemont, H., Gerke, V., and Weber, K. (1993). Characterization of the tubulin-tyrosine ligase. J Cell Biol 120, 725-732.
- Sharma, N., Berbari, N.F., and Yoder, B.K. (2008). Ciliary dysfunction in developmental abnormalities and diseases. Curr Top Dev Biol 85, 371-427.
- Westermann, S., and Weber, K. (2003). Post-translational modifications regulate microtubule function. Nat Rev Mol Cell Biol 4, 938-947.



Immunofluorescence of wild type *Drosophila* testis. Actin is stained with TRIC-conjugated phalloidin (red) while polyglycylated tubulin is revealed with PolyG antibodies (green). The nuclei are stained with DAPI (blue) and detyrosinated tubulin is labeled by delta1-tubulin antibodies (grey).



Systemic impact of small regulatory RNAs

HERVE SEITZ
herve.seitz@igh.cnrs.fr

Hervé Seitz
Research Scientist CNRS

Natalia Pinzon,
Post-doctoral Fellow

Anna Sergeeva,
PhD student

Laura Martinez,
Engineer

MicroRNAs (miRNAs) are small regulatory RNAs that repress specific target genes through base-pairing with the target mRNA. Computational analyses aim at identifying miRNA targets by searching miRNA binding sites that have been conserved in evolution; such algorithms predict thousands of miRNA targets in animal models. While they seem to have many targets, miRNAs usually repress them very modestly (less than 2-fold in general), hence they have been proposed to fine-tune these numerous genes, precisely setting protein abundance to its optimal level.

We proposed an alternative hypothesis: as most genes in animals are robust to small changes in gene expression (for example, most genes are haplo-sufficient in animals), we expect most predicted "miRNA targets" to be insensitive to the miRNA-mediated <2-fold repression. Yet their interaction with miRNAs has been conserved in evolution, hence it must have a function: we proposed that these "pseudo-targets" rather act as competitive inhibitors, repressing miRNAs by titrating them. Just a small subset of predicted targets would actually be functionnally targeted by miRNAs: these "real targets" would be the most dose-sensitive genes among predicted targets (Seitz, 2009).

Our laboratory is confronting the two hypotheses, testing their predictions by experimental and computational methods (see figures 1 and 2). Our work suggests that the number of real miRNA targets (hence, the physiological impact of miRNAs) has been vastly over-estimated.

In addition to that major project, our group is also involved in several collaborations related to the biogenesis or the function of small regulatory RNAs: understanding the molecular mechanisms of miRNA biogenesis (collaboration with Y. Tomari, university of Tokyo; Kawamata et al., 2009; Tsutsumi et al., 2011); dissecting the origins of phenotypic robustness to perturbation of gene regulators (collaboration with J. Turner, MRC, London); exploring small regulatory RNA biology in emerging model organisms (collaborations with P.D. Zamore, UMass Medical School; D. Tagu, INRA; and H. Escriva, CNRS and UPMC) (see figure 3).

- Tsutsumi, A., Kawamata, T., Izumi, N., Seitz, H. and Tomari, Y. (2011) Recognition of the pre-miRNA structure by Drosophila Dicer-1. **Nat Struct Mol Biol,** *18,* 10, 1153-1158

- Seitz, H., Tushir, J.S. and Zamore, P.D. (2011) A 5´-uridine amplifies miRNA/miRNA* asymmetry in Drosophila by promoting RNA-induced silencing complex formation. **Silence,** *2*, 4.

- Seitz, H. (2010) siRNAs: the hidden face of the small RNA world. **Curr Biol,** *20*, 3, R108-110

Kawamata, T., Seitz, H. and Tomari, Y. (2009) Structural determinants of miRNAs for RISC loading and slicer-independent unwinding. **Nat Struct Mol Biol,** *16,* 9, 953-960.

- Seitz, H. (2009) Redefining microRNA targets. **Curr Biol**, *19*, 10, 870-873.

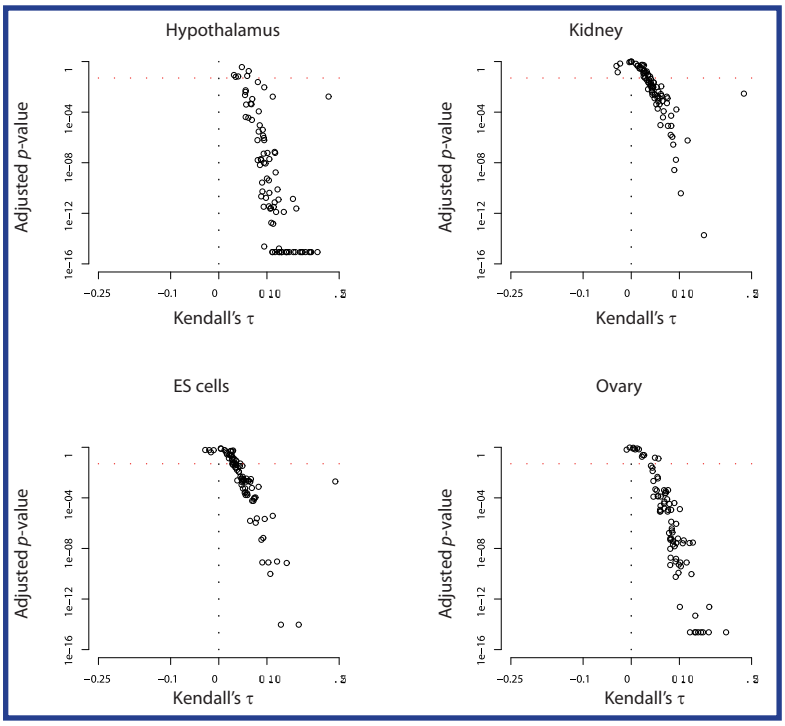


Figure 1. For predicted miRNA targets, mRNA abundance correlates positively with miRNA binding site conservation. Each point represents a murine miRNA family. Correlation between mRNA abundance and conservation of miRNA binding sites was assessed across all predicted miRNA targets (these volcano plots show the correlation coefficients and their p-values). mRNA abundance was extracted from published microarray datasets and miRNA binding site conservation was evaluated using TargetScan's «probability of conserved targeting» (described in Friedman et al. (2009) Genome Research 19: 92). A positive correlation between mRNA abundance and target site conservation was predicted by the pseudo-target hypothesis, and cannot be explained by the genome-wide fine-tuning hypothesis.

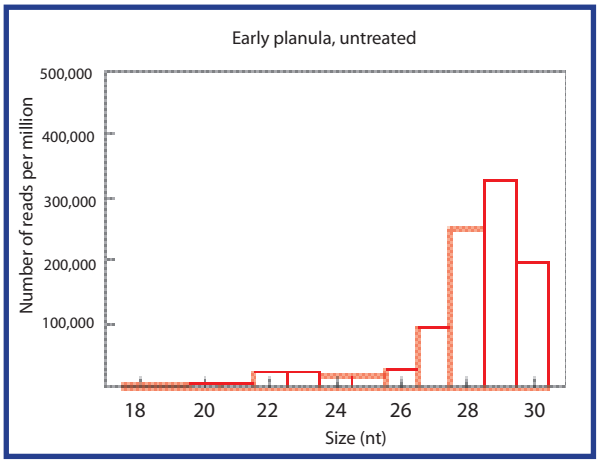


Figure 3. Size distribution of small RNAs from Nematostella vectensis early planula. Small RNAs were sequenced on an Illumina GAII sequencer. Genomic annotation reveals three classes of small RNAs: piRNAs (25 to 30 nt long), miRNAs (22 to 23 nt long) and endogenous siRNAs (20 nt long).

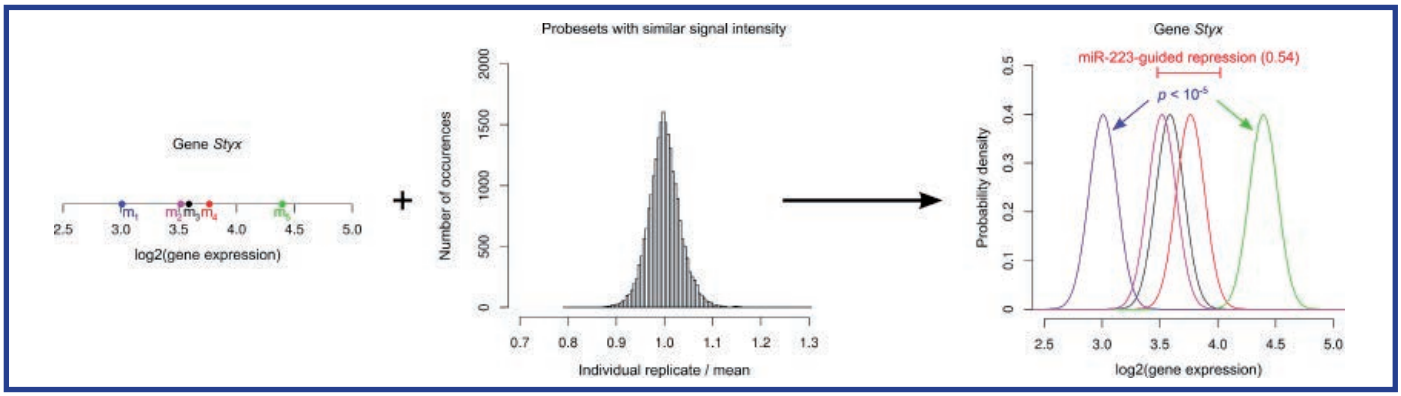


Figure 2. For most predicted miR-223 targets, inter-individual fluctuations in a wild-type population exceeds miR-223-guided repression. We measured gene expression in neutrophils in five wild-type mice by microarray (left panel) and measured technical variability of the complete experimental procedure (middle panel). The right panel shows probability distributions of the underlying biological values for the expression of that gene (calculated based on the measured technical variability of the experiment). The p-value (shown in blue) measures the probability that the underlying differences in gene expression among the five mice is smaller than miR-223-guided repression of that gene (shown in red; taken from Baek et al. (2008) Nature 455: 64). For 168 out of 189 analyzed miR-223 predicted targets, inter-individual variations in gene expression appear to be larger than miR-223-guided repression ($p < 0.05$), suggesting that these genes are not functionnally affected by miR-223.

mRNA Regulation and Development

MARTINE SIMONELIG
Martine.Simonelig@igh.cnrs.fr

Martine Simonelig
Research Director CNRS

Isabelle Busseau,
Research Scientist CNRS

Catherine Papin,
Research Scientist CNRS

Aymeric Chartier,
Research Engineer CNRS

Bridlin Barckmann,
Post-doctoral Fellow

Anne-Laure Bouge,
Post-doctoral Fellow

Jérémy Dufourt,
Post-doctoral Fellow

Cécile Ribot,
Post-doctoral Fellow

Willy Joly,
Engineer

Stéphanie Pierson,
Engineer

Post-transcriptional regulations have a huge impact in the control of gene expression and are crucial for many developmental processes. We are using *Drosophila*, a genetically tractable organism, as a model to investigate the regulations of mRNA 3'-end processing and poly(A) tail length, and their roles in the control of gene expression during development and disease.

Translational control of early development by poly(A) tail length: cytoplasmic polyadenylation and deadenylation

In many species, early steps of development occur in the absence of transcription and depend on maternal mRNAs and on their regulation at the level of localization, translation and stability. A major mechanism of control of translation and mRNA stability involves changes in the length of mRNA poly(A) tails. Poly(A) tail elongation by cytoplasmic polyadenylation leads to translational activation, whereas poly(A) tail shortening by deadenylation leads to mRNA decay, or translational repression. In *Drosophila*, regulations of mRNA poly(A) tail lengths are crucial for anterior-posterior patterning of the embryo as these regulations control the synthesis and localization of morphogens: Bicoid at the anterior pole and Nanos at the posterior pole. We are investigating the molecular mechanisms and the roles of these regulations during oogenesis, meiosis, stem cell biology in the female germline and axis formation in the embryo.

We are currently studying the role of the RNA silencing pathways (siRNA, microRNA and piRNA) in the decay of maternal mRNAs in the early embryo and we have recently shown that the piRNA pathway is involved. This pathway is known to repress the transposition of transposable elements. Moreover, piRNAs are themselves produced from transposable elements. Our finding proposes the first example of a role for transposable elements through piRNAs in gene regulation and embryo patterning.

***Drosophila* as a model for understanding human diseases: the *Drosophila* model of oculopharyngeal muscular dystrophy (OPMD)**

Oculopharyngeal muscular dystrophy (OPMD) is an adult-onset syndrome characterized by progressive degeneration of specific muscles. OPMD is caused by short GCG repeat expansions within the gene encoding the nuclear poly(A) binding protein 1 (PABPN1) that extend an N-terminal poly-alanine tract in the protein. PABPN1 has a role in mRNA polyadenylation. Mutant PABPN1 molecules aggregate as nuclear inclusions in OMPD patients' muscles. We have generated a *Drosophila* model of OPMD that recapitulates the features of the human disorder: progressive muscle degeneration and formation of PABPN1 nuclear inclusions. Strikingly, the RNA binding domain of PABPN1 and its function in RNA binding are required for muscle degeneration, demonstrating that OPMD results from an intrinsic property of PABPN1. We are using this model and a set of complementary genetic and molecular approaches to identify the molecular mechanisms underlying the disease. We are also investigating the potential of novel therapeutic strategies, including the utilization of anti-PABPN1 intrabodies, and the identification of beneficial drugs.

- Barbezier, N., Chartier, A., Bidet, Y. , Buttstedt, A., Voisset, C., Galons, H., Blondel, M., Schwarz, E. and Simonelig, M. (2011). Antiprion drugs 6-aminophenanthridine and guanabenz reduce PABPN1 toxicity and aggregation in oculopharyngeal muscular dystrophy. **EMBO Molecular Medicine**, *3*, 35-49.

- Rouget, C., Papin, C., Boureux, A., Meunier, A.C., Franco, B., Robine, N., Lai, E.C., Pélisson, A. and Simonelig, M. (2010). Maternal mRNA deadenylation and decay by the piRNA pathway in the early Drosophila embryo. **Nature,** *467*, 1128-1132.

- Chartier, A., Raz, V., Sterrenburg, E., Verrips, T.C., van der Maarel, S. and Simonelig, M. (2009). Prevention of oculopharyngeal muscular dystrophy by muscular expression of Llama single-chain intrabodies in vivo. **Human Molecular Genetics**, *18,* 1849-1859.

- Benoit, P., Papin, C., Kwak, J.E., Wickens, M. and Simonelig, M. (2008). PAP- and GLD-2-type poly(A) polymerases are required sequentially in cytoplasmic polyadenylation and oogenesis in Drosophila. **Development,** *135,* 1969-1979.

- Chicoine, J., Benoit, P., Paliouras, M., Gamberi, C., Simonelig, M. and Lasko, P. (2007). Bicaudal-C recruits CCR4-NOT deadenylase to target mRNAs and regulates oogenesis, cytoskeletal organization, and its own expression. **Developmental Cell**, *13*, 691-704.

- Chartier, A., Benoit, B. and Simonelig, M. (2006). A Drosophila model of oculopharyngeal muscular dystrophy reveals intrinsic toxicity of PABPN1. **EMBO J.**, *25*, 2253-2262.

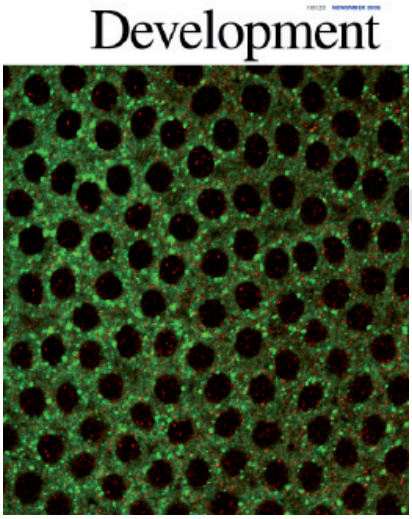


Figure 1: P bodies in the *Drosophila* embryo. The CCR4 deadenylase (red) and the Smaug RNA binding protein (green), localize in foci or processing bodies (P bodies) in *Drosophila* embryos (Zaessinger et al. 2006, Development, 133, cover).

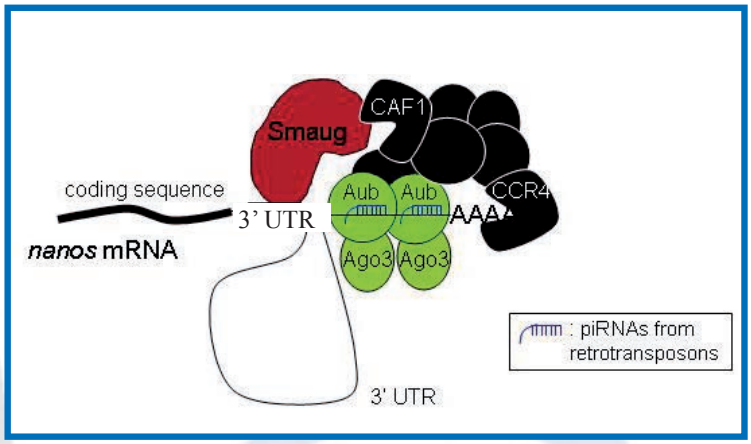


Figure 2: Model of *nanos* mRNA regulation by the piRNA pathway. SRE: Smaug recognition elements. The Smaug RNA binding protein (red) binds to the SRE and recruits the deadenylation complex (proteins in black). piRNAs from retrotransposons target *nanos* 3'UTR and guide the interaction with Argonaute proteins (green) which stabilize the complex.

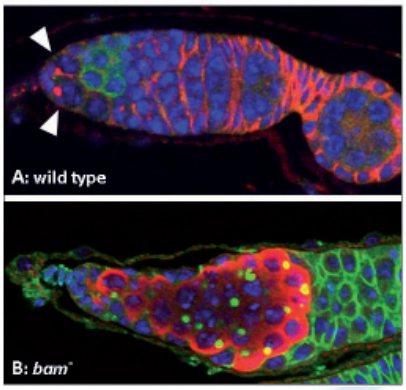


Figure 3: Germaria in the *Drosophila* ovary.
A: wild-type. All germline cells derive from two germline stem cells (marked by a dot with the 1B1 marker (red), arrowheads). Bam (green) is expressed in cystoblasts and is required for their differentiation. DAPI (blue).
B: In the *bam* mutant, germline stem cells cannot differentiate and form a tumor of stem cells. 1B1 (green). Vasa marks all germline cells (red). DAPI (blue).

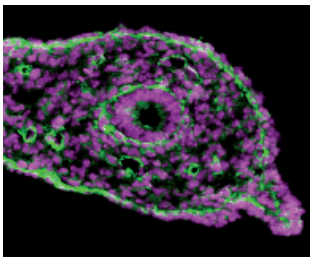
Figure 4 : *Drosophila* thoracic muscles.
A: diagram of dorso-longitudinal indirect flight muscles.
B: normal dorso-longitudinal muscles in a control fly.
C: *Drosophila* model of OPMD. Muscles expressing mutant PABPN1 degenerate (arrowhead).

Molecular Bases of Human Diseases Department

Director : Monsef Benkirane

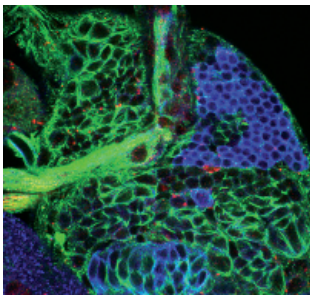
General Statement about the Department

Research in the department of Molecular Bases of Human Diseases strives to shed light on the etiology of cancer, AIDS and neuro-degenerative diseases. Supported by strong collaborations with the academic hospitals, our objective is to translate novel biological concepts and molecular insights into new therapies.



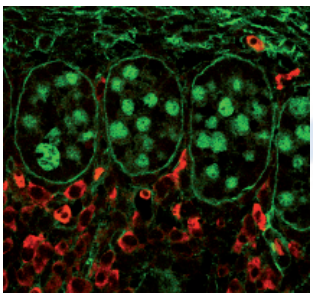
Genome instability and cancer.

Five research groups use complementary model systems (yeast, Xenopus and human cells) to explore two major topics in cancer biology: the origin of genomic instability in cancer development and the cellular responses to DNA damage. Since defects in DNA replication are increasingly recognized as a major source of genomic instability, the "Maintenance of Genome Integrity during DNA Replication" group aims at identifying the origin of replication stress. Exploring how cells respond to and tolerate stress during DNA replication are the objectives of the group "Responses to DNA Replication Stress and Associated Diseases". Meanwhile, the team "Genome Surveillance and Stability" explores the molecular mechanisms by which checkpoint signals are generated in the presence of DNA lesions, particularly during early embryogenesis. Deciphering the transcriptional reprogramming induced by DNA lesions is one of the aims of the "Molecular Virology" team. Finally, understanding the physical and functional interactions between cell cycle regulators and the DNA damage response is the aim of the "Microtubules and Cell Cycle" group.



Infectious diseases.

Infectious diseases are a major public health problem world-wide. HIV/AIDS constitutes one of the public health issues of the Millennium Development Goals. Understanding the intimate interaction between HIV and its host is an important challenge which, if achieved, may lead to the development of effective therapies and/or a vaccine. Major efforts in the department are channeled towards a better understanding of the physical and functional interactions between HIV and its co-receptors (CCR5 and CXCR4). This is the main objective of the team "Homing, Immune Activation and Infection". Moreover, improving our understanding of HIV gene expression regulation at the transcriptional and post-transcriptional levels is the major aim of the "Molecular Virology" group.



IMGT®, the ImMunoGeneTics Information System®.

Created in 1989, IMGT®, the international ImMunoGeneTics information system® (Montpellier 2 University and CNRS) is the global reference in immunogenetics and immunoinformatics. IMGT® is a CNRS registered trademark (EU, Canada and USA). The group's research interests concern molecular immunogenetics, immunoinformatics, bioinformatics and rare human genetic diseases in consanguineous families. IMGT® is used globally by academic and industrial scientists involved in fundamental and medical research as well as in antibody engineering for humanization of therapeutic antibodies.

