

# 33<sup>rd</sup> annual French Drosophila conference



## INVITED SPEAKERS

Erika BACH, New York University, USA  
Thomas FLATT, University of Fribourg, Switzerland  
Ronald KÜHNLEIN, University of Graz, Austria  
Matthias LANDGRAF, University of Cambridge, UK  
Ingrid LOHMANN, University of Heidelberg, Germany  
Alain VINCENT, CBI Toulouse, France  
Paula I WATNICK, Harvard Medical School, USA

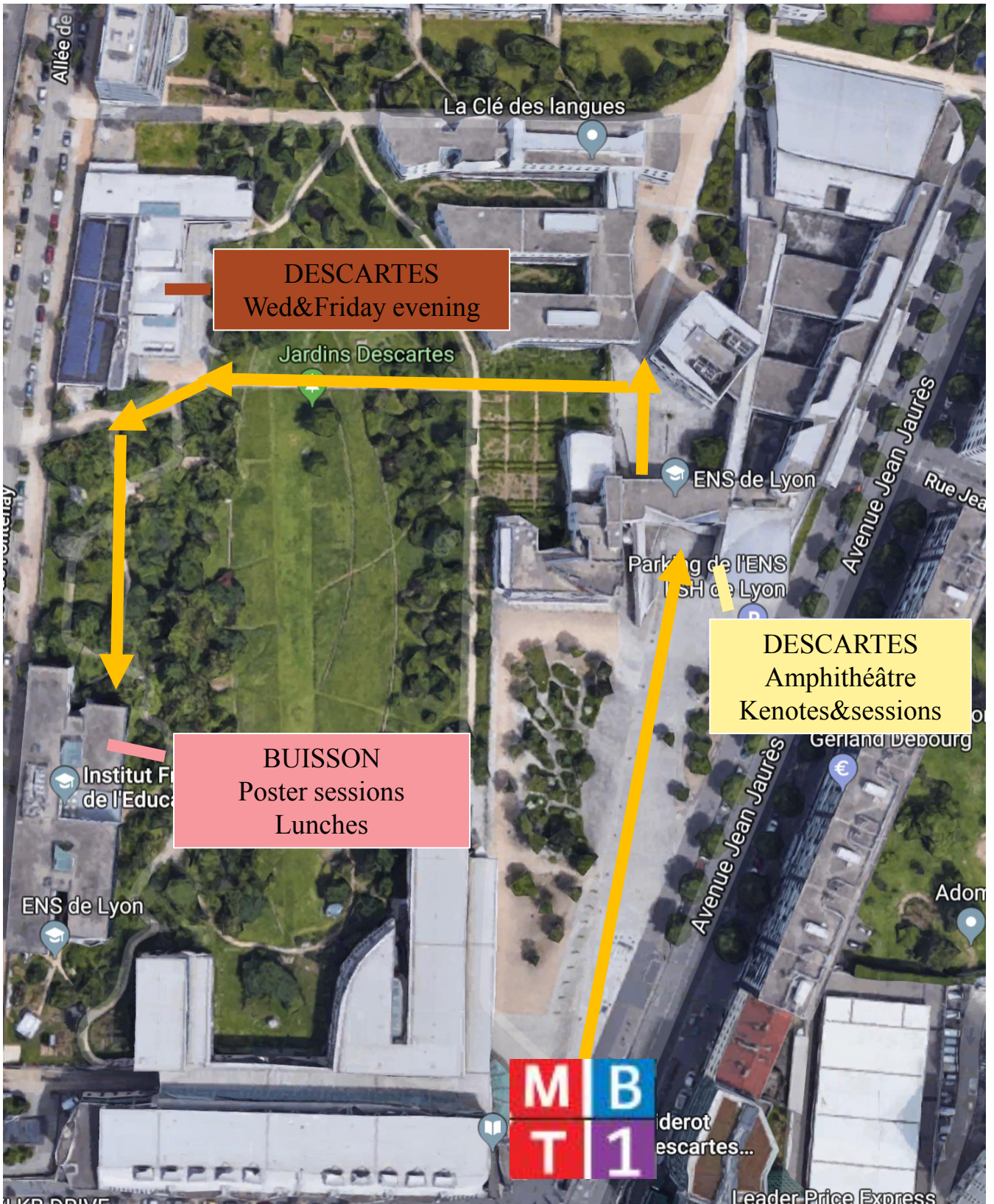
November 6-9, 2019 - ENS de Lyon (France)

**deadline for abstract submission:** September 29, 2019  
**deadline for registration:** October 18, 2019

website: [drosoconf.sciencesconf.org](http://drosoconf.sciencesconf.org)



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**DESCARTES**  
Wed&Friday evening

Jardins Descartes

**BUISSON**  
Poster sessions  
Lunches

**DESCARTES**  
Amphithéâtre  
Kenotes&sessions

**MIB**  
**T1**

Wednesday Nov 6th	Thursday Nov 7th	Friday Nov 8th	Saturday Nov 9th
<p>This program is colour coded to reflect the conference venues. Please see map.</p> <p>NB Entry and exit the conference sites by the main entrance only.</p>	<p>09:00-11:00 <b>S2: Metabolism</b> <b>Ronald KÜHNLEIN</b> Bruno HUDRY Nathalie DAVOUST-NATAF Mickaël POIDEVIN</p>	<p>09:00-11:00 <b>S5: Development</b> <b>Erika BACH</b> Jacques MONTAGNE Emmanuèle MOUCHEL-VIELH Vincent LOREAU</p>	<p>09:30-11:00 <b>S9: Cell Biology (continued)</b> Hammed BADMOS Jérôme BOHERE Chantal ROUBINET Hadi BOUKHATMI</p>
<p><b>DESCARTES AMPHITHEATRE</b> Main conference proceedings (Sessions, key-notes, and coffee breaks @amphi_mezzanine)</p>	<p>Coffee Break @BUISSON</p> <p>11:30-13:15 <b>Posters Session 1</b></p>	<p>Coffee Break @amphi-mezzanine</p> <p>11:30-12:15 <b>S6: Behavior</b> Alain GARCES Julien ROYET Maroua FERDENACHE</p>	<p>Coffee Break @amphi-mezzanine</p> <p>11:30-12:00 <b>Organisation of 34th Annual French Drosophila Conference Meeting</b></p>
<p><b>BUISSON</b> All poster sessions, lunches and some coffee breaks.</p>	<p>12:15-13:15 <b>S7: Disease models</b> Laurent SEUGNET Anissa SOUIDI Victor GIRARD Pierre DOURLEN</p>	<p>12:00-12:30 <b>Prizes (for posters and talks)</b></p>	<p>12:00-12:30 <b>Prizes (for posters and talks)</b></p>
<p>14:00-16:00 <b>Arrivals</b> <b>Registration @Descartes_entrance</b></p>	<p>13:30-14:00 <b>Lunch @Buisson</b></p> <p>14:00-15:20 <b>S3: RNA and transcription</b> <b>Ingrid LOHMANN</b> Solène VANDERPERRE Benjamin LOPPIN</p>	<p>13:30-14:00 <b>Lunch @Buisson</b></p> <p>14:00-15:20 <b>Posters Session 3</b></p>	<p>12:30 <b>End of conference</b></p>
<p>16:15 <b>Welcome address</b></p>	<p>15:20 -16:40 <b>S4: Evolution</b> <b>Thomas FLATT</b> Natacha KREMER Abderrahman KHILA</p>	<p>15:20-16:40 <b>S8: Developmental Neurobiology</b> <b>Mathias LANDGRAF</b> Wenyue GUAN Filipe PINTO-TEIXEIRA</p>	
<p>16:30-18:20 <b>S1: Host-Microbes interactions</b> <b>Paula WATNICK</b> Armel GALLET Juliette SCHNEIDER Roubba JNEID Théodore GRENIER</p>	<p>Coffee Break @Buisson</p> <p>17:15-19:00 <b>Posters Session 2</b></p>	<p>Coffee Break @Buisson</p> <p>17:15-18:00 <b>S8: Developmental Neurobiology (continued)</b> Caroline MEDIONI Jean-Maurice DURA Iryna MOHYLYAK</p>	
<p>18:30-22:00 <b>Mixer &amp; Dinner @Descartes_CROUS</b></p>	<p>18:00-18:50 <b>S9 : Cell Biology (keynote only)</b> <b>Alain VINCENT</b></p>	<p>18:00-18:50 <b>S9 : Cell Biology (keynote only)</b> <b>Alain VINCENT</b></p>	
	<p>No program after 19:00. You are free to explore #Lyon. See organisers and locals for suggestions.</p>	<p>19:00-00:00 <b>Festive Dinner @Descartes_CROUS</b></p>	



# Detailed Program

**Wednesday November 6th**

14:00-16:00

*Arrivals and Registration at Descartes main entrance*

16:15

**Welcome address**

*Jonathan ENRIQUEZ*

**16:30-18:30 Session 1 Host-Microbes interactions**

*Keynote: Dr Paula Watnick*

Associate Professor, Pediatrics, Harvard Medical School; Attending Physician, Medicine, Boston Children's Hospital, USA

How the host listens and responds to the whispers of its intestinal microbiota

*Dr Armel Gallet*

Université Côte d'Azur, CNRS, INRA, ISA, Fr

*Bacillus thuringiensis* bioinsecticide induces developmental defects by disturbing larval gut homeostasis.

*Dr Juliette Schneider*

Institut de biologie moléculaire et cellulaire, University of Strasbourg, Fr

The evolutionarily conserved factor STING regulates a broad antiviral response in drosophila.

*Dr Rouba Jneid*

Faculty of Sciences III and Azm Center for Research in Biotechnology and its Applications, Lebanon

Btk toxins influence progenitor cells fate of intestinal stem cell by modulating cell adhesion

*Théodore Grenier*

IGFL, Ecole Normale Supérieure de Lyon, Fr

Probing the mechanistical basis of nutritional mutualism between host and facultative bacterial commensals using holidic diets in *Drosophila*

**18:30-22:00 Mixer and Dinner on Descartes Site**

***Thursday November 7th***

**9:00-11:00            Session 2 Metabolism**

*Keynote: Pr Ronald Kühnlein*

Institute of Molecular Biosciences; UNIVERSITY OF GRAZ, Austria  
Drosophila storage lipid metabolism – energy management and more?

*Dr Bruno Hudry*

Université Côte d'Azur, CNRS, Inserm, iBV, Fr  
Gut-testis crosstalk controls sex differences in intestinal sugar metabolism to promote food intake and sperm maturation.

*Dr Nathalie Davoust*

LBMC, Ecole Normale Supérieure de Lyon, Fr  
Split-ends confers resistance to paraquat neurotoxicity and modulates glial lipid droplet contents in adult *Drosophila*.

*Mickael Poidevin*

Institute for Integrative Biology of the Cell, Gif-sur-Yvette, Fr  
Nutrient-Activation of S6Kinase Provides Competence for Starvation-Induced Autophagy.

**11:00-11:30 Coffee Break on Buisson Site**

**11:30-13:00 Poster Session 1**

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



***Thursday November 7th***

14:00-15:20      **Session 3 RNA and Transcription**

Keynote: *Pr Ingrid Lohmann*  
COS Heidelberg, University of Heidelberg, Germany  
How Lineages get different: a Hox Perspective

*Solene Vanderperre*  
IGFL, Ecole Normale Supérieure de Lyon, Fr  
Visualization of Hox-Cofactor protein complexes on DNA at the super resolution scale.

*Dr Benjamin Loppin*  
LBMC, Ecole Normale Supérieure de Lyon, Fr  
The Lid/KDM5 histone demethylase complex activates a critical effector of the oocyte-to-zygote transition.

15:20-16:40      **Session 4 Evolution**

Keynote: *Pr Thomas Flatt*  
Department of Biology, University of Fribourg, Fribourg, Switzerland  
The Genomic Basis of Clinal Adaptation

*Dr Natacha Kremer*  
LBBE, UMR CNRS 5558, Université de Lyon, Fr  
Experimental evolution of the Drosophila-Wolbachia symbiosis under oxidative stress and viral infection.

*Dr Abderrahman Khila*  
IGFL, Ecole Normale Supérieure de Lyon, Fr  
Co-option of the pteridine biosynthesis pathway underlies the diversification of embryonic colours in water striders.

16:45-17:15 **Coffee Break on Buisson Site**

17:15-19:00 **Poster Session 2**

***Friday November 8th***

**9:00-11:00            Session 5 Development**

*Keynote: Dr Erika Bach*

New York University School of Medicine, USA

Stem cell-niche interactions: lessons from the *Drosophila* testis.

*Dr Jacques Montagne*

Institute for Integrative Biology of the Cell, Gif-sur-Yvette, Fr

A Fatty Acid anabolic pathway in specialized-cells of female *Drosophila* remotely controls sperm delivery to the oocytes.

*Pr Emmanuèle Mouchel-Vielh*

Institut de Biologie Paris Seine, Sorbonne Université, Fr

Deciphering the gene regulatory network mediating thermal plasticity of abdominal pigmentation in *D. melanogaster*.

*Vincent Loreau*

Aix Marseille University, CNRS, IBDM, Marseille, Fr

Quantifying the impact of titin elasticity on sarcomere architecture during muscle development.

**11:00-11:30 Coffee Break**

**11:30-12:15            Session 6 Behavior**

*Dr Alain Garces*

IGFL, Ecole Normale Supérieure de Lyon, Fr

A GABAergic Maf-expressing interneuron subset regulates the speed of locomotion in *Drosophila*.

*Pr Julien Royet*

Aix Marseille University, CNRS, IBDM, Marseille, Fr

Peptidoglycan sensing by octopaminergic neurons modulates *Drosophila* oviposition.

*Maroua Ferdenache*

Faculty of Sciences, University of Badji Mokhtar Annaba, Algeria

Effects of single larval exposure to azadirachtin and its antifeedant potential on two successive generations.

**12:15-13 :15            Session 7 Disease models**

*Dr Laurent Seugnet*

Centre de recherche en Neurosciences de Lyon, Fr

In search for a link between chronic sleep/wake disorders, endosomes and amino-acids.

*Anissa Souidi*

Université Clermont Auvergne, Fr

Analysis of miR-1 and its potential target Multiplexin deregulated in myotonic dystrophy type 1 (DM1).

