Impact of Bt bioinsecticides on the Drosophila gut physiology

Rihab Loudhaief, Olivia Benguettat, Alexandra Brun-Barale, Marie-Paule Esposito, Marcel Amichot, Armel Gallet

27th Annual French Drosophila Conference

Obernai – 26-29th November 2013

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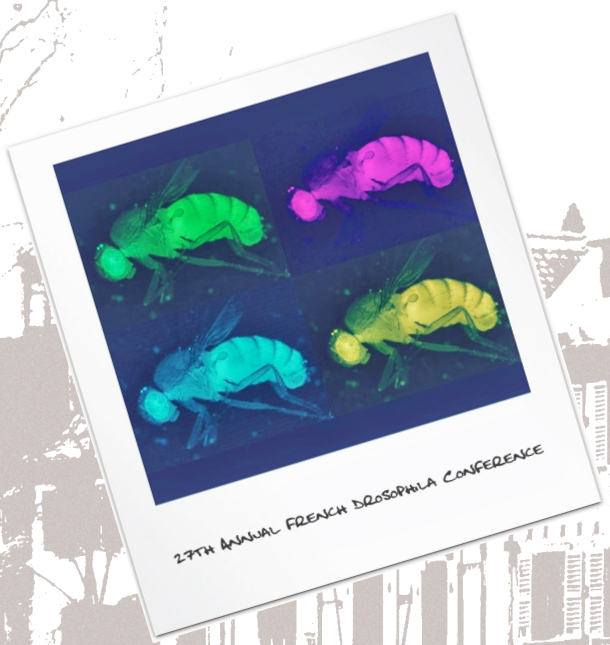

Invited Speakers:

Ilan Davis
Bruce Edgar
Thomas Préat
Martine Simonelig
Luisa Di Stefano
Julien Colombani
Jean-René Huynh
François Leulier

We are pleased to announce that there will be an evening out in Strasbourg on Thursday.

The evening will start by a river trip around the historical Alsatian capital & the European institutions, offered by the City of Strasbourg.

The evening will continue in the heart of Strasbourg with a dinner at "Gurtlerhoft vault" restaurant, nested by the famous cathedral.

Buses will be chartered for transfers.

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Organizing committee: **Carine Meignin, Nicolas Matt,** Dominique Ferrandon, Angela Giangrande, Adrien Franchet and Jelena Patrnogic

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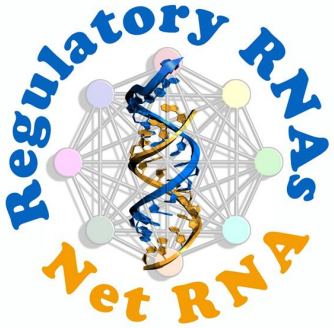
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UPR 9022
IBMC Immune Response and Development in Insects


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biologie moléculaire et cellulaire

Invited speakers

The control of long-term memory formation.

Thomas Préat

Genes and Dynamics of Memory Systems
Neurobiology Unit
CNRS-ESPCI
Paris

Syncrip: The missing link between neuronal activation and localized translation at the synapse?

Ilan Davis

Department of Biochemistry
The University of Oxford
United Kingdom

« pre-pairing » chromosomes for meiosis.

Jean-René Huynh

Développement des cellules germinales
Génétique et biologie du développement
Institut Curie / UMR 3215 CNRS / U934 Inserm
Paris

Searching for novel pathways involving LSD1 in vivo.

Luisa Di Stefano

LBCMCP
Université Paul Sabatier - Toulouse III
Toulouse

Host/Lactobacilli mutualism: "learning on the fly"

François Leulier

Functional Genomics of Host/ Intestinal bacteria interactions
Functional Genomics Institute of Lyon (IGFL)
UMR 5242 CNRS/ENS Lyon
Lyon

mRNA regulation by deadenylation and small non-coding RNAs during early development

Martine Simonelig

mRNA Regulation and Development
Institut de Genetique Humaine
Montpellier

The Drosophila TNF receptor Grindelwald couples loss of cell polarity with neoplastic growth.

Julien Colombani

Institut de Biologie Valrose (iBV)
CNRS UMR 7277 / INSERM U1091
Université Nice Sophia Antipolis
Nice

Homeostatic and tumorous growth of Drosophila intestinal stem cells

Bruce Edgar

Cell growth and proliferation
DKFZ-ZMBH Alliance
Heidelberg, Germany

Program

Tuesday, 26th November 2013

14:00-16:15 **Registration and Welcome!**

16:15-16:45 ***Break***

16:45-19:00 Session I ***Nervous system***

16:45 **Introduction**

16:55-17:35 **Thomas Préat**
The control of long-term memory formation.

17:35-17:55 **Clémence Levet** (Bertrand Mollereau)
ER stress inhibits neuronal death by promoting autophagy. 1

17:55-18:15 **Maria Capovilla** (Alain Robichon)
Functional gustatory receptors in Drosophila wings and their role in flight-associated chemoperception. 2

18:15-18:35 **Jean-Maurice Dura**
Extrinsic DRL guides DRL-2-expressing Drosophila mushroom body axons by localizing WNT5. 3

18:35-18:55 **Pierre Cattenoz** (Angela Giangrande)
A Genome-wide screen reveals a new function for Gcm transcription factor. 4

Wednesday, 27th November 2013

9:00-9:40 **Ilan Davis**
Syncrip: The missing link between neuronal activation and localized translation at the synapse?

09:40-11:55 Session II ***Oogenesis***

9:40-10:00 **Jean-Antoine Lepesant** (Antoine Guichet)
Relationship between microtubules and the positioning of the nucleus during the polarisation of the Drosophila egg chamber. 5

10:10:20 **Geordie Zimniak** (Stéphane Noselli)
A novel hemocyte- niche association controls Collagen IV and basement membrane assembly, essential for germline stem cell homeostasis. 6

10:20-10:40 **Hervé Alegot** (Vincent Mirouse)
Study of the ovarian follicles elongation mechanisms during the early stages. 7

10:40-11:15 ***Break***

11:15-11:55 **Jean-René Huynh**
« pre-pairing » chromosomes for meiosis.

11:55-12:55 Session III ***Chromatin***

11:55-12:35 **Luisa Di Stefano**
Searching for novel pathways involving LSD1 *in vivo*.

12:35-12:55 **François Bonnay** (Nicolas Matt)
NF-κB selectivity during the innate immune response in Drosophila requires an Akirin - dependent recruitment of the (SWI/SNF) BAP chromatin-remodeling complex. 8

13:00-14:30 ***Lunch***

14:30-16:10 Session IV ***The digestive tract in growth and disease***

14:30-15:10 **François Leulier**
Host/Lactobacilli mutualism: "learning on the fly"

15:10-15:30 **Kwang-Zin Lee** (Dominique Ferrandon)
Resilience of the Drosophila intestinal epithelium upon oral infection with *Serratia marcescens*. 9

15:30-15:50 **Gilles STORELLI** (François Leulier)
Lactobacilli mutualism: a promising model to characterize the molecular mechanisms governing host/intestinal microbes interactions. 10

15:50:16:10 **Michael Rera** (Hervé Tricoire)
New insight on aging. 11

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16:45:18:45 **Poster session I**

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mRNA regulation by deadenylation and small non-coding RNAs during early development.

9:40-10:00 **Jean-René Martin**
A new small nucleolar RNA (jouvence) extends lifespan and protects against neurodegeneration in Drosophila. 12

10:00-10:20 **Xia Sun** (Marie-Laure Samson)
The *fne* gene (found in neurons) links post-transcriptional regulation to synaptic function. 13

10:20-10:40 **Pascal Heitzler**
Genetics of miRNA clusters and families: new insights on Notch lateral signaling. 14

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11:15-11:35 **Rami Makki** (Alex Gould)
A glance at oenocyte function. 15

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Fatty acid metabolism protect against sugar toxicity. 16

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Study of the microsporidia *Tubulinosema ratisbonensis*, an intracellular parasite of *Drosophila melanogaster*. 17

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Pastrel, a restriction factor for picorna like viruses in Drosophila. 18

12:35-12:55 **Berra Erkosar** (François Leulier)
The impact of commensal bacteria on Drosophila transcriptome: a molecular crosstalk between immunity and metabolism. 19

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The pan-glial homeotic gene *repo* represses hemocyte differentiation. 20

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Diedel, an immunomodulator molecule, involved in resilience to viral infection in Drosophila. 22

15:30-15:50 **Frank Touret** (Christophe Terzian)
The endogenous retrovirus *gypsy* and the endosymbiotic bacteria wolbachia : a struggle for transmission. 23

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16:00-16:20 ***Business meeting***

16:00-16:45 ***Break***

16:45-17:45 Poster session II

17:45 Bus departure for an evening in Strasbourg

Friday, 29th November 2013

09:00-10:00 Session VIII *Cellular biology*

09:00-9:40 **Julien Colombani**
The Drosophila TNF receptor Grindelwald couples loss of cell polarity with neoplastic growth.

