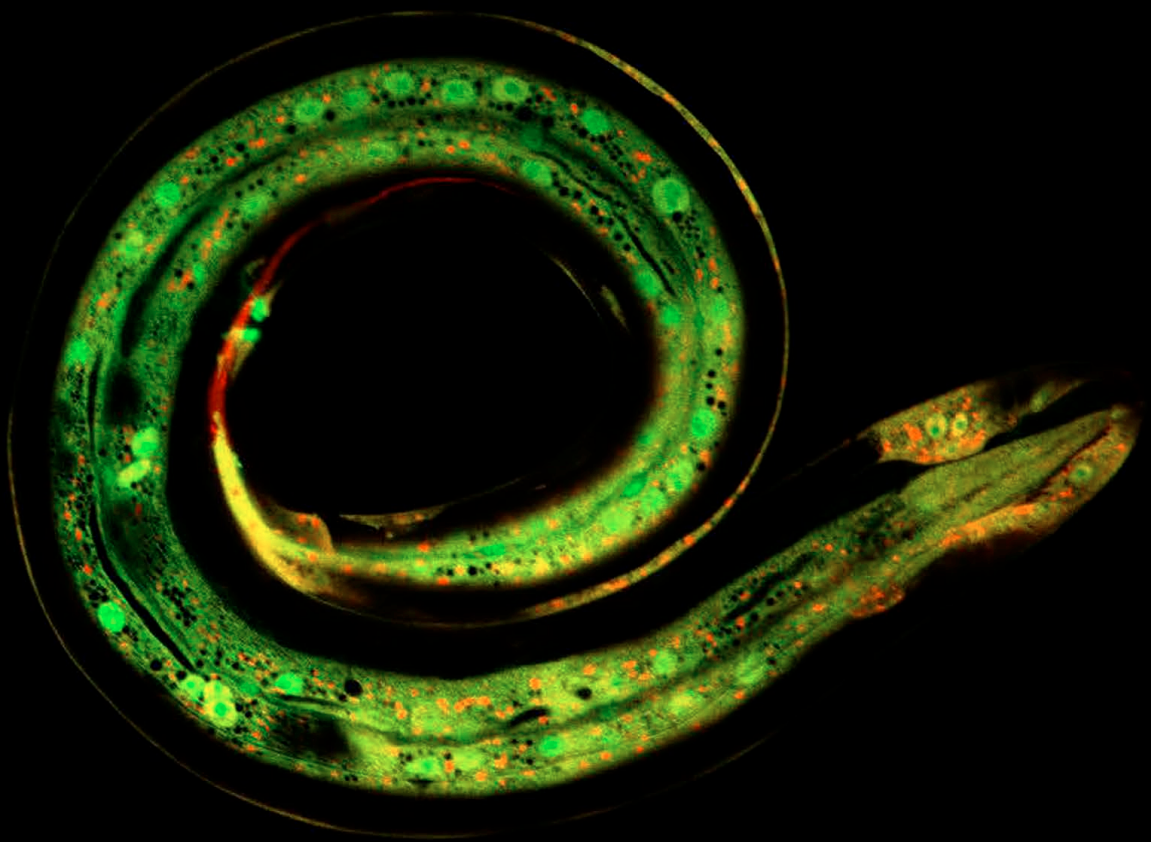
VerMidi XXI



26th January 2018

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VerMidi XXI - 26th January 2018 - CIML

09:30 - 9:55 Welcome coffee

09:55 - 10:00 Opening Remarks

Session 1

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Amhed Vargas Velazquez, Institut de biologie de l'école normale supérieure - Paris

10:20 - 10:40 › Why would females produce males whose DNA is not passed on to females ?
Manon Grosmaire, Laboratoire de Biologie et Modélisation de la Cellule - Lyon

10:40 - 11:00 › Wolbachia in filarial nematodes: a passenger holding the steering wheel in oogenesis through control of germline stem cell fate and differentiation
Vincent Foray, Centre de recherche de Biologie cellulaire de Montpellier

11:00 - 11:20 › A novel correction mechanism regulates nuclear position and ensures proper DNA segregation during late cytokinesis
Anne Pacquelet, Institut de Génétique & Développement de Rennes

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Henrik Bringmann - Max Planck Institute for Biophysical Chemistry (Gottingen)

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14:20 - 14:40 › A ratchet process powers *C. elegans* embryo axis elongation
Alicia Lardennois, Institut de Biologie Paris-Seine

14:40 - 15:00 › Epidermal Response to sterile injury and fungal infection in *C. elegans*
Clara Taffoni, Centre d'Immunologie de Marseille - Luminy

15:00 - 15:20 › Bridging extra- and intracellular synaptic scaffolds at GABA synapses in *C. elegans*
Xin Zhou, Institut NeuroMyogène - Lyon

15:20 - 15:40 › A protein disulfide isomerase linked to congenital cardiac defects is required in the endoplasmic reticulum for acetylcholine receptor biogenesis
Manuela D'Alessandro, Institut NeuroMyogène - Lyon

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16:20 - 16:40 › Adenylosuccinate Lyase deficiency in the recycling pathway is responsible for post-embryonic developmental delay, germline maintenance and muscle defects
Roxane Marsac, Institut de biochimie et génétique cellulaires - Bordeaux

16:40 - 17:00 › You are what you experience: The impact of environment on cellular identity
Sarah Becker, Institut de Génétique et de Biologie Moléculaire et Cellulaire - Strasbourg

17:00 - 17:20 › Chromatin organisation : a novel function for H3K4 methylation in the *C. elegans* germline
Marion Herbette, Laboratoire de Biologie et Modélisation de la Cellule - Lyon

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Arnaud Hubstenberger, Institute of Biology Valrose - Nice

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Invited talk

Regulation and regenerative functions of sleep

Henrick Bringmann [*†] [1]

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Sleep is a behavior that affects the physiology of the entire organism. It is essential and likely serves many functions from higher brain functions to basic cell biological functions including learning and memory, development, and regeneration. However, little is known about how sleep is controlled and how it exerts its functions. Central to the control of sleep are sleep-active sleep-promoting neurons that are active at the onset of sleep and that actively induce sleep through inhibitory transmitters such as GABA and neuropeptides. *Caenorhabditis elegans* is one of the most simple organisms that sleeps. Sleep is induced by just one single sleep-active neuron called RIS, which depolarizes at the onset of sleep to induce this state. To understand how sleep is generated we need to understand how the depolarization of this neuron is controlled by circuits and molecular pathways. For example RIS activity is under the control of homeostatic mechanisms. To study sleep functions, RIS can be ablated and the phenotypes caused by sleep loss can be studied. Because of its simplicity, the molecular basis of sleep regulation and functions should be straightforward to solve in the worm.

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Session 1

Molecular identification of vulval developmental defects in the non-model nematode Oscheius tipulae via mapping-by-sequencing

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Oscheius tipulae is a common free-living nematode, phylogenetically closer to the model species *Caenorhabditis elegans* than the outgroup *Pristionchus pacificus*. This species is thus enlightening for comparative genetics, developmental and evolutionary studies despite not being a model organism.

In model species with fully assembled and annotated genomes, mapping-by-sequencing has become a standard method to map and identify phenotype-causing mutations. Candidate variants are pinpointed using a cross to a divergent mapping strain and sequencing of a pool of mutant segregants. Here we show that we can apply the mapping-by-sequencing approach with a draft genome assembly of *O. tipulae* to identify mutations responsible for vulval and other morphological defects.

The only Vulvaless mutant we found corresponds to a cis-regulatory deletion in the *lin-3* gene. Combining single-molecule FISH, laser ablation and CRISPR-Cas9 deletion results, we demonstrate the role of LIN-3 in vulval induction by the anchor cell in *O. tipulae*. In contrast, mutants with an excess of vulva induction correspond unexpectedly to the plexin/semaphorin pathway, a signaling pathway not previously found in *C. elegans* vulva development screens. We will present the analysis of these mutants and several others (Wnt pathway, etc.).

Our success suggests that a draft assembly of a non-model organism is sufficient to perform mapping-by-sequencing thus bringing non-model species firmly into genomics-enabled science, and providing tools to investigate the evolution of developmental mechanisms.

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Why would females produce males whose DNA is not passed on to females ?