Molecular Virology

MONSEF BENKIRANE
Monsef.Benkirane@igh.cnrs.fr

Monsef Benkirane
Research Director CNRS

Yamina Bennasser,
Research Scientist, INSERM
Nadine Laguette,
Research Scientist, INSERM
Bijan Sobhian,
Research Scientist, INSERM

Nathalie Malirat,
Engineer CNRS

Post-doctoral fellows :
Sabine Chabalier,
Alexandra Cribier,
Benjamin Descours,
Gaël Petitjean,
Bernd Stadelmayer,

PhD students :
Tania Louis,
Oussama Meziane,
Mathieu Ringeard,
Ahmad Yatim,
Ke Zhang,

Pauline Hue,
Engineer

Human Immunodeficiency Virus type 1 (HIV-1), the causative agent of AIDS, is a retrovirus that primarily infects cells of the immune system. The outcome of HIV-1 infection is the result of complex interactions between viral proteins and host cell factors. In most cases, HIV-1 successfully hijacks cellular pathways and bypasses cellular restriction factors for optimal replication, leading to continuous rounds of infection, replication and cell death. Ongoing viral replication causes the loss of CD4+ T cells and progression to immunodeficiency in infected individuals. Major advances in HIV/AIDS treatment regimens have fundamentally altered the natural history of the disease and sharply reduced HIV-related morbidity and mortality in countries where such treatments are accessible. The most notable advance is the use of combination antiretroviral therapy or ART. However, after 15 years of treatment it is clear that ART is unable to achieve complete virus eradication or "sterilizing cure". Indeed, in most if not all cases, viral rebound is observed rapidly after ART interruption. Thus, life-long treatment is currently needed to control HIV. Drug resistance, cumulative side effects and high cost, represent major drawbacks of such treatments. Moreover, residual harmful inflammation and accelerated immune aging is observed even under optimized ART regimens. The persistence of HIV in treated patients results from the establishment of a viral reservoir insensitive to ART and poorly visible to the immune system. Thus, understanding HIV persistence and developing drugs able to flush out HIV, in order to achieve viral eradication or to decrease the need for continuous ART remain outstanding challenges. Our main objectives are to understand the complex interaction between HIV-1 and its host leading to viral persistence and escape from immune sensing. We are particularly interested in deciphering the molecular mechanisms involved in the regulation of HIV-1 gene expression and the role of host restriction factors in innate immune sensing of HIV.

1- Understanding HIV-1 gene expression through the identification of key regulatory host factors involved in activating or repressing the viral promoter.

Studying the HIV-1 transcriptional activator Tat has led to important progress in our understanding of transcription elongation by RNAPII, a key regulatory step of gene expression. To gain insight into the regulation of transcription elongation, we purified HIV-1 Tat-associated factors from HeLa nuclear extracts. We found that HIV-1 Tat assembles a multifunctional transcription elongation complex, which consists of the core active P-TEFb, MLL-fusion partners involved in leukemia (AF9, AFF4, AFF1, ENL and ELL) and PAF1/CDC73. Importantly, Tatcom1 formation relies on Cyclin T1 and CDK9, while optimal CDK9 CTD-kinase activity depends on the presence of AF9. Surprisingly, we found that Tat also associates and remodels the 7SK snRNP (Inactive PTEFb). Tat remodels 7SK snRNP by interacting directly with 7SKRNA in vivo, leading to the formation of stress-resistant 7SK snRNP particles (Sobhian et al. Mol Cell 2010). Besides the identification of new factors that are important for P-TEFb function and are required for Tat transcriptional activity, our data show a coordinated control of RNAPII elongation by different classes of transcription elongation factors acting at the same promoter.

- Laguette, N., Sobhian, B., Casartelli, N., Ringeard, M., Chable-Bessia, C., Ségéral, E., Emiliani, S., Schwartz, O., Benkirane, M. (2011) SAMHD1 is the dendritic- and myeloid-cell-specific HIV-1 restriction factor counteracted by Vpx. **Nature,** http://dx.doi.org/10.1038/nature10117
- Bennasser, Y., Chable-Bessia, C., Triboulet, R., Gibbings, D., Gwizdek, C., Dargemont, C., Kremer, E.J., Voinnet, O., and Benkirane, M. (2011). Competition for XPO5 binding between Dicer mRNA, pre-miRNA and viral RNA regulates human Dicer levels. **Nat Struct Mol Bio**l *18,* 323-327.
- Sobhian, B., Laguette, N., Yatim, A., Nakamura, M., Levy, Y., Kiernan, R., and Benkirane, M. (2010). HIV-1 Tat assembles a multifunctional transcription elongation complex and stably associates with the 7SK snRNP. **Mol Cell** *38*, 439-451.
- Laguette, N., Rahm, N., Sobhian, B., Chable-Bessia, C., Münch, J., Snoeck, Sauter, D., Switzer, WM., Heneine, W., Kirchhoff, F., Delsuc, F., Telenti, A. and Benkirane, M. (2012) Evolutionary and Functional Analyses of the Interaction between the Myeloid Restriction Factor SAMHD1 and the Lentiviral Vpx Protein. **Cell Host & Microbe**, *11,* 2, 205-217. PMID 22305291
-Wagschal, A., Rousset, E., Basavarajaiah, P., Contreras, X. , Harwig, A., Laurent-Chabalier, S. , Nakamura, M., Chen, X., Zhang, K., Meziane, O., Boyer, F., Parrinello, H., Berkhout, B., Terzian, C., Benkirane, M., Kiernan, R. (2012) Microprocessor, Setx, Xrn2 and Rrp6 Co-Operate to Induce Premature Termination of Transcription by RNAPII. **CELL**, *150*, 6, 1147-1157. doi: 10.1016/j.cell.2012.08.004. PMID: 22980978
-Yatim, A., Benne, C., Sobhian, B., Laurent-Chabalier, S., Deas, O., Judde, JG., Lelievre, JD., Levy, Y., Benkirane, M. (2012) NOTCH1 Nuclear Interactome Reveals Key Regulators of Its Transcriptional Activity and Oncogenic Function. **Mol Cell** (http://dx.doi.org/10.1016/j.molcel.2012.08.022).

More recently, in collaboration with Rosemary Kiernan's lab (IGH), we described a novel mechanism regulating RNAPII pausing and premature termination of transcription at the HIV-1 promoter. We found that microprocessor (consisting of Drosha and DGCR8) initiates premature termination by RNAPII at the HIV-1 promoter through cleavage of the stem-loop RNA, TAR and orchestrate the recruitment of the termination factors SETX and XRN2, and Rrp6 (Wagschal A. Rousset E. Basavarajaiah P. el al. Cell 2012).

2- Understanding the crosstalk between HIV-1 replication and RNAi.

The rate of HIV-1 gene expression is a key step that determines the kinetics of virus spread and AIDS progression. Viral entry and gene expression are considered to be the key determinants for cell permissiveness to HIV. Recent reports highlighted the involvement of miRNAs in regulating HIV-1 replication post-transcriptionally (Triboulet et al. Science 2007). In this study we explored the role of cellular factors required for miRNA-mediated mRNA translational inhibition in regulating HIV-1 gene expression. We showed that HIV-1 mRNAs associate and co-localize with components of the RNA Induced Silencing Complex (RISC), and we characterized some of the proteins required for miRNA-mediated silencing (miRNA effectors). RCK/p54, GW182, LSm-1 and XRN1 negatively regulate HIV-1 gene expression by preventing viral mRNA association with polysomes. Interestingly, knockdown of RCK/p54 or DGCR8 resulted in virus reactivation in peripheral blood mononuclear cells (PBMCs) isolated from HIV-infected patients treated with suppressive HAART.

microRNAs (miRNAs) are a class of small non-coding RNAs (sncRNAs) that function by regulating gene expression post-transcriptionally. Alterations in miRNA expression can dramatically influence cellular physiology and are associated with human diseases, including cancer. Here, we demonstrated cross-regulation between two components of the RNA interference machinery. Specific inhibition of Exportin-5, the karyopherin responsible for pre-miRNA export, down-regulates Dicer expression, the RNase III required for pre-miRNA maturation. This effect is post-transcriptional and results from increased nuclear localization of Dicer mRNA. In vitro assays and cellular RNA immunoprecipitation experiments showed that Exportin-5 directly interacts with Dicer mRNA. Titration of Exportin-5 by over-expressing either pre-miRNA or the adenoviral VA1 RNA resulted in loss of the Dicer mRNA/Exportin-5 interaction and reduction of Dicer level. This saturation also occurs during adenoviral infection and enhances viral replication. Our study reveals an important cross-regulatory mechanism between pre-miRNA or viral small RNAs and Dicer through XPO5 (Bennasser et al. Nat Struct Mol Biol. 2011).

3-Identification of host cell restriction factors.

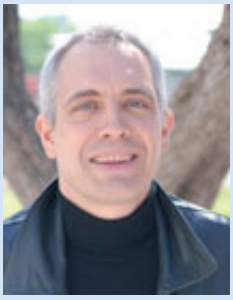
In addition to the information required for the production of structural and enzymatic proteins essential for mature viral particles production, lentiviral genomes also encode auxiliary proteins that regulate viral fitness in hosts. Although these auxiliary proteins are mostly unnecessary for viral replication in permissive cells in vitro, disruption of open reading frames (ORFs) corresponding to individual viral auxiliary proteins results in inefficient viral spread ex vivo in non-permissive cells and in vivo in hosts. The primate lentivirus auxiliary protein Vpx counteracts an unknown restriction factor that renders human dendritic and myeloid cells largely refractory to HIV-1 infection. Here we identified Samhd1 as this restriction factor. Samhd1 is a protein involved in Aicardi-Goutière Syndrome (AGS), a genetic encephalopathy with symptoms mimicking congenital viral infections (Laguette et al. Nature 2011).
Eukaryotic organisms have been exposed to viral infections for millions of years. This co-evolutionary process has driven the development and adaptation of immune responses against invading viruses. In turn, viruses have evolved countermeasures to escape immune control. Through evolutionary studies, we found that SAMHD1 experienced strong positive selection episodes during primate evolution that occurred in the Catarrhini ancestral branch prior to the separation between hominoids (gibbons and great apes) and Old World monkeys. Importantly, we found that while SAMHD1 restriction activity towards HIV-1 is evolutionarily conserved, antagonism of SAMHD1 by Vpx is species-specific. The distinct evolutionary signature of SAMHD1 sheds light on the development of its antiviral specificity (Laguette et al Cell Host & Microbes 2011. Laguette and Benkirane. Trends immunology 2012).

4- NOTCH1 nuclear interactome reveals key regulators of its transcriptional activity and oncogenic function.

The Notch pathway is a master regulator of embryonic development and adult tissues homeostasis. Given its prominent role, dysfunctions and mutations in this pathway are associated with various human diseases including cancers. Despite important advances in our understanding of Notch signal transduction, the regulation of Notch functions in the nucleus remains unclear. Using immuno-affinity purification we identified NOTCH1 nuclear partners in T-ALL cells and showed that beyond the well characterized core activation complex (ICN1-CSL-MAML1) NOTCH1 assembles a multifunctional complex containing the transcription coactivator AF4p12, the PBAF nucleosome remodeling complex and the histone demethylases LSD1 and PHF8 acting through their demethylase activity to promote epigenetic modifications at Notch-target genes. Remarkably, LSD1 functions as a corepressor when associated with CSL-repressor complex and as a NOTCH1 coactivator upon Notch activation. Our work provides new insights into the molecular mechanisms that govern Notch transcriptional activity and represents the first glimpse into NOTCH1 interaction landscape, which will help deciphering mechanisms of NOTCH1 functions and regulation (Yatim et al. Mol Cell 2012).

Responses to DNA Replication Stress and Associated Diseases

ANGELOS CONSTANTINOU
Angelos.Constantinou@igh.cnrs.fr



Angelos Constantinou
Research Director INSERM

Jihane Basbous,
Research Scientist CNRS

Gerald Lossaint,
Post-doctoral fellow

Maria Moriel-Carretero,
Post-doctoral fellow

Cyril Ribeyre,
Post-doctoral fellow

Ramhari Kumbhar,
PhD student

Sophie Vidal-Eychenie,
Technician CNRS

Marion Larroque,
Engineer

The DNA damage response: In S phase, the DNA damage response (DDR) orchestrates the repair of DNA lesions and the resolution of problems arising during DNA replication in physiological conditions. The DDR is implemented by sensors, transducers, and effector proteins. Failure to correctly sense or repair DNA lesions and/or aberrant DNA replication structures is the underlying cause of a number of human diseases with a wide range of clinical manifestations (from neurological defects, immunodeficiency, congenital abnormalities, premature ageing to cancer predisposition).

Fanconi anemia: During the last five years, our focus has been on the cancer-prone disorder Fanconi anemia (FA). FA genes encode proteins that play crucial roles in the maintenance of genomic stability and in cell tolerance to replication stress. Cells derived from patients with FA are hypersensitive to chemotherapeutic cross-linking agents and prone to chromosome breakage and promiscuous repair during DNA replication. We found that the FA protein FANCM binds to and remodels branched DNA structures, such as replication forks, and facilitates DNA replication in cells exposed to DNA damaging agents.

Research goals: The activation of growth signaling pathways in an evolving population of tumor cells induces constitutive stress during DNA replication. As a consequence, replication forks collapse and double-strand breaks are formed. This characteristic feature distinguishes normal cells from tumor cells, and can be exploited therapeutically through stress overload or stress sensitization.

We wish to understand how pathological replication structures are sensed and signaled, how DNA replication is regulated in response to stress during DNA chain elongation and how the activities of DNA caretaker proteins are coordinated and regulated in chromatin. We believe that this knowledge will help understanding how tumor cells can resist to chemotherapeutic treatments and proliferate at a furious pace in the presence of persistent stress during DNA replication.

To unveil the molecular mechanisms of replication stress tolerance, we are taking advantage of a wide repertoire of biochemical, molecular biology and cell biology (confocal, high resolution imaging) approaches, single molecule analysis (molecular combing), proteomics (mass spectrometry) and genomics (CHIP-Seq).

- Constantinou A (2012) Rescue of replication failure by Fanconi anaemia proteins. **Chromosoma** *121,* 21-36- Z.

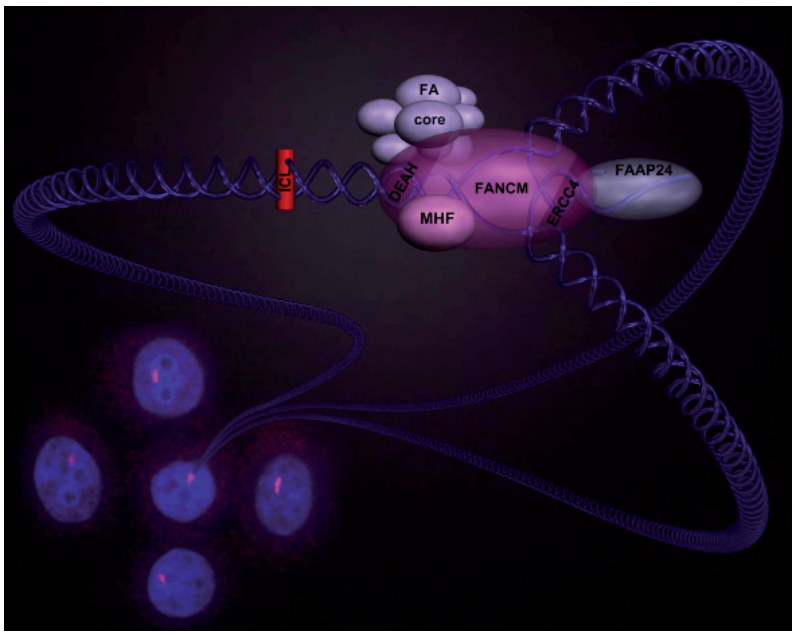
- Yan, M. Delannoy, C. Ling, D. Daee, H. Du, A.B. Oostra, T. Lin, C. Décaillet, A. Stasiak, A. Stasiak, B. Schuster, C. Woodcock, D. Schindle, H. Joenje, J. de Winter, R. Sen, M.C. Whitby, K. Myung, A. Constantinou*, and W. Wang* (2010). A Novel Histone-Fold Complex Cooperates with the Fanconi Anemia Protein FANCM to Maintain Genome Stability. **Molecular Cell**, *37,* 865-878. * Co-correspondence-authors.

- Luke-Glaser, S., Luke, B., Grossi, S. and Constantinou, A. (2010). FANCM regulates DNA chain elongation and is stabilized by S-phase checkpoint signalling. **The EMBO Journal,** *29,* 795-805.

- Roques, C., Coulombe, Y., Delannoy, M., Vignard, J., Grossi, S., Brodeur, I., Rodrigue, A., Gautier, J., Stasiak, A.Z., Stasiak, A., Constantinou, A. and Masson, J.Y. (2009) MRE11-RAD50-NBS1 is a critical regulator of FANCD2 stability and function during DNA double-strand break repair. **The EMBO Journal,** *28,* 2400-2413.

- Gari, K., Décaillet, C., Delannoy, M., Wu, L., and Constantinou, A. (2008) Remodeling of DNA replication Structures by the Branchpoint Translocase FANCM. **Proc. Natl. Acad. Sci. U. S. A.**, *105,* 16107-16112.

- Gari, K., Décaillet, C., Stasiak, A.Z., Stasiak,A., and Constantinou, A. (2008). The Fanconi Anemia Protein FANCM Can Promote Branch Migration of Holliday Junctions and Replication Forks. **Molecular Cell**, *29,* 141-148.

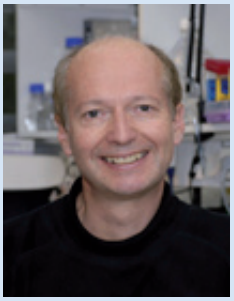


FANCM and MHF form a conserved DNA-remodeling complex that protects replication forks from yeast to humans.

Acknowledgment: This image is by courtesy of Dr. Julien Dorier (University of Lausanne) and incorporates immunofluorescence images provided by Drs. Parameswary Muniandy and Michael Seidman (National Institute on Aging/NIH) and the model in Figure 7E of Yan et al. (2010).

Homing, Immune Activation and Infection

PIERRE CORBEAU
Pierre.Corbeau@igh.cnrs.fr



Pierre Corbeau
Lecturer,
Hospital Practitioner,
University Montpellier 1

Vincent François,
Research Scientist CNRS

Laurence Guglielmi,
Lecturer, University Montpellier 1

Clément Mettling,
Research Scientist CNRS

Thierry Vincent,
Hospital Assistant,
University Montpellier 1

Sandrine Gimenez,
Technician,
University Montpellier 1

Charline Duquenne,
PhD student

Katerina-Christina Psomas,
PhD student

Our research interests are focused on the roles played by the chemokine receptors CCR5 and CXCR4 in Human Immunodeficiency Virus type 1 (HIV-1) infection. CCR5 is used as a co-receptor in addition to CD4 by the vast majority of HIV-1 virions ("R5 strains"), whereas CXCR4-using ("X4 strains") HIV-1 strains emerge eventually in some infected individuals, preferentially at later stages of the disease.

We have previously shown that:
- the level of CCR5 and CXCR4 expression at the surface of CD4+ T lymphocytes drastically determines the level of productive infection of these cells by the R5 and X4 strains, respectively
- CCR5 and CXCR4 are used by the virus not only to bind to the target cell but also to activate it in order to optimize its own replication.
A distinctive feature of our team is that we study these roles both at the basic and clinical levels.

We are currently working on three themes.

Theme 1: Effect of the CCR5 signaling induced by HIV virions on reverse transcription.
We have previously shown that the interaction between the HIV envelope and CCR5 triggers a signal via the proteins GAI1 and ERK1/2 that boosts the reverse transcription of the viral RNA. Our aim is to understand the molecular mechanisms linking ERK1/2 and reverse transcription.

Theme 2: Roles of the chemokine receptor CCR5 in immune activation.
In addition to being a chemokine receptor, CCR5 might also work as a co-activation molecule at the surface of lymphocytes. Therefore, our working hypothesis is that CCR5 could be involved in the immune activation observed in HIV-infected individuals. To test this hypothesis, we are analyzing in vitro the role of CCR5 in T cell activation. Moreover, we are looking for correlations between the level of expression of CCR5 at the surface of CD4+ T lymphocytes and the level of immune activation in HIV-positive subjects. Finally, we are monitoring the in vivo effects of a CCR5 antagonist on the immune system.

- Corbeau, P and Reynes, J. (2009) CCR5 antagonism in HIV infection: ways, effects, and side effects. **AIDS,** *23,* 15, 1931-1943.

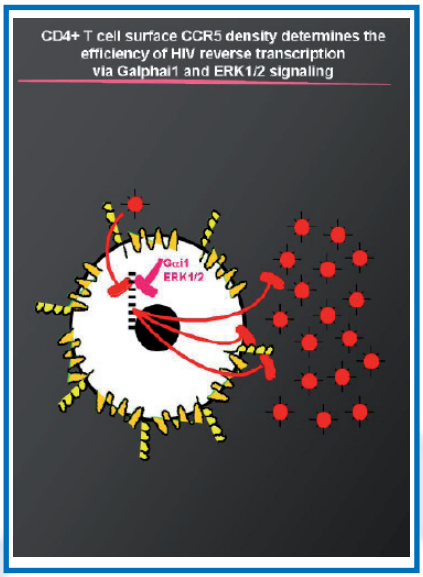
- Fiser, AL., Vincent, T., Brieu, N., Lin, YL., Portalès, P., Mettling, C., Reynes, J., Corbeau, P. (2010) High CD4+ T-Cell Surface CXCR4 Density as a Risk Factor for R5 to X4 Switch in the Course of HIV-1 Infection. **J. AIDS**. *55,* 5, 529-535.