9:40-10:00 **Amandine Clavier** (Isabelle Guénal)
Rbf/dE2F2, together in the dREAM complex, downregulate anti-apoptotic genes to induce cell death.

10:00-10:30 Coffee break

10:30-11:30 Concluding lecture

Bruce Edgar

Homeostatic and tumorous growth of Drosophila intestinal stem cells

12:00 Lunch

Short talks

ER stress inhibits neuronal death by promoting autophagy

Clémence Levet (Bertrand Mollereau)

Clémence Levet, Antoine Fouillet, Marion Robin, Pierre Dourlen and Bertrand Mollereau

Laboratory of Molecular Biology of the Cell, Ecole Normale Supérieure de Lyon.

Endoplasmic Reticulum (ER) stress has been implicated in neurodegenerative diseases but its relationship and role in disease progression remain unclear. Using genetic and pharmacological approaches, we showed that mild ER stress ("preconditioning") is neuroprotective in the retina and a model of Parkinson disease in Drosophila. In addition, we found that combination of mild ER stress and apoptotic signals triggers an autophagic response. We showed that when autophagy is impaired, ER-mediated protection is lost. We further demonstrated that autophagy inhibits apoptosis. In addition, we showed that caspases act as inhibitor of autophagy. Together, we propose that autophagy and apoptosis antagonize each other and that activating autophagy has a potential therapeutic value for the treatment of neurodegenerative diseases.

Functional gustatory receptors in Drosophila wings and their role in flight-associated chemoperception

Maria Capovilla (Alain Robichon)

UMR INRA/CNRS/UNS 7254, Institut Sophia Agrobiotech, 400 route des Chappes, P. O. Box 167, 06903 Sophia Antipolis, France

Insects are able to detect highly diverse families of molecules like sugars, various bitter molecules, toxins, water, carbon dioxide and also a large panel of "xenobiotics". This chemoperception guides exploration of ecological niches. Surprisingly, Drosophila wings contain taste neuronal elements, which function is unknown. Here we show the expression of gustatory receptors also in the wings of the aphid Acyrtosiphon pisum and the honeybee *Apis mellifera*. The apparent universality of insect wing gustatory receptors supposes a major role associated to flight. Both sweet and bitter molecules stimulate an increase of the cytosolic Ca2+ levels in the nerve of the anterior wing margin. Sugars also cause an increase in cAMP levels, but this is not seen for bitter molecules. Moreover, a water/glucose solution pulverized in air without odorants provokes fly aggregation and Bayesian conditioning to food tastants is affected in genetically modified flies presenting transformed wing chemosensory cells. Wing neuronal elements are organized to allow the optimal environment perception through the air vortex that spirals off along the wing anterior margin during flight allowing the subsequent capture and detection of molecules trapped in this micro whirlwind. We hypothesize that during their stationary flight over a food source, insects nebulize molecules which are funneled by the air vortex over the wing margin chemosensors, making the exploratory process highly efficient.

Extrinsic DRL guides DRL-2-expressing Drosophila mushroom body axons by localizing WNT5

Jean-Maurice Dura

Elodie Reynaud[1], Liza L Lahaye[2], Adrien Flandre[1], Iveta M Petrova[2], Ana Boulanger[1], Jasprina N Noordermeer[2], Lee G Fradkin[*2], Jean-Maurice Dura[*1]

[1]CNRS, Institute of Human Genetics, Montpellier, 34396, France.

[2]Leiden University Medical Center, Molecular Cell Biology, Leiden, 2300RC, Netherlands.

Neurons often innervate multiple distinct targets via axon branching, however, how differential guidance of branched axons occurs remains unclear. We therefore studied the Drosophila mushroom bodies (MBs) whose α - and β -branches arise from ~2000 bifurcating axons and target different brain structures. We show that the Ryk pseudokinase family WNT5 receptor, DRL (derailed), expressed outside the MBs, is required for α -branch guidance. DRL likely acts to capture and present WNT5 to MB axons rather than transduce a WNT5 signal since DRL's cytoplasmic domain is not required. Supporting this, WNT5 is delocalized from its normal sites in *drl* mutant MBs. DRL-2, another Ryk, is expressed within MB axons and functions as a repulsive WNT5 signaling receptor. Thus, MB intrinsic and -extrinsic Ryk receptors act together to guide α-branch axons. To the best of our knowledge, this is the first description of such a mechanism in the developing adult brain where the capture and localization of a widely-expressed repulsive ligand to the surfaces of nearby cells ensures the guidance of axons required to form a distinct brain structure.

A Genome-wide screen reveals a new function for Gcm transcription factor.

Pierre Cattenoz (Angela Giangrande)

Pierre CATTENOZ and Angela GIANGRANDE

Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), Centre National de la Recherche Scientifique, Institut de la Santé et de la Recherche Médicale, Université de Strasbourg, ILLKIRCH, France

Glial cell missing (Gcm) is the molecular trigger of the differentiation of glia and hemocytes. In the nervous system, the transcription factor Gcm induces the choice between glia and neurons, presents a tightly regulated expression and its activity relies on co-factors including Polycomb. Its prolonged expression triggers glial over proliferation in the central nervous system and in the peripheral nervous system. In hemocytes, Gcm acts as a key player during the immune response by triggering the differentiation of plasmatocytes. Even though the role of Gcm in hemocytes and glial cells is undeniable, few targets of Gcm have been identified so far. To identify the direct targets of Gcm, we performed a DAM-ID screen, a genome-wide method used to characterize the binding sites of proteins on the genomic DNA. The experiment returned more than 1000 genes bound by Gcm in embryo. As expected, genes involved in the development of the hemocytes and the nervous system were enriched in our dataset. Surprisingly, the DAM-ID screen also revealed a set of genes involved in the development of the reproductive system. Further analysis of Gcm expression pattern revealed that Gcm is expressed in the mature spermathecae and Gcm loss of function showed that Gcm is indispensable for the normal development of these structures.

Relationship between microtubules and the positioning of the nucleus during the polarisation of the Drosophila egg chamber

Jean-Antoine Lepesant (Antoine Guichet)

Jean-Antoine Lepesant, Nicolas Tissot, Maïté Coppey, Antoine Guichet

Institut Jacques Monod. CNRS and Université Paris-Diderot. Paris. France.

Controlling the position of the nucleus is essential for a variety of cellular functions in a broad range of organisms. In the Drosophila oocyte, molecular motor-based transport of mRNA cargoes along microtubules (MTs) is critical for the establishment of the future embryo axes. MTs polymerisation recovery assays after cold-induced disassembly have revealed that the centrosome-nucleus complex acts as an active MTs nucleation centre in the oocyte. During stage 6 of oogenesis the oocyte nucleus migrates from a posterior to an anterior position. This migration of the nucleus is essential for the determination of the anterodorsal polarity of the egg chamber and for the reorganization of the MTs array that controls the asymmetric transport of determinants of the polarity axes. Although cytoskeleton disruption mediated by various treatments has revealed that MTs but not actin are important for the final positioning of the nucleus, little remains known on the molecular mechanisms involved. We have developed a 3D live-imaging assay, which allows us to monitor the migration of the nucleus. We have shown that migration is completed within 2,5 h on average at a speed of 0,13µm/ min. Live imaging analysis of MTs distribution and laser-mediated local ablation have revealed that the nucleus is pushed rather than pulled by MTs. In addition laser-mediated or RNAi-induced ablation of the centrosomes have shown that they do not play an essential role in the migration.

A novel hemocyte- niche association controls Collagen IV and basement membrane assembly, essential for germline stem cell homeostasis .

Geordie Zimniak (Stéphane Noselli)

Zimniak Geordie, Van De Bor Véronique, Juan Thomas, Cerezo Delphine and Noselli Stéphane

1iBV – institut de Biologie Valrose – UMR 7277 – CNRS INSERM Université Nice Sophia-Antipolis

The Basement Membrane (BM) provides essential structural support for epithelia and organ morphogenesis. Recent studies have shown that Collagen IV, a major BM component, is able to actively modulate cell signaling. Our lab uses the ovarian follicle to study the function of Collagen IV during development. Egg chambers are made of germ line cells surrounded by a monolayer epithelium. Oogenesis is a highly active and dynamic process in which egg chambers are produced steadily from the germ line stem cell niche, further differentiating into different cell types. Using new specific markers developed in the lab, cell biology techniques and targeted genetic approaches, we could show that ovarian collagen IV originates from three different cell types: the adult fat body cells, the follicular epithelial cells, and from previously uncharacterized cells scattered in the ovary. These cells correspond to a new population of hemocytes. These “ovarian hemocytes” are preferentially located around the germarium, a structure housing the adult germline stem cell niche. Using controlled expression of fluorescently tagged forms of collagen IV, we show that hemocytes specifically deposit collagen IV around the germarium. Furthermore, our data show that the interaction between hemocytes and the germarium starts during larval stages and plays a crucial role in the maintenance of the germline stem cell niche. Preventing collagen IV production by the hemocytes, using RNAi or inducing hemocyte apoptosis, severely impairs the number of stem cells, mimicking a loss of decapentaplegic/TGF-beta activity, whose activity is essential to control the stem cells population. These results reveal a yet unknown interaction between circulating blood cells and the germline stem cell niche to control homeostasis and the rate of egg chamber production. We are further investigating the signaling pathways involved in this association.

