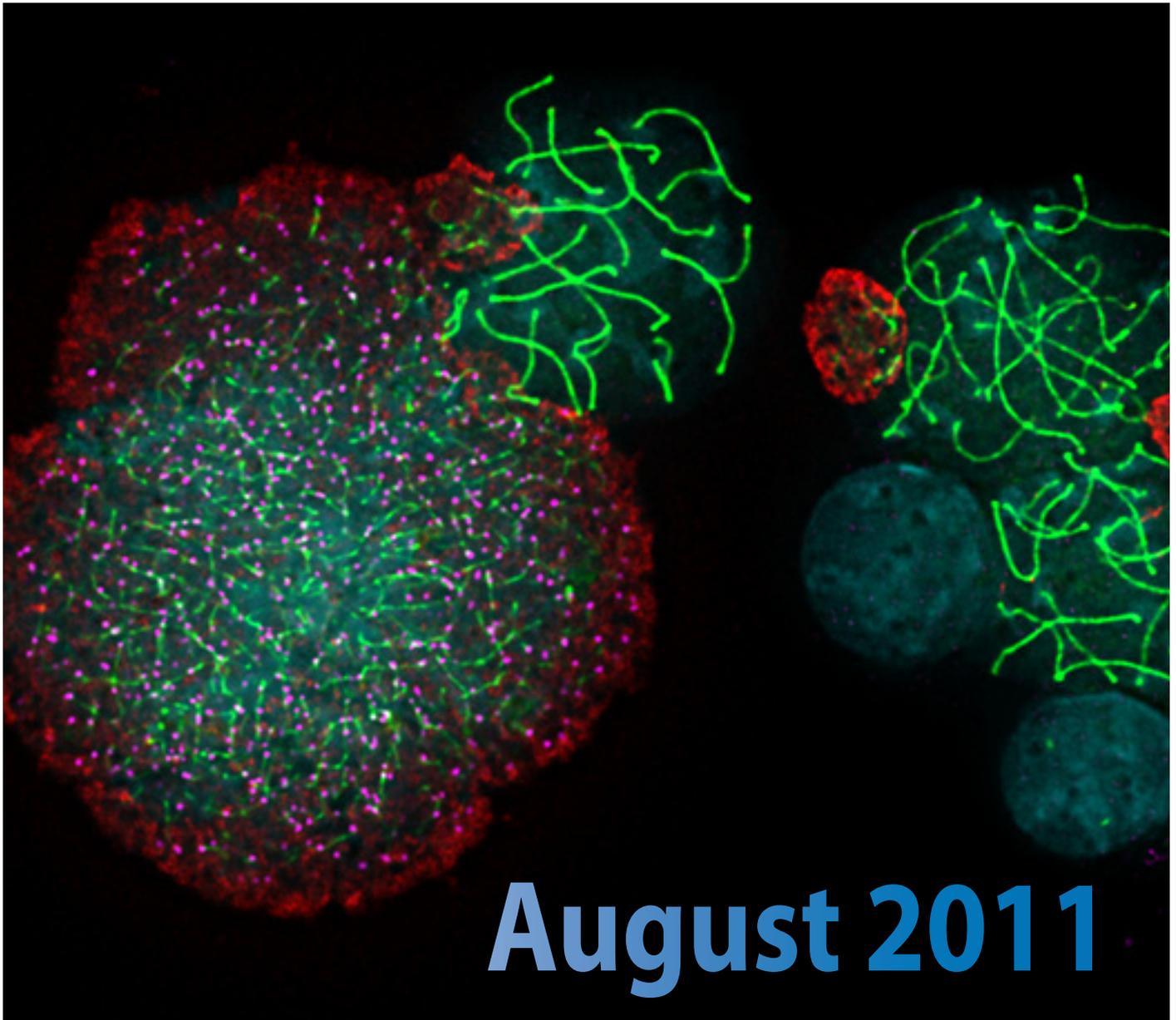


INSTITUTE OF HUMAN GENETICS

Scientific Report



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Contents

Introduction	2
GENOME DYNAMICS Department	8
Ounissa Aït Ahmed	9
Giacomo Cavalli	11
Séverine Chambeyron	13
Jérôme Déjardin	15
Bernard de Massy	17
Nicolas Gilbert	19
Rosemary Kiernan	21
Marcel Méchali	23
GENETICS & DEVELOPMENT Department	26
Brigitte Boizet	27
Jean-Maurice Dura	29
Anne Fernandez & Ned Lamb	31
Krzysztof Rogowski	33
Martine Simonelig	35
MOLECULAR BASES OF HUMAN DISEASES Department	38
Monsef Benkirane	39
Angelos Constantinou	41
Pierre Corbeau	43
Dominique Giorgi & Sylvie Rouquier	45
Marie-Paule Lefranc	47
Sylvain Lehmann	49
Domanico Maiorano	51
Philippe Pasero	53
ADMINISTRATION AND OTHER SERVICES	56
SEMINAR SPEAKERS	66
PUBLICATIONS	73





GIACOMO CAVALLI

Director



PHILIPPE PASERO

Associate 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 m².

It hosts more than 200 people, including scientists (31 CNRS, 9 INSERM and 14 University and Hospital researchers), engineers, technical and administrative staff (36), post-doctoral fellows (47), graduate students (26), 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 IGH is a high-profile, large institute devoted to basic biomedical research. Throughout its 12 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 perfectly supports the high scientific output of the IGH. Below, I discuss the main facts about life at IGH and the recent improvements that have been implemented to further improve the IGH working environment.

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 scientists in developmental genetics are invited to give timely up-dates on their research work. Until now, there was only an annual series on Genetics and Development, but, starting from 2011 there will be also series on Genome Dynamics and Molecular Bases of Human Diseases;
- weekly «internal» seminars where scientists, post-doctoral fellows and PhD students expose their results and research projects;
- 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» (June 2008), with lectures by 11 outstanding scientists including the Nobel laureate David Baltimore (see <http://congres.igh.cnrs.fr/IGH/IGH10ans.pdf> for an overview of the program);
- IGH group leaders have organized prestigious international conferences (such as EMBO conference series and others) and the IGH has acted as a co-organizer institution, providing financial support, secretariat and infrastructure. Typically, the IGH sponsors every year at least one of these events (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 University of Montpellier South of France (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 m² imaging facility. This facility, called MRI – IGH, has imaging equipment which is worth more than 3 millions Euros, including 3 confocal microscopes and more than 10 top-level epifluorescence microscopes. We have recently acquired a Macroconfocal microscope (Macrofluor Confocal from Leica) that allows performing confocal microscopy of very large tissue samples with a field of view up to 16 mm and magnification up to 630X.

Furthermore, the recent installation of the OMX super-resolution fluorescence microscope 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 Ix 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.

IGH Highlights of the last year

This has been a very exciting time for the IGH. We have witnessed a flurry of exciting discoveries and welcomed two new groups. We also opened a call for selecting a new junior group leader and will welcome the new team in October 2011. Our institute was evaluated in January 2010 by the AERES agency (<http://www.aeres-evaluation.fr/index.php/Etablissements/UNIVERSITE-MONTPELLIER-1>, see Institut de Génétique Humaine). Following the panel's recommendations, we have set up clear policies concerning laboratory space and the status of junior groups. In order to accompany the development of the Institute and to follow the implementation of its policies, an external scientific advisory board (SAB) has been established. The new director and associate director and the scientific advisory board took up their positions in January 2011. I briefly discuss below these main points.

A year of thrilling science

Last year's scientific achievements have been perhaps the most striking since the opening of the Institute. It would be too long to discuss all the main discoveries published by the IGH groups and I will thus mention only four of them, as examples that highlight the impact of the IGH research on a very broad research community that includes the fields of meiosis, early embryonic development, nuclear organization and HIV/AIDS. I strongly recommend reading carefully the scientific summaries of the individual research groups for more information about all the exciting recent advances made by the IGH teams in genome function, development and disease.

Focusing on the regulation of DNA recombination, the laboratory of Bernard de Massy has identified PRDM9 as the main mammalian protein that determines the position of meiotic recombination hot spots along the genome (Baudat, F., et al. (2010), *Science*: 327, 5967, 836-840). Indeed, meiotic recombination events cluster into narrow segments of the genome, defined as hotspots. They found that two mouse strains that differ in hotspot usage are polymorphic for the zinc finger DNA binding array of PRDM9, a chromosomal protein that is able to trimethylate lysine 4 of histone H3 and is expressed specifically in germ cells during meiotic prophase. Turning to humans, they found that the consensus PRDM9 allele is predicted to specifically recognize the 13-mer motif enriched at human hotspots and verified this DNA binding specificity by *in vitro* studies. Finally, they discovered that allelic variants of PRDM9 zinc fingers are significantly associated with variability in genome-wide hotspot usage among humans. These results, therefore, provide a molecular basis of the distribution of meiotic recombination in mammals, in which binding of PRDM9 to specific DNA sequences targets the initiation of recombination at specific locations in the genome. The specific features of the PRDM9 protein carry major implications for hotspot variability and genome evolution and, moreover, these studies open a new avenue to precisely understand the molecular basis of initiation of meiotic recombination.

The eukaryotic genomes encode a plethora of small non-coding RNAs. In particular, Piwi-associated RNAs (piRNAs), a specific class of 24- to 30-nucleotide-long RNAs produced by the Piwi-type of Argonaute proteins, have a specific germline function in repressing transposable elements. This repression is thought to involve heterochromatin formation and transcriptional as well as post-transcriptional silencing. The laboratory of Martine Simonelig has identified an unexpected function for piRNAs in driving mRNA deadenylation and decay in early *Drosophila* embryos (Rouget, C. et al. (2010), *Nature*: 467, 7319, 1128-1132). A subset of maternal mRNAs is degraded in the embryo at the maternal-to-zygotic transition. In *Drosophila*, maternal mRNA degradation depends on the RNA-binding protein Smaug and the deadenylase CCR4 as well as the zygotic expression of a microRNA cluster. Using mRNA encoding the embryonic posterior morphogen Nanos (Nos)

as a paradigm to study maternal mRNA decay, Rouget et al. found that CCR4-mediated deadenylation of Nos depends on components of the piRNA pathway, including piRNAs complementary to a specific region in the Nos 3' untranslated region. Based on these and other results, the authors propose that piRNAs and their associated proteins act together with Smaug to recruit the CCR4 deadenylation complex to specific mRNAs, thus promoting their decay. Because the piRNAs involved in this regulation are produced from transposable elements, this identifies a direct developmental function for transposable elements in the regulation of gene expression. This may be one additional reason for the maintenance of these elements in eukaryotic genomes.

The laboratory of Giacomo Cavalli has identified a role for the regulation of the three-dimensional chromosome architecture by Polycomb proteins in modulating gene expression (Bantignies, F. et al. (2011), *Cell*: 144, 214-226). The positional organization of genes within nuclei has long been thought to play a role in the regulation of gene expression. In particular, several loci that are linearly distant on a chromosome are known to come in close three-dimensional contact within the cell nucleus. By studying Polycomb target genes in *Drosophila*, Bantignies et al. have shown that two Hox loci, which are located 10 Mb apart on chromosome 3R, colocalize in nuclear compartments called Polycomb bodies. They further demonstrated that these contacts are evolutionarily conserved and contribute to Polycomb-mediated silencing of the interacting loci in flies. These studies open the possibility that many other types of chromosomal contacts may exist in the nucleus, with similar gene-regulatory properties.

A fourth discovery came from the laboratory of Moncef Benkirane (Laguette, N., et al. (2011) *Nature*, <http://dx.doi.org/10.1038/nature10117>) who is interested in HIV biology and in its relation with the host genome. One of the mysterious properties of this host-virus interaction is that dendritic cells, although they express the viral receptors, are refractory to HIV-1 infection. Laguette et al. identified Samhd1 as the dendritic and myeloid cell-specific HIV-1 restriction factor. Samhd1 is a protein that is involved in Aicardi-Goutière Syndrome (AGS), a genetic encephalopathy with symptoms that mimic those of a congenital viral infection, and that has been proposed to act as a negative regulator of the interferon response. These new results demonstrate that Samhd1 is an anti-retroviral protein expressed in cells of the myeloid lineage that inhibits an early step of the viral life cycle. When asked to comment on Laguette's manuscript, Professor Françoise Barré-Sinoussi, 2008 Nobel Laureate in Medicine and IAS President-elect, said, "The new findings on innate control of HIV have implications for treatments and can provide insight into therapeutic vaccine development, bringing us one step closer to finding better strategies to address HIV infection." These findings open new perspectives for the development of DC-targeted vaccines against HIV/AIDS.

New groups, institute governance and organization

In 2010, the Institute went through major changes in the composition of the research groups. On the "departure" side, Frédéric Gachon, former junior group leader at the IGH, moved to the University of Lausanne to take up a professor position. His work at the IGH was very successful and just before leaving he published his latest results in *Cell Metabolism*. The IGH congratulates him and his group for their work and wishes Frédéric to continue his successful career in his new institute. Alain Bucheton, a senior group leader, is going to retire this year. Severine Chambeyron applied for a junior group leader position and, based on the results of the IGH evaluation process, she was granted this position, for which we congratulate her and wish her the best success. Two more groups have to be counted on the "arrival" side, as we welcomed two new externally recruited teams at IGH. The senior group "Responses to DNA replication stress and associated diseases", headed by Angelos Constantinou, who previously ran a laboratory at the Institute of Biochemistry of the University of Lausanne, Switzerland, aims at understanding how cells sense, signal and process DNA lesions and how signaling orchestrates the activity of effector proteins involved in DNA repair and replication. They also hope to exploit the DNA damage response for therapeutic purposes. The junior group "Tubulin code", headed by Krzysztof Rogowski, former post-doctoral researcher in the laboratory of Carsten Janke, will focus on the understanding of post-translational modifications of cytoskeletal components. In particular, they have identified enzymes involved in the generation and removal of Tubulin poly-glycylation and poly-glutamylolation and their projects will focus on understanding the functional role of both poly-modifications.

Finally, the IGH has issued a joint junior group leader recruitment call with the neighboring Institut of Functional Genomics in mid 2010. This call was extremely well received and, out of 110 applicants coming from all over the world, 7 were shortlisted for interview. Finally, the position was offered to Hervé Seitz, a non-coding RNA specialist who carried out his post-doctoral training in the laboratory of Philip Zamore, and now will join our Institute in October 2011 with an ATIP/AVENIR grant. We are very happy with the success of this call and look forward to be doing great science with this new group in the coming years.

On the governance side, the new 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.

This year, a new governance body was added, namely the Scientific Advisory Board (SAB). The SAB includes Hervé Chneiweiss, University Paris Descartes, Paris, France; Denis Duboule, University of Geneva, Switzerland; Edith Heard, Institut Curie, Paris, France; Ron Laskey, University of Cambridge, UK; and Stéphane Noselli, Institute of Developmental Biology and Cancer, Nice, France. These five distinguished scientists are experts in the research fields of the three departments. They will examine the overall Institute activity every two years, by participating 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. The SAB composition will evolve and new members will be added when needed.

