UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Master 2

Parcours

Biologie Intégrative & Physiopathologies

Track

Integrative Biology & Physiopathologies

Propositions de stages

Internship proposals

Année
2025-2026

UNIVERSITÉ Clermont Auvergne

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Laboratoires :

iGReD	Institut Génétique Reproduction et Développement
IMoST	Imagerie Moléculaire et Stratégies Théranostiques
M2iSH	Microbes Intestin Inflammation et Susceptibilité de l'Hôte
LPCA	Laboratoire de Physique de Clermont Auvergne
Neurodol	Neurosciences et Douleur
UNH	Unité de Nutrition Humaine
LMGE	Laboratoire Microorganismes: Génome Environnement
MEDIS	Microbiologie Environnement Digestif Santé

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	Responsable	Laboratoire	Sujet du Stage
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23	Antoine Molaro	iGReD	Consequences of Short Histone H2A Rapid Evolution on Chromatin Organization
24	Céline Nourrisson	M2iSH	Impact of the co-infection with microsporidia and colibactin-producing Escherichia coli (CoPEC) on colonic carcinogenesis
25	Caroline Peyrode	iMoST	Identification of new therapeutic targets of interest in chondrosarcoma
26	Aurélien Pommier	iMoST	Preclinical development of theranostic radioconjugates for the treatment of cancers resistant to the anti-tumor immune response.
27	Aline V. Probst	iGReD	Chromatin dynamics during the developmental transition from the seed to the seedling
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29*	Paul Rouzaire	CHELTER	Development of a Murine Model to Study Interactions Between CAR-T Cells and Respiratory Pathogens
30	Vincent Sapin	iGReD	Study of the influence of a pollutants cocktail present in the amniotic fluid of pregnant women on the signaling pathways of nuclear receptors in the human fetal membranes.
31	Laurence Vandel	iGReD	Mechanistic Insights into Gene Expression Control by the Epigenetic Regulator Ten-Eleven Translocation (TET).
32*	Marjolaine Vareille-Delarbre	LMGE	Interactions between Klebsiella pneumoniae and inflammasomes in intestinal epithelial cells
33	Eric Wersinger	NeuroDol	Characterization of a Human IPSCs-derived sensory nerve platform to model neuropathic pain associated with cancer treatment
34*	Mickael Zbili	NeuroDol	In vivo and in vitro characterization of cortical plasticity development in facial neuropathic pain.

Laboratoires :

iGReD	Institut Génétique Reproduction et Développement
IMoST	Imagerie Moléculaire et Stratégies Théranostiques
M2iSH	Microbes Intestin Inflammation et Susceptibilité de l'Hôte
Neurodol	Neurosciences et Douleur
UNH	Unité de Nutrition Humaine
CHELTER	Role of intra-Clonal HEterogeneity and Leukemic environment in ThErapy Resistance of chronic leukemias

*Sujet de stage proposé également dans le parcours NHM

UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : **Plant protein and health prevention: role of an intermittent amino acid restriction**

Laboratory : UNH UMR1019 INRAE/UCA
Laboratory director : Didier Remond
Address : Centre de Recherche INRAE, 63122 Saint Genès Champanelle

Internship tutor : Julien Averous
Tel : 04 73 62 42 04
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Summary :
In rodents, it has been established that a chronic dietary restriction in methionine is effective to prevent the onset of obesity and its related metabolic diseases such type 2 diabetes (T2D). Methionine is one of the nine essential amino acids (EAA) that share two important characteristics: (i) they cannot be synthetized de novo by the organism and (ii) they have no dedicated storage. Therefore, if dietary EAA supply is low, the organism engages an adaptive response. The signaling pathway involving the kinase GCN2 and the transcription factor ATF4 plays a major role in this adaptive response. In the context of a chronic dietary restriction in methionine, there is not a clear consensus concerning the role of the GNC2/ATF4 pathway in the effects of this nutritional strategy on obesity/T2D. However, the expression of the FGF21 is increased by ATF4, this hormone has been described as major actor in the beneficial effects of methionine restriction. In human, the permanent consumption of a synthetic diet (containing free amino acids) restricted in methionine as performed in rodent's studies is not conceivable. Moreover, long-term consumption of such a diet leads to undesirable effects such as a decrease of muscle mass. In the objective to transfer the restriction of methionine to human nutrition, we have set-up in mice an intermittent methionine restriction using specific plant proteins, whose methionine contents are low, instead of using free amino acid diet. Our initial results indicate a protective effect of this strategy on weight gain and glucose tolerance in the context of a high-fat diet. A more detailed analysis of how methionine restriction influences cellular functions and metabolism will be conducted in different organs, with particular focus on the liver. The underlying mechanisms of these effects will be explored, including investigation of the GCN2/ATF4 pathway using a transgenic mouse model.

Methodologies (key words) : Animal experimentation, RT-qPCR, Western Blot, Elisa.