Study of the ovarian follicles elongation mechanisms during the early stages

Hervé Alegot (Vincent Mirouse)

Alegot Hervé, Fritsch Cornelia, Aigouy Benoit, Bardot Olivier, Couderc Jean-Louis, Mirouse Vincent

Laboratoire GRED, 28 place Henri-Dunant 63000 Clermont-Ferrand

The Drosophila ovarian follicle is a model to study tissue elongation. Its elongation normally takes place from stage 4 to 14 of oogenesis, and it has recently been shown that ovarian follicles undergo rotation around their antero-posterior (AP) axis during stage 4 to 8. According to current model, this rotation allows the deposition of polarized collagen fibers perpendicular to the AP axis acting as a molecular corset constraining the growth along the elongation axis. However we found that dystrophin mutant follicles show no polarized collagen fibers but elongate normally until stage 14 of oogenesis. Moreover, despite they do not rotate, we observed that fat2 mutant follicles elongate almost normally until stage 7, Therefore, neither rotation nor corset played a role in elongation before stage 7-8. Though we are looking for the mechanism(s) that drives elongation during these "early" stages. We found that the elongation axis is defined by a group of cell situated at each pole of the follicles called the polar cells. Moreover we found that the early elongation defective mutants previously described pak and myospheroid (Beta-integrin) affect the location of the polar cell, explaining their phenotype. We then investigated which cellular mechanism(s) play(s) a role during early elongation. We observed that cell elongation does not contribute to follicle elongation and that cell divisions are randomly oriented. We found that cell intercalation happens in the ovarian follicle epithelium during early stages. Moreover, we saw that disrupting cell–cell adhesion using α-catenin mutant clones leads to rounded follicles where the clone is situated. So, we propose that early elongation of the follicles is driven by a polarized intercalation mechanism and that the corset is required for elongation only after stage 8.

NF-κB selectivity during the innate immune response in Drosophila requires an Akirin-dependent recruitment of the (SWI/SNF) BAP chromatin-remodeling complex

François Bonnay (Nicolas Matt/Jean-Marc Reichhart)

IBMC - CNRS-UPR9022, 15 Rue Descartes 67000 Strasbourg, France

NF-κB signaling pathways are crucial among metazoans to fight pathogens by triggering a rapid and robust immune response. Nevertheless, these pathways can also be inappropriately activated in numerous diseases such as auto-immunity, chronic inflammation and cancers, and are therefore the target of therapeutic inhibitors. Such commercially available inhibitors block NF-κB pathways upstream of NF-κB itself, provoking a complete shut down of the pathway and leading to numerous adverse effects. Akirins are nuclear factors conserved from fly to human, required for NF-κB targets transcription in the Drosophila IMD pathway and in mice, downstream of IL-1R and TLRs pathways. Using Drosophila as a model, we showed that Akirin is recruited to certain NF-κB target promoters and is required for their transcription. We also showed that Akirin physically interacts with the SWI/SNF Brahma Associated Protein 60 (Bap60) upon immune stimulation. This interaction orchestrated the NF-κB selective gene activation in adult flies and was required to respond and survive to a Gram (-) bacterial threat. Our data suggest a role for Akirin and the Brahma complex to transcribe selectively a subset of NF-κB target genes mostly composed of immune effectors (AMPs) to face a microbial infection in Drosophila. In mammals, Akirin-2 was shown to be crucial for some key pro-inflammatory cytokines production but was not required for several other NF-κB targets including anti-inflammatory factors. We therefore anticipate that Akirin could be used as a potent therapeutic target in mammals to selectively attenuate the NF-κB-dependent transcription of pro-inflammatory genes involved in cancer and chronic inflammatory diseases.

Resilience of the Drosophila intestinal epithelium upon oral infection with *Serratia marcescens*

Kwang-Zin Lee (Dominique Ferrandon)

Kwang-Zin Lee, Matthieu Lestradet, Samuel Liégeois, Stefanie Limmer, Richard Bou Aoun and Dominique Ferrandon

UPR9022-CNRS, IBMC, Strasbourg, France

The intestine plays a pivotal role in the digestion and absorption of food. It reflects also the first line of defense against orally ingested pathogens. Upon oral infection intestinal host defenses invoke the coordinated action of 1) local immune response (IMD and ROS activation) and 2) renewal/repair of damaged gut epithelium, inflicted either by the pathogen or the host own immune response. We are particularly interested in the mechanism maintaining the integrity of the intestinal epithelium during infection and to understand the molecular basis regulating homeostasis of intestinal epithelium, which we term resilience. We use an oral infection model with the entomopathogenic Gram(-) bacterium *Serratia marcescens*. A genome wide RNAi screen established the importance of resilience during oral infection, yielding around 150 genes. The exact function of most of the genes and the associated molecular pathways underlying resilience remains to be elucidated. In our model, we report a striking degradation of the epithelium in the early phase (EP) of infection, followed by a steady-state phase, in which the epithelium appears normal. Surprisingly, the repair in EP appears to be stem-cell proliferation independent. Correlative electron microscopy was applied to study the effects of Serratia during the early phase of infection. We show that the Serratia pore forming toxin hemolysin is required for multiple alterations during EP, e.g. thinning and flattening of the midgut epithelium. The infection leads also to degenerated mitochondria and disorganized rough ER. We are analyzing candidate genes potentially involved in resilience. We use transcriptomics approaches to investigate the temporal transcriptional response of the midgut of Serratia infection. Our combined approaches will allow us to better understand the cellular and molecular bases of resilience after oral infection.

Lactobacilli mutualism: a promising model to characterize the molecular mechanisms governing host/intestinal microbes interactions

Gilles Storelli (Leulier François)

Storelli Gilles and Leulier François

Institute of Functional Genomics, Lyon (France)

It is now widely recognized that intestinal microbiota influences its host biology, with impacts on metabolic, tissular and immune homeostasis. However, despite the increasing number of studies tying intestinal mutualism with health and diseases, the complexity of intestinal ecosystems in high metazoans may hamper our understanding of the basic mechanisms governing these interactions. During the last decades the fruit fly has been an invaluable model to understand the molecular mechanisms governing host/pathogens interactions. Taking advantage of its tractability, we decided to follow the lead and use Drosophila to characterize the genetic networks involved in intestinal mutualism. Our previous studies confirmed that the fruit fly is a relevant model to study these aspects: its microbiota is relatively simple (in terms of composition) and strongly impacts its physiology, with the sustainment of larval growth upon nutrient scarcity. Moreover, flies monoassociation with Lactobacillus plantarum, a single species of this bacterial consortium, can recapitulate this growth promoting effect, via the enhancement of host nutrient-sensitive hormonal signals. Using flies monoassociated with a set of Lactobacillus plantarum strains, we are now following a gene-trait matching approach to pinpoint the bacterial loci that could stem for different mutualistic aspects such as growth promotion, gut colonization and persistence. This conference will give us the opportunity to present our experimental approaches and our latest results addressing these burning questions.

New insight on aging.

Michael Rera (Hervé Tricoire)

Michael Rera[1], Rebecca I. Clark[2] and David W. Walker[2,3]

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[2]Department of Integrative Biology and Physiology and [3]Molecular Biology Institute, University of California, Los Angeles, CA 90095

Aging is a complex process affecting a wide range of organisms, driving a progressive decrease in individual's fitness and ultimately leading to death. A large set of age-related changes is conserved across species; Homo sapiens included, such as increased chronic inflammation, metabolic defects, increased intestinal permeability. I will present a new tool developed in D. melanogaster that allows us to identify individual flies that are about to die of natural causes. Based on the in vivo measurement of intestinal barrier function, this test allows the identification, among a population of synchronized individuals of the same genotype, of a subpopulation of individuals characterized by a dramatic increase of their intestinal permeability, systemic inflammation and metabolic defects. More than chronological age, the dramatic increase of intestinal permeability is a strong predictor of impending death in Drosophila melanogaster. These recent data give a new insight on the aging process and open new questions relative to the molecular and physiological changes preceding death in flies.