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 last year 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 launched an application as a Center of Excellence (submitted by Giacomo Cavalli) that includes other major research centers in Montpellier. The project title is 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 10 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 start in the second half of 2011 and will run for 10 years 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. The 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 fantastic year to come to all IGH members.



Genome Dynamics Department

Director : Bernard De Massy

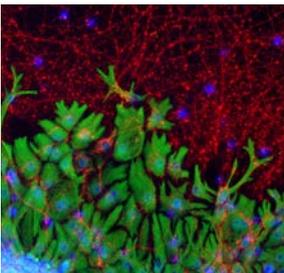
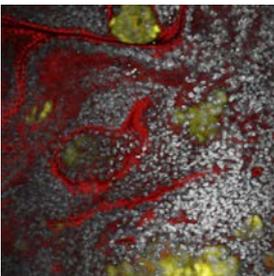
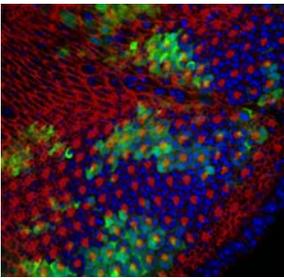
General Statement about the Department

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. (Gilbert is listed as part of the "Molec. Bases of diseases dept" in the organogram)

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.





Meiosis and Chromosome Segregation

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Foreword

During the past four years my group has focused on two research projects: 1) Post-transcriptional Regulation/DM1 Modeling in *Drosophila*; and 2) Meiosis and Chromosome Segregation. Both projects are summarized here, but our current research is specifically dedicated to « Meiosis and Chromosome Segregation » and related aspects.

From post-transcriptional control of maternal mRNAs to DM1 modeling in *Drosophila*

In the framework of our previous interests in maternal mRNA regulation, my group has shown that the EDEN element functions as a translational repressor in *Drosophila* oocytes and has characterized Bru-3 as the *Drosophila* EDEN-BP/CUG-BP homolog. CUG-BP is considered a major player in the multi-systemic disorder known as Steinert's myotonic dystrophy (DM1). DM1 is caused by expansion of CTG repeats in the 3'UTR of DMPK. Since the mechanisms underlying the pathology are still unclear, we planned to model DM1 in the fly. Transgenic flies that express inducible repeats of various type (CUG or CAG) and length (16, 240, 480 repeats) were generated to address the question of the importance of repeat type, length, RNA rate and RNA insertion context in foci formation and expansion toxicity. A deleterious phenotype upon (CUG)240 induction was observed in a single transgenic line, (CTG)240.4. (CUG)240 and (CUG)480 expansions formed nuclear foci regardless of whether they had a toxic effect or not. The toxicity of (CUG)240.4 expansion correlated with the formation of a fusion transcript between (CUG)240.4 and an endogenous RNA. Although other publications reported toxicity of (CUG)480 expansions in *Drosophila*, we are confident that our results will contribute to the still open debate on the role of the expansions per se in *Drosophila* and in the pathogenesis of RNA-dominant human diseases (Le Mée et al, 2008). Yemanuclein-alpha (yem-alpha), a new player in *Drosophila* female meiosis

Sexual reproduction relies on two key events: formation of cells with a haploid genome (the gametes) and restoration of diploidy after fertilization. We have identified and characterized yem1, the first yem-alpha mutant allele (V478E), which to some extent affects diploidy reduction and restoration. My group has identified Yem-alpha in molecular screens for genes specifically expressed in the female germ line (Aït Ahmed et al, 1987; 1988). We reported its specificity for the oocyte nucleus and its DNA binding properties (Aït Ahmed et al, 1992). Yem-alpha is a conserved protein and a member of the Ubinuclein/HPC2 family of proteins that has recently been implicated in replication-independent chromatin remodeling in concert with the histone H3.3 chaperone HIRA. Yem1 mutant females exhibit disrupted chromosome behavior in the first meiotic division and produce very few viable progeny. Moreover, their offspring do not display paternal chromosome markers, suggesting that they develop from diploid gametes that undergo gynogenesis, a form of parthenogenesis that requires fertilization. The analysis of the meiotic defects of yem1 oocytes strongly suggests that yem1 affects chromosome segregation presumably by hindering kinetochores function in the first meiotic division. Accordingly Yem-alpha colocalizes with CID, the centromeric histone variant (Meyer et al, 2010).

This work paves the way to further investigations on the evolution of the mechanisms that support sexual reproduction.

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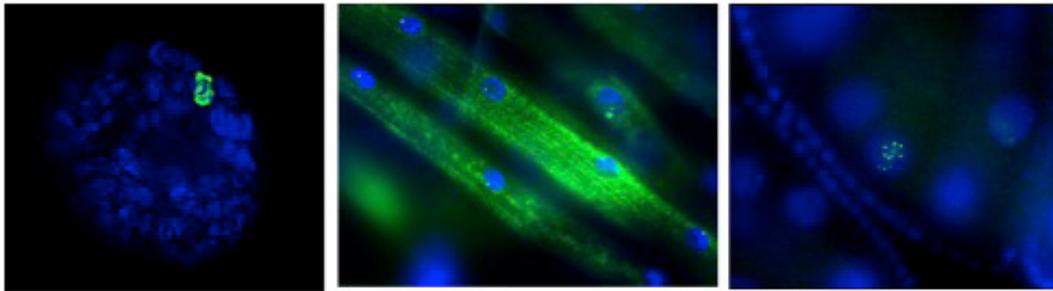
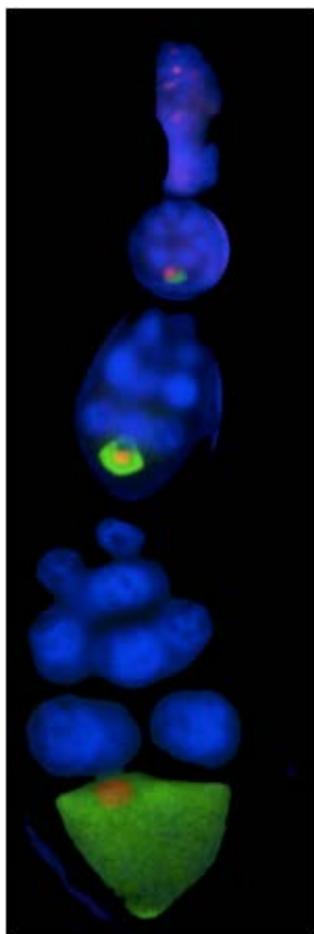
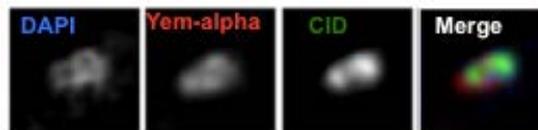


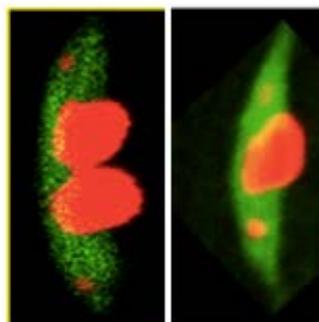
Figure 1 - RNA-FISH revealing expression of expanded CUG repeats in various tissues
CUG repeat foci form within the nuclei of larval salivary glands (left), muscle cells (middle) and ovaries (right). These RNAs are expressed upon induction of transgenic lines



Drosophila ovariols stained for DNA (DAPI; blue), Orb (green) and Yemanuclein-alpha (red). Yem-alpha is specifically expressed in the oocyte nucleus.



Yemanuclein-alpha (red) and CID (green) colocalize at the kinetochores of the metaphase I oocyte spindles



Metaphase I stage 14 wild type (left) and *yem1* mutant (right) oocytes stained for Tubulin (green) and phospho-histone H3 (red). The chromosome mass is disorganized in the mutant

Figure 2 - Yemanuclein-alpha localization in wild type and *yem-alpha* mutant *Drosophila* oocytes.



Chromatin and Cell Biology

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Proteins of the Polycomb and Trithorax groups are key regulators of the expression of major developmental genes and they 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. They are able to maintain the memory of gene regulatory states through successive mitotic divisions in the different cell lineages and our laboratory wishes to understand their function in normal development and disease, using flies as a model system.

Research in our laboratory has highlighted the importance of the nuclear architecture and developed the concept of 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 (Bantignies et al., 2010; Grimaud et al., 2006). 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 (Comet et al., 2006; Dejardin et al., 2005).

Moreover, our laboratory performed the first large-scale mapping of the distribution of Polycomb group proteins along *Drosophila* chromosomes at different developmental stages (Negre et al., 2006; Schuttengruber et al., 2009). We have then recently demonstrated that polyhomeotic, a Polycomb group gene, is a tumor suppressor that controls cell proliferation by regulating Notch signaling (Martinez et al., 2009). In the coming years, we will be pursuing these lines of research in order to deep. missing something

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Engineer

Visiting scientist
David Voadlo

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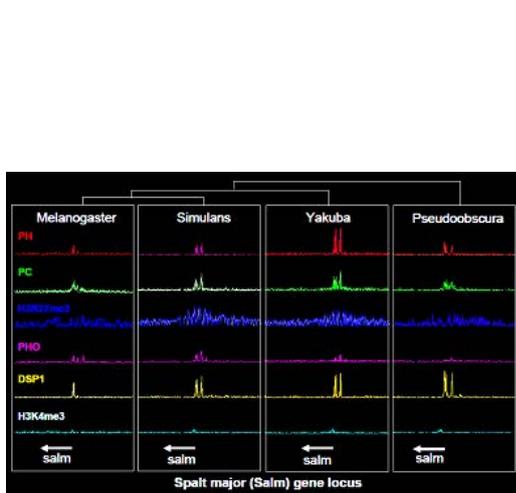


Figure 1. ChIP-Seq techniques are used to determine the distribution of Polycomb proteins in different *Drosophila* species. They allow identifying crucial sequences that target Polycomb proteins to the genome and their evolution.

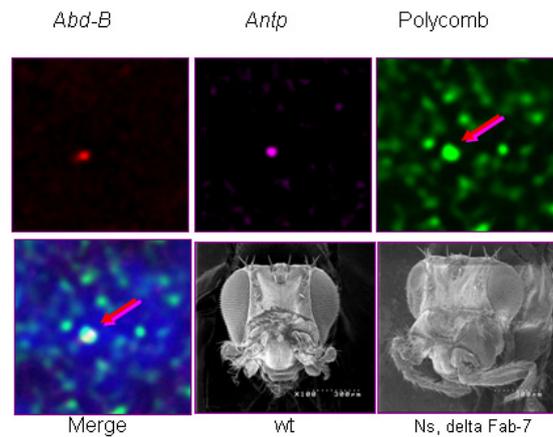


Figure 2. Microscopy analysis shows that co-repressed genes like *Abd-B* and *Antp* colocalize in the cell nucleus even if they are 10 Mb away in linear distance. Mutation in *Abd-B* can induce *Antp* phenotypes. Thus, long-distance gene contacts control phenotypes.

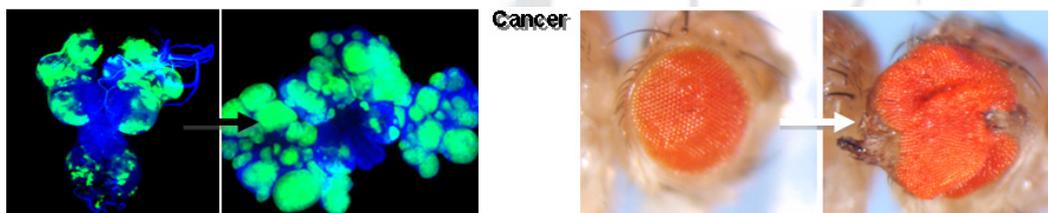


Figure 3. Mutation of the polyhomeotic locus (second panel from the left) induces over-proliferation of the mutant tissue (in green, compare to control on the left). Most larvae die but around 10% survive and, in that case, the mutant tissue over-proliferates (the mutant eye in the second panel from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



JUNIOR LABORATORY

RNA Silencing & Control of Transposition

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

piRNAs may be considered as key elements of a sort of bipartite immune system: one genetic component is encoded by heterochromatic loci that contain defective copies of TEs (piRNAs clusters) producing antisense piRNAs; the other component corresponds to the sense piRNAs produced by the functional copies of TEs located in euchromatin. In the proposed repression model associated with piRNAs, primary anti-sense piRNAs, produced by an unknown mechanism from piRNA clusters, target the transcripts of functional TEs that are cut to produce sense piRNAs. These sense piRNAs then target the transcripts of the piRNAs clusters that are cut this time to produce secondary, anti-sense piRNAs.

Our recent results provide evidence that such amplification loop is likely to occur in the female germline to repress the I element, a *Drosophila* retrotransposon, in the female germline. The I element is an excellent model because it is one of the rare transposable elements which can be de-silenced and mobilized in vivo through appropriate crosses.

Our data also show that this amplification loop does not occur in somatic ovarian cells, where only the primary piRNAs are present.

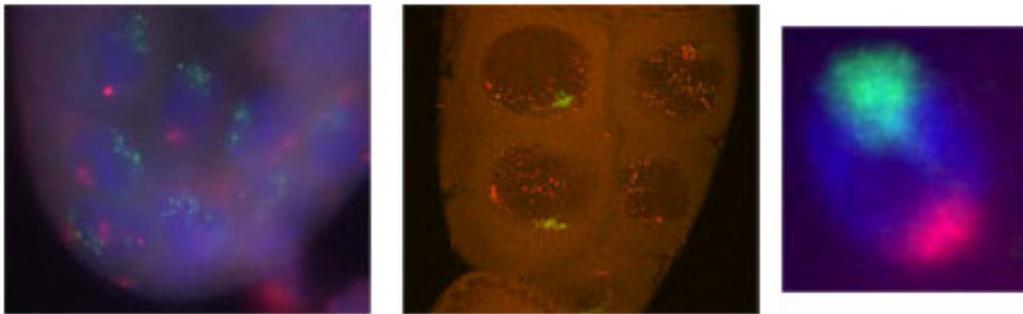
Based on our knowledge on two retrotransposons, the I element in the germline and the gypsy element in the soma, we are now studying the biogenesis of the primary piRNAs, the role of piRNAs in TE repression, and the epigenetic mechanisms involved in the maternal inheritance of this silencing. We are focusing on the biogenesis of the primary piRNAs in the ovarian somatic tissue by testing possible candidates for the processing of the putative long heterochromatic transcripts of the piRNA cluster.