Publications of the research group on the proposed topic (3 max.)
Decreased ATF4 expression as a mechanism of acquired resistance to long-term amino acid limitation in cancer cells. Mesclon F, et al Oncotarget. 2017 Apr
GCN2 contributes to mTORC1 inhibition by leucine deprivation through an ATF4 independent mechanism. Averous J et al. Sci Rep. 2016 Jun

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title: Deciphering bile acid synthesis pathway in germline stem cell homeostasis: from reproductive health to fertility disorders and cancer.

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: Claude Beaudoin, PhD HDR
Tel: 04 73 40 53 40
e-mail: claude.beaudoin@uca.fr

Summary: The germline plays a major role in the maintenance of a species as it provides a link between generations. Throughout the adult life of mammals, spermatogenesis relies on the existence of a pool of spermatogonial stem cells (SSCs) that involves a delicate balance between self-renewal, mitosis and differentiation. Our data show that BA produced by the liver and the intestinal microbiota play crucial roles in hepato-testicular disorders[14].

We demonstrated that testis is a bile acid producing tissue, but the roles of this intra-testicular production remain undefined. Our project aims to elucidate the role of this intra-testicular bile acid production in the development of the urogenital tract, in the establishment and maintenance of spermatogonial stem cells and in turn in the onset of reproductive disorders (fertility issues, testicular germ cell tumors) as well as in the transmission of (reproductive and metabolic) pathologies to offspring. We will analyze the correlation of the incidence of these disorders with qualitative/quantitative changes in the composition of plasma and testicular bile acid pools. To achieve our goals, we will take advantage of genetically engineered mouse models for the initial bile acid synthesis enzymes Cyp7a1 and/or Cyp27a1; in combination with SSC cell lines either treated by pharmacological agents or modified by genome editing (Crispr/CAS9).

The data obtained will shed light on the gene networks that drive stem cell fate and help to better understand the impact of local bile acid homeostasis, cellular metabolism and epigenetics for regulating stem cell homeostasis, cell state and differentiation capacity. This project will enable us to reconsider our understanding of the control of testicular function, by identifying new players in gonadal development, sexual maturation and the quantitative/qualitative homeostasis of gametes. This work should allow defining biomarkers of stem cell alterations and giving novel cues to understand the molecular mechanisms that imprint long-term memories of metabolic stresses by the SSC leading to fertility disorders and/or transgenerational inheritance of disease to offspring.

Methodologies (key words) , mouse models, cell culture, viral transduction, transient transfection, germ cell transplantation, histology/imaging, molecular biology. 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- Baptissart et al. "*Multigenerational impacts of bile exposure are mediated by TGR5 signaling pathways.*", ***Scientific reports***, vol. 8 (1), pp. 16875, 2018.

3- Martinot et al. "The Bile Acid Nuclear Receptor FXRα Is a Critical Regulator of Mouse Germ Cell Fate." **Stem Cell Reports**. 2017 Jul 11;9(1):315-328. doi: 10.1016/j.stemcr.2017.05.036

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title: Interactions of plant extracts containing polyphenols designed to reduce hypertension with human gut microbiota in an *in vitro* model of the human gut

Laboratory: UMR454 MEDIS
Laboratory director: Mickael DESVAUX
Address: Faculté de Pharmacie - Bâtiment CBRV 5ème étage-28, Place Henri Dunant - BP38-63001 Clermont-Ferrand Cedex 1

Internship tutor: Stéphanie BLANQUET-DIOT
Tel: +33 (0)4 73 17 83 90
e-mail: stephanie.blanquet@uca.fr

Summary:
High blood pressure is a multifactorial disease leading to the increase risk of heart attack, stroke and metabolic syndrome, associated to gut microbiota perturbations. Totum-854 is a unique combination of polyphenol rich plant extracts, developed as an innovative nutritional solution for the overall management of hypertension. The preclinical evaluation of active compounds can be carried out *in vivo* using rodents, yet this approach remains limited by significant differences between animal and human digestive physiology, as well as increasing regulatory and societal constraints. A relevant alternative is the use of complex and dynamic *in vitro* models of the human digestive environment, such as the M-SHIME (Mucosal-Simulator of Human Intestinal Microbial Ecosystem. This model has been recently adapted to simulate both the lumen and mucus-associated microbes from the ileal and colon compartments.
In this context, the objective of the internship will be to evaluate the bilateral interactions of Totum-854 with human and colon microbiota in the M-SHIME, i.e., the effects of vegetal extracts on microbiota composition and metabolic activities, but also their metabolization by gut microbes. The first part of the internship will be dedicated to a literature review on the role of human gut microbiota in the etiology of hypertension. Then, *in vitro* experiments will be performed in the M-SHIME inoculated with stools from different healthy donors to assess the effects of Totum-854 on microbiota composition (qPCR and 16S metabarcoding) and gas/short chain fatty acids production. Plant metabolites will also be followed by UPLC-UV-MS.
This training will be performed in partnership with Valbiotis company and CMET laboratory from Ghent University in Belgium, in the frame of the international associated laboratory HOMIGUT.