A new small nucleolar RNA (jouvence) extends lifespan and protects against neurodegeneration in Drosophila

Jean-René Martin

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Longevity is one of the most complexes biological processes influenced both by genetic and environmental factors. It is also generally related to neurodegenerative lesions in aged organisms. In Drosophila some mutations as mathuselah, Indy, InR (insulin receptor), chico (insulin receptor substrate), as well as anti-oxydant enzyme, like Cu/Zn superdismutase, have been shown to extend the longevity. However, though several genes and metabolic factors have been shown to play a role in longevity, biological mechanisms from molecular up to organismal level still remain largely unknown. Here, we have characterized a new small nucleolar RNA named jouvence (jou) and showed that its mutation reduces the lifespan and leads to neurodegenerative lesions in old flies. In contrast, a transgene containing the DNA genomic region of the snoRNA rescues these phenotypes both longevity and neurodegeneration, as well as it protects against deleterious effect of aging, as the decline of sensory-motor parameters. In addition, as longevity genes have often been related to increase stress resistance, the over-expression of snoRNA also increases resistance to stress tests. Moreover, in-situ hybridisations have revealed that the expression of snoRNA in the epithelial cells of the gut is required and sufficient to rescue and extend lifespan. Similarly, targeted expression of the snoRNA specifically in the enterocytes rescues the phenotype and increases lifespan. Altogether, these results reveal a new link between a snoRNA expressed in the epithelium of the gut, the increased lifespan and neuroprotection.

The *fne* gene (found in neurons) links post-transcriptional regulation to synaptic function.

Xia Sun (Marie-Laure Samson)

Xia Sun[1], David Sturgill[2], John Malone[2], Brian Oliver[2], Leonard Rabinow[1], Marie-Laure Samson[1]

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[2]NIH, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 20892

We are exploring the function of members of the ELAV/Hu family which are conserved RNA binding proteins involved in post-transcriptional regulation. They are early markers of neuronal differentiation first identified in Drosophila melanogaster. We focus on two members of the gene family, *fne* and *rbp9* because of (1) their close relationship to the vertebrate orthologs, (2) the availability of viable null mutants. We are using an evolutionary approach, performing parallel analyses of the fne and rbp9 paralogs, which will allow us to distinguish newly evolved functions (specific) from those which are shared and thus more likely to be ancestral. *fne* and *rbp9* have both gene-specific functions (relevant to brain anatomy, innate behaviour and longevity) and overlapping function(s), as is evident from the lethality in early adulthood of the double mutants. In collaboration with the laboratory of B. Oliver, NIH, Bethesda, MD, USA, we used RNA-Seq, a quantitative method of high throughput sequencing of non-cloned cDNA libraries, to compare the transcriptomes of normal and fne- Drosophila in order to identify functional networks controlled by FNE. Only about 30 genes have been identified and validated as fne targets so far, 20 among them being affected both in *fne* and *rbp9* mutants. A gene ontology (GO analysis) shows a significant enrichment for genes involved in synaptic transmission, neurotransmitter secretion and synaptic vesicle exocytosis. We detected defects in the innate behaviour of the mutants, including chaining of the fne males. Further, we found that the *fne* and *fru* genes share similar sex-specific splicing patterns (alternative 5′ donor).

Genetics of miRNA clusters and families: new insights on Notch lateral signaling

Pascal Heitzler

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During neurogenesis, dosage-dependent events play critical role for patterning and differentiation. We identified 4 conserved miRNAs as antineural or proneural based on gain-of-function experiments. Unfortunately, any of these interesting miRNA is produced by 2 or 3 gene copies, suggesting functional redundancy and defining miRNA families. To overcome the complexity, we develop new tools to delete accurately every single miRNA, families or clusters, a method that respects genomic environment in contrast to the antisense technics. It is not obvious to find the true miRNA expression pattern, especially in situation where the miRNAs are tightly packed in small introns in a host gene that displays alternative splicing. To unravel the problem, we improve the P[acman] enginery in collaboration with Koen Venken and Hugo Bellen (Houston, Texas), introducing a sensor within large genomic inserts that contain the whole set of the required natural regulatory elements. It is now possible to define the hierarchy of the members for each miRNA family by comparing their exact individual phenotypes. Our results show clear redundancy within a given family, since triple mutants are lethal whereas single are viable, and since the specific pattern of expression are mostly similar, despite the distinct hairpin locus. We have explored the quantitative impact of the individual miRNAs, clusters, and families on Notch lateral signaling, using a cell by cell analysis in mitotic clones. Our results indicate that cluster can contain molecularly unrelated miRNA that have nevertheless convergent and additive effects on lateral inhibition. We propose a model in which, the miRNAs are involved in a complex network that regulates Notch feedback loops. The accurate genetics of the miRNAs in Drosophila would help to explore new areas of functional and developmental neurogenesis that might be conserved throughout animal evolution and involved in human neurodegenative diseases.

A glance at oenocyte function

Rami Makki (Alex Gould)

Rami Makki and Alex Gould

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Oenocytes are cells that are found in most, if not all, pterygote insects. These mysterious cells were documented as early as 1856, and while their development has been well described, especially thanks to contemporary molecular genetic studies in Drosophila melanogaster and Tribolium castaneum, their function remains unclear. Indeed, they have been implicated in a bewildering variety of processes, including larval growth and nutrition, the histolysis of larval tissues, oxygen uptake/respiration, the elimination of toxic waste products, the regulation of haemolymph composition, cuticle synthesis, and the production of ecdysteroids. Our studies, among others, enable us to support some of these hypotheses. We have shown that oenocytes express genes implicated in lipid metabolism and I will discuss their role in desiccation resistance, cuticle formation, and detoxification.

Fatty acid metabolism protect against sugar toxicity

Damien Garrido (Jacques Montagne)

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Fatty acids are key components for cell signaling, energy storage, membrane components and homeostasis. Fatty Acids metabolism is deregulated in several human diseases, including obesity, diabetes, neurological disorder and most cancers. To assess the role of fatty acid metabolism in maintaining body homeostasis, we took advantage of the power of Drosophila genetics. We have investigated the consequences of inactivating the FAS (Fatty Acids Synthase) enzyme, which catalyze the synthesis of long chain fatty acids (LCFA). To this end, we have generated null FAS mutant fly and tissue targeted knock-down through RNAi strategy. Homozygous FAS mutants exhibit a lethal phenotype at L1 stage, which can be rescued by feeding dietary lipids. Importantly, these rescued mutants do not support moderate increase in dietary sugar. In this context, we have observed the deregulation of metabolic pathway including glycogenesis. We have analyzed the cellular defect in the Fat Body that retains hepatic and adipose functions. In this way, we have observed a cell size reduction of FAS mutant cells. We propose that FAS control cellular growth through metabolic perturbation.

Study of the microsporidia *Tubulinosema ratisbonensis* an intracellular parasite of Drosophila melanogaster.

Adrien Franchet (Dominique Ferrandon)

Adrien FRANCHET, Sebastian NIEHUS and Dominique FERRANDON

CNRS – IBMC Strasbourg

With over 1200 species described, microsporidia represent a diverse group that parasitizes hosts from invertebrates to vertebrates. Microsporidia are a highly derived group of fungi that have evolved toward efficient intracellular parasitism. Microsporidia are important pathogens afflicting AIDS patients and also cause important economic damages to aquaculture and to beekeeping. The mechanism of infection and its host-pathogen interactions remain poorly understood. We focus on the microsporidial parasite *Tubulinosema ratisbonensis*. We use Drosophila as a host model, with powerful genetic tools and an evolutionary conserved innate immunity. We have developed an in vivo infection model by directly injecting spores into adult flies. We report the virulence of the parasite in survival tests under different conditions. For the first part, we have observed the impact of host nutrition on parasite growth with dry yeast addition on food medium. The infected flies died faster with this energetic supplementation on food and the parasite load is also higher. These results suggest that the parasite can hijack the energetic resource of the host to proliferate faster. The next question is to find what is the limiting component for parasite growth coming from yeast. Our data indicate the fatty acids as limiting factor so we decided to focus on lipid droplets of fat body cells. As expected, the spores infect the fat body cells and the amount of lipid droplets is significantly decreasing with the time after infection. The fat body could be the preferential tissue target of parasite just after injection. In Drosophila, the fat body is more than an energetic storage tissue with is active role in innate immunity. So we were interesting for this second part to the in vivo cellular host defense against the parasite. Our experiments demonstrate that the parasite endures the defense mechanisms of the host and the innate immune system response only slows down the parasite proliferation.

Pastrel, a restriction factor for picorna--like viruses in drosophila.