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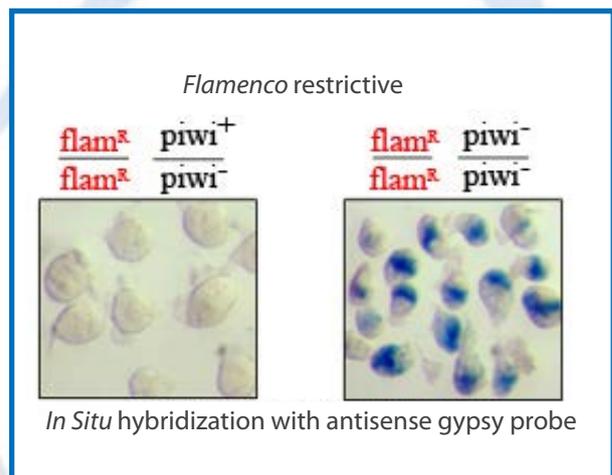
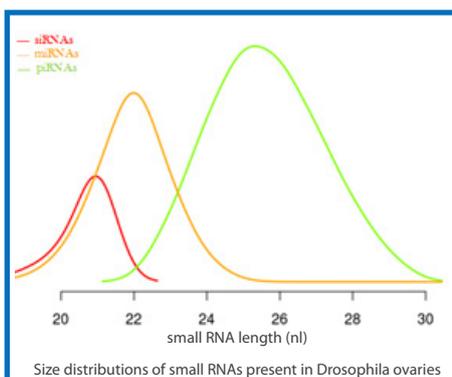
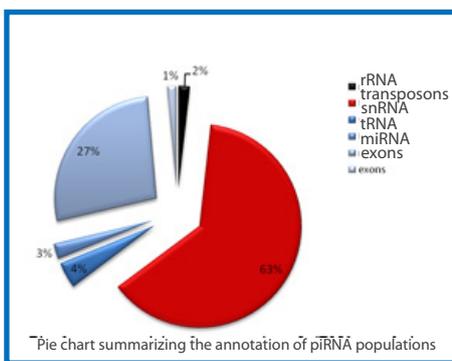
We are also studying the relationship between piRNAs and the siRNA pathway in the regulation of somatic TEs.

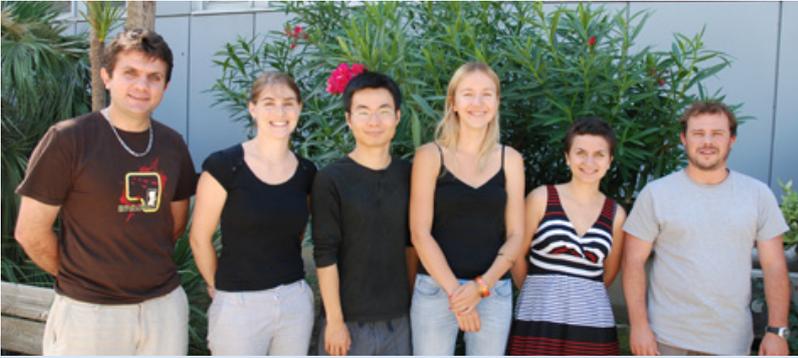
Moreover, the repression level of the I element in the female germline depends on ageing and various environmental conditions, for instance temperature. Its variations are maternally transmitted through generations. Hence, this element offers the opportunity to study epigenetic features that are maternally transmitted over many generations.

The molecular mechanisms of this trans-generational transmission are still unknown and piRNAs (some of which are maternally deposited in the embryo) could be the maternally transmitted epigenetic factors. We are characterizing quantitatively and qualitatively the piRNA population that is maternally deposited in the embryos.



In Situ hybridization on Drosophila ovaries





Biology of Repetitive Sequences

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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. The current view is that 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:

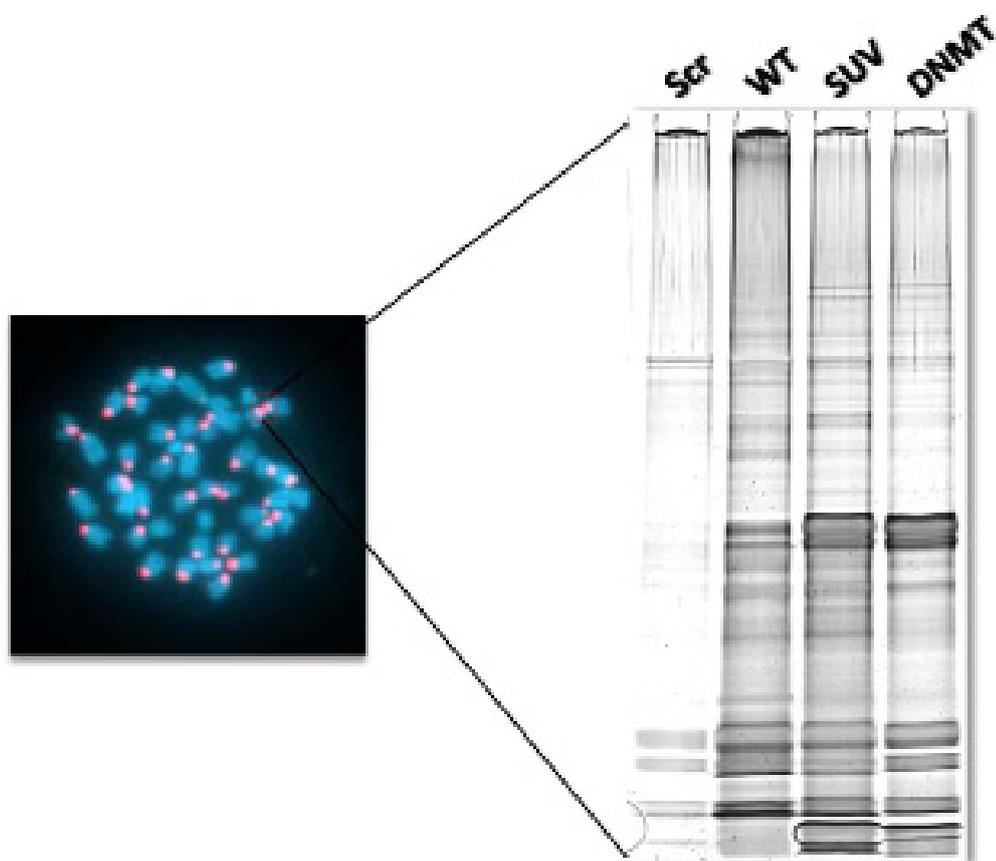
- (i) How telomere compositional changes upon loss of heterochromatin function can explain the appearance of the ALT (Alternative Lengthening of Telomeres) pathway observed in certain cancers.
- (ii) How the situation at ALT telomeres can be compared to the changes observed at human satellite 2 sequences 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 a new heterochromatin protein which possibly links DNA methylation and non-coding RNAs.
- (v) How is rDNA expression regulated?

We have initiated these studies using the PICh technology (Déjardin and Kingston, 2009), which 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 this research will uncover important determinants of gene expression and genome stability.

For more information, please, see:

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

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Purification of pericentric chromatin from mouse stem cells. The panel on the left shows the specificity of the PICh probes used for purification (in red). The panel on the right shows the protein profile of purified gamma satellite regions in wild type (WT) and in two heterochromatin mutant backgrounds (SUV and DNMT).



Meiosis and Recombination

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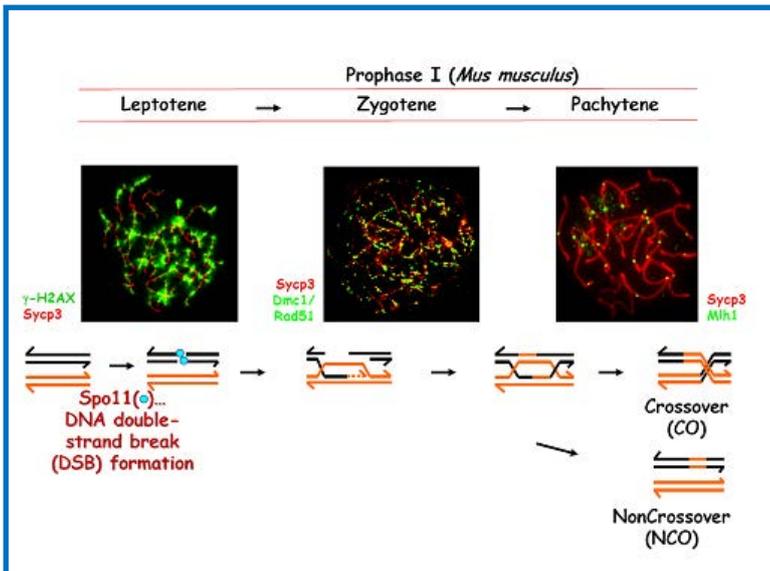
In sexually reproducing species, meiosis allows the formation of haploid gametes from diploid cells. The halving of the DNA content results from a specialized cell cycle, where a single phase of DNA replication is followed by two divisions. In most species, the proper segregation of chromosomes at the 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.

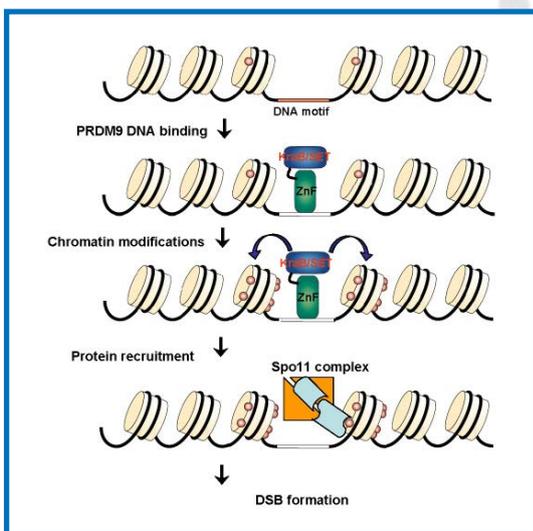
We are interested in understanding how the frequency and distribution of these DSBs are regulated, and how DSB formation and repair are coordinated. We have recently discovered a major component that determines the sites where DSBs are formed in mammals: the Prdm9 gene. This gene encodes a protein with 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 are required for DSB formation (Fig. 3). We are currently investigating the activities and functions of these proteins using biochemical, molecular, cytological and genetic approaches.

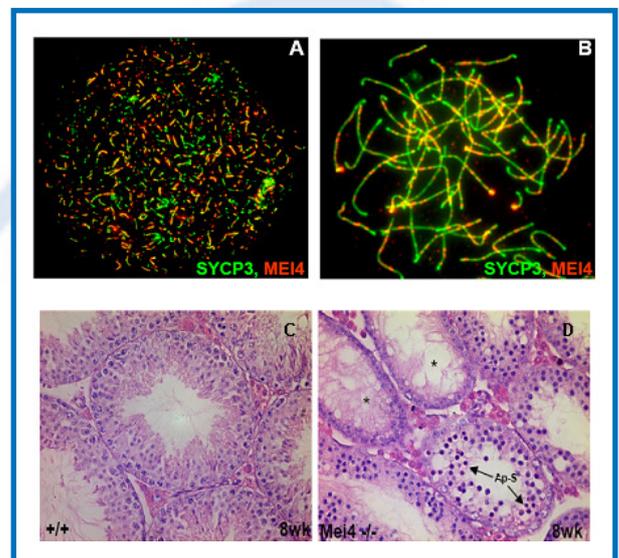
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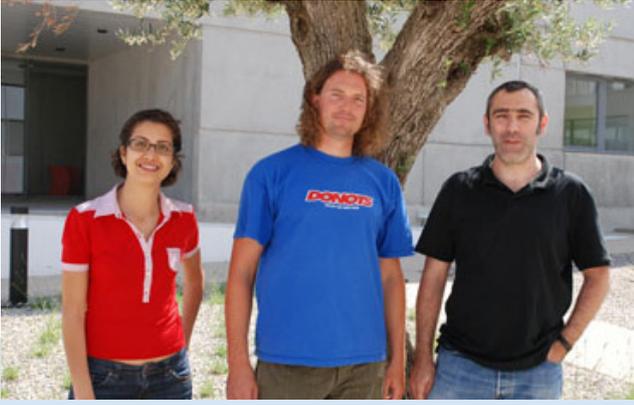
- **Fig.1.** DNA and cytological events during meiotic prophase. Meiotic recombination is initiated by DSBs, which are catalyzed by SPO11 and visualized by the appearance of γ H2AX (the phosphorylated form of H2AX). DSB repair, with the strand exchange activity of RAD51 and DMC1, leads to crossover (CO) 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 apoptosis are observed in *Mei4*^{-/-} mice. *, empty tubules; Ap-S, Apoptotic spermatocytes.



Mobile elements, Integrity and Plasticity of the Human Genome

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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.

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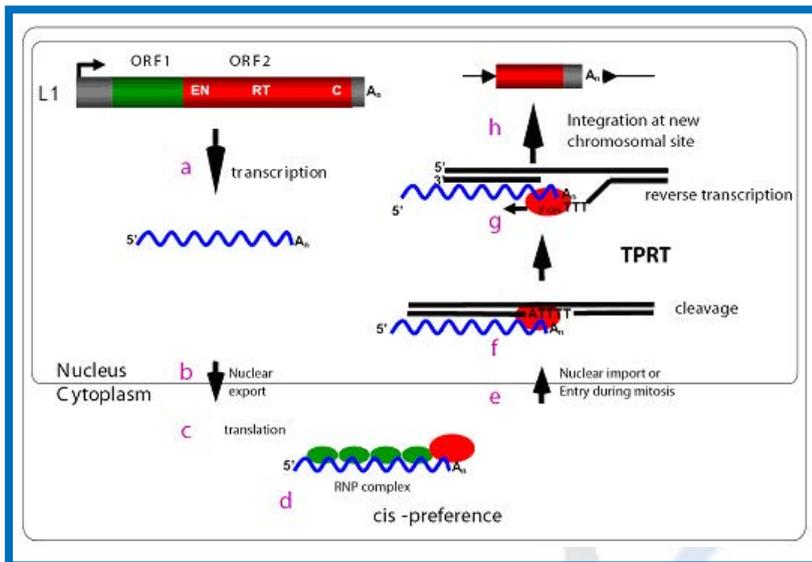


Figure 1: Structure of an L1 and model of retrotransposition.