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Sperm-dependent parthenogenesis, also called pseudogamy, is a reproductive strategy in which females use the sperm of males, usually from another species, to activate their oocytes. The sperm DNA does not participate to the development of the zygote, which produces only females. We discovered a novel and unique reproductive strategy in the pseudogamous nematode species *Mesorhabditis belari,* which produces its own males. While fertilization is needed to activate all oocytes, 92% of oocytes undergo a single meiotic division, do not decondense the male DNA and develop into diploid females by gynogenesis. The remaining 8% of the oocytes undergo two rounds of meiotic divisions, the paternal DNA decondenses and mixes with the female DNA, and develop exclusively into diploid male individuals. Using game theory, we developed a model that explains why 8% of males may be maintained in these populations while their genetic material does not participate to the female fitness. Such a reproductive strategy is efficient only if sons are more likely to mate with their sisters. We experimentally tested this prediction and show that *M. belari* females are indeed more often fertilized when mated with their brothers than with unrelated males. In parallel, we sequenced and assembled the genome and the transcriptome of *M. belari*. We will present our analysis of the genome and the recent experiments that we have designed in order to decipher i) the sex determination system of *M.belari*, ii) the different possible mechanisms of female meiosis.

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Wolbachia in filarial nematodes: a passenger holding the steering wheel in oogenesis through control of germline stem cell fate and differentiation

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Understanding intimate symbiotic interactions is of a huge interest because many pests and vectors live in multipartite associations with viruses and bacteria and their control poses significant challenges to the medical communities. The mutualism of *Wolbachia* bacteria *(Wb)* with highly debilitating or lethal parasitic filarial nematode species has triggered a resurgence of interest for these endosymbionts. While *Wb* are present in adult somatic tissues, they colonize the female germline to be passed onto the next generation. *Wb* depletion induces female sterility and eventually kills the adult worms, unlike current anti-helminth drugs. From eradication of neglected tropical diseases to marketable veterinary drugs, interests converge towards *Wb*. However, how the bacteria control the worm's fertility and survival is still a mystery. Massive apoptosis in embryos has been reported as the first consequence of *Wb* depletion in *Brugia malayi* a causative agent of human elephantiasis. We postulated a major role of *Wolbachia* during oogenesis because of their heavy colonization of the ovaries. Using novel approaches and techniques to deal with these large and unwieldy nematodes, we explored the making of an egg in filarial species, focusing on defects occurring during gamete production after *Wb* depletion, to determine which key cell mechanisms are controlled by the endosymbionts during normal development. Our data suggest that *Wb* influence the female germline in a cell-autonomous manner as early as the germline stem cell pool maintenance, and stimulate the proliferation in parallel of the known key controllers. We will present the cellular defects following *Wb*-depletion and suggesting that the endosymbionts are essential to maintain a proper germline developmental program in order to produce viable eggs and embryos.

*Speaker

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A novel correction mechanism regulates nuclear position and ensures proper DNA segregation during late cytokinesis

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Ensuring correct DNA segregation is an essential feature of cell division which relies on the proper assembly of the mitotic spindle and its coordination with the cytokinetic machinery. Here we present a novel mechanism which corrects DNA segregation defects due to cytokinetic furrow mispositioning.

We recently showed that tight regulation of myosin is required to coordinate furrow and spindle positions during the first division of *C. elegans* embryos: abnormal accumulation of myosin at the anterior cortex induces a strong displacement of the furrow towards the anterior, thereby uncoupling cytokinetic furrow and spindle positions and leading to DNA segregation defects (Pacquelet et al;, J Cell Biol, 210,1085). However, we unexpectedly found that these DNA segregation defects can be corrected at the end of cytokinesis. This correction occurs when the mitotic spindle midzone is being disassembled and after nuclear envelop reformation. It relies on the concomitant displacement of the furrow and of the anterior nucleus towards the posterior and anterior poles, respectively. We also found that nucleus and furrow displacements coincide with an anteriorly directed flow of cytoplasmic particles, likely revealing the existence of a higher tension in the posterior region of the embryo compared to the anterior region. Genetic experiments demonstrated that the displacement of the anterior nucleus requires the interaction of the nucleus with microtubules as well as myosin activity. Moreover, both furrow displacement and cytoplasmic flow also require myosin activity. These results lead us to propose that myosin regulates nuclear position by inducing furrow displacement, which in turn increases intracellular pressure in the posterior region of the embryo and creates an anteriorly directed cytoplasmic flow.

Altogether, our work reveals the existence of a so far undescribed correction mechanism which ensures that DNA segregation defects due to the mispositioning of the cytokinetic furrow are corrected during late cytokinesis. This correction involves the regulation of nuclear position by the concomitant action of microtubules and myosin and is critical to ensure the robustness of cell division.

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Session 2

A ratchet process powers *C. elegans* embryo axis elongation

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Body axis elongation represents a fundamental morphogenetic process in development, which involves cell shape changes. While it is clearly established that mechanical forces play a critical role in driving these changes, proper understanding of how cells respond to such forces is lacking. To understand the interplay between cell elasticity and its response to forces we are studying axis elongation of *C. elegans* embryos, which depends on muscle contractions during the 2nd phase of axis elongation. To gain a global view of this process, we used Lightsheet Microscopy, focusing on epidermal adherens junctions and muscle nuclei. First, by measuring the distance between two dorsal or ventral muscle nuclei, respectively, we found that dorsal and ventral muscles mostly contract alternatively, causing embryos to rotate. Second, we observed that the length of the embryo gradually increases after each muscle contraction. Taken together these results suggest that *C. elegans* embryos extend in a ratchet mode. A classical ratchet works with a lock preventing the system to go backwards. To identify the potential morphogenetic lock that would counteract elasticity, we focused on the kinase PAK-1 which we previously found to mediate a mechanotransduction system downstream of muscle contractions. We performed a yeast two-hybrid screen and an RNAi screen in a *pak-1(Ø)* mutant background, from which α-spectrin SPC-1 came out as a strong candidate. We found that *spc-1(-) pak-1(-)* mutant embryos elongate up to the 1.5-fold stage and then retract to 1-fold. Further, muscle defective *spc-1(-) pak-1(-)* embryos failed to retract, implying that muscle contractions induce the retraction phenotype. At the subcellular level, we found that circumferential actin filament bundles are discontinuous and not fully oriented perpendicular to adherens junctions in *spc-1(-) pak-1(-)* embryos. Strikingly, it was previously shown that actin depolymerization induces embryo retraction (Priess & Hirsh 1986), suggesting that actin rearrangement could account for the lock in the ratchet. To test if it was the case, we modelled the embryo as a Kelvin-Voigt material experiencing acto-myosin force from the epidermis plus muscle tension. We could predict embryo lengthening by introducing a viscoplastic component in the system, which we propose corresponds to actin shortening. Altogether our data identify a cellular network that confers mechanical plasticity (in physical terms, implies an irreversible deformation under stress) that stabilizes cell shapes during morphogenesis.

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Epidermal Response to sterile injury and fungal infection in *C. elegans*

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Epithelia are the interface that separates animal tissues from the external environment. Epithelial membranes are easily damaged, by physical injury and chemical stress, compromising cell integrity. A perforated plasma membrane can be repaired through activation of a resealing process. In parallel, changes in gene expression provide protection against opportunistic infection and aid in restoring homeostasis. In the epidermis of *C. elegans*, wounding provokes an immediate Ca2+ burst that promotes actin ring formation at the wound site, enabling wound closure, and an increase in the transcription of antimicrobial peptide (AMP) genes in the epidermis. The coordination and interdependence of these two responses are, however, not fully understood. We developed a model where we wound the *C. elegans* epidermis with a laser under a spinning disk microscope to monitor in vivo the subcellular changes that lead to both wound healing and immune activation. After the Ca2+ burst, we observed a fast membrane reorganization and a recruitment of EB1/EBP-2, a protein that binds the + end of growing microtubules. This precedes and seems to trigger the formation of the actin ring necessary for wound closure, that is independent of the classic contractile purse string machinery. At the same time, the SLC6 bioamine transporter SNF-12, which is a key player in the epidermal immune response, gets locally activated. We propose a model where upon wounding SNF-12 first dissociates from apical clusters, get rapidly cleaved and its released C tail translocate into the nucleus to activate the innate immune response with the STAT-like transcription factor STA-2. Subsequently, the SNF-12 proteins will be recruited towards the wound site. Experimental disorganization of microtubules disrupts the constitutive SNF-12 positioning and its dynamics upon wounding, leading to the absence of an immune response. Thus, the process of cytoskeleton reorganization during wound closure seems to be closely linked to immune activation. Our work has revealed an unexpected role for a bioamine transporter in immune activation. Future investigations will uncover whether a similar epithelial response is also activated upon infection.