Vincent Barbier (Jean-Luc Imler)

Vincent Barbier, Laurent Daeffler, Akira Goto, Carine Meignin, Karim Majzoub, Jean-Luc Imler

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Since the discovery of the evolutionarily conserved TOLL and IMD pathways, involved in anti-fungal and anti-bacterial immune responses, the fruit fly Drosophila melanogaster is used as a model to study the molecular mechanisms of innate immunity. To defend against viral pathogens, Drosophila relies on two main facets: the RNA interference (RNAi) pathway, which plays a broad role in the control of viruses, and virus specific inducible responses (Kemp *et al*., 2013). We also observed that the fly genetic background can modulate the resistance to infection by Drosophila C Virus (DCV), a natural pathogen of Drosophila. A genome wide association study recently showed that polymorphisms in the gene named *pastrel*, localized on the left arm of the third chromosome, affect the resistance to DCV infection (Magwire *et al*., 2012). We are now deciphering the role of this uncharacterized gene in the control of DCV infection. Our loss of function and gain of function experiments indicate that pastrel encodes a molecule opposing DCV infection, raising the question of the mechanism involved. Co-localization experiments indicate that Pastrel is localized in lipid droplets. All together, our data suggest a connection between lipid droplets and restriction of viral infection in Drosophila, as already described in mammals between the restriction factor Viperin, present on lipid droplets, and the replication of the human pathogen Hepatitis C Virus (Helbig *et al*., 2011).

The impact of commensal bacteria on drosophila transcriptome: A molecular crosstalk between immunity and metabolism

Berra Erkosar (François Leulier)

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Intestinal microbiota plays a major role in host physiology. However, the consequences of host-microbiota interactions regarding immunity and metabolism are still not fully revealed. To address this question, we use Drosophila, an animal model that has a relatively simple microbiota and useful genetic tools. We have shown that certain Drosophila gut commensal species impact juvenile growth. Although nutrient sensing pathways (Insulin and TOR) were shown to be involved in this process, how host gene expression is affected still remains unknown. We will present our latest results including transcriptome analysis of host response to its commensal bacteria, and our recent efforts to dissect the molecular pathways underlying host gene regulations. Our results indicate that metabolic and immunity genes are significantly impacted by commensal bacteria, through common cis-regulatory modules involving NF-kB response elements. Our results point to a crosstalk between intestinal microbiota, host metabolism and immunity through shared signaling modules.

The pan-glial homeotic gene repo represses hemocyte differentiation

Guillaume Trebuchet (Angela Giangrande)

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In Drosophila, glial cells play the role of resident macrophages in the central nervous system (for a review, see Kurant, 2011). They clear apoptotic bodies and sculpt neuronal circuits, resembling to vertebrate microglial cells. Moreover, the embryonic glial cells and hemocytes require the same transcription factor (TF), Glial cell missing (Gcm), to differentiate (for a review, see Trebuchet and Giangrande, 2012). To study the mechanisms underlying the glial immune properties, we focus on Gcm pathway regulation. Factors specific to each cell type must regulate the choice between the hemocyte and the glial fates. Among the Gcm target genes, the homeotic gene reversed polarity (repo) is required for glial fate determination (Xiong et al., 1994). In contrast, serpent and u-shaped, encoding Drosophila GATA and friend-of-GATA (FOG) TFs respectively, play key roles in hematopoiesis (for a review, see Lebestky *et al.*, 2000). Using gain-of-function (GOF) and loss-of-function (LOF) mutations and imaging techniques, we find that repo represses serpent and u-shaped expression in glial cells. On the other hand, serpent can inhibit gliogenesis. All together, these data highlight a mechanism controlling the mutual exclusion of the glial and the hemocyte fates.

Hematopoiesis and Cellular Immune Response: role of the NF-kappaB transcriptional factors Dif and Dorsal

Isabelle Louradour (Michèle Crozatier)

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In adult mammals, hematopoiesis occurs in the bone marrow and gives rise to different blood cell types involved in the cellular immune response. In our lab, we use parasitism of Drosophila larvae by the parasitoid wasp Leptopilina boulardi as a model system to decipher the cellular immune response. The wasp lays its eggs inside the fly larva. This induces a massive production of lamellocytes, a specialized immune cell type required to encapsulate the wasp egg and block its development. Lamellocytes are massively produced in the larval Drosophila hematopoietic organ called the lymph gland. Interestingly, the encapsulation of the wasp egg does not occur in larvae mutant for components of the Toll signaling pathway, such as one of the NF-kappaB transcriptional factors, Dorsal-related Immunity Factor (Dif). These data strongly suggest a key role for this pathway in controlling the Drosophila cellular immune response. The Toll pathway has an evolutionarily conserved r ole in humoral immunity, and in particular it plays a key role in Drosophila by activating the production of anti-microbial peptides in response to gram-positive bacteria and fungi. However, its role in controlling the Drosophila cellular immune response remains unknown. We are currently investigating the role of Dif and Dorsal in the lymph gland, during both normal hematopoiesis and in response to wasp parasitism.

Diedel, an immunomodulator molecule, involved in resilience to viral infection in Drosophila.

Olivier Lamiable (Jean-Luc Imler)

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Viral infection is a major threat for all living organisms, which have evolved efficient antiviral defense mechanisms. Innate immunity is the first-line defense program, which operates in all animals to inhibit growth of microorganisms and increase host survival. Viral infections are particularly challenging for the immune system because viruses replicate within cells, using molecules from the host. Using the fruit fly Drosophila melanogaster as a model, we have shown that viral infection triggers both RNA interference, and an inducible response. Whereas the former has been quite extensively studied, the latter remains poorly characterized. Here, we provide evidence that viral infection triggers production of cytokine regulating homeostasis, thus allowing flies to survive the stress of the infection. Using genome-wide microarrays, we identified the gene Diedel which is strongly induced during Sindbis (SINV) and Vesicular Stomatitis Virus (VSV) infection. We show that Diedel encodes a 12 kDa circulating protein secreted by the fat body upon infection. The induction of Diedel is controlled by NF-KB transcription factor Dif, but does not depend on Myd88, suggesting that it is regulated by a non-canonical Toll pathway or a completely different pathway. Diedel mutant flies exhibit increased lethality upon infection by SINV, but the viral load is not affected by the mutation. These results indicate that Diedel is involved in resilience, rather than resistance (i.e. immune response) to infection. Interestingly, several lepidopteran DNA viruses express orthologs of Diedel, and we show that ortholog of Spodoptera frugipe rda ascovirus 1a can rescue the lethality of Diedel mutant flies. This suggests that this gene was hijacked by DNA viruses to limit their impact on the mortality of their hosts. Finally, we will present a genome-wide microarray analysis of the transcriptome of SINV infected Diedel mutant flies, which suggest that Diedel act as an immunomodulator cytokine.

The endogenous retrovirus *gypsy* and the endosymbiotic bacteria wolbachia : a struggle for transmission.

Franck Touret (Christophe Terzian)

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Insect endogenous retroviruses (IERVs) are present in the genome of several insect species. It was previously shown that gypsy is an active endogenous retrovirus in Drosophila melanogaster, which could be transmitted to individuals fed with gypsy-containing extracts. Gypsy replication involved follicular cells to oocyte transfer in permissive mother resulting in new copies insertion in the offspring Interestingly this maternal effect is not restricted to IERVs: indeed the endosymbiotic bacteria wolbachia (wmel) is transmitted to the next generation via the oocyte cytoplasm. The fact that wmel and gypsy uses the same transmission pathway raises the question of a possible interaction or interference between wmel and gypsy. Moreover it has been well described that wmel can induce resistance or tolerance to insect RNA viruses. Our results indicate that: a) wmel modify gypsy pattern of expression in the follicular cells b) gypsy new copies insertion rate is significantly reduced in wmel permissive vs. permissive antibiotic treated individuals.

Rbf/dE2F2, together in the dREAM complex, downregulate anti-apoptotic genes to induce cell death

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rb is the first tumor suppressor gene identified in human cells. It is an essential gene involved in many cellular processes such as cell cycle, DNA stability, differentiation or apoptosis. Over 200 pRb partners have been identified, allowing it to modulate the transcription of more than one thousand targets. Only pRb activity in cell cycle control is well described: rb (with transcription factors of E2F family) inhibits cell proliferation by controlling G1/S transition. Unlike, rb role in apoptosis is complex and molecular mechanisms involved are poorly understood. Indeed, depending on the cellular context, rb displays either pro- or anti-apoptotic effects. Studies led in the laboratory on rbf, the Drosophila counterpart of the mammalian rb gene, highlighted that rbf role on apoptosis depends on the cell proliferation status. rbf overexpression in proliferating tissues induces caspase-dependent cell death, whereas no cell death is triggered by rbf in post-mitotic tissues. Since the mechanism of Rbf-induced apoptosis is not well known, we initially studied through genetic interaction test the involvement of E2F family members. In Drosophila, there are 2 members: dE2F1 (activator) and dE2F2 (repressor). We were able to show that dE2F2 and its cofactor dDP are needed for Rbf-induced cell death while dE2F1 only plays an indirect role. RT-qPCR experiment combined with ChIP-qPCR analyses helped us to identify two new transcriptional targets of Rbf/dE2F2 heterodimer. We confirmed that these transcriptional regulations are important for Rbf-induced apoptosis. Further, Rbf and dE2F2 belong to a multiprotein complex called dREAM involved in transcriptional regulation. We have studied the involvement of this complex in Rbf-induced apoptosis. Thus our study has helped to better characterize the mechanism of Rbf-induced apoptosis in proliferating cells, which could in the longer term allow considering means of restoring apoptosis in cells deficient for *rb* tumor suppressor gene.