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).

pAD3TE1 T7 TAP MS2

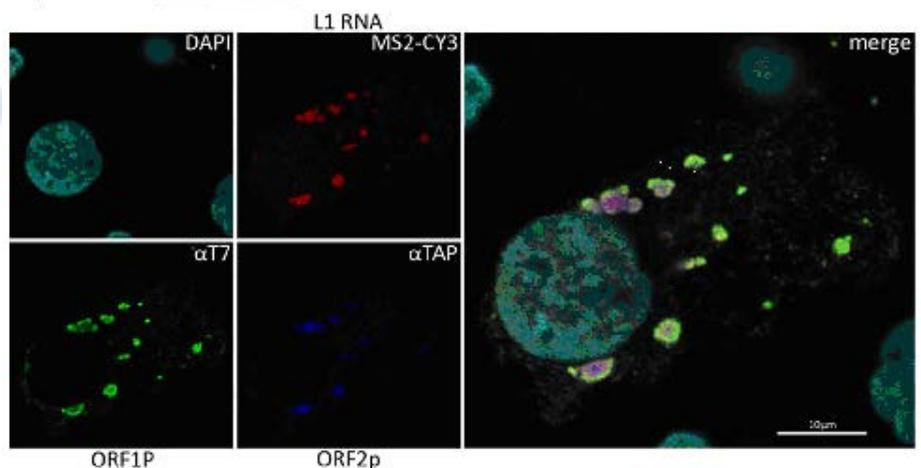


Figure 2: Cell localization of L1-encoded proteins and RNA. Immunofluorescence/RNA FISH was carried out using pAD3TE1-transfected U-2 OS cells 48 hours post-transfection. T7-tagged ORF1p (green), TAP-tagged ORF2p (blue), L1 RNA (red) and DAPI (turquoise) staining are shown in the four micrographs on 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.



Gene Regulation

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

Disregulation 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.

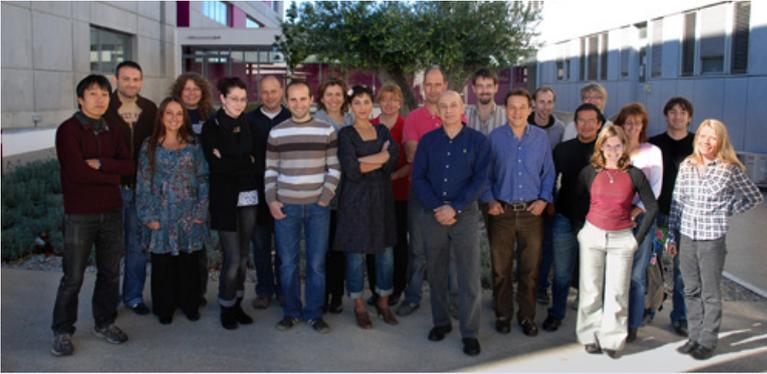
Finally, transcription of a gene is linked to cellular processes required for the maturation and export of the mRNA in order to achieve gene expression.

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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 shown that the HIV-1 promoter is repressed by HP1 γ -dependent heterochromatin formation. We are further characterizing the repressive mechanisms that down-regulate HIV-1 transcription, and we want to determine whether similar mechanisms operate at cellular promoters



Replication & Genome Dynamics

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Paradoxically, the faithful duplication of the genome (a major cell function) remains poorly understood in metazoans, and deciphering its rules is an ambitious challenge. Chromosomes should be duplicated while maintaining memory of the specific ongoing transcription programs in the embryo, 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 50 000 sites along chromosomes, called DNA replication origins. They do not share a detectable consensus sequence, and their common features remain to be unveiled. 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 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 embryonic stem cells and differentiating cells as well as *Drosophila* cells. Nascent strands synthesized at replication origins were purified and their distribution along chromosomes identified by micro-arrays and high-throughput sequencing. Several new features of replication origins were characterized and found to be conserved, including CpG elements. We also analyzed the global organization of origins by DNA combing methods (Figure 1). Bioinformatic simulations using the data obtained suggest a replicon model in which origins are organized in groups of potential and flexible adjacent origins that define each replicon. 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 replication complexes. 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 acting as an ON/OFF switch at replication origins. Two new members of the MCM helicase family were found to be active during DNA replication: MCM8, which acts at the replication fork, and MCM9, which participates in the formation of the pre-replication complex. New functions of these two genes are being characterized.

The dissociation of replication complexes at the end of S phase is also 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 necessary for its disassembly at mitotic entry. Specifically, MCM-BP, a protein that interacts with the MCM2-7 helicase, contributes to ORC complex dissociation from DNA at the end of DNA synthesis. In the coming years we will explore how DNA replication origins contribute to chromosome structures and cell identity and how they are regulated in mammalian cells, with the aim of understanding how this regulation might be perturbed in human pathologies. Further information is available at: <http://www.igh.cnrs.fr/equip/mechali/>

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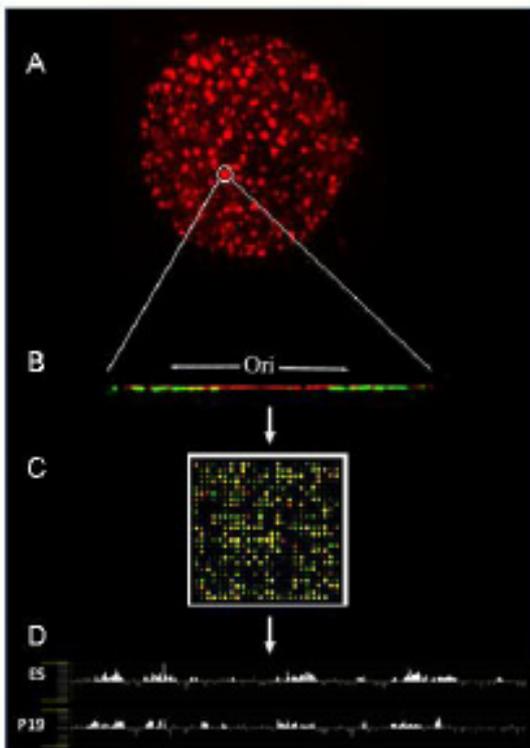


Fig.1. From replication foci to the replication origin code.

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 microarray 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).

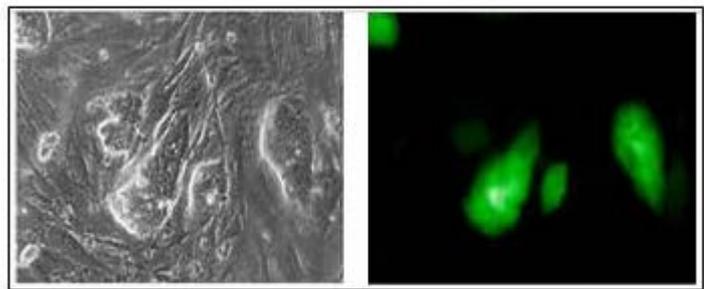


Fig.2. Mouse embryonic fibroblasts reprogrammed by *Xenopus* egg extracts express OCT4, a marker of pluripotency. Left, phase-contrast image. Right, fluorescence image showing cell clones expressing GFP under the control of the Oct4 promoter.

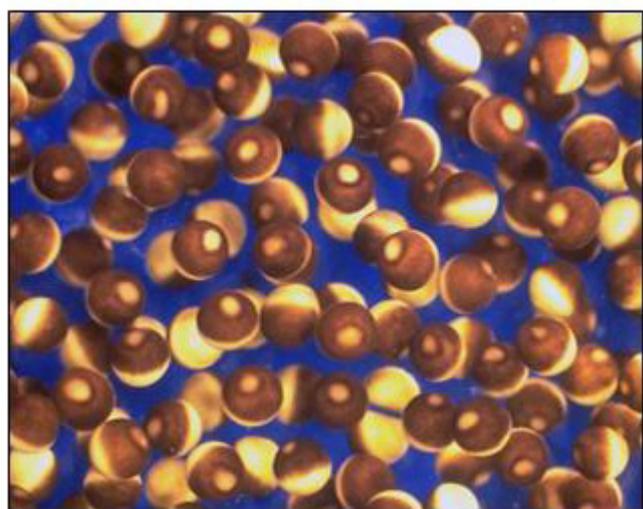
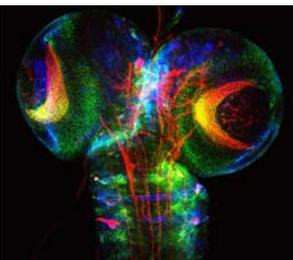
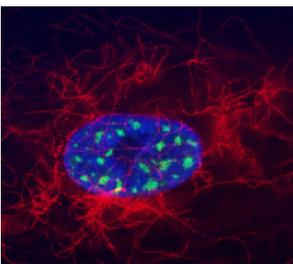
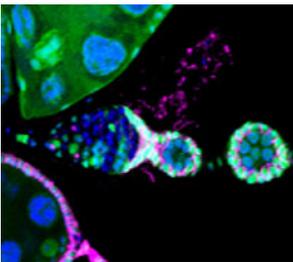


Fig.3. *Xenopus* eggs

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, motoneuronal 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

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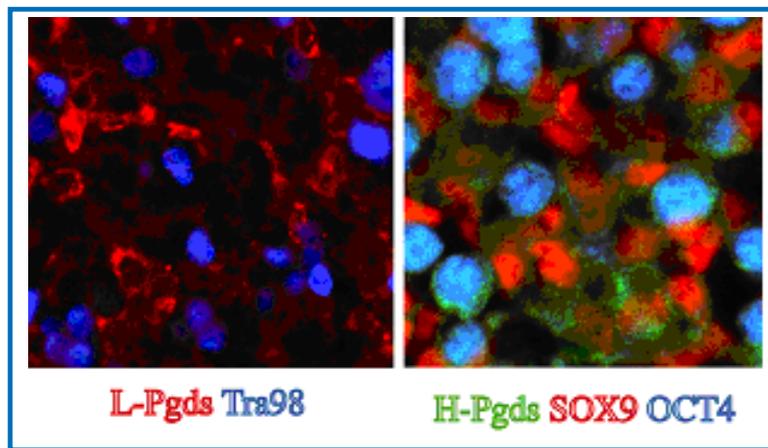
Massilva Rahmoun,
Post-doctoral Fellow

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.

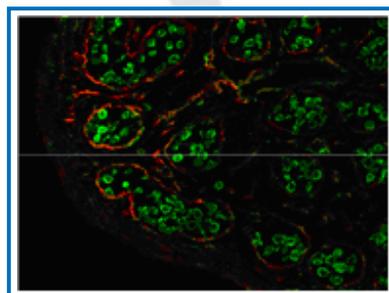
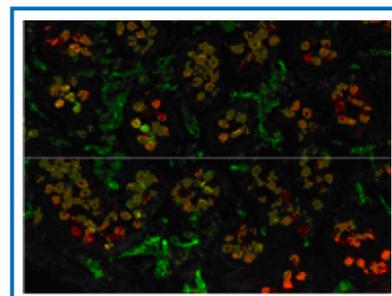
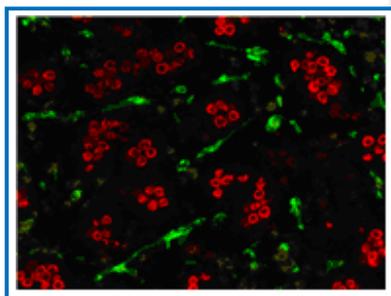
In mammals, testicular differentiation is controlled by the gene *Sry* located on the Y-chromosome. This gene, which encodes a HMG (High Mobility Group) domain-containing transcription factor of the SOX family, induces a variety of morphogenetic events, including cell proliferation, cell migration and 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 gene by *SOX9*; L-Pgds and H-Pgds, two genes encoding PGD2-producing enzymes, belong to a regulatory loop that is independent of the *FGF9/SOX9* loop and both contribute to maintaining *Sox9* expression and induce testis formation. We have recently described the expression of H-Pgds in the embryonic gonad. By analyzing gonads from mouse embryos in which both L- and H-Pgds were knocked down, we found that both activities are required for normal differentiation of Sertoli cells and of the germ cell lineage. We also identified an H-Pgds mutation in a cryptorchid patient, indicating that PGD2 signaling is involved in the testicular descent process. Moreover, we have also shown that PGD2, through H-PGDS expression, is a positive effector of the activity of the FSH and LH hormones in the normal adult ovary, whereas in the pathological ovary, PGD2, through L-PGDS expression, has an anti-proliferative effect.

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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).





Neurogenetics and Memory

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Developmental molecular genetics of *Drosophila* adult brain.

Developmental molecular genetics of *Drosophila* adult brain is a young science which 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 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 $\alpha'\beta'$ and finally the $\alpha\beta$ 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 as 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 will divide 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 (homolog of the oncogene H-Ryk), its ligand *wnt5* and the cytoplasmic oncogene *Src*. We want to understand how *Src* integrates the signals from the new transduction pathway in order to regulate axonal growth, fasciculation and guidance in MBs.

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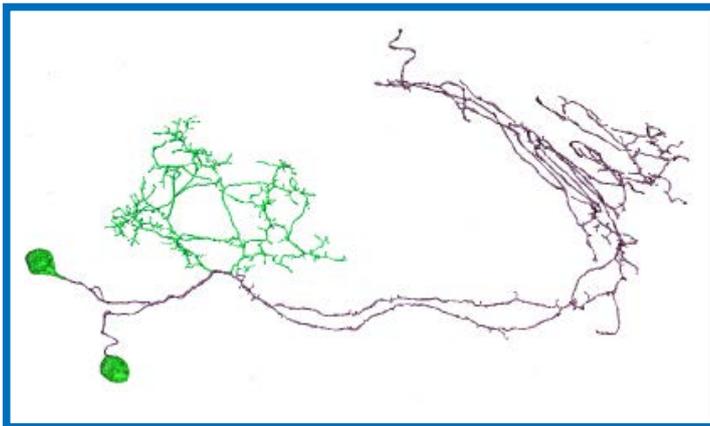


Fig 1 : 2 γ neuron clone in a larval brain (in green the cell bodies and the dendrites).

Development



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

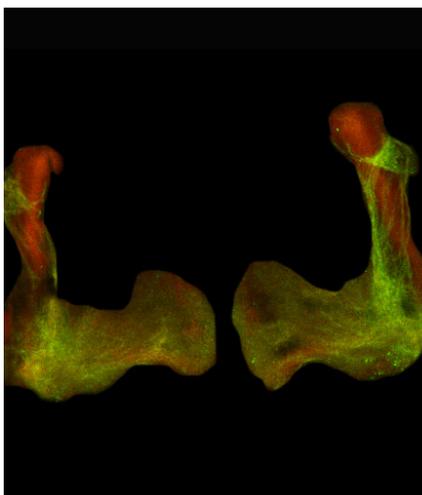


Fig 3 : Adult MB with un-remodelled γ axons (green) and normal $\alpha\beta$ axons (red).