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Bridging extra- and intracellular synaptic scaffolds at GABA synapses in *C. elegans*

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Positioning type A GABA receptors (GABAARs) in front of GABA release sites set the strength of inhibitory synapses and consequently the excitability of neuronal networks. The *C. elegans* inhibitory neuromuscular junction (NMJ) provides a genetically tractable model to analyze the clustering of GABAARs because muscle cells receive inhibitory innervation from GABAergic motor neurons. We previously identified an anterograde synaptic organizer, Ce-Punctin/MADD-4, that governs the molecular composition of post-synaptic domains at the NMJs. A short isoform of Punctin is secreted by the inhibitory motoneurons and localizes in the extracellular matrix at NMJs. Punctin controls the clustering of the synaptic adhesion molecule neuroligin (NLG-1) at inhibitory synapses, which in turns recruits the GABAAR UNC-49. In addition, Punctin activates the netrin receptor UNC-40/DCC (Deleted in Colorectal Cancer), which promotes the recruitment of UNC-49 by NLG-1. In a forward screen for UNC-49-RFP mislocalization, we also identified FRM-3, a FERM domain containing protein, and LIN-2/CASK that were shown to associate with UNC-49 at inhibitory NMJ. We demonstrated that UNC-40 acts at postsynaptic sites to stabilize an intracellular scaffold that includes FRM-3, LIN-2/CASK, NLG-1, and UNC-49. Based on the previously characterized modes of action of UNC-40/DCC in cell migration, we propose a model in which UNC-40 acts downstream of Punctin and controls subsynaptic actin dynamics and/or phosphorylation of intracellular scaffold components to regulate the stability of GABAARs at inhibitory synapses.

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A protein disulfide isomerase linked to congenital cardiac defects is required in the endoplasmic reticulum for acetylcholine receptor biogenesis.

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Ionotropic acetylcholine receptors (AChR) are pentameric transmembrane proteins that are assembled in the endoplasmic reticulum (ER). AChR assembly is known to be generally inefficient and limits the number of receptors delivered to the plasma membrane. To characterize further the machinery required for AChR biogenesis, we performed a genetic screen in *Caenorhabditis elegans* for mutants partially resistant to the AChR agonist levamisole and identified *crld-1*, the ortholog of the human genes Creld1 and Creld2 . Creld1 mutations are associated with developmental cardiac defects and Creld2 is implicated in ER stress response. Here we show that CRLD-1 is an ER-resident protein specifically required for the expression of levamisole-sensitive AChR (LAChR) in muscle cells. CRLD-1 physically interacts with L-AChR and regulates the stability of unassembled L-AChR subunits. We demonstrate that CRLD-1 contains a protein disulfide activity (PDI) required for L-AChR expression in vivo . We also found that expression of both murine and human Creld1 in *C. elegans* body-wall muscle rescues the decreased expression of L-AChR in crld-1 KO mutants (based on levamisole response) to the same extent as the nematode gene. W have then extended our analysis to mammalian systems, and we confirmed that Creld1 function in AChR biosynthesis is conserved in vertebrate muscle cells.

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Session 3

Adenylosuccinate Lyase deficiency in the recycling pathway is responsible for post-embryonic developmental delay, germline maintenance and muscle defects.

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The purine biosynthesis pathway is a metabolic network conserved from prokaryotes to humans, ensuring ATP and GTP homeostasis. This pathway is well characterized in microorganisms, but little is know about its regulation in metazoans. Different diseases are associated with deficiencies in purine synthesis enzymes leading to neuromuscular defects, autistic spectrum behaviors and psychomotor delay. ADSL enzyme plays a role in both the de novo and the recycling pathway. Its substrates are known to act as signal metabolites regulating gene expression. Study ADSL deficiency in multicellular organisms is extremely challenging in comparison to microorganisms. In ADSL deficiency patients, the most severe symptoms are neuromuscular indicating neurons and muscles may require the purine pathway differently. Purines can be transported across tissues and purine metabolism could have different regulations during development. To address this issues we established *C. elegans* as metazoan model organism.
We studied the phenotypes caused by ADSL deficiency and sought to distinguish their causes. Specifically, our goal was to understand what ADSL deficiency phenotypes are caused by an accumulation of an intermediate, a lack of purines, or an imbalance in purine synthesis. We aim to establish whether ADSL activity is required in the de novo or recycling pathway. So, we also study other purine pathway *C. elegans* mutants in order to separate the origins of phenotypes. By sequence alignment, HPLC profiling and functional complementation in yeast, we have shown that both the de novo and the recycling pathway are functionally conserved in *C. elegans*. Likewise, we observed sterility in *adsl-1* mutant, with less than 10 germline nuclei. We also observed a reduced adult size indicating a potential role for ADSL during post-embryonic development. So, we studied developmental timing using a novel high-throughput technique and shown that in *adsl-1* mutant post-embryonic development is increasingly delayed as larval stages progress. We also observed a strong locomotion defect in *adsl-1* mutant, associated with myosin fiber misalignment but no neuronal defect. Through genetic analysis, we can conclude that ADSL deficiency in the recycling pathway causes these different phenotypes. Our analysis shows that ADSL activity in the recycling pathway plays a crucial role, in a tissue specific manner and during the post-embryonic development. Hence, *C. elegans* is an amenable metazoan model to study the purine metabolism.

*Speaker

You are what you experience: The impact of environment on cellular identity

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The balance between maintenance of cellular identity and cellular plasticity (as the potential of identity change on a functional and morphological level) is a major challenge for tissues inside an organism. Unbalanced, uncontrolled cell fate changes can cause several dysfunctional cellular behaviors such as cancer and degenerative diseases. Unraveling the mechanisms behind cell type conversion will help to develop a safe environment for regenerative medicine. Here, we describe how several external factors can impact on cellular identity and increase its potential of plasticity.
We use a natural cell identity conversion in the worm to determine how a cell can change or maintain its identity. *C. elegans* rectal to neuronal Y-to-PDA transition is a *bona fide* transdifferentiation event: During L2 larval stage the epithelial identity of the Y rectal cell is erased completely, followed by a very robust and unipotent redifferentiation into a fully functional motoneuron, PDA.

We previously described a subset of essential factors that are crucial for the inititation of Td such as *egl-27*/MTA, *sem-4*/SALL, *ceh-6*/OCT and *sox-2*, whose loss of function lead to severe defects in PDA formation. We identified two novel regulators in Td: *lin-15A* and *lin-56*. Their null mutants show a lower penetrance of PDA defects and are highly variable under different environmental conditions. We found starvation and caloric restriction, as well as virulence or different food sources to decrease PDA defects in these mutants and thus to increase the potential of cellular plasticity.
We have indications that there is a general mechanism underlying the effect of these environmental factors and that this might be a more general concept not only in the worm, that could impact the field of cell identity conversions as a tool in regenerative medicine.

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Chromatin organisation : a novel function for H3K4 methylation in the *C. elegans* germline.

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H3 lysine 4 methylation (H3K4me) is a conserved histone post-translational modification associated with the promoter of actively transcribed genes and which regulates gene expression. In addition, H3K4me is associated with DNA repair, recombination and chromatin organisation. However the molecular mechanisms supporting these different context-dependent functions remain poorly understood. H3K4me is catalyzed by histone methyltransferases of the SET1/MLL family. SET-2, one of the two SET1/MLL family members encoded by the *C. elegans* genome, is required to catalyze H3K4me3 in the soma and H3K4me2/3 in the germline. A *set-2* loss-of-function mutant shows genome instability at 20∘C and a mortal germline phenotype (Mrt) associated with germline transdifferentiation at 25∘C. My PhD project aims at a better understanding of the role of H3K4 methylation in the *C. elegans* germline. I will present RNAseq experiments performed on dissected germlines showing that H3K4me is associated with both gene repression and activation. Genetic analysis suggests that, in addition to influencing transcription, SET-2 dependent H3K4 methylation cooperates with condensin II to ensure proper chromosome segregation. Using a novel FLIM FRET approach, I will present evidence suggesting that SET-2/SET1 is required for proper chromatin compaction of germ cells. These results reveal a novel, unexpected role for *set-2/*SET1 dependent H3K4 methylation in chromatin organisation in the germline of *C. elegans*.

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RNP phase transitions and the coordination of RNA expression

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Gene networks are coordinated with organism development and adapted to environmental changes. Nucleic acids organization and the control of its expression on a large scale remain poorly understood. We and others introduced phase transitions as a framework to study co-assemblies of nucleic acids and proteins, which are a common feature of gene expression path-ways. Using *C. elegans* germline as model, we showed that cytosolic ribonucleoproteins (RNPs) can switch from a diffuse soluble state to condensed liquid droplets, semi-liquid hydrogels or solid aggregates (1). These phase transitions regulate RNP exchange, sort and compartmental-ize RNA during development and in response to the environment. Genetic screen approaches further identified regulators of these RNP phase transitions (2). For example, we showed that supramolecular polymerization of polyQ rich RNA binding proteins play a structural role in RNP super-assemblies. Furthermore, RNP condensation may reinforce mRNA translation re-pression in an adaptive response to quiescence or stress that is critical for oocyte fitness. We recently developed an RNP droplet purification method that identifies large RNA regulons whose translation is coordinated by phase transitions (3). We are utilizing this method in *C. elegans* to further dissect how RNP super-assemblies adapt RNA expression to the environment during early development.

