

## Master 2

Parcours

*Biologie Intégrative  
& Physiopathologies*

Track

*Integrative Biology  
& Physiopathologies*

**Propositions de stages**

**Internship proposals**

Année  
2024-2025

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### Laboratoires :

<b>iGReD</b>	Institut Génétique Reproduction et Développement
<b>IMoSt</b>	Imagerie Moléculaire et Stratégies Théranostiques
<b>M2iSH</b>	Microbes Intestin Inflammation et Susceptibilité de l'Hôte
<b>LPCA</b>	Laboratoire de Physique de Clermont Auvergne
<b>Neurodol</b>	Neurosciences et Douleur
<b>UNH</b>	Unité de Nutrition Humaine

\*Sujet de stage proposé également dans le parcours NHM

	Responsable	Laboratoire	Sujet du Stage
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33	Waltzer L	iGReD	Analysis of the impact of TET epigenetic enzyme in gene expression regulation: an epitranscriptomic view.
34*	Zbili M	NeuroDol	Characterization of cortical homeostatic plasticity associated with facial neuropathic pain in rodent.
35*	Ranchon-Cole I	NeuroDol	Light and migraine pain

#### Laboratoires :

<b>iGReD</b>	Institut Génétique Reproduction et Développement
<b>iMoST</b>	Imagerie Moléculaire et Stratégies Théranostiques
<b>M2iSH</b>	Microbes Intestin Inflammation et Susceptibilité de l'Hôte
<b>Neurodol</b>	Neurosciences et Douleur
<b>UNH</b>	Unité de Nutrition Humaine

\*Sujet de stage proposé également dans le parcours NHM

## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :**

Impact of the hormonal cycle on the therapeutic effect of motor cortex neurostimulation in an animal model of migraine

**Laboratory :** Inserm/UCA, U1107, Neuro-Dol, Trigeminal Pain and Migraine

**Laboratory director :** Radhouane DALLEL

**Address :** Faculté de Chirurgie dentaire, 2 rue de Braga, 63000 Clermont-Ferrand

**Internship tutor :** Myriam Antri

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**Summary :**

Migraine is a pathology with a high female prevalence, often linked to the hormonal cycle, and affecting about 15% of the population. Despite recent progress, pharmacological treatments for attacks remain unsatisfactory for many patients. Neurostimulation, such as transcranial direct current stimulation (tDCS), offers a promising approach, though little is known about its effect on migraine.

We recently conducted a study in an animal model of migraine induced by injection of an "inflammatory soup" (IS) into the meninges of female rats. We show that the intensity of cephalic pain induced by the IS injection varied depending on the phase of the hormonal cycle at the time of injection. We also found that the activation of neurons located in the trigeminal-cervical complex (TCC), the first sensory relay for meningeal and facial cutaneous information, also differed based on the hormonal cycle phase at the time of injection.

The project aims to evaluate the therapeutic efficacy of tDCS in our animal model of migraine and to determine whether the hormonal cycle at the time of stimulation influences migraine symptoms. Using behavioral approaches, we will investigate whether tDCS neurostimulation prevents migraine symptoms such as allodynia (pain following a non-painful stimulation) and, by combining *ex vivo* electrophysiology techniques (patch-clamp recordings) and immunohistochemistry, we will decipher the underlying physiological and cellular mechanisms, focusing particularly on TCC neurons.

**Methodologies (key words) :** Behavioral, Patch-clamp electrophysiological recordings, immunohistochemistry, pharmacology

**Publications of the research group on the proposed topic (3 max.)**

1. Compromised trigemino-coerulean coupling in migraine sensitization can be prevented by blocking beta-receptors in the locus coeruleus. *J Headache Pain*. 2023. Signoret-Genest J, Barnet M, Gabrielli F, Aissouni Y, Artola A, Dallel R, Antri M, Tovote P, Monconduit L. Dec 8;24(1):165.
2. GABAA and Glycine Receptor-Mediated Inhibitory Synaptic Transmission onto Adult Rat Lamina III PKC $\gamma$ -Interneurons: Pharmacological but Not Anatomical Specialization. *Cells*. 2022. El Khoueiry C, Alba-Delgado C, Antri M, Gutierrez-Mecinas M, Todd AJ, Artola A, Dallel R. Apr 15;11(8):1356. doi: 10.3390.
3. 5-HT<sub>2A</sub> Receptor-Induced Morphological Reorganization of PKC $\gamma$ -Expressing Interneurons Gates Inflammatory Mechanical Allodynia in Rat. *J Neurosci*. 2018. Alba-Delgado C, Mountadem S, Mermet-Joret N, Monconduit L, Dallel R, Artola A, Antri M. Dec 5;38(49):10489-10504. doi: 10.1523

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## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :** Deciphering the multiscale regulation of imprinted genes during mouse neural commitment

**Laboratory :** iGReD

**Laboratory director :** Krzysztof JAGLA

**Address :** Faculté de Médecine, 28, Place Henri Dunant, 63 000 Clermont-Ferrand

**Internship tutor:** P .Arnaud

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**Summary :**

Genomic imprinting is a key epigenetic process in which about 150 mammalian genes are expressed on only one allele, depending on their parental origin. Most of these are required for key biological processes, including brain function and behaviour.

Allele-specific expression along each imprinted domain is regulated by a key region, the imprinting control region (ICR). In addition to DNA methylation imprints that constitutively mark ICRs on their maternal or paternal alleles, other levels of regulation, including histone modification and chromatin looping, account for the complex and specific spatio-temporal expression patterns of imprinted genes. However, how ICR dynamically orchestrates allele-specific coordination between these regulatory layers along large imprinted domains and fine-tunes the allelic expression of distal genes during lineage commitment remains poorly understood.

The aim of this internship, to be followed by a PhD, is to characterise the details of the fine-tuned regulation of the imprinted domain *Peg13* during neural commitment.

It will use a multiscale integrative allelic resource being established by the host team on a brain organoid model based on hybrid mouse embryonic stem cells to explore how transcription factors, chromatin signatures and 3D conformation interact to regulate imprinted expression during neural commitment. A regulatory model will be built from the exploration of this resource and further tested using a range of molecular, cellular, cell imaging and functional in cell approaches.

By identifying novel players in the fine-tuned regulation of imprinted genes in the brain, this work will provide a relevant framework for understanding the causes of imprinting-related neurobehavioural disorders.

**Methodologies (key words) :** Brain organoid, ES cell differentiation, Omic related to epigenetic analyses (HiC-capture, Cut&Run..), FISH, RT-qPCR, bioinformatics,

**Publications of the research group on the proposed topic (3 max.)**

Rengifo Rojas C et al., (2024) “Biallelic non-productive enhancer-promoter interactions precede imprinted expression of *Kcnk9* during mouse neural commitment”. *HGG Adv.*30:100271. doi: 10.1016/j.xhgg.2024.100271.

Montibus B et al. (2021). « TET3 controls the expression of the H3K27me3 demethylase *Kdm6b* during neural commitment.” *Cell Mol Life Sci.* 78(2):757-768.

S. Maupetit-Mehouas et al, (2016) “Imprinting control regions (ICRs) are marked by mono-allelic bivalent chromatin when transcriptionally inactive.”, *Nucleic Acids Res* 44 (2):621-635

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**Track « Integrative Biology, Physiopathologies »****Proposal for a Master 2 internship – 2024-2025**

**Title :** Characterization of new virulence factors of Adherent-Invasive *Escherichia coli* (AIEC) bacteria using a Tn-Seq approach without a priori.

**Laboratory :** M2iSH (Microbes, intestine, inflammation and Susceptibility of the Host), UMR 1071 Inserm/Université Clermont Auvergne, USC INRAE 1382

**Laboratory director :** Professor Nicolas Barnich

**Address :** CRBV, 28 Place Henri Dunant, 63000 Clermont-Ferrand

**Internship tutor :** Pr. Nicolas Barnich (PhD, HDR)

**Tel :** 0473178376

**e-mail :** nicolas.barnich@uca.fr

**Summary :**

Crohn's disease is a chronic inflammatory bowel disease, in which it is now well established that Adherent-Invasive *Escherichia coli* (AIEC) bacteria plays a key role in the initiation and/or maintenance of intestinal inflammation. We recently published that these bacteria are associated with early post-surgery relapses, and that the presence of these bacteria on the surgical specimen at the time of surgery is a factor in relapse 6 months post-surgery. Therefore, targeting these bacteria represents a complementary strategy to current therapies which only target the symptoms, and not the origin, of Crohn's disease.

The proposed project aims to better understand the virulence of AIEC bacteria isolated from patients with Crohn's disease, using the non-targeted Tn-Seq strategy recently developed in the Unit which consists of creating libraries of mutants by insertion of transposons provided by a conjugative plasmid. These mutant banks will be tested on intestinal epithelial cells in culture, and on macrophages, in order to characterize new virulence factors *in vitro*, but also in a mouse model overexpressing CEACAM6 in order to identify new virulence factors *in vivo* using an approach without a priori.

Thus, we should identify new virulence factors which will allow the development of more specific anti-AIEC strategies.

**Methodologies (key words):** Microbiology (creation of mutant bank), molecular biology (DNA extraction and sequencing, including analysis), cell biology (culture of intestinal epithelial cells and macrophages) and animal experimentation (infection of mice overexpressing CEACAM6).

**Publications of the research group on the proposed topic (3 max.)**

1- Sivignon A, Chervy M, Chevarin C, Ragot E, Billard E, Denizot J, **Barnich N**. An adherent-invasive *Escherichia coli*-colonized mouse model to evaluate microbiota-targeting strategies in Crohn's disease. *Dis Model Mech*. 2022 Oct 1;15(10):dmm049707. PMID: 36172858.

2- Buisson A, Sokol H, Hammoudi N, Nancey S, Treton X, Nachury M, Fumery M, Hébuterne X, Rodrigues M, Hugot JP, Boschetti G, Stefanescu C, Wils P, Seksik P, Le Bourhis L, Bezault M, Sauvanet P, Pereira B, Allez M, Remind study group, **Barnich N**. Role of adherent and invasive *Escherichia coli* in Crohn's disease: lessons from the postoperative recurrence model. *Gut*. 2023 Jan;72(1):39-48. PMID: 35361684 *Clinical Trial*.

3- Agus A, Richard D, Faïs T, Vazeille E, Chervy M, Bonnin V, Dalmasso G, Denizot J, Billard E, Bonnet R, Buisson A, **Barnich N**, Delmas J. Propionate catabolism by CD-associated adherent-invasive *E. coli* counteracts its anti-inflammatory effect. *Gut Microbes*. 2021 Jan-Dec;13(1):1-18. PMID: 33769191.

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## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title:** Direct involvement of PLP deregulation in the development of chronic pain symptoms in MS model?

**Laboratory:** UMR UCA/INSERM U1107, Neuro-Dol

**Laboratory director:** Radhouane DALLEL

**Address:** Faculté de Médecine et de Pharmacie, 28 place Henri Dunant, 63000 CLERMONT-FERRAND

**Internship tutor:** Méлина BEGOU

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#### **Summary :**

Multiple sclerosis (MS) is a multifactorial autoimmune disease of the central nervous system (CNS), characterized by demyelination and chronic inflammation, as well as axonal and neuronal loss, affecting 2–3 million people worldwide - specifically 115,000 in France. Among the numerous neurological symptoms of MS, pain is a common disabling symptom often not improved by available drugs. Recent data suggested the involvement of demyelination in the development of chronic pain in which the proteolipid protein (PLP), the major protein of CNS myelin, could be an underestimated but important actor. We notably showed that loss of PLP expression in mice lead to sensitive dysfunctions (pain hypersensitivity and mechanical allodynia) well before motor dysfunctions development. Later, another team described that PLP underexpression could be linked to thermal hypersensitivity and that restoring PLP expression could correct this behavioral alteration. Based on these recent data, and because PLP is highly underexpressed in MS demyelinating lesions, the general objective of our project is to better understand the involvement of this protein in the development of sensitive dysfunctions in MS and to propose new therapeutic target.

To achieve this objective, the master 2 internship will be divided in 2 workpackages. One evaluating the corrective effect of PLP spinal overexpression (using viral vector induced gene therapy) in an animal model of MS, namely the experimental autoimmune encephalomyelitis (EAE) mice. The second further characterizing involvement of PLP in sensitive perception modulation using mice with conditional deletion of Plp1 gene (neuronal vs oligodendroglial inactivation).