*Victor Girard*

LBMC, Ecole Normale Supérieure de Lyon, Fr

Lipid droplet accumulation promotes Alpha-synuclein aggregation in a *Drosophila* model of Parkinson Disease.

*Dr Pierre Dourlen*

INSERM U1167, Institut Pasteur de Lille, Université de Lille, Fr

Isoform-dependent neurotoxicity of the Alzheimer Disease risk factor BIN1 in *Drosophila*.

13:30-14:00 **Lunch on Buisson Site**

14:00-15:20 **Poster Session 3**

15:20-16:40 **Session 8 Developmental Neurobiology**

Keynote: *Dr Matthias Landgraf*

University of Cambridge, England

Regulation of adaptive plasticity in the nervous system by metabolic reactive oxygen species.

*Dr Wenyue Guan*

IGFL, École Normale Supérieure de Lyon, Fr

Establishing a mechanistic relationship between neuronal stem cell identity and progeny motor neurons morphologies.

*Dr Filipe Pinto-Teixeira*

Center for Genomics and Systems Biology, New York University Abu Dhabi, Abu Dhabi, United Arab

Emergence of neural network organization during brain development.

*Dr Caroline Medioni*

Institut National de la Santé et de la Recherche Médicale, Nice, Fr

Identifying new actors of axonal remodeling using *Drosophila* Bursicon neurons.

*Dr Jean-Maurice Dura*

IGH, Université de Montpellier, Fr

The chemokine-like Orion protein is a “find-me/eat-me” signal for glia infiltration during neuronal remodeling.

*Dr Iryna Mohylyak*

Institut du Cerveau et de la Moelle épinière, Fr

Molecular profiling of neuronal circuit development.

18:00-18:50      **Session 9 Cell Biology**

Keynote: *Dr Alain Vincent*

Centre de Biologie Intégrative, Toulouse, Fr

Alary muscles and TARMS, a novel type of striated muscles  
maintaining internal organs positions

19:00-00:00 **Dinner on Descartes Site**

***Saturday November 9th***

9:30-11:00            **Session 9 Cell Biology (continued)**

*Hammed Badmos*

Department of Biochemistry and Centre for Cell Imaging, University of Liverpool, England

Interrogating the requirement of *non-stop* in *Drosophila* border cell migration

*Dr Jérôme Bohère*

University of Cambridge, England

Identifying how intestinal cell fate is controlled by Integrin-mediated mechano-transduction.

*Dr Chantal Roubinet*

MRC-LMCB, UCL, England

Asymmetric nuclear division of fly neural stem cells generates daughter nuclei with distinct identities.

*Dr Hadi Boukhatmi*

Dept of Physiology Development & Neuroscience, U of Cambridge, England

Molecular mechanisms mediating inter-tissue communication and promoting tumorigenesis.

11:00-11:30 **Coffee Break**

11:30-12:00 **34th Annual French Meeting Organisation**

12:00-12:30 **Poster and Talk Prizes**



# Oral Abstracts

# Session 1: Host-Microbes Interactions

**Keynote:** Paula Watnick

Harvard Medical School

How the host listens and responds to the whispers of its intestinal microbiota.

How the host listens and responds to the whispers of its intestinal microbiota  
Bat-Erdene Jugder, Layla Kamareddine, and Paula Watnick Boston Children's Hospital/Harvard Medical School A healthy intestinal microbiota provides resistance against intestinal pathogen invasion, while a dysbiotic microbiota may accelerate the development of chronic metabolic diseases such as obesity and diabetes. At the present time, most of our mechanistic knowledge of the interaction of the microbiota with the host revolves around an understanding of the composition of the intestinal bacterial community and the interactions between these bacteria. We have harnessed the power of the model organism *Drosophila melanogaster* with its extensive and accessible genetic tools to dissect the intestinal innate immune response to commensal microbes at the cellular and genetic levels. These studies describe the paths through which microbial metabolites activate host intestinal innate immunity and provide a mechanistic understanding of the influence of our intestinal microbiota on host metabolic homeostasis and susceptibility to infection. Such studies may lead to the development of therapeutics that restore infection resistance and mitigate chronic metabolic diseases such as diabetes and obesity in hosts that respond inappropriately to their microbiota or are afflicted by dysbiosis



# Session 1: Host-Microbes Interactions

## *Bacillus thuringiensis* bioinsecticide induces developmental defects by disturbing larval gut homeostasis

**Armel Gallet**

Université Côte d'Azur, CNRS, INRA, ISA, France

Bioinsecticides made of the bacterium *Bacillus thuringiensis* (Bt) are the bioinsecticide best sale worldwide. Because of the governmental policies and the public opinion, the use of such products has been exponentially increased during this last decade and this trend is continuing. Among Bt bioinsecticides, those based on the strain Bt var. *kurstaki* (Btk) are widely used in organic farming to fight lepidopteran pests. Although many data have demonstrated the short-term safety of Btk products on non-target animals, only scarce data are available on their unintended long-term effects. Therefore, using the non-target *Drosophila melanogaster* (a diptera), we investigated the putative impacts of the ingestion of environmental doses of Btk products on development. We first showed that Btk products delayed development and impaired growth. We further demonstrated that these effects were mediated by the synergism between Btk bacteria and Btk toxins and were independent of an interference with the commensal flora. We then showed that Btk products disturbed the cellular homeostasis of the midgut, reducing protein digestion. Finally, we showed that larval gut maintained its epithelial barrier function thanks to an incomplete process of regeneration. We assume that this abortive regeneration limits the digestive capacities of the intestine, thus causing a development delay and a growth defect.

# Session 1: Host-Microbes Interactions

## The evolutionarily conserved factor STING regulates a broad antiviral response in drosophila.

**Juliette Schneider**

Institut de biologie moléculaire et cellulaire, University of Strasbourg

Viral infections are a threat to all living organisms who developed diverse mechanisms to control them. Insects evolved powerful systems to fight against viruses, among which the best known is the RNA interference pathway. However, it is now clear that insects also developed other strategies to resist viral infections, including inducible responses. Working on the model organism *Drosophila melanogaster*, we recently discovered a new antiviral pathway involving the ortholog of the well-known mammalian antiviral protein STING (Stimulator of interferon genes). We showed that *drosophila* STING (dSTING) acts upstream of two components involved in the IMD pathway, the kinase IKK $\beta$  and the NF- $\kappa$ B-like transcription factor Relish, to regulate expression of antiviral genes. In mammals, the STING pathway is activated after recognition of DNA by the enzyme cyclic-GMP-AMP-synthase (cGAS), which synthesizes the cyclic dinucleotide (CDN) 2'-3'-cyclicGMP-AMP (2'-3'-cGAMP). This second messenger binds to and activates STING, leading to induction of interferons. We have now identified a CDN that activates the STING-IKK $\beta$ -Relish pathway in *drosophila*. We show that co-injection of this STING agonist together with several viruses belonging to different families results in significantly reduced viral replication. The protective effect of the CDN is abolished in Relish mutant flies, but not in AGO2 and Atg7 null mutant flies, indicating that it does not require RNAi or classical autophagy. Altogether, our results reveal that, besides RNAi, an inducible transcriptional response controlled by STING participates in immunity against a broad range of viruses in flies.

# Session 1: Host-Microbes Interactions

## Btk toxins influence progenitor cells fate of intestinal stem cell by modulating cell adhesion

**Rouba Jneid**

Faculty of Sciences III and Azm Center for Research in Biotechnology and its Applications (Lebanon)

*Bacillus thuringiensis* var *kurstaki* (Btk) is the most used biopesticide around the world. Btk is a Gram-positive soil bacterium. When resources are limited, vegetative Btk cells undergo sporulation, synthesizing a protein crystal during spore formation. Proteins contained in this crystal are called Cry endotoxins. Those proteins were described to be entomopathogenic toward lepidopteran pests. My PhD project aims to study the impacts of Btk on the gut homeostasis of the non-target organism *Drosophila melanogaster*. In the *Drosophila* midgut, Intestinal Stem Cells (ISCs) are required for maintenance of the proper cell composition in the adult intestine. An ISC undergoes asymmetric cell division that generates one ISC itself and one progenitor cell. Then, the level of Notch pathway activation in the progenitor cell will commit it toward enterocyte (at high Notch activation) or enteroendocrine cell (at low Notch activation) differentiation. My work revealed that the number of enteroendocrine cells (EEC) increases after an intoxication by the commercialized form of Btk. I have shown that this EEC increase is dependent on the Cry toxins. I am currently deciphering how Btk induces an increase in EECs and the putative link between Cry toxins and the inhibition of Notch pathway.

# Session 1: Host-Microbes Interactions

## Probing the mechanistical basis of nutritional mutualism between host and facultative bacterial commensals using holidic diets in *Drosophila*

**Théodore Grenier**

Institut de Génomique Fonctionnelle de Lyon (IGFL) Ecole Normale Supérieure de Lyon

Animals have evolved and are living in constant association with microbes. One of the most consequential features of such symbiosis is the optimization of host nutrition, but how symbionts achieve this remains partly elusive. In this study, we mono-associated *Drosophila melanogaster* with strains of its natural bacterial commensals, *Acetobacter pomorum* and *Lactobacillus plantarum*, as a model of facultative nutritional mutualism. Indeed unlike obligate symbiosis, *Drosophila* larvae can survive and develop in the absence of their commensals. However, when they face a nutritional challenge, Germ-Free (GF) larvae show important developmental delay and this delay can be buffered by the activity of *A. pomorum* or *L. plantarum*. To better comprehend the nutritional basis of this beneficial association, we replaced the commonly used laboratory diet based on inactivated yeast and cornmeal flour with a holidic diet, i.e. a diet entirely composed of chemically pure nutrients. This approach enabled us to specifically remove each nutrient and compare the nutritional requirements of germ-free and mono-associated animals. We observed that removing essential amino acids, vitamins, certain metal ions from the diet prevented development of GF larvae. However, the lack of these nutrients could be differentially compensated by each commensal bacteria: *L. plantarum* compensates the lack of only some nutrients, whereas *A. pomorum* compensates the lack of nearly all nutrients tested. We measured the ability of *L. plantarum* and *A. pomorum* to produce these nutrients by two methods: testing bacterial growth in auxotrophic conditions and measuring amino-acid production by high-pressure liquid chromatography. In most conditions, the ability of a symbiont to compensate the lack of a nutrient correlated with its ability to produce this nutrient. This suggests that *L. plantarum* and *A. pomorum* can provide essential nutrients to their host. Moreover, we focused on *L. plantarum* to investigate the mechanisms of its interaction with *Drosophila*. Valine is essential to both *Drosophila* and *L. plantarum*. Therefore *L. plantarum* cannot grow in the absence of Valine and it cannot compensate the effects of the absence of Valine on the host. We manipulated Valine concentration in the holidic diet so that *L. plantarum* could grow, but GF larvae were not able to develop. Surprisingly, in this condition, *L. plantarum* was able to compensate the effect of Valine deficiency on the host. Since *L. plantarum* does not produce Valine, these results bring to light an additional mechanism of compensation of nutrient deficiency that does not rely on the specific nutrient provision to the host. To dissect this mechanism, we are currently performing a genetic screen using a loss-of-function mutants library of *L. plantarum*. Our system therefore provides a powerful model to dissect the nutritional basis of how facultative symbionts shape their animal host's nutrition and development.

## Session 2: Metabolism

### **Keynote: Ronald Kühnlein**

University of Graz

## **Drosophila storage lipid metabolism – energy management and more?**

Storage and mobilization of lipids are evolutionarily conserved cellular processes that are required in all animals to maintain energy and membrane homeostasis in responses to changing developmental and environmental conditions. *Drosophila* engages a distinct set of lipogenic and lipolytic enzymatic activities to control the accumulation and breakdown of lipids at specialized intracellular organelles termed lipid droplets. Dynamic changes in lipid droplet size and number witness an intricate lipid metabolism control at the tissue as well as at the systemic level. However, these regulatory mechanisms are incomprehensively understood; in part because not even all lipolytic and lipogenic enzymes are characterized in the fly.

This lecture will summarize our current knowledge on the regulators and mechanisms of storage lipid homeostasis in the adult fly, which show remarkable similarities but also distinct differences to the control of the corresponding processes in mammals. Moreover, possible roles of neutral lipid metabolism during a non-feeding ontogenetic stage like embryogenesis will be discussed. In this context the maternally deposited lipid pool might be the regulatory hub to orchestrate fueling, cellularization and instructive signaling during morphogenesis due to the interconversion capability of storage lipids, structural lipids and signaling lipids.

## Session 2: Metabolism

### Gut-testis crosstalk controls sex differences in intestinal sugar metabolism to promote food intake and sperm maturation

**Bruno Hudry**

Université Côte d'Azur, CNRS, Inserm, iBV, France (France)

Physiology and metabolism are often sexually dimorphic, but the underlying mechanisms remain incompletely understood. Here, we use the adult intestine of *Drosophila melanogaster* to investigate how gut-derived signals contribute to sex differences in whole-body physiology. Using newly generated genetic and metabolic tools, we find that intestinal carbohydrate handling is male-biased and spatially confined to defined intestinal portions. In contrast to known sexual dimorphisms in invertebrates, the sex differences in intestinal sugar handling are extrinsically controlled by the adjacent male gonad, which activates JAK-STAT signalling in enterocytes within this intestinal portion. Sex reversal experiments uncover key roles for this male-biased intestinal metabolic state in controlling food intake and sperm production through gut-derived citrate. Our work uncovers a novel male gonad-gut axis, and reveals that metabolic communication across organs is physiologically significant. The instructive role of citrate in inter-organ communication may be active in more biological contexts than previously recognized.

## Session 2: Metabolism

### Split-ends confers resistance to paraquat neurotoxicity and modulates glial lipid droplet contents in adult *Drosophila*.