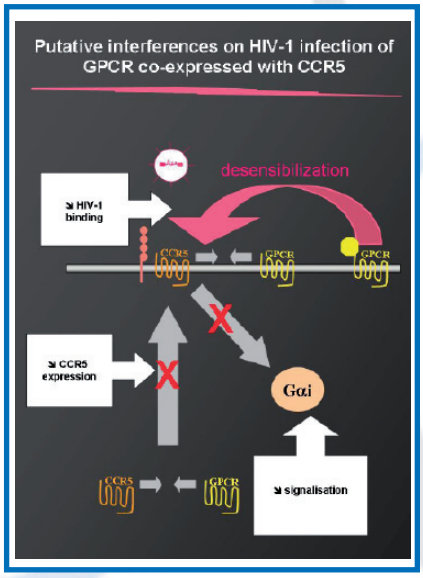
- Brieu, N., Portalès, P., Carles, MJ., Corbeau, P (2011) IL-7 induces Human Immunodeficiency Virus type 1 R5 to X4 switch. **Blood**, *117,* 6, 2073-2074

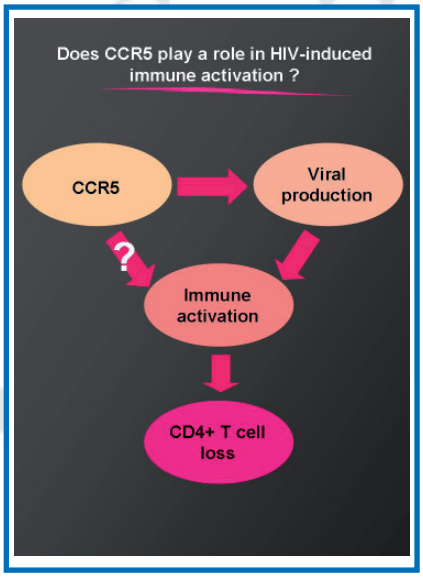
- Guglielmi, L., Gimenez, S., Larroque, M., Tong, X., Portalès, P., Corbeau, P. (2011) Circulating human CD4+ T cells have intracellular pools of CCR5 molecules **Blood,** *118,* 4, 1177-1178.

- Corbeau, P., Reynes, J. (2011) Immune reconstitution under antiretroviral therapy: the new challenge in HIV-1 infection. **Blood**, *117,* 21, 5582-5590.

Theme 3: Identification of G protein-coupled receptors that interfere with CCR5 function.
G protein-coupled receptors (GPCR) may heterodimerize and this heterodimerization could modify their capacity to bind to ligands and therefore to signal. We have identified GPCR that are co-expressed with CCR5 at the surface of CD4+ T lymphocytes and that can inhibit the function of CCR5 as an HIV co-receptor. We are studying the mechanism of this anti-viral effect and are looking for ligands capable of increasing it.







Microtubules and Cell Cycle

DOMINIQUE GIORGI
SYLVIE ROUQUIER
Dominique.Giorgi@igh.cnrs.fr
Sylvie.Rouquier@igh.cnrs.fr

Dominique Giorgi
Research Director CNRS

Sylvie Rouquier
Research Director CNRS

Cell division needs error-free DNA replication and correct chromosome segregation mediated by the mitotic spindle, which is mainly formed by microtubules (MT) and MT-associated proteins (MAPs).

Centrosomes are the main site of MT nucleation in animal cells, and are essential for chromosome segregation. Defects in the duplication of centrosomes lead to abnormal spindles, abortive mitoses and segregation defects that cause aneuploidy as observed in many cancers. Different kinases and their substrates, particularly proteins of the Cdk, Aurora and Plk families, are essential for controlling cell cycle progression, centrosome regulation and spindle assembly. Deregulation or mutation of centrosomal and mitotic proteins, such as the regulatory mitotic kinases Aurora-A (AurA) and Plk1 as well as the tumor suppressors p53 and BRCA1, leads to chromosome instability. Furthermore, centrosomes are now considered as a control center for the DNA damage response (DDR). We have characterized ASAP (MAP9), a new protein associated with the mitotic spindle and the centrosomes, the deregulation of which induces severe mitotic defects leading to aneuploidy and/or cell death. We have shown that: a) phosphorylation of ASAP by the oncogenic kinase AurA is required for bipolar spindle assembly and is essential for correct mitotic progression; and b) phosphorylation by Plk1 regulates both ASAP localization and its role in spindle pole integrity. BRCA1 and p53 are phosphorylated by AurA and are involved in DDR, whereas BRCA1 also play a role in centrosomal amplification and mitotic spindle assembly. Many proteins play a role in both DDR and mitotic events, and ASAP, BRCA1, AurA and Plk1 may belong to this pool of proteins. We are investigating whether ASAP is involved in DDR and through which mechanistic pathways it regulates DDR.

We have also shown that ASAP is highly expressed in various adult tissues, in particular in microtubule-rich and ciliated tissues. The function of MAPs in neurons and in some degenerative diseases is well established. A growing number of MAPs play a dual role, i.e. they might be involved in mitosis at the cellular level and in specific developmental steps in a living organism, suggesting they could be candidates for various developmental defects. We have shown in zebrafish that ASAP is involved in the early steps of development, and that its depletion leads to profound defects and death of the embryos prior the end of gastrulation. In combination with an ASAP conditional KO mouse model, we are investigating the role of ASAP in these different physiological/developmental processes and its potential implication in various syndromes.

ASAP plays thus a crucial role in different cell cycle events. We aim at determining the cellular mechanisms in which ASAP and its partners are involved by focusing our efforts on ASAP role in development in normal and pathological conditions.

- Basbous, J., Knani, D., Bonneaud, N., Giorgi, D., Brondello, JM., Rouquier, S. (2012) Induction of ASAP (MAP9) contributes to p53 stabilization in response to DNA damage. **Cell Cycle** , *11*, 12, 2380-90

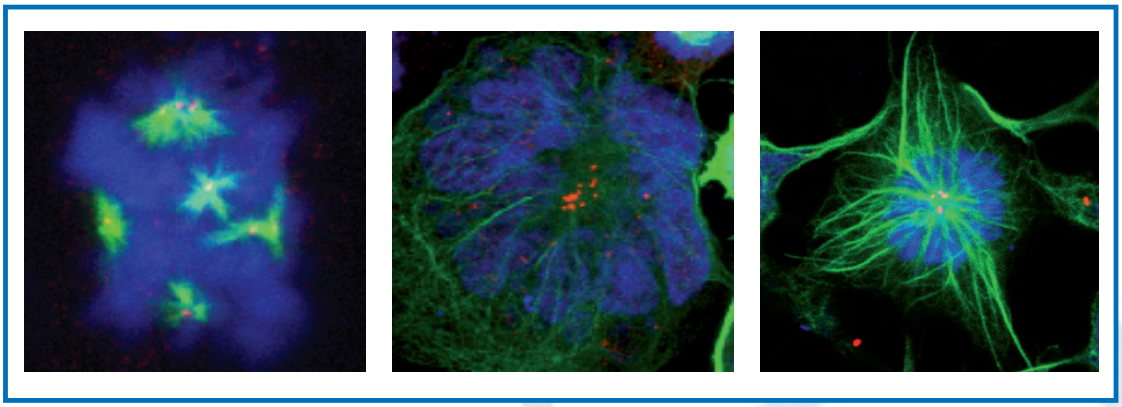
- Eot-Houllier, G., Venoux, M., Vidal-Eychenié, S., Hoang, M-T., Giorgi, D., Rouquier, S. (2010) Plk1 regulates both ASAP localization and its role in spindle pole integrity. **J. Biol. Chem**., *285*, 29556-29568.

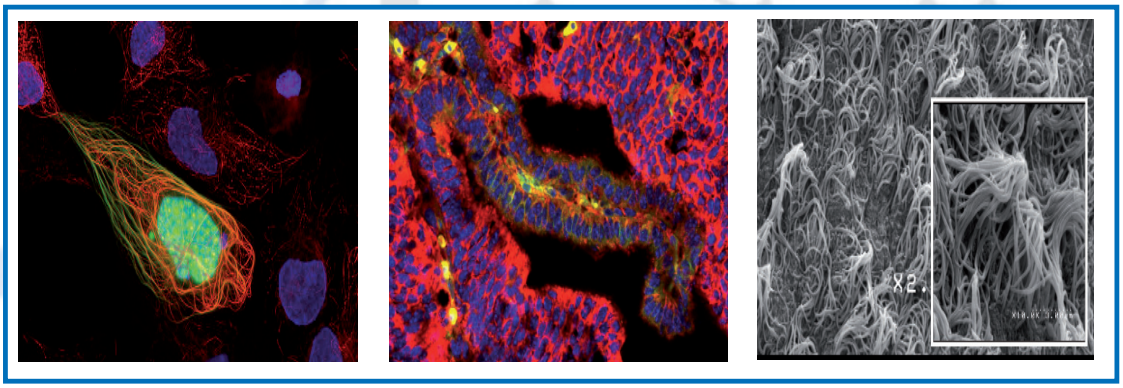
- Venoux, M., Basbous, J., Berthenet, C., Prigent, C., Fernandez, A., Lamb, N. J., Rouquier, S. (2008) ASAP is a novel substrate of the oncogenic mitotic kinase Aurora-A : phosphorylation on Ser625 is essential to spindle formation and mitosis. **Hum. Mol. Genet.**, *17*, 215-224.

- Venoux, M, Delmouly, K, Milhavet, O, Vidal-Eychenié, S, Giorgi, D, Rouquier, S. (2008). Gene organization, evolution and expression of the microtubule-associated protein ASAP (MAP9). **BMC Genomics,** *9,* 406

- Giorgi, D.; Gaillard, I. and Rouquier, S. (2007) Olfactory Receptors. In: ENCYCLOPEDIA OF LIFE SCIENCES. John Wiley & Sons, Ltd: Chichester http://www.els.net/

- Rouquier S, Giorgi D. (2007) Olfactory receptor gene repertoires in mammals. **Mutat. Res**., *616*, 95-102.





IMGT®, the international ImMunoGeneTics information system®

MARIE-PAULE LEFRANC
Marie-Paule.Lefranc@igh.cnrs.fr

Marie-Paule Lefranc
Emeritus Professor,
University Montpellier 2

Gérard Lefranc,
Emeritus Professor
University Montpellier 2

Patrick Duroux,
Research Engineer CNRS

Véronique Giudicelli,
Research Engineer UM2

Géraldine Folch,
Engineer CNRS

Joumana Jabado-Michaloud,
Engineer CNRS

Chantal Ginestoux,
Technician CNRS

Souphatta Sasorith,
Post-doctoral Fellow

Eltaf Alamyar,
PhD student

Engineers :
Fatena Bellahcene,
Emilie Carillon,
Nelly Jouffre,
Amandine Lacan,
Denis Moreno,
Claire Poiron,
Mansour Saljoqi,
Saida Saljoqi,
Caroline Tournier

Our research activities are focused on molecular immunogenetics, immunoinformatics, bioinformatics and rare human genetic diseases, more particularly Primary ImmunoDeficiencies (PID). We are studying the genetics, structures, functions, as receptors and initiators of signaling pathways, and repertoires of the immunoglobulins (IG) of B lymphocytes and plasmocytes, and of the T cell receptors (TR) on T lymphocytes, which are essential components of the adaptive (specific) immunity in humans and other vertebrates.

In 1989, we created IMGT®, the international ImMunoGeneTics information system® (Montpellier 2 University and CNRS). IMGT®, a CNRS registered trademark (EU, Canada and USA), is the global reference in immunogenetics and immunoinformatics.

This high-quality integrated knowledge resource is specialized in the IG, TR and major histocompatibility (MH) proteins of vertebrate species, and in the immunoglobulin superfamily (IgSF), MH superfamily (MhSF) and related proteins of the immune system (RPI) of any species. IMGT® provides a common access to expertly annotated nucleotide and protein sequences, structural data and genetic information. IMGT® includes seven databases (IMGT/LIGM-DB, a comprehensive database of more than 168,000 IG and TR sequences from human and 300 other vertebrate species in July 2012; IMGT/GENE-DB, IMGT/CLL-DB, IMGT/PRIMER-DB, IMGT/2Dstructure-DB, IMGT/3Dstructure-DB and IMGT/mAb-DB), seventeen interactive tools and more than 10,000 pages of web resources. IMGT/HighV-QUEST analyses Next-Generation Sequencing (NGS) High Throughput Sequencing (HTS)/Next-Generation Sequencing (NGS) data of IG and TR by batch of up to 150,000 sequences.

IMGT/DomainGapAlign is widely used for antibody engineering and design of humanized antibodies as it allows the precise definition of FR-IMGT and CDR-IMGT and the easy comparison of amino acid sequences between the nonhuman (mouse, rat…) V domains and the closest human germline genes. Since July 1995, IMGT® is available on the web at http://www.imgt.org. IMGT® is used by academic and industrial scientists involved in fundamental research, medical research (autoimmune and infectious diseases, AIDS, leukemia, lymphoma, myeloma), veterinary research, genomics (genome diversity and evolution of the adaptive immune system), biotechnology related to antibody engineering for humanization of therapeutic antibodies, diagnostics (detection of minimal residual diseases) and therapeutic approaches (grafts, immunotherapy, vaccinology).

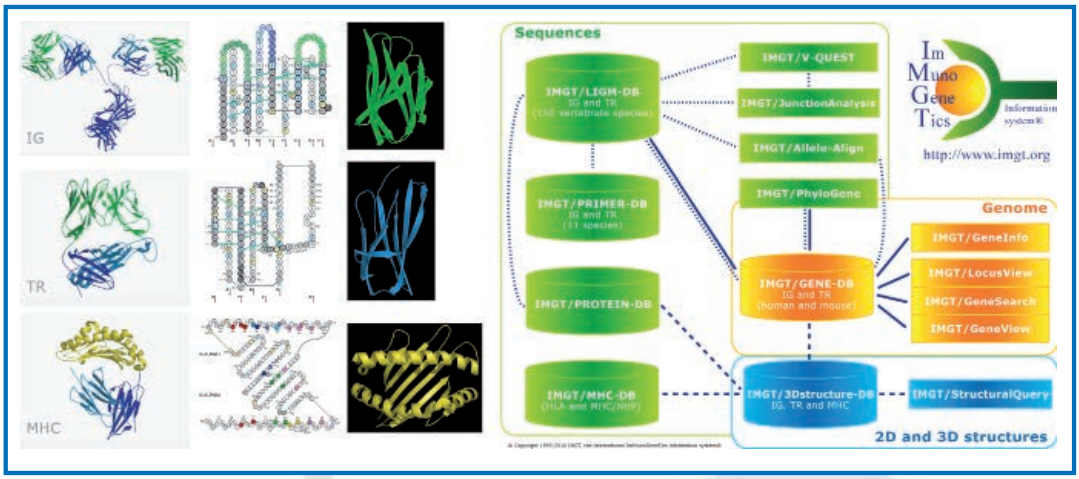
- Alamyar, E., Giudicelli, V., Shuo, L., Duroux, P., Lefranc, M-P. (2012) IMGT/HighV-QUEST: the IMGT® web portal for immunoglobulin (IG) or antibody and T cell receptor (TR) analysis from NGS high throughput and deep sequencing. **Immunome Res.**, *8*, 1, 26.

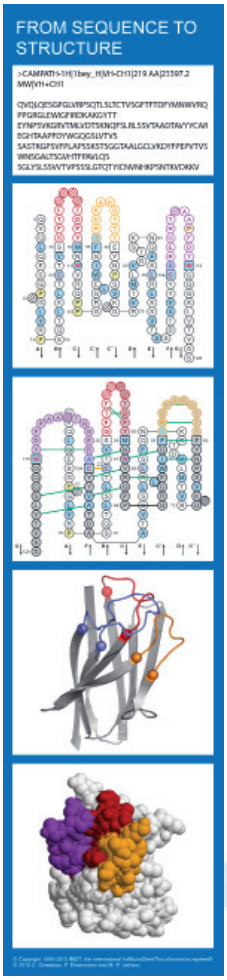
- Giudicelli, V., Lefranc, M-P. (2012) IMGT-ONTOLOGY 2012. Frontiers in Bioinformatics and Computational Biology. **Front. Genet.**, *3*, 79.

- Jabara, HH., McDonald, DR., Janssen, E., Massaad, MJ., Ramesh, N., Borzutzky, A., Rauter, I., Benson, H., Schneider, L., Baxi, S., Recher, M., Notarangelo, LD., Wakim, R., Dbaibo, G., Dasouki, M., Al-Herz, W., Barlan, I., Baris, S., Kutukculer, N., Ochs, HD., Plebani, A., Kanariou, M., Lefranc, G., Reisli, I., Fitzgerald, KA., Golenbock, D., Manis, J., Keles, S., Ceja, R., Chatila, TA., Geha, RS. (2012) DOCK8 functions as an adaptor that links TLR-MyD88 signaling to B cell activation. **Nat Immunol.,** *13*, 6, 612-620.

- Lana, E., Mégarbané, A., Tourrière, H., Sarda, P., Lefranc, G., Claustres, M., De Sario, A. (2012) DNA replication is altered in Immunodeficiency Centromeric instability Facial anomalies (ICF) cells carrying DNMT3B mutations. **Eur J Hum Genet**. *20, 10*, 1044-1050.

- Lefranc, M-P., Lefranc, G. (2012) Human Gm, Km and Am allotypes and their molecular characterization: a remarkable demonstration of polymorphism. **Methods Mol Biol.,** *882,* 635-680.

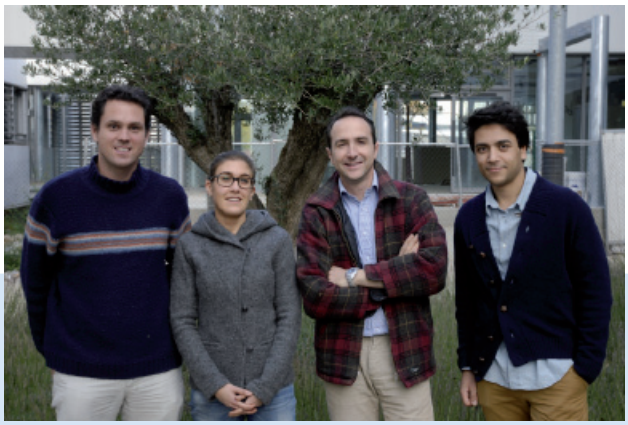




The IMGT® web server at Montpellier is accessed by more than 80,000 sites per year. IMGT® has an exceptional response with more than 150,000 requests per month. The IMGT® platform has been certified ISO 9001:2008 by LRQA France, in October 2010.

Antibodies represent a large number of the pharmaceutical substances submitted to the World Health Organization/International Nonproprietary Names (WHO/INN) Programme. The INN definition of antibodies is based on the IMGT-ONTOLOGY concepts. Since 2008, amino acid sequences of monoclonal antibodies (mAb, INN suffix -mab), of fusion proteins for immune applications (FPIA, INN suffix -cept) and composite proteins for clinical applications (CPCA) from WHO/INN have been entered into IMGT®. These therapeutic applications emphasize the importance of the IMGT-ONTOLOGY concepts in bridging the gap between antibody sequences and 2D and 3D structures.

Another great research interest, in collaboration with the Unit of Medical Genetics, St-Joseph University, Beirut (Pr A. Mégarbané), concerns very rare autosomal recessive genetic diseases in consanguineous Lebanese families. Patients are autozygous (homozygous by descent) for a very rare mutated gene present in the common ancestor of their parents who are cousins. These pathologies, almost unknown in panmictic populations, are invaluable starting points from which to identify unknown genes, their products and functions as well as links, unsuspected in populations without consanguinity, with cell physiology. For examples, the ICF (Immunodeficiency, Centromeric region instability and Facial anomalies) syndrome results from mutations either in the DNA methyltransferase 3B (DNMT3B) gene in most cases (type 1) or in the ZBTB24 gene (type 2); there are two forms of the Hyper IgE syndrome: a sporadic-dominant form due to dominant negative mutations of STAT3 and a recessive form due to mutations in the Dedicator Of CytoKinesis 8 (DOCK8) gene; mutations of SP110 are responsible for the hepatic veno-occlusive disease with immunodeficiency (VODI-ID); many candidate genes for adaptive and innate immunodeficiencies have been investigated; recessive infantile osteopetrosis, a bone disease with neural involvement in the most severe form, results from mutations of the TCIRG1 (Atp6a3), CLCN7 or OSTM1 (grey lethal) genes. The genome evolution (Alu sequences, mtDNA, Y chromosome) is analyzed in Lebanon and in Tunisia, along the paths of human expansion out of Africa. We study also markers of positive selection or, conversely, of susceptibility towards infectious diseases. In these cases also, as well as in complex genetic diseases, consanguineous families are powerful and time-saving sources of information.



Genome Surveillance and Stability

DOMENICO MAIORANO
Domenico Maiorano@igh.cnrs.fr

Domenico Maiorano
Research Scientist INSERM

Siem Van Der Laan,
Post-doctoral Fellow

Dana Hodroj,
PhD student

Chames Kermi,
PhD student

Our team is interested in the regulation of DNA damage and replication checkpoints. This surveillance mechanism is crucial for the maintenance of genomic stability when DNA integrity is compromised. Exposure to chemical compounds, replication fork (the functional units of DNA synthesis) arrest and endogenous cues, such as free oxygen radicals or the metabolism of the DNA itself, constitute major sources of mutations that continuously threaten the integrity of the cell genome. Checkpoint signals are generated in order to block cell division and activate repair pathways necessary to regenerate the normal DNA state. In the presence of high levels of damaged DNA this signaling pathway can promote the activation of programmed cell death, or apoptosis.

The experimental model systems we employ are in vitro extracts derived from activated eggs of the amphibian Xenopus laevis as well as mammalian cells. Xenopus egg extracts faithfully reproduce the cell cycle in vitro and particularly the regulated activation of replication-independent and -dependent checkpoint signaling induced by different DNA damaging agents, such as UV rays, gamma radiations and genotoxic agents (cys-platin, methyl methanesulfonate).

Although the genes that control the DNA damage and replication checkpoints are well conserved throughout evolution, a number of them are only found in vertebrates, and these are often mutated in several cancers. We are using a functional in vitro screen as well as in silico approaches to search for new, vertebrate-specific checkpoint genes.