**Methodologies (key words):** Human neurologic disease mouse model, mouse behavioral evaluation, viral gene therapy, intrathecal injection, western-blot analysis.

#### **Publications of the research group on the proposed topic (3 max.)**

Mabrouk M, ..., Bégou M. The antioxidant effect of grape seed extract (GSE) corrects experimental autoimmune encephalomyelitis behavioural dysfunctions, demyelination and glial activation. *Frontiers in Immunology*. 2022; 13:960355.

Démsthènes A, ..., Bégou M. In-Depth Characterization of Somatic and Orofacial Sensitive Dysfunctions and Interfering-Symptoms in a Relapsing-Remitting Experimental Autoimmune Encephalomyelitis Mouse Model. *Front Neurol*. 2022 Jan 17;12:789432.

Petit B, ..., Bégou M. Mice with a deletion of the major central myelin protein exhibit hypersensitivity to noxious thermal stimuli: involvement of central sensitization. *Neurobiol Dis*. 2014 May;65:55-68.

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## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :** Comprehensive investigation of transposable element expression during the development : detrimental or beneficial effect

**Laboratory :** Institut GReD, CNRS UMR 6293, UCA, Inserm U1103

**Laboratory director :** Krzysztof JAGLA

**Address :** Faculté de médecine, CRBC, 28 place Henri Dunant, 63000 Clermont-Ferrand

**Internship tutor :** Brassset Emilie

**Tel :** 0473160427

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**Summary :**

Transposable Elements (TE), often called "jumping genes," are DNA sequences that can move or replicate themselves to a new position within the genome. Their ability to move make them highly mutagenic thereby influencing genetic diversity and adaptation but their mobilization can also have detrimental effect. The resulting selective pressure has driven the evolution of many epigenetic mechanisms to silence their expression thus limiting their mobilization.

Interestingly, recent research points to the existence of developmental window where TEs are not repressed. Surprisingly, these TEs are not just genomic parasites but might play significant and beneficial roles within their host genomes. We have recently discovered, using *Drosophila* as a model, that during embryogenesis, many transposable elements resembling viruses are not repressed since RNAs and proteins of these elements are detected. The project aims to investigate the expression of Transposable Elements (TEs) under physiological conditions, in order to elucidate their possible roles in developmental processes where they may exert advantageous function.

**Methodologies (key words) :** To carry out this project we will use *Drosophila* as a model organism. Molecular biology, genetics, omics analysis, immunostaining, smFISH, FACS, will be used to achieve this project.

**Publications of the research group on the proposed topic (3 max.)**

-Akkouche A, Kneuss E, Bornelöv S, Renaud Y, Eastwood EL, van Lopik J, Gueguen N, Jiang M, Creixell P, **Maupetit-Mehouas S**, Czech Nicholson B\*, **Brassset E\***, Hannon GJ\*. A dual histone code specifies the binding of heterochromatin protein Rhino to a subset of piRNA source loci. bioRxiv 2024.01.11.575256; doi: <https://doi.org/10.1101/2024.01.11.575256>,

-Yoth M, **Maupetit-Méhous S**, Akkouche A, Gueguen N, Bertin B, Jensen S, **Brassset E\***. Reactivation of a somatic errantivirus and germline invasion in *Drosophila* ovaries. Nat Commun. 2023 Sep 29;14(1):6096. PMID: 37773253

-Yoth M, Jensen S, **Brassset E\***. The Intricate Evolutionary Balance between Transposable Elements and Their Host: Who Will Kick at Goal and Convert the Next Try? Biology (Basel). 2022 May 6;11(5):710. doi: 10.3390/biology11050710. PMID: 35625438;

## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :** Preclinical relevance of SPECT Imaging with [<sup>99m</sup>Tc]-NTP-15-5 for the evaluation of chondrosarcoma response to immunotherapy.

**Laboratory :** Unité Mixte de Recherche INSERM/UCA,,Imagerie Moléculaire et Stratégies théranostiques”

**Laboratory director :** Elisabeth Miot-Noirault

**Address :** 58 rue Montalembert. BP 184 – 63005 Clermont-Ferrand cedex

**Internship tutor :** Arnaud Briat-Le Mest

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**Summary:**

Classified as a musculoskeletal tumour, chondrosarcoma (CHS), the most common primary bone cancer after osteosarcoma in adults, is very often described as chemo- and radio-resistant. As CHS is characterized in multiple histological forms, this therapeutic impasse is mainly due to a complex tumour microenvironment due to its chondrogenic nature, low vascularization and hypoxic environment. The growing interest in cancer immunotherapy, however, has reached the field of sarcomas and a number of molecular profiling studies have identified immunotherapeutic targets in bone sarcomas: PD1 expression appears to have prognostic and therapeutic implications in CHS, while PD-L1 and T-cell infiltrate are highly expressed. Unfortunately, the clinical responses in the different trials remain unsatisfactory to date, suggesting the need to better characterize and understand the tumour microenvironment of CHS in order to improve the immunotherapy approach. Based on this observation, this project will aim to compare the performance of the [<sup>99m</sup>Tc]-NTP 15-5 radiotracer with ex vivo tissue characterization techniques, for the longitudinal follow-up of the remodelling of the extracellular matrix of the CHS, in response to an immunotherapy targeting the PD-1/PD-L1 couple. This preclinical study will exploit a humanized mouse model available from licensed breeders, mice that have been the subject of numerous publications on the evaluation of immunotherapies in different cancers. This study will complement our ongoing studies and should allow us to prove concept that the radiotracer [<sup>99m</sup>Tc]-NTP 15-5 is a companion tracer for CHS immunotherapy.

**Methodologies (key words) :** CHS preclinical model ; Immunohistochemistry (PD-1/PD-L1, lymphocytes infiltrate) ; Immunotherapy ; SPECT/CT.

**Publications of the research group on the proposed topic (3 max.)**

-Miot-Noirault E, et al. <sup>99m</sup>Tc-NTP 15-5 assessment of the early therapeutic response of chondrosarcoma to zoledronic acid in the Swarm rat orthotopic model. EJNMMI Res. 2013, 3 :40.

-Peyrode C et al. Proteoglycans as target for an innovative therapeutic approach in chondrosarcoma: preclinical proof of concept. Mol. Cancer Ther. 2016, 15 : 2575-85.

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## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :** Assessing long-term exposure to a chemical mixture representative of the dietary inorganic exposome on the gut microbiota-immune system and gut-brain axes: toward susceptibility to chronic diseases?

**Laboratory :** U1107 INSERM/UCA NeuroDOL – Laboratoire de Pharmacologie Fondamentale et Clinique de la Douleur

**Laboratory director :** Pr Radhouane Dallel

**Address :** Faculté de Médecine et de Pharmacie, 28 place Henri Dunant 63000 Clermont-Ferrand

**Internship tutor :** Dr Frédéric CARVALHO

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#### **Summary :**

The human exposome through the diet represents the array of nutrient and non-nutrient factors to which an individual is daily exposed. Among the non-nutrient factors, chemicals of various sources and of organic or inorganic nature (i.e., metals and minerals) come from production (phytosanitary products, grain storage) to food transformation (auxiliary agents, food additives, food contact materials). They composed the dietary chemical exposome, a group of agents that can have a negative impact on human physiology due to chronic exposure, including immune and metabolic health. Many animal studies suggest that long-term oral exposure and systemic absorption of inorganic particles have deleterious impacts on the development and maturation of intestinal, immune and metabolic functions, as well as on stress-linked gut disorders, predisposing to chronic diseases in Human, and that gut dysbiosis induced by these agents may have a central role in these effects. However, because these data concern individual chemicals not representative of the complex inorganic cocktail to which the consumers are exposed, the present project will expose mice from conception to adult offspring to a mixture of common metal and mineral food additives (E141/E171/E172/E551/E554). **Our aim is to assess the hazards of this representative subset of inorganic agents as part of the human exposome on the development of gut microbiota-immune-metabolic and gut-brain axes, and whether this could predispose to the risk of developing immune-related diseases in offspring, i.e., inflammatory bowel diseases (IBD) and/or food allergies, stress-induced gut-brain disorders (irritable bowel syndrome, IBS), and metabolic disorders (diabetes, obesity).**

**Methodologies (key words) :** Behavioral assessment in mice (colonic sensitivity, anxiety, depression,...), Calcium imaging, ELISA, Histological studies, Immunostaining, RT-qPCR

#### **Publications of the research group on the proposed topic (3 max.)**

1. Meynier M., *et al.*, 2024. Pasteurized *Akkermansia muciniphila* improves irritable bowel syndrome-like symptoms and related behavioral disorders in mice. *Gut microbes*, 16(1), 2298026. [PMID: 38170633](https://pubmed.ncbi.nlm.nih.gov/38170633/).
2. Gervason S, *et al.*, 2023. Antihyperalgesic properties of gut microbiota: Parabacteroides distasonis as a new probiotic strategy to alleviate chronic abdominal pain. *Pain*, [PMID: 37756665](https://pubmed.ncbi.nlm.nih.gov/37756665/).
3. Meynier M., *et al.*, 2022. AhR/IL-22 pathway as new target for the treatment of post-infectious irritable bowel syndrome symptoms. *Gut microbes*, 14(1):2022997. [PMID: 35090380](https://pubmed.ncbi.nlm.nih.gov/35090380/).

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## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :** Pathological role of D-serine metabolism in microbiota-gut-brain axis dysfunction in intestinal inflammatory disorders

**Laboratory :** U1107 INSERM/UCA NeuroDOL – Laboratoire de Pharmacologie Fondamentale et Clinique de la Douleur

**Laboratory director :** Pr Radhouane Dallel

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**Summary :** The gut-brain communication involves different signaling metabolites routing through the systemic and vagus nerve pathways. At the core of this dialogue, the gut microbiota plays a key role in regulating the metabolism of these mediators and in maintaining intestinal homeostasis and host “well-being”. Accordingly, the gut microbiota dysbiosis leads to several gastrointestinal (GI) disorders and associated comorbidities as anxiety and depression. Changes in the microbiota-gut-brain axis have been described in chronic intestinal disorders, such as irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD). These modulations may promote the development of anxio-depressive symptoms. Despite many progresses, the signaling pathways involved in this inter-organ dialogue are not well identified. Remarkably, right-handed amino acids (D-AAs) which are metabolized by microorganisms but also directly by the host are emerging as an important class of signaling molecules in the brain but also in peripheral organs. In particular, D-Ser is an effective co-agonist of the N-methyl-D-aspartate subtype of glutamate receptors (NMDARs) which are essential for the healthy settling and functioning of brain circuits. D-Ser is synthesized from L-Ser by serine racemase (SR) and degraded by D-AA oxidase (DAAO). Noteworthy, D-Ser metabolism disruption has been consistently linked to inflammatory disorders, anxiety and depression. Preliminary results indicate that D-Ser is metabolized by enteric neurons and that the molecule regulates GI motility and transit. Gut microbiota has a large genetic capacity of producing D-AAs. However, the mechanisms of action of the impact of microbiota and gut D-AAs on the brain remains unexplored. We postulate that **D-AAs and particularly D-Ser support interconnection of microbiota, gut and brain and play a key role in GI disorders and altered brain functions**. We make the hypothesis that any alteration in D-Ser metabolism in the gut may promote the development of colitis and the associated brain symptoms.

**Methodologies (key words) :** Behavioral assessment in mice (colonic sensitivity, anxiety, depression,...), Calcium imaging, ELISA, Histological studies, Immunostaining, RT-qPCR

**Publications of the research group on the proposed topic.**

1. Meynier M., *et al.*, 2024. Pasteurized *Akkermansia muciniphila* improves irritable bowel syndrome-like symptoms and related behavioral disorders in mice. *Gut microbes*, 16(1), 2298026. [PMID: 38170633](https://pubmed.ncbi.nlm.nih.gov/38170633/).
2. Gervason S., *et al.*, 2023. Antihyperalgesic properties of gut microbiota: Parabacteroides distasonis as a new probiotic strategy to alleviate chronic abdominal pain. *Pain*, [PMID: 37756665](https://pubmed.ncbi.nlm.nih.gov/37756665/).
3. Meynier M., *et al.*, 2022. AhR/IL-22 pathway as new target for the treatment of post-infectious irritable bowel syndrome symptoms. *Gut microbes*, 14(1):2022997. [PMID: 35090380](https://pubmed.ncbi.nlm.nih.gov/35090380/).