**Nathalie Davoust**

Laboratoire de Biologie et de Modélisation de la Cellule  
Ecole Normale Supérieure de Lyon

Glial cells are early sensors of central nervous system injury and recent reports suggest that lipid droplets expansion in glia might promote cellular communications affecting neuronal integrity. Using *Drosophila* retina to model neuron-glia interactions, we previously identified Spen as a cell survival factor for inter-ommatidial glial cells during retina development. Spen belongs with spenito to the evolutionary conserved SPEN proteins family and is implicated in multiple cellular processes, including neuronal and glial cell fate during nervous system development. Here we studied the role of Spen in a model of Parkinson's disease induced in adult *Drosophila* by systemic exposure to the neurotoxic molecule paraquat. We found that the brain expression of spen mRNA is modulated by paraquat treatment and that flies heterozygous for a spen loss-of-function mutation exhibit an enhanced vulnerability to paraquat-induced neurotoxicity. Importantly, a glial-restricted silencing of spen similarly increased *Drosophila* sensitivity to paraquat, while conversely, an over-expression of spen in glial cells had a protective effect. Interestingly, spen loss-of-function was associated with the accumulation of large lipid droplets in the astrocyte-like glial cellular processes located in the neuropil. We then performed a meta-analysis of microarray data sets comparing substantia nigra tissue samples deriving from Parkinson's disease (PD) patients vs control subjects. We found that SHARP the human spen ortholog, was significantly up regulated in the substantia nigra of PD patients along with a number of genes involved in lipid metabolism and fatty acid elongation. Altogether, our results highlight the importance of lipid metabolism and lipid droplet formation in glia during neurodegenerative processes.

## Session 2: Metabolism

### Nutrient-Activation of S6Kinase Provides Competence for Starvation-Induced Autophagy

**Mickael Poidevin**

Institute for Integrative Biology of the Cell, Gif-sur-Yvette, France

Animal physiology adjusts to environmental variations with periods of food abundance and scarcity. Nutrients activate the mechanistic-Target-of-Rapamycin (mTOR) to promote cellular growth and to impede autophagy, a recycling process induced by fasting to maintain homeostasis. Conversely, downregulation of mTOR induces autophagy and dephosphorylation of its downstream effector target S6Kinase. Previous studies reported that *Drosophila*S6Kinase(dS6K) mutants are disabled for fasting-induced autophagy, suggesting that kinase-inactive dS6K is required for autophagy. However, we observed that kinase-active—but not inactive—dS6K is required for autophagy. dS6K is dispensable during the autophagic process, but is required prior to nutrient deprivation, suggesting that a nutritional phase integrated through S6K must precede fasting so that cells undergoing autophagy contain nutrient stores. We identified a dS6K downstream target that mediates this yet unknown process. The mechanism of this novel regulatory loop will be presented.



# Session 3: RNA and Transcription

## **Keynote: Ingrid Lohmann**

University of Heidelberg

## How Lineages get different: a Hox Perspective

A central dogma in biology is that transcription factors (TFs) control cell fates by precisely orchestrating spatiotemporal gene expression programs. However, how individual TFs promote cell type diversity with high precision remains unclear. We use Hox TFs as a model to explore how a single TF specifies multiple cell types. To this end, we study Ultrabithorax (Ubx) in two tissue lineages, the mesodermal and neuronal lineages, using transcriptomic, epigenetic and proteomics approaches. Building on the hypothesis that functional diversity emerges from specific protein interactions, we systematically identified Ubx interactomes *in vivo* using proximity dependent Biotin IDentification (BioID) in *Drosophila* embryos. We find that Ubx interacts with largely non-overlapping sets of proteins in each tissue lineage. Among the lineage restricted interactors only few have cell-specific RNA expression or were annotated as TFs. Instead the majority of Ubx interactors are components of protein complexes active in many cell types. Intriguingly, regulators controlling gene expression at multiple levels, ranging from chromatin remodelling to the initiation of translation, were over-represented. Even more important, despite their general function and broad expression, genetic interaction assays *in vivo* confirm that these regulators act with Ubx in a strictly lineage- and process-specific manner. Thus, functional specificity of Ubx seems to play out at several regulatory levels and to result from a controlled restriction of its promiscuous interaction potential by the cellular environment. By studying one of the interactions in more detail, we discovered that Ubx stabilizes binding of the Polycomb complex to specific chromatin sites, which we show to be critical for the repression of alternative fate gene expression and thus the maintenance of lineage identity. As the Hox code is preserved throughout the lifecycle, our data indicate that the Hox mediated suppression of multipotency encoded in the genome could set a life-long block to trans-differentiation in adult cells.

## Session 3: RNA and Transcription

### Visualization of Hox-Cofactor protein complexes on DNA at the super resolution scale

**Solene Vanderperre**

Institut de Génomique Fonctionnelle de Lyon (IGFL), ENS de Lyon

Analysing live organisms tends to push the limits of the resolution in fluorescence microscopy. Nowadays, it is possible to reach the nanometric scale in this field thanks to the work of Eric Betzig and William Moerner. This advanced microscopy is called «super-resolution microscopy» (SR microscopy) and allows the visualization of single fluorescent molecules. By using particular fluorescent proteins it enables the quantification and/or the tracking of those individual molecules in live cells and tissues. Achieving this high resolution is promising to study more in details structural features but also gene regulation. In our team, we aim to explain how Hox proteins (a family of developmental transcription factors) cooperate with cofactors to regulate their specific target genes. The goal of my PhD project is to directly visualize Hox-cofactor single complexes at a specific genomic locus. In this perspective, I am developing Photo-Activated-Bimolecular-Fluorescent-Complementation (PA-BiFC) to reveal Protein-Protein Interactions (PPIs) with SR microscopy and reach the nanoscale binding of Hox-cofactor complexes on specific enhancers. Moreover, to tackle the question in vivo, I adapted the Int/ParB system for SR. Combining PA-BiFC with the Int/ParB system should allow us to quantify a specific enrichment of Hox-cofactor complexes on specific target enhancers.

## Session 3: RNA and Transcription

### The Lid/KDM5 histone demethylase complex activates a critical effector of the oocyte-to-zygote transition

**Benjamin Loppin**

Laboratoire de Biologie et de Modélisation de la Cellule  
Ecole Normale Supérieure de Lyon

Following fertilization of a mature oocyte, the formation of a diploid zygote involves a series of coordinated cellular events that ends with the first embryonic mitosis. In animals, this complex developmental transition is entirely controlled by maternal gene products. How such a crucial transcriptional program is established during oogenesis remains poorly understood. Here, we have performed a shRNA-based genetic screen in *Drosophila* to identify genes required to form a diploid zygote. We found that the Lid/KDM5 histone demethylase and its partner, the Sin3A/Rpd3 deacetylase complex, are necessary for sperm nuclear decompaction and karyogamy. Surprisingly, our transcriptomic analyses revealed that these histone modifiers are required for the massive transcriptional activation of deadhead (dhd), which encodes a maternal thioredoxin involved in sperm chromatin remodeling. We propose that Lid/KDM5 and Sin3A cooperate to establish a local chromatin environment compatible with the unusual expression of Dhd, a key effector of the oocyte-to-zygote transition.

## Session 4: Evolution

**Keynote:** Thomas Flatt

University of Fribourg

### The Genomic Basis of Clinal Adaptation

One of the central goals of evolutionary genetics is to understand how organisms adapt to environmental heterogeneity. A promising approach towards this end is to investigate systematic, gradual phenotypic and genotypic changes along environmental (e.g. climatic) gradients, so-called clines, which are thought to be driven by spatially varying selection. Over the past 7 years we have been using next-generation sequencing, population genetics and laboratory assays to identify and characterize candidate genes and polymorphisms that might contribute to variation in fitness-related (life-history) traits among populations of the fruit fly, *Drosophila melanogaster*, situated along a latitudinal cline spanning the North American east coast. Our genomic analyses suggest that spatially varying selection is pervasive and acts on numerous loci and pathways, with many candidates implicated in life-history regulation and exhibiting parallel differentiation along the parallel Australian cline. In my talk, I will focus on our recent work on two clinal polymorphisms, namely an inversion polymorphism that harbors an excess of clinal SNPs and a clinal allele in the insulin signaling transcription factor *foxo*. In both cases we have experimental evidence that both polymorphisms make a causative contribution to the observed phenotypic clines in fitness-related traits.

## Session 4: Evolution

### Experimental evolution of the *Drosophila*-*Wolbachia* symbiosis under oxidative stress and viral infection.

**Natacha Kremer**

Laboratoire de Biométrie et Biologie Evolutive, UMR CNRS 5558, Université de Lyon

Animals are living in symbiosis with tightly regulated bacterial communities that can strongly impact their phenotype. Indeed, while bacteria were classically associated with pathogenesis, recent work on microbiota shows that they can also benefit to their host, notably by providing nutrients or protection against infection by other pathogens. For instance, the maternally-inherited bacterium *Wolbachia* is known to interfere with RNA-viruses replication and is currently used in biological control against viruses such as zika or dengue virus, transmitted by mosquitoes. However, the mechanisms by which *Wolbachia* protects its host and the potential evolution of the *Wolbachia*-virus-insect interaction are still unclear. Symbiotic associations also face stressful situations, such as temperature shifts or exposure to pesticides. These stresses may impact the host directly, but also impact the host extended phenotype, through an alteration of the symbiotic community. It is thus important to study the evolution of symbiotic associations after stress exposure to determine how they can adapt to new environments, and if symbiosis will favor or constraint the adaptive process. To tackle these questions, we performed experimental evolution of flies, infected or not by *Wolbachia*, under different stress conditions (oxidative stress and/or infection by the *Drosophila C* virus) for 24 generations. We will present the impact of these stresses on the physiology of both partners by measuring various life-history traits, directly after stress or all during the experimental selection process. Experimental evolution may also help to identify mechanisms under selection, and highlight mechanisms involved in the response to stress(es), including those involved in host immunity or competition. In the context of the use of *Wolbachia* in vector-control strategies, understanding better the mechanisms of interaction, but also the influence of environmental changes on the regulation of symbiosis, may help to improve our way to manage infectious disease, notably vector-borne diseases.

## Session 4: Evolution

### Co-option of the pteridine biosynthesis pathway underlies the diversification of embryonic colours in water striders

**Abderrahman Khila**

Institut de Génomique Fonctionnelle de Lyon (IGFL), ENS de Lyon

Naturalists have been fascinated for centuries by animal colours and colour patterns. While widely studied at the adult stage, we know little about colour patterns in the embryo. Here we study a new trait consisting of colouration that is specific to the embryo and absent from post-embryonic stages in water striders (Gerromorpha). By combining developmental genetics with chemical and phylogenetic analyses across a broad sample of species, we uncovered the mechanisms underlying the emergence and diversification of embryonic colours in this group of insects. We show that the pteridine biosynthesis pathway, which ancestrally produces red pigment in the eyes, has been recruited during embryogenesis in various extra-ocular tissues including antennae and legs. In addition, we discovered that this co-option is common to all water striders and initially resulted in the production of yellow extra-ocular colour. Subsequently, six lineages evolved bright red colour and two lineages lost the colour independently. Despite the high diversity in colours and colour patterns, we show that the underlying biosynthesis pathway remained stable throughout the 200 million years of Gerromorpha evolutionary time. Finally, we identified erythropterin and xanthopterin as the pigments responsible for these colours in the embryo of various species. These findings demonstrate how novel traits can emerge through the activation of a biosynthesis pathway in new developmental contexts.

## Session 5: Development

**Keynote:** Erika Bach

New York University School of Medicine

### Stem cell-niche interactions: lessons from the *Drosophila* testis.

My lab is focused on understanding stem cell-niche interactions, and we use the *Drosophila* testis as a model. This tissue has a dedicated niche consisting of 12 quiescent somatic cells that supports germline stem cells (GSCs), which ultimately produce sperm, and somatic cyst stem cells (CySCs), which support GSCs and produce somatic support cells. Since GSCs transmit genetic information to the next generation, GSCs with a competitive advantage could promote their biased inheritance in offspring. This may underlie human paternal age effect disorders, but no experimental models exist to test this. We have identified a mutation in the gene *chinmo* that when homozygous mutant endows the mutant GSC with a competitive advantage. Overtime the *chinmo*-mutant GSC and its descendants cause the expulsion of all wild-type GSCs from the niche. Our work shows that these competitive *chinmo*-mutant GSCs remodel the niche to their advantage by secreting the heparin sulfate proteoglycan Perlecan (Pcan) into the niche milieu. This leads to the formation of an ectopic extracellular matrix around the endogenous niche, which causes the loss of wild-type GSCs. The *chinmo*-mutant GSCs remain in this remodeled niche because they upregulate Pcan-binding proteins. Moreover, when wild-type GSCs are supplied with increased Pcan-binding proteins, they, too, can stay in the altered niche and are no longer out-competed. Finally, the *chinmo*-mutant allele is inherited in a biased manner at super-Mendelian frequencies.

Niches provide a distinct microenvironment for stem cells through the production of short-range self-renewal cues that promote 'stemness' in the resident populations. However, whether stem cells also secrete signals that reciprocally maintain the niche remains an intriguing question. Prior work has shown that genetic ablation of all CySCs in the *Drosophila* testis causes niche cells to exit quiescence and transdifferentiate into CySCs (Hetie, *Cell Reports* 2014). This study demonstrated that CySCs non-autonomously maintain niche cells, but the identity of the factors that regulate this process are still not known. We find that the secreted Activin antagonist Follistatin (Fs) is expressed in CySCs, and its depletion from CySCs causes the progressive and complete loss of niche cells, followed by a loss of all GSCs and catastrophic collapse of spermatogenesis. These data indicate that CySC-produced Fs protects niche cells from local Activin ligands. Consistent with this finding, autonomous stimulation of Activin signaling in niche cells causes all of them to transdifferentiate into fully functional CySCs. We show that in CySCs, expression of *Fs* is positively regulated by the Dp/E2f1 transcription factor complex. Depletion of Dp/E2f1 from CySCs results in the non-autonomous loss of all niche cells. Importantly, ectopic mis-expression of *Fs* in CySCs depleted for Dp/E2f1 prevents the niche-loss phenotype. Thus, TGF $\beta$ /Activin signaling in niche cells triggers a regenerative response to replenish lost CySCs, at the cost of reducing the niche population.