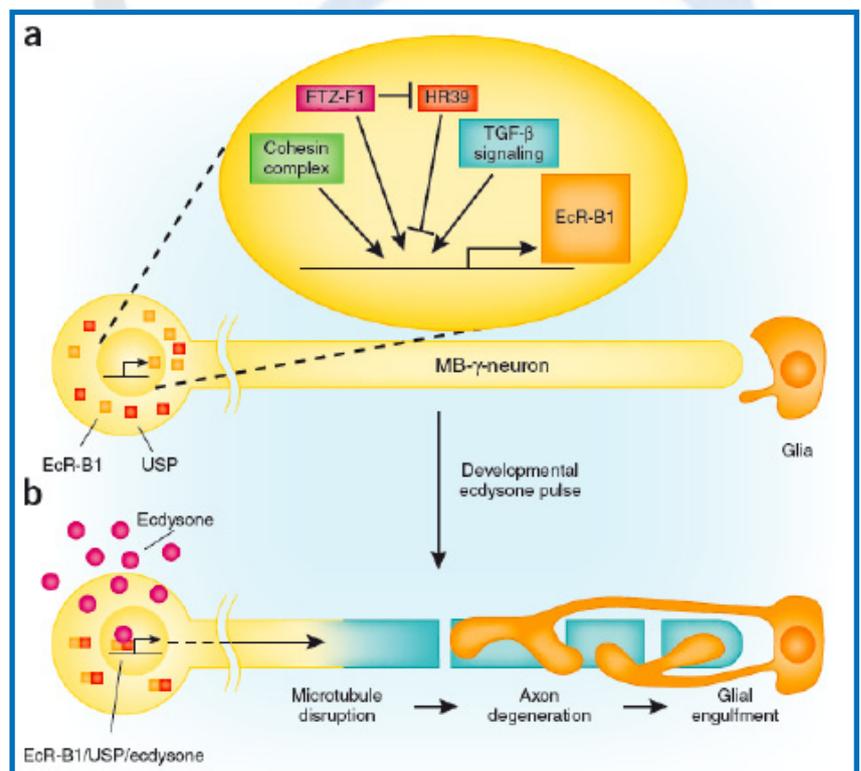


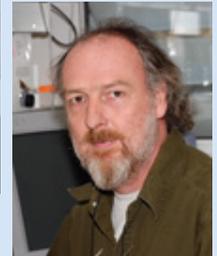
Fig 4 : Model for EcR-B1 activation in MB neuron remodeling. After a News and Views by Awasaki and Lee introducing Boulanger *et al.*, 2011.



Cell Cycle and Myogenesis

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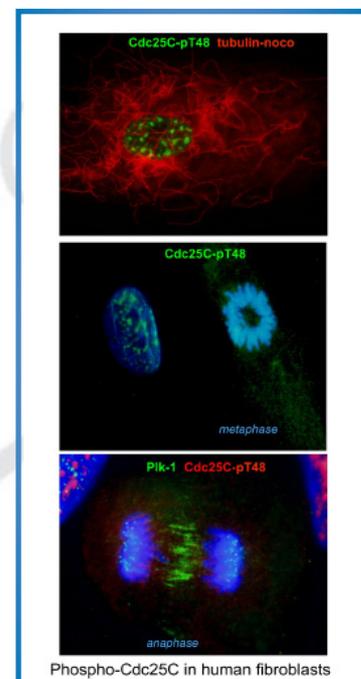
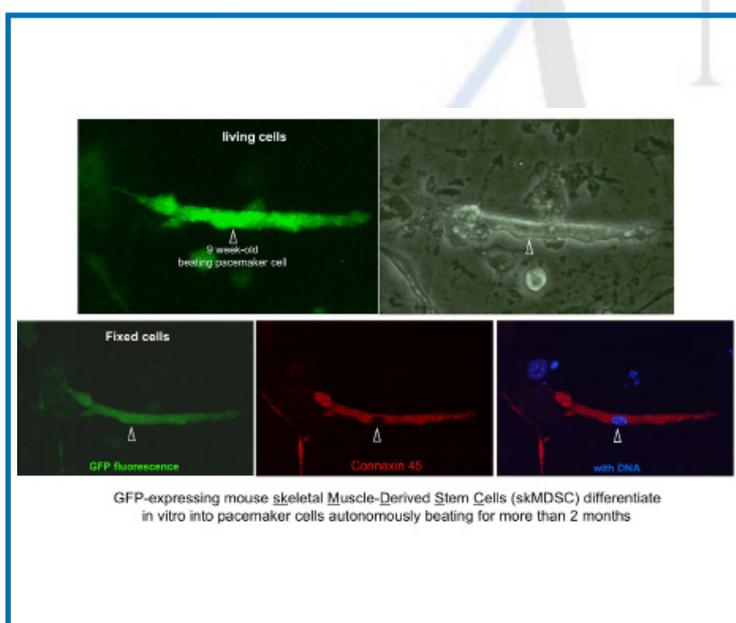
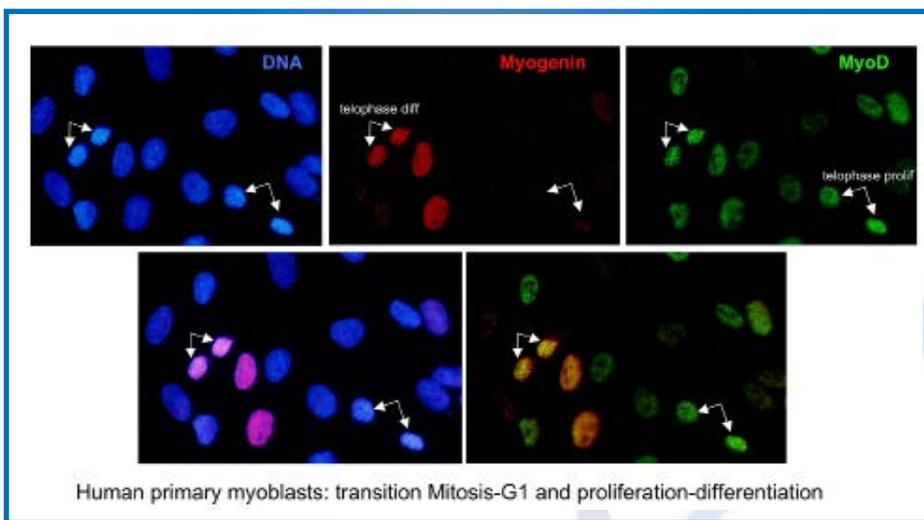
Using primary and established cultured mammalian cells (human, rodent), our group applies cell biological and biochemical approaches to the study of signaling pathways, investigating their impact on transcriptional and post-translational regulation of the cell division cycle and the transition from cell proliferation to terminal differentiation, in particular muscle cell differentiation.

In the study of cell cycle control, we are examining the modulation involving Cyclin-Dependent Kinases (CDK), the activating Cdc25C phosphatase and their crosstalk with some major multi-task enzymes, such as cAMP-dependent Protein Kinase (PKA), Akt/PKB family kinases and phosphatase 2A (PP2A). 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, in addition to studying the regulation of MyoD, the only myogenic factor expressed and involved in both myoblast proliferation and differentiation, we are also 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.

The last aspect we have developed from the study of skeletal muscle progenitor and stem cells involves the isolation and characterization of a new population of adult stem cells derived from skeletal muscle and capable of multipotent differentiation, particularly into spontaneously beating cardiac muscle cells and neuronal lineages. Transplantation experiments in mutant mice show that these multipotent stem cells possess a very promising repair and regeneration potential and thus represent a valuable source of autologous stem cells for cell therapy approaches in the treatment of numerous degenerative and traumatic diseases.

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Tubulin Code

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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-glutamylolation 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.

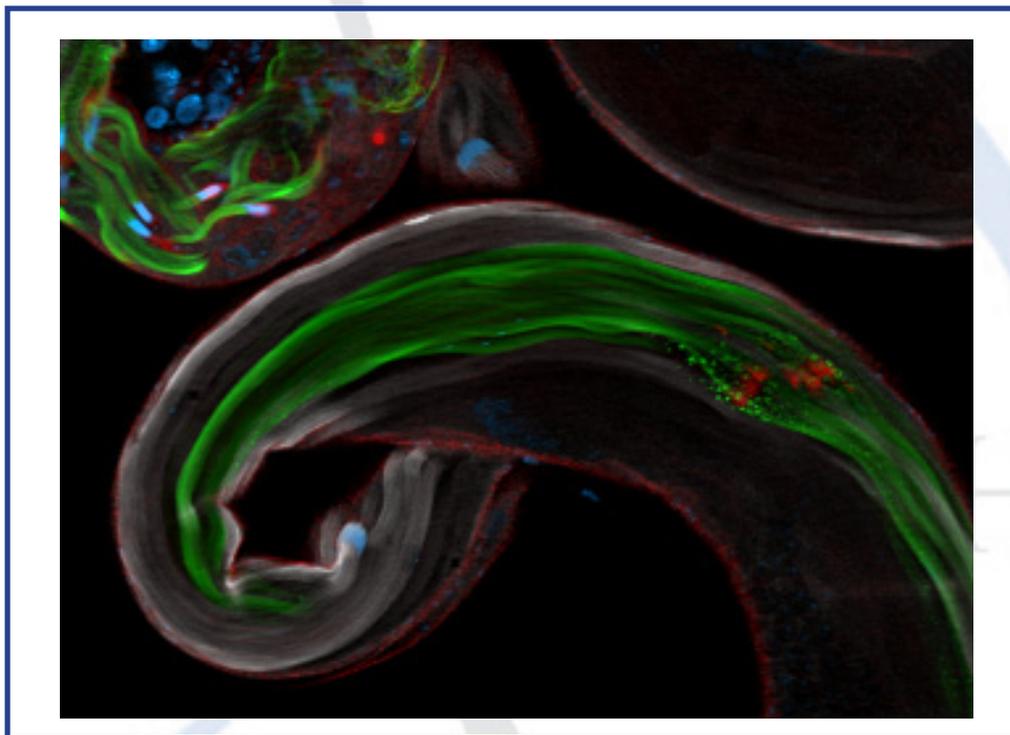
Given the range of signals that the Tubulin C-terminal modifications can generate, it is not surprising that particularly high levels of these post-translational marks are present in complex and sophisticated MT-based structures, such as the ones found in neurons or in cilia and flagella. However, until 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-glutamylolation 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-glutamylolation, 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-glutamylolation 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 dyskinesia, polycystic kidney disease, situs inversus, retinal degeneration, obesity, hypergenitalism and polydactyly as well as cancer (Sharma et al., 2008).

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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.

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



mRNA Regulation and Development

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mRNA Regulation and Development

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 OPMD patients' muscles. We have generated a *Drosophila* model of OPMD that recapitulates the features of the human disorder: progressive muscle degeneration, with muscle defects proportional to the number of alanines in the N-terminal tract of PABPN1, 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.

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Development

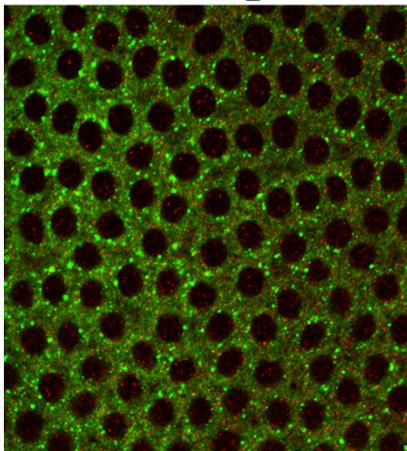


Figure 1: P bodies in the *Drosophila* embryo. The CCR4 deadenylase (red) and the Smaug RNA binding protein (green), localize in foci or processing bodies (P bodies) in *Drosophila* embryos (Zaessinger et al. 2006, *Development*, 133, cover).

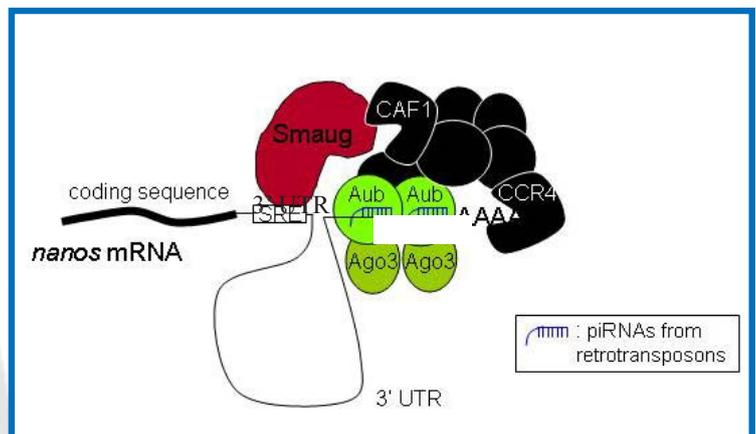


Figure 2: Model of *nanos* mRNA regulation by the piRNA pathway. SRE: Smaug recognition elements. The Smaug RNA binding protein (red) binds to the SRE and recruits the deadenylation complex (proteins in black). piRNAs from retrotransposons target *nanos* 3'UTR and guide the interaction with Argonaute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

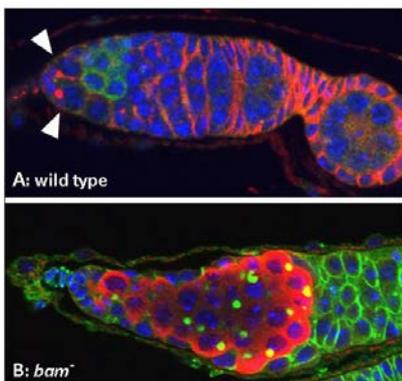


Figure 3: Germaria in the *Drosophila* ovary.
A: wild-type. All germline cells derive from two germline stem cells (marked by a dot with the 1B1 marker (red), arrowheads). Bam (green) is expressed in cystoblasts and is required for their differentiation. DAPI (blue).
B: In the *bam* mutant, germline 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).

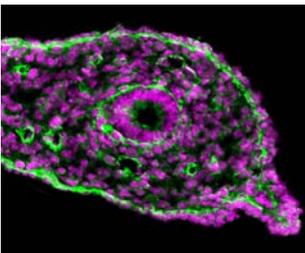
Molecular Bases of Human Diseases Department

Director : Monsef Benkirane

General Statement about the Department

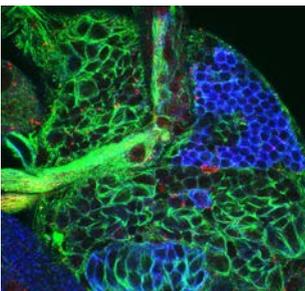
Research in the department of Molecular Bases of Human Diseases strives to shed light on the etiology of cancer, AIDS and neuro-degenerative diseases. Supported by strong collaborations with the academic hospitals, our objective is to translate novel biological concepts and molecular insights into new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

Genome instability and cancer.



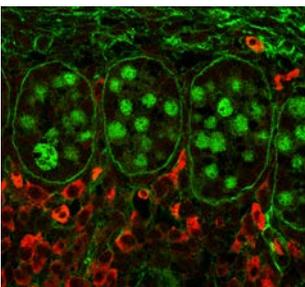
Five research groups use complementary model systems (yeast, *Xenopus* and human cells) to explore two major topics in cancer biology: the origin of genomic instability in cancer development and the cellular responses to DNA damage. Since defects in DNA replication are increasingly recognized as a major 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 and neuro-degenerative 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. Prion diseases or transmissible spongiform encephalopathies (TSEs) are a group of fatal neurodegenerative disorders. The team "Neurological Disorders and Stem Cells" aims at understanding the effect of prion replication on cell fate and on the function of PrP. The team is also developing gene and cell therapy approaches to TSEs based on "lentiviral expression vectors" and on the use of neural stem cells.