We are also interested in identifying the molecular mechanism of sensor activation, the proteins that recognize the lesions and, particularly, the structures recognized by the sensors and the consequences of this recognition on the sensor functions. We have recently shown that the DNA repair protein XRCC1 halts DNA replication forks in front of unrepaired single stranded DNA lesions by interacting with the DNA primase, the enzyme that catalyzes the initiation of DNA synthesis. This regulatory mechanism would prevent conversion of single stranded into double stranded DNA breaks, which are highly recombinogenic and can induce strong genomic instability. More recently, we have analyzed the specific role of the single stranded DNA binding protein RPA in S-phase checkpoint activation and surprisingly found that, in contrast to what previously thought, its nucleation onto single stranded DNA generated at arrested forks, nor its phosphorylation, is dispensable for checkpoint activation. We have also observed that in these conditions replication slows down and activates spontaneously the checkpoint through the production of single stranded DNA. Hence, generation of single stranded DNA can be considered as a general cellular response to replication stress that functions in checkpoint activation independently of RPA. We are currently analyzing the role of RPA binding to single stranded DNA in genome stability during replication stress.

For more information see the team web page: http://www.igh.cnrs.fr/equip/domenico.maiorano/

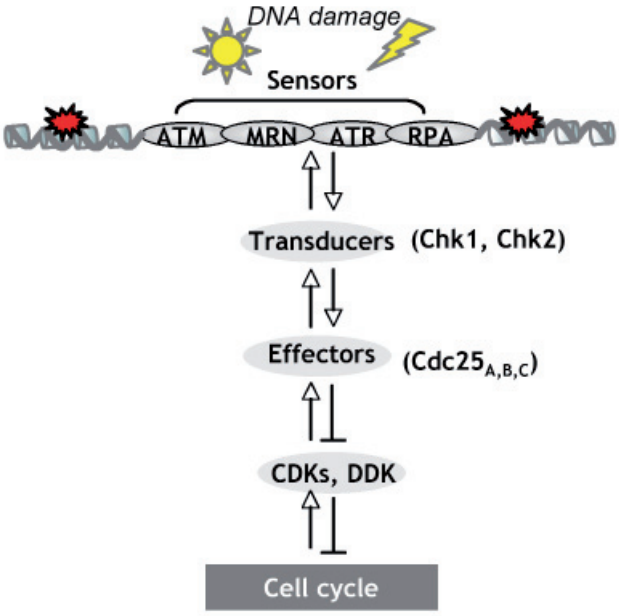
- Recolin, B. and Maiorano, D. (2012). Implication of RPA phosphorylation in S-phase checkpoint signalling at replication forks stalled with aphidicolin in Xenopus egg extracts. **Biochemical and Biophysical Research Communications**. October 6 (in press) doi: 10.1016/j.bbrc.2012.09.139.

-Recolin, B., Van der Laan, S., Maiorano, D (2011). Role of replication protein A as sensor in activation of the S-phase checkpoint in Xenopus egg extracts. **Nucleic Acids Research** Dec 22. [Epub ahead of print].

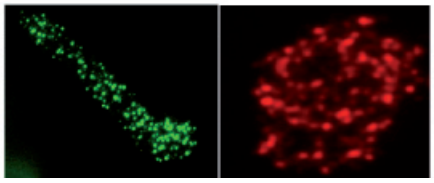
- Levy, N., Oehlmann, M., Delalande, F., Nasheuer, HP., Van Dorsselaer, A., Schreiber, V., De Murcia, G., Ménissier-de Murcia, J., Maiorano, D*, Bresson, Anne*. (2009) XRCC1 interacts with the p58 subunit of DNA Pol α-primase and may coordinate DNA repair and replication during S phase». **Nucleic Acids Research**, *37*, 3177-3188. (*corresponding authors)

- Recolin, B., Maiorano, D. (2009) Regulation of S phase during early embryonic Xenopus development. In « **Cell Cycle and Development in vertebrates** ». Ed. Research Signpost.

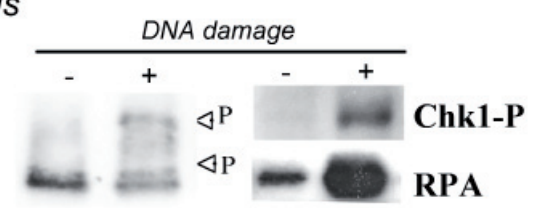
- Auziol, C., Méchali, M. and Maiorano, D. (2007) Geminin is cleaved by caspase 3 during apoptosis in Xenopus egg extracts. **Bioch. Bioph. Res. Comm**., *361*, 276-280.



Xenopus

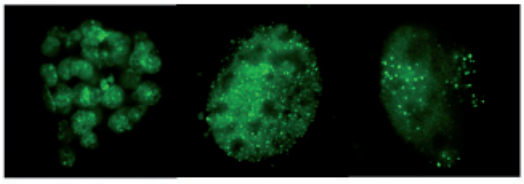


Recruitment of the RPA protein to replication-independent DNA damage foci induced by DNA double strand breaks (green) or replication-dependent damage foci induced by UV irradiation (red) in nuclei reconstituted in vitro in Xenopus egg extracts. RPA is visualized by indirect immunofluorescence.



Recruitment of the phosphorylated form of the RPA protein to damaged chromatin (left) or to single stranded DNA produced by replication fork uncoupling upon UV irradiation (right) in Xenopus egg extracts. RPA and Chk1 phosphorylation are visualized by western blot.

Mammalian cells



Detection of DNA damage foci in nuclei of mouse-embryonic stem cells upon UV irradiation (left) and in whole (center) or locally-damaged (right) mammalian cells nuclei.

Maintenance of Genome Integrity during DNA Replication

PHILIPPE PASERO
Philippe.Pasero@igh.cnrs.fr

Philippe Pasero
Research Director INSERM

Armelle Lengronne,
Research Scientist CNRS
Yea-Lih Lin,
Research Scientist CNRS
Hélène Tourrière,
Research Scientist CNRS

Julie Saksouk,
Technician CNRS

Benjamin Pardo,
Post-doctoral Fellow

Mireille Tittel-Elmer
Post-doctoral Fellow

Kazumasa Yoshida,
Post-doctoral Fellow

Axel Delamarre,
PhD student
Jérôme Poli,
PhD student
Alexy Promonet,
PhD student
Maria-Joao Silva,
PhD student

Julien Bacal,
Engineer
Damien Desmarais,
Engineer

Genomic instability is a hallmark of cancer cells. Recent studies indicate that DNA damage accumulates in pre-cancerous lesions as a consequence of spontaneous replication defects. This in turn promotes genomic instability and activates checkpoint pathways driving cells to apoptosis or senescence. Defects in the p53 pathway allow pre-cancerous cells to bypass these anti-cancer barriers and to progress through the cancer process. An important goal in cancer research is therefore to understand why replication stress arises spontaneously at early stages of tumorigenesis.

We use yeast and human cell lines as model organisms to identify regions of the genome that are intrinsically difficult to replicate and that induce spontaneous replication stress. We also investigate the cellular responses to replication stress in normal cells and in cancer cell lines. To this end, we take advantage of powerful new technologies, such as DNA combing, ChIP-chip and ChIP-seq, to monitor origin firing and replication fork progression both in individual molecules and genome-wide (Poli et al., 2012; Tittel-Elmer et al., 2012).

Using these technologies, we have recently identified a novel mediator of the DNA replication checkpoint (DRC) in yeast that is essential for the timely activation of the DRC in HU-treated cells (Crabbé et al., 2010). We also monitor the activation of the replication checkpoint during normal S phase, using gamma-H2AX as a marker for spontaneous replication stress. This analysis indicates that gene expression interferes with DNA replication. This is consistent with an earlier report from our laboratory showing that DNA-RNA hybrids accumulate in the human genome when mRNP assembly is perturbed, thus hindering replication fork progression and inducing chromosome breaks (Tuduri et al., 2009). Whether replication/transcription interference also occurs in pre-cancerous lesions is an important question that remains to be addressed.

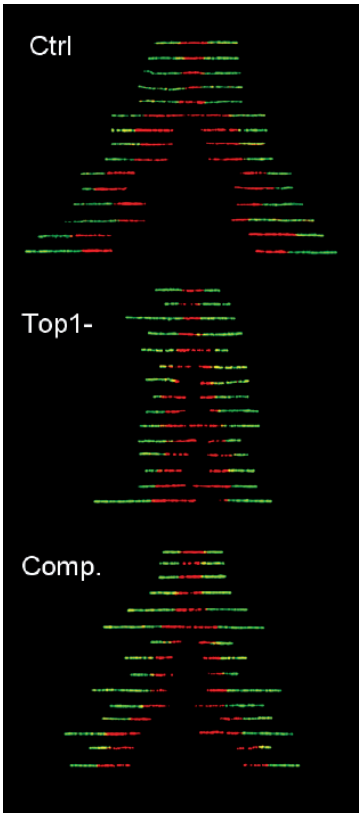
- Tittel-Elmer, M#, Lengronne, A#, Davidson, MB., Bacal, J., François, P., Hohl, M., Petrini, J., Pasero, P* and Cobb, JA* (2012) Cohesin association to replication sites depends on Rad50 and promotes fork restart. **Mol Cell,** *48,* 1, 98-108 (# equal contribution, * corresponding authors)

- Poli, J., Tsaponina, O., Crabbe, L., Keszthelyi, A., Pantesco, V., Chabes, A., Lengronne, A* and Pasero, P* (2012). dNTP pools determine fork progression and origin usage under replication stress. **EMBO J,** *31,* 883-894 (* corresponding authors)

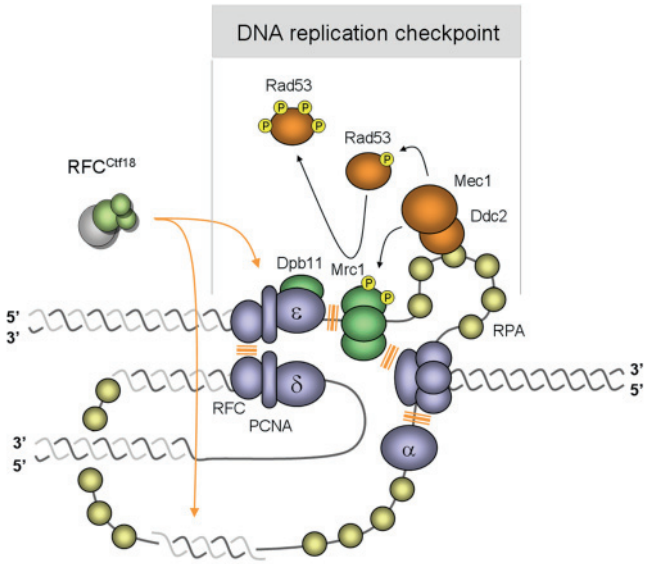
- Crabbé, L., Thomas, A., Pantesco, V., De Vos, J, Pasero, P* and Lengronne, A.* (2010) Genomic analysis of replication profiles identifies RFCCtf18 as a key mediator of the replication stress response. **Nat. Struct. Mol. Biol.,** *17*, 11, 1391-1397 (* equal contribution)

- Tuduri, S., Crabbé, L., Conti, C., Tourrière, H., Holtgreve-Grez, H., Jauch, A., Pantesco, V., de Vos, J., Theillet, C., Thomas, A., Pommier, Y., Tazi, J., Coquelle, A.* and Pasero, P.* (2009) Topoisomerase 1 suppresses replication stress and genomic instability by preventing interference between replication and transcription. **Nat Cell Biol**, *11*, 1315-1324 (* equal contribution)

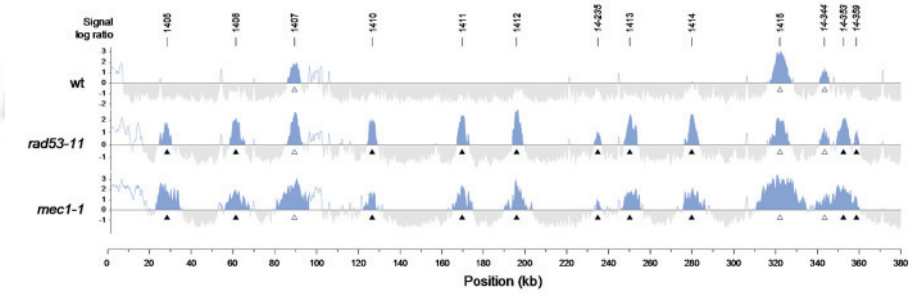
- Alabert, C., Bianco, J. and Pasero, P. (2009) Differential regulation of homologous recombination at DNA breaks and replication forks by the Mrc1 branch of the S-phase checkpoint. **EMBO J.**, *28*, 1131-1141



DNA combing analysis of replication forks progression and pausing in Top1-deficient mouse cells. Control mouse P388 cells (Ctrl), Top1-deficient cells (Top1-) and Top1-deficient cells complemented with human Top1 were analysed by DNA combing after two pulses of IdU (red) and CldU (green). Replication forks progress more slowly and pause more frequently in Top1- cells (Tuduri et al., 2010).



Activation of the DNA replication checkpoint in budding yeast. Accumulation of ssDNA at stalled forks is detected by the ATR-homolog Mec1, which activates the effector kinase Rad53. Amplification of the checkpoint response depends on the checkpoint mediator Mrc1. Recent evidence also indicate that the RFC-Ctf18 complex, best known for its role in the establishment of sister-chromatid cohesion, is also essential for the Mrc1-dependent activation of Rad53 (Crabbé et al., 2010).



BrdU-IP-chip analysis of origin activity in checkpoint mutants. Yeast wt, rad53-11 and mec1-1 cells were synchronized in G1 with alpha factor and were released for 90 min in fresh medium containing BrdU to label replication origins and HU to block elongation. BrdU-labeled DNA was immunoprecipitated and hybridized on Affymetrix tiling arrays. A map of a fraction of chromosome XIV is shown. Empty arrowheads: early origins. Filled arrowheads: late origins.

ADMINISTRATION

General secretariat : BRIGITTE MANGONI

Brigitte.Mangoni@igh.cnrs.fr

Executive secretariat : ANNE-PASCALE BOTONNET
Anne-Pascale.Botonnet@igh.cnrs.fr

Financial Management : Sahondra RAKOTONDRAMASY
Marie-Claire MERRIOT
Harizakanirina RAJAONARIVELO

FINANCIAL MANAGEMENT OF THE LABORATORIES :

- Order forms (5000/year), invoices, travel reimbursements (500/year), incomes, notifications;
- Agreements, equipment purchase and tenders;
- Help with the preparation of the budget, and follow-up of the budget implementation.

Administrative secretariat : Silke CONQUET
Stéphanie MARTINETTI

COMPUTING FACILITY

GUILLAUME GIELLY

Guillaume.Gielly@igh.cnrs.fr

Guillaume Gielly
Engineer CNRS

Jacques Faure,
Technician CNRS

Alfred Vriese,
Engineer CNRS

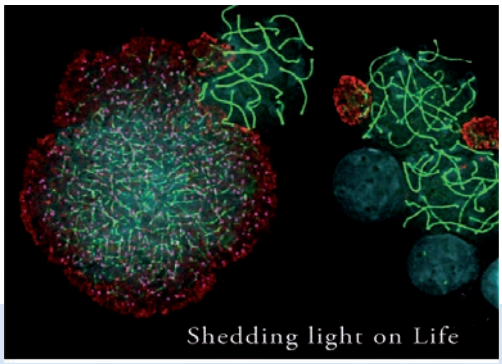
The computing staff assures the smooth running of the computing facility (network infrastructures and services, database servers, grid computing servers, backup and virtualization servers), offers help and advice to the users at the Institute of Human Genetics (IGH) and is involved in IT research and development.

The computing facility includes three full-time employees who run the IT infrastructure, offer computational support and assure the technological monitoring. The different activities of the service include:

- The choice and daily installation of common resources for the exploitation systems and network software: DNS (Domain Name System), mail, anti-spam, web homepages, backup, virtualization, diffusion lists, users' directories, and compute server for data analysis. About one hundred physical and virtual servers are housed at the Institute.
- The management of the local server, the remote groups at the CHU and IURC sites as well as the security: +600 Ethernet sockets, definition and implementation of the security policy.
- Hosting the FTP mirrors: GNU & Savannah, Debian-Multimedia; the GNU/Linux and BSD (0linux, Nutyx, PC-BSD) distributions and the software forge for the free NetBSD project
- Users' support: advice, troubleshooting, training
- Development of innovative solutions to answer to specific users' needs.
- Purchase of IT equipment and software for the Institute after having taken into consideration the users' preferences and requirements
- Management of the IP telephony infrastructure
- Management of the groups' web servers and databases
- Software licensing
- Technological monitoring activity

Moreover, we are playing an active role in a new scientific facility (MAGMA: Make Analysis in Montpellier fAcilities) that offers the opportunity to the research groups in the Languedoc-Roussillon region of carrying out powerful analyses of sequencing data. A cluster system has been set up in partnership with the Institute of Functional Genomics (Institut de Génomique Fonctionnelle, IGF) in order to offer high speed access with high availability. An original data storage system (4U-high, 90To in ZFS) has been developed by the IGH computing staff to answer to the need of an important disk volume.

We host also several databases to make scientific data available to the scientific community.



CELL IMAGING FACILITY

JULIEN CAU

Julien.Cau@igh.cnrs.fr

Julien Cau,
Engineer CNRS

Julio Mateos-Langerak,
Engineer CNRS

The cell imaging facility of the Arnaud de Villeneuve/IFR3 campus is located on the basement floor of the Institute of Human Genetics. On its premises (approx. 100 m^2) state-of-the-art image acquisition and analysis workstations are housed under the supervision of two-three scientific officers.

The facility is part of the Montpellier RIO Imaging distributed facility. This structure is dedicated to light/electron microscopy, X-ray tomography and flow cytometry. The facility is managed within an ISO:9001 framework (i.e., its main aims are increased users' satisfaction and continuous improvement). The whole facility is used by about 600 active users over the city and the site at the Institute of Human Genetics by approximatively 150 people.

The facility hosts the equipment previously located within the building (5 widefield microscopes). It also offers three confocal microscopes for high resolution observation of thick samples: a regular one, a macro-confocal (for observation of sample up to 19mm wide) and a high sensitivity set-up (with GaAsP detectors). The facility recently entered the super-resolution path following the acquisition of a structured illumination microscope. This piece of equipment, under the supervision of a dedicated engineer, allows the observation of specimens with a lateral resolution of 100nm and an axial resolution of 300nm. Thus the observation volume is 8 times smaller, allowing super-resolution imaging of samples. Images and the derived data from any workstation can be further analyzed on dedicated computers (deconvolution, 3D rendering, 3D image processing and measurements, analysis automation). The detailed list of the services provided by each workstation is included in the facility web site (see www.mri.cnrs.fr).

Beside this state-of-the-art equipment, a set of good quality microscopes (stereomicroscope, upright and inverted microscopes) are available on a free-access basis (no booking required) for rapid inspection of samples or sample preparation/dissection at the laboratory bench.

New users are encouraged to contact the facility manager in order to have a brief introduction about the facility rules and to better identify their needs in cell imaging before they prepare their samples.

INFORMATIC DEVELOPMENT FOR RESEARCH SUPPORT

CYRIL SARRAUSTE de MENTHIERE

Cyril.Sarrauste@igh.cnrs.fr

Cyril Sarrauste
Engineer CNRS

Eric Stossel
Assistant
Engineer CNRS

The mission of the service is to design and develop programs or databases for "dynamic access" applications available on the web.

Our work involves the maintenance and development of the institute website with programs and intranet tools for both scientific and administrative operations within the institute. For example, these comprise an institute booking system for all common equipment, seamless updating of the institute publication database, various administrative directory services including the personnel directory, the research groups' directory and the secretarial and administrative staff's directory. In addition, thanks to these tools, the different services and group leaders can manage and update the databases and / or the information of their own web pages.

Concerning the development side, when a research group or department has specific projects with needs beyond the strict confines of the IGH, we analyze the project requirements to design, develop and implement tools both web-based and at the workstation level.

For example,

* TraCSEH: a traceability tool for human embryonic stem cells,
* WebCongress: a complete environment for managing the organization of seminars up to international conferences, ranging from speakers' registration, abstract submission and review to automatic badge generation, abstract book production and the management of room assignment and billing.
* EpiGeneSys: tools tailored to the management of European project (7th FP) coordinated by IGH scientists.
* BioCampus Montpellier network of technological platforms for life sciences in Montpellier.
* Labex EPIGENMED a BioHealth research program selected by the French Ministry of Research and Education in the framework of the "Laboratoires d'Excellence" initiative.

The relevance of many of these tools, which have been specifically developed initially for the IGH (in particular WebCongress), is shown by their deployment now by regional and national institutions for their specific and own uses.

The facility also develops and supervises special projects for external laboratories, for instance:

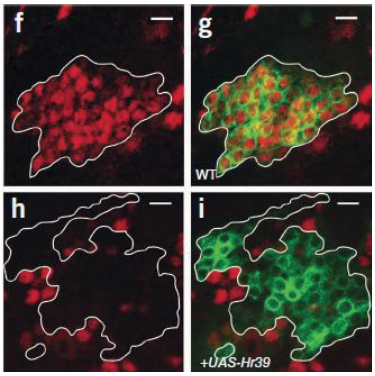
* Design of the RHEM Website for the Network of Experimental Histology in Montpellier.
* Consultant for R@M (Network of the animal house facilities of Montpellier) for the control of software deployment and management of animal welfare facilities.
* Design of CQE ACLF: quality control software for French cytogenetic laboratories.

Finally, the service provides full user's support for all desktop softwares, bibliographic management tools, computer aided design (CAD) and computer aided publication (CAP).