## Session 5: Development

### A Fatty Acid Anabolic Pathway in Specialized-Cells of Female *Drosophila* Remotely Controls Sperm Delivery to the Oocytes

**Jacques Montagne**

Institute for Integrative Biology of the Cell, Gif-sur-Yvette, France

Fitness of multicellular species depends on cooperative activities between specialized organs to adjust homeostasis, animal behavior and reproductive functions. Meeting mates is a critical issue for sexual reproduction that requires specific courtship behavior and pheromonal signals between individuals of the same species. In *Drosophila melanogaster*, the pheromones derive from fatty acids produced in specialized cells called oenocytes. After mating, sperm transferred from males remains in the female genital tract, where its survival duration greatly varies amongst species. Mating also elicits behavioral and physiological changes in females that converge to favor their offspring. In well-fed fertilized *Drosophila* females, eggs are continuously produced and spermatozooids stored in female spermathecae and seminal receptacle are synchronously delivered to fertilize the oocytes. A neuromodulator-dependent regulatory loop previously described in *Drosophila*, controls both spermatozoid delivery and egg laying, implying that these processes are coordinated. Here, we identified a set of lipid-anabolic enzymes required in the oenocytes for the synthesis of a peculiar fatty acid that controls spermatozoid delivery. Oenocyte knockdown of this metabolic pathway resulted in female sterility due to sperm retention. Our study supports the notion that oenocytes coordinate reproductive functions through lipid-dependent signals including a pheromone-independent regulatory loop that controls spermatozoid release from storage organs in *Drosophila* female.



## Session 5: Development

### Deciphering the gene regulatory network mediating thermal plasticity of abdominal pigmentation in *Drosophila melanogaster*

**Emmanuèle Mouchel-Vielh**

Institut de Biologie Paris Seine, Sorbonne Université

Phenotypic plasticity is the ability of a given genotype to produce different phenotypes in response to distinct environmental conditions. This phenomenon is widespread and has major implications, notably in medicine or agronomy. It is often an adaptation to fluctuating and predictable environmental conditions such as seasonal variations. Furthermore, phenotypic plasticity is thought to facilitate evolution, as it broadens the range of phenotypes produced by a given genotype. As a model of phenotypic plasticity, we study the posterior abdominal pigmentation of *Drosophila melanogaster* females. This trait is temperature sensitive, as females are darker when raised at 18°C than 29°C. Our previous studies showed that temperature dramatically modulates the expression of tan and to a lesser extent those of yellow and Ddc, all three genes encoding pigmentation enzymes [1,2]. We have already identified some of the actors and molecular mechanisms involved in tan thermal plasticity, such as the modulation of the active histone mark H3K4me3 on its promoter or its repression by the Bab transcription factor, whose expression is also modulated by temperature [2,3]. Our goal is now to identify the whole gene regulatory network responsible for this difference of pigmentation in response to temperature. To do so, we have performed a genetic screen to identify transcription factors and chromatin regulators involved in the establishment of abdominal pigmentation. The second step will be to identify, among these genes, those involved in thermal plasticity of abdominal pigmentation. Results of this screen as well as preliminary study of some candidate genes identified by the screen will be presented.

## Session 5: Development

### Quantifying the impact of titin elasticity on sarcomere architecture during muscle development

**Vincent Loreau**

Aix Marseille University, CNRS, IBDM, Marseille, France

Sarcomeres are the force producing molecular machines of muscles. Each sarcomere consists of a quasi-crystalline assembly of cross-linked parallel actin filaments with bipolar myosin filaments, both of which are linked by gigantic titin molecules. Members of the titin family are essential for sarcomere formation across evolution and are proposed to determine sarcomere length by spanning from the sarcomeric Z-disc to the M-band. While this titin ruler model is well supported for mammalian sarcomeres, titin isoforms in insects are shorter and thus may not simply rule sarcomere length. Here, we are investigating the two *Drosophila* titin homologs Sallimus and Projectin, both of which are essential for the formation of sarcomeres in *Drosophila*. Using CRISPR-based genome engineering we modified the large elastic PEVK (Pro-Glu-Val-Lys) domains, which act as molecular springs within the I-band of sarcomeres. Interestingly, we find that reducing the PEVK domain length by half results in viable animals with functional muscles. Yet, these muscles display a shorter sarcomere length, surprisingly caused by length reduction of both I-band and A-band. This suggests that titin elasticity in the I-band region generates a mechanical feedback impacting A-band organization. In conclusion, our work demonstrates that the titin elastic PEVK domains determine sarcomere length across animal evolution using a biomechanical rather than a simple ruler mechanism.

## Session 6: Behavior

### A GABAergic Maf-expressing interneuron subset regulates the speed of locomotion in *Drosophila*

**Alain Garces**

Institut de Génomique Fonctionnelle de Lyon (IGFL), ENS de Lyon

Interneurons (INs) coordinate motoneuron activity to generate appropriate patterns of muscle contractions, providing animals with the ability to adjust their body posture and to move over a range of speeds. In *Drosophila* larvae several IN subtypes have been morphologically described and their function well documented. However, the general lack of molecular characterization of those INs prevents the identification of evolutionary counterparts in other animals, limiting our understanding of the principles underlying neuronal circuit organization and function. Here we characterize a restricted subset of neurons in the nerve cord expressing the Maf transcription factor Traffic Jam (TJ). We found that TJ<sup>+</sup> neurons are highly diverse and selective activation of these different subtypes disrupts larval body posture and induces specific locomotor behaviors. Finally, we show that a small subset of TJ<sup>+</sup> GABAergic INs, singled out by the expression of a unique transcription factors code, controls larval crawling speed.

## Session 6: Behavior

### Peptidoglycan sensing by octopaminergic neurons modulates *Drosophila* oviposition.

**Julien Royet**

IBDM, Marseille

Since eukaryotes live in an environment heavily contaminated by microorganisms, it is not surprising that they have forged, over the times, extremely complex and intimate relationships. It is also expected that eukaryotes have developed mechanisms to perceive the presence of bacteria and to adapt their immune response, their physiological status or even their compartment accordingly. Many reports have shown that bacteria can interact with eukaryote nervous system, either for the benefit of the microbe that alters the host's behavior or to the benefit of the host that adapts its behavior to the infection. However, in most cases, the molecules and mechanisms underlying the dialog between bacteria and their host nervous system were not identified and their mode of action poorly understood. I will present our latest data dissecting the cellular and molecular mechanisms by which one single microbiota-derived compound, called peptidoglycan, influences the behavior of infected hosts by directly acting on some specific brain neurons.

## Session 6: Behavior

### Effects of single larval exposure to azadirachtin and its antifeedant potential on two successive generations of *Drosophila melanogaster*

**Maroua Ferdenache**

Laboratory of Applied Animal Biology Department of Biology, Faculty of Sciences, University of Badji Mokhtar Annaba, Algeria.

Among the plant derived product, azadirachtin, a neem-based insecticide with board mode of action including deterrent and antifeedant effects. If considerable progress on the physiological and biological activities and agricultural application of azadirachtin has been achieved, its exact mechanism of action remains uncertain. In the present study, the lethal and sublethal behavioral effects of azadirachtin on food choice selection and consumption in *D. melanogaster* were evaluated in two consecutive generations, parental (P:exposed) and first generation (F1: non-exposed). Azadirachtin was applied topically at two doses LD25(0.28 $\mu$ g) and LD50 (0.67 $\mu$ g) on early third instar larvae. Different concentrations of azadirachtin solution (0.1 $\mu$ g, 0.25 $\mu$ g and 1 $\mu$ g) mixed with sugar (30mM of sucrose) were used. Our results demonstrate dazadirachtin reduced significantly flies consumption only for P generation as compared as control. In addition, previously treated flies preferentially consume sugar rather than azadirachtin mixed with sugar. Choice food assays showed a clear preference of all tested flies (treated and control) of both generations for less concentrated solution of azadirachtin than the high stone. However, the antifeedant activity were increased with increasing concentration. our results revealed that the antifeeding effect of azadirachtin was more marked in the previously treated flies compared to “naïve” flies, suggesting that previous experience may affects feeding behavior of adults of *D. melanogaster*. This finding suggests a long term antifeedancy action which may reinforce behavioral avoidance of azadirachtin and contribute as push-pull strategies in integrated pest management programs using antifeedants as a safer alternative crop protectant.

## Session 7: Disease Model

### In search for a link between chronic sleep/wake disorders, endosomes and amino-acids

**Laurent Seugnet**

Centre de recherche en Neurosciences de Lyon (CRNL) (France)

Narcolepsy is a lifelong disease characterized by excessive daytime sleepiness and sleep/wake instability. To reveal genes involved in the cellular mechanisms of the disease, we conducted a transcriptomic analysis in a mouse model of narcolepsy. We then used the flexible genetic tools of *Drosophila* to functionally assess the role of a subset of the differentially expressed genes in sleep/wake regulation. This led us to focus on pallidin, which encodes a lysosomal protein known to regulate the trafficking of cellular transporters. In *Drosophila*, this gene is required in surface glia for proper sleep/wake regulation and may facilitate the transport of amino-acids involved in monoamine synthesis. Surface glia constitutes the *drosophila* hemolymph-brain barrier, and controls nutrients access to the brain. In narcoleptic mice, pallidin is massively upregulated in the brain, including cells of the Blood-Brain-Barrier, and is associated with significant changes in monoaminergic systems.

## Session 7: Disease Model

### Analysis of miR-1 and its potential target Multiplexin deregulated in myotonic dystrophy type 1 (DM1)

**Anissa Souidi**

Université Clermont Auvergne

Myotonic dystrophy type 1 (DM1) is an autosomal dominant, multisystemic disease, caused by an expansion of CTG repeats in 3'-untranslated region of the *dystrophia myotonica protein kinase gene* (DMPK), and leading to conduction defects, dilated cardiomyopathy and cardiac arrhythmias. Healthy individuals have 5 to 37 CT repeats. Whereas, DM1 patients carry from >50 to ≈4,000 CTG repeats. The mutated Dmpk transcripts sequesters MBNL1 (Muscleblind-like1) and stabilizes CELF1 (Elav-Like Factor1), two alternative splicing factors that bind to 3'UTR of their target genes. MBNL1 regulates the maturation of miR-1, muscle and heart-specific microRNA, conserved between *Drosophila* and human, involved in cardiogenesis, decreased in DM1 context. In our study, we used *Drosophila* model to perform a functional analysis of miR-1 and its potential target multiplexin (Mp) (Collagen XV/XVIII in mammals), deregulated in DM1. First, we analyzed the expression of Mp in DM1 context by immunostaining. Then, we tested Mp gain of function effects on cardiac structure and physiology by the Semi-intact Optical Heartbeat Analysis (SOHA) approach. Second, we analyzed miR-1 loss of function effects on cardiac structure and physiology and on Mp expression. Finally, we tested the rescue of heart tube dilatation observed in DM1 context by inhibiting Mp. Our results show an increase of Mp in DM1 context. Mp overexpression leads to dilated cardiomyopathy and to arrhythmias with slow-down heartbeat. Mp inhibition rescues dilated cardiomyopathy observed in DM1 context. Finally, miR-1 loss of function in heart causes dilated cardiomyopathy and an increase in Mp, similar to DM1 symptoms. Actually, we are testing the direct regulation of Mp by miR-1 in vivo using GFP-Mp 3'UTR transgenic *Drosophila* reporter lines. Overall, our data suggest that DM1 associated dilated cardiomyopathy is due to a reduced level of miR-1 and concomitant up-regulation of Mp, a miR-1 target.

## Session 7: Disease Model

### Lipid droplet accumulation promotes Alpha-synuclein aggregation in a *Drosophila* model of Parkinson Disease

**Victor Girard**

Laboratoire de Biologie et de Modélisation de la Cellule  
Ecole Normale Supérieure de Lyon

Lipid metabolism dysregulation has been reported in neurodegenerative disorders such as Alzheimer and Parkinson's diseases (PD). Recent studies including ours suggest that lipid storage organelles (lipid droplets, LD) accumulate and function not only as lipid stores but also as dynamic regulators of the neuronal stress response. PD is characterized by neuronal accumulation of alpha-synuclein (aSyn) aggregates and locomotor dysfunction. Recent evidences indicate that aSyn expression leads to the accumulation of LD in yeast cells and mammalian cell culture. However, the mechanism by which aSyn expression leads to the accumulation of LD remains elusive. Here, we use a *Drosophila* model in which aSyn is expressed in photoreceptor-neurons to further elucidate LD and aSyn interactions in vivo. We show that expression of human aSyn induces progressive accumulation of triacylglycerol and LD, revealed by lipidomic profiling and imaging analyses of *Drosophila* retina. Interestingly, LD accumulation does not require dFatpormidway (*dgat1*) suggesting that aSyn promotes LD independently of *de novo* lipid synthesis. Finally, we found that genetic ablation of LD regulates the levels of age-dependent aSyn aggregation. Taken together our results suggest that the accumulation of LD induced by aSyn expression contributes to the progression of PD.



## Session 7: Disease Model

### Isoform-dependent neurotoxicity of the Alzheimer Disease risk factor BIN1 in *Drosophila*

**Dourlen Pierre**

INSERM U1167, Institut Pasteur de Lille, Université de Lille

Using genome-wide association studies, BIN1 was identified as the most important genetic risk gene for Alzheimer's Disease (AD) after APOE. BIN1 has more than 10 isoforms and the contribution of BIN1 and its isoforms to AD pathogenesis remains unclear. The aim of this work was to assess the neurotoxicity of BIN1 isoforms. We generated *Drosophila* transgenic lines expressing 3 representative BIN1 isoforms, brain isoform1, muscular isoform8 and ubiquitous isoform9. We analyzed the neurotoxicity of BIN1 isoforms using cornea neutralization, immunofluorescence, electrophysiology and electron microscopy in the fly eye. We showed that expression of the different human BIN1 isoforms during eye development (GMR driver) induced dose-dependent rhabdomere morphogenesis defects, phenocopying *Drosophila* BIN1, called amph, and suggesting functional evolutionary conservation. Adult eye-specific expression of the brain BIN1 isoform 1 (Rh1 driver) resulted in an age-dependent loss of photoreceptor neurons. Interestingly, this effect was isoform-specific and required the CLAP domain of BIN1 isoform1. On electroretinograms, although not affected in young flies, expression of BIN1 isoform1 affected synaptic transmission and phototransduction with age. Photoreceptor neurodegeneration was characterized by a strong vacuolization at the ultrastructural level with early and late endosomal markers and could be rescued by modulators of the intracellular vesicular trafficking. Of note, endosome enlargement is one of the first cytopathological markers of Alzheimer disease. Altogether, our results reveal that human BIN1 isoform1 can be neurotoxic in adult *Drosophila* photoreceptor neurons. They suggest it originates from an alteration of the intracellular vesicular trafficking. Finally they support a role for BIN1 in AD pathogenesis.