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Molecular Virology

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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. However, in certain situations, the virus replication can be successfully controlled. First, HAART (Highly Active Anti-Retroviral Therapy) treatment revealed the existence of a pool of resting memory CD4+ T cells harboring integrated, but silent HIV-1 proviruses. Although this situation occurs in a small number of cells, it suggests that the intracellular defense mechanisms can be effective against HIV. This long lived viral reservoir is believed to be the major obstacle against HIV-1 eradication by HAART. Second, HIV-infected individuals, who can control the virus to undetectable levels for many years in the absence of any treatment, have been identified and referred to as Elite HIV Controllers, "EC". Again, this is a rare situation observed in 0.5% of infected patients. Still, it demonstrates that it is possible to naturally and effectively control HIV replication and disease progression. A common feature of these two situations is that viral replication is controlled at the gene expression level. A major challenge in the HIV field is to understand how, in these naturally occurring situations, the intracellular defense and/or immune response win the battle against HIV. Our main objectives are to identify the host factors and define the molecular mechanisms involved in the regulation of HIV-1 gene expression and to explore the involvement of cellular small non-coding RNAs in virus replication. We also use viruses as tools to understand important cellular processes, such as transcription and RNAi.

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

HIV-1 Tat assembles a multifunctional transcription elongation complex and stably associates with the 75K snRNP (Sobhian et al. 2010. Mol Cell 38, 439-451). 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. In this study, we purified HIV-1 Tat-associated factors from HeLa nuclear extracts and showed by biochemical analysis that HIV-1 Tat forms two distinct and stable complexes. The first one is Tatcom1, 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. MLL-fusion partners and PAF1 are required for Tat-mediated transactivation of the HIV-1 promoter.

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The second complex, Tatcom2, is composed of CDK9, Cyclin T1 and 7SK snRNP containing LARP7 and MEPCE. Tat remodels 7SK snRNP by interacting directly with 7SKRNA *in vivo*, leading to the formation of stress-resistant 7SK snRNP particles. 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.

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

Suppression of HIV-1 replication by microRNA effectors (Chable-Bessia, Meziane et al. 2009. *Retrovirology* 6, 26). 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. 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.

Competition between Dicer mRNA, pre-miRNA, viral RNA for Exportin-5 binding strikes a regulatory balance in cellular miRNA levels. (Bennasser et al. 2011. *Nat Struct Mol Biol* 18, 323-327).

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.

3-Identification of host cell restriction factors.

Samhd1 is the dendritic and myeloid cell-specific HIV-1-restriction factor counteracted by Vpx. (Laguette et al. 2011. *Nature* <http://dx.doi.org/10.1038/nature10117>)

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 that has been proposed to act as a negative regulator of the interferon response 7. We show that Vpx induces proteasomal degradation of Samhd1. Silencing of Samhd1 in non-permissive cell lines alleviates HIV-1 restriction and is associated with a significant accumulation of viral DNA in infected cells. Concurrently, over-expression of Samhd1 in sensitive cells inhibits HIV-1 infection. The putative phosphohydrolase activity of Samhd1 is likely to be required for HIV-1 restriction. Vpx-mediated relief of restriction is abolished in Samhd1 negative cells. Finally, silencing of Samhd1 dramatically increases the susceptibility of monocytic-derived dendritic cells to infection. Altogether, our results demonstrate that Samhd1 is an anti-retroviral protein expressed in cells of the myeloid lineage that inhibits an early step of the viral life cycle. Our findings should be integrated in the development of DC-targeted vaccines against HIV/AIDS.



Responses to DNA Replication Stress and Associated Diseases

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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).

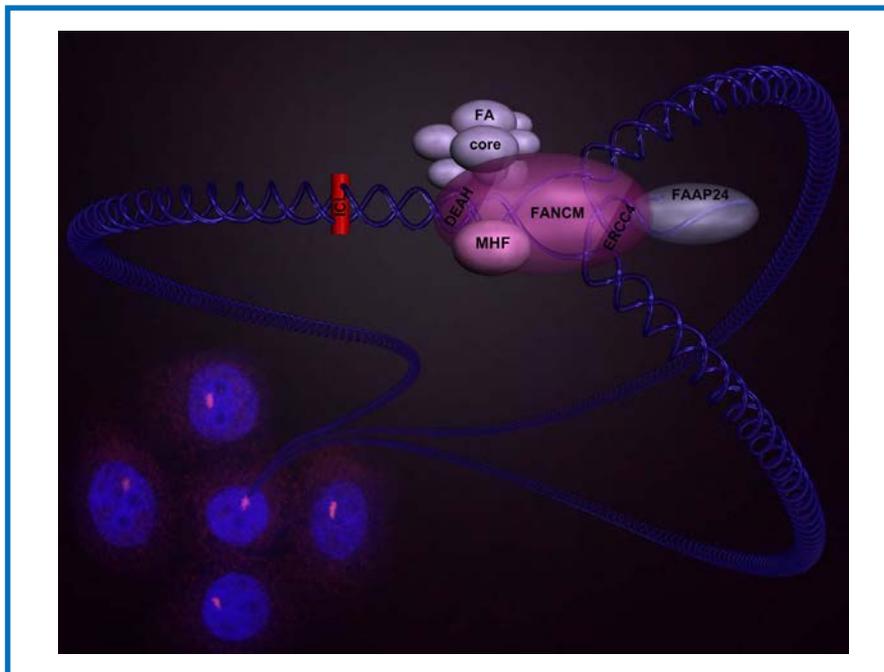
Fanconi anemia: During the last five years, our focus has been on the cancer-prone disorder Fanconi anemia (FA). FA genes encode proteins that play crucial roles in the maintenance of genomic stability and in cell tolerance to replication stress. Cells derived from patients with FA are hypersensitive 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).

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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

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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.

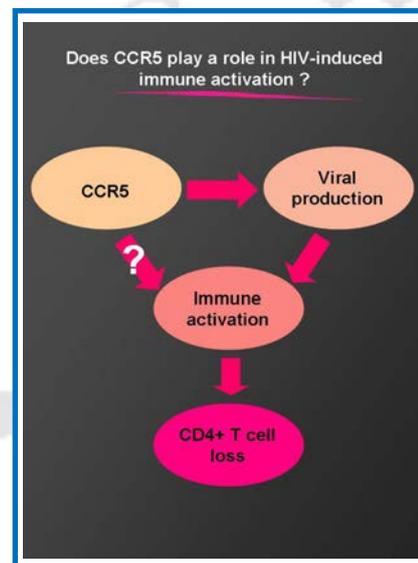
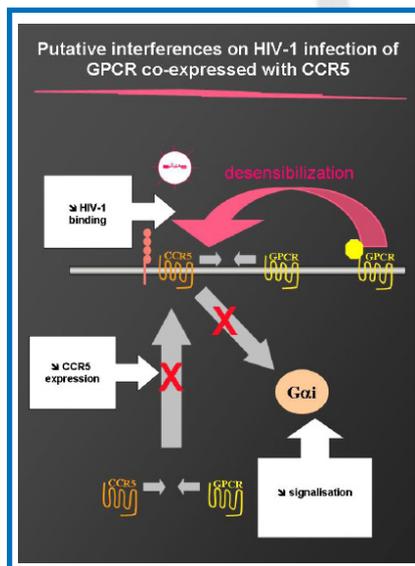
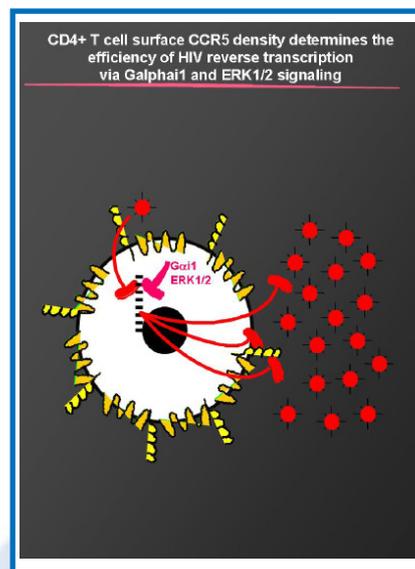
Theme 2: Roles of the chemokine receptor CCR5 in immune activation.

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.

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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

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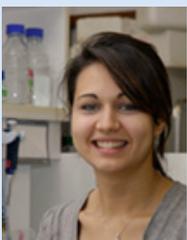


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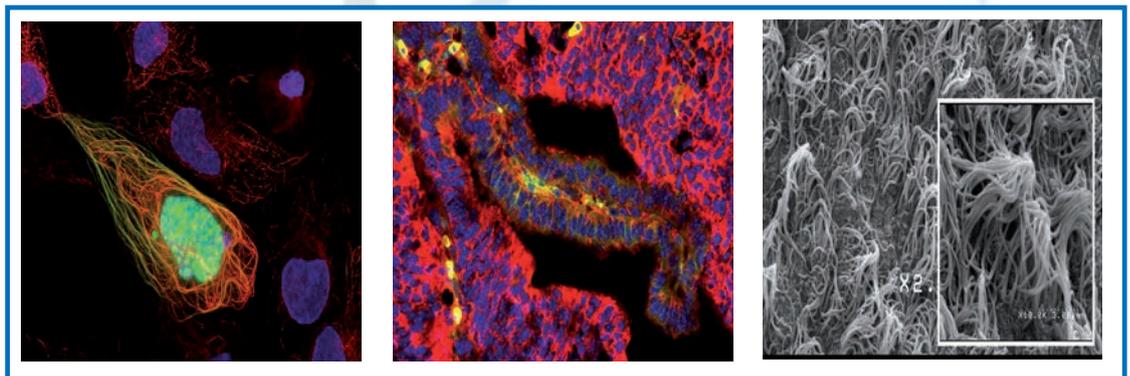
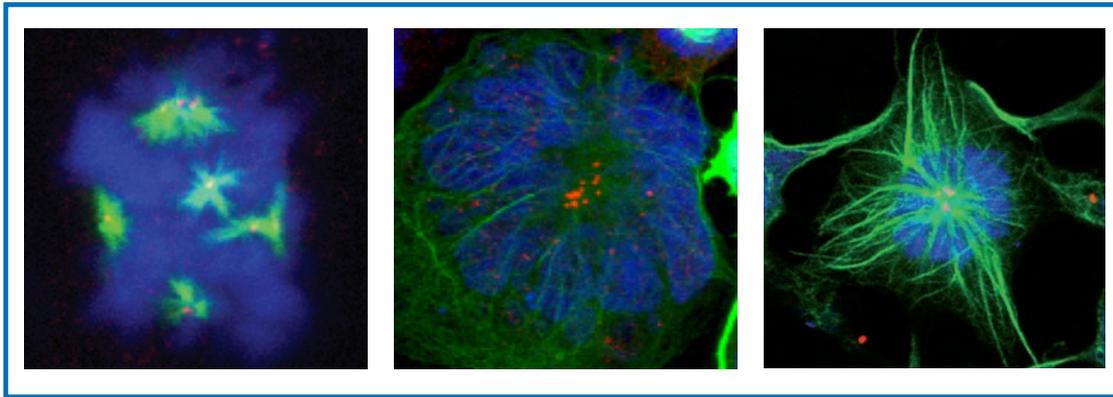
Cell division needs error-free DNA replication and correct chromosome segregation mediated by the mitotic spindle, which is mainly formed by microtubules (MT) and MT-associated proteins (MAPs).

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 neurons of adult brain. 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 are not only associated with mitosis and involved in the development of the central nervous system, but they may also lead to neurodegenerative diseases, when misexpressed/mutated (Huntingtin, for example). ASAP could be involved in different functions, such as neuron architecture, dendritic and axonal protein transport, neuron migration/maturation, etc. Based mainly on 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 and in brain function. We aim at determining the cellular mechanisms in which ASAP and its partners are involved by focusing our efforts on ASAP role in DDR, mitotic spindle assembly, centrosome amplification and central nervous system development in normal and pathological conditions.

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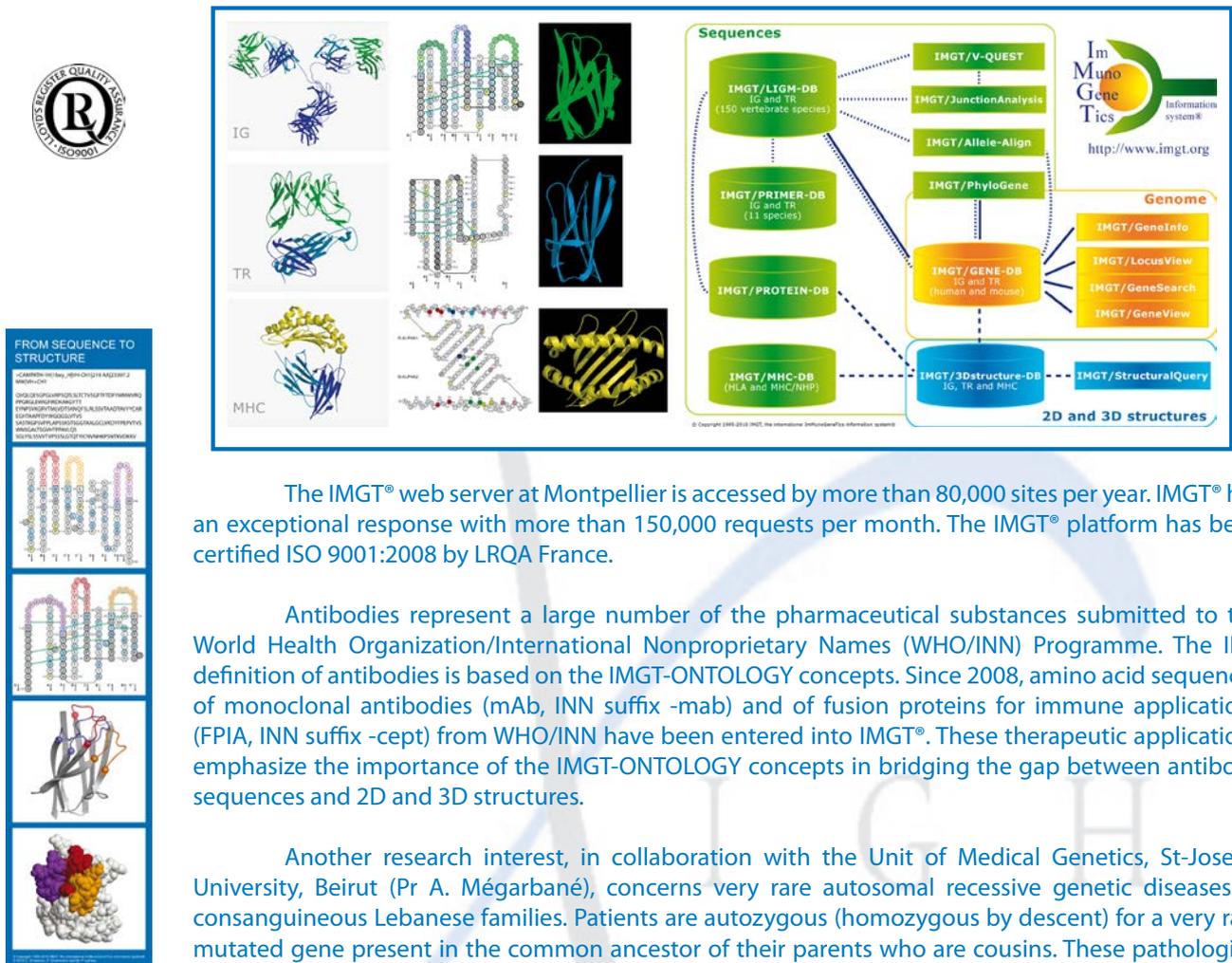
Our research activities are focused on molecular immunogenetics, immunoinformatics, bioinformatics and rare human genetic diseases. We are studying the genetics, structures, functions and repertoires of the immunoglobulins (IG) of B lymphocytes and plasmocytes, and of the T cell receptors (TR) on T lymphocytes, 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 six databases (IMGT/LIGM-DB, a comprehensive database of more than 150,000 IG and TR sequences from human and 260 other vertebrate species in November 2010; IMGT/GENE-DB, IMGT/PRIMER-DB, IMGT/2Dstructure-DB, IMGT/3Dstructure-DB and IMGT/mAb-DB), fifteen interactive tools and more than 15,000 pages of web resources. IMGT/HighV-QUEST analyses Next-Generation Sequencing (NGS) High-throughput IG and TR sequencing data 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).