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## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :** *Stem cells in the embryo: analysis of novel factors important for preimplantation in mice.*

**Laboratory :** iGReD

**Laboratory director :** Christophe Jagla

**Address :** UFR Médecine, CRBC. 28 place Dunant. 63000 Clermont-Ferrand

**Internship tutor :** Claire Chazaud

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**Summary :** Our team analyzes the genetic mechanisms of cell lineage differentiation in the mouse embryo during pre-implantation. We are particularly interested in the differentiation between epiblast cells (Epi) and primitive endoderm cells (PrE), which takes place during the first 3 days in mice, corresponding to the first 6 days in humans.

Epiblast cells will produce all the cells of the future individual and its descendants. Epi is also the source of the famous ES pluripotent stem cells ("Embryonic Stem cells, Nobel Prize 2007 by Evans, Smithies, Capecchi) or similar to iPS reprogrammed cells ("induced Pluripotent Stem cells, Nobel Prize 2012 by Yamanaka). These cells can give rise to any embryonic or adult cell type, and therefore have great potential for cell therapy.

In the course of our recent single-cell RNAseq analyses, we have discovered new factors potentially involved in epiblast or PrE differentiation. The student will characterize the expression of these new factors by various techniques such as immunofluorescence and fluorescent in situ hybridization (smFISH), protein interactions (Proximity ligation assay) or transcriptomic analyses. Functional analyses (RNAi or CRISPR/CAS9) will then be carried out in the embryo or in *in vitro* models of differentiation such as ES stem cells.

Understanding the mechanisms underlying this "developmental program" is of paramount importance both from a fundamental point of view and for therapeutic applications aimed at using stem cells in regenerative medicine or improving *in vitro* fertilization techniques.

**Methodologies (key words) :** The project will potentially involve various techniques: embryo culture and electroporation, gene expression analysis (RTqPCR, immunofluorescence, FISH, PLA), single-cell analysis, confocal microscopy (fixed tissue and live-imaging), transgenesis, cell culture, RNAi, CRISPR/CAS9...

**Publications of the research group on the proposed topic (3 max.)**

- Allègre N, Chauveau S, Dennis C, Renaud Y, Meistermann D, Valverde Estrella L, Pouchin P, Cohen-Tannoudji M, David L and Chazaud C (2022). A Nanog-dependent gene cluster initiates early embryonic lineage segregation. *Nature Communications* 13, 3550. doi: 10.1038/s41467-022-30858-8. IF: 15.

- Huyghe A, Furlan G, Ozmadenci D, Galonska C., Charlton J., Gaume X., Combémourel N., Allègre N., Zhang J.Y., Wajda P., Rama N., Vieugué P., Durand I., Brevet M., Gadot N., Merrill B.J., Koch M., Mehlen P., Chazaud C., Meissner A. and F. Lavial (2020). Control of naive pluripotency by the netrin-1/Neol/Unc5B signalling axis. *Nature Cell Biology* 22:389-400. IF: 17

- Azami T\*, Bassalart C\*, Allègre N, Valverde Estrella L, Pouchin P, Ema M and Chazaud C (2019). Regulation of ERK signalling pathway in the developing mouse blastocyst. *Development* 146: dev177139.

\* equal contribution IF: 6

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**Track « Integrative Biology, Physiopathologies »**  
**Proposal for a Master 2 internship – 2024-2025**

<p><b>Title</b> : Development of a preclinical model of ocular rosacea: study of pathophysiology and development of new treatments</p>
<p><b>Laboratory</b> : NeuroDol UMR 1107 Inserm UCA - team 1 « Pharmacologie Fondamentale et Clinique de la Douleur » (PFCD)  <b>Laboratory director</b> : Pr Radhouane Dallel  <b>Address</b> : Faculté de Médecine et de Pharmacie, 28 place Henri Dunant 63000 Clermont-Ferrand</p>
<p><b>Internship tutor</b> : Dr David CIA  <b>Tel</b> : 04 73 17 79 83  <b>e-mail</b> : <a href="mailto:david.cia@uca.fr">david.cia@uca.fr</a></p>
<p><b>Summary</b> :</p> <p>Ocular rosacea is a chronic inflammatory disease characterized by inflammation of ocular surface tissues, including the eyelid margin and cornea. In the most severe cases, corneal inflammation can lead to ulceration and infection which, if left untreated, may perforate the eye and result in vision loss. Currently, available treatments are mainly symptomatic and often ineffective, based on the use of antibiotics, corticoids and artificial tears. Despite these treatments, the frequency of relapses remains high. Among possible therapeutic targets, the intestinal and/or ocular surface microbiota could represent an interesting candidate. It could play a role in the development of inflammation and/or sensitization of the cornea in patients with ocular rosacea.</p> <p>The internship is part of a global project to study the pathophysiological mechanisms of inflammation and corneal sensitivity observed in ocular rosacea, in order to propose new therapeutic strategies. Preliminary work has been undertaken to establish a preclinical animal model of ocular rosacea. Two models are currently being developed in mice: one induced by exposure of the eyes to ultraviolet B (UVB), and one induced by ocular exposure to the antimicrobial peptide of cathelicidin (LL-37). First results show the development of corneal inflammation in both models, which seems to be associated with an increase in ocular surface sensitivity; and an increase in corneal expression levels of various genes related to innate immunity or ocular surface microbiota. The objectives of the internship will be to confirm these results and further characterize the two models. Particular attention will be paid to the study of intestinal and ocular surface microbiota, in order to identify the “microbiota imprint” linked to the disease, and to develop new therapeutic approaches based on the use of probiotics or prebiotics.</p>
<p><b>Methodologies (key words)</b> : Behavioral assessment of ocular sensitivity in mice (eye-wiping test, von-Frey test, ...), ELISA, Histological studies, Immunostaining, RT-qPCR</p>
<p><b>Publications of the research group on the proposed topic (3 max.)</b></p> <p>Jacquemot, N., Wersinger, E., Brabet, P., &amp; Cia, D. (2023). Hydrogen Peroxide Affects the Electroretinogram of Isolated Perfused Rat Retina. <i>Current Eye Research</i>, 48(12), 1179-1188.</p> <p>Hassel, C., Couchet, M., Jacquemot, N., Blavignac, C., Loï, C., Moinard, C., &amp; Cia, D. (2022). Citrulline protects human retinal pigment epithelium from hydrogen peroxide and iron/ascorbate induced damages. <i>Journal of Cellular and Molecular Medicine</i>, 26(10), 2808-2818.</p> <p>Meynier, M., Daugey, V., Mallaret, G., Gervason, S., Meleine, M., Barbier, J., ... &amp; Carvalho, F. A. (2024). Pasteurized akkermansia muciniphila improves irritable bowel syndrome-like symptoms and related behavioral disorders in mice. <i>Gut microbes</i>, 16(1), 2298026.</p>

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## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title** : Regulation of 5-HT<sub>6</sub> receptors in primary cilia of spinal cord neurons and astrocytes in experimental models of neuropathic pain

**Laboratory** : INSERM UMR1107/UCA, NeuroDol, Equipe Pharmacologie fondamentale et clinique de la Douleur

**Laboratory director** : Pr Radhouane Dallel

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**Internship tutor** : Stéphane Doly

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**e-mail** : stephane.doly@uca.fr

**Summary** : Chronic neuropathic pain is a highly disabling syndrome affecting ~7-10% of adult population. It is especially problematic because of the limited efficacy of currently available drugs. Therefore there is an urgent need for new therapeutics. The serotonin type 6 (5-HT<sub>6</sub>) receptor has recently emerged as a promising target for the treatment of neuropathic pain: i) blocking the constitutive activity of 5-HT<sub>6</sub> receptor produces anti-allodynic, anti-hyperalgesic effects in traumatic, toxic and diabetic neuropathy, ii) 5-HT<sub>6</sub> receptors physically interact with mTOR and, (iii) central administration of Rapamycin (an mTOR inhibitor) produces anti-allodynic effects in models of neuropathic pain in rats. Previous findings revealed the expression of 5-HT<sub>6</sub> receptor in the dorsal horn spinal cord of 5-HT<sub>6</sub>-GFP KI mice and its localization in the primary cilium of dorsal spinal cord neurons, corroborating previous observations in striatal neurons where 5-HT<sub>6</sub> receptors were found to finely regulate cilia length and signaling. Little is known about its precise subcellular and spatiotemporal localization during development of neuropathic pain. We propose to compare the expression of spinal 5-HT<sub>6</sub> receptors in primary cilia of dorsal spinal cord neurons and astrocytes and their regulation in models of traumatic (spared nerve injury), toxic (Paclitaxel-induced peripheral neuropathy) and metabolic (STZ-diabetes) neuropathic pain in 5-HT<sub>6</sub>-GFP KI mice using a combination of pharmacological, biochemical and cell biology approaches. This project will provide a better understanding of the role of 5-HT<sub>6</sub> receptors in the pathophysiology of neuropathic pain.

**Methodologies (key words)** : neuropathic pain, in vivo behavioral tests (von frey hair test, paw immersion test), Immunohistochemistry, western-blotting, RNAscope

**Publications of the research group on the proposed topic (3 max.)**

- ✓ Martin et al., **2020**. mTOR activation by constitutively active serotonin<sub>6</sub> receptors as new paradigm in neuropathic pain and its treatment. *Progress in Neurobiology* 193: 101846
- ✓ Drop et al., **2021**. Neuropathic pain-alleviating activity of novel 5-HT<sub>6</sub> receptor inverse agonists derived from 2-aryl-1H-pyrrole-3-carboxamide. *Bioorganic Chemistry* 115 : 105218
- ✓ Mokhtar et al., **2023**. The Constitutive Activity of Spinal 5-HT<sub>6</sub> Receptors Contributes to Diabetic Neuropathic Pain in Rats. *Biomolecules* 13 : 364 : 103390

## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :** Characterization of modulators of mitochondrial replisome activity in healthy individuals or in pathological conditions

**Laboratory :** UMR 6533 CNRS-UCA – LPCA - Equipe Santé  
**Laboratory director :** Dominique Pallin  
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**Internship tutor :** Géraldine Farge  
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**Summary :**

Mitochondrial DNA, our “other genome,” is replicated by a relatively simple enzymatic machinery, the mitochondrial replisome, comprising an helicase, a single-stranded DNA binding protein and a DNA polymerase POLG. Dysfunctions in this replication system can lead to the development of mitochondrial pathologies such as myopathies. In particular, POLG mutations are among the most common causes of mitochondrial diseases and are associated with a range of phenotypes. However, treatments for these diseases are currently almost non-existent and remain largely limited to symptomatic and supportive care.

This Master internship is part of a project which intends to characterize compounds modulating the activity of the mitochondrial replisome in order to attenuate the phenotype of patients. Recently, new molecules capable of stimulating POLG activity were identified by our Swedish collaborators (Pr. M. Falkenberg, Gothenburg).

During this internship, 1-3 of these molecules will be tested to finely characterize their mode of action on the activity of POLG and on pathogenic POLG mutants. These tests will be carried out by combining molecular biology, biochemistry and microscopy techniques. The results will be discussed and validated with clinicians working on mitochondrial diseases. They will open new avenues towards targeted therapies for POLG-related mitochondrial diseases.

**Methodologies (key words) :** Molecular biology, Biochemistry and Microscopy

**Publications of the research group on the proposed topic (3 max.)**

Martucci M et al., The mutation R107Q alters mtSSB ssDNA compaction ability and binding dynamics, under revision at NAR, 2024

Debar L, et al. NUDT6 and NUDT9, two mitochondrial members of the NUDIX family, have distinct hydrolysis activities. Mitochondrion. 2023

Mehmedović M et al., Disease causing mutation (P178L) in TFAM results in impaired mitochondrial transcription initiation. BBA Mol Basis Dis. 2023

## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title : Effects of macrophage polarization modulated by sevoflurane in vitro on epithelial alveolar viability**

**Laboratory:** iGReD, Université Clermont Auvergne, CNRS, INSERM (Team « Translational approach to epithelial injury and repair »)

**Laboratory director:** Krzysztof Jagla

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#### **Summary :**

Acute respiratory distress syndrome (ARDS) is a major cause of respiratory failure and death, such as during COVID-19, that still lacks specific therapy. The fibro-proliferative phase allows alveolar repair, but dysfunction can lead to refractory ARDS and fibrotic sequelae. Repair depends on epithelial viability and the interaction between macrophages and epithelial cells.