## Session 8: Developmental Neurobiology

### **Keynote: Matthias Landgraf**

University of Cambridge

### Regulation of adaptive plasticity in the nervous system by metabolic reactive oxygen species

Neurons are inherently plastic, and in response to changes in activity adjust their electrical and transmission properties, as well as the size of their synaptic terminals and numbers of synaptic connections. Such adjustments are usually homeostatic. We recently identified metabolic reactive oxygen species (ROS) as signals that are necessary for activity-regulated plasticity in the developing nervous system in *Drosophila*. For example, activity-regulated ROS signalling leads to structural changes in terms of synaptic terminal size and synapse number. We also find ROS directing adjustments of synaptic transmission at the neuromuscular junction. At the circuit level, ROS signalling is required for network adjustment, with disturbances in ROS levels leading to maladaptive networks, manifested by changes in behaviour and network stability. Interestingly, different sub-cellular sources of ROS regulate distinct aspects of activity-dependent plasticity. For example, ROS generated at the plasma membrane by NADPH oxidases regulate the growth of pre- and postsynaptic terminals via DJ-1 $\beta$ -PTEN-PI3Kinase signalling; while mitochondrial ROS determine changes in synapse number. Intriguingly, pre- versus postsynaptic terminals seem to use distinct NADPH oxidases (Nox and Duox).

## Session 8: Developmental Neurobiology

### Establishing a Mechanistic Relationship between Neuronal Stem Cell Identity and Progeny Motor Neurons Morphologies

**Wenyue Guan**

Institut de Génomique Fonctionnelle de Lyon, ENS de Lyon

Locomotion is essential for animal survival. *Drosophila* locomotion requires the coordinated excitation of muscles by motor neurons (MNs). In *Drosophila*, each of the six legs is innervated by 50 MNs having a unique morphology that is highly stereotyped between animals. Here, we propose to understand how single MNs acquire their morphologies by dissecting their transcriptional program. All these unique MNs are derived from 11 stem cells, called neuroblasts (NBs). Among these 11 stem cells, one (Lin A NB) generates 29 MNs while another (Lin B NB) generates 7 MNs. Previous study has shown that each of the 7 Lin B MNs expresses a combinatorial code of morphological transcription factors (mTFs) specifying its unique morphology. We have recently demonstrated that a unique transcription factor (TF) code for a given MN is also true for the 29 MNs generated by Lin A NB. How the huge amount of TF code diversity is generated? Two groups of TFs identified in NBs, termed spatial and temporal selectors, defining their spatial and temporal identities and contribute to changes of their progeny identity to generate neuronal diversity. We hypothesize that spatial/temporal selectors control the expression of mTF codes, which in turn control individual motor neuron morphology.

## Session 8: Developmental Neurobiology

### Emergence of neural network organization during brain development

**Filipe Pinto-Teixeira**

Center for Genomics and Systems Biology, New York University Abu Dhabi,  
Abu Dhabi, United Arab

What developmental strategies do nervous systems use to wire complex circuits? Neural circuit assembly requires coordination between distinct processes: the specification of neural identities, their numbers, and the precise wiring between these neurons. It is accepted that the identity of a neuron is tightly linked to its connectivity, however we do not yet understand how each determines the other, nor by which mechanisms. In both vertebrates and invertebrates, visual input from the retina is mapped onto the brain so that neighboring points in space are represented as neighboring regions on the retinotopic map. In the *Drosophila* optic lobes, information from each of 800 ommatidia is processed in distinct ganglia, themselves subdivided into 800 stereotypical matching retinotopic columns. In the developing optic lobes, d-IPC neuroprogenitors transit through two competence windows to first produce C&T neurons, and then the 8 subtypes of motion sensing direction selective T4/T5 neurons. Importantly, each matching retinotopic column is enervated by one of each C/T neurons and by each one of the 8 subtypes of T4/T5 neurons. We found that single neuroprogenitors divide to produce clonally related C/T and T4/T5 neurons with the correct stoichiometry and retinotopic matching among all optic lobe ganglia. We show that the neurogenic program installed in each neuroprogenitor simultaneously establishes neuronal identities and retinotopic organization with spatial, and numerical precision. We show that neuronal diversity and circuit formation are established by the same mechanism which depends on neuronal birth order and neuroprogenitor division pattern. Our work provides an example of how complex hardwired neuronal circuits can be built from simple developmental rules. These results will be presented as an entry point to discuss how the establishment of connectivity within a neural circuit can only be fully understood in its developmental context.

## Session 8: Developmental Neurobiology

### Identifying new actors of axonal remodeling using *Drosophila Bursicon* neurons

**Caroline Medioni**

Institut National de la Santé et de la Recherche Médicale, Nice, France.

During brain maturation, neurons undergo extensive remodeling and change their morphology, in particular by reorganizing their dendrites and axons, to integrate into mature functional neuronal networks. In human, this process is much employed during early development as well as at puberty. Furthermore, neuronal remodeling is altered in many pathologies or mental disorders such as Autism and Schizophrenia. To date, however, the mechanisms underlying the different steps of neuronal remodeling are still poorly understood. Here, we focused on axonal remodeling and looked for new actors involved in this process *in vivo*, using *Bursicon* neurons located in the *Drosophila* central nervous system. These neurons are born during embryogenesis, and undergo extensive remodeling during metamorphosis, including a strong reorganization of their terminal axonal arbors. Interestingly, defective remodeling of *Bursicon* neurons leads to external phenotypes easy to observe, such as wing expansion defects, cuticle tanning and head eversion problems. In this system, we have observed strong wing expansion defects when inhibiting the function of the RNA binding protein *Imp*, suggesting that *imp* may control axonal remodeling, as described in gamma mushroom body neurons. To identify functional interactors of *imp*, we are starting a “modifier” screen in which the dosage of all fly genes will be altered, in a context where *imp* function is impaired via RNAi. To this end, we are taking advantage of available collections of deficiencies uncovering 98% of the genome. Genes coding for molecules identified in the laboratory as potential *Imp* partners via mass spectrometry experiments will be particularly studied first. With this work, we hope to improve our knowledge on the molecular and cellular mechanisms underlying neuronal remodeling in a living organism.

## Session 8: Developmental Neurobiology

### The chemokine-like Orion protein is a “find-me/eat-me” signal for glia infiltration during neuronal remodeling

**Jean-Maurice Dura** IGH, Université de Montpellier

The remodeling of neurons is a conserved fundamental mechanism underlying nervous system maturation and function. Developmental axon pruning of mushroom body (MB)  $\gamma$ neurons occurs by a degenerative mechanism during metamorphosis in *Drosophila*. The glia surrounding the MB has an active role in the process; blocking glia infiltration into the MBs prevents remodeling. It has been widely proposed that a signal emanating from the degenerating  $\gamma$ neurons is necessary for glia infiltration. However, the nature of this long sought-after glial recruitment signal is unknown. We performed an EMS mutagenesis screen based on an adult MB  $\gamma$ axon pruning defect. We have identified a new neuronal gene, that we name orion, which is required non-cell autonomously, for MB  $\gamma$ axon pruning. We identified a missense mutation (orion1) with a clear and highly penetrant  $\gamma$ axon pruning defect phenotype. We have also produced a CRISPR/Cas mutation in the orion gene that deletes the common domain (orion $\Delta$ C) which displays the same pruning phenotype as orion1. The presence of a debris clearance defect in the mutant is strongly indicative of a defect in glial cell activity. Interestingly, at 6h after puparium formation (APF), no glia infiltration is detected on MB axons of mutant brains unlike in the wild type. Rescue and RNAi experiments indicated that orion expression is required in the MBs and not in the glia. Orion encodes two likely secreted isoforms as evidenced by the presence of signal peptides at their amino-termini. In addition, Myc-tagged Orion protein expressed in 6h APF MB showed Orion secretion on both the tip and the hole-like structures of the  $\gamma$ bundle, where Orion colocalizes with glial membranes. Orion bears some chemokine features, i.e. a CX3C motif. Chemokines are a family of chemoattractant cytokines and CX3C, in particular, is involved in neuron-glia communication suggesting that both isoforms likely act as signaling molecules. Supporting this view, we observed that the removal of the signal peptide or the change of the CX3C motif into CX4C or AX3C blocked the Orion function necessary for the MB pruning. Glycosaminoglycans (GAGs) belong to a family of highly anionic polysaccharides that occur both at the cell surface and within the extracellular matrix. All chemokines bind to GAGs, ensuring that these signaling proteins are presented at the correct site and time in order to mediate spatially and temporally defined specific function. We identified, in the common part of Orion3 typical GAG binding consensus sequences, that are required for its function. We propose that the Orion proteins are members of the proposed, but still not identified, “find-me/eat-me” class of signals sent by the degenerating  $\gamma$ neurons that promote the glial infiltration required for  $\gamma$ axon pruning. We hypothesize, and are looking for, an as-yet-undefined Orion receptor on the surface of the glial cells. The study of the role of these novel proteins should help to decipher the crucial molecular and cellular steps in the neuron-glia crosstalk necessary for neuronal remodeling

## Session 8: Developmental Neurobiology

### Molecular profiling of neuronal circuit development

**Mohylyak, Iryna**

Institut du Cerveau et de la Moelle épinière

Individual variation in behavior is a key feature of personality. The crucial question of whether and how this individuality of behavior and its variability in the population might be reflected in the brains of single animals remains unknown. The brain works as an interconnected system where different specialized areas continuously exchange information through stable synchronous connectivity patterns. This connectivity map is unique to every individual and arise during development through intrinsically variable wiring mechanisms. Using a group of cells in the *Drosophila* brain called the Dorsal Cluster Neurons (DCNs) it was shown that the development of higher order neural circuits in the fly visual system is intrinsically variable, resulting in a range of possible circuit diagrams among genetically identical individuals. Ongoing work in the laboratory shows that the variation in circuit wiring predicts the stable innate orientation behavior of an individual fly in an object fixation task. The goal of the project is to reveal molecular mechanisms involved in stochastic wiring pattern formation in different individuals. We performed RNA seq of DCN circuits (~80 cells/brain) isolated with Laser Micro Capture technique. Transcriptome analysis revealed 1190 differentially expressed genes, with 310 upregulated genes within DCNs. We've performed an RNAi-screen of 75 highly upregulated genes to study their input into DCN circuit development, wiring formation and function. We've found 10 candidates, which impair circuit innervation, some of them in sexually dimorphic manner. Among them, CG7101 encoding transcriptional factor, which is homologous to mammalian ZBTB48/TZAP known to be involved in telomeres length control and transcriptional regulation of mitochondrial fission process 1 (MTFP1) gene. Downregulation of CG7101 /TZAP and its mammalian target gene homologue CG7772 /MTFP1 expression in DCNs changes circuit wiring which leads to changes in individual behavior. We obtained first evidence that lack of CG7101 in DCNs leads to dramatic loss of postsynaptic connectivity of these cells, which could arise due to mitochondria homeostasis impairments

## Session 9 : Cell Biology

### **Keynote: Alain Vincent**

Centre de Biologie Intégrative Toulouse

**Alary muscles and TARMS, a novel type of striated muscles maintaining internal organs positions.**

Locomotion of the soft-bodied *Drosophila* relies upon a stereotypical pattern of 30 distinct body wall muscles per each hemi-segment. In addition, abdominal Alary muscles (AMs) connect the exoskeleton to the cardiac system. While described in various arthropods, AMs function has remained obscure. A few years ago, we discovered the existence of "Thoracic Alary-Related Muscles" (TARMS), connecting the exoskeleton to specific regions of the gut (Boukhatmi et al., 2014). Asymmetrical attachments of AMs and TARMS to the skeleton on one end, and internal organs on the other, suggested an architectural function for these muscles. At the 33rd *Drosophila* Research Conference, at Lyon, I will report the morphological and functional characterization of AMs and TARMS in crawling larvae. Elimination of AMs and TARMS by targeted apoptosis shows that AMs are required for suspending the heart in proper intra-hemocelic position and opening of the heart lumen, and constrain the curvature of the respiratory trachea. TARMS are required for proper positioning of visceral organs and efficient food transit.

*Drosophila* TARMS and AMs represent novel multinucleate striated muscles connecting the skeleton to the cardiac and visceral systems in bilaterians, with multiple physiological functions. This instates novel anatomical and evolutionary perspectives.



## Session 9 : Cell Biology

### Interrogating the requirement of *non-stop* in *Drosophila* border cell migration.

**Hammed Badmos**

Department of Biochemistry and Centre for Cell Imaging, University of Liverpool

Cell migration is central to normal development, whilst aberrant migration is involved in a number of human diseases, including cancer. We are interested in understanding the mechanisms that drive collective cell migration using the fruit fly, *Drosophila*, where a specialized group of epithelial cells migrates through the egg chamber in a developmentally-controlled manner. In an RNAi-based screen for deubiquitinases, we identified *non-stop* (*Drosophila* USP22) as a gene required for border cell migration. Notably, we find that *non-stop* is required for the normal expression and distribution of Hippo signalling components; this leads to abnormal F-actin localisation at the cortex of migrating clusters and premature tumbling of the border cell cluster. Taken together, our results uncover novel roles for *non-stop*/USP22 in Hippo-mediated collective cell migration, which may help guide studies in more complex organisms where USP22 has been implicated in cell motility and invasion.