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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.

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) and of fusion proteins for immune applications (FPIA, INN suffix -cept) 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 research interest, in collaboration with the Unit of Medical Genetics, St-Joseph University, Beirut (Pr A. M egarban ), 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 unsuspected links with cell physiology. For examples, the ICF (Immunodeficiency, Centromeric region instability and Facial anomalies) syndrome results from mutations in the DNA methyltransferase 3B (DNMT3B) gene in most cases (type 1); a recessive form of Hyper-IgE syndrome is due to mutations in the Dedicator Of CytoKinesis 8 (DOCK8) gene; 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, consanguineous families are powerful and time-saving sources of information.



Neurological Disorders and Stem Cells

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Prion diseases or transmissible spongiform encephalopathies (TSE) are fatal, transmissible neurodegenerative diseases, which include mainly Creutzfeldt–Jakob disease in humans, scrapie in sheep and bovine spongiform encephalopathy (BSE) in cattle. They are characterized pathologically by widespread neuronal loss, spongiform changes and accumulation of PrP^{Sc}, the pathological conformational variant of the host-encoded prion protein PrP^C. The pathologic molecular events occurring in these disorders are still elusive and no treatment is yet available for humans. TSE represent therefore an important scientific and medical challenge. They are also a relevant model of neurodegenerative disorders and of pathologies linked to protein aggregation (e.g., Alzheimer's, Parkinson's disease). To address these scientific issues, our laboratory has developed a strong expertise in stem cell research, while keeping prion diseases as a major model to test therapeutic strategies and to investigate common molecular mechanisms of neurodegenerative disorders.

Specifically, we are using cultures of neural stem cells (NSC) to study the physiological role of the prion protein in neuronal differentiation and to investigate the patho-physiological events occurring in TSE. NSC can be isolated from fetal and adult wild type or PrP KO mice and we demonstrated that they can be infected in vitro with infectious prions. Hence, we use them to study the influence of PrP expression on neuronal differentiation and the ex vivo transmission of prions from different species. These models are also invaluable for screening therapeutic agents, performing proteomic research to identify new (diagnostic, patho-physiological) biomarkers, and for testing for the presence of infectious prions in decontamination programs.

In parallel, we are investigating the role of adult neurogenesis and the implication of endogenous NSC during the course of the disease in mice. The goal is to find whether adult neurogenesis is activated, inhibited and/or contributes to a transient repairing activity in the brain. This might lead to new therapeutic strategies. As a matter of fact, therapeutic strategies using stem cells have shown encouraging results for the treatment of neurodegenerative diseases. We are therefore pursuing an ambitious cell therapy program of regenerative medicine in TSE in which we propose to combine cell therapy and gene therapy.

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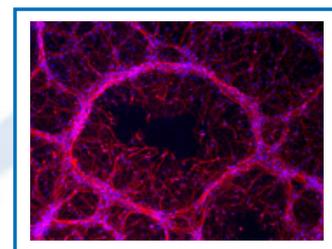
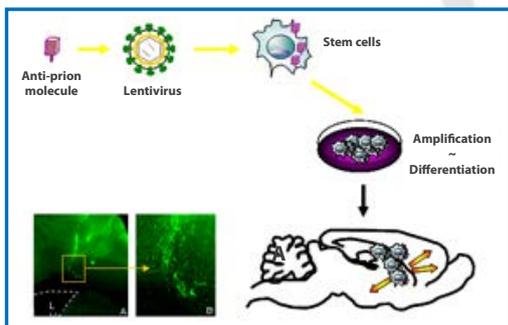
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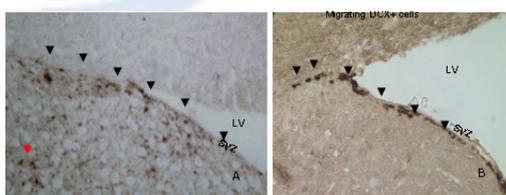
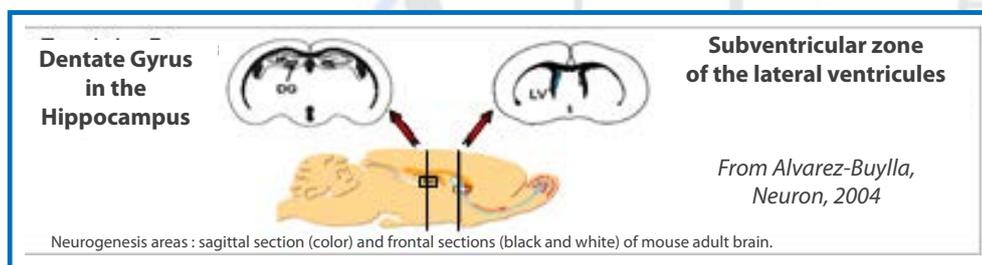
Our general objective is to use NSC from embryonic (i.e., differentiated from embryonic stem cells (ESC)), fetal or adult origin and graft them as a “drug” not only to orchestrate a functional recovery of the damaged zones, but also to deliver anti-prion molecules. For that purpose, NSC can be genetically modified (via lentiviral vectors) to express anti-prion molecules (dominant negative mutants of PrP, scFV). Pre-clinical trials can then be performed using an experimental mouse model infected with prions. Initial results are very encouraging showing significant delay in the appearance of the disease and a reduction of the TSE-linked neuropathological changes. Importantly, we are moving toward the adaptation of these therapeutic approaches to humans thanks to the authorization from the “Agence de Biomédecine” to perform research with several human ESC lines.

Finally, as prion diseases and Alzheimer’s disease share common pathological mechanisms and molecular events, we are investigating the possible crosstalk between functional and metabolic pathways of prion and amyloid protein/peptides using human material in collaboration with the hospital biochemistry and neurology units.



Neuronal differentiation of Human Embryonic Stem Cells (nucleus : Blue hoechst staining, Neuron : beta III tubulin, red immunostaining)

Schematic representation of the “gene and cell therapy strategy”. Stem cells are genetically modified (via lentivirus) to express anti-prion molecules. The resulting cells are then grafted in the brain of prion infected mice. (A) Visualisation of the NSC-GFP cells grafted in the mouse cortex. (B) magnification of (A) It is possible to see the cellular processes. (LV : lateral ventricle)



A. PrPSc immunostaining (brown + arrow) using Saf84 anti-PrP antibody in the “corn” of the lateral ventricle (LV) and the SVZ.
B. Doublecortin (DCX) immunostaining (brown + arrow) showing neuroblasts exiting the SVZ of the lateral ventricle .



MOLECULAR BASES OF HUMAN DISEASES

JUNIOR LABORATORY

Genome Surveillance and Stability

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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 (cisplatin, methyl methanesulfonate, MMS).

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.

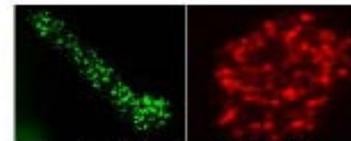
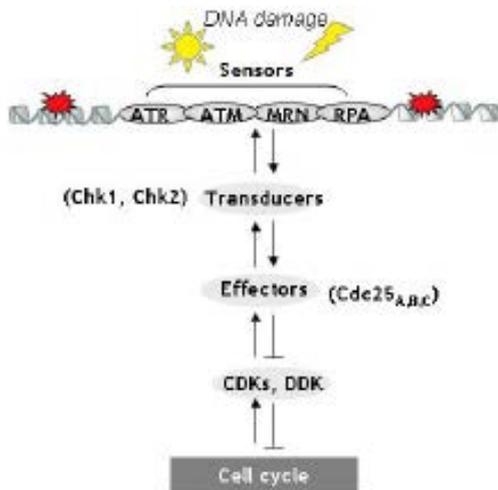
We are also interested in identifying the molecular mechanism of sensor activation, the proteins that recognize the lesions and, particularly, the structures recognized by the sensors and the consequences of this recognition on the sensor functions. We have recently shown that the DNA repair protein 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.

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

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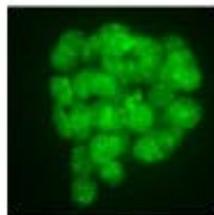
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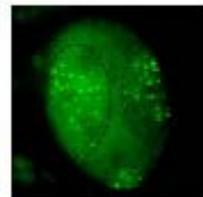
Recruitment of the RPA protein to replication-independent DNA damage foci induced by DNA double strand breaks (green) or replication-dependent damage foci induced by UV irradiation (red) of nuclei reconstituted in vitro in Xenopus egg extracts. RPA is visualised by indirect immunofluorescence.



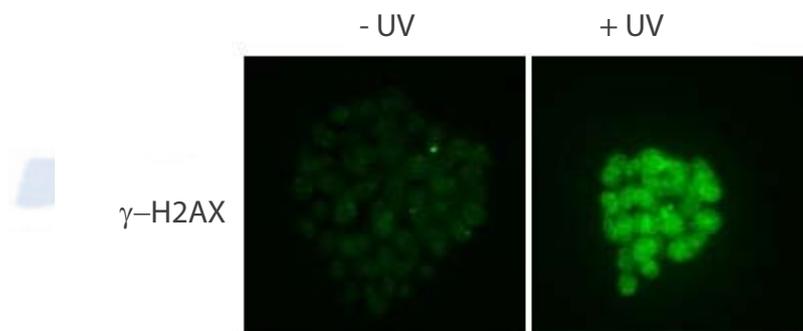
Recruitment of the phosphorylated form of the RPA protein to damage chromatin (left) or to single stranded DNA produced by replication fork uncoupling upon UV irradiation (right) in Xenopus egg extracts. RPA is visualised by western blot.



Detection of DNA damage foci in nuclei of mouse embryonic stem cells upon UV irradiation.



Detection of locally-induced DNA damage (shaded lines) in mammalian cells nuclei.



Detection of DNA damage in mouse embryonic stem cells upon UV irradiation. Individual nuclei are shown.



Maintenance of Genome Integrity during DNA Replication

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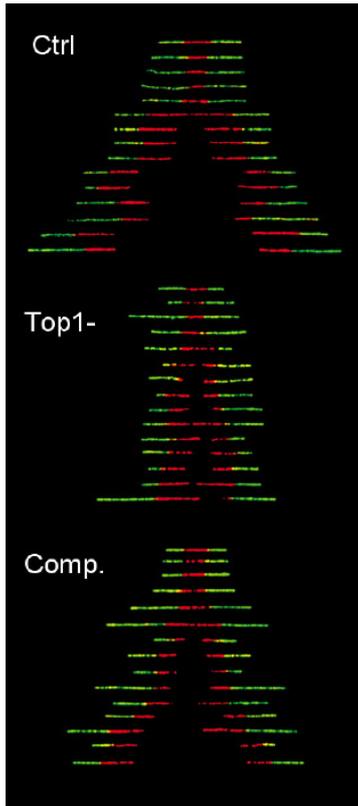
Julien Bacal,
Engineer

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.

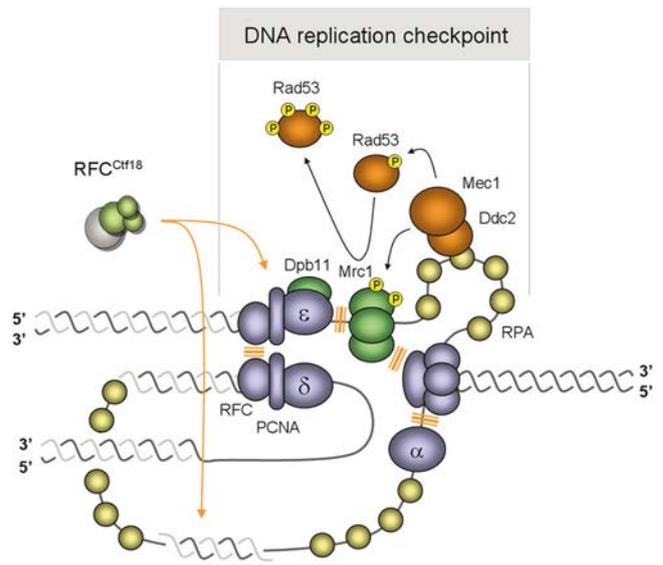
We use yeast and human cell lines as model organisms to identify regions of the genome that are intrinsically difficult to replicate and that induce spontaneous replication stress. We also investigate the cellular responses to replication stress in normal cells and in cancer cell lines. To this end, 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.

Using these technologies, we have recently identified a novel mediator of the replication checkpoint in yeast (Crabbé et al., 2010). We also monitor the activation of the replication checkpoint during normal S phase, using γ 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.