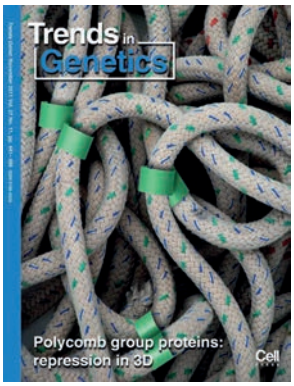
Keywords: programming, databases, interfaces, bioinformatics, DAO

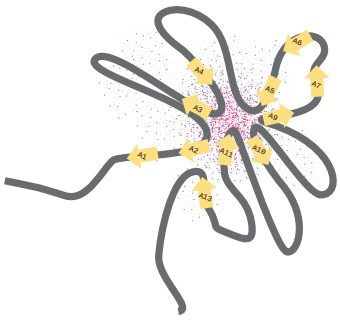
- C. Cartier, C. Sarrauste de Menthière inventors. (2009). Patentee: CNRS. "TraCSEH: Tool for Traceability of Human Embryonic Stem Cells". IDDN: FR.001.090013.001.SP2007.000.10000
- Milhavet F. Sarrauste de Menthière C., Touitou I. (2008). "The international society for systemic auto-inflammatory diseases (ISSAID)". Clinical and Experimental Rheumatology, *26,* 222 DD1
- Milhavet, F. Cuisset, L., Hoffman, H., Slim, R., El-Shanti, H., Aksentijevich, I., Lesage, S., Waterham, H., Wise, C., Sarrauste de Menthière , C., Touitou, I. (2008). "The auto-inflammatory Infevers mutation online registry: update with new genes and functions". HUM. TRANSFER, *29,* 803-808.

Some user's support in CAP / CAD

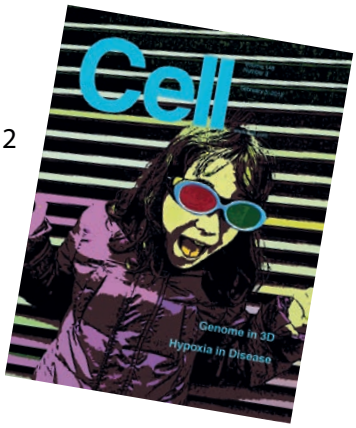


Published in Boulanger *et al.* Nat Neurosci. 2010





Trends Genet. 27(11) 2011 cover and published in Bantignies *et al.*



Cover of Cell 148(3) 2012

Some projects

Data flow poster, shown in Vienna, dec. 2011

EPIGENMED

BioCampus Montpellier

ACLF

Some uses of the «WebCongresses» tool

COMMUNICATION & TRAINING PROGRAM

CATHERINE LAROSE

Catherine.Larose@igh.cnrs.fr

The Communication department of the Institute serves as an interface between various audiences:
• internally, to facilitate the scientists, Institute and IGH staff interactions;
• externally, to connect the scientists and the Institute with different groups (e.g., citizens, decision makers, associations and economic stakeholders).

The IGH Communication Department co-operates with the Communication Department at the CNRS regional office (DR 13)

These actions aim at:
- Increasing the visibility of the Institute,
- Informing the scientific community on the scientific life of the Institute
- Informing the public about the activities of our Institute
The department contributes to both the internal and external IGH / CNRS communication and harmonizes projects with our partners.

We have focused our work specifically on:
• Organizational support for international meetings organized by IGH scientists on different topics, such as Epigenetics and Meiosis
• Development of relationships between academic institutions and scientists (Fête de la Science)

Institutions involved:
- DR 13 (CNRS regional office)
- CNRS communication department
- ADR 8 / INSERM (National)
- Universities 1 and 2 of Montpellier

Its missions include:

- Monitoring the implementation of the IGH science policy
- Relationship with the CNRS communication department and with other research institutes to facilitate the organization of events of scientific interest, especially directed towards young people (Fête de la Science ...) at the national and regional level.
- Preparation of scientific information to be used for communication, working closely with the IGH management
- The multidisciplinary perspective of scientific information.

TECHNICAL SUPPORT

Health & Safety : Robert Orti

The health and safety engineer (ACMO) plans, implements and coordinates the institute safety programs to prevent and correct unsafe environmental working conditions

Technical Servicing : Daniel Bellenoue

Store : Faiza Laachir - Stéphane Raoulx

The IGH stores contribute to the smooth running of the institute research activities and therefore improve the life of the IGH staff. Products and materials required by the research groups and the common facilities are available. The stock composition is mainly organized based on the researchers' requirements and proposals.

The catalog contains 1600 references.

Washing/Sterilization Service & Preparation of Laboratory Media

Scientific Leader : Francis Poulat
- Marie-Thérèse Molinier
- Séverine Nadaud

Drosophila Facility :

Scientific manager : Martine Simonelig
- Stéphanie Chalmeton
- Mustapha Hanyn
- Fabienne Mazur

Animal Housing Facilities :

Scientific manager : Anne Fernandez
- Audrey Combe-Sainseau

ANIMAL HOUSING FACILITY

Barrier Unit
Animal Housing Facility

Scientific manager
Anne Fernandez

Manager : Florence Arnal

- Audrey Combe-Sainseau

- Segolene Debiesse
- Luc Forichon
- Frederic Gallardo
- Elodie Gavois
- Jennifer Guillemin
- Florent Paillasse
- Alain Sanchez

Microbiological status and hosted species:

- 140 m^2 dedicated to the breeding and housing of genetically modified mice, under a specific pathogen-free (SPF) status. The entry into this SPF zone is strictly limited to the zootechnicians who take care of the animals. It is located in the IGH building and hosts about 6 000 mice permanently. 15 000 new animals per year are tagged for 22 user teams. The genotyping service spares tedious and time-consuming bench work for researchers, and ensures the timely delivery of genotype identification to the personnel taking care of the animals.

- 30 m^2 for housing rabbits and Xenopus frogs under a conventional status. This zone, located in the IGH building, hosts rabbits used for the production of antibodies against specific epitopes, and Xenopus frogs to produce ovocytes for developmental biology or for the study of ionic channels.

- 60 m^2 for rodents under a conventional status, in the IGF building. This facility hosts wild type mice and rats, and is also dedicated to short-time housing of class I genetically modified animals in view of quick testing of well-defined scientific hypotheses (promising mouse lines are then decontaminated and transferred into the SPF zone for long-term research projects). Moreover, the facility also provides help to researchers with injection protocols or small surgery (orchydectomy, ovariectomy...). We recently established an Ethics Committee for animal experimentation. Affiliated with the Ethics Committee of the Languedoc Roussillon region (CEEA-LR), this local committee is devoted to provide advice for designing experiments with animals and filling in the protocol forms to be submitted to the CEEA-LR.

DROSOPHILA FACILITY



Scientific manager :
Martine Simonelig

- Stéphanie Chalmeton
- Mustapha Hanyn
- Fabienne Mazur

The IGH fly facility is a state-of-the-art fly-pushing and genetic manipulation service where all fly laboratories can grow flies, perform genetic and developmental biology experiments and maintain their stocks.

In terms of space, the facility has three rooms at different temperatures (18°C, 21°C and 25°C) and several high-precision incubators. Two more rooms are dedicated to the work with binocular microscopes, with 15 workstations equipped with CO2. A GFP-binocular is also available, as well as injection equipment for production of transgenic fly lines.

The facility personnel are in charge of maintaining the *Drosophila* laboratory stocks for each *Drosophila* group at the IGH. In total about 3.500 different *Drosophila* stocks are maintained permanently.

Furthermore, the *Drosophila* facility provides fly food to the whole Montpellier *Drosophila* community spread over four different institutes. The facility produces 10.000 ready-to-use *Drosophila* vials per week. As such, the services provided by the facility personnel are essential to the whole *Drosophila* community in Montpellier.

JANUARY

27.01.11
Mark Wainberg
Mc Gill University - USA
Bases moléculaires pour des distinctions entre différentes soutypes de VIH dans le développement des mutations associées a la résistance aux antiretroviraux

28.01.11
Blanche Capel
Duke University Medical Center - Durham - USA
Vascular Patterning of Gonad Development

FEBRUARY

04.02.11
Cyril Ribeyre
Dept Biologie Moléculaire - Genève - SWITZERLAND
Multiple functions of telomere capping proteins in budding yeast

18.02.11
Monica Bettencourt-Dias
Institute Gulbenkian de Cienca - Oeiras - PORTUGAL
Centrosome and cilia biogenesis and evolution

MARCH

08.03.11
Antoine Peteers
Friedrich Miescher Institute for Biomedical Reserach - Basel - SWITZERLAND
Intergenerational epigenetic control of mammalian early embryonic development

24.03.11
Wolfgang Fischle
Max Planck Institute for Biophysical Chemistry - Goëttingen - GERMANY
Molecular analysis of histone methylation readout

25.03.11
Wolf-Dietrich Heyer
University of California, Davis, USA
Functions of the human breast and ovarian tumor suppressor protein BRCA2 in recombinational DNA repair

APRIL

01.04.11
Olivier Pourquié
Institut de Génétique et de Biologie Moléculaire et cellulaire - Strasbourg - FRANCE
Patterning the vertebrate axis: clocks and scoliosis

08.04.11
Christian Eckmann
Max Planck Institute of Molecular cell biology and genetics - Dresden - GERMANY
Germ Cell fate determination by RNA regulatory circuits

04.04.11
Katherine Jones
The Salk Institute for Biological Studies - LA JOLLA
Transcription elongation and the integration of nuclear events

15.04.2011
Jean-Marc Egly
IBMC Strasbourg
The NER factors are part of the transcription process

22.04.2011
William Vainchenker
Institut Gustave Roussy, Villejuif
Syndromes myéloprolifératifs de JAK2 à TET2

MAY

06.05.2011
Germain Gillet
Centre de recherche en cancérologie de Lyon Université Claude Bernard Lyon I INSERM U1052- CNRS UMR 5286
The role of the Bcl- 2 family of apoptosis regulators in neoplastic transformation and early development : a zebrafish case

13.05.2011
Gérard Roizes
énomique et maladies communes

20.05.11
David Glover
Dept Genetics - University of Cambridge - UNITED KINGDOM
Poles of Polo, PIk4 and Greatwall kinases in the centrosome duplication cycle

27.05.2011
Dr Paula Vazquez-Pianzola
Institute of Cell Biology, University of Bern, Switzerland
Bic-D's little helpers in localizing mRNAs in Drosophila

JUNE

10.06.2011
Lothar Schermelleh
Ludwig Maximilien University of Munich
Towards multi-dimensional epigenomics - super resolution imaging of nuclear topology with 3D-SIM

14.06.2011
Nicolas Bertin
Genome-wide promotome-transcriptome profiling from nanogram-scale samples : application to the mouse olfactory epithelium

2011

17.06.2011
Jose L. Garcia-Perez
Spanish Stem Cell Bank - University of Granada
Epigenetic control of human LINE-1 retrotransposition

28.06.2011
Alain Robichon
AgroBiotech Sophia-Antipolis
Heritability of epigenetic marks in insects

JULY

08.07-2011
Frank Kirchhoff
Ulm University Medical Center
Role of Vpu and Nef in HIV transmission and pathogenesis

21.07/.2011
Frédéric Pontvianne
Epigenetic mechanisms of repetitive gene dosage control: the case of rRNA genes in plants

SEPTEMBER
06-09-2011
Steffen DIETZEL
Ludwig-Maximilians-Universität München
Label-free deep tissue imaging with second and third harmonic generation microscopy

07-09-2011
Pr. Yoshihiro Nakatani
Dysfunction of p600/UBR4 induces caspase-independent cell death in various types of cancer cells

16.09.2011
Akira Shinohara
Osaka University
Mediators of two RecA homologs, Rad51 and Dmc1 in recombination

22-09-2011
Benjamin Prado
Centro Andaluz de Biología Molecular y Medicina Regenerativa - Universidad de Sevilla (Spain)
Branch structure nuclease functions during Break-Induced Replication

23-09-2011
Maria Moriel-Carretero
Centro Andaluz de Biología Molecular y Medicina Regenerativa), Universidad de Sevilla (Spain))
Genetic instability associated to defects in the TFIIH complex

23-09-2011
Dan Camerini-Otero
National Institute of Health, Bethesda, USA
Early chromosomal events in mammalian meiosis

26-09-2011
John Lis
Molecular Biology and Genetics, Cornell University, Ithaca, USA
The Dynamic Interplay of Transcription Regulation and Chromatin Structure

04-11-2011
Klaus Scherrer (Institut J. Monod, CNRS and Univ Paris Diderot, Paris)
About 3D Genome Organisation and Gene Expression: Unified Matrix Hypothesis and Genon Concept

04-11-2011
Antoine Graindorge (Center for Genomic Regulation (CRG), Barcelona)
Sex-specific translational control : identification of SXL co-factors and targetsJULY

21-11-2011
Fuyuki ISHIKAWA (Kyoto University)
Meiotic mRNA elimination system directs facultative heterochromatin formation in fission yeast

DECEMBER

02-12-2011
Nick J Proudfoot (Sir William Dunn School of Pathology - University of Oxford)
Gene punctuation in eukaryotes : Gene loops, R-loops and Non coding RNASEPTEMBER

08-12-2011
Marie-Claude Blatter (Swiss-Prot, Swiss Institute of Bioinformatics, Geneva)
Protein sequence databases: use and pitfalls

09-12-2011
Carla SALEH (Institut Pasteur PARIS)
RNAi and reverse transcription control viral persistence in Drosophile

16-12-2011
Noam KAPLAN (Weizmann Institute, Israel)
Principles of directional regulation in bidirectional promoters

JANUARY
06-01-2012
Deborah BOURC'HIS (Institut Curie, PARIS)
The fates of oocyte-inherited methylation04-11-2011

17-01-2012
Frédérique MAGDINIER (INSERM UMR 910 - MARSEILLE)
Telomeric silencing in human cells as a sensor of telomere integrity21-11-2011

20-01-2012
Jérémy Dufourt (GReD UMR INSERM 931 CNRS 6247 Clermont Universités)
Epigenetic germline regulation story of a "somatic" transposable element.

27-01-2012
Cristina CARDOSO (Technische Universität Darmstadt - Germany)
Duplicating the mammalian epigenome

FEBRUARY
09-02-2012
Caroline Jacquier-Labroche
Screening genes and chemical suppressors of miRNA silencing pathway in Drosophila

10-02-2012
Simon BOULTON (Clare Hall, Cancer Research, UK)
Genome stability: from worms to human disease

15-02-2012
Jérome Moreaux (Institut de Recherche en Biothérapies, INSERM Unité 1400, Hôpital Saint-Eloi, CHU de Montpellier)
Identification of new pathophysiological mechanisms in multiple myeloma and therapeutic applications

17-02-2012
Andrei Chabes (Dept. Of Medical Biochemistry and Biophysics - Umeå University - Sweden)
dNTPs and maintenance of genome stability

MARCH
02-03-2012
Dirk SCHUBELER (University of Basel, Switzerland)
Sequence grammar of the epigenome

07-03-2012
Frédéric CHIBON (Institut Bergonié - Bordeaux)
Instabilité chromosomique et potentiel métastatique des sarcomes

09-03-2012
Benjamin LOPPIN (Centre de Génétique et Physiologie Moléculaire et Cellulaire, Villeurbanne)
Paternal chromatin assembly in the drosophila zygote

16-03-2012
Yanick CROW (Genetic Medicine - St Mary's Hospital - Manchester UK)
Mendelian interferonopathies

26-03-2012
Olivier VOINNET (ETH, Zürich)
Caught in the Act – The Awakening and Demise of a Plant Retrotransposon: When, Where, How?

27-03-2012
Domenico MAIORANO (IGH - UPR 1142 CNRS)
Molecular mechanims of activation of the DNA damage response in embryos and somatic cells

28-03-2012
Julian SALE (MRC - Cambridge)
Replication of structured DNA and epigenetic stability

APRIL
02-04-2012
Roderic GUIGO (CRG Barcelone)
RNA Seq in the Encode project

04-04-2012
Massimo LOPES (Institute of Molecular Cancer Research - Zurich)
Structural and molecular insights into DNA replication stress

06-04-2012
Nicolas Nègre (INRA UMR1333-UMII - Montpellier)
Understanding transcriptional regulation through the annotation of the Drosophila epigenome

13-04-2012
Patrick HEUN (Max Planck Institute of Immunobiology and Epigenetics Freiburg, Germany)
Towards understanding the epigenetic identity of centromeres

20-04-2012
Yukihide TOMARI (Institute of Molecular and Cellular Biosciences - The University of Tokyo)
Making RISC

27-04-2012
Thomas PREAT (UMR7637 Laboratoire de neurobiologie - PARIS)
Three pairs of dopaminergic neurons gate long-term memory in Drosophila

MAY
03-05-2012
Reina FERNANDEZ DE LUCO (National Cancer Institute, NIH, Bethesda, USA)
A non-coding RNA regulates chromatin-mediated modulation of alternative splicing

11-05-2012
Hilary ASHE (University of Manchester - Faculty of Life Sciences)
BMP signalling and cell fate specification in Drosophila

29-05-2012
Razq HAKEM
Ubiquitylation, DNA damage response and cancer

JUNE
01-06-2012
Ian ADAMS (MRC Human Genetics Unit -Edinburgh - UK)
Preventing aneuploidy in the developing mammalian germline

08-06-2012
Ronald T. Hay (Wellcome Trust Centre for Gene Regulation and Expression - DUNDEE)
Role of SUMO-targeted ubiquitin E3 ligase RNF4 in the DNA damage response

12-06-2012
Nicolas Bertin (Omics Science Center (OSC), RIKEN Yokohama Institute - Japan)
ZENBU: secured scientific collaborations, data integration and omics visualization

15-06-2012
Michael Emerman
Evolution and Function of Restriction Factors Against HIV and Related Viruses

22-06-2012
Marc YCHOU (Directeur du Cancéropole Grand Sud-Ouest CRLC Val d'Aurelle)
Actualités et perspectives en recherche et thérapeutique du cancer colorectal

29-06-2012
ANAIS BARDET (Research Institute of Molecular Pathology (I.M.P.) Vienna)
Conservation of transcriptional regulation in Drosophila

JULY
04-07-2012
Maria Elena TORRES-PADILLA (INSTITUT DE GENETIQUE ET DE BIOLOGIE MOLECULAIRE ET CELLULAIRE (IGBMC))
Heterochromatin dynamics in early mammalian embryogenesis

05-07-2012
Robert Fuchs (Institut de Microbiologie de la Méditerranée, Marseille)
Molecular mechanisms of mutagenesis: the critical choice between Translesion Synthesis and Damage Avoidance

06-07-2012
Bruno LEMAITRE (Ecole Polytechnique fédérale de lausanne, Switzerland)
The Drosophila gut: a new paradigm for epithelial immune response

06-07-2012
Dalibor BLAZEK (CEITEC-Masaryk University - BRNO - Czech Republic)
transcription cycle-related cyclin-dependent kinases and their role in the maintenance of genomic stability

13-07-2012
Kim BAEK (Department of Microbiology and Immunology / University of Rochester Medical Center / Rochester USA)
Non-dividing Macrophages: A "Funny" Place for DNA Synthesis and Lesson from HIV Replication in Macrophages

SEPTEMBER

03-09-2012
Patrick MURPHY (Cornell University, Ithaca, NY, USA)
Novel Single Molecule Methods and Classic Techniques to Characterize Epigenetic Mark Regulation

26-09-2012
Stéphane Ronsseray (UMR7622 - BIOLOGIE du DEVELOPPEMENT CNRS - University Pierre et Marie CURIE (Paris 6) Lab)
Paramutation and piRNAs in Drosophila

28-09-2012
Pascal CARRIVAIN (Laboratoire de Physique Théorique de la Matière Condensée - Univ Pierre & Marie Curie)
Single-molecule manipulation application of the physics engine

OCTOBER

03-10-2012
Jean-Christophe Andrau (CIML)
From enhancer of transcription to transcription at enhancers and promoters, new insights to old dogmas

05-10-2012
Brendan Battersby (FinMIT)
Mitochondrial surveillance and the importance to cellular homeostasis

10-10-2012
Hironori Funabiki (The Rockefeller University, New York, USA)
Chromatin as a reaction platform: from the spindle to the nucleus

10-10-2012
Takehiko Ogawa (Yokohama University)
From spermatogonial transplantation to in vitro spermatogenesis

12-10-2012
Laurent Farinelli (Founder and CEO FASTERIS SA (http://www.fasteris.com/) - Plan les Ouates - Switzerland)
Illumina sequencing: overview and applications

16-10-2012
Nathalie ARHEL (Trafficking Avenir Group, U941, Génétique et Ecologie des Virus, Paris)
Intracellular trafficking of incoming HIV complexes to the nucleus and through the nuclear pore

18-10-2012
Nicolas Tricaud (INM)
Myelin sheath growth in space and axo-glial molecular crosstalk

19-10-2012
Karim BOUAZOUNE (Harvard Med. school - BOSTON)
Chromatin remodeling by the CHD7 protein is impaired by mutations that cause human developmental disorders

22-10-2012
Kerstin GARI (London Research Institute)
MMS19 links cytoplasmic iron-sulphur cluster assembly to DNA metabolism

26-10-2012
Rabih Murr (FMI, Bâle - CH)
DNA-binding factors mediate DNA methylation turnover at active distal regulatory regions

Abu-Raddad, LJ., Hilmi, N., Mumtaz, G., Benkirane, M., Akala, FA., Riedner, G., Tawil, O., Wilson, D. (2010) Epidemiology of HIV infection in the Middle East and North Africa. **AIDS**. *24* Suppl 2, S5-23. PMID: 20610949.

Baudat, F., Buard, J., Grey, C., Fledel-Alon, A., Ober, C., Przeworski, M., Coop, G., de Massy, B. (2010) PRDM9 is a Major Determinant of Meiotic Recombination Hotspots in Humans and Mice. **Science**. *327,* 5967, 836-840, PMID: 20044539.

Baudat, F., Buard, J., Grey, C., de Massy, B. (2010) Prdm9, a key control of mammalian recombination hotspots. **Med. Sci. (Paris)**, *26*, 5, 468-470. PMID: 20510143.

Benkirane, M., Sardet, C, Coux,O. (2010) Lessons from interconnected ubiquitylation and acetylation of p53: think metastable networks. Biochem. **Soc. Trans.,** *38*, Pt 1, 98-103. PMID: 20074043.

Bermúdez-López, M., Ceschia, A., de Piccoli, G., Colomina, N., Pasero, P., Aragón, L., Torres-Rosell, J. (2010) The Smc5/6 complex is required for dissolution of DNA-mediated sister chromatid linkages. **Nucleic Acids Res**. *38*, 19, 6502-6512, PMID: 20571088.