## Session 9 : Cell Biology

### Identifying how intestinal cell fate is controlled by Integrin-mediated mechano-transduction

**Jérôme Bohère**

University of Cambridge

To maintain gut size and function, intestinal stem cells (ISC) integrate dynamic chemical and mechanical signals from the surrounding cells and environment to decide whether to proliferate or differentiate. Failure to do so may result in tissue integrity loss and development of degenerative diseases. Integrins are transmembrane proteins linking the extracellular matrix to the cytoskeleton via associated proteins such as Talin and Vinculin. Integrins are also able to trigger downstream signaling cascade activation ultimately regulating gene expression and thus cell behavior. However, Integrin associated proteins and signaling cascade specific functions remain to be identify and precisely characterized .In *Drosophila*, genetic ablation of the ubiquitous  $\beta$ PS Integrin sub-unit in gut stem cells prevents them to proliferate therefore affecting their maintenance, but the precise function of Integrins in proliferation control and its role in ISC mechano-sensing remains unknown. Our aim is to identify and understand *in vivo* the mechanisms causing mechanical signals to regulate ISC proliferation. We take advantage of the structural and genetic simplicity of the *Drosophila* gut to investigate how integrin-mediated mechano-transduction regulates stem cell fate as the whole gut remodels in response to physiological and abnormal physical constraints. By combining genetic tools, clonal analyses and measurements of tissue stiffness, we show that homeostatic ISC fate relies on distinct requirements of Integrin associated proteins in a region-specific manner. Moreover, we demonstrate that Integrins role is not restricted to its adhesive properties. Finally, we are testing if similar mechanisms regulate stem cell proliferation in regeneration and tumour growth.

## Session 9 : Cell Biology

Asymmetric nuclear division of fly neural stem cells generates daughter nuclei with distinct identities.

**Chantal Roubinet**

MRC-LMCB, UCL

Asymmetric cell division generates cellular diversity through unequal partitioning of cell fate determinants. Fly neural stem cells rely on asymmetric cell division to generate a self-renewing stem cell and a smaller differentiating sibling cell. Although the role of the cortical polarity on cell fate has been well documented, the contribution of the nuclear division in this context remains to be explored. Here, using live cell imaging of asymmetric divisions in intact and dissociated brains, together with electron microscopy, mutant analysis and drug treatments, I show that the nucleus compartment retains its identity during division. Second, I show that nuclear division does not require cell division, but is rendered asymmetric by the asymmetric division furrow. Third, I find that the generation of two daughter nuclei with a distinct size and composition occurs in two-steps – establishment and growth. Finally, I show how the coupling of nuclear division with the release of cortical cell fate determinants help to establish two different nuclear identities that contribute to generation of distinct cell fates during a neuroblast division.

## Session 9 : Cell Biology

### Molecular mechanisms mediating inter-tissue communication and promoting tumorigenesis.

**Hadi Boukhatmi**

Dept of Physiology Development & Neuroscience, University of Cambridge

How normal stromal cells are influenced by a tumor environment and contribute to tumor development is not fully understood. We have addressed this question using a *Drosophila* tumor model, which involves cross-talk between tumorous epithelial cells and unmodified mesenchymal cells. We show here that Notch/Zfh1 regulation hijacks the mesenchymal cells by preventing their differentiation and promoting their proliferation. In addition, we show that the mesenchymal Notch activation is mediated via high Delta-expressing epithelial cells. We also provide the evidence that long range communication can occur between aberrant Delta-expressing epithelial cells and the neighboring mesenchyme to activate Notch. We thus propose that high Notch activity coordinates the cross-talk between the cancerous epithelial and unmodified mesenchymal cells to promote tumorigenesis.



# Poster Abstracts

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2	BENHRA Najate	TmY neurons: Targeting multiple neuropils in the visual system
3	BOUMARD Benjamin	Replication stress in adult intestinal stem cells
4	CARNESECCHI Julie	Transcriptional interactive networks revealed by close-pr(H)OXimity biotinylation
5	CHAZAL Fanny	Elucidating the mode of action of the Chinmo/Broad transcription factor module in the developing wing imaginal disc
6	DAVOUST-NATAF Nathalie	Split-ends confers resistance to paraquat neurotoxicity and modulates glial lipid droplet contents in adult <i>Drosophila</i> .
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8	GIRAUD Guillaume	A Biotin-based approach to capture dose-dependent Hox cofactors involved in flight appendage specification
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12	LAMBERT Erwan	Characterization of the neurotoxicity of the Alzheimer Disease risk factor BIN1 in <i>Drosophila</i>
13	LEFEVRE Benedicte	<i>D. pachea</i> as a model to unravel the development of left/right asymmetry
14	LOPPIN Benjamin	The Lid/KDM5 histone demethylase complex activates a critical effector of the oocyte-to-zygote transition
15	MATOS Renata	<i>Lactobacillus plantarum</i> cell envelope and <i>Drosophila</i> linear growth promotion
16	MOHYLYAK Iryna	Molecular profiling of neuronal circuit development
17	PRET Anne-Marie	Regulation of the JAK/STAT signaling pathway during <i>Drosophila</i> oogenesis
18	QUINTANA Rio Laura	Modular transcriptional programs diversify neuronal circuit connectivity
19	RAMOS Cathy	<i>Drosophila</i> larval tissues growth and maturation: how does commensal bacteria impact their coordination upon undernutrition
20	ROUSSET Raphaël	Impact of <i>Bacillus thuringiensis</i> bioinsecticides on the development of intestinal pathologies
21	SAVIJÁ Tatjana	The pattern of antioxidant defense in <i>Drosophila subobscura</i> adults after exposure to extremely low frequency magnetic field (50 Hz)
22	TAILLEBOURG Emmanuel	Regulation of MYC-dependent cell growth by a specific isoform of the <i>Drosophila</i> ubiquitin specific protease dUSP36
23	THOMASSIN-BOURREL Helene	Understanding the function of the methylation of lysine 3 on the ribosomal protein uL11/RPL12
24	VINCENT Stephane	DPP signaling and dorsal closure
25	YUE Xiaojing	Study on the role of the gut-brain axis in Parkinson's disease in the <i>Drosophila</i> model

Poster number 1

## Localization of viral RNAs and proteins during infection in *Drosophila melanogaster*

Matthieu Bellet & Carine Meignin

Université de Strasbourg

Viral infections are a threat to all living organisms who developed several mechanisms to control them. In invertebrates and plants, the main antiviral defense is the RNA interference (RNAi) pathway. In the model organism *Drosophila melanogaster*, the core of the RNAi pathway is composed of three main proteins: Dicer-2, R2D2 and Argonaute2 (Ago2). More precisely, Dicer-2 recognizes viral double stranded RNA and cleaves it in 21-nucleotides duplex. Then, Dicer-2 along with its cofactor R2D2, load the RNA duplexes onto Ago2. Ago2 is the catalytic unit of the RNA induced silencing complex (RISC) and is responsible for the degradation of the viral RNAs through its endonuclease activity. To understand the dynamics of host-pathogen interactions, tools have been developed to label Dicer-2, R2D2 and Ago2 with fluorescent proteins. Thanks to these tools it is possible to evaluate the dynamics of the innate antiviral immunity during the infection. However, very few techniques allow real-time detection of viral RNAs. It is therefore important to develop approaches for the detection of these molecules. In order to track the dynamics of the viral infection, a replicon, called FHV-RdRp-GFP and coding for RdRp tagged with GFP (RdRp::GFP) was constructed. The RdRp is the enzyme that allow viral replication by synthesizing RNA from a viral RNA template. Therefore, we can extrapolate that the localization of RdRp correlates with the site of viral replication and synthesis of viral double-stranded RNAs. I have shown that RdRp::GFP allows the viral replication steps by synthesizing sense and antisense RNAs. This result open the door to the development of viruses coding for a functional fluorescent RdRp, making it possible to detect the localization of viral RNAs synthesis. I also started the optimization of an RNA labeling approach with fluorogenic aptamers to follow their dynamics in real-time. The latter approach, although very promising, still needs some fine tuning.



Poster number 2

## TmY neurons: Targeting multiple neuropils in the visual system

Najate Benhra and Claude Desplan

New York University Abu Dhabi, CGSB

Drosophila visual system has proved to be a useful model to study how neuronal diversity and wiring are generated. The optic lobe is one of the largest structures in the Drosophila brain comprising of ~60,000 neurons. Interestingly, a large number of specialized neurons innervating the optic lobe terminate in the appropriate neuropil layer, following a consistent neuronal topology- a process known as retinotopy. However, the molecular cues involved in the proper targeting of neurons to their final site remain unknown. To answer some of these questions, we focused our studies on a particular cell type called transmedullary (TmY) neuron, which connect the medulla (the most complex optic lobe ganglion) to the lobula and the lobula plate. Very little is known about these neurons and our goal is to characterize in detail their morphology. In addition, we aim to determine the genetic program underlying their dendritic and axonal growth and pathfinding throughout development, as well as to assess their function in visual processing. Furthermore, we are presenting data for a specific subset of TmY neurons, termed TMY14, which project to the central brain in addition to targeting the lobula and lobula plate.

Poster number 3

## Replication stress in adult intestinal stem cells

Benjamin Boumard, Nick Riddiford, Katarzyna Siudeja, Allison Bardin

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Genome integrity in long-lived tissue stem cells is essential to maintain tissue function and prevent cancer initiation. How stem cells cope with DNA lesions determines their mutation rate, susceptibility to cancer, and likely age-related functional decline. Using adult *Drosophila* intestinal stem cells we aim to understand what are the DNA damage causing factors, and what mechanisms are acting in adult stem cells to prevent spontaneous mutation.

Our previous work in *Drosophila*, demonstrated that in aging intestinal stem cells, frequent gene inactivation leads to neoplastic growth. Using whole-genome sequencing, we find that the stem cell genome accumulates a large number of somatic mutations, including large genomic rearrangements and other structural variants. A subset of deletions and more complex structural rearrangements are reminiscent of Fork Stalling and Template Switching (FoSTeS) events, suggesting a contribution of replication stress in stem cell genome instability.

Here, we are investigating the consequences of replication stress on the stem cells and the type of genome structural variants it promotes. We are combining various genetic techniques with whole-genome sequencing and DamID approaches to identify genomic region of replication stress in the stem cell and the consequence of replication fork collapse on genome integrity. I will present preliminary results on this ongoing investigation.

Poster number 4

## Transcriptional interactive networks revealed by close-pr(H)OXimity biotinylation

Carnesecchi J.1, Sigismondo G.2, Domsch K.1, Clara EP. Baader1, Rafiee MR.2, Krijgsveld J.2, Lohmann I.1

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Cell type diversity is controlled by transcription factors (TFs), which activate variable yet specific gene expression programs depending on the cellular environment. However, how TFs promote such diversity with high precision is still unknown. We used the Hox TF Ultrabithorax (Ubx) as a model to elucidate how a single TF specifies multiple cell types. We explored protein interactomes of Ubx in three different tissue lineages using proximity dependent Biotin IDentification (BioID) in combination with the UAS-GAL4 system in *Drosophila* embryos. We find that Ubx interactomes are highly specific, as Ubx interacts with a largely non-overlapping set of proteins within each tissue. Intriguingly, this specificity does not primarily come from Ubx interactions with lineage-restricted proteins. Instead, Ubx interacts in a lineage-specific manner with many ubiquitously expressed subunits of protein complexes that control general aspects of gene expression, including chromatin remodelling and RNA processing. In sum, our study reveals that a key developmental TF achieves in vivo specificity not only at the enhancer level but to a large extent by tissue-specifically fine-tuning the assembly of general transcription machineries. Thus, Hox TFs seem to act as versatile platforms which allow the integration of diverse regulatory inputs, from transcriptional initiation to translation, into cell fate decisions in vivo.

Poster number 5

## Elucidating the mode of action of the Chinmo/Broad transcription factor module in the developing wing imaginal disc

CHAZAL Fanny and Cédric Maurange

Institut de Biologie du Développement de Marseille (France)

In the developing *Drosophila* wing imaginal discs, epithelial cells commit to differentiation around midL3, just after the larva reaches the critical weight (CW). This switch coincides with the increasing production of a steroid hormone called ecdysone which regulates, in imaginal disc cells, a bistable loop between two ZBTB transcription factors (TF) expressed sequentially: Chinmo and Broad (Br). Before the CW, only chinmo is expressed, maintaining a default self-renewing undifferentiated state. However, upon production of ecdysone, broad becomes progressively expressed and represses chinmo, switching cells to a differentiation-permissive state. Interestingly, Chinmo<sup>+</sup> epithelial cells are competent for regeneration, while Broad<sup>+</sup> epithelial cells exhibit a restricted regenerative potential. While the mechanisms involved in the regulation of the Chinmo-to- Broad switch are now better understood, the mode of action of these two TFs remains unclear. Our aim is to understand how Chinmo and Broad respectively impose a self-renewing and a differentiation-permissive state to epithelial progenitor cells. I will present our strategy and preliminary data using a combination of transcriptomic, ATAC-seq, TaDa (targeted DamID) and Yeast-2-Hybrid approaches.

Poster number 6

## Split-ends confers resistance to paraquat neurotoxicity and modulates glial lipid droplet contents in adult *Drosophila*.

Victor Girard<sup>1\*</sup>, Valérie Goubard<sup>1\*</sup>, Matthieu Querenet<sup>1</sup>, Laurent Seugnet<sup>4</sup>, Laurent Pays<sup>2,3</sup>, Serge Nataf<sup>2,3</sup>, Eloïse Dufourd<sup>1</sup>, David Cluet<sup>1</sup>, Bertrand Mollereau<sup>1</sup> and Nathalie Davoust<sup>#1</sup>

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Glial cells are early sensors of central nervous system injury and recent reports suggest that lipid droplets expansion in glia might promote cellular communications affecting neuronal integrity. Using *Drosophila* retina to model neuron-glia interactions, we previously identified Spen as a cell survival factor for inter-ommatidial glial cells during retina development. Spen belongs with spenito to the evolutionary conserved SPEN proteins family and is implicated in multiple cellular processes, including neuronal and glial cell fate during nervous system development. Here we studied the role of Spen in a model of Parkinson's disease induced in adult *Drosophila* by systemic exposure to the neurotoxic molecule paraquat. We found that the brain expression of spen mRNA is modulated by paraquat treatment and that flies heterozygous for a spen loss-of-function mutation exhibit an enhanced vulnerability to paraquat-induced neurotoxicity. Importantly, a glial-restricted silencing of spen similarly increased *Drosophila* sensitivity to paraquat, while conversely, an over-expression of spen in glial cells had a protective effect. Interestingly, spen loss-of-function was associated with the accumulation of large lipid droplets in the astrocyte-like glial cellular processes located in the neuropil. We then performed a meta-analysis of microarray data sets comparing substantia nigra tissue samples deriving from Parkinson's disease (PD) patients vs control subjects. We found that SHARP the human spen ortholog, was significantly up regulated in the substantia nigra of PD patients along with a number of genes involved in lipid metabolism and fatty acid elongation. Altogether, our results highlight the importance of lipid metabolism and lipid droplet formation in glia during neurodegenerative processes.