Posters

Control of blood cell diversity and homeostasis in Drosophila

Benoit Augé (Lucas Waltzer)

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Several features of blood cell development have been conserved from mammals to Drosophila. In particular transcriptional regulators of the GATA and RUNX and FOG families, which are involved in haematopoiesis and leukaemia in humans, play key roles in the control of Drosophila blood cell lineages development. One aspect of our work consists in deciphering how cross-regulatory interaction between these 3 factors regulate differentiation along the three larval haematopoietic lineages (plasmatocytes, crystal cells and lamellocytes). Schematically, the GATA factor Serpent (SRP) is required for all blood cells. In combination with the RUNX factor LZ it induces crystal cell differentiation whereas its interaction with the FOG factor USH is required to prevent the transdifferentiation of the plasmatocytes into lamellocytes. To gain molecular insights into the processes of differentiation/trans-differentiation, we wish to characterise the binding site repertoire and transcriptional response to these three factors. In parallel, we are characterizing the function and molecular mechanisms of action of two conserved regulators of GATA/RUNX activity that we have identified, MLF and ENOK, which are both controlling hemocyte homeostasis. Finally, while embryonic and larval blood cells have been the focus of many studies, adult hemocytes have been largely overlooked. We thus embarked into a systematic characterization of the adult hematopoietic system that will account for its origin, diversity and function.

Analyses of muscle diversification processes by new cell specific approaches in Drosophila.

Benjamin BERTIN (Guillaume JUNION)

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Cell diversification is an essential process for proper organism development. Understanding genetic and molecular mechanisms conferring the individual characteristics of each muscle during development remains a major challenge. Our current knowledge about the control of cell diversification is only based on functional analyses of individual genes in whole embryo. However, this strategy is not adapted to define gene networks that control the acquisition of individual properties of muscle cells. For studying muscle diversification process we apply new cell specific approaches and use them in Drosophila model. Indeed, muscle network in Drosophila embryos represents an attractive system for studying cell diversification. It is composed of 30 muscle fibers and 6 stem cells (AMPs) per hemisegment, which are easy to detect and to follow during development. Currently we take advantage from the newly generated and tested drivers targeting muscle subtypes and a cell specific transcriptomic method to define a transcriptional signature that specifies different subsets of muscle cells at different stages. We first performed translational ribosome affinity purification (TRAP) on specific muscle cells to isolate mRNA engaged in translation. The preliminary results from microarray analyses show enrichment of muscle specific genes. Furthermore biological process gene ontology showed that the majority of enriched genes are linked to muscle development. According to those results, TRAP method seems to be efficient to identify transcriptional signatures in subsets of muscle cells. This study should provide insights into genes acting as realisators of muscle identity code of individual muscles.

Vap, a negative effector of autophagy deregulates cellular Vps34 activity

Marc Bourouis (Pierre Léopold)

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Autophagy supplies for recycled nutrients which are essential for animals to survive on episodes of food deprivation. In RNAi screenings for modifiers of a fat body-directed starvation phenotype, we found vap (vacuolar peduncle), a member of the five rasGAP genes in Drosophila.

Vap null adult flies were unable to resist to food deprivation suggesting some failure during the normal autophagic response.

In the search for defects in the starvation response through the analysis of larval fat bodies, a major storage organ, we found paradoxally that the loss of vap caused enhanced induction of acidified lysosomes as well as increased PI(3)P production which signs initiation of autophagic vesicles nucleation.

However, in accordance to the starvation sensitivity of vap flies, the apparent enhancement of autophagosome early biogenesis was not followed by proper maturation into catabolically active autolysosomes.

Conversely, the excess of vap resulted into either a partial or a full suppression of cellular PI(3)P production and lysosome induction. Similar phenotypes (including the functional starvation sensitivity) were observed by either increasing or respectively inhibiting the expression of the lipid kinase Vps34, a class III PI3-kinase.

We concluded that vap somehow negatively regulated Vps34 activity or distribution. The requirements for vap parallels those for the several Vps34-Complexes involved both throughout autolysosome progression and in the course of the formation of endosomal vesicles.

Sprint, a GEF for Rab5 was recovered as a SH2-binding partner of vap could provide a closer link to the vesicular events where Vps34-C activity is acting.

Interestingly, Sprint was able to fully suppress mutant vap starvation sensitivity suggesting that deregulation of sprint is instrumental to vap dependent phenotypes.

Identification and characterization of new proteins involved in mitosis in Drosophila melanogaster

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During mitosis, the mitotic spindle, a microtubule-based structure plays a crucial role to ensure the proper segregation of sister chromatids and cortical cell fate determinants into the two daughter cells. Errors in spindle formation can lead to improper chromosome segregation and aneuploidy, a common hallmark of most cancers. In addition, failure in spindle orientation along the apico basal axis of neural stem cells (Neuroblast, Nb) can contribute to loss of cell identity, acquisition of the Nb fate and tumor formation. Therefore, regulation of microtubule (Mt) dynamics is crucial during cell division. The regulation of microtubule network is ensured by microtubule-associated proteins (MAPs) that associate with Mts. In order to identify new putative mitotic MAPs or spindle regulators, Mts and MAPs were purified from syncytial (mitotic) and older (interphasic) Drosophila embryos. 96 poorly characterized proteins, enriched with the mitotic fraction or present in interphasic fraction, were selected for further studies by RNAi in vivo using Drosophila central nervous system neuroblasts, to monitor mitotic spindle and chromosome.

Our results show 22 candidates required for mitotic spindle assembly. The use of mutants and video-microscopy will be used to investigate spindle and chromosome segregation defects in space and time.

Relations between epithelial morphogenesis and basement membrane during *Drosophila melanogaster* oogenesis.

Julien CHLASTA (MURIEL GRAMMONT)

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Epithelial cells interact with basement membrane for instance through integrins. During early development, they can take different shapes (morphogenesis). We can observe these epithelial changes in ovarian follicles of Drosophila melanogaster. Each follicle is composed of a monolayer of epithelial cells. At stage 9, these cells flatten around the follicle from the most anterior pole to the middle of the follicle. This flattening stops at the beginning of stage 10.

Basement membrane is composed by collagen IV, perlecan and syndecan (etc.) and surrounds the follicle. My objective is to determine the molecular and biophysic relations between epithelial cells and basement membrane during this cell stretching. My first results show a difference in the rigidity along the antero-posterior axis at stage 9 (Atomic Force Microscopy). Observations of mutations in integrin signal (BPS or aPS1/2) or JNK pathway enable me to observe a delay of stretching (genetics). Hence, these results are beginning to demonstrate the important link between epithelial cells and basement membrane in the morphogenesis of epithelia tissues.

Molecular mechanisms of CNS sparing in Drosophila

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Growing organs are differentially sensitive to suboptimal levels of dietary nutrients. For example, it has long been known that intrauterine growth restriction (IUGR) during the third trimester of human pregnancy can lead to an elevated brain/body ratio. This reflects sparing of the growth of the brain at the expense of other organs. Although brain sparing is an important survival response that appears to be highly conserved during evolution, its underlying mechanisms are still unclear. In our lab, a Drosophila model to study brain sparing during dietary nutrient restriction was recently established. Early during larval development, sparing of CNS growth does not occur as dietary amino acids are needed to stimulate neural stem cell (neuroblast) growth via glial-dependent activation of Insulin-like Receptor/Tor signaling. However, at later larval stages, neuroblast growth is very efficiently spared during nutrient restriction despite no overall body mass gain. This late CNS sparing, is powered by Anaplastic Lymphoma Kinase (Alk) and its glial-derived ligand, Jelly Belly (Jeb). We have now begun to investigate the developmental timing mechanism underlying the switch from diet-sensitive to diet- insensitive modes of neuroblast growth. We will present data suggesting that at least part of this switch mechanism involves temporal transcription factor transitions within the neuroblast.

Functional dissection of the IMD/TNF-R pathway in Drosophila antiviral immunity.