Sevoflurane, a volatile anesthetic, could have protective effects on ARDS pathogenesis. Preclinical and clinical studies suggest decreased inflammation, improved oxygenation, and modulation of macrophage polarization towards an anti-inflammatory phenotype.

The current project aims to test the hypothesis that sevoflurane could have a protective effect on alveolar epithelial viability, notably through an anti-apoptotic effect, by inducing anti-inflammatory macrophage polarization and thus promoting the beneficial effects of such polarization on epithelial cells during ARDS. Freshly isolated primary human alveolar epithelial type 2 cells, exposed or not to pro-inflammatory cytokines and treated or not with sevoflurane, will be cultured in complete medium or sevoflurane-treated, primary human macrophage-conditioned medium to assess epithelial viability and markers of apoptosis.

This project fully aligns with the desire from our team to pursue collaborative translational research in the era of precision medicine.

**Methodologies (key words):** cell culture; immunocytochimie; multi-analyte ELISA (ELLA); western blot; viability assay; cytotoxicity assay.

#### **Publications of the research group on the proposed topic (3 max.)**

- Jabaudon M et al. Inhaled sedation in the intensive care unit. *Anaesth Crit Care Pain Med* (2022).
- Garnier M. et al. Macrophage polarization favors epithelial repair during acute respiratory distress syndrome. *Crit Care Med.* (2018).
- Zhai R. et al. Effects of sevoflurane on lung epithelial permeability in experimental models of acute respiratory distress syndrome. *J Transl Med.* (2023).

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## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :** Development of an alternative in vivo model for the evaluation of radiobiological effects in targeted radionuclide therapy (TRT).

**Laboratory :** UMR1240 IMoST  
**Laboratory director :** Pr Elisabeth Miot Noirault  
**Address :** 58 rue Montalembert 63000 Clermont-Ferrand, France

**Internship tutor :** Dr Elodie Jouberton  
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**Summary :**

In line with the 3Rs principles (reduction, replacement, refinement), it's important to develop alternative models for evaluating radiopharmaceuticals. One alternative is the use of chicken embryo tumor models. Because of its textures and functions, as well as the complex character of its vascular system, the CAM (ChorioAllantoic Membrane) is a well-suited platform for conducting experiments such as tumor growth, tissue grafts, drug delivery, and toxicological analysis. In this context, we have the emergence of the use of these models for nuclear imaging. For example, Dr Löffler's team compared PET/MRI accumulation of [<sup>18</sup>F]-siPSMA-14 or [<sup>68</sup>Ga]-PSMA-11 in prostate tumor xenografts on the HET-CAM model and mouse models. They were able to demonstrate a PSMA-specific accumulation in the HET-CAM model and similar accumulation of radiotracers in the HET-CAM model and mouse model obtained by PET quantification and  $\gamma$ -counter measurements. Studies of tumor growth monitoring by bioluminescent imaging on these models have also been documented.

The aim of this internship is to assess the relevance of this new model for the evaluation of new radiopharmaceuticals in TRT. We will take as an example the [<sup>177</sup>Lu]-PSMA treatment in TNBC combined with PARPi. To this end, it will be necessary to (i) develop and characterize the model, (ii) carry out a dosimetric study on our models and (iii) assess the radiobiological effects of [<sup>177</sup>Lu]-PSMA treatment alone or combined with PARPi.

**Methodologies (key words):** Following the development of three HET-CAM models (two *BRCAmut* TNBC and one *BRCAwT* TNBC), the study will begin by characterizing PSMA expression in the model using PET imaging, autoradiography, histological studies and flow cytometry. Then, the several PARPi will be tested alone or in combination with a PSMA-TRT injection. The variation in tumor volume over time will be evaluated and completed by mechanistic studies to characterize therapeutic response by histological study.

**Publications of the research group on the proposed topic (3 max.)**

Jouberton, E. *et al.* [<sup>18</sup>F]ML-10 PET imaging fails to assess early response to neoadjuvant chemotherapy in a preclinical model of triple negative breast cancer. *EJNMMI Res.* 10, 2 (2020)

Fortin, S., Brasseur, K., Morin, N., Asselin, É. & Bérubé, G. New platinum(II) complexes conjugated at position 7 $\alpha$  of 17 $\beta$ -acetyl-testosterone as new combi-molecules against prostate cancer: design, synthesis, structure-activity relationships and biological evaluation. *Eur. J. Med. Chem.*(2013)

## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :** Deciphering the function of the RNA-binding protein Boule in normal and DM1-like contexts

**Laboratory :** Institut GReD  
**Laboratory director :** Krzysztof Jagla  
**Address :** CRBC- 28 Place Henri Dunant 63000 Clermont-Ferrand

**Internship tutor :** Guillaume Junion  
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#### **Summary :**

The specific properties of muscles depend not only on the differential expression of genes, but also strongly on the type of protein isoforms produced by the cells. This is particularly true for sarcomeric structure, in which the genes involved are the same, but the content of protein isoforms has an impact on muscle fiber identity and function. However, the extent to which specific transcription isoforms are differentially translated during development and the posttranscriptional mechanisms involved are not fully understood. In particular, this mode of regulation involves RNA-binding proteins (RBPs) which modulate RNA processing such as splicing, export, RNA stability or translation. Mutations in genes encoding RBPs are known to lead to several muscle diseases, such as cardiomyopathy or myotonic dystrophy type 1 (DM1). Myotonic dystrophy type 1 (DM1) is a common neuromuscular disease affecting 1 in 2,100 people worldwide and can present a congenital form. DM1 patients present with myotonia, muscle weakness and degeneration, as well as insulin resistance, cataracts, cardiac conduction defects and hypogonadism. Interestingly, DM1 affects muscle types with different severity but the reason is still elusive. The mechanism of DM1 pathogenesis is not fully understood, but several lines of evidence indicate that the expansion of CUG or CCUG repeats in some RNAs disrupts the normal processing of other mRNAs through the deregulation of several RBPs. Among these RBPs, the most extensively studied are muscleblind (mbl) and members of the Celf (Bruno) family. Our laboratory has recently demonstrated, using our *Drosophila* models of DM1, that it can mimic the muscle phenotypes observed in human<sup>1-3</sup> and have shown an important link between Mbl deregulation and microRNAs function<sup>3</sup>. In parallel, recent single nucleus RNA-seq data in the *Drosophila* embryo have enabled us to identify clusters of variable expression of mbl, bru1,2,3 and a newly identified RBP conserved in human called Boule (Bol). Boule was found to be down-regulated in mbl knockdown experiments<sup>1</sup> (a *drosophila* model of DM1), but its functions in muscle and its potential link to DM1 pathogenesis are still unknown. The proposed project aims to characterize the function of Boule during myogenesis and assess the link with Mbl deregulation, microRNAs and DM1 congenital disease, particularly with regard to muscle type-specific impact.

**Methodologies (key words):** genetics, confocal imaging, single molecule FISH, locomotor behavior, RNA-seq

**Publications of the research group on the proposed topic (3 max.)**

- 1) Picchio, L. et al., (2013). Novel *Drosophila* model of myotonic dystrophy type 1 : phenotypic characterization and genome-wide view of altered gene expression. **Human Mol Genet** 22, 2795-2810.
- 2) Auxerre-Plantié, E., et al., (2019) Straightjacket/a2d3 deregulation is associated with cardiac conduction defects in myotonic dystrophy type 1. **Elife** 8, e51114.
- 3) Souidi, A., et al., (2023). Deregulation of miR-1 and its target Multiplexin promote dilated cardiomyopathy associated with myotonic dystrophy type 1. **EMBO Rep** 24, e56616.

## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :**

Liver X Receptors acts as a promoter of epithelial-mesenchymal transition in advanced prostate cancer

**Laboratory :** Institut de Génétique Reproduction et Développement – iGReD, INSERM U1103, CNRS 6293, Université Clermont Auvergne-UCA

**Laboratory director :** Dr Christophe Jagla

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**Internship tutor :** Ayhan KOCER

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**Summary :**

*Cholesterol Metabolism plays a crucial role in the progression and development of cancer. For several years we are studying the Liver X Receptors (LXR), which belong to the nuclear receptor superfamily and play a key role in the control of cholesterol homeostasis in the cell. They act as inducible transcription factors controlling a large number of genes directly involved in cholesterol efflux and storage. It is known that the development of prostate cancer is associated with an alteration in cellular cholesterol homeostasis. Thus, our study model is more specifically prostate cancer in the advanced stages and resistance to hormonal therapy. The Master 2 internship will be based on the identification of the mechanisms involved in the invasion and migration of carcinoma cells in connection with LXR signaling. The investigations will be conducted on preclinical in vivo models of prostate cancer and in vitro (cancer cell lines) or spheroids by using different molecular approaches (qRT-PCR, Western Blot, Immunocytology, ...).*

**Methodologies (key words) :** Cell culture, CRISP-Cas, qRT-PCR, invasion, migration, prostate cancer.

**Publications of the research group on the proposed topic (3 max.)**

- Bouchareb E., Dallel S., De Haze A., Damon-Soubeyrand C., Re-Naud Y., Baabdaty E., Vialat M., De Joussineau C., Degoul F., Sanmukh S., Gendronneau J., Sanchez P., Gonthier-Gueret C., Trousson A., Morel L., Lobaccaro JM., Kocer A.\*, Baron S\*. Liver X receptors enhances epithelial to mesenchymal transition in metastatic prostate cancer cells (soumis Cancers 2024)
- Buñay J1,2,3, Kossai M., Damon-Soubeyrant C., De Haze A., Saru JP., Trousson A., De Joussineau C., Bouchareb E., Kocer A., Vialat M., Dallel S., Degoul F., Bost F., Penault-Llorca F., Valli MP., Guy L., Matthews J., Renaud Y., Sreekumar A., Gohlke J., Ittmann M., Jones J., Morel L., Lobaccaro JM., Baron S. DIOXIN and PCB-153, two persistent organic pollutants, promote aggressiveness in prostate cancer by a mechanism dependent of acat1 overexpression. (oncogene, accepted 2023)
- Bousset L, Septier A, Bunay J, Voisin A, Guiton R, Damon-Soubeyrant C, Renaud Y, De Haze A, Sapin V, Fogli A, Rambur A, De Joussineau C, Kocer A, Trousson A, Henry-Berger J, Höring M, Liebisch G, Matysik S, Lobaccaro JA, Morel L, Baron S. Absence of nuclear receptors LXRs impairs immune response to androgen deprivation and leads to prostate neoplasia. PLoS Biol. 2020 Dec 7;18(12):e3000948

## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title:**

Role of central and peripheral TREK1 potassium channels in pain and itch

**Laboratory:** UMR 1107 INSERM/Université Clermont Auvergne, NEURODOL lab

**Laboratory director:** Pr Radhouane Dallel

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**Internship tutor:** Dr Stéphane Lolignier

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**Summary :**

We have shown that the TREK1 potassium channel, known to be involved in pain sensitivity and widely expressed in the nervous system, is involved in the analgesic effect of morphine but not in its adverse effects. This makes it a particularly interesting target for the development of new analgesic drugs with an improved benefit/risk ratio. However, questions remain regarding the mechanisms involving TREK1 in pain and, given TREK1 widespread expression, we need to explore its possible role in other physiological functions to better evaluate the safety of future drugs acting on TREK1. We also recently discovered a role of TREK1 channels in the perception of itch which must be explored further. To better understand the contribution of TREK1 channels to the pathophysiology of pain and itch, and the possible adverse effects triggered by pharmacological modulation of TREK1, we wish to study its expression in the nervous system and various organs, and to perform functional studies aiming at characterizing the role of peripheral and central TREK1 channels in neuronal activity, in physiological functions and in pain/itch perception. Accordingly, the objectives of this internship are as follows:

- Study TREK1 expression in nervous and non-nervous tissues using a fluorescent reporter mouse and immunohistochemistry, tissue clearing and light sheet microscopy.
- Determine the role of peripheral and central TREK1 channels in pain and itch in vivo using behavioral analyses in conditional knock-out mice (constitutive and/or induced using viral vectors) as well as in vivo two-photon calcium imaging in sensory neurons.

**Methodologies (key words):** behavioral assessment of pain, transgenic mice, in vivo calcium imaging, immunohistochemistry, tissue clearing

**Publications of the research group on the proposed topic (3 max.)**

Devilliers et al., Activation of TREK-1 by morphine results in analgesia without adverse side effects. Nat Commun. 2013;4:2941. doi: 10.1038/ncomms3941.