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Posters

Asymmetric cell division and the acto-myosin cytoskeleton in nematodes

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The first division of the *Caenorhabditis elegans* embryo is a classic example of asymmetric cell division. Much has been learned from this model concerning the role of the acto-myosin cortex in symmetry breaking and polarity establishment, and the role of astral microtubules in spindle positioning. Although they undergo similar asymmetric divisions, nematode embryos from other genera appear to be lacking key characteristics observed for *Caenorhabditis*, including cortex behavior. In this project, we will characterize the acto-myosin cytoskeleton in three nematode embryos evolutionarily distant from *C. elegans*, in order to understand how acto-myosin organization and dynamics is modified in embryos of non-*Caenorhabditis* genera. We chose three species that showed interesting cortical activity and were sequenced: *Oscheius tipulae*, *Pristionchus pacificus* and *Diploscapter coronatus*.

As a first step, since these species are not amenable to easy genetic manipulation like *C. elegans*, we performed phalloidin staining on fixed embryos to observe the actin network in these species. The embryos of *O. tipulae* and *P. pacificus* have enhanced cortical shape changes at the anterior pole of the embryo as observed by DIC microscopy. However phalloidin staining showed that there did not appear to be an enhanced actin signal at the anterior pole, and that the asymmetry in cortical actin was similar in *C. elegans*, *P. pacificus* and *O. tipulae*. There were qualitative differences in the organization of cortical actin however, with *P. pacificus* and *O. tipulae* displaying more bundles and long-range structures, and more cytoplasmic actin in the case of *O. tipulae*. Similar cortices were also observed with *D. coronatus*, despite the fact that this species undergoes very little cortical shape change prior to division, as observed by DIC microscopy. In order to measure dynamics, we are currently working on introducing fluorescently-labeled actin probes into *P. pacificus* by transgenesis via bombardment in an *unc-119* mutant background. Bombardment should side-step some of the issues associated with other techniques of genetic modification in *P. pacificus*. With the widespread application of CRISPR to nematodes for making gene knock-outs, we hope that corresponding *unc-119* mutants in other species will be forthcoming, allowing us to label the actin cytoskeleton in the other species as well.

Results of this study will shed light on why non-*Caenorhabditis* embryos display different shape change dynamics during the first cell division, and yet still succeed in dividing asymmetrically.

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Physical and functional interaction between the SET1 complex component CFP-1/CXXC and the Sin-3S/HDAC complex in *C. elegans* embryos

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H3K4 methylation, a universally conserved mark associated with active promoters in all species, is catalyzed by the highly conserved SET1/MLL family methyltransferases acting in large multisubunit complexes known as COMPASS in yeast and SET1/MLL in mammals. COMPASS-related complexes from yeast to mammals contain either a SET1- or MLL-related catalytic subunit, and the common subunits ASH2, RbBP5, WDR5 and DPY30. In addition, the CFP1/CXXC1 zinc finger protein is unique to SET1 complexes. *C. elegans* contains a single homologue of SET1, named SET-2, and single homologues of all additional subunits, including CFP-1. All subunits contribute to global H3K4 methylation and share common phenotypes, but the biochemical composition of the complex has not been described. In order to purify the SET-2/SET1 complex from *C. elegans*, we undertook a proteomic approach in *C. elegans* embryos. In immunoprecipitation experiments using tagged components of the SET1 complex, followed by tandem MS/MS, we identified all common as well as unique subunits of SET1 and MLL-related complexes. In addition, we identified a previously unknown link between the SET-2/SET1 complex and the highly conserved Sin3S histone deacetylase complex, which we identify for the first time in *C. elegans*. We show that CFP-1 directly interacts with SIN-3 and additional subunits of the Sin3S complex through a conserved domain. Using genome-wide transcriptional profiling and binding studies, we further show that CFP-1, SET-2 and SIN-3 co-regulate common genes, and that CFP-1 and SIN-3 colocalize on a subset of promoter regions. Finally, phenotypic analysis of animals lacking *set-2*, *cfp-1*, or *sin-3* complex subunits reveals a common function in maintaining fertility and promoting cell divisions in intestinal cells. Our results support a mechanism whereby SET-2/SET1 and SIN-3/HDAC physically interact and cooperate to maintain correct patterns of gene expression in a context-dependent manner, and perhaps directly influence chromatin compaction.

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Intestinal polarity is maintained by the V0-ATPase in *C. elegans*

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Food absorption relies on the strong polarity of intestinal epithelial cells and the array of microvilli forming a brush border (BB) at their apical pole. Some rare genetic enteropathies, characterized by BB defects leading to food malabsorption, are caused by mutations in genes coding for membrane traffic factors (Myo5B and STX3 in microvillus inclusion disease/MVID; Munc18-2 in FHL-5). We and others have recently shown that enterocytes from MVID patients display mispolarized polarity modules and BB structural proteins. Despite this functional link, little is known about the interaction between membrane traffic, polarity components and BB structural proteins, especially *in vivo*.

Combining genetic and *in vivo* imaging tools in the *C. elegans* intestine, we uncovered that depletion of the V0 transmembrane sector of the V-ATPase (V0-ATPase), a H+ pump necessary for endosomes acidification and transmembrane proteins trafficking, affects both the intestinal polarity and the BB. Indeed, V0-ATPase depletion leads to a basolateral mislocalization of apical polarity determinants (CDC-42/PAR module) and BB components (actin, ERM-1), defects in BB maintenance and formation of microvillus inclusions in the cytoplasm. Further characterization of this complex in polarity maintenance showed that: 1) this V0-ATPase role is independent from the acidification function, 2) V0-ATPase specifically controls a trafficking step involving RAB-11-positive apical recycling endosomes, 3) V0-ATPase genetically interacts with the glycosphingolipids biosynthesis pathway and 4) V0-ATPase depletion phenotype is dependent on cholesterol concentration.

Overall, our results suggest that the V0-ATPase has a function in apical polarity involving RAB-11 recycling endosomes and lipids to ensure the correct polarization of polarity determinants and BB components. Notably, polarity loss, microvillus inclusions and RAB-11-endosomes defects are hallmarks of MVID and FHL-5 enteropathies. Thus the V0-ATPase likely belongs to a trafficking complex essential for intestinal epithelium integrity and characterization of its role will help to better understand the mechanisms leading to absorption disorders.

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Molecular basis of natural variation in *C. elegans* dauer formation

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Virtually all organisms possess the capacity to flexibly adjust their development in response to environmental changes, a phenomenon called developmental plasticity. A prime example of developmental plasticity is the process of dauer formation in the nematode *C. elegans*, during which larvae can adopt an alternative, stress-resistant larval stage (termed dauer) in response harsh environmental conditions (high population density, starvation, or high temperature). The molecular mechanisms regulating dauer induction have been well-characterized and involve insulin, TGF-β and steroid signalling. In contrast, few studies have focused on characterizing the molecular variants explaining differences in dauer induction among natural *C. elegans* isolates. Here we characterized a *C. elegans* isolate (JU751, France), which shows an unusually strong tendency to form dauers compared to most other *C. elegans* isolates. We therefore quantified dauer formation in F2 recombinant inbred lines (RILs) generated from an intercross between JU751 and another isolate displaying dauer induction only under harsh environmental conditions (JU1200, UK). RILs were SNP-genotyped at 150 loci across the whole genome to allow for QTL (Quantitative Trait Locus) analysis, which identified a single, highly significant QTL on chromosome III, spanning approximately 700kb. We have confirmed the effect of this QTL region on dauer formation through establishment of near-isogenic lines (NILs. We further restricted the target region, within which we currently investigate a key candidate variant affecting expression of a gene known to affect dauer induction.

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Identification of new regulators of Acetylcholine receptor function in *C. elegans*

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Acetylcholine receptor (AChR) is an essential component of central and peripheral nervous responsible in particular for the coupling between nervous and muscular system at the neuromuscular junction. At cholinergic synapses, AChRs are clustered in front of neurotransmitters release sites to insure fast excitatory neurotransmission. Despite extensive work to decipher the molecular properties of the receptor itself, how the activity of the receptor and the signal following its activation are modulated is still bot fully understood; In *C. elegans*, a subclass of AChR is sensitive to the agonist levamisole. Prolonged exposure to levamisole induces irreversible worm paralysis. Forward genetic screens based on the ability of worms to overcome such levamisole exposure lead to the identification of genes coding for AChR subunits or involved in AChR biosynthesis and clustering.