Castro, R., Bernard, D., Lefranc, MP., Six, A., Benmansour, A., Boudinot, P. (2010) *Fish Shellfish Immunol* ., in press, PMID: 20804845

Cayrou, C., Coulombe, P., Méchali, M. (2010) Programming DNA replication origins and chromosome organization. **Chromosome Res**., *18,* 1, 137-145, PMID: 20066560.

Chouery, E., Pangrazio, A., Frattini, A., Villa, A., Van Wesenbeeck, L., Piters, E., Van Hul, W., Coxon, F., Schouten, T., Helfrich, M., Lefranc, G., Mégarbané, A. (2009) A new familial sclerosing bone dysplasia. **Journal of Bone and Mineral Research**, *25,* 3, 676-680. PMID 20422625.

Crabbe, L., Thomas, A., Pantesco, V., De Vos, J., Pasero, P. and Lengronne, A.(2010) Analysis of replication profiles reveals key role of RFC-Ctf18 in yeast replication stress response. **Nat. Struct. Mol. Biol.**, *17*, 11 , 1391-1397. PMID: 20972444.

Cretenet, G., Le Clech, M., Gachon, F. (2010) Circadian Clock-coordinated 12 Hr period rhythmic activation of the IRE1 alpha pathway controls lipid metabolism in mouse liver. **Cell Metabolism,** *11,* 1, 47-57. PMID: 20074527.

Denden, S., Lakhdar, R., Leban, N., Daimi, H., El Hayek, D., Knani, J., Perrin, P., Lefranc, G., Ben Chibani, J. and Haj Khelil, A. (2010) Mise au point: déficit en alpha 1 antitrypsine. A review: alpha1 antitrypsin deficiency. **Rev. Med. Genet. Hum.**, *1*, 26-33.

Doucet AJ, Hulme AE, Sahinovic E, Kulpa DA, Moldovan JB, Kopera HC, Athanikar JN, Hasnaoui M, Bucheton A, Moran JV, Gilbert N. (2010) Characterization of LINE-1 Ribonucleoprotein Particles. **PLoS Genet**., *6*, 10, pii: e1001150. PMID: 20949108

Ehrenmann, F., Kaas, Q., Lefranc, MP. (2010) IMGT/3D Structure-DB and IMGT/DomainGapAlign: a database and a tool for immunoglobulins or antibodies, T cell receptors, MHC, IgSF and MhcSF. **Nucleic Acids Res.,** *38* (Database issue):D301-7., PMID: 19900967

Ehrenmann, F., Duroux, P., Giudicelli, V. and Lefranc, M.-P. (2010) Standardized sequence and structure analysis of antibody using IMGT®. In: **Antibody engineering,** Vol. 2, Kontermann R. and Dübel S. (eds), Springer-Verlab Berlin Heidelberg, chap. 2, pp. 11-31. ISBN: 978-3-642-01146-7

Eot-Houllier, G., Venoux, M., Vidal-Eychenie, S., Hoang, MT., Giorgi, D., Rouquier, S. (2010) PLK1 regulates both ASAP localization and its role in spindle pole integrity. **J. Biol. Chem**. In Press. PMID: 20615875.

Fiser, AL., Lin, YL., Portalès, P., Mettling, C., Clot, J., Corbeau, P. (2010) 1. Pairwise Comparison of Isogenic HIV-1 Viruses: R5 Phenotype Replicates More Efficiently Than X4 Phenotype in Primary CD4+ T Cells Expressing Physiological Levels of CXCR4. **J. Acquir. Immune Defic. Syndr.**, *53*, 2, 162-166, PMID: 20051874.

Fradkin, LG., Dura, JM., Noordermeer, JN. (2010) Ryks: new partners for Wnts in the developing and regenerating nervous system. **Trends Neurosci.,** *33,* 2, 84-92, PMID: 20004982.

Franckhauser, C., Mamaeva, D., Heron-Milhavet, L., Fernandez, A., Lamb, NJ. (2010) Distinct Pools of cdc25C Are Phosphorylated on Specific TP Sites and Differentially Localized in Human Mitotic Cells. **PLoS One**., *5,* 7, e11798. PMID: 20668692.

Gabelle, A., Roche, S., Gény, C., Bennys, K., Labauge, P., Tholance, Y., Quadrio, I., Tiers, L., Gor, B., Chaulet, C., Vighetto, A., Croisile, B., Krolak-Salmon, P., Touchon, J., Perret-Liaudet, A., Lehmann, S. (2010) Correlations between soluble alpha/beta forms of amyloid precursor protein and Abeta38, 40 and 42 in human cerebrospinal fluid. **Brain Res**., *1357*, 175-183, PMID: 20713025.

Giannattasio M, Follonier C, Tourrière H, Puddu F, Lazzaro F, Pasero P, Lopes M, Plevani P, Muzi-Falconi M. (2010) Exo1 competes with repair synthesis, converts NER intermediates to long ssDNA gaps, and promotes checkpoint activation. **Mol Cell.,** *40*, 1, 50-62. PMID: 20932474.

Godin, JD., Poizat, G., Hickey, MA., Maschat, F., Humbert, S. (2010) Mutant huntingtin-impaired degradation of beta-catenin causes neurotoxicity in Huntington's disease. **EMBO J**., *29,* 14, 2433-2445. PMID: 20531388.

Haj Khelil, A., Denden, S., Leban, N., Daimi, H., Lakhdhar, R., Lefranc, G., Ben Chibani, J., Perrin , P.(2010) Hemoglobinopathies in North Africa: a review. **Hemoglobin**. *34,* 1, 1-23. PMID: 20113284.

Halling-Brown, M., Pappalardo, F., Rapin, N., Zhang, P., Alemani, D., Emerson, A, Castiglione, F., Duroux, P., Pennisi, M., Miotto, O., Churchill, D., Rossi, E., Moss, DS., Sansom, CE., Bernaschi, M., Lefranc, MP., Brunak, S., Lund, O., Motta, S., Lollini, PL., Murgo, A., Palladini, A., Basford, KE., Brusic, V., Shepherd, AJ. (2010) ImmunoGrid: towards agent-based simulations of the human immune system at a natural scale. Philos. Transact. **A Math. Phys. Eng. Sci.** *368,* 1920, 2799-2815. PMID: 20439274.

Heron-Milhavet, L., Mamaeva, D., Leroith, D., Lamb, NJ., Fernandez, A. (2010) Impaired muscle regeneration and myoblast differentiation in mice with a muscle-specific KO of IGF-IR. . **J. Cell Physiol.** *225*, 1, 1-6. PMID: 20458740.

Herzig, CT., Lefranc, MP., Baldwin, CL. (2010) Annotation and classification of the bovine T cell receptor delta genes. **BMC Genomics**, *11*, 1, 100. PMID: 20144200.

Kalfa, N., Méduri, G., Philibert, P., Patte, C., Boizet-Bonhoure, B., Thibaut, E., Pienkowski, C., Jaubert, F., Misrahi, M., Sultan, C. (2010) Unusual Virilization in Girls with Juvenile Granulosa Cell Tumors of the Ovary Is Related to Intratumoral Aromatase Deficiency. **Horm. Res. Paediatr.** *74,* 2, 83-91. PMID: 20395670.

Kumar, R., Bourbon, HM., De Massy, B. (2010) Functional conservation of Mei4 for meiotic DNA double-strand break formation from yeasts to mice. **Genes and Development**, *24*, 12, 1266-1280. PMID 20551173.

Lakhdar, R., Denden, S., Knani, J., Leban, N., Daimi, H., Hassine, M., Lefranc, G., Ben Chibani, J., Haj Khelil, A. (2010) Relationship between glutathione S-transferase P1 polymorphisms and chronic obstructive pulmonary disease in a Tunisian population. **Genet. Mol. Res**. *9*, 2, 897-907. PMID: 20467983.

Lakhdar, R., Denden, S., Knani, J., Leban, N., Daimi, H., Hassine, M., Lefranc, G., Ben Chibani, J., Haj Khelil, A. (2010) Association of GSTM1 and GSTT1 polymorphisms with chronic obstructive pulmonary disease in a Tunisian population. **Biochem Genet.,** *48*, 7-8, 647-657. .PMID: 20495862

Lakhdar, R., Denden, S., Knani, J., Leban, N., Daimi, H., Hassine, M., Lefranc, G., Chibani, J.B. and Khelil, AH. (2010) Microsomal epoxide hydrolase gene polymorphisms and susceptibility to chronic obstructive pulmonary disease in the tunisian population. **Genet. Test. Mol. Biomarkers** *14,* 6, 857-863. PMID: 20932192

Lane, J., Duroux, P., Lefranc, MP. (2010) From IMGT-ONTOLOGY to IMGT/LIGMotif: the IMGT(R) standardized approach for immunoglobulin and T cell receptor gene identification and description in large genomic sequences. **BMC Bioinformatics**. *11*, 1, 223. PMID: 20433708.

Leban, N., Aloui, S., Touati, D., Lakhdhar, R., Skhiri, H., Lefranc, G., Achour, A., Elmay, M., Lopez-Trascasa, M., Sanchez-Corral, P., Chibani, J. and Haj Khelil, A. (2010) Atypical hemolytic uremic syndrome in the Tunisian population. **Int. Urol. Nephrol.**, *43,* 2, 559-564. PMID: 20499172

Malki S, Boizet-Bonhoure B, Poulat F. (2010) Shuttling of SOX proteins . **Int. J. Biochem. Cell Biol.**, *42,* 3, 411-416. PMID: 19808100

Martinez, AM., Cavalli, G. (2010) Uncovering a tumor-suppressor function for Drosophila polycomb group genes. **Cell Cycle**., *9,* 2. 215-216. PMID: 20046098.

Méchali, M. (2010) Eukaryotic DNA replication origins: many choices for appropriate answers. **Nat. Rev. Mol. Cell Biol**., *11,* 10, 728-738. PMID: 20861881.

Meyer, RE., Delaage, M., Rosset, R., Capri, M., Ait-Ahmed, O. (2010) A single mutation results in diploid gamete formation and parthenogenesis in a Drosophila yemanuclein-alpha meiosis I defective mutant. **BMC Genet.**, *11,* 1, 104. PMID: 21080953

Mougenot, AL., Bétemps, D., Hogeveen, KN., Kovacs, GG., Chouaf-Lakhdar, L., Milhavet, O., Lehmann, S., Legastelois, S., Pin, JJ., Baron, TG. (2010) Production of a monoclonal antibody, against human alpha-synuclein, in a subpopulation of C57BL/6J mice, presenting a deletion of the alpha-synuclein locus. **J. Neurosci. Methods.,** *192*, 2, 268-276, PMID: 20709102.

Muhlstein J, Golfier F, Frappart L, Poulizac G, Abel F, Touitou I, Hajri T, Raudrant D. (2010) Review: Repetitive hydatidiform moles. **Gynecol Obstet Fertil.** *38,* 11, 672-676 . PMID: 20965770.

Pallares-Ruiz, N., Philibert, L., Dumont, B., Fabre, A., Cuisset, L., Cointin, E., Rittore, C., Soler, S., Touitou, I. (2010) Combined mutation and rearrangement screening by quantitative PCR high-resolution melting: is it relevant for hereditary recurrent Fever genes? **PLoS One.** *5*, 11, e14096.PMID: 21124859

Pappalardo, F., Lefranc, MP., Lollini, PL., Motta, S. (2010) A novel paradigm for cell and molecule interaction ontology: from the CMM model to IMGT-ONTOLOGY. **Immunome Res.,** *6,* 1, 1. PMID: 20167082.

Pillaire, M.J., Selves, J., Gordien, K., Gouraud, P.A., Gentil, C., Danjoux, M., Do, C., Negre, V., Bieth, A., Guimbaud, R., Trouche, D., Pasero, P., Méchali, M., Hoffmann, JS, and Cazaux, C (2010) A DNA replication signature of progression and negative outcome in colorectal cancer. **Oncogene**, *29,* 6, 876-887. PMID: 19901968.

Pironon N, Puechberty J, Roizes G. (2010) Molecular and evolutionary characteristics of the fraction of human alpha satellite DNA associated with CENP-A at the centromeres of chromosomes 1, 5, 19, and 21. **BMC Genomics**., *11,* 1, 195.

Piwko, W., Olma, MH., Held, M., Bianco, JN., Pedrioli, PG., Hofmann, K., Pasero, P., Gerlich, DW., Peter, M. (2010) RNAi-based screening identifies the Mms22L-Nfkbil2 complex as a novel regulator of DNA replication in human cells. **EMBO J.** *29,* 24, 4210-4222. PMID: 21113133.

Poveda, AM., Le Clech, M., Pasero, P. (2010) Transcription and replication: Breaking the rules of the road causes genomic instability. **Transcription**.*1*, 2, 99-102. PMID:21326900

Provansal, M., Roche, S., Pastore, M., Casanova, D., Belondrade, M., Alais, S., Leblanc, P., Windl, O., Lehmann, S. (2010) Proteomic consequences of expression and pathological conversion of the prion protein in inducible neuroblastoma N2a cells. **Prion**, *4*, 4. PMID: 20930564

Robert, R., Lefranc, MP., Ghochikyan, A., Agadjanyan, MG., Cribbs, DH., Van Nostrand, WE., Wark, KL., Dolezal, O. (2010) Restricted V gene usage and VH/VL pairing of mouse humoral response against the N-terminal immunodominant epitope of the amyloid β peptide **Mol. Immunol.**, in press, PMID: 20970857.

Rouget, C., Papin, C., Boureux, A., Meunier1, AC. , Franco, B., Robine, N., Lai, E.C., Pelisson, A., & Simonelig, M. (2010) Maternal mRNA deadenylation and decay by thepiRNA pathway in the early Drosophila embryo. **Nature**, *467*, 7319, 1128-1132. PMID: 20953170.

Schuettengruber, B., Cavalli, G. (2010) The DUBle life of polycomb complexes. **Dev. Cell.** *18*, 6, 878-880. PMID: 20627069

Shahab-Osterloh, S., Witte, F., Hoffmann, A., Winkel, A., Laggies, S., Neumann, B., Seiffart, V., Lindenmaier, W., Gruber, AD., Ringe, J., Häupl, T., Thorey, F., Willbold, E., Corbeau, P., Gross, G. (2010) Mesenchymal stem cell-dependent formation of heterotopic tendon-bone insertions (osteotendinous junctions). **Stem Cells**., *28,* 9, 1590-1601.PMID: 20882636

Sobhian, B., Laguette, N., Yatim, A., Nakamura, M., Levy, Y., Kiernan, R ., Benkirane, M. (2010) HIV-1 Tat assembles a multifunctional transcription elongation complex and stably associates with the 7SK snRNP. **Molecular Cell.** *38,* 3, 439-451. PMID: 20471949.

Soler, S., Rittore, C., Touitou, I., Philibert, L. (2010) A comparison of restriction fragment length polymorphism, tetra primer amplification refractory mutation system PCR and unlabeled probe melting analysis for LTA+252 C>T SNP genotyping. **Clin. Chim. Acta**. in press, PMID: 21094154

Temme, C., Zhang, L., Kremmer, E., Ihling, C., Chartier, A., Sinz, A., Simonelig, M., Wahle, E. (2010) Subunits of the Drosophila CCR4-NOT complex and their roles in mRNA deadenylation. **RNA**, *16,* 7, 1356-1370. PMID : 20504953.

Tuduri, S., Tourrière, H., Pasero, P. (2010) Defining replication origin efficiency using DNA fiber assays. **Chromosome Res**., *18*, 1, 91-102, PMID: 20039120.

Tuduri, S., Crabbe, L., Tourrière, H., Coquelle, A., Pasero, P. (2010) Does interference between replication and transcription contribute to genomic instability in cancer cells? **Cell Cycle**. *9,* 10. PMID: 20495385.

Tuduri, S., Crabbé, L., Conti, C., Tourrière, H., Holtgreve-Grez, H., Jauch, A., Pantesco, V., De Vos, J., Thomas, A., Theillet, C., Pommier, Y., Tazi, J., Coquelle, A., Pasero, P.(2010) Topoisomerase I suppresses genomic instability by preventing interference between replication and transcription. **Nat. Cell Biol**., *12*, 11, 1122.. PMID: 21045805.

Abdel-Samad, R., Zalzali, H., Rammah, C., Giraud, J., Naudin, C., Dupasquier, S., Poulat, F., Boizet-Bonhoure, B., Lumbroso, S., Mouzat, K., Bonnans, C., Pignodel, C., Raynaud, P., Fort, P., Quittau-Prévostel, C., Blache, P. (2011) MiniSOX9, a dominant-negative variant in colon cancer cells. **Oncogene**, *30*, 22, 2493-2503. PMID:21297661

Antonacci, R., Mineccia, M., Lefranc, MP., Ashmaoui, HM., Lanave, C., Piccinni, B., Pesole, G., Hassanane, MS., Massari, S., Ciccarese, S. (2011) Expression and genomic analyses of Camelus dromedarius T cell receptor delta (TRD) genes reveal a variable domain repertoire enlargement due to CDR3 diversification and somatic mutation. **Mol. Immunol.,** *48,* 12-13, 1384-1396, PMID: 21511341

Anvar, SY., Hoen, PA., Venema, A., van der Sluijs, B., van Engelen, B., Snoeck, M., Vissing, J., Trollet, C., Dickson, G., Chartier, A., Simonelig, M., van Ommen, GJ., van der Maarel, SM,, Raz, V. (2011) Deregulation of the ubiquitin-proteasome system is the predominant molecular pathology in OPMD animal models and patients. **Skelet Muscle,** *1,* 1, 15. PMID:21798095

Ayrolles-Torro, A., Imberdis, T., Torrent, J., Toupet, K., Baskakov, IV., Poncet-Montange, G., Grégoire, C., Roquet-Baneres, F., Lehmann, S., Rognan, D., Pugnière, M., Verdier, JM., Perrier, V. (2011) Oligomeric-Induced Activity by Thienyl Pyrimidine Compounds Traps Prion Infectivity. **J. Neurosci**., *31*, 42, 14882-14892. PMID: 22016521

Bantignies, F., Cavalli, G. (2011) Polycomb group proteins: repression in 3D. **Trends Genet.** *27*, 11, 454-464. PMID: 21794944

Bantignies, F., Roure, V., Comet, I., Leblanc, B., Schuttengruber, B., Bonnet, J., Tixier, V., Mas, A., Cavalli, G. (2011) Polycomb-dependent Regulatory Contacts between Distant Hox Loci in Drosophila. **CELL,** *144,* 2, 214-226. PMID: 21241892

Barbezier, N., Chartier, A., Bidet, Y., Buttstedt, A., Voisset, C., Galons, H., Blondel, M., Schwarz, E., Simonelig, M. (2011) Antiprion drugs 6-aminophenanthridine and guanabenz reduce PABPN1 toxicity and aggregation in oculopharyngeal muscular dystrophy. **EMBO Mol Med**., *3,* 1, 35-49. doi: 10.1002/emmm.201000109.PMID: 21204267

Baudat F, Buard J, Grey C, de Massy B.(2011) What determines the localisation of spots of meiotic recombination? **Med Sci (Paris)** *27,* 12, 1053-1055. PMID:22192738

Bennasser, Y., Chable-Bessia, C., Triboulet, R., Gibbings, D., Gwizdek, C., Dargemont, C., Kremer, EJ., Voinnet, O., Benkirane, M. (2011) Competition for XPO5 binding between Dicer mRNA, pre-miRNA and viral RNA regulates human Dicer levels. **Nat. Struct. Mol. Biol.,** *18,* 3, 323-327. PMID:21297638.

Boulanger, A., Clouet-Redt, C., Farge, M., Flandre, A., Guignard, T., Fernando, C., Juge, F., Dura, JM. (2011) ftz-f1 and Hr39 opposing roles on EcR expression during Drosophila mushroom body neuron remodeling. **Nat. Neurosci.**, *14,* 1, 37-44. PMID: 21131955

Braoudaki, M., Katsibardi, K., Giudicelli, V., Karamolegou, K., Papathanassiou, Ch., Lefranc, MP., Tzortzatou-Stathopoulou, F. (2011) Analysis of somatic hypermutations of immunoglobulin gene rearrangements in childhood acute lymphoblastic leukemia. **Cancer Invest.** *29*, 5, 360-364. PMID: 21599512

Brieu, N., Portalès, P., Carles, MJ., Corbeau, P. (2011) Interleukin-7 induces HIV type 1 R5-to-X4 switch. **Blood.**, *117*, 6, 2073-2074. PMID:21310936

Brun, M.-E., Lana, E., Rivals, I., Lefranc, G., Sarda, P., Claustres, M., Mégarbané, A. and de Sario, A. (2011) Heterochromatic genes undergo epigenetic changes and escape silencing in Immunodeficiency, Centromeric Instability, Facial Anomalies (ICF) Syndrome. **PLOS One** *vol.6*, issue 4, e19464. PMID: 21559330

Cavalli, G. (2011) From linear genes to Epigenetic inheritance of three dimensional Epigenomes. **J. Mol. Biol.**, *409,* 1, 54-61. PMID: 21392507.