Akira Goto

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UPR9022 du CNRS, Institut de Biologie Moléculaire et Cellulaire (IBMC), Strasbourg, France

Recent breakthroughs demonstrated that RNA interference is a potent cellular antiviral defense in Drosophila. In addition, circumstantial evidence indicates that a yet poorly defined inducible response contributes to antiviral immunity. The IMD/TNF-R signaling pathway appears to participate in this response.

Here, we focus on analyzing the precise roles of the IMD/TNF-R pathway genes in antiviral defenses. To achieve this, we set up two research strategies, a target-focused approach to directly examine the role of the canonical components of the IMD/TNF-R signaling pathway (Research strategy 1) and a discovery-based approach to functionally characterize candidate molecules recently identified as interactants of the IMD/TNF-R pathway by a proteomic approach (Research strategy 2).

Research strategy 1 identified a novel antiviral role for the kinase IKKβ (Ird5). Depletion of IKKβ (Ird5) in Drosophila S2 cells as well as in mutant flies leads to a significant increase of Drosophila C virus (DCV) replication. Interestingly, in contrast to the antibacterial response, this anti-DCV role of IKKβ (Ird5) is independent of the regulatory subunit IKKγ (key). A DNA microarray analysis comparing wild-type with IKKβ (Ird5) mutant flies led to the identification of a subset of genes regulated by IKKβ (Ird5) upon DCV infection.

For research strategy 2, we conducted an RNAi screen on 378 candidate molecules and identified a number of candidates involved in the activation of the IMD pathway. Among those, we have further discovered DMAP1 for DNA methyltransferase associated protein 1, which contributes to both antibacterial and antiviral responses.

Overall, this research has discovered a new IKKγ (key) independent function for IKKβ (Ird5) in the control of a viral infection in Drosophila, and we are currently dissecting this new pathway. In addition, I have identified several new regulators of the IMD/TNF-R signaling pathway, many of which are highly conserved in mammals.

gcm: Impact of a fate determinant in collective glia migration

Tripti GUPTA (Angela GIANGRANDE)

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Nervous system comprises of a vast and complex neuronal network, which is very essential for its proper functioning. To construct complicated neuronal networks, glial cells undergo temporal based collective migration from the place of their birth to the final destination. Collective cell migration is a widely conserved process that plays a key role in several physiological processes, from development to homeostasis. It requires a higher degree of complexity than single-cell migration since cells must coordinate their movements to maintain their reciprocal positions and to correctly reach their final destination. glide/gcm encodes an atypical zinc finger transcription factor, which is expressed in all the lateral glial cells. Its mutation causes presumptive glia to convert into neurons whereas its over-expression causes vice versa. My project aims at studying the role of such an early fate determinant in later aspects of development such as collective glia migration. In order to study the process of collective migration I make use of the developing Drosophila wing as a model system. So far my results while studying the role of gcm in collective glia migration indicate that gcm directly affects migration in a dosage dependent manner.

Occurrence of the non-LTR I element in *Drosophila mojavensis* and *Drosophila arizonae* and their hybrids.

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The I non-LTR retronsposon, which belongs to the I superfamily of non-LTR retrotransposon well known in Drosophila melanogaster because it transposes in high frequency in the germ line cells and drives the I-R system of hybrid dysgenesis in this species. Here we report the occurrence of this element in hybrids of two sister species belonging to the repleta group of the genus Drosophila, Drosophila mojavensis and Drosophila arizonae, which display variable degree of pre- and post-zygotic isolation, depending on the geographic origin of the strains. We took the advantage of these features for exploring the transposable element dynamics in interspecific crosses. We here examined the presence of the I element in the sequenced genome of D. mojavensis and identified the occurrence of at least one complete copy, which belongs to a different I family than that of D. melanogaster. We showed that this element is transcriptionally active in ovaries and testis of both specie s and in their hybrids. Most interesting, we showed that this element is more expressed in hybrid males than in females and in females the expression is restricted to the ovary nurse cells.

Cell-specific protection against brain aging by expression of mitochondrial uncoupling proteins in Drosophila.

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Brain aging plays an important role in general body senescence but the molecular and cellular mechanisms controlling this process are still poorly understood. Reactive oxygen species (ROS) play a central role both in aging and neurodegenerative diseases. The oxidative stress they produce causes progressive macromolecular and cell membrane damages. Mitochondria are the main source of ROS in cells and their dysfunction can lead to accelerated aging and the onset of neurodegeneration. Thus, controlling mitochondrial ROS production could be relevant to longevity and healthspan. The uncoupling proteins (UCPs) can mitigate ROS production by mitochondria. Recent studies demonstrated that enhancing mitochondrial uncoupling can decrease ROS-induced phenotypes in Drosophila. To further investigate these effects, we expressed human and Drosophila forms of UCPs in the Drosophila nervous system. We observed positive or detrimental effects on healthspan when these proteins wer e overexpressed in specific neuronal subsets. Our current project aims at identifying nerve cells involved in healthspan improvement when mitochondrial uncoupling is enhanced, both in normal and Parkinson's disease-like conditions.

Characterization of subtelomeric regions in *Drosophila melanogaster*

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During the last century, the Drosophila melanogaster genome has been invaded by the P element. Then, a mechanism of repression of P transposition has been established and led to the discovery of the P cytotype. One copy of the P element inserted in Telomeric Associated Sequence (TAS) at the cytologic 1A site of the chrosomome X is able to repress the expression of 80 euchromatic copies of P element in the genome.

Parralel to this, a transgenic model mimicking the repression by the P element has been shown: a P-transgene inserted in the TAS, can repress in the female germline, in trans, a homologous euchromatic P-transgene. This mechanism has been called the trans-silencing effect (TSE) and involved the PIWI-interacting RNAs (piRNA) pathway as well as heterochromatin formation. Those piRNAs are implicated in the regulation of transposable elements in gonads.

TAS are subtelomeric regions composed of non coding repeated sequences and are also known to be a producer locus of piRNA.

Since the TAS locus seems to be a key player in the silencing involved during the P element repression and the TSE, we are studying structure and molecular properties of this locus and some preliminary results will be presented.

Impact of Bt bioinsecticides on the Drosophila gut physiology.

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The digestive tract is continuously subjected to multiple aggressions through virus, bacteria, toxins and chemicals mixed in the feed. Therefore the gut lining has established a mechanism of replenishment in order to maintain the physiological function of the organ called the gut homeostasis. This homeostatic equilibrium is based on the existence of intestinal stem cell (ISC) that are able to give rise to all the cell types of the epithelium to maintain the integrity and the function of the organ. Upon aggression, a complex network of signaling pathways is taking place between the different cell types, allowing the appropriate differentiation of the ISC daughter cells (the enteroblasts, EB) in order to replace the defective epithelial cells.

Among the aggressors hidden in the feed, there is the bacterium Bacillus thuringiensis (Bt). Bt is a soil bacterium that is widely used worldwide as bioinsecticides. Indeed all together the multitude of Bt strains produces a broad range of crystalline toxins, named Cry toxins, which certain have been selected in organic farming owing to their lethal properties against specific pests. Because of incentive programs for sustainable development, the use of Bt bioinsecticides as an alternative to chemical pesticides will further increase in the next decades. Cry toxins target the intestinal epithelium of sensitive organisms causing osmotic lysis and cell death. Insects dye after 2-3 days. Although the specificity of the acute toxicity of these toxins has been proved since many years, with no acute toxicity observed towards non-target species ranging from honey bees to human, data are scarce on adverse effects that could result from chronic exposure. The question now is how far no n-target organisms will be potentially impacted by the resulting augmentation of the Bt bacterium and its Cry toxins in the environment?

To answer this challenge, we are using drosophila (a non-target organism) to study the impacts of the most common Bt bio.

Methylene blue rescues heart defects in a Drosophila model of Friedreich's ataxia

Véronique Monnier

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Friedreich's Ataxia (FRDA), the most common hereditary ataxia, is characterized by progressive degeneration of the central and peripheral nervous system, hypertrophic cardiomyopathy and a high risk of diabetes. FRDA is caused by abnormally low levels of frataxin, a highly conserved mitochondrial protein. Drosophila appears as an adequate animal model to study pathogenic mechanisms involved in FRDA and has been previously successfully used to model FRDA in various cell types, including neurons and glial cells. We have developed a Drosophila cardiac model of FRDA. In vivo heart imaging revealed profound impairments in heart function in frataxin depleted Drosophila, including a strong increase in end-systolic and end-diastolic diameters and a decrease in fractional shortening. These features, reminiscent of pathological phenotypes in humans, are fully rescued by complementation with human frataxin, suggesting conserved cardiac functions of frataxin between the two organisms. Oxidative stress is not a major factor of heart impairment in frataxin-depleted flies, suggesting the involvement of other pathological mechanisms notably mitochondrial respiratory chain dysfunction. Accordingly, we report that methylene blue (MB), a compound known to act as an alternative electron carrier that bypasses mitochondrial complexes I-III, was able to prevent heart dysfunction. MB also partially rescued the phenotype when administered post-symptomatically. Analysis of MB derivatives demonstrates that only compounds with electron carrier properties are able to prevent the heart phenotype. Thus MB, a compound already used for several clinical applications, appears promising for the treatment of the heart dysfunctions that are a major cause of death of FRDA patients. This work provides the grounds for further evaluation of MB action in mammals.