Taking advantage of the potent and specific effect of levamisole, we conducted in parallel a structure/function analysis of a AChR partner and a genetic screen based on the ability of some mutants to adapt to levamisole. This two approaches both aimed to characterize new regulatory mechanisms of AChR function.In one hand, we focused on LEV-10, a protein identified as a key player in AChR clustering and levamisole sensitivity. Indeed, *lev-10* mutants display unclustered AChR and are able to adapt to levamisole suggesting a critical role for AChR clustering in the response to levamisole. However, preliminary work revealed that a CUB domain of LEV-10 may play a role in levamisole sensitivity without affecting receptor clustering. This suggests that this CUB domain could recruit a regulator of AChR function involved in levamisole response. Using CRISPR/Cas9 technic, we then edited the endogenous *lev-10* loci to delete this domain and studied the effect of this deletion.

On the other hand, we aim to identify new regulators of AChR function by performing an EMS mutagenesis screen based on the identification of mutant able to adapt to levamisole. To identify genes regulating AChR function we used a knock-in strain expressing a RFP-tagged AChR and focused on mutants with a receptor clustering pattern similar to wild-type. A first screen for adaptation was conducted, followed by genetic complementation and additional levamisole adaptation tests. All the interesting strains were sequenced and strains carrying mutations in the AChR subunits or already known candidates were discarded. This screen finally isolated 7 strains with no mutation in the already known candidates but able to adapt to levamisole. We are currently conducting experiments to simultaneously map and identify mutations responsible for the levamisole adaptation phenotype which will eventually lead to the characterization of unknown regulators of acetylcholine signaling.

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Comparison of active forces governing spindle positioning in different species of nematodes

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In many nematode species, the first embryonic cell division gives rise to two daughter cells of different size. This is due to the asymmetric positioning of the mitotic spindle towards the posterior side of the cell. In the one-cell embryo of *C. elegans*, force generators that are present on the cell cortex pull on astral microtubules. Because they are slightly enriched on the posterior side of the cell compared to the anterior side at the onset of anaphase, they generate asymmetric pulling forces towards the posterior of the cell. These force generators are also responsible for oscillations of the spindle on the transverse axis of the cell. In *C. elegans*, the amplitude and frequency of these oscillations are directly correlated with the strength of the cortical pulling forces.

By analyzing spindle movements during the first embryonic division of 42 different nematode species, we uncovered large inter-species variations in spindle oscillation, elongation, and displacement (Valfort & al. Plos Biology 2018). Interestingly, we found several species for which spindle displacement was not accompanied by spindle oscillations, suggesting a reduction of the strength of cortical pulling forces compared to *C. elegans*. In order to further analyze the force balance in these species, we performed laser ablation of the spindle or of astral microtubules in 4 species that do not display spindle oscillations: *C. species 1* which is at the basis of the *Caenorhabditis* genus and is the only *Caenorhabditis* species that does not display spindle oscillations during mitotis, *Diploscapter corronatus*, *Pristionchus pacificus* and *Oscheius tipulae*. In all species, except *D. corronatus*, we found that the spindle was submitted to pulling forces during mitosis. These forces were more pronounced towards the posterior side of the cell compared to the anterior side, as previously shown for *C. elegans*, for *C. species 1*. However, we found that the forces were symmetric in *P. pacificus*. In *O. tipulae* wild-type embryos the spindle moved back and forth on the anterio/posterior axis of the cell during mitosis before reaching its final position on the posterior side of the cell. We found that several reversion of the net pulling forces towards the anterior or the posterior of the cell were responsible for these oscillations. Our results show the many different mechanisms allow the asymmetric positioning of the spindle depending on the species, because it can happen in the absence of pulling forces (in *D. corrona-tus*), when forces are symmetric (*P. pacificus*) or when the asymmetry of forces is oscillating between the anterior and the posterior of the cell (*O. tipulae*). We are now developing tools to explore these three species into more details.

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Unbiased genetic screen to identify paternal factors involved in the regulation of the maternal mitochondrial transmission

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The genomic DNA is inherited from both parents (one copy each) upon fertilization, making it a biparental transmission. Mitochondrial DNA, however, follows a uniparental transmission, typically maternal. It has been shown that the paternal mitochondria in *C. elegans* are degraded by postfertilization autophagy but the activating signal is yet to be determined (Al Rawi et Al, 2011).
In order to identify the paternal factors involved in the regulation of paternal/spermatic mitochondrial clearance, we will conduct an unbiased genetic screen on EMS mutagenized worms. We aim to identify male mutants able to transmit their mitochondria.

To achieve this goal, we designed the screen on the basis of a positive selection of worms that keep the paternal mitochondrial genome. We use hermaphrodite worms that carry a genomic mutation in *ctb-1* and therefore have a dysfunctional respiratory chain and show slow growth. These worms are crossed with mutated males harboring a mitochondrial mutation in *isp-1* that has the potential to rescue the slow growth phenotype.

Furthermore, since this screen requires a large number of males, we also developed a high throughput method to rapidly and efficiently sort males from a large worm population.
This screen will allow us to identify the marks that are specific to paternal mitochondria and could be recognized by a maternal mechanism that will activate the mechanism of autophagy.

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Heparan sulfate proteoglyans, a sugar code at the neuromuscular junction?

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Heparan sulfate proteoglycans (HSPGs) are composed of a core protein and one or several chains of unbranched sugars that consist in many repeats of disaccharides units of glucuronic acid and N-acetylglucosamine. Modification of these sugars by 6 enzymes (HST-1, HSE-5, HST-2, HST-3.1, HST-3.2 and HST-6) leads to a complex code of HSPGs displaying saccharides with various levels of 2-, 3- and 6-O-sulfation and epimerization.
Caenorhabditis elegans is an ideal model to assess the role of specific modifications because, contrary to mammals, there is little redundancy among the enzymes achieving specific modifications. Moreover, *in vivo* expression of single chain fragment variant (scFv) antibodies, which have been fused to the green fluorescent protein (GFP), allows the detection of specific HSPG modifications at the neuromuscular junction. Two such strains show specific synaptic patterning across GABAergic and cholinergic synapses along the ventral and dorsal cords. In L4 larvae, most of the GFP signal detected in these two lines comes from modifications present on syndecan (SDN-1), as revealed by the loss of signal upon crossing to *sdn-1(zh20)* null mutants. In *sdn-1(zh20)* mutants, levels of cholinergic receptors (UNC-29) and GABA receptors (UNC-49) are decreased at the nerve cords (see the poster of Camille Vachon *et al.*).
The aim of this project is to assess a potential role for specific HSPG modifications in the organization of the neuromuscular junction. To do so, specific mutants of each modification enzyme will be crossed to knock-in strains that express either GABAergic or cholinergic receptors fused to the TagRFP-T (*unc-49(kr296)* and *unc-29(kr208)*, respectively) and potential changes in receptor expression will be quantified at the dorsal and ventral nerve cords. Moreover, the distribution of Punctin, an extracellular synaptic organizer, is also affected by the loss of syndecan. A visual screen for Punctin mislocalization is currently being conducted in order to identify novel regulators of synapse organization. Preliminary results will be presented at the meeting.

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Formin dynamics and cortical actomyosin contractility the early *C. elegans* embryo

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Proper development and morphogenesis relies on fine-tuned spatial and temporal deployment of forces inside cells. The actomyosin cytoskeleton is determinant for the deployment of these forces and so, for the mechanical properties of embryonic cells and tissues.
In *C. elegans* early embryos, the cell cortex includes at least two types of cytoskeletal structures that simultaneously coexist, competing for the actin monomer pool as well as for their various binding partners. Strikingly, these structures co-exist in space and time, competing for the actin monomer pool as well as for their various binding partners. Indeed, actin network homeostasis is not only a balance between cytoplasmic G- and cortical F-Actin, but also a tug-of-war between these different actin structures for the control of the actin monomer pool (Burke et al, 2014). The distribution between these different populations is critically important for the mechanical properties of the cortex (Pujol et al, 2012; Chaigne et al, 2013).

Formins are responsible for the polymerization of new actin filaments. Using HILO imaging and the SmPReSS method (Robin et al. 2014), we can track single molecules of actin or actin-binding partners (such as the processive formin CYK-1) in order to understand the biochemical interactions in vivo within cortical actomyosin and the organisation of the active meshwork during contractility pulses (orientation of actin filaments).Furthermore, I will present results of the analysis of CYK-1 at the cortex, as proxy for measuring actin filament length in vivo and how it is scaled with cell size in the embryo.