Vivier et al., Development of the First Two-Pore Domain Potassium Channel TWIK-Related K<sup>+</sup> Channel 1-Selective Agonist Possessing in Vivo Antinociceptive Activity. J Med Chem. 2017 Feb 9;60(3):1076-1088. doi: 10.1021/acs.jmedchem.6b01285.

Busserolles et al., TREK1 channel activation as a new analgesic strategy devoid of opioid adverse effects. Br J Pharmacol 2020 Oct;177(20):4782-4795. doi: 10.1111/bph.15243

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## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :** The *Myc* oncogene as a transcriptional amplifier of sex dimorphism in the adrenal gland

**Laboratory :** institut GReD, CNRS UMR6293 - Inserm U1103 - UCA

**Laboratory director :** Krzysztof JAGLA

**Address :** Faculté de médecine, CRBC, 28 place H. Dunant, 63001 Clermont-Ferrand

**Internship tutor :** Antoine MARTINEZ

**Tel :** +33 4 73 40 74 09

**e-mail :** antoine.martinez@uca.fr

**Summary :**

Benign or malignant adrenocortical lesions have a greater prevalence in women. The reasons for this sexual dimorphism (SD) remain unexplained but different mouse genetic models recreate this prevalence bias and suggest a hormonal cause rather than a chromosomal one. Indeed, the female mice show a bigger adrenal cortex with faster cell renewal, a better capacity to mobilise the progenitor cells and a greater production of corticosterone than males. Experiments using gonadectomies and hormone substitution or sex reversal models, have shown that the core of this SD depends on the inhibitive action of androgens. To elucidate the mechanisms mobilised by androgen signalling in the physiological or pathological manifestations of SD, we have performed the genetic inactivation of the androgen receptor (AR) in the postnatal adrenal cortex of mice. These experiments established that the targeted loss of AR in male mice is sufficient to induce a feminisation of the adrenal gland in most aspects of the cortex homeostasis and endocrine function. RNA-seq was performed on the adrenals of wild-type and AR deficient mice to identify common differentially expressed genes (DEG) influenced by both sex and AR. Using bioinformatic prediction tools, we identified transcription factors (TF) potentially enriched within promoter regions of members of this DEG list. Among these TF, cMyc oncogene whose expression is repressed by AR, appears to be the best candidate to support SD of the adrenal genetic program. The project will aim at testing this hypothesis *in vivo* by monitoring cMyc expression during development and functional differentiation of the adrenal gland using *Myc*-EFGP knock-in mice and by exploring the consequences of its invalidation using *Myc* floxed allele and adrenal-specific Cre drivers. This project is supported by ANR2023 ADD-SEX grant.

**Methodologies (key words) :** handling (genetically-modified) mice, hormonal manipulation and dosage, immunohistology, microscopic imaging, gene expression analyses, omic data analysis

**Publications of the research group on the proposed topic (3 max.)**

- Dumontet *et al.* PKA signalling drives reticularis differentiation and sexually dimorphic adrenal cortex renewal. JCI Insight. 2018 Jan 25;3(2). pii: 98394. doi: 10.1172/jci.insight.98394.
- Grabek *et al.* The adult adrenal cortex undergoes rapid tissue renewal in a sex-specific manner. Cell Stem Cell. 2019 Aug 1;25(2):290-296.e2. doi: 10.1016/j.stem.2019.04.012.
- Wilmoth *et al.* Sexually dimorphic activation of innate antitumor immunity prevents adrenocortical carcinoma development. Sci Adv. 2022 Oct 14;8(41):eadd0422. doi: 10.1126/sciadv.add0422.

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## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :** Studying the contribution of ATF4 to adaptive changes in amino acid transport and metabolism in the liver during catabolic inflammatory states.

**Laboratory :** Human Nutrition Unit, UMR 1019

**Laboratory director :** Didier Rémond

**Address :** INRAE Centre de Theix, Route de Theix, 63122 Saint-Genès Champanelle

**Internship tutor :** Anne-Catherine Maurin

**Tel :** 06-67-46-33-14

**e-mail :** anne-catherine.maurin@inrae.fr

#### Summary :

Inflammatory states such as cancer and sepsis are often associated with cachexia, a systemic wasting syndrome accelerating the deterioration of health. Advanced cachexia leads to functional impairments and a general weakness state that reduces tolerance and response to treatments. Understanding the etiology of cachexia is needed to develop new therapeutic approaches targeting early stages of the syndrome. Using a mouse model of cancer cachexia, our recent results highlighted that, as early as the pre-cachectic phase, cancer progression was associated with induced production of IL-6 and reduced circulating levels of most AA, while in the liver, positive acute-phase protein expression was strongly induced and autophagy was upregulated. Then, the onset of cachexia was associated with activation of the stress-related eIF2 $\alpha$  signaling in the liver, with increased expression of ATF4-target genes involved in AA synthesis and -transport, as well as autophagy. Thus, the eIF2 $\alpha$ -ATF4 signaling pathway is likely to contribute to adaptive gene expression-regulatory mechanisms aimed at promoting AA availability in the liver from the earliest stages of cachexia (Chaouki et al., under review). Our current goal is to functionally evaluate the role of ATF4 in adaptive changes in liver amino acid transport and metabolism in response to catabolic inflammatory situations. To this end, mice with an inducible genetic ablation of ATF4 in the liver will be subjected to an acute catabolic inflammatory situation resulting from the administration of bacterial lipopolysaccharide (LPS). The aim of the internship is to contribute to this project.

**Methodologies (key words) :** RT-qPCR, western-blot, AA assay, Elisa, histology.

#### Publications of the research group on the proposed topic (3 max.)

Pre-cachectic alterations in amino acid homeostasis precede activation of eIF2 $\alpha$  signaling in the liver at the onset of C26 cancer-induced anorexia-cachexia. Chaouki *et al.*, under review.

GCN2 upregulates autophagy in response to short-term deprivation of a single essential amino acid. Maurin *et al.*, 2022. *Autophagy Reports*, 1 (1), 119-142.

The eIF2 $\alpha$ /ATF4 pathway is essential for stress-induced autophagy gene expression. B'chir *et al.*, 2013. *Nucleic Acids Res*, 41(16):7683-99.

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## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title:** Evaluation of PET radioligands for imaging of mutant Isocitrate DeHydrogenase 1 (mIDH1) in solid tumours

**Laboratory:** IMoST UMR1240 INSERM UCA  
**Laboratory director:** Pr Elisabeth Miot-Noirault  
**Address:** 58, rue Montalembert 63000 Clermont-ferrand

**Internship tutor:** Dr Leslie Mazuel  
**Tel :** 04 73 15 08 15  
**e-mail :** leslie.mazuel@uca.fr

#### **Summary:**

Isocitrate dehydrogenase (IDH) enzymes catalyze the conversion of isocitrate to  $\alpha$ -ketoglutarate ( $\alpha$ -KG) in the tricarboxylic acid cycle. IDH mutations (mIDH) are a common genetic alteration in glioma (80%) and in chondrosarcomas (60%) leading to the acquisition of a new enzymatic activity. mIDH enzymes catalyze the conversion of  $\alpha$ -KG into the oncometabolite D-2-hydroxyglutarate (D2HG) involved in tumorigenesis. Currently, mIDH is an important biomarker for glioma classification and a potential target for new therapeutic approaches. However, current clinical methods for detecting mIDH1 require invasive tissue sampling and cannot be used for follow-up examinations or longitudinal studies. In order to detect directly, non-invasively and quantitatively mIDH1 *in vivo*, the IMoST laboratory (UMR1240 INSERM UCA) is developing mIDH1 specific radiotracers for positron emission tomography (PET) imaging. mIDH1 PET imaging could represent a promising approach for non-invasive assessment of the mIDH1 status in solid tumors.

The objectives of this internship will be to establish subcutaneous model tumors expressing different mIDH1 mutation in mice. The evaluation of mIDH radiotracers biodistribution will be done *in vivo* by nuclear imaging and *ex vivo* by gamma counting. To carry out this project, the student will be in charge of cell culture, implementation of the animal model, analysis of mIDH expression by western blot, genomic sequencing and D2HG dosage. The student will participate in nuclear imaging acquisitions and perform data analysis.

**Methodologies (key words):** Cell culture, animal model, nuclear imaging, biodistribution, dosage

#### **Publications of the research group on the proposed topic (3 max.)**

Lai TH, Wenzel B, Dukić-Stefanović S et al., Radiosynthesis and biological evaluation of [18F]AG-120 for PET imaging of the mutant isocitrate dehydrogenase 1 in glioma. *Eur J Nucl Med Mol Imaging*. 2024 Mar;51(4):1085-1096. doi: 10.1007/s00259-023-06515-7.

Weber V, Arnaud L, Dukic-Stefanovic S et al., Novel Radioiodinated and Radiofluorinated Analogues of FT-2102 for SPECT or PET Imaging of mIDH1 Mutant Tumours. *Molecules*. 2022 Jun 11;27(12):3766. doi: 10.3390/molecules27123766. PMID: 35744895; PMCID: PMC9228733.

## Track « Integrative Biology, Physiopathology »

### Proposal for a Master 2 internship – 2024-2025

**Title** : Ovarian tissue homeostasis: Study of the molecular mechanism of follicular dormancy from *Drosophila* to human

**Laboratory** : Institute of Genetics, Reproduction and Development

**Laboratory director** : K Jagla

**Address** : CRBC, Medecine School, place Henri Dunant, 63000 Clermont-fd

**Internship tutor** : Vincent Mirouse

**Tel** : 04 73 17 81 71

**e-mail** : vincent.mirouse@uca.fr

**Summary** :

Human ovarian development represents one of the most spectacular examples of homeostatic control in the living world. Indeed, after the definition of a large stock of primordial follicles during development, these can be kept dormant for decades while only one can escape this dormancy to enter the steroid phase leading to the formation of a mature oocyte. The mechanisms explaining, 1) this dormancy and 2) the escape from this dormancy, remain very poorly understood. *Drosophila* is considered to have a different reproductive strategy with the continuous production of large numbers of mature follicles. However, we have defined physiological conditions, which can be genetically mimicked, in which females accumulate the mature steroidogenic stages without laying them. This accumulation causes early follicle dormancy similar to mammals. Using transcriptomic studies and the genetic potency of *Drosophila* we have identified a paracrine factor produced by mature stages and which inhibits the growth of young stages. The purpose of this internship will therefore be to study 1) the control of the expression of this factor 2) to confirm its impact on the dormancy of the follicles 3) to define the signaling pathway explaining the dormancy. Since this factor is conserved in humans, where it is also expressed in the follicular cells of mature stages, this work will be done, in parallel and in collaboration, on human follicles in culture, with the aim to solve an important enigma of animal physiology.

**Methodologies (key words)** : Cell imaging, CRISPR genome editing, tissue culture, *Drosophila* genetics

**Publications of the research group on the proposed topic (3 max.)**

Vachias C, Fritsch C, Pouchin P, Bardot O, Mirouse V. Tight coordination of growth and differentiation between germline and soma provides robustness for *drosophila* egg development. *Cell Reports*. 2014 Oct 23;9(2):531-41.

Vachias C, Tournalias C, Grelee L, Gueguen N, Renaud Y, Venugopal P, Richard G, Brassat E, Mirouse V. Promotion of germ cell growth by gap junction-dependent amino acid transfer. *BioRxiv* 2024.

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## Track « Integrative Biology, Physiopathology »

### Proposal for a Master 2 internship – 2024-2025

**Title :** Study of the dynamics of the actin cytoskeleton during epithelial morphogenesis in *Drosophila*

**Laboratory :** Institut de Génétique, Reproduction et Développement (iGRéD)

**Laboratory director :** Krzysztof Jagla

**Address :** CRBC, Faculté de médecine, Place Henri Dunant, 63000 Clermont-Ferrand.

**Internship tutor :** Vincent Mirouse

**Tel :** 04 73 17 81 71

**e-mail :** vincent.mirouse@uca.fr

**Summary :**

How cells change their relative position to give a particular shape to a tissue is a major question in developmental biology with important implications for regenerative medicine. Our team studies the mechanisms allowing the morphogenesis of epithelial tissues using the *Drosophila* model and more particularly the elongation of ovarian follicles because of the power of the genetic tools available and the cellular imaging possibilities it offers.