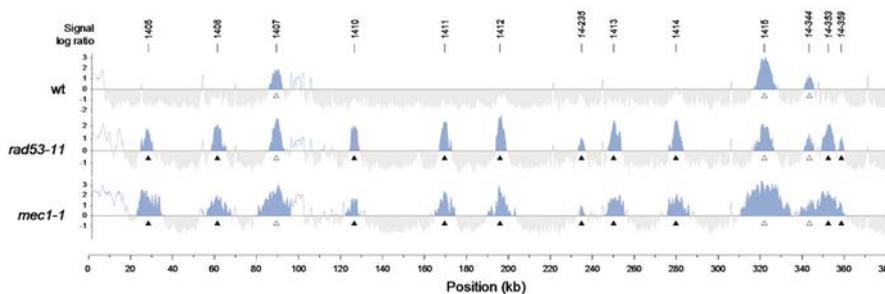
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DNA combing analysis of replication forks progression and pausing in Top1-deficient mouse cells. Control mouse P388 cells (Ctrl), Top1-deficient cells (Top1-) and Top1-deficient cells complemented with human Top1 were analysed by DNA combing after 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.

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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.

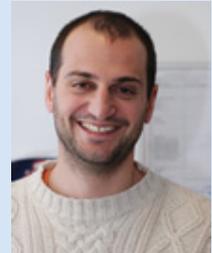
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COMPUTING FACILITY

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The 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.

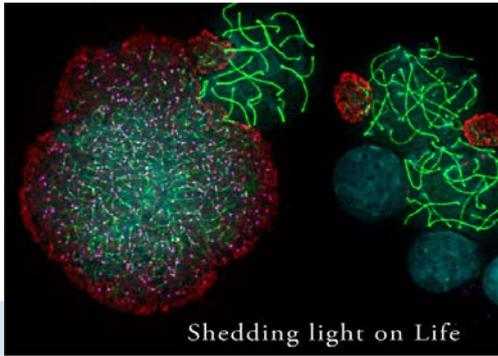
The computing facility includes three full-time employees who run the IT infrastructure, offer computational support and assure the technological monitoring. The different activities of the service include:

- 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 (Olinux, 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.

The computing service is also in charge of running the servers of the on line IFR3 library. This is a structure that groups together about 176 researchers and nine INSERM, CNRS, University and Hospital laboratories of Montpellier.

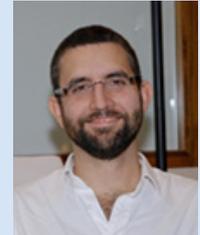
We host also several databases to make scientific data available to the scientific community.



CELL IMAGING FACILITY

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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 m²) 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 approximately 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.

WEB DEVELOPMENT & INFOGRAPHY

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The mission of the “Web Development & Infography (Iconography)” facility 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, GenomeIntegrity: tools tailored to the management of European projects coordinated by IGH scientists.

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 national or international meetings.

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.

More recently, we have been developing imagery applications to favor the use of a common iconographic background that exploits the web as a communication unit within the IGH.

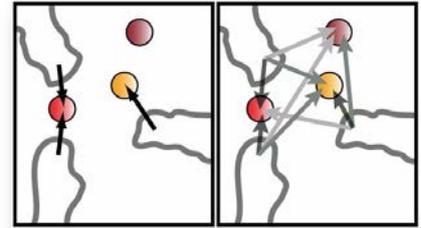
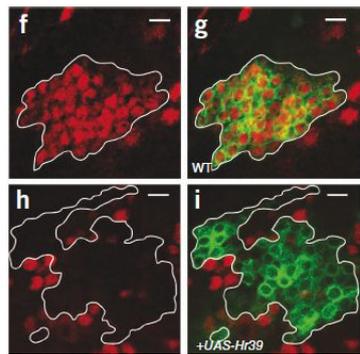
The facility also provide the IGH users with common services for poster design and production and formatting /reformatting interchange services for production of scientific figures for publications.

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

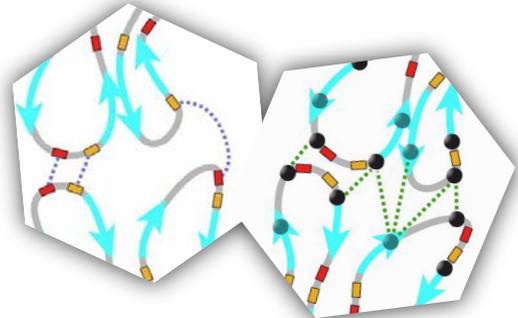
Keywords: programming, databases, interfaces, bioinformatics, CAD/CAP.

- C. Cartier, C. Sarrauste de Menthère 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 Menthère C, Toutou 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 Menthère, C., Toutou, I. (2008). "The auto-inflammatory Infevers mutation online registry: update with new genes and functions". *HUM. TRANSFER*, 29, 803-808.
- C. Cartier, C. Sarrauste of Menthère inventors. (2007). Patentee: CNRS. "TraCSEH: Tool for Traceability of Human Embryonic Stem Cells". IDDN: FR.001.090013.000.SP2007.000.10000

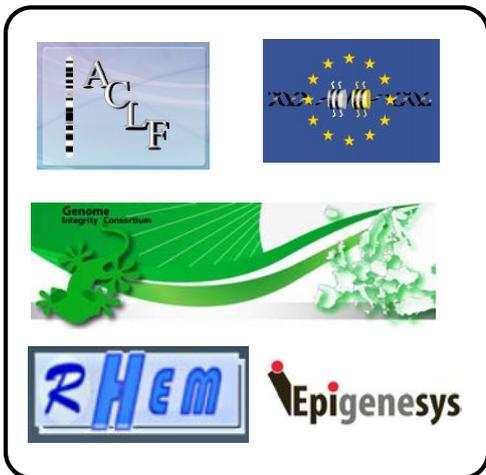
Some drawings:



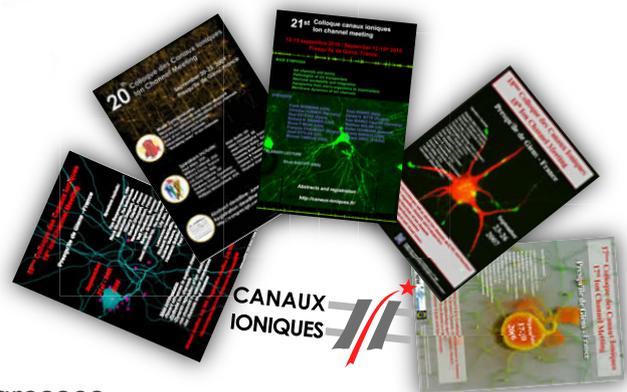
Published in Boulanger *et al.*, *Nat. Neurosci.* 2010



In press Cheutin *et al.*, *CSHSQB* 2011



Some web projects



Some WebCongresses



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.

In 2009-2010, 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.

General Secretary of the Doctoral School: CBS2: HEALTH, BIOLOGY and CHEMICAL SCIENCES

<http://ecole-doctorale-cbs2.igh.cnrs.fr/>

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 Hanyin
- Fabienne Mazur



Animal Housing Facilities :

Scientific manager : Anne Fernandez

- Audrey Combe-Sainseau





ANIMAL HOUSING FACILITY

Our animal facility is a common infrastructure that is part of the IFR3.

Barrier Unit
Animal Housing Facility

Scientific manager
Anne Fernandez

Manager : Florence Arnal



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

Microbiological status and hosted species:

- 140 m² 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 m² 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 oocytes for developmental biology or for the study of ionic channels.

- 60 m² 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 (orchidectomy, 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 (fluorescence microscope?) 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

15.01.10 Thierry Heidmann
Institut Gustave Roussy - Villejuif - FRANCE
Les rétrovirus endogènes: du virus infectieux au gène placentaire

26.01.10 Susan Martinez
UMR CNRS 6204, Université de Nantes - FRANCE
Inhibition de l'activité d'échange de brins de hRad51 par des aptamères ADN

FEBRUARY

12.02.10
Bernard Klein
IRB Montpellier - FRANCE
Tumor stem cells involved in multiple myeloma

19.02.10
Jean-Pierre de Villartay
Hôpital Necker Enfants Malades - INSERM U 768 - PARIS - FRANCE
DNA Repair in the immune system

MARCH

12.03.10
Jiri Forejt
Institute of Molecular Genetics - Prague - CZECH REPUBLIC
Positional cloning of hybrid sterility genes in mouse inter subspecific hybrids

19.03.10
François Payre
Centre de Biologie du Développement - Toulouse - FRANCE
Small peptides join the game of transcriptional regulation

26.03.10
David Margolis
Mickael Hooker Research Center - University of North Carolina at Chapel Hill - USA
Epigenetic targeting of proviral latency in HIV infection

26.03.10
Laurence Hurst
Evolution & Structure of genetic Systems - University of bath - UNITED KINGDOM
The evolution of gene order

APRIL

02.04.10
Kristi Wharton
Brown University 6 Providence - USA
Differential regulation of BMP signaling during development

09.04.10
Daniel Grimanelli
IRD - Montpellier - FRANCE
To be or not sexual; control of germ cell development by small RNA pathways in plants

16.04.10

Hervé Seitz

Laboratoire de Biologie Moleculaire des Eucaryotes LBME -Toulouse - FRANCE

Redefining the biological function of small regulatory RNAs in animals

30.04.10

Raul Mendez

CRG Barcolona - SPAIN

A CPEB-mediated translational control circuit regulates meiosis, mitosis and tumor development

MAY

07.05.10

Amanda Swain

Institute of cancer Research - London - United Kingdom

Molecular pathways in gonad and adrenal development

21.05.10

Niels de Wind

Leiden University Medical Center - THE NETHERLANDS

Mutatis mutandis: roles of mutagenic translesion synthesis in fitness and disease

26.05.10

Thomas Lecuit - IBDML - Marseille - FRANCE

The mechanics of tissue morphogenesis

28.05.10

Christophe Antoniewski

Institut Pasteur - Paris - FRANCE

Function of Drosophila non-coding small RNAs in heterochromatin dynamics

JUNE

09.06.10

Thomas Robert

IFOM - Milan - ITALY

Mechanisms that control the DNA damage checkpoint response in *S. cerevisiae*

15.06.10

Stefano de Renzis

Developmental Biology Unit - EMBL - Heidelberg - GERMANY

Developmental modulation of intracellular trafficking during tissue morphogenesis

16.06.10

Pei-Yun Jenny Wu

Rockefeller University - New York - USA

Establishing the S phase program of origin usage in fission yeast

18.06.10

Alicia Hidalgo

School of Biosciences - University of Birmingham - UNITED KINGDOM

Plastic fruit-flies

23.06.10

Sofia Francia

Fabrizio d'Adda di Fagagna's Lab IFOM - Milan - ITALY

A novel role for the RNA-interference machinery in the regulation of the DNA-damage response

25.06.10

John de Vos - INSERM U 847 - Montpellier - FRANCE

Creating pluripotency in vitro : highlights from whole genome gene expression profiling

28.06.10

Rodney Rothstein

Columbia University - New York - USA

Kinetochore components define a single lineage in budding yeast and also affect the DNA damage response

SEPTEMBER

07.09.10

Karlene Cimprich

Stanford University School of Medicine - USA

Mechanisms for Maintaining Genome Stability

09.09.10

Nick Proudfoot

Sir Williams Dunn School of Pathology - University of Oxford - UNITED KINGDOM

Gene punctuation: multiple roles of transcriptional termination in regulating eukaryotic gene expression

30.09.10

Maria Jasin

Sloan Kettering Cancer Center - New York - USA

Double-strand break repair in meiotic and mitotic mammalian cells

OCTOBER

01.10.10

Acaimo Gonzalez-Reyes

Centro Andaluz Biología del Desarrollo CABD - Sevilla - SPAIN

Extracellular matrix and signalling in a stem cell niche: a view from *Drosophila*

08.10.10

Sarah Lambert

Institut Curie Orsay - FRANCE

Homologous Recombination and blocked replication forks: from fork restart to Genome Instability

27.10.10

Gaetano Verde

Istituto di Genetica e Biofisica - Adriano Buzzati traverso - Milan - ITALY

KAP1 orchestrates the deposition of H3K9me3 and the maintenance of DNA methylation at imprinting control regions in embryonic stem cells

NOVEMBER

05.11.10

Sara Hardy

Institut Pasteur - Lille - FRANCE

The euchromatic and heterochromatic landscapes are shaped by antagonizing effects of transcription on H2A.Z deposition

10.11.10

Chris Jopling

Centre de Medicina Regenerativa de Barcelona, SPAIN

Heart Regeneration

12.11.10

Jose Alcami

Unidad de Immunopatologia del SIDA - Madrid - SPAIN

NF- κ B and Tat, major players driving HIV-host relationship

12.11.10

Massimo Lopes

Institute of Molecular Cancer Research - University of Zuerich - SWITZERLAND

Towards the structural visualization of genome instability during DNA replication

19.11.10

Sun Fei

LMDE - Toulouse - FRANCE

microRNA-383: bridging male infertility and testicular germ cell tumor

22.11.10

Alessio Zippo

University of Siena - ITALY

Deciphering a new histone code that drives transcription elongation

24.11.10

Michael Chang

Columbia University - New York - USA

Characterizing the multiple ways to solve the end-replication problem

26.11.10

Yehezkel Ben-Ari

INMED INSERM U901- Parc scientifique de Luminy - Marseille - FRANCE

Genes and environment in brain development and neurological disorders

DECEMBER

01.12.10

Holger Richly

Center for Genomic Regulation (CRG) - Barcelona - SPAIN

Dissecting a Molecular Mechanism for Transcriptional Activation

03.12.10

Maria Fernandez de Luco

NCI / NIH, Bethesda - USA

Epigenetics in alternative splicing

JANUARY

27.01.11

Mark Wainberg

Mc Gill University - USA

Bases moléculaires pour des distinctions entre différents sous-types de VIH dans le développement des mutations associées à 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 Ciencia - Oeiras - PORTUGAL

Centrosome and cilia biogenesis and evolution

MARCH

08.03.11

Antoine Peteers

Friedrich Miescher Institute for Biomedical Research - Basel - SWITZERLAND

Intergenerational epigenetic control of mammalian early embryonic development

24.03.11

Wolfgang Fischle

Max Planck Institute for Biophysical Chemistry - Goettingen - 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, Plk4 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

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

2008

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2008

- Denden, S., Haj Khelil, A., Perrin, P., Daimi, H., Leban, N., Ouaja, A., Mahdouani, K., Hlioui, L., Lefranc, G., Ben Chibani, J. (2008) Alpha 1 antitrypsin polymorphism in the tunisian population with special reference to pulmonary disease. **Pathol. Biol. (Paris)**, 6, 3, 106-110, PMID: 18031952.
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LAYOUT & DESIGN

Catherine Larose

PICTURES

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COVER ILLUSTRATIONS

Immunolocalization of chromosome axes (SYCP3, green), DNA double-strand break repair foci (DMC1, purple), phosphorylation of histone H2AX (γ H2AX, red) and DNA stained by DAPI (blue), on mouse spermatocyte nuclei.

Photo: B. de Massy

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HOW TO FIND US

Plane:

Montpellier Méditerranée 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.





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