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Arp2/3 complex-based actin assembly produces forces to drive basement membrane invasion

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During cell invasion, it remains unclear if actin polymerization is applying force to make holes in basement membranes (BMs), or if actin filaments play a passive role as scaffolding for targeting invasive machinery. Here using the developmental event of anchor cell (AC) invasion as a model of BM invasion, we provide evidence that actin polymerization in the AC pushes down on the BM before invasion, exerting forces in the tens of nN range. Arp2/3 complex-driven actin nucleation at the invasive membrane is absolutely required for invasion, and both Arp2/3 complex activators, N-WASP and WAVE, are present and play a role in the invasive protrusion. Delays in invasion upon actin perturbation are not caused by defects in trafficking, as proteases and other invasive components are shown to be correctly localized. Overall we provide evidence that Arp2/3 complex-driven actin polymerization is producing forces to facilitate hole formation in BM during cell invasion.

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Robustness in the transcriptional programs that maintain neuronal cell fates

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During nervous system development, neurons with specific functions are generated. The acquisition and maintenance of their differentiated state are achieved by terminal transcription factors (TFs) that are expressed throughout the life of the neurons and often autoregulate their own expression via positive feedback loops. To produce an invariable output this transcriptional network has to be strictly controlled and needs to be robust to internal and external perturbations. The objective of this study is to determine how the specific fate of a neuron is maintained during the life of the animal in a reliable manner despite the inherent stochasticity in gene expression levels. To address this question, we use a specific class of cholinergic neurons of *C. elegans*, the pair of AIY cholinergic interneurons, whose differentiation network is well characterized. In our lab it has been shown that the expression of the terminal TFs is noisy and that chromatin factors, members of the PRC1 complex, display a protective role on the fate of AIY neurons. A stochastic and progressive loss of the identity of AIY neurons is observed when components of the PRC1 complex are mutated. In the current study, we are testing whether PRC1 protects neurons against environmental perturbations. In addition, we will perform a genome-wide RNAi screen to identify new regulators that buffer the variability of gene expression in the maintenance phase.

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Evolution of *Caenorhabditis* sperm size within and between species

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Sperm competition is a key force driving evolutionary diversification of sperm morphology. In *Caenorhabditis* nematodes, sperm size is a major factor determining sperm competitiveness: male sperm is larger and consistently outcompetes hermaphrodite sperm, and larger male sperm outcompetes smaller male sperm. To generate an in-depth overview of sperm size variation in *Caenorhabditis* nematodes, we quantified male sperm size in 100 *C. elegans* wild isolates from a world-wide collection and in the 26 currently described *Caenorhabditis* species, including the three androdioecious species.
Analysis of *C. elegans* wild isolates indicates significant levels of heritable variation in mean male sperm size, but Genome-Wide Association Mapping did not allow detection of any significant QTL underlying this variation. The observed sperm size distributions across strains indicate a complex genetic basis involving many loci of small effect. This survey of intraspecific variation also uncovered a strongly reduced mean male sperm size in LSJ1 and LSJ2 strains, recently derived from the reference strain N2. We show through quantitative complementation tests that a *nurf-1* deletion in LSJ strains is responsible for reduced male sperm size, suggesting a role of the Nucleosome Remodeling Factor (NURF)-like complex in *C. elegans* spermatogenesis.

Our quantification of sperm size evolution in different *Caenorhabditis* species confirmed earlier reports that mean sperm size of gonochoristic species is globally larger than in males of androdioecious species, although exceptions occur. While species of the elegans group all display relatively small, and similar, male sperm size, several gonochoristic species outside this group show convergent evolution of distinct, extremely large male sperm. In addition, within-species genetic variation in male sperm size is considerable in all examined gonochoristic and androdioecious species. We present experimental results aimed at understanding how germline and sperm development shape such dramatic variation in sperm size across species, isolate, sex and individual.

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Functional characterization of a 9 transmembrane domain protein involved in GABA receptor trafficking

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In the central nervous system (CNS), the inhibitory system plays a key role in neuronal network excitability. To identify novel genes and mechanisms involved in the formation and regulation of inhibitory synapses, we use the inhibitory GABAergic neuromuscular junction of *C. elegans* as a genetically tractable model. At these synapses, fast neurotransmission is ensured by type A ionotropic GABA receptors (GABAAR), which form post-synaptic clusters in front of GABAergic buttons.

We performed an unbiased EMS genetic screen based on *in vivo* visualization of fluorescently-tagged GABAAR in a knock-in strain. We identified 56 mutants with abnormal GABAAR localization. For 36 mutants, we used a novel WGS strategy to simultaneously map and identify causative mutation without any prior time-consuming genetic mapping. We found 9 alleles of genes already known to be involved in synaptogenesis, such as genes encoding master regulators of neuronal identity (the transcription factors UNC-30*, a* Pitx family member, and UNC-3*,* a COE motif family member*)*, presynaptic organizers (SYD-2/liprin), postsynaptic scaffold proteins (FRM-3*,* an ERM domain protein*,* and LIN-2/CASK) and the netrin receptor UNC-40/DCC. For 11 mutant strains, we are currently completing the validation of candidate genes, which are known to be involved in various cellular processes, such as transcription factors, motor proteins or extracellular matrix components.

We started the functional characterization of a novel candidate gene, tentatively named *nsp-3,* which encodes an evolutionarily conserved transmembrane protein. *nsp-3* mutation causes a severe reduction of synaptic GABAAR and the presence of small ectopic punctae, partially colocalized with endosomal markers, in muscle cells. We reproduced this phenotype by generating a complete *nsp-3* deletion using CRISPR technology. A transcriptional reporter showed that it is expressed in many tissues among which muscle cells, hypodermis and motoneurons. We are now investigating its subcellular localization and role in GABAAR dynamics and localization. Though a few publications showed that other members of this family were involved in cellular adhesion, phagocytosis and immune response in *Drosophila*, nothing is known about their function in the CNS. Our data should identify novel functions of these proteins in the traffic or synaptic localization of neurotransmitter receptors in the nervous system.

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New insights on the Katanin, a prototype of microtubule-severing enzyme essential for *C. elegans* meiosis

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Microtubules (MTs) are dynamic cytoskeletal polymers with instrumental functions in cell division (meiosis and mitosis), morphogenesis, motility and signaling. MTs constantly polymerize and shrink and this dynamic behavior, which is critical for their function, is regulated by a large family of MT-interacting proteins. Whereas most of these proteins interact with the microtubule plus or minus ends, another class interacts with the MT lattice and severs MTs along their length, thereby controlling MTs size and density. Three evolutionarily conserved MT-severing enzymes have been identified: Fidgetin, Spastin and Katanin. Mutation of these enzymes has been linked to various defects and pathologies including developmental defects, neurodegenerative disorders such as hereditary spastic paraplegia (HSP) and the Fidget disease. In this project, we are using use *Caenorhabditis elegans* Katanin as prototype of microtubule severing-enzymes. Katanin is a heterodimer composed of a catalytic subunit (p60 –MEI-1 in *C. elegans*) and a regulatory subunit (p80 –MEI-2), but the relative contribution of both subunits to the MT-severing activity is unclear. Moreover, the mechanism by which Katanin is interacting with and is severing MTs is currently unknown. Using complementary biochemical and genetic approaches, we provide new insights into the molecular mechanism by which Katanin severs the microtubules.

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Wnt ligands regulate the asymmetric divisions of neuronal precursors in the *C. elegans* embryo.

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Wnt/beta-catenin signaling has been implicated in the terminal asymmetric divisions of neuronal precursors in both vertebrates and invertebrates. However, the role of Wnt ligands in this process remains poorly characterized. Here we used the terminal divisions of the embryonic neuronal precursors in *C. elegans* to characterize the role of Wnt ligands during this process focusing on a lineage that produces the cholinergic interneuron AIY. We observed that during interphase the neuronal precursor is elongated along the anteroposterior axis, and then divides along its major axis, generating an anterior and a posterior daughter with different fates. Using time-controlled perturbations, we show that three Wnt ligands (CWN-1, CWN-2 and MOM-2), which are transcribed at higher levels at the posterior of the embryo, regulate the orientation of the neuronal precursor and its asymmetric division. We also identified a role for a Wnt receptor (MOM-5) and a cortical transducer APC (APR-1) in this process, while PCP proteins do not seem to be involved. MOM-5 is enriched at the posterior pole and APR-1 at the anterior pole of the neuronal precursor. Our study establishes a role for Wnt ligands in the regulation of the shape and terminal asymmetric divisions of neuronal precursors, and characterizes the role of downstream components.

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Identification of various pseudogamous species from the Mesorhabditis genus

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Pseudogamy is a mode of reproduction in which the fertilization of an oocyte by a sperm cell is necessary even though the male DNA does not contribute to the zygote genome in female embryos. Several pseudogamous species of nematodes within the Rhabditidae family have been described in the first half of the 20th century (Nigon, 1949), in particular in the Mesorhabditis genus. These species were characterized by a very low percentage of males in the population (around 10%).
From soil sampling around the world, we have recently isolated 57 new strains of Mesorhabditis based on their morphology (small body size, posterior vulva, dark intestine...). We found 39 pseudogamous strains (showing also around 10% of males), and 18 strains showing a classic male/female mode of reproduction (gonochoristic strategy).
Genetic crosses between strains combined with morphological description defined 11 pseudogamous species and 2 gonochoristic species. Sequencing of ITS, 18S and 28S allowed us to obtain a first phylogeny, indicating that those pseudogamous species- which were found world-wide- constituted a monophyletic group.
We are currently exploring the origin of the reproductive isolation between pseudogamous species.