Our team has recently identified a new actin subpopulation within epithelial cells which is necessary for cell intercalation and tissue elongation. Intercalations correspond to exchanges of neighbors in the plane of the tissue and are one of the basic mechanisms explaining how cells rearrange themselves during morphogenesis. Our current data show that this dynamic population is generated by a polymerization complex called Wave Regulatory Complex (WRC), that it is specifically localized at the junction points between several cells. The project will be to explain how WRC activity is controlled in time and space and how tissue elongation emerges from this control. For this, a combination of a living cell imaging approach, genetics and protein interaction will be carried out. This project aims to functionally link events occurring at the molecular (actin polymerization), cellular (intercalation) and tissue (elongation) scales and to bring a multi-scale and integrative mechanism to an important biological question.

**Methodologies (key words) :** Cell live quantitative imaging, ex vivo culture, *Drosophila* genetics, CRISPR genome editing

**Publications of the research group on the proposed topic (3 max.)**

**Calvary et al.**, Tricellular junction recruitment of Wave regulatory complex by Sidekick and Lar induces protrusive activity resolving cell intercalation, **BioRxiv**, 2024

**Alegot et al.**; Jak-Stat pathway induces *Drosophila* follicle elongation by a gradient of apical contractility. **Elife** 2018 Feb 8;7. pii: e3294

**Cerqueira-Campos et al.**; Oriented basement membrane fibrils provide a memory for F-actin planar polarization via the Dystrophin-Dystroglycan complex during tissue elongation. **Development**. 2020 Apr 8;147(7)

## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :** Consequences of Short Histone H2A Rapid Evolution on Chromatin Organization

**Laboratory :** Institute of Genetics Reproduction and Development (iGReD); Team:  
“[Evolutionary Epigenomics and Genetic Conflicts](#)”

**Laboratory director :** Krzysztof Jagla

**Address :** Faculté de Médecine 28 Place Henri Dunant, 63000, Clermont-Ferrand.

**Internship tutor :** Antoine Molaro (Group Leader)

**Tel :** 0473178177

**e-mail :** antoine.molaro@uca.fr

**Summary :**

**Background:** Histones are evolutionary conserved proteins that package genetic information into nucleosomes - the basic unit of chromatin. In placental mammals, including in humans, a unique class of short H2A histone variants are incorporated in the chromatin of reproductive cells. The loss of short H2As in mouse models affects fertility and development. In addition, their ectopic activation in cancer cells leads to chromatin reorganization. Unlike other histones, short H2As are subject to dramatic evolutionary innovations. Although these innovations occur over protein domains predicted to impact histone function, their functional consequences on chromatin structure have never been explored *in vivo*.

**Project:** This Master project is aimed at identifying and comparing the chromatin features of cells expressing specific short H2A orthologs. This will help understand their role during reproduction and cancer. Using phylogenetics we will identify and clone human and non-human primate short H2As sequences for expression in cell culture. Using microscopy, qPCR and high-resolution chromatin profiling we will compare the chromatin alterations induced by specific short H2A orthologs. During her/his time in the lab, the student will develop skills in: evolution-guided hypothesis testing, molecular and cell biology, epigenomics and bioinformatics. The student will work in a diverse and inclusive environment. This project uniquely combines evolutionary and chromatin biology and is well-suited for students seeking to pursue a career in laboratory research or a doctorate in biological sciences.

**Requirements:** good command of research literature; prior experience with laboratory techniques and protocols (e.g. internship...); comfortable with note-keeping and oral presentations.

**Methodologies (key words) :** *phylogenetics; vector design and building; transfections in human and chimpanzee cell lines; microscopy; qPCR; CUT&RUN*

**Publications of the research group on the proposed topic (3 max.)**

1. Chew et al., 2021. Short H2A variants are expressed in cancer. *Nature Comm.* PMID: 33473122
2. Molaro A et al., 2020. Biparental contributions of the H2A.B histone variant control embryonic development in mice. *PLOS BIOLOGY.* PMID: 33362208
3. Molaro A et al., 2018. Evolutionary origins and diversification of testis-specific short histone H2A variants in mammals. *Genome Research.* PMID: 29549088

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**Track « Integrative Biology, Physiopathologies »**  
**Proposal for a Master 2 internship – 2024-2025**

**Title :** Organization of trigeminal meningeal and cutaneous afferents in a murine model of migraine.

**Laboratory :** INSERM U1107 Neuro-Dol, Team Trigeminal Pain and Migraine  
**Laboratory director :** Pr Radhouane DALLEL  
**Address :** 2 rue de Braga, 63000 Clermont-Ferrand

**Internship tutor :** Lénaïc MONCONDUIT  
**Tel :** 04 73 17 73 14  
**e-mail :** lenaic.monconduit@uca.fr

**Summary :**

Migraine presents as a neurovascular condition characterized by pulsatile, unilateral headaches ranging from moderate to severe intensity. It is accompanied by symptoms such as cutaneous hypersensitivity (cutaneous allodynia) and can progress to a chronic state. We developed a murine migraine model, applying inflammatory substances onto the meninges' surface induces temporary then persistent allodynia. Allodynia is underpinned by central sensitization in the trigeminal sensitive complex. We hypothesize that sensitization might originate as early as the peripheral ganglion relay and not only in central level. Specifically, sensitization of cutaneous ganglion neurons could occur via meningeal ganglion neurons. To test this theory, we plan to examine the organization of trigeminal ganglion neurons projecting onto both the meninges and the cutaneous territory using tracer and virus injections on the meninges and subcutaneously in the ophthalmic region. Alongside this anatomical tracing, we will administer inflammatory substance infusions on the meninges to study how meningeal and cutaneous peripheral neurons organize under pathological conditions. Additionally, we will investigate the expression of connexins, pannexins, and markers of satellite cell activation surrounding ganglion neurons to observe any changes following meningeal neuron activation.

**Methodologies (key words) :** virus injections, surgery, behavior studies, anatomical labeling

**Publications of the research group on the proposed topic (3 max.)**

Signoret-Genest J, et al. J Headache Pain. 2023 doi: 10.1186/s10194-023-01691-1.  
Boyer N, et al. Pain. 2017 doi: 10.1097/j.pain.0000000000001007.  
Descheemaeker A, et al. Brain. 2022 doi: 10.1093/brain/awac139.

**Track « Integrative Biology, Physiopathologies »****Proposal for a Master 2 internship – 2024-2025**

**Title :** Targeting autophagy by physical activity to attenuate the deleterious effects of Western diet and pathogenic bacteria on intestinal homeostasis and gut microbiota.

**Laboratory :** M2iSH (Microbes, intestine, inflammation and Susceptibility of the Host), UMR 1071 Inserm/Université Clermont Auvergne, USC INRAE 1382

**Laboratory director :** Professor Nicolas Barnich

**Address :** CRBV, 28 Place Henri Dunant, 63000 Clermont-Ferrand

**Internship tutor :** Dr. Hang Nguyen (PhD, HDR)

**Tel :** 0473178345

**e-mail :** hang.nguyen@uca.fr

**Summary :**

Crohn's disease (CD) is a chronic inflammatory bowel disease, of which the etiology involves environmental, genetic and microbial factors. Despite recent advances, the mechanism favoring the onset of CD is largely unknown, and to date, there is no medication cure for this disease.

Among the genetic factors, single nucleotide polymorphisms (SNPs) in the autophagy-related genes, which lead to dysregulated autophagy, have been associated with an increased risk to develop CD. Autophagy, a cellular process that degrades dangerous cytoplasmic materials and invasive pathogens, is central for the maintenance of organism's homeostasis. Among the environmental factors, the spread of Western diet during the latter 20<sup>th</sup> century has been revealed as a risk factor for CD. Among the microbial factors, alterations in the gut microbiota composition, also called intestinal dysbiosis, have been involved in CD etiology. One example of intestinal dysbiosis in CD patients is the high prevalence of adherent-invasive *E. coli* (AIEC), which are able to inhibit autophagy to replicate inside host cells, to colonize the gut and induce intestinal inflammation in genetically susceptible mouse models.

Physical activity (PA) is a fundamental intervention that confers remarkable health benefits and disease risk reduction. PA has been linked with a decreased risk of developing Crohn's disease (CD), however the underlying mechanisms remain unclear. Exercise has been shown to induce autophagy in different tissues, exerting beneficial effects for the organism. However, it is not known yet whether PA can effectively induce autophagy in the intestine, and whether PA can suppress the deleterious effects of Western diet and pathogenic bacteria on intestinal homeostasis and gut microbiota *via* modulating autophagy.

The objectives of the proposed internship are (i) to investigate the impact of PA on autophagy in the intestine, and (ii) to examine the ability of PA to, *via* activating autophagy, restore intestinal homeostasis, including gut microbiota, attenuate host susceptibility to AIEC infection and decrease intestinal inflammation during Western diet consumption. If successful, this project will contribute to the development of a novel personalized strategy for CD management.

**Methodologies (key words):** molecular biology (RNA extraction, cDNA synthesis, qRT-PCR); biochemistry (Western blot, ELISA); cell biology (cell culture, fluorescent microscopy); infection of susceptible mouse models of CD: determination of bacterial colonization in the intestine.

**Publications of the research group on the proposed topic (3 max.)**

-Larabi A, Barnich N, **Nguyen HT\***. New insights into the interplay between autophagy, gut microbiota and inflammatory responses in IBD. *Autophagy*. 2020; 16(1):38-51. DOI: 10.1080/15548627.2019.1635384.

-**Nguyen HT\***, *et al.* Crohn's disease-associated adherent invasive *Escherichia coli* affect levels of microRNAs in intestinal epithelial cells to reduce autophagy. *Gastroenterology*. 2014, 146(2):508-19. DOI: 10.1053/j.gastro.2013.10.021.

-Lucas C, Salesse L, Hoang MHT, Bonnet M, Sauvanet P, Larabi A, Godfraind C, Gagnière J, Pezet D, Rosenstiel P, Barnich N, Bonnet R, Dalmaso G, **Nguyen HT\***. Autophagy of intestinal epithelial cells inhibits colorectal carcinogenesis induced by colibactin-producing *Escherichia coli* in *Apc*<sup>Min/+</sup> mice. *Gastroenterology*. 2020, 158(5):1373-1388. DOI: 10.1053/j.gastro.2019.12.026. IF = 33.4.

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## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title** : Deciphering the molecular mechanism underpinning the antero-posterior axis establishment in the early mouse embryo.

**Laboratory** : iGReD

**Laboratory director** : Christophe Jagla

**Address** : UFR Médecine, CRBC. 28 place Dunant. 63000 Clermont-Ferrand

**Internship tutor** : Pierre Osteil

**Tel** : 0473138383

**e-mail** : pierre.osteil@uca.fr

#### **Summary** :

At the time of implantation, at 4.5 days of development or **blastocyst stage**, the mouse embryo is made up of three tissues: the trophectoderm, the epiblast and the hypoblast or primitive endoderm (PrE). The epiblast is at the origin of the cells that make up the individual, while the PrE is an extraembryonic tissue at the origin of the yolk sac. At around 6 days, the epiblast then specialises into the three embryonic layers, the mesoderm, endoderm and ectoderm, during gastrulation, which defines the **antero-posterior**, left-right and dorso-ventral axes. The anteroposterior (AP) axis is induced in epiblast-derived cells by a gradient of Wnt (WNT3) and Tgf $\beta$  (NODAL) from weakest in the anterior to strongest in the posterior. This gradient is generated by the secretion of inhibitors of Wnt (DKK1) and Tgf $\beta$  (CER1 and **LEFTY1**) from a group of adjacent cells in the PrE. The absence of these cells and therefore of the inhibitors leads to anterior truncations (headless embryos) because the anterior tissues are not induced.

By tracing the cascade of events leading to the appearance of these secretory cells, studies using cell lineages tracking have shown that they emerge in the PrE at the blastocyst stage, which is already polarised. Currently, only one marker for these cells, *Lefty1*, has been identified at day 4.5 and the molecular mechanisms involved in the specialisation of these cells remain unknown.

The project will aim at understanding how these cells specialise within the PrE tissue within the mouse embryo and in embryonic stem cells organoids, mimicking the embryo. We will use CRISPR editing and confocal microscopy to answer these questions.