Castro, R., Bernard, D., Lefranc M.-P., Six ,A., Benmansour, A., Boudinot, P. (2011) T cell diversity and TcR repertoires in teleost fish. **Fish Shellfish Immunol**., *31,* 5, 644-654. PMID: 20804845

Cayrou, C., Coulombe, P., Vigneron, A., Stanojcic, S., Ganier, O., Peiffer, I., Rivals, E., Puy, A, Laurent-Chabalier, S., Desprat, R., Méchali, M. (2011) Genome-scale analysis of metazoan replication origins reveals their organization in specific but flexible sites defined by conserved features. **Genome Res**, *21*, 9, 1438-1449. PMID:21750104

Cheutin, T., Bantignies, F., Leblanc, B., Cavalli, G. (2011) Chromatin folding : from linear chromosomes to the 4D nucleus. **Cold Spring Harb Symp Quant Biol.** *75*, 461-473. PMID: 21447815

Comet, I., Schuettengruber, B., Sexton, T., Cavalli, G. (2011) A chromatin insulator driving three-dimensional Polycomb response element (PRE) contacts and Polycomb association with the chromatin fiber. **Proc. Natl. Acad. Sci. U S A.,** *108*, 6, 2294-2299. PMID: 21262819

Corbeau, P., Reynes, J. (2011) Immune reconstitution under antiretroviral therapy: a new challenge in HIV-1 infection. **Blood**, *117,* 21, 5582-5590. PMID: 21403129

Delmouly, K., Belondrade, M., Casanova, D., Milhavet, O., Lehmann, S. (2011) HEPES inhibits the conversion of the Prion protein in cell culture. **J. Gen. Virol.,** *92*, Pt 5, 1244-1250. PMID: 21289158

De Vidi, I., Boursier, G., Delouche, N., Portalès, P., Cadars, E., Bouthier, M., Mettling, C, Lin, YL., Thouvenot, E., Carlander, B., Camu, W., Antel, JP., Bar-Or, A., Zephir, H., Vermersch, P., De Seze, J., Corbeau, P., Eliaou, JF., Vincent, T. (2011) Strategy for anti-aquaporin-4 auto-antibody identification and quantification using a new cell-based assay. **Clin. Immunol.,** *138*, 3, 239-246. PMID: 21190899

Dievart, A., Gilbert, N., Droc, G., Attard, A., Gourgues, M., Guiderdoni E., Perin, C. (2011) Leucine-Rich Repeat Receptor Kinases are sporadically distributed in eukaryotic genomes. **BMC Evolutionary Biology,** *11*, 367. PMID : 22185365

Dumond, H., Al-Asaad, I., Chesnel, A., Chardard, D., Boizet-Bonhoure, B., Flament, S., Kuntz, S. (2011) Temporal and spatial SOX9 expression patterns in the course of gonad development of the caudate amphibian Pleurodeles waltl. **J. Exp. Zool. B Mol. Dev. Evol.** *316B,* 3, 199-211. doi: 10.1002/jez.b.21390. PMID:21462314

Ehrenmann, F., Lefranc, MP. (2011) IMGT/DomainGapAlign: IMGT Standardized Analysis of Amino Acid Sequences of Variable, Constant, and Groove Domains (IG, TR, MH, IgSF, MhSF). **Cold Spring Harb Protoc**., *6,* pii: pdb.prot5636. doi: 10.1101/pdb.prot5636. PMID: 21632775

Ehrenmann, F., Lefranc, MP. (2011) IMGT/3Dstructure-DB: Querying the IMGT Database for 3D Structures in Immunology and Immunoinformatics (IG or Antibodies, TR, MH, RPI, and FPIA). **Cold Spring Harb Protoc**., *6,* pii: pdb.prot5637. doi: 10.1101/pdb.prot5637. PMID: 21632774

Ehrenmann, F., Giudicelli, V., Duroux, P., Lefranc, MP. (2011) IMGT/Collier de Perles: IMGT Standardized Representation of Domains (IG, TR, and IgSF Variable and Constant Domains, MH and MhSF Groove Domains). **Cold Spring Harb Protoc**., *6*, pii: pdb.prot5635. doi: 10.1101/pdb.prot5635. PMID: 21632776

Farhat, A., Philibert, P., Sultan, C., Poulat, F., Boizet-Bonhoure, B. (2011) Hematopoietic-Prostaglandin D2 synthase through PGD2 production is involved in the adult ovarian physiology. **J. Ovarian. Res**., *4,* 3. PMID:21352547

Gabelle, A., Roche, S., Gény, C., Bennys, K., Labauge, P., Tholance, Y., Quadrio, I., Tiers, L., Gor, B., Boulanghien, J., Chaulet, C., Vighetto, A., Croisile, B., Krolak-Salmon, P., Perret-Liaudet, A., Touchon, J., Lehmann, S. (2011) Decreased sAβPPβ, Aβ38, and Aβ40 Cerebrospinal Fluid Levels in Frontotemporal Dementia. **J. Alzheimers Dis**., *26*, 3, 553-563. PMID:21709372

Ganier, O., Bocquet, S., Peiffer, I., Brochard, V., Arnaud, P., Puy, A., Jouneau, A., Feil, R., Renard, JP., and Méchali, M. (2011) Synergic reprogramming of mammalian cells by combined exposure to mitotic Xenopus egg extracts and transcription factors. **Proc. Natl. Acad. Sci. USA,** *108*, 42,, 17331-6 - PMID 21908712

Gongora, C., Vezzio-Vie, N., Tuduri, S., Denis, V., Causse, A., Auzanneau, C., Collod-Beroud, G., Coquelle, A., Pasero, P., Pourquier, P., Martineau, P., Del Rio, M. (2011) New Topoisomerase I mutations are associated with resistance to camptothecin. **Mol Cancer.**, *10*, 1, 64. PMID: 21619602

Grad, I., Cederroth, CR., Walicki, J., Grey, C., Barluenga, S., Winssinger, N., De Massy, B., Nef, S., Picard, D. (2011) The Molecular Chaperone Hsp90α Is Required for Meiotic Progression of Spermatocytes beyond Pachytene in the Mouse. **PLoS One**, *5*, 12, e15770. PMID: 21209834

Grey, C., Sommermeyer, V., Borde, V., de Massy, B. (2011) What defines the genetic map? The specification of meiotic recombination sites. **Med Sci (Paris)**., *27*, 1, 63-69. PMID:21299964

Giudicelli, V., Brochet, X., Lefranc, MP. (2011) IMGT/V-QUEST: IMGT Standardized Analysis of the Immunoglobulin (IG) and T Cell Receptor (TR) Nucleotide Sequences. **Cold Spring Harb Protoc**., *6,* pii: pdb.prot5633. doi: 10.1101/pdb.prot5633. PMID: 21632778

Giudicelli, V., Lefranc, MP. (2011) IMGT/JunctionAnalysis: IMGT Standardized Analysis of the V-J and V-D-J Junctions of the Rearranged Immunoglobulins (IG) and T Cell Receptors (TR). **Cold Spring Harb Protoc**. , *6*, pii: pdb.prot5634. doi: 10.1101/pdb.prot5634. PMID: 21632777

He, N., Chan, CK., Sobhian, B., Chou, S., Xue, Y., Liu, M., Alber, T., Benkirane, M., Zhou, Q. (2011) Human Polymerase-Associated Factor complex (PAFc) connects the Super Elongation Complex (SEC) to RNA polymerase II on chromatin. **Proc. Natl. Acad. Sci. U S A** , *108,* 36, E636-645. PMID 21873227

Heron-Milhavet, L., Khouya, N., Fernandez, A., Lamb, N.J. (2011) Akt1 and Akt2: differenciating the action. **Histol. Histopathol.,** *26*, 5, 651-662. PMID 21432781

Hetzer, M., Cavalli, G. (2011) Eukaryotic cells - Editorial Review. **Curr. Opin. Cell Biol**., *23,* 3, 255-257, PMID: 21592757

Iovino, N., Cavalli, G. (2011) Rolling ES Cells Down the Waddington Landscape with Oct4 and Sox2. **CELL**., *145,* 6, 815-817. PMID: 21663785

Kostareli E, Gounari M, Janus A, Murray F, Brochet X, Giudicelli V, Pospisilova S, Oscier D, Foroni L, di Celle PF, Tichy B, Pedersen LB, Jurlander J, Ponzoni M, Kouvatsi A, Anagnostopoulos A, Thompson K, Darzentas N, Lefranc MP, Belessi C, Rosenquist R, Davi F, Ghia P, Stamatopoulos K (2011) Antigen receptor stereotypy across B-cell lymphoproliferations: the case of IGHV4-59/IGKV3-20 receptors with rheumatoid factor activity. **Leukemia** : doi: 10.1038/leu.2011.311. PMID: 22051533

Laguette, N., Sobhian, B., Casartelli, N., Ringeard, M., Chable-Bessia, C., Segeral, E., Emiliani, S., Schwartz, O., Benkirane M. (2011) SAMHD1 is the dentritic and myeloid-cell-specific HIV-1 restriction Factor counteracted by Vpx. Nature, 474, 7353, 654-657 http://dx.doi.org/10.1038/nature10117/ PMID: 21613998

Lakhdar, R., Denden, S., Kassab, A., Leban, N., Knani, J., Lefranc, G, Miled, A., Ben Chibani, J.B., Haj-Khelil, A.H. (2011) Update in chronic obstructive pulmonary disease: role of antioxidant and metabolizing gene polymorphisms. **Exp Lung Res.** *37,* 6, 364-375. PMID: 21721950

Lakhdar, R., Denden, S., Knani, J., Leban, N., Daimi, H., Hassine, M., Lefranc, G., Chibani, J.B., Khelil, A.H. (2011) Combined analysis of EPHX1, GSTP1, GSTM1 and GSTT1 gene polymorphisms in relation to chronic obstructive pulmonary disease risk and lung function impairment. **Dis. Markers.** *30,* 5, 253-63. doi: 10.3233/DMA-2011-0782. PMID: 21734345

Lakhdar, R., Denden, S., Mouhamed, M.H., Chalgoum, A., Leban, N., Knani, J., Lefranc, G., Miled, A., Chibani, J.B. and Khelil, A.H. (2011) Correlation of EPHX1, GSTP1, GSTM1, and GSTT1 genetic polymorphisms with antioxidative stress markers in chronic obstructive pulmonary disease. **Exp Lung Res**., *37,* 4, 195-204. PMID: 21309732

Lapasset, L., Milhavet, O., Prieur, A., Besnard, E., Babled, A., Aït-Hamou, N., Leschik, J., Pellestor, F., Ramirez, JM., De Vos, J., Lehmann, S., Lemaitre, JM.. (2011) Rejuvenating senescent and centenarian human cells by reprogramming through the pluripotent state. **Genes Dev**. , *25*, 21, 2248-2253. PMID: 22056670

Lefranc, MP. (2011) Antibody nomenclature: From IMGT-ONTOLOGY to INN definition. **MAbs**., *3*, 1,1-2. PMID: 21099347

Lefranc, MP. (2011) From IMGT-ONTOLOGY IDENTIFICATION Axiom to IMGT Standardized Keywords: For Immunoglobulins (IG), T Cell Receptors (TR), and Conventional Genes. **Cold Spring Harb Protoc.**, *6*, pii: pdb.ip82. doi: 10.1101/pdb.ip82. PMID:21632792

Lefranc, MP. (2011) From IMGT-ONTOLOGY DESCRIPTION Axiom to IMGT Standardized Labels: For Immunoglobulin (IG) and T Cell Receptor (TR) Sequences and Structures. **Cold Spring Harb Proto***c., 6*. pii: pdb.ip83. doi: 10.1101/pdb.ip83. PMID: 21632791

Lefranc, MP., From IMGT-ONTOLOGY CLASSIFICATION Axiom to IMGT Standardized Gene and Allele Nomenclature: For Immunoglobulins (IG) and T Cell Receptors (TR). **Cold Spring Harb Protoc**., *6*, pii: pdb.ip84. doi: 10.1101/pdb.ip84. PMID: 21632790

Lefranc, MP.,(2011) IMGT Unique Numbering for the Variable (V), Constant (C), and Groove (G) Domains of IG, TR, MH, IgSF, and MhSF. **Cold Spring Harb Protoc**., *6,* pii: pdb.ip85. doi: 10.1101/pdb.ip85. PMID: 21632789

Lefranc, MP., (2011) IMGT Collier de Perles for the Variable (V), Constant (C), and Groove (G) Domains of IG, TR, MH, IgSF, and MhSF. **Cold Spring Harb Protoc**., *6,* pii: pdb.ip86. doi: 10.1101/pdb.ip86. PMID: 21632788

Lefranc, MP., IMGT, the International ImMunoGeneTics Information System. **Cold Spring Harb Protoc.**, *6*, pii: pdb.top115. doi: 10.1101/pdb.top115. PMID: 21632786

Lehmann, S. (2011) CSF proteins: useful markers in Alzheimer's diseases. **Rev. Prat.**, *61*, 7, 928. PMID : 22039728

Lichten, M., de Massy, B. (2011) The Impressionistic Landscape of Meiotic Recombination. **CELL** Vol. *147*, Issue 2, pp. 267. PMID 22000007

Medlej-Hashim, M., Chouery, E., Salem, N., Delague, V., Lefranc, G., Loiselet, J. and Mégarbané, A. (2011) Familial Mediterranean fever in a large Lebanese family: Multiple MEFV mutations and evidence for a Founder effect of the p.[M694I] mutation. **Eur. J. Med. Genet**. *54,* 1, 50-54. PMID: 20937419

Moniot, B., Farhat, A., Aritake, K., Declosmenil, F., Nef, S., Eguchi, N., Urade, Y., Poulat, F., Boizet-bonhoure, B. (2011) Hematopoietic prostaglandin D synthase (H-Pgds) is expressed in the early embryonic gonad and participates to the initial nuclear translocation of the SOX9 protein. **Dev Dyn.**, *240*, 10, 2335-2343. doi: 10.1002/dvdy.22726. PMID: 21887724

Nishiyama A, Frappier L, Méchali M. (2011) MCM-BP regulates unloading of the MCM2-7 helicase in late S phase. **Genes Dev**., *25,* 2, 165-175. PMID: 21196493

Papin, C., Simonelig, M. (2011) Embryonic development is controlled by small non-coding RNAs derived from transposable elements. **Med. Sci. (Paris)**, *27,* 12, 1050-1052. PMID: 22192737

Provansal, M., Jorgensen, C., Lehmann, S., Roche, S. (2011) Two Dimensional Gel Electrophoresis Analysis of Mesenchymal Stem Cells. **Methods Mol. Biol**. *698,* 431-442. PMID: 21431536

Relaño-Ginés, A., Lehmann, S., Bencsik, A., Herva, ME., Torres, JM., Crozet, CA. (2011) Stem cell therapy extends incubation and survival time in prion-infected mice in a time window-dependant manner. **J. Infect. Dis.** *204*, 7, 1038-1045. PMID: 21998645

Romero, Y., Meikar, O., Papaioannou, MD., Conne, B., Grey, C., Weier, M., Pralong, F., De Massy, B., Kaessmann, H., Vassalli, JD., Kotaja, N., Nef, S. (2011) Dicer1 depletion in male germ cells leads to infertility due to cumulative meiotic and spermiogenic defects. **PLoS One,** *6,* 10, e25241. PMID: 21998645

Schuettengruber, B., Martinez, AM., Iovino, N., Cavalli, G. (2011) Trithorax group proteins: switching genes on and keeping them active. **Nat. Rev. Mol. Cell Bio**l.,*12*, 12, 799-814. doi: 10.1038/nrm3230. PMID: 22108599

Seitz, H., Tushir, JS., Zamore, PD. (2011) A 5´-uridine amplifies miRNA/miRNA* asymmetry in Drosophila by promoting RNA-induced silencing complex formation. **Silence**, *2*, 4 PMID: 21649885

Shen, MY., Liu, YJ., Don, MJ., Liu, HY., Chen, ZW., Mettling, C., Corbeau, P., Chiang, CK., Jang, YS., Li, TH., Young, P., Chang, CL., Lin, YL., Yang, WC. (2011) Combined Phytochemistry and Chemotaxis Assays for Identification and Mechanistic Analysis of Anti-Inflammatory Phytochemicals in Fallopia japonica. **PLoS One**, *6,* 11, e27480. PMID: 22087325

Sim, H., Argentaro, A., Czech, DP., Bagheri-Fam, S., Sinclair, AH., Koopman, P., Boizet-Bonhoure, B., Poulat, F., Harley, VR. (2011) Inhibition of SRY-Calmodulin Complex Formation Induces Ectopic Expression of Ovarian Cell Markers in Developing XY Gonads. **Endocrinology**, *152*, 7, 2883-2893, PMID: 21558314

Simonelig, M. (2011) Developmental functions of piRNAs and transposable elements: A Drosophila point-of-view. **RNA Biol**. *8*, 5, PMID: 21712652

Trannoy, S., Redt-Clouet, C., Dura, JM., Preat, T. (2011) Parallel processing of appetitive short- and long-term memories in Drosophila. **Curr. Biol.**, *21*, 19, 1647-1653. PMID: 21962716

Tsutsumi, A., Kawamata, T., Izumi, N., Seitz, H., Tomari Y. (2011) Recognition of the pre-miRNA structure by Drosophila Dicer-1. **Nat. Struct. Mol. Biol.**, *18,* 10, 1153-1158. PMID: 21926993

Villard, E., Pe, C., Gary, F., Proust, C., Dilanian, G., Hengstenberg, C., Ruppert, V., Arbustini, E., Wichter, T., Germain, M., Dubourg, O., Tavazzi, L., Aumont, MC., DeGroote P., Fauchier, L., Trochu, JN., Gibelin, P., Aupetit, JF., Stark, K., Erdmann, J., Hetzer, R., Roberts A., Barton, P., Regitz-Zagrosek, V., CardioGenics Consortium, Aslam, U., Duboscq-Bidot, L., Meyborg, M., Maisch, B., Madeira, H., Waldenstrom, A., Galve, E., Cleland, J.G., Dorent, R., Roizes, G., Zeller, T., Blankenberg, S., Goodall, A.H., Cook, S., Tregouet, D.A., TIret, L., Isnard, R., Komajda, M., Charron, P., Cambien, F. (2011) A genome-wide association study identifies two loci associated with heart failure due to dilated cardiomyopathy. **European Heart Journal,** *32*, 1065-1076. PMID: 21459883

Agathangelidis, A., Darzentas, N., Hadzidimitriou, A., Brochet, X., Murray, F., Yan, XJ., Davis, Z., van Gastel-Mol, EJ., Tresoldi, C., Chu, CC., Cahill, N., Giudicelli, V., Tichy, B., Pedersen, LB., Foroni, L., Bonello, L., Janus, A., Smedby, K., Anagnostopoulos, A., Merle-Beral, H., Laoutaris, N., Juliusson, G., di Celle, PF., Pospisilova, S., Jurlander, J., Geisler, C., Tsaftaris, A., Lefranc, MP., Langerak, AW., Oscier, DG., Chiorazzi, N, Belessi, C., Davi, F., Rosenquist, R., Ghia, P., Stamatopoulos, K.. (2012) Stereotyped B-cell receptors in one third of chronic lymphocytic leukemia: towards a molecular classification with implications for targeted therapeutic interventions. **Blood.**, *119,* 19, 4467-4475, PMID: 22415752.

Alamyar, E., Duroux, P., Lefranc, MP, Giudicelli, V. (2012) IMGT(®) tools for the nucleotide analysis of immunoglobulin (IG) and T cell receptor (TR) V-(D)-J repertoires, polymorphisms, and IG mutations: IMGT/V-QUEST and IMGT/HighV-QUEST for NGS. **Methods Mol Biol**., *882*, 569-604. PMID: 22665256

Alamyar, E., Giudicelli, V., Li, S., Duroux, P., Lefranc, MP. (2012) IMGT/HighV-QUEST: the IMGT® web portal for immunoglobulin (IG) or antibody and T cell receptor (TR) analysis from NGS high throughput and deep sequencing. **Immunome Res**., *8,* 1, 26. PMID: 22647994

Basbous, J., Knani, D., Bonneaud, N., Giorgi, D., Brondello, JM., Rouquier, S. (2012) Induction of ASAP (MAP9) contributes to p53 stabilization in response to DNA damage. **Cell Cycle**, *11*, 12. PMID: 22672907

Bianco, JN., Poli, J., Saksouk, J., Bacal, J., Silva, MJ., Yoshida, K., Lin, YL., Tourrière, H., Lengronne, A., Pasero, P. (2012) Analysis of DNA replication profiles in budding yeast and mammalian cells using DNA combing. **Methods,** *57,* 2, 149-157. PMID 22579803

Boulanger, A., Farge, M., Ramanoudjame, C., Wharton, K., Dura, JM. (2012) Drosophila Motor Neuron Retraction during Metamorphosis Is Mediated by Inputs from TGF-β/BMP Signaling and Orphan Nuclear Receptors. **PLoS One**, *7*, 7, e40255. PMID: 22792255

Brandariz-Nuñez A, Valle-Casuso JC, White TE, Laguette N, Benkirane M, Brojatsch J, Diaz-Griffero F (2012) Role of SAMHD1 nuclear localization in restriction of HIV-1 and SIVmac. **Retrovirology**, *9,* 1, 49. PMID: 22691373

Buonocore, F., Castro, R., Randelli, E., Lefranc, M.-P., Six, A., Kuhl, H., Reinhardt, R., Facchiano, A., Boudinot, P., Scapigliati, G. (2012) Diversity, molecular characterization and expression of T cell receptor gamma in a teleost fish, the sea bass (Dicentrarchus labrax, L). PLoS One, 7, 10, e47957. PMID: 23133531

Cayrou, C., Coulombe, P., Puy, A., Rialle, S., Kaplan, N., Segal, E., Méchali, M. (2012) New insights into replication origin characteristics in metazoans. **Cell Cycle,** *11,* 4. 658-667. PMID: 22307000

Cayrou ,C., Grégoire, D., Coulombe, P., Danis, E., Méchali, M. (2012) Genome-scale identification of active DNA replication origins. **Methods** *57*, 2, 158-164. PMID: 22796403

Chartier, A, Simonelig, M. (2012) Animal models in therapeutic drug discovery for oculopharyngeal muscular dystrophy. **Drug Discovery Today : Technologies** :doi.org/10.1016/j.ddtec.2012.07.002

Cheutin, T., Cavalli, G. (2012) Progressive Polycomb Assembly on H3K27me3 Compartments Generates Polycomb Bodies with Developmentally Regulated Motion. **PLoS Genet.**, *8*, 1, e1002465. PMID: 22275876

Chou J., Hanna-Wakim R., Tirosh I., Kane J., Fraulino D., Lee Y.N., Ghanem S., Mahfouz I., Mégarbané A., Lefranc G., Inati A., Dbaibo G., Giliani S., Notarangelo L.D., Geha R.S., Massaad M.J. (2012) A novel homozygous mutation in recombination activating gene 2 in 2 relatives with different clinical phenotypes: Omenn syndrome and hyper-IgM syndrome. **J. Allergy Clin. Immunol**. in press, PMID: 22841008