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Mechanisms of immune activation after cuticle damage

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We are studying the innate immune response of *C. elegans* to infection by a natural fungal pathogen. Through genetic and RNAi screens, we have defined several signaling pathways that act in the adult epidermis to regulate the expression of defense genes, including genes encoding antimicrobial peptides (AMP). We have shown that infection provokes the conversion of tyrosine to hydroxyphenyllactic acid (HPLA) and this in turn activates the G-protein coupled receptor DCAR-1 that acts upstream of a PKC-p38 MAPK pathway and the STAT-like transcription factor STA-2. Not only are *dcar-1* mutants deficient in their response to infection, but they also fail to switch on AMP expression following physical injury. Thus HPLA appears to be a damage-associated molecular pattern (DAMP), and DCAR-1 to be the first DAMP receptor identified in *C. elegans* [1-3]. Just how infection or injury leads to an increase in HPLA is, however, unknown.

We are currently dissecting the mechanism leading to its production through a forward genetic screen. Interestingly, we found that mutants lacking annuli, the structure on the cuticle that delineates the furrows, exhibit a high constitutive expression of AMP genes (3-5). We know for one of them, *dpy-10*, that the level of HPLA is elevated, and for all of them that the high AMP gene expression is dependent on *dcar-1*. Thus, we designed a genetic screen using a furrow mutant (*dpy-7*) background in which an infection-inducible AMP reporter gene is constitutively turned on, from the early larval stage. To avoid isolating mutants for components downstream of the GPCR, the strain used also expresses a constitutively active Ga protein (GPA-12) specifically in the adult epidermis. Screening for mutants that block reporter gene expression in larvae but not in adults will identify genes acting upstream of GPA-12 and hence potentially reveal the initial steps leading to the production of HPLA. We have screened over 60,000 genomes and obtained 7 candidate mutants. 3 have been successfully outcrossed and further phenotypically characterised and whole-genome sequenced to identify the underlying molecular lesion(s). We hope that it will give insights into how infection and injury is recognised in the worm.

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UNC-120/SRF independently controls muscle aging and lifespan in *C. elegans*

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Aging is commonly defined as the loss of global homeostasis, which results from progressive alteration of all organ function. This model is currently challenged by recent data showing that interventions that extend lifespan do not always increase the overall fitness of the organism. These data suggest the existence of tissue-specific factors that regulate the pace of aging in a cell-autonomous manner. Here, we investigated aging of *Caenorhabditis elegans* striated muscles at the subcellular and the physiological level. Our data show that muscle aging is characterized by a dramatic decrease in the expression of genes encoding proteins required for muscle contraction, followed by a change in mitochondria morphology, and an increase in autophagosome number. Myofilaments, however, remain unaffected during aging. We demonstrated that the conserved transcription factor UNC-120/SRF regulates muscle aging biomarkers. Interestingly, the role of UNC-120/SRF in the control of muscle aging can be dissociated from its broader effect on lifespan. In *daf-2* /insulin/IGF1 receptor mutants, which exhibit a delayed appearance of muscle aging biomarkers and are long-lived, disruption of *unc-120* accelerates muscle aging but does not suppress the lifespan phenotype of *daf-2* mutant. Conversely, *unc-120* overexpression delays muscle aging but does not increase lifespan. Overall, we demonstrate that UNC-120/SRF controls the pace of muscle aging in a cell-autonomous manner downstream of the insulin/IGF1 receptor.

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Cellular response to Wnt signals: an in vitro approach using *C. elegans* embryonic cells

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Embryonic development is finely tuned by a group of secreted proteins known as morphogens. They signal to the cell through their specific receptors present on the plasma membrane and are thought to define cell identity. One of the well-studied morphogens is Wnt that signals through its receptor Frizzled. In *C. elegans,* Wnt signalling controls various asymmetric divisions along the anterior-posterior axis. However, the localization and dynamics of the Frizzled receptor are largely unknown, although they are essential to the spatial and temporal control of Wnt signalling. The objective of this study is to understand individual cellular response in presence of imposed Wnt signals. In particular, we want to understand how Wnt polarizes individual neuronal precursor cells prior cell division, by modifying Frizzled localization and dynamics. To tackle these questions, we use the primary culture of *C. elegans* embryonic cells. These cells are exposed to artificial Wnt gradients generated by microfluidic devices. This approach combined with high-resolution imaging enables us to visualize fluorescently tagged Frizzled, at endogenous levels, on the membrane of single cells.

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Highlighting of the molecular mechanisms involved in probiotic properties of Lactobacillus rhamnosus Lcr35®

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Probiotics are defined by the World Health Organization as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host (1). Although their beneficial effects on health are proven, knowledge on their mechanisms of action is becoming a priority today. This is the case with *L. rhamnosus* Lcr35®, whose probiotic and anti-*Candida albicans* properties have been demonstrated (2, 3). Lcr35® is genetically and physiologically well-characterized and it has been proven that ingredients included in the formulations is able to potentialize Lcr35® probiotic effect. In order to investigate the molecular mechanisms involved in the Lcr35® strain probiotic properties, *in vivo* studies have been carried out in *C. elegans*: the analysis of the nematode survival in the presence of the probiotic strain potentialized or not for the anti- *C. albicans* properties, and a preliminary analysis of the modulation of the immune response by Lcr35®.

The survival analyzes showed that the strain Lcr35® allowed a significant increased lifespan of the nematode in comparison with *E. coli* OP50 whereas *C. albicans* impaired survival. The activation of insulin and p38 MAPK pathways has been shown using RT-qPCR. Then we will go further into the investigations to understand the molecular mechanisms related to these properties by studying in particular the preventive and curative effects of Lcr35® with respect to a *C. albicans* infection. In addition, a complete analysis of the transcriptome of *C. elegans* will be carried out by RNA sequencing in order to precisely identify the signaling pathways involved in the interaction between the host and the probiotic or the pathogen microorganisms.Moreover, because of *C. elegans* genetic homology with humans and in particular its intestinal physiology close to humans, our work lead us to evaluate the potential of *C. elegans* to be a relevant *in vivo* model to characterize the molecular mechanisms involved in the probiotic potential of a microorganisms and then to screen microorganisms collections for their potential probiotic capacities.

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The SET-2/SET1 histone H3K4 methyltransferase maintains cell fate in the *C. elegans* germline

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Maintenance of germ cell fate is of critical importance for species survival. In *C. elegans*, translational repression, P granules, chromatin factors and histone tail modifications have been shown to be essential to maintain germ cell identity. We previously showed that the conserved SET-2/SET1 histone H3K4 methyltransferase plays a crucial role in maintaining germline immortality and totipotency, two defining features of germline identity. *set-2* mutant animals grown at 25∘C become sterile over several generations, which is reminiscent of what happens in mortal germline (*mrt*) mutants. This sterility, which is reversible when animals are switched back to 20∘C, is associated with a loss of germline-specific markers, transcriptional derepression of somatic genes, and transdifferentiation of the germline into soma. To look at how the transcriptional landscape changes in the absence of SET-2 across generations and to identify pathways involved in germline maintenance, we performed transcriptome analysis of germlines dissected from fertile animals grown for 2 generations at 25∘C and on both fertile and sterile animals grown for 4 generations at 25∘C. We are currently analyzing these transcriptome data and performing RNAi to identify triggering events of transdifferentiation and transcriptional networks deregulated in transdifferentiated germlines. I will present preliminary results of this analysis.

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DRP-1-mediated apoptosis induces muscle degeneration in dystrophin mutants

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[3] Plateforme "Biologie de Caenorhabditis elegans" – CNRS : UMS3421 – Université Claude Bernard Lyon 1 Faculté de Médecine et de Pharmacie - 3ème étage 69008 Lyon, France

Mitochondria are double-membrane subcellular organelles with highly conserved metabolic functions including energy production. Mitochondria shapes change continually through the combined actions of fission and fusion events rendering mitochondrial network very dynamic. Mitochondrial fission and fusion processes are tightly regulated by GTPases of the dynamin family that are well conserved between species. Mitochondria are largely implicated in pathologies and mitochondrial dynamics is often disrupted upon muscle degeneration in various models.
Currently, the exact roles of mitochondria in the molecular mechanisms that lead to muscle degeneration remain poorly understood. Here we report a role for DRP-1 in regulating apoptosis induced by dystrophin-dependent muscle degeneration. We found that: *(i)* dystrophin-dependent muscle degeneration was accompanied by a drastic increase in mitochondrial fragmentation that can be rescued by genetic manipulations of mitochondrial dynamics *(ii)* the loss of function of the fission gene *drp-1* or the overexpression of the fusion genes *eat-3* and *fzo-1* provoked a reduction of muscle degeneration and an improved mobility of dystrophin mutant worms *(iii)* the functions of DRP-1 in apoptosis and of others apoptosis executors are important for dystrophin-dependent muscle cell death *(iv)* DRP-1-mediated apoptosis is also likely to induce age-dependent muscle degeneration.
Collectively, our findings point toward a mechanism involving mitochondrial dynamics to impact muscle degeneration through apoptosis in *Caenorhabditis elegans*.