**Methodologies (key words)** : Mouse Embryonic stem cells, CRISPR, embryo dissection, confocal microscopy, Immunostaining, FISH-HCR, bioinformatics, RT-qPCR, organoid models

#### **Publications of the research group on the proposed topic (3 max.)**

Allegre, et al. (2022). NANOG initiates epiblast fate through the coordination of pluripotency genes expression. Nat. Com. 10.1038/s41467-022-30858-8

Azami et al. (2019). Regulation of the ERK signalling pathway in the developing mouse blastocyst. Development. 10.1242/dev.177139

Bessonard et al. (2018). Gata6, Nanog and Erk signaling control cell fate in the inner cell mass through a tristable regulatory network. Development. 10.1242/dev.109678

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## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :**

Identification and characterization of a molecule with anti-atrophic potential.

**Laboratory:** Human Nutrition Unit, UMR1019

**Laboratory director:** Didier REMOND

**Address:** INRAE de Theix – 63122 St Genès Champanelle

**Internship tutor:** Cécile POLGE

**Tel:** 04 73 62 42 18

**e-mail:** cecile.polge@inrae.fr

**Summary:**

A common feature of many diseases (cancer, sepsis, heart failure, ...) is a catabolic state leading to significant muscle atrophy. This muscle atrophy contributes to the deterioration of patients' health, compromises treatments and is associated with high mortality. Muscle atrophy results from a strong increase in the degradation of contractile proteins by the ubiquitin proteasome system (UPS).

The targeting of substrates for degradation by the 26S proteasome results from the sequential action of three enzymes: the E1 enzyme, which activates ubiquitin (Ub) and transfers it to an E2 conjugating enzyme (among 35). In the presence of an E3 ubiquitin ligase (> 700), E2 covalently binds Ub to a lysine residue of the substrate. We and others have identified the only E3 ligase known to target muscle contractile proteins for degradation during catabolic states, namely MuRF1 (Polge et al, 2011 FASEB J). This was consistent with the phenotype of MuRF1 knockout mice, which were resistant to muscle atrophy in several catabolic situations. Thus, MuRF1 appears to be a good candidate for pharmacological inhibition to limit muscle atrophy.

We have identified one molecule as a potential MuRF1 inhibitor in a previous screen. The first part of the internship will be to confirm the effect of this molecule on MuRF1 targets in cellulo. Secondly, we will test and characterize variants of this molecule synthesized by collaborators (Pr Taillefumier, Institut de Chimie de Clermont-Fd, ICCF). This project is part of a multidisciplinary project considered promising by the AFM-Telethon (regular support since 2013) and Europe (Marie Curie Innovative Training Network 2019-2023). This project involves a high-quality consortium (Paris-Sorbonne; CRCT Toulouse; LUMC Leiden; ICCF).

**Methodologies (key words):** cell culture, cell viability assay, western blot, interactomics

**Publications of the research group on the proposed topic (3 max.)**

**Peris-Moreno**, et al (2021) UBE2L3, a Partner of MuRF1/TRIM63, Is Involved in the Degradation of Myofibrillar Actin and Myosin. *Cells*.10(8):1974.

**Polge**, et al. (2018). A muscle-specific MuRF1-E2 network requires stabilization of MuRF1-E2 complexes by telethonin, a newly identified substrate. *J Cachexia Sarcopenia Muscle*. doi: 10.1002/jcsm.12249

**Peris-Moreno**, et al (2020). MuRF1/TRIM63, Master Regulator of Muscle Mass. *Int. J. Mol. Sci.* 2020, 21, 6663; doi:10.3390/ijms21186663

## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :** Development of theranostic radioconjugates for the treatment of cancers resistant to immunotherapy

**Laboratory :** IMOST UMR1240  
**Laboratory director :** Pr. Elisabeth Noirault  
**Address :** 58 Rue Montalembert, 63000 Clermont-Ferrand (France)

**Internship tutor :** Dr. Aurélien Pommier  
**Tel :** +33 (0)6 07 69 28 60  
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#### **Summary :**

Immunotherapies such as immune checkpoint blockers or CAR-T cell adoptive transfer have seen unprecedented therapeutic success in recent years, but an objective clinical response is still observed only in a minority of patients. Despite the promising potential of radiotherapy (RT) to enhance the antitumor immune response, many clinical studies investigating conventional external beam RT as a combination for immunotherapy failed to reveal a therapeutic benefit over either treatment modality. These results may be explained by a robust local and systemic immunosuppression in response to high and fractionated radiation doses which could be overcome by changing RT regimens to optimally sustain the immune response.

The mid-term aim of this project is to develop Radionuclide Antibody Conjugates (RAC) which are bio-vectors enabling to deliver a dose of radioactive particles specifically in tumors which can limit the immunosuppression induced with current RT regimens. The originality of this approach relies on both, the identification of novel cancer specific antigens, ideally associated with low chance of response to immunotherapy, and the design of the RAC which combine selected radionuclides with the most relevant tumor specific antibodies. The proposed project has high translational and industrial potentials since there is a huge interest of the main pharmaceutical industry players in this field, as demonstrated by their recent investment in the underlying biotechnologies.

The internship will be focused on the generation and validation of biological therapeutic tools such as novel antibodies and recombinant proteins which will be used to design the RAC.

**Methodologies :** Molecular biology (PCR, sequencing), bacteriology (cloning), cell-based pharmacology assays (antibody binding by FACS/ELISA, cell viability by MTT).

#### **Publications of the research group on the proposed topic**

Phase I study of <sup>131</sup>I-ICF01012, a targeted radionuclide therapy, in metastatic melanoma : MELRIV-1 protocol. Thivat E et al., BMC Cancer 2022, 22 (1) : 417.

Tetraspanin 8 (TSPAN 8) as a potential target for radio-immunotherapy of colorectal cancer. Maisonia-Besset A et al., Oncotarget. 2017; 8:22034-22047.

Novel Radioiodinated and Radiofluorinated Analogues of FT-2102 for SPECT or PET Imaging of mIDH1 Mutant Tumours. Weber V. et al., Molecules 2022, 27(12), 3766

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**Track « Integrative Biology, Physiopathologies »**  
**Proposal for a Master 2 internship – 2024-2025**

**Title :** Chromatin dynamics during Arabidopsis seed germination

**Laboratory :** Institute of Genetics, Reproduction and Development (iGReD)

**Laboratory director :** K. Jagla

**Address :** iGReD, CRBC, UFR Médecine, 28 Place Henri Dunant, 63001 Clermont-Ferrand  
Cedex. France

**Internship tutor :** Aline V. Probst

**Tel :** 04 73 40 74 01

**e-mail :** aline.probst@uca.fr

**Summary:**

The organization of genomic DNA into chromatin helps to structure and compact the genome and contributes to the control of gene expression. To accommodate the substantial changes in gene expression patterns that occur during developmental transitions, chromatin structure is remodeled by the exchange of histone variants and the deposition of new histone modifications. Given the importance of histones in epigenetic inheritance, the removal of old and deposition of new histones during replication and transcription is coordinated by a network of specific histone chaperone complexes.

This project will study the dynamics of histones H3 and H2B during the developmental transition from seed to seedling. Using epitope-tagged H3 and H2B histones expressed under the control of developmentally regulated promoters in the model plant *Arabidopsis thaliana*, the candidate will study the eviction of old and deposition of new histones during seed germination in different chromatin contexts such as heterochromatin and genes induced or repressed during seed germination. To this end, the candidate will use various molecular approaches and microscopic imaging. The results from wild type plants will be compared to mutants lacking the histone chaperone complexes HIRA and FACT, which are known to show altered seed germination, to elucidate their respective roles in histone dynamics and transcription.

This project is expected to provide new insights into the mechanisms that ensure epigenetic inheritance and epigenetic reprogramming.

**Methodologies:** *Chromatin Immuno-precipitation, Histone extraction and Western Blot, Immunofluorescence staining and confocal microscopy, Reverse Transcription coupled to quantitative PCR, seed germination phenotyping*

**Publications of the research group on the proposed topic**

Probst AV. Deposition and eviction of histone variants define functional chromatin states in plants. *Curr Opin Plant Biol.* 2022 Oct;69:102266.

Layat E, Bourcy M, Cotterell S, Zdzieszynska J, Desset S, Duc C, Tatout C, Bailly C, Probst AV. The Histone Chaperone HIRA Is a Positive Regulator of Seed Germination. *Int J Mol Sci.* 2021 Apr 14;22(8):4031.

Benoit M, Simon L, Desset S, Duc C, Cotterell S, Poulet A, Le Goff S, Tatout C, Probst AV. Replication-coupled histone H3.1 deposition determines nucleosome composition and heterochromatin dynamics during Arabidopsis seedling development. *New Phytol.* 2019 Jan;221(1):385-398.

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## Track « Integrative Biology, Physiopathologies » Proposal for a Master 2 internship – 2024-2025

**Title :** Genetic and epigenetic control of DNA recombination

**Laboratory :** Genetics, Reproduction and Development Institute (iGReD)  
UMR CNRS 6293 – INSERM U1103 – Clermont Auvergne University

**Laboratory director :** Krzysztof JAGLA

**Address :** Centre de Recherche BioClinique, 28 Place Henri Dunant, 63001 Clermont-Ferrand

**Internship tutor :** Heidi SERRA

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**Summary :** **Meiosis** is a specialized cell division that produces **gametes** and is thus at the heart of sexual reproduction in Eukaryotes. During meiosis, chromosomes pair and recombine, i.e. exchange genetic material with each other. **Meiotic recombination** has two main biological functions: it increases genetic diversity of gametes and ensures balanced segregation of chromosomes within the daughter cells. Any abnormality at meiosis can be responsible for **sterility** or **major genetic disorders** in the offspring.

We have recently shown in the model plant *Arabidopsis suecica* (a polyploid species which contains two sub-genomes, like durum wheat, rapeseed, and cotton) that recombination not only occurs between homologous chromosomes but also between chromosomes from different sub-genomes (Chéron et al, 2023). These events lead to important genomic and chromosomal rearrangements that can directly impact fitness and fertility of the plants.

Based on these data, the proposed project has two main objectives: (1) identify how often and where does recombination occur at local and genome scales and (2) how genetic and epigenetic contexts influence recombination profiles. It involves the generation of high-resolution maps of meiotic recombination (using Nanopore sequencing) and the analysis of DNA methylation and/or histone marks (isolation of meiocytes, chromatin immunoprecipitation...). This study seeks to provide insights into the **dynamics of polyploid genomes** and its regulation.

**Methodologies (key words):** Genetics, Molecular biology, Microscopy, Chromatin Immunoprecipitation, High throughput sequencing (Nanopore technology), Bioinformatics.

**Publications of the research group on the proposed topic**

- Chéron F, Petiot V, Lambing C, White C, Serra H (2023) Incorrect recombination partner associations contribute to meiotic instability of neo-allopolyploid *Arabidopsis suecica*. **New Phytologist** 241(5), 2025-2038
- Serra H, Svačina R, Baumann U, Whitford R, Sutton T, Bartoš J, Sourdille P (2021) *Ph2* encodes the mismatch repair protein MSH7-3D that inhibits wheat homoeologous recombination. **Nature Communications** 12, 1-10
- Serra H, Lambing C, Griffin CH *et al.* (2018) Massive crossover elevation via combination of HEI10 and *recq4a* *recq4b* during *Arabidopsis* meiosis. **PNAS** 115(10):2437-2442

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## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title : Aseptic abscess syndrome : Host-microbiota relationship**

**Laboratory :** M2iSH (Microbes, intestine, inflammation and Susceptibility of the Host),  
UMR 1071 Inserm/Université Clermont Auvergne, USC INRAE 1382

**Laboratory director :** Professor Nicolas Barnich

**Address :** CRBV, 28 Place Henri Dunant, 63000 Clermont-Ferrand

**Internship tutor :** Dr Ludovic Trefond

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#### **Summary :**

Aseptic abscess (AA) syndrome is a rare disease whose pathophysiology is unknown. It is often associated with inflammatory bowel disease and characterised by sterile inflammation with collections of neutrophils affecting several organs, especially the spleen. Microbiota are known to influence local and systemic immune responses, and both gut and oral microbiota perturbations have been reported in diseases associated with AA syndrome. However, interactions between these factors have never been studied in AA syndrome. The purpose of this translational case-control study (ABSCESSBIOT) is to investigate gut and/or oral microbiota in patients with AA syndrome compared with healthy controls. Moreover, microbiota associated metabolites quantification and Treg/Th17 balance characterisation will give a mechanistic insight on how microbiota may be involved in the pathophysiology of AA syndrome.