Poster number 7

## Lipid droplet accumulation promotes Alpha-synuclein aggregation in a *Drosophila* model of Parkinson Disease

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Lipid metabolism dysregulation has been reported in neurodegenerative disorders such as Alzheimer and Parkinson's diseases (PD). Recent studies including ours suggest that lipid storage organelles (lipid droplets, LD) accumulate and function not only as lipid stores but also as dynamic regulators of the neuronal stress response. PD is characterized by neuronal accumulation of alpha-synuclein (aSyn) aggregates and locomotor dysfunction. Recent evidences indicate that aSyn expression leads to the accumulation of LD in yeast cells and mammalian cell culture. However, the mechanism by which aSyn expression leads to the accumulation of LD remains elusive. Here, we use a *Drosophila* model in which aSyn is expressed in photoreceptor-neurons to further elucidate LD and aSyn interactions in vivo. We show that expression of human aSyn induces progressive accumulation of triacylglycerol and LD, revealed by lipidomic profiling and imaging analyses of *Drosophila* retina. Interestingly, LD accumulation does not require dFatp or midway (dgat1) suggesting that aSyn promotes LD independently of de novo lipid synthesis. Finally, we found that genetic ablation of LD regulates the levels of age-dependent aSyn aggregation. Taken together our results suggest that the accumulation of LD induced by aSyn expression contributes to the progression of PD.

Poster number 8

## A Biotin-based approach to capture dose-dependent Hox cofactors involved in flight appendage specification

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Dipterans are characterized by small balancing organs called “halteres” in place of posterior wings observed in other insects. The formation of halteres is directly under the control of the Hox gene Ultrabithorax (Ubx). Recent work in our laboratory showed that the haltere- specification program was tightly dependent on a striking high dose of Ubx, and low doses of Ubx are sufficient to promote back the formation of wings instead of halteres.

My PhD project aims at understanding how dosage variation of a single Hox gene product could lead to the formation of two distinct flight appendages in *Drosophila*. To this end, I am combining three complementary experimental approaches to identify Ubx- and dosage- specific cofactors. First, I have established a candidate RNAi approach to screen for genes that could affect the Ubx-dependent haltere specification program in a sensitized genetic background. Second, I am establishing a biotin-dependent purification method to isolate proteins that could specifically interact with different doses of Ubx in the haltere primordium. Last, we are analyzing cis-regulatory sequences of genes regulated by Ubx in the haltere to identify candidate DNA-binding partners.

Altogether, the three different approaches should identify cofactors involved in the Ubx- and dosage-specific haltere specification program. Capturing these interactions will provide unprecedented molecular insights to understand how wings evolved into an innovative balancing organ during insect evolution.

Poster number 9

## Building and maintaining a functional neuromuscular system

Camille GUILLERMIN, Mathilde BOUCHET, Alain GARCES, and Jonathan ENRIQUEZ

IGFL ENS de Lyon

Every species possesses its stereotypical mode of locomotion which is under the control of the neuromuscular system. Locomotion results in movements that are essential for animal survival. Diseases of the locomotor system are at the origin of many handicaps with severe economic and social consequences. Hence, the study of the neuromuscular system has become a key challenge for the science community in order to develop different forms of therapies. The long-term project of the team is to understand the coordinated development and maintenance of the *Drosophila melanogaster* neuromuscular system components. My project is to elucidate the cellular and molecular mechanisms at the origin of the communication between motoneurons axons and their muscles target in order to understand how the specific innervation is generated during development, and how these specific connections are maintained during adulthood. To achieve the first part of this project, I make the hypothesis that each muscle, and motoneurons, express differentially molecules that are at the origin of the specific recognition. For this part of the project, I will perform transcriptomic experiments of individual muscle leg to discover molecules playing a role in the specific axon-muscle recognition. I began by generating flies labelling specifically subpopulation of muscles. Then, to understand how the specific connections are maintained during adulthood, I study the function of morphological transcription factors (mTF) which are known to control the innervation of motoneurons during development. I confirmed the maintenance of one mTF, OLI, at adulthood. The following step will be to demonstrate its role in the preservation of the neuromuscular system during the fly life by mutating Oli only at adulthood. Altogether, this project will lead to novel biological concepts that will increase our fundamental knowledge on developmental biology.



Poster Number 10

## Cellular mechanisms of astrocytes plasticity in *Drosophila* ventral nerve cord

Imene HAMMOUM, Anne LAURENCON and Jonathan ENRIQUEZ

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In the ventral nerve cord, *Drosophila* astrocytes are characterized by their highly ramified processes deep into the neuropil regions where they are in close contact with synapses and play a critical role for the development and function of these synapses. Based on morphological, molecular and functional criteria, *Drosophila* astrocytes are very similar to their mammalian counterparts. In the ventral nerve cord, two of the 11 stem cells, called neuroblasts, produce Motor neurons (Lin A and D) and give rise also to all astrocytes. Moreover, these cells have a unique mode of development that is highly stochastic. The gliogenesis phase is plastic and highly adaptable: when gliogenesis in one lineage is compromised, other lineages compensate to maintain the correct number of astrocytes. This plasticity is explained by a neutral competition where these cells compete to invade different regions of the central nervous system.

Our purpose is to understand the cellular mechanisms of astrocyte cell competition and how astrocytes can adapt their number of division and their processes morphologies to invade different regions of the neuropil. In early stage of development, the number of glia progenitor surrounding the immature neuropil is identical. However, in the adult stage, the number of astrocytes is variable between neuropil. Is the final number of astrocytes is under the control of the neuropil size? To answer this question, we starved the flies to make them smaller and have smaller VNCs, count the number of astrocytes, and measure the neuropil volume at the larval and adult stages. We show that the number of astrocytes and the neuropil volume decreased significantly in smaller flies compared to controls which confirms our hypothesis that the neuropil volume who dictates the final number of astrocytes.

Poster number 11

## The role of Ire1/Fatp in the formation of lipid droplets

Jin Haixiu and Bertrand Mollereau

LBMC ENS de Lyon

Endoplasmic reticulum (ER) stress and dysregulated lipid metabolism are hallmarks of several neurodegenerative diseases. ER stress is caused by the overload of misfolded proteins, which promotes the unfolded protein response (UPR) that results in the activation of Ire1, Perk and Atf6 pathways. Ire1 is an endoribonuclease that splices and activates Xbp-1 transcription factor and promotes mRNA Regulated Ire1-dependent decay (RIDD). It was shown that RIDD degrades specific mRNA such as Fatp (Fatty Acid Transport Protein), that is an important regulator of lipid storage organelles, lipid droplets in *Drosophila* glial cells. In contrast, it was shown that Xbp1 activates lipid biosynthesis pathway. This indicates that Ire1 activation may results in an antagonistic regulation of lipid metabolism. Here, we investigate the roles of Ire1/Xbp1 and Ire1-dependent degradation of Fatp pathways in the regulation of lipid droplet formation in retina with a physiological or pathological activation of Ire1 pathway. We show that the RIDD pathway is activated in physiological or mild ER stress but not in severe ER stress conditions. Further study will aim to address the pathophysiological relevance of Ire1/Xbp1 and Ire1-dependent degradation of Fatp pathways in neurodegeneration.

## Characterization of the neurotoxicity of the Alzheimer Disease risk factor BIN1 in *Drosophila*

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BIN1 is the second Alzheimer's disease genetic risk factor but its role still remains poorly understood. BIN1 has notably more than 10 isoforms. Preliminary results have shown that the expression of the brain-specific isoform (BIN1-1) specifically induces photoreceptor neuron degeneration in the *Drosophila* eye. However the mechanism by which BIN1-1 induces neurodegeneration is unknown. The first objective of this work was to identify the domain of BIN1-1 responsible for the degeneration. We tested truncated BIN1-1 forms and showed that the only construction which was able to abolish the degeneration was the one without the CLAP domain, indicating that this domain is necessary for the BIN1-1 induced toxicity. This domain is involved in endocytosis, a process related to the endosome-lysosome pathway. In addition the degeneration is characterized by endosome-positive large vesicles. For these reasons, the second objective of this work was to evaluate the impact of the endosome-lysosome pathway regulation on the BIN1-1 induced toxicity. We tested the effect of the modulation of this pathway on BIN1-1 associated degeneration. We found that modulation of Rab5, Rab4 and Rab11, respectively involved at the level of the early and recycling endosomes, abrogated photoreceptor degeneration, suggesting that BIN1-1 toxicity is likely due to an alteration of the endosome-lysosome pathway. Altogether, these results suggest that an increase of the BIN1 isoform 1 could impair the endosome-lysosome pathway, leading to neuronal death and thus contribute to Alzheimer's disease.

## *D. pachea* as a model to unravel the development of left/right asymmetry

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We study the establishment of morphological left-right asymmetry using *Drosophila pachea* as a new model system. Males of this species have a pair of asymmetric external genital lobes, with the left lobe being about 1.5 times longer than the right lobe. Lobes are not found in closely related species and present an evolutionary novelty. First developmental changes in genitalia development with respect to closely related sister species of *D. pachea* are observed when the lobes start to grow during pupal development, between 24 h and 36 h after puparium formation (APF). Cell number but not cell size increases in the left lobe compared to the right lobe, which grow to about 410 cells and 220 cells, respectively. However, no differences in cell division rates were detected at various time points of development by immuno-fluorescence staining of mitotic cells. We are preparing life- imaging of developing genitalia in transgenic *D. pachea* that express fluorescent markers in the nucleus or cell membrane. We want to test, if cell number differences result from a pulse or short time period of proliferation, differential cell death or cell recruitment from the flanking tissues. Lobe outgrowth occurs while male genitalia rotate clockwise during pupal development between 25 h and 40 h APF. This is a conserved and asymmetric developmental process in many fly species and might be important for asymmetric lobe development because a *D. pachea* mutant with variable left lobe length reveals premature rotation timing of 6 h compared to wildtype stocks. Asymmetric growth thus likely depends on intrinsic asymmetric cellular growth processes inside the genitalia, but also on a particular (rotating) tissue context.

Poster number 14

## The Lid/KDM5 histone demethylase complex activates a critical effector of the oocyte-to-zygote transition

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Following fertilization of a mature oocyte, the formation of a diploid zygote involves a series of coordinated cellular events that ends with the first embryonic mitosis. In animals, this complex developmental transition is entirely controlled by maternal gene products. How such a crucial transcriptional program is established during oogenesis remains poorly understood. Here, we have performed a shRNA-based genetic screen in *Drosophila* to identify genes required to form a diploid zygote. We found that the Lid/KDM5 histone demethylase and its partner, the Sin3A/Rpd3 deacetylase complex, are necessary for sperm nuclear decompaction and karyogamy. Surprisingly, our transcriptomic analyses revealed that these histone modifiers are required for the massive transcriptional activation of deadhead (*dhd*), which encodes a maternal thioredoxin involved in sperm chromatin remodeling. Furthermore, this remarkably specific regulation is not mediated by the demethylase activity of Lid, as revealed by our ChIP-Seq profiling of H3K4me<sub>3</sub>, its target mark. We propose that Lid/KDM5 and Sin3A cooperate to establish a local chromatin environment compatible with the unusual expression of *Dhd*, a key effector of the oocyte-to-zygote transition.

Poster number 15

## Lactobacillus plantarum cell envelope and Drosophila linear growth promotion

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Metazoans establish complex interactions with their resident microorganisms for mutual benefits. When in homeostasis, these interactions contribute to different aspects of host physiology. In the gut, microbial communities enhance digestive efficiency by providing enzymatic functions that help their hosts optimize extraction of dietary energy and nutrients. Despite the renewed interest in understanding the functional impact of gut microbiota on host physiology, a clear view of the molecular dialogue engaged upon host/microbiota interaction remains elusive. Therefore, the use of simple animal models, such as *Drosophila*, may help unravel the evolutionarily conserved mechanisms underlying the impact of intestinal bacteria in their host physiology, since it combines genetic and experimental tractability with a cultivable microbiota. Previously, we showed that upon chronic undernutrition, strains of *Lactobacillus plantarum*, a major commensal partner of *Drosophila*, promote host juvenile growth and maturation partly via enhanced expression of intestinal peptidases. By screening a transposon insertion library of *Lactobacillus plantarum* in gnotobiotic *Drosophila* larvae, we identified a bacterial cell wall modifying machinery encoded by the *pbpX2-dlt* operon that is critical to enhance host digestive capabilities and promote animal growth and maturation. Deletion of this operon leads to bacterial cell wall alteration with a complete loss of teichoic acids D-alanylation. We show that *L. plantarum* cell walls bearing D-alanylated teichoic acids are directly sensed by *Drosophila* enterocytes to ensure optimal intestinal peptidase expression and activity, juvenile growth and maturation upon chronic undernutrition. In this work, we analyze *L. plantarum* mutant strains for their peptidoglycan and teichoic acids composition and how those changes correlate with *Drosophila*'s linear growth, further demonstrating cell envelope importance for *L. plantarum-Drosophila* symbiosis.