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Analysis of syndecan function at the *C. elegans* neuromuscular junction.

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The extracellular matrix (ECM) plays an essential role in the development and function of organs and tissues. Syndecan is an ECM component that belongs to the heparan sulfate proteoglycan (HSPG) family. It is composed of 3 polysaccharidic chains linked to a core transmembrane protein. In *C. elegans* syndecan is coded by a single gene *sdn-1*. It is required for gonad arm migration and neuritic growth and guidance. Sugar chains are extensively modified including sulfation, acylation and epimerisation of individual sugar residues. Recent reports suggest that some modifications are cell specific supporting the hypothesis of an HS code.
HSPG are present at neuromuscular junctions (NMJ) but their synaptic functions remain uncharacterized. In *C. elegans* body-wall muscle cell receive excitatory and inhibitory innervation from cholinergic and GABAergic motoneurons, respectively. Ce-punctin (also known as MADD-4) is an ECM protein secreted by motoneurons in the synaptic cleft. Specific combinations of Ce-punctin isoforms trigger the clustering of acetylcholine or GABAA receptors at synaptic sites.

We used a BFP knock-in allele generated by the B́ulow lab to detect SDN-1 and we observed that SDN-1 is present at NMJs and seems to be enriched at cholinergic neuro-muscular synapses. Using single-chain antibodies to label specific HS modifications *in vivo* suggests that some modifications could be prevalent at cholinergic junctions. *sdn-1* disruption affects the localization of acetylcholine receptors and impacts Ce-punctin.
Insertion of a SL2-Scarlet reporter cassette in the *sdn-1* locus will be used to analyse *sdn-1* expression pattern. In addition, we used CRISPR/Cas9 to tag SDN-1 with a DEGRON sequence. Using the Auxin Inducible Degradation, we will identify the tissue-specific requirement and developmental window of SDN-1 expression required for proper formation and maintenance of synaptic structures.

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Analysis of activity-dependent synaptogenesis at the SAB neuromuscular junction.

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Activity of neurons or muscle can shape network connectivity, thus providing the basis for learning and memory. The nematode *Caenorhabditis elegans* is a powerful system to study the mechanisms of synapse formation and maintenance. We chose to analyze the development of the three SAB motor neurons that are innervating muscles in the head of the worm. In this system, it was shown that electrical silencing of the muscle cells during development can regulate SAB morphology (Zhao and Nonet, *Development*, 2000).

We observed SAB overgrowth and ectopic synapse formation in *unc-13* and *unc-18* mutant worms where neuromuscular transmission is disrupted. We could confirm that this effect is not due to the loss of movement as there is no SAB overgrowth in the myosin heavy chain *unc-54* mutants that are completely paralyzed. Silencing of muscle cell electrical activity through expression of the *Drosophila* HisCl1 histamine-gated chloride channel causes SAB overgrowth, suggesting that retrograde factor(s) control SAB development. Spatially restricted inhibition of the head muscles innervated by the SAB is sufficient to induce overgrowth, suggesting that this effect is controlled locally. We could further pinpoint a critical developmental window at the first larval stage during which SAB development is plastic.

To find genes involved in the overgrowth of the SAB, we used RNA-Seq to detect genes differentially expressed upon electrical manipulation of the muscle cells. However, the differentially expressed genes were dominated by a developmental delay, hindering the detection of meaning-ful variations. Additionally, we used RNAi-induced gene silencing to screen 40 candidate genes. Unfortunately, the RNAi treatment failed to produce a robust suppression of SAB overgrowth. We are now testing candidate genes using *bona fide* mutant strains of candidate genes.

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Genetic mechanisms regulating TWK-40, a potassium channel controlling the locomotion of *C. elegans*

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Two-pore domain potassium channels (K2P) form a large family of well-conserved ion channels that play a central role in the establishment and maintenance of the resting membrane potential of almost all animal cells. They regulate neuronal excitability, hormone secretion, respiratory and cardiac functions. Despite the fundamental role of K2P channels, some very basic questions about their biology are still largely unexplored. In particular, we still know very little about the molecular and cellular processes that determine the number of active channels and their distribution at the cell surface in different cell types. To address this simple yet fundamental question, our group uses the powerful genetic tools available in the nematode *C. elegans* to discover genes and cellular pathways that control the biology of K2P channels in their native cellular context. The goal of my thesis project is to identify the molecular factors and cellular mechanisms that are required for the biosynthesis, trafficking and function of the TWK-40 channel. TWK-40 is expressed in several interneurons and is required for the proper locomotion of *C. elegans*. In collaboration with the lab of Mei Zhen in Toronto, we use calcium imaging to observe the activity of AVA interneurons that control backward locomotion and express TWK-40. We find that the level of TWK-40 activity determines the level of excitability of the AVA neuron. A direct way to identify genes that are required for the function of the TWK-40 channel is to perform genetic screens for gene mutations that suppress the phenotype of hyperactive channel mutants. By combining protein structure data and two-electrode voltage-clamp electrophysiology in *Xenopus* oocytes, we have recently identified a key conserved amino acid that can be mutated to strongly increase the activity of vertebrate and invertebrate K2P channels. By inserting these mutations into the *C. elegans twk-40* gene, we have been able to generate a new mutant strain with a striking behavioral phenotype. This "gain of function" mutation causes a very strong locomotor defect that was an ideal starting point for a genetic suppressor screen based on recovery of locomotion. We isolated 69 independent suppressor mutants with different levels of locomotion recovery. To rapidly clone the candidate mutants, we will take advantage of whole-genome sequencing technology. Candidate genes will then be validated by standard genetic tests. We will also use calcium imaging to directly measure the impact of different suppressor mutants on the excitability of AVA interneurons.

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Exploring fungal virulence using *C. elegans*

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In the laboratory, we use the interaction between *C. elegans* and the nematophagous fungi *Drechmeria coniospora* as a model system to investigate fungal pathogenesis and the host response to infection. Our aim for this project is to characterise fungal virulence factors and thus understand fungal pathogenesis in an *in vivo* setting.
The obligate fungal pathogen *D. coniospora* adheres to the host cuticle, germinates, penetrates the cuticle, grows into the epidermis and underlying tissues and eventually kills its host. Using transcriptome data for different stages of *D. coniospora*'s life-cycle, we identified genes that are preferentially expressed during infection. In order to dissect the function of these genes, we have established methods for fungal transgenesis to knock-out and knock-in the chosen candidates. In parallel, we are expressing selected fungal virulence genes directly in *C. elegans*. For those that provoke an effect (e.g. on survival and/or on the expression of host defence genes), we will use co-immunoprecipitation and Y2H screens to identify host proteins that interact specifically with selected fungal effectors. We hope to identify novel virulence strategies.

Related publication:
- Lebrigand, *et al.* (2016). Comparative Genomic Analysis of *Drechmeria coniospora* Reveals Core and Specific Genetic Requirements for Fungal Endoparasitism of Nematodes. PLoS Genet.,12(5):e1006017

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C. elegans as a model to study protein persulfidation (RSSH): effects on development and aging

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Oxidative posttranslational modification of cysteine residues, called protein persulfidation (RSSH), has been proposed as a unifying mechanism behind the numerous physiological/pathophysiological effects ascribed to H2S. Therefore development of a selective detection method for protein persulfides is of utmost importance. We developed a new method for protein persulfide labelling and detection. The selectivity of the method was tested and confirmed in various models (*D. melanogaster, C. elegans, M. musculus*, human cell lines). Recent publications showed that H2S has an important role in numerous physiological processes, as well as aging, in *C.elegans*. We particularly focused on *C. elegans* knockouts for the enzymes of the transsulfuration pathway, as well as antioxidant enzymes, trying to understand how persulfidation changes during aging and development. Pharmacological interventions to increase persulfidation levels result in longer lifespan and healthspan. Our results suggest that persulfidation represents an evolutionary conserved mechanism for rescuing cysteine residues from overoxidation on one hand, and a new signaling mechanism on the other.

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