Samples from AA patients and healthy controls have been collected. The M2 student will perform experiments to analyse microbiota (DNA extraction, 16S data analysis), T cell balance (flow cytometry, qPCR) and microbial metabolite quantifications (short-chain fatty acids, tryptophan derivatives).

If specific bacterial species, abnormal microbiota-associated metabolites and/or Treg/Th17 imbalance are associated to AA syndrome, other studies could be conducted to demonstrate their role in the pathophysiology. All these data could thus constitute a basis for the future development of therapies targeting microbiota or the immune response in AA syndrome.

**Methodologies (key words) :** microbiota profiling, microbial metabolites, T cell phenotyping.

#### **Publications of the research group on the proposed topic (3 max.)**

1. **Trefond L**, Frances C, Costedoat-Chalumeau N, Piette JC, Haroche J, Sailler L, et al. Aseptic Abscess Syndrome: Clinical Characteristics, Associated Diseases, and up to 30 Years' Evolution Data on a 71-Patient Series. *J Clin Med.* 2022 Jun 25;11(13):3669.
2. **Trefond L**, Billard E, Pereira B, Richard D, Vazeille E, Bonnet R, et al. Host-microbiota relationship in the pathophysiology of aseptic abscess syndrome: protocol for a multicentre case-control study (ABSCESSBIOT). *BMJ Open.* 2023 Aug 4;13(8):e073776.

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## Track « Integrative Biology, Physiopathologies » Proposal for a Master 2 internship – 2024-2025

**Title :** Identification of the crosstalk between metabolic and epigenetic processes in stem cell homeostasis and their involvement in fertility disorders and/or testicular cancer as well as in their chemoresistance.

**Laboratory :** Team VOLLE ; Institute GReD, CNRS UMR6293/UCA/Inserm U1103  
**Laboratory director :** Krzysztof Jagla  
**Address :** Centre de Recherche BioClinique, Faculté de Médecine, 28 Place Henri Dunant, 63037 Clermont-Ferrand, France

**Internship tutor :** Dr David VOLLE  
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**Summary:** Understanding the mechanisms that drive stem cell fate decision is of major importance with clinical in the etiology of diseases such as infertility or cancer as well as in regenerative medicine and tissue rehabilitation after cancer therapy. Growing evidence show that metabolic pathways influence epigenetic changes associated with lineage commitment, specification, and self-renewal. In the other way round, epigenetic is also important in metabolic decision. However, the interplay between metabolism and epigenetics in deciding the fate of spermatogonial stem cells (SSC) remains largely unexplored. The study of SSC that self-renew while giving rise to differentiated germ cells appears as a useful strategy to decipher the mechanisms involved in stem cell homeostasis associated with cell fate specification and outcome of potential diseases. Our goal is to decipher the metabolic-epigenetic interplays through the study of "candidate genes" identified using RNAseq approaches. We will take advantage of genetically engineered mouse models in combination with cell culture experiments either treated by pharmacological agents or modified by genome editing (Crispr/CAS9). Our objectives are: **1/** to analyze the role of yet unidentified genes in the etiology of fertility disorders or germ cell cancers; **2/** to study the interaction between metabolic-epigenetic pathways in germ cell homeostasis and chemoresistance; and **3/** to transpose these data on human. The data obtained will shed light on the gene networks that drive stem cell fate and help to better understand the interaction between cellular metabolism and epigenetics for regulating stem cell homeostasis, cell state and differentiation capacity. This work should allow defining biomarkers of stem cell alterations leading to germ cell cancer, fertility disorders and/or transgenerational inheritance of disease to offspring. This project might also offer opportunities to develop new therapeutics in regenerative medicine following anti-cancer treatment.

**Methodologies (key words) :** Modèles murins, culture cellulaire, transduction virale, transfection transitoire, transplantation CSS tumorales, histologie/Imagerie, biologie moléculaire.

**Publications of the research group on the proposed topic (3 max.)**

- 1- Thirouard et al. "Identification of a Crosstalk among TGR5, GLIS2, and TP53 Signaling Pathways in the Control of Undifferentiated Germ Cell Homeostasis and Chemoresistance." *Adv. Sci (Weinh)* 2022 Apr 18; e2200626. doi: 10.1002/advs.202200626.
- 2- Thirouard et al. "Analysis of the Reversible Impact of the Chemodrug Busulfan on Mouse Testes.", *Cells*, vol. 10 (9), 2021.
- 3- Baptissart et al. "Multigenerational impacts of bile exposure are mediated by TGR5 signaling pathways.", *Scientific reports*, vol. 8 (1), pp. 16875, 2018.

## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :** Analysis of the impact of TET epigenetic enzyme in gene expression regulation: an epitranscriptomic view.

**Laboratory :** iGReD – Institut de Génétique Reproduction et Développement ; UMR6293  
CNRS-UCA / UMR1103 Inserm-UCA

**Laboratory director :** Dr K. Jagla

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**Internship tutor :** Dr Lucas Waltzer

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**Summary :**

Enzymes of the Ten Eleven Translocation (TET) family play a crucial role in the regulation of gene expression and are involved in different cancers in human, notably in the hematopoietic and nervous systems. These enzymes are well known for their function in the oxidation and demethylation of 5-methylCytosines (5mC) on DNA, a widespread epigenetic mark in mammalian genomes. Yet, these proteins also have non-canonical functions beyond 5mC DNA oxidation. In particular, it was proposed that they also act as epitranscriptomic regulators by targeting m5C on RNA, thereby regulating gene expression at the post-transcriptional level. Notably, many tRNA are methylated on m5C and this modification controls their maturation and the formation of tRNA fragments with diverse biological functions. However, the impact of TET on tRNA processing and biology remains largely unknown.

Interestingly, the drosophila genome codes for a TET enzyme but is devoid of 5mC DNA. Thus, this insect provides an excellent model organism to study the non-canonical mode of actions of TET. Thanks to the genetic tools that we developed and using a combination of transcriptomic and ChIP-seq approaches, we recently showed that TET plays an important role in the regulation of transcription in the drosophila larval brain and that this function is largely independent of its enzymatic activity. Yet we also found that TET exhibits catalytic-dependent functions, and our data suggest that these effects are post-transcriptional. As a follow-up of these results, this internship will aim to characterize further the catalytic-dependent functions of TET. The main objective of the internship will be to establish the impact of TET on tRNA expression and maturation its relationship with other epitranscriptomic enzymes.

**Methodologies (key words) :** transcriptomics, bioinformatics, confocal imaging, drosophila genetics

**Publications of the research group on the proposed topic (3 max.)**

Gilbert *et al.*, Drosophila TET acts with PRC1 to activate gene expression independently of its catalytic activity. Science Advances (2024), in press.

Boulet *et al.*, Adenine methylation is very scarce in the Drosophila genome and not erased by the ten-eleven translocation dioxygenase. Elife (2023), doi: 10.7554/eLife.91655.

**Track « Integrative Biology, Physiopathologies »**  
**Proposal for a Master 2 internship – 2024-2025**

**Title :** Characterization of cortical homeostatic plasticity associated with facial neuropathic pain in rodent.

**Laboratory :** Neuro-Dol, Université Clermont-Auvergne, INSERM UMR 1107  
**Laboratory director :** Radhouane Dallel  
**Address :** Faculté de chirurgie dentaire - 2, Rue de Braga 63100 CLERMONT-FERRAND

**Internship tutor :** Mickael Zbili  
**Tel :** 04 73 17 73 17  
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**Summary :**

Neuropathic pain is a major public health problem affecting 7–10% of the general population. It often arises from a primary lesion in the nervous system, such as a nerve or spinal cord injury, but are characterized by a persistence of the pain sensation after the lesion disappearance. While, repetitive transcranial cortical stimulations display an analgesic effect on neuropathic pain, the mechanism of neuropathic pain emergence is still poorly understood. It has been proposed that neuropathic pain originated from an overcompensating homeostatic plasticity in cortical sensory networks. Homeostatic plasticity is a compensatory mechanism allowing the neuronal networks to maintain their global electrical activity despite perturbations. When a neuronal network experiences a decrease in electrical activity due to a inputs reduction, it can compensate via an increase in synaptic connectivity and neuronal excitability, ultimately returning to its original basal activity level. However, homeostatic plasticity can entail an overcompensation leading to hyperexcitable neuronal networks resulting in some pathologies such as epilepsy. In the case of neuropathic pain, a peripheral nerve injury could lead to a decrease of inputs into primary sensory cortex (S1), resulting in hyperexcitability of this network via homeostatic plasticity which causes a persistent pain sensation. We propose to test this hypothesis in a rodent model of facial neuropathic pain, the lesion of the infraorbital nerve in young adult rats. Combining in vivo and ex vivo electrophysiological recordings as well as immunochemistry of neuronal ion channels, we will characterize the homeostatic plasticity occurrence in S1 Layer 2/3 pyramidal neurons. This preliminary study will pave the way to the unraveling of new molecular targets for neuropathic pain treatment.

**Methodologies (key words) :** *Extracellular in vivo electrophysiological recordings, Patch-clamp ex vivo electrophysiological recordings, Von Frey pain test, immunohistochemistry*

**Publications of the research group on the proposed topic (3 max.)**

1. Moisset X, Lefaucheur J.P (2018) Non pharmacological treatment for neuropathic pain : Invasive and non-invasive cortical stimulation. *Revue Neurologique*. doi: 10.1016/j.neurol.2018.09.014.
2. Zbili M, Rama S, Benitez MJ, Fronzaroli-Molinieres L, Bialowas A, Boumedine-Guignon N, Garrido JJ, Debanne D (2021) Homeostatic regulation of axonal Kv1.1 channels accounts for both synaptic and intrinsic modifications in CA3 circuit. *PNAS*. doi: 10.1073/pnas.2110601118.
3. Moisset X, Bouhassira D, Attal N (2021) French guidelines for neuropathic pain: An update and

## Track « Integrative Biology, Physiopathologies »

### Proposal for a Master 2 internship – 2024-2025

**Title :** Light and migraine pain

**Laboratoire d'accueil :** Trigeminal pain and migraine

**Directeur du laboratoire :** R. Dallel

**Adresse :** UFR Odontologie, UMR 1107, NeuroDol, 2 rue Braga, Clermont Ferrand

**Directeur de stage :** Isabelle Ranchon-Cole

**Tel :** 04-73-17-79-80 ou 04-73-17-73-20

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**Summary :**

Migraine is considered one of the most common neurological conditions and is the 6th leading cause of disability worldwide. It is characterized by headaches, nausea and vomiting that can last from 4 to 72 h if left untreated. It preferentially affects women: 18% compared to an incidence of 6% in men. In addition, migraine patients have emotional disorders (depression, anxiety) but also sensory disorders including an increase in sensitivity to visual stimuli both during and between migraine attacks. In addition, light can trigger a migraine attack. Historically, this hypersensitivity has been attributed to hyperexcitability of the cortex. However, the retina seems to play a key role. On the one hand, alterations of the retina, particularly at the level of the ganglion cells, have been demonstrated in migraine subjects. On the other hand, the relatively recent discovery of melanopsin ganglion cells intrinsically photosensitive has generated numerous studies highlighting the link between retina and photophobia in migraine. However, the pathophysiological mechanisms remain to be elucidated. In the laboratory, we have developed a model of migraine in mice. We have been able to show that chronic injection of ISDN leads to a decrease in facial pain sensitivity thresholds as well as an increase in aversion to light. Therefore, we will use this same model to assess the effects of light as a function of wavelength on light aversion and pain sensitivity. At the same time, studies will be conducted to determine the role of the retina and the areas of the brain involved in modulation as well as the activated mechanisms.

**Methodologies (key words) :** *Méthodologies envisagées (mots-clés) : Immunohistochemistry retina and brain, Von Frey, Electrophysiology*

**Publications of the research group on the proposed topic (3 max.)**

Thierry E ; Bourgeat A, Avan P, Dallel R, Ranchon-Cole I., Alba-Delgado C. Sex differences in light sensitivity in a mice model of migraine. 11ème FENS, Forum of Neuroscience 7-11 Juillet 2018, Berlin Germany.

Dallel R, Descheemaeker A, Luccarini P (2018) Recurrent administration of the nitric oxide donor, isosorbide dinitrate, induces a persistent cephalic cutaneous hypersensitivity: A model for migraine progression. Cephalalgia. 38(4):776-785.

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