Poster number 16

## Molecular profiling of neuronal circuit development

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Individual variation in behavior is a key feature of personality. The crucial question of whether and how this individuality of behavior and its variability in the population might be reflected in the brains of single animals remains unknown. The brain works as an interconnected system where different specialized areas continuously exchange information through stable synchronous connectivity patterns. This connectivity map is unique to every individual and arise during development through intrinsically variable wiring mechanisms. Using a group of cells in the *Drosophila* brain called the Dorsal Cluster Neurons (DCNs) it was shown that the development of higher order neural circuits in the fly visual system is intrinsically variable, resulting in a range of possible circuit diagrams among genetically identical individuals. Ongoing work in the laboratory shows that the variation in circuit wiring predicts the stable innate orientation behavior of an individual fly in an object fixation task. The goal of the project is to reveal molecular mechanisms involved in stochastic wiring pattern formation in different individuals. We performed RNAseq of DCN circuits (~80 cells/brain) isolated with Laser Micro Capture technique. Transcriptome analysis revealed 1190 differentially expressed genes, with 310 upregulated genes within DCNs. We've performed an RNAi-screen of 75 highly upregulated genes to study their input into DCN circuit development, wiring formation and function. We've found 10 candidates, which impair circuit innervation, some of them in sexually dimorphic manner. Among them, CG7101 encoding transcriptional factor, which is homologous to mammalian ZBTB48/TZAP known to be involved in telomeres length control and transcriptional regulation of mitochondrial fission process 1 (MTFP1) gene. Downregulation of CG7101 /TZAP and its mammalian target gene homologue CG7772 /MTFP1 expression in DCNs changes circuit wiring which leads to changes in individual behavior. We obtained first evidence that lack of CG7101 in DCNs leads to dramatic loss of postsynaptic connectivity of these cells, which could arise due to mitochondria homeostasis impairments.

Poster number 17

## Regulation of the JAK/STAT signaling pathway during *Drosophila* oogenesis

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The JAK/STAT signaling pathway is essential to numerous cellular and developmental processes, which are often conserved between vertebrates and invertebrates. In our model, the egg chamber of the *Drosophila* ovary, the JAK/STAT signaling pathway plays various roles for which its mechanisms of action and targets remain largely unknown. Our team has shown that apoptotic extrusion of specialized follicular epithelial cells (polar cells) is controlled by the JAK/STAT pathway non-cell autonomously. Here we show that Arp3 and MRLC, two regulators of the Acto-Myosin network, are also required non-cell autonomously for the apoptotic extrusion of polar cells and interact with JAK/STAT pathway components at the genetic level. We have also unexpectedly identified a new positive regulator of JAK/STAT signaling in the ovary. These results are opening new prospects in understanding regulation of the JAK/STAT pathway.



Poster number 18

## Modular transcriptional programs diversify neuronal circuit connectivity

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The assembly of functional neural circuits requires precise patterns of synaptic connectivity. Such neuronal wiring patterns appear to be genetically hardwired in flies. Likewise, patterns of synaptic connectivity in the mammalian Central Nervous System are largely genetically determined before plasticity modifies these circuits. However, we lack a good understanding of how developmental programs act in individual neurons to establish proper neurocircuitry. Here we focus on the T4/T5 motion detection circuitry in the *Drosophila* optic lobe to identify the molecular and developmental programs underlying synaptic specificity. The T4/T5 circuitry is built from eight subtypes of lineage related T4 and T5 neurons. Each neuron is morphologically defined by three parameters: 1) the localization of their dendrites in either the Medulla (T4) or Lobula (T5) neuropiles, 2) the orientation of their dendritic arbors in one of the four cardinal directions, and 3) organization of axonal outputs in one of four differentiated layers. These morphological attributes sustain the motion detection computation for each neuronal subtype. Using single cell mRNA-sequencing to define the transcriptome of developing T4/T5, we found that the eight cell types have distinct transcriptomes, defined by combinations of few transcription factors and cell surface proteins. Gain and loss of function experiments revealed developmental modules composed of transcriptional programs, and downstream batteries of cell surface proteins that independently establish dendritic and axonal wiring properties. We propose that combinations of developmental modules diversify patterns of neuronal connectivity.

Poster number 19

## *Drosophila* larval tissues growth and maturation: how does commensal bacteria impact their coordination upon undernutrition

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The juvenile growth period is crucial since acute and chronic undernutrition lead to severe wasting, stunting and in extreme cases, childhood mortality. Until recently no study had informed us to what extent and how the microbiome activities govern juvenile growth, let alone the molecular mechanism behind. Using gnotobiotic models, our team has recently revealed the evolutionarily conserved impact of the intestinal microbiota and selected lactobacilli strains on the promotion of linear growth in animals and has started identifying some molecular players of the intricate and multi-factorial dialog engaged during the beneficial symbiosis between host and commensal bacterial species. We now aim to elucidate the cellular and molecular mechanisms that forge the mutualistic interaction between the fly larvae and its commensal gut bacteria *L.plantarum*.

In this context, this study focuses on highlighting a possible effect of the bacteria mono-association to the coupling of systemic growth with organ growth. Thus, we found that at equal longitudinal size, the *L.plantarum* mono-associated larvae possess a longer gut than the germ-free animals, strongly suggesting that the bacteria affect organ growth coordination. In order to understand this gut specific phenotype, we imaged entire guts and gut region-specific cells to characterize this growth promotion. Also, we performed an unbiased study via tissue measurements through developmental time, leading to RNAseq analyses and identification of gut-specific transcriptomes.

Together, these data pave the way for a new tissue-specific role mediated by the fly commensal *L.plantarum* regulating gut growth upon undernutrition.

Poster number 20

## Impact of *Bacillus thuringiensis* bioinsecticides on the development of intestinal pathologies

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*Bacillus thuringiensis* (*Bt*) products are the main bioinsecticides used in organic farming. *Bt* is a sporulating Gram-positive bacterium that belongs to the *Bacillus cereus* group. *Bt* bioinsecticides, which are made of *Bt* spores producing entomopathogenic toxins, target pests by destroying their intestinal epithelium. Although studies have shown the safety of *Bt* for non-target organisms over a short period of time (acute toxicity), the potential adverse effects of chronic exposure are not known. Our laboratory uses *Drosophila melanogaster* as a non-target model to study the unintended effects of *Bt* intake on gut homeostasis. We already established that ingestion of a low amount of *Bt* (environmental dose found on vegetables) triggers a transitory inflammation and hyperplasia of the midgut involving the JNK, JAK/STAT and HIPPO pathways (Loudhaief et al., Development 2017). However, chronic inflammation in the intestine is known to promote the development of inflammatory pathologies (Crohn's Disease, Ulcerative Colitis), and even cancers. We therefore wonder whether repetitive ingestion of *Bt* could favour a chronic inflammation and tumorigenesis in the gut, especially in fragile individuals prone to develop these pathologies. We are analysing the impact of chronic ingestion of *Bt* on adult flies, as well as on new born, old and genetically predisposed flies by monitoring in vivo the fitness, growth, proliferation, differentiation of the intestinal cells, as well as the initiation/progression of tumorigenesis. This project should strengthen our knowledge about the relationship between allochthone bacteria, inflammation and tumour development and should lead to an objective assessment of the risks after ingestion of organic food treated with *Bt* bioinsecticides.

Poster number 21

## The pattern of antioxidant defense in *Drosophila subobscura* adults after exposure to extremely low frequency magnetic field (50 Hz, 0.5 mT) at different developmental stages

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Nowadays, it is of importance to perceive the benefits and costs of enhanced technological development which implies the presence of various forms of magnetic fields in the living and working environment. Living organisms are confronted with that influence and it is useful to find out how we can minimize costs and reap the benefits. The aim of this research was to consider the pattern of antioxidant defense in *Drosophila subobscura* adults exposed at different developmental stages (embryons or just eclosed adults) to extremely low frequency magnetic field (ELF MF; 50 Hz, 0.5 mT, 48 h). The consequences of this treatment were evaluated by measuring the activity of superoxide dismutase (SOD) and catalase (CAT), as well as the content of total glutathione (GSH). The obtained results indicated different pattern of antioxidant defense in females and males after exposure to ELF MF. In females, decreased SOD activity together with increased CAT activity and GSH content were observed regardless of whether they were exposed to ELF MF as embryos or just eclosed individuals. In males, SOD activity was increased after exposure of embryos, while CAT activity and GSH content were increased after exposure of just eclosed individuals. In conclusion, ELF MF could be considered as a stressful factor affecting the pattern of antioxidant defense in *D. subobscura*.

Poster number 22

## Regulation of MYC-dependent cell growth by a specific isoform of the *Drosophila* ubiquitin specific protease dUSP36

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The c-Myc oncogene encodes a pleiotropic transcription factor controlling the expression of a large number of genes involved mainly in cell growth and proliferation. MYC is estimated to be overexpressed in more than 50% of human tumors and is degraded by the ubiquitin- proteasome system. The SCF<sup>Fbw7</sup> E3 ligase promotes MYC ubiquitination and degradation whereas MYC is deubiquitinated and stabilized by two DUBs of the Ubiquitin Specific Protease (USP) family: USP28 and USP36. In *Drosophila*, the only DUB known to regulate dMYC stability is encoded by the puffeye gene and is orthologous to human USP34. While no obvious homolog of human USP28 is present in the *Drosophila* genome, USP36 has a clear *Drosophila* ortholog known as dUsp36 (or scrawny) which is involved in immunity, stem cell maintenance and cell growth. The aim of this study is to understand the role of dUSP36 in the regulation of cell growth. First, we show that the dUsp36 gene generates three isoforms with different subcellular localizations. To address their respective functions, isoform-specific loss-of-functions alleles have been generated by CRISPR/Cas9 and one of them was shown to play a major role in cell and organismal growth. We then show that this dUSP36 isoform interacts with dMYC and AGO (the *Drosophila* Fbw7 ortholog), regulating the stability and ubiquitination levels of both proteins. These results lead us to propose that dMYC, AGO and dUSP36 are part of the same macromolecular complex with AGO ubiquitinating itself, dUSP36 and dMYC and dUSP36 deubiquitinating itself, AGO and dMYC. We provide genetic evidence supporting this model. This complex thus represents a regulatory node that tightly controls dMYC ubiquitination levels and stability in *Drosophila* as well as in humans. Its evolutionary conservation opens new avenues in studying its role and regulation in a genetically tractable organism such as *Drosophila*.

Poster number 23

## Understanding the function of the methylation of lysine 3 on the ribosomal protein uL11/RPL12

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Post-translational modifications, such as phosphorylation, ubiquitylation, acetylation and methylation, are key contributors to protein structure and function. Until recently, methylation of lysine has been studied mainly on histone proteins and has been shown to affect gene transcription and chromatin remodelling. Beyond histones, recent advances in proteomic techniques, in particular in mass-spectrometry, have considerably expanded the list of lysine methylation sites on non-histone proteins. However, the biological functions as well as the lysine methyltransferases (KMTs) that control the majority of these methylations are not yet identified.

The ribosomal protein uL11/RPL12 can be tri-methylated on the conserved residue lysine 3. We discovered that, when tri-methylated on lysine 3, the *Drosophila* ribosomal protein uL11 interacts with the chromodomain of Corto, a member of the Enhancer of Trithorax and Polycomb (ETP) family of epigenetic cofactors. uL11 and Corto bind chromatin at the same loci on polytene chromosomes and regulate a subset of genes implicated in ribosome biogenesis (Coleno-Costes et al., PLoS Genetics 2012). Hence, in addition to its bona fide role in ribosome biogenesis and translation, uL11 also participates in transcriptional regulation of ribosomal protein genes and could be involved in the dynamic coordination of ribosome biogenesis.

We used two complementary approaches to elucidate the function of the tri-methylation of uL11 lysine 3. First, we used the CRISPR/Cas9 technology to specifically address the role of this modification in vivo, and generated uL11 variant proteins whose lysine 3 has been deleted or replaced by another residue. While K3Y alleles have no obvious phenotypes,  $\Delta$ K3 or K3A alleles exhibit developmental delay, small body size, short and thin bristles, poor fertility and viability, all referred to as Minute phenotypes usually attributed to a reduced overall protein synthesis. Second, we look at the KMT responsible for the methylation of uL11K3. In *S. pombe*, Set11, a SET domain-containing protein, specifically modifies uL11 (Sadaie et al., J Biol Chem, 2008). We found that CG33230, the *Drosophila* ortholog of Set11, specifically methylates uL11K3 in vitro. We are currently investigating the biological function of the KMT CG33230 determining in particular whether its deletion phenocopy uL11 mutation or not. The latter possibility would suggest the existence of additional substrate for CG33230.

Poster Number 24

## DPP signaling and dorsal closure

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Dorsal closure is a morphogenetic event during late *Drosophila* embryogenesis that is often used as a wound healing model. Indeed, the left and right dorsal epidermis migrate toward the embryos dorsal midline and fuse. The Bone Morphogenetic Protein homologue Decapentaplegic is required for dorsal closure as mutants lacking Decapentaplegic signaling undergo evisceration. Here, we characterize the different steps leading to evisceration of embryos carrying an amorphic version of thickveins, that codes for the type I Decapentaplegic receptor. Surprisingly, our data show that the evisceration is not due to a migration defect. Based on the characterization of the evisceration dynamics, we propose several hypotheses to explain the cellular basis of the thickveins phenotype.

Poster Number 25

## Study on the role of the gut-brain axis in Parkinson's disease in the *Drosophila* model

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Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. It is estimated that more than 6 million people worldwide suffer from it. The PD motor symptoms (resting tremor, bradykinesia, rigidity and postural instability) are attributed to the loss of dopaminergic neurons (DANs) in the substantia nigra pars compacta (SNpc). The PD patients also suffer from non-motor symptoms, such as impaired olfaction, constipation and dementia. The degeneration or death of the DANs in the SNpc is characterized by the formation of large cytoplasmic inclusions named Lewy bodies. The main component of these Lewy bodies is  $\alpha$ -Synuclein ( $\alpha$ -Syn), a 140-amino acid protein present in the nucleus and presynaptic terminals. The Ala30Pro mutation ( $\alpha$ -SynA30P) modifies the aggregation properties of this protein and has been linked to familial PD. A current hypothesis is that  $\alpha$ -Syn oligomers or small aggregates could spread from cell to cell or organ to organ in a prion-like manner to propagate the disease. It has also been proposed that in some cases PD originates in the gut before it reaches the brain. We have expressed human  $\alpha$ -SynA30P either in neurons, in the gut or both in neurons and gut to explore whether the accumulation of  $\alpha$ -SynA30P in the gut could trigger or exacerbate the PD-like phenotypes in the fly. We found that  $\alpha$ -SynA30P expression in the gut accelerated locomotor ageing and decreased oxidative stress resistance but had no effect on lifespan. Interestingly, we observed that these flies also had higher spontaneous activity during the night, suggesting a disturbance in dopaminergic signalling. Our results to this point indicate that the expression of  $\alpha$ -Syn in the *Drosophila* gut could by itself trigger symptoms associated with PD pathogenesis.



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