The post-translational of Akirin is required for its function in the IMD pathway

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A conserved nuclear factor, Akirin is required for the activation of NF-κB in both Drosophila melanogaster and mammals. However, the mechanisms involved in the Akirin function are unknown. Here we present evidence that Akirin is tightly regulated by ubiquitination and proteasomal degradation. Akirin acquires K63-linked polyubiquitin during the induction of IMD pathway, while at later times K48-linked polyubiquitin targets them for proteasomal degradation. Mutation of specific lysine residues in the N-terminal region of Akirin abrogates activation of Akirin-dependent gene expression and disrupts K63-polyubiquitinated Akirin accumulation while promoting Akirin degradation by proteasome. Since akirin is strictly localized to the nucleus, these results suggest that the IMD signaling in the nucleus level is modulated by Akirin post-translational modification.

Tissue-specific function of Patj in regulating the Crumbs complex and epithelial polarity

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Epithelial polarity is characterized by the asymmetric localization of proteins that exclude each other to separate the plasma membrane in three cortical domains: apical, lateral and basal. Among the polarity proteins network, Crumbs (Crb) plays a key role, as its overexpression is sufficient to induce extension of the apical domain. We generated the null mutants for Drosophila patj, a core component of the Crb complex. These mutants are lethal. patj mutation has no effect on Crb in embryo, whereas in the follicular epithelium it induces decrease of the Crb complex from the apical domain and morphogenetic phenotypes. Moreover, gain of function of Crb and patj mutation genetically suppress each other in follicular cells. We show that PDZ1 domain of Patj associated with the L27 domain (that binds to Sdt) are sufficient to rescue both Drosophila viability and Crb localization. Therefore, critical function of Patj hinges on the ability of L27-PDZ1 to positively regul ate Crb complex (Pénalva and Mirouse, 2012). I will present our recent results suggesting the identification of a PDZ1 protein interactor. We obtained in vivo evidences that such interaction can provide an explanation on how Patj regulates Crb at the apical membrane and suggests that it might participate to a positive feed-back loop stabilizing Crb complex.

ER stress induces PERK/JNK/Dilp8-dependent tissue regeneration

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The endoplasmic reticulum (ER) is known to play a major role in protein maturation and folding. The accumulation of unfolded proteins in this organelle triggers an adaptive response known as the unfolded protein response (UPR) to resolve this induced stress. If the ER-stress remains unresolved, the UPR induces apoptosis as observed in a great number of devastating diseases including neurodegenerative diseases, diabetes, atherosclerosis and renal diseases. To understand how cells activate apoptosis and promote tissue homeostasis after ER-stress, we have developed a novel chronic ER-stress Drosophila model. We chose to overexpress the, Presenilin protein (Psn) that contains multiple transmembrane domains in part of the vestigial expression domain of the wing imaginal disc. Indeed, overexpression of Presenilin (Psn) is already known to trigger ER stress in mammalian models. We have shown that in our system, the UPR PERK/ATF4 pathway (i) is activated, (ii) promotes caspase-dependent apoptosis and (iii) counterbalances ER-stress induced loss-of-tissue-homeostasis through a Dilp8-dependent general developmental delay controlled by the induction of the c-Jun N-terminal kinase (JNK) pathway. This Drosophila chronic ER-stress model offers new perspectives for future investigations, including the identification of novel regulators of the UPR-dependent tissue and organismal homeostasis.

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Host-microbiota interactions: Effects of Lactobacillus plantarum on Drosophila melanogaster physiology

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Metazoans are naturally associated with bacterial communities, which establish commensalistic or mutualistic relationships with each other and with the host organism. These interactions play a crucial role in different aspects of the host physiology while providing the microbiota a nutrient-rich environment. When deregulated, the relationships can lead to pathological situations, such as inflammatory chronic disease, metabolic disorders or even cancers, and despite recent progress, the characteristics and molecular basis of the beneficial impact microbiota has on its host remain largely unknown.

In order to elucidate the fine-tuned dialogue governing the relationships between intestinal bacteria and their host, we use a system based on the association of the model organism Drosophila melanogaster with one of its natural commensals, Lactobacillus plantarum. This rather simple gnotobiotic model allowed us to reveal a growth-promoting effect mediated by L. plantarum in nutritionally challenged drosophila larvae and will now give us the ability to see whether this commensal bacteria has a beneficial role on its host physiology throughout it's entire life, by studying the effects of the association at the adult stage. We study different life history traits such as fecundity, fertility and resistance to full starvation as an indication of L. plantarum effects on the adult fly metabolism and will give you an overview of the first data.

TEs can escape host piRNA silencing in the "Piwiless pocket" during early oogenesis

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During Drosophila oogenesis, transposable element (TE) repression involves the Piwi-interacting RNA (piRNA) pathway which ensures genome integrity for the next generation. We have developed a transgenic model to study repression of the Idefix retrotransposon in the germline. We shown that, during early oogenesis, in the dividing cysts in the germarium, Idefix anti-sense transgenes escape host control and this is associated with very low piwi expression. Silencing of P-element-based transgenes is also strongly weakened in these cysts. This region, termed the "Piwiless pocket" or Pilp, may ensure that new TE insertions may occur and be transmitted to the next generation, thereby contributing to genome dynamics. In contrast, since piRNA-mediated PTGS is strong in germline stem cells, TE mobilization with potentially deleterious effects is repressed ensuring the continued production of viable germline cysts.

Exploring interactions between circadian rhythms and neurodegeneration in a Drosophila model of Parkinson's disease

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Parkinson's disease (PD) affects 1-2% of the population over the age of 65. It is characterized by a progressive loss of midbrain dopaminergic neurons and the presence of cytoplasmic inclusions composed of α-synuclein (α-syn) aggregates. Although PD is likely a multifactorial disease, evidence suggests that α-syn plays a central role in PD pathogenesis. Moreover, PD most visibly affects locomotor control, but non-motor symptoms are numerous, e.g. sleep and/or circadian rhythm disruptions that may occur before motor deficits. Since such disruptions decrease quality of life and may even negatively impact the course of the disease, it is important to understand, and if possible alleviate, them.

PD-like symptoms can be partly reproduced in Drosophila melanogaster by transgenic expression of human wild-type or mutant pathogenic α-syn. Recently, mutant α-syn expression in serotoninergic and dopaminergic neurons was shown to affect locomotor activity rhythms in old flies and increase sleep latency in young flies long before locomotion is impaired. Consequently, the goal of the present study is to look for both anatomical and functional interactions between the circadian system and the PD-like phenotypes observed in α-syn flies.

As a first step in examining how clock mutations/disruptions may interact with dopaminergic control of locomotion and α-syn neurotoxicity, we evaluated the impact of circadian clock dysfunction on locomotor ability in young and old flies. An overview of this ongoing work will be presented.

Origin, assembly and function of Collagen IV in the ovary

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Basement membranes (BMs) provide a specialized network of extracellular matrix (ECM) proteins essential for tissue morphogenesis and function. Their structure and composition is well documented but little is known about the origin of their components and their biogenesis. BMs are mainly composed of the highly conserved type IV Collagen. Our lab uses the Drosophila ovary to study the biosynthesis and function of Collagen IV during development. Drosophila Collagen type IV is made of 2 alpha chains, alpha1 (Cg25c) and alpha2 (Viking), assembling and forming an organized network around the different ovarian tissues: the germarium, housing the stem cells niche; the egg chambers, giving rise to the future embryo; and, the muscle sheath cells surrounding the egg chambers. In order to determine the origin of ovarian Collagen, we developed new tools and combined cell biology and genetics approaches to spatially and temporally control the expression or knockout of Collagen IV. We found that ovarian Collagen IV originates from different cell types: the follicular epithelial cells, the adult fat body cells and a group of scattered cells that we have identified as hemocytes. Interestingly, the Collagen IV produced by follicular epithelium accumulates cell autonomously around mature egg chambers and is essential for embryonic morphogenesis. Collagen IV secreted from hemocytes led to a short range, specific BM assembling around the stem cell niche selectively and plays a key role in stem cell proliferation. Finally, the Collagen IV produced by the fat body is required for a long-range deposition in the muscular sheath cells providing elasticity. Hence, Type IV Collagen can originate from diverse cell types and assemble specifically on selected target tissues. Our data reveal a previously unknown complex pattern of BM assembly, leading to specialized matrices of diverse origin and function. We are currently investigating the targeting mechanisms to ward the different tissues.