Chouery, E., Abou-Ghoch, J., Corbani, S., El Ali, N., Korban, R., Salem, N., Castro, C., Klayme, S., Azoury-Abou Rjeily M., Khoury-Matar, R., Debo, G., Germanos-Haddad, M., Delague, V., Lefranc, G., Mégarbané, A. (2012) A novel deletion in ZBTB24 in a Lebanese family with immunodeficiency, centromeric instability, and facial anomalies syndrome type 2 **Clin Genet**. *82,* 5, 489-493. doi: 10.1111/j.1399-0004.2011.01783.x. PMID: 21906047

Cliffe, S.T., Bloch, D.B., Suryani, S., Kamsteeg, E.J., Avery, D.T., Palendira, U., Church, J.A., Wainstein, B.K., Trizzino, A., Lefranc, G., Akatcherian, C., Mégarbané, A., Gilissen, C., Moshous, D., Reichenbach, J., Misbah, S., Salzer, U., Abinun, M., Ong, P.Y., Stepensky, P., Ruga, E., Ziegler, J.B., Wong, M., Tangye, S.G., Lindeman, R., Buckley, M.F., Roscioli, T. (2012) Clinical, molecular, and cellular immunologic findings in patients with SP110-associated veno-occlusive disease with immunodeficiency syndrome. **J. Allergy Clin. Immunol**., *130,* 3, 735-742.e6. PMID: 22621957

Constantinou, A. (2012) Rescue of replication failure by Fanconi anaemia proteins. **Chromosoma** , *121*, 1, 21-26, PMID: 22057367

Cuzin, L., Trabelsi, S., Delobel, P., Barbuat, C., Reynes, J., Allavena, C., Peytavin, G., Ghosn, J., Lascoux-Combe, C., Psomas, C., Corbeau, P., Flandre, P., the ANRS 145 MARIMUNO Study group. (2012) Maraviroc intensification of stable antiviral therapy in HIV-1-infected patients with poor immune restoration: MARIMUNO-ANRS 145 study. , **J. Acquir. Immune Defic. Syndr**. In press, PMID: 22986949

Dechavanne, C., Guillonneau, F., Chiappetta, G., Sago, L., Lévy, P., Salnot, V., Guitard, E., Ehrenmann, F., Broussard, C., Chafey, P., Le Port, A., Vinh, J., Mayeux, P., Dugoujon, JM., Lefranc, MP., Migot-Nabias, F. (2012) Mass Spectrometry Detection of G3m and IGHG3 Alleles and Follow-Up of Differential Mother and Neonate IgG3. **PLoS One.,** *7*, 9, e46097. doi: 10.1371/journal.pone.0046097. PMID : 23049948

Dejardin, J. (2012) How chromatin prevents genomic rearrangements: Locus colocalization induced by transcription factor binding. **Bioassays** : doi: 10.1002/bies.201100122. *34*, 2, 90-93; PMID: 22086436

Delest, A., Sexton, T., Cavalli, G. (2012) Polycomb: a paradigm for genome organization from one to three dimensions. **Curr. Opin. Cell Biol**., *24*, 3, 405-414. PMID: 22336329

Descours, B., Cribier, A., Chable-Bessia, C., Ayinde, D., Rice, G., Crow, Y., Yatim, A., Schawartz, O., Laguette, N., Benkirane, M. (2012) SAMHD1 restricts HIV-1 reverse transcription in quiescent CD4+ T-cells. **Retrovirology**, *9,* 1, 87. PMID : 23092122

Ehrenmann, F., Lefranc, MP. (2012) IMGT/DomainGapAlign: the IMGT® tool for the analysis of IG, TR, MH, IgSF, and MhSF domain amino acid polymorphism. **Methods Mol Biol.**, *882*, 605-633. PMID: 22665257

Estefanía, MM., Ganier, O., Hernández, P., Schvartzman, JB., Mechali, M., Krimer, DB. (2012) DNA replication fading as proliferating cells advance in their commitment to terminal differentiation. **Sci. Rep**., *2,* 279. PMID: 22359734

Flachs, P., Mihola, O., Simeček, P., Gregorová, S., Schimenti, JC., Matsui, Y., Baudat, F., de Massy, B., Piálek, J., Forejt, J., Trachtulec, Z. (2012) Interallelic and intergenic incompatibilities of the prdm9 (hst1) gene in mouse hybrid sterility. **PLoS Genet.**, *8,* 11, e1003044. doi: 10.1371/journal.pgen.1003044. PMID: 23133405

Giest, S., McWhinnie, A., Lefranc, MP., Little, AM., Grace, S., Mackinnon, S., Madrigal, JA., Travers, PJ. (2012) Cytomegalovirus-specific CD8+ T cells targeting different peptide/HLA combinations demonstrate varying T-cell receptor diversity. **Immunology.** *135*, 1, 27-39. doi: 10.1111/j.1365-2567.2011.03508.x. PMID: 22044339

Giudicelli V, Lefranc MP. (2012) IMGT-ONTOLOGY 2012, **Front.Genet.,** *3*, 79. PMID: 22654892

Grentzinger, T., Armenise, C., Brun, C., Mugat, B., Serrano, V., Pelisson, A., Chambeyron, S. (2012) piRNA mediated transgenerational inheritance of an acquired trait. **Genome Res**., *22,* 10, 1877-1888, PMID: 22555593

Jabara, H.H., McDonald, D.R., Janssen, E., Massaad, M.J., Ramesh, N., Borzutzky, A., Rauter, I., Benson, H., Schneider, L., Baxi, S., Recher, M., Notarangelo, L.D., Wakim, R., Dbaibo, G., Dasouki, M., Al-Herz, W., Barlan, I., Baris, S., Kutukculer, N., Ochs, H.D., Plebani, A., Kanariou, M., Lefranc, G., Reisli, I., Fitzgerald, K.A., Golenbock, D., Manis, J., Keles, S., Ceja, R., Chatila, T.A., Geha, R.S. (2012) DOCK8 functions as an adaptor that links TLR-MyD88 signaling to B cell activation. **Nat Immunol.** *13,* 6, 612-620. doi: 10.1038/ni.2305. PMID: 22581261

Kostareli, E., Gounari, M., Janus, A., Murray, F., Brochet, X., Giudicelli, V., Pospisilova, S., Oscier, D., Foroni, L., di Celle, PF., Tichy, B., Pedersen, LB., Jurlander, J., Ponzoni, M., Kouvatsi, A., Anagnostopoulos, A., Thompson, K., Darzentas, N., Lefranc, MP., Belessi, C., Rosenquist, R., Davi, F., Ghia, P., Stamatopoulos, K. (2012) Antigen receptor stereotypy across B-cell lymphoproliferations: the case of IGHV4-59/IGKV3-20 receptors with rheumatoid factor activity. **Leukemia**. *26,* 5, 1127-1131. doi: 10.1038/leu.2011.311. PMID: 22051533

Laguette, N., Benkirane, M. (2012) How Samhd1 changes our view of viral restriction. **Trends Immunol**., *33*, 1, 26-33. PMID:22177690

Laguette, N., Rahm, N., Sobhian, B., Chable-Bessia, C., Münch, J., Snoeck, Sauter, D., Switzer, WM., Heneine, W., Kirchhoff, F., Delsuc, F., Telenti, A. and Benkirane, M. (2012) Evolutionary and Functional Analyses of the Interaction between the Myeloid Restriction Factor SAMHD1 and the Lentiviral Vpx Protein. **Cell Host & Microbe**, *11,* 2, 205-217. PMID 22305291

Lahouassa, H., Daddacha, W., Hofmann, H., Ayinde, D., Logue, EC., Dragin, L., Bloch, N., Maudet, C., Bertrand, M., Gramberg, T., Pancino, G., Priet, S., Canard, B., Laguette, N., Benkirane, M., Transy, C., Landau, NR., Kim, B., Margottin-Goguet, F. (2012) SAMHD1 restricts the replication of human immunodeficiency virus type 1 by depleting the intracellular pool of deoxynucleoside triphosphates. **Nat. Immunol.**, *13,* 3, 223-228, doi: 10.1038/ni.2236, PMID: 22327569

Lin, YL., Pasero, P. (2012) Interference between DNA replication and transcription as a cause of genomic instability. **Curr Genomics.,** *13*, 1, 65-73. PMID: 22942676

Lana, E., Mégarbané, A., Tourrière, H., Sarda, P., Lefranc, G., Claustres, M., De Sario, A. (2012) DNA replication is altered in Immunodeficiency Centromeric instability Facial anomalies (ICF) cells carrying DNMT3B mutations. **Eur J Hum Genet.,** *20,* 10, 1044-1050. doi:10.1038/ejhg.2012.41. PMID: 22378288

Lefranc, MP., Lefranc, G. (2012) Human Gm, Km, and Am allotypes and their molecular characterization: a remarkable demonstration of polymorphism. **Methods Mol Biol**., *882,* 635-680. PMID: 22665258

Lefranc, MP., Ehrenmann, F., Ginestoux, C., Giudicelli, V., Duroux, P. (2012) Use of IMGT(®) databases and tools for antibody engineering and humanization. **Methods Mol. Biol.**, *907*, 3-37. PMID: 22907343

Lefranc M.-P., Ehrenmann F., Ginestoux C., Duroux P., Giudicelli V. (2012) Use of IMGT® databases and tools for antibody engineering and humanization In: P. Chames (Ed.), **Antibody engineering**, chap 1, Humana Press, Springer, New York, USA. Methods Mol Biol. 907:3-37. PMID: 22907343

Lutzmann, M., Grey, C., Traver, S., Ganier, O., Maya-Mendoza, A., Ranisavljevic, N., Bernex, F., Nishiyama, A., Montel, N., Gavois, E., Forichon, L., de Massy, B., Méchali, M. (2012) MCM8- and MCM9-Deficient Mice Reveal Gametogenesis Defects and Genome Instability Due to Impaired Homologous Recombination. **Mol. Cell,** *47*, 4, 523-534. PMID 22771120

Méchali, M. (2012) Methods in DNA replication. **Methods,** *57,* 2, 139. PMID:22935726

Nakamura, M., Basavarajaiah, P., Rousset, E., Beraud, C., Latreille, D., Henaoui, IS., Lassot, I., Mari, B., Kiernan, R. (2012) Spt6 levels are modulated by PAAF1 and proteasome to regulate the HIV-1 LTR. **Retrovirology**, *9*, 1, 13. PMID: 22316138

Philibert, P., Boizet-Bonhoure, B., Bashamboo, A., Paris, F., Aritake, K., Urade, Y., Leger, J., Sultan, C., Poulat, F. (2012) Unilateral Cryptorchidism in Mice Mutant for Ptgds. **Hum. Mutat.,** doi: 10.1002/humu.22231. PMID : 23076868

Poli, J., Tsaponina, O., Crabbé, L., Keszthelyi, A., Pantesco V., Chabes, A., Lengronne, A., Pasero, P. (2012) dNTP pools determine fork progression and origin usage under replication stress. **EMBO J**., *31*, 4, 883-894 : doi: 10.1038/emboj.2011.470. PMID: 22234185

Portales, P., Psomas, KC., Tuaillon, E., Mura, T., Vendrell, JP., Eliaou, JF., Reynes, J, Corbeau, P. (2012) The intensity of immune activation is linked to the level of CCR5 expression in human immunodeficiency virus type 1-infected persons. **Immunology,** *137*, 1, 89-97. PMID: 22862553

Recolin, B., Van der Laan, S., and Maiorano, D. (2012) Role of RPA as sensor in activation of the S-phase checkpoint in Xenopus egg extracts. **Nucleic Acids Research**, *40*, 8, 3431-3442.doi: 10.1093/nar/gkr1241. PMID: 22187152

Recolin, B., Maiorano, D. (2012) Implication of RPA32 phosphorylation in S-phase checkpoint signalling at replication forks stalled with aphidicolin in Xenopus egg extracts. **Biochemical and Biophysical Research Communications,** pii: S0006-291X(12)01917-1. doi: 10.1016/j.bbrc.2012.09.139, PMID: 23047005

Redt-Clouet, C., Trannoy, S., Boulanger, A., Tokmatcheva, E., Savvateeva-Popova, E., Parmentier, ML., Preat, T., Dura, JM. (2012) Mushroom body neuronal remodelling is necessary for short-term but not for long-term courtship memory in Drosophila. **Eur. J. Neurosci**., *35*, 11, 1684-1691. : doi: 10.1111/j.1460-9568.2012.08103.x. PMID 22571719

Roesch, F., Meziane, O., Kula, A., Nisole, S., Porrot, F., Anderson, I., Mammano, F., Fassati, A., Marcello, A., Benkirane, M., Schwartz, O. (2012) Hyperthermia Stimulates HIV-1 Replication. **PLoS Pathog**., *8,* 7, e1002792. PMID: 22807676

Romero, Y., Vuandaba, M., Suarez, P., Grey, C., Calvel, P., Conne, B., Pearce, D., de Massy, B., Hummler, E., Nef, S. (2012) The Glucocorticoid-Induced Leucine Zipper (GILZ) Is Essential for Spermatogonial Survival and Spermatogenesis. **Sex Dev.** *6*, 4, 169-177. PMID : 22571926

Schwartz, JC., Lefranc, MP., Murtaugh, MP. (2012) Evolution of the porcine (Sus scrofa domestica) immunoglobulin kappa locus through germline gene conversion. **Immunogenetics**, *64*, 4, 303-311. PMID : 22109540

Schwartz, JC., Lefranc, MP., Murtaugh, MP. (2012) Organization, complexity and allelic diversity of the porcine (Sus scrofa domestica) immunoglobulin lambda locus. **Immunogenetics**. *64*, 5, 399-407. PMID: 22186825

Sexton, T., Yaffe, E., Kenigsberg, E., Bantignies, F., Leblanc, B., Hoichman, M., Parrinello, H., Tanay, A., Cavalli, G. (2012) Three-Dimensional Folding and Functional Organization Principles of the Drosophila Genome. **CELL,** *148,* 3, 458-472. PMID: , 22265598

Shen, MY., Liu, YJ., Don, MJ., Liu, HY., Chen, ZW., Mettling, C., Corbeau, P., Chiang, CK., Jang, YS., Li, TH., Young, P., Chang, CL., Lin, YL., Yang, WC. (2012) Correction: Combined Phytochemistry and Chemotaxis Assays for Identification and Mechanistic Analysis of Anti-Inflammatory Phytochemicals in Fallopia japonica. **PLoS One**, *7*, 6. doi: 10.1371/annotation/e81927cf-e940-4604-acfa-44b5655e40a3. PMID: 22723826

Simonelig, M. (2012) Maternal-to-zygotic transition: soma versus germline. **Genome Biol**., *13,* 2, 145. PMID: 22356804

Simonelig, M. (2012) PABPN1 shuts down alternative poly(A) sites. **Cell Res**.,*22*, 10, 1419-1421. doi: 10.1038/cr.2012.86. PMID: 22641371

The International AIDS Society Scientific Working Group on HIV Cure, Deeks SG, Autran B, Berkhout B, Benkirane M, Cairns S, Chomont N, Chun TW, Churchill M, Mascio MD, Katlama C, Lafeuillade A, Landay A, Lederman M, Lewin SR, Maldarelli F, Margolis D, Markowitz M, Martinez-Picado J, Mullins JI, Mellors J, Moreno S, O'Doherty U, Palmer S, Penicaud MC, Peterlin M, Poli G, Routy JP, Rouzioux C, Silvestri G, Stevenson M, Telenti A, Lint CV, Verdin E, Woolfrey A, Zaia J, Barré-Sinoussi F. (2012) Towards an HIV cure: a global scientific strategy. **Nat Rev Immunol.**, *12,* 8, 607-614. doi: 10.1038/nri3262. PMID: 22814509

Tittel-Elmer, M., Lengronne, A., Davidson, MB., Bacal, J., François, P., Hohl, M., Petrini, JH., Pasero, P., Cobb, JA. (2012) Cohesin Association to Replication Sites Depends on Rad50 and Promotes Fork Restart. **Mol Cell**., *48,* 1, 98-108. doi: 10.1016/j.molcel.2012.07.004. PMID: 22885006

Wagschal, A., Rousset, E., Basavarajaiah, P., Contreras, X. , Harwig, A., Laurent-Chabalier, S. , Nakamura, M., Chen, X., Zhang, K., Meziane, O., Boyer, F., Parrinello, H., Berkhout, B., Terzian, C., Benkirane, M., Kiernan, R. (2012) Microprocessor, Setx, Xrn2 and Rrp6 Co-Operate to Induce Premature Termination of Transcription by RNAPII. **CELL**, *150,* 6, 1147-1157. doi: 10.1016/j.cell.2012.08.004. PMID: 22980978

Wurtele, H., Schalck Kaiser, G., Bacal, J., St-Hilaire, E., Lee, EH., Tsao, S., Dorn, J., Maddox, P., Lisby, M., Pasero, P., Verreault, A. (2012) Histone H3 lysine 56 acetylation and the response to DNA replication fork damage. **Mol. Cell Biol.**, *32,* 1, 154-172. PMID: 22025679

Yatim, A., Benne, C., Sobhian, B., Laurent-Chabalier, S., Deas, O., Judde, JG., Lelievre, JD., Levy, Y., Benkirane, M. (2012) NOTCH1 Nuclear Interactome Reveals Key Regulators of Its Transcriptional Activity and Oncogenic Function. **Molecular Cell.,** *48*, 3, 445-458. pii: S1097-2765(12)00740-X. doi: 10.1016/j.molcel.2012.08.022. PMID : 23022380.

HOW TO FIND US

Plane:

Montpellier Méditérannée Airport about 3km to the South of Montpellier. (about 1/2 an hour from the IGH).

Train :

Montpellier SNCF train station - St Roch (downtown). The Bus Station is at the same place. (20 minutes away from the IGH).

Car:

* from A9 Toll highway, exit 29 Montpellier-Est (East) or exit 31 Montpellier-Ouest (West) : Follow North direction (20 minutes away from the IGH).

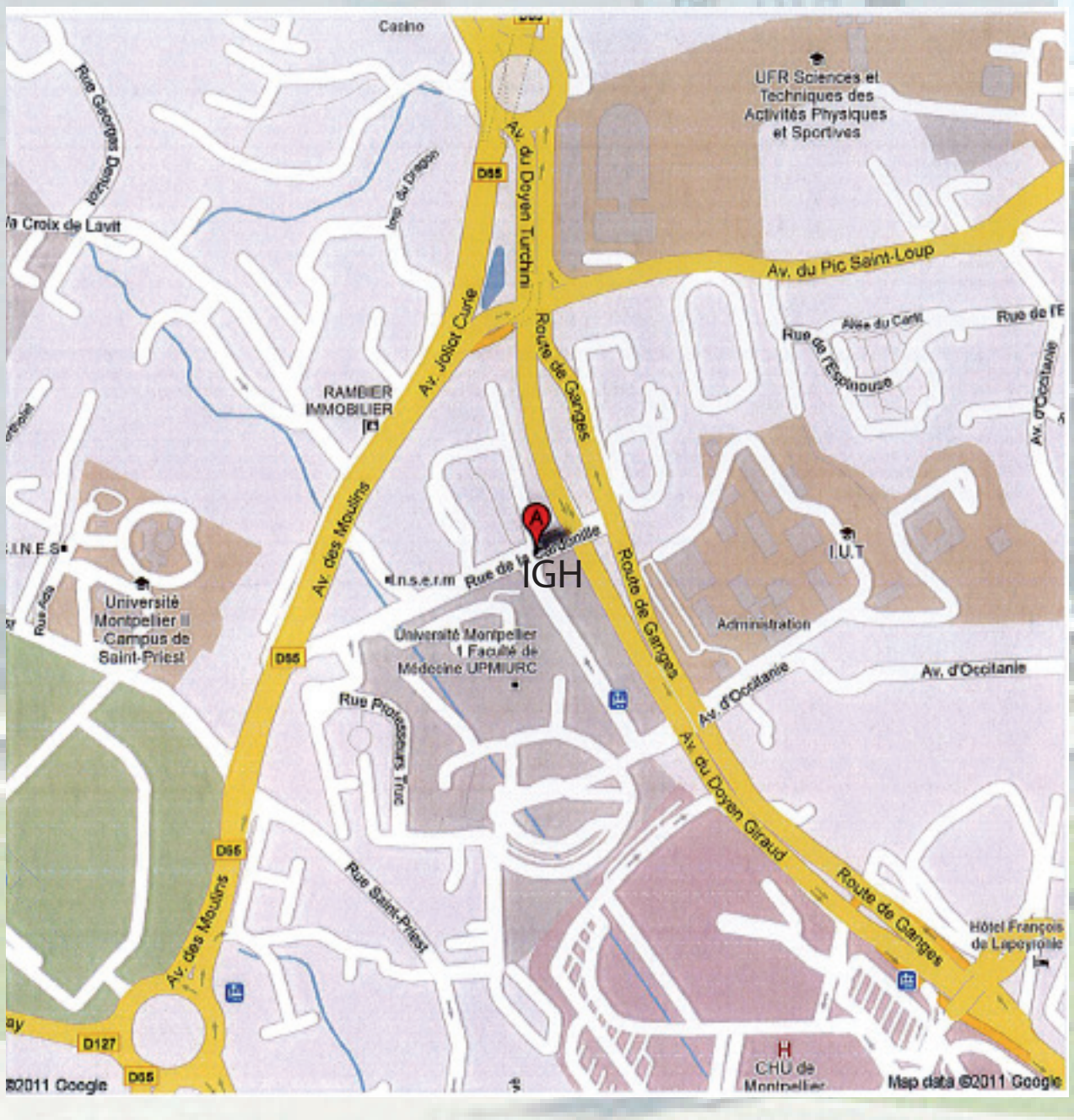
* from downtown : take the direction « Hôpitaux-Facultés » (10 minutes away from the IGH).

Bus-Tramway:

TAM network (From Downtown to the IGH) :

* Bus service N° 16 in the direction of "Euromédecine" get out at the "Occitanie" stop. about 25 min.

* Tramway service N° 1 in the direction of "Mosson" get out at the "Occitanie" stop. about 15 min.



INSTITUTE OF HUMAN GENETICS
UPR 1142 CNRS

141 RUE DE LA CARDONILLE
34396 MONTPELLIER CEDEX 5

TÉL +33 (0)4 34 35 99 04
FAX +33 (0)4 34 35 99 99

http://www.igh.cnrs.fr