Methodologies (key words): M-SHIME, *in vitro* fermentation, flow cytometry, molecular biology (qPCR, sequencing), chromatography analysis, bioinformatics

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

- Delbaere K, Roegiers I, Bron A, Durif C, Van de Wiele T, Blanquet-Diot S, Marinelli L. The small intestine: dining table of host-microbiota meetings. FEMS Microbiol Rev. 2023 19;47(3).
- Langhi C, Vallier M, Bron A, Otero Y, Maura M, Le Joubioux F, Blomberg N, Giera M, Guigas B, Maugard T, Chassaing B, Peltier S, Blanquet-Diot S, Bard JM, Sirvent P. A polyphenol-rich plant extract prevents hypercholesterolemia and modulates gut microbiota in western diet-fed mice. Frontiers in Cardiovascular Medicine. 2024 11:1342388.
- Esmail GA, Uriot O, Mottawea W, Denis S, Sultan S, Njoku EN, Chiba M, Tosh S, Blanquet-Diot S*, Hammami R* (*co-senior authors). Western diet-based NutriCol medium: A high-pectin, low-inulin culture medium promoted gut microbiota stability and diversity in PolyFermS and M-ARCOL continuous in vitro models. Food Res Int. 2025 206:115993.

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »
Track « Nutrition, Health, Mobility »

Proposal for a Master 2 internship – 2025-2026

Title : Role of L-serine on the pro-carcinogenic effect of Colibactin-positive *E.coli*

Laboratory : M2iSH
Laboratory director : Mathilde Bonnet
Address : Faculté de médecine. CBRV 3ème étage. 28 place H.Dunant. 63000 Clermont Ferrand.

Internship tutor : Mathilde Bonnet
Tel : 04-73-17-83-81
e-mail : mathilde.bonnet@uca.fr

Summary :
Colonic tissues in colorectal cancer (CRC) patients are colonized by colibactin-producing *Escherichia coli* (CoPEC). Colibactin is a genotoxin synthesized by the *pks* genomic island. Metabolomic studies have revealed that CoPEC infection leads to a reprogramming of intestinal epithelial cell metabolism, resulting in a decrease in L-serine. In a previous study, we showed that L-serine contributes to CoPEC persistence in the gastrointestinal tract and enhances its pro-carcinogenic functions.
The objective of this internship is to understand how L-serine influences the pro-carcinogenic effects of CoPECs, with a focus on the tumor microenvironment and oxidative stress. The first aim will be to study the impact of an L-serine-depleted (SD) diet on immune cell populations in the intestinal mucosa and tumors of CoPEC-infected animals, using immunostaining or flow cytometry. These studies will focus specifically on neutrophils, T lymphocytes ($CD8_+$), and ILC3s. The modulation of these cell populations will be correlated with tissue and serum cytokine levels, measured by multiplex cytometry (KC, IL-10, IL-4, IL-22, IL17A), as well as with tumor development. Moreover, induction of oxidative stress and inflammation during the infection was evaluated using optical *in vivo* imaging (IVIS spectrum- IMOST IVIA platform), and MPO and lipocalin-2 levels determination by ELISA. Same experiment will be performed using a CoPEC mutant unable to metabolize L-serine.
This work will allow to better understand the impact of nutrition factor on pro-carcinogenic properties of CoPEC in colorectal cancer.

Methodologies (key words) : Immunohistochemistry (fluorescent microscopy***), imaging,*** molecular biology (RNA extraction, cDNA synthesis, qRT-PCR); biochemistry (ELISA), preclinical model of infection

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

1- Devaux et al. L-serine promotes pro-carcinogenic effects of colibactin-producing E. coli. *In revision*
2-Lopès A et al. Colibactin-positive Escherichia coli induce a procarcinogenic immune environment leading to immunotherapy resistance in colorectal cancer. Int J Cancer. 2020 Feb 9.
3- Gagnière J et al. Interactions between microsatellite instability and human gut colonization by Escherichia coli in colorectal cancer. Clin Sci (Lond). 2017 Mar 1;131(6):471-485.

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : Study of cellular and molecular responses following reactivation of an endogenous retrovirus

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 : Brasset Emilie
Tel : 0473160427
e-mail : emilie.brasset@uca.fr

Summary :

Endogenous retroviruses (ERVs), a particular class of transposable elements, are relics of ancient retroviruses and represent an important part of metazoan genomes. It is well established that they contribute to the variability and evolution of genomes. Moreover, since they are able to move (transpose), they are powerful mutagenic agents. Their mobilization is potentially responsible for gene disruption or chromosomal rearrangements. To ensure the stability of the genome, sophisticated mechanisms involving epigenetic regulation exist. However, in some pathologies this regulation is lost and TE/ERVs are expressed.

How this control is set up and accidently lost and what is the first response of the organism to an ERV reactivation remains poorly studied.

The objective of the project is to study the cellular and molecular responses upon an ERV reactivation.

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.)

Yoth M, Gueguen N, Maupetit-Mehouas S, Bertin B, Jensen S, Brasset E. Germline piRNAs counteract endogenous retrovirus invasion from somatic cells bioRxiv 2022.08.29.505639; https://doi.org/10.1101/2022.08.29.505639

Duc C, Yoth M, Jensen S, Mouniée N, Bergman CM, Vaury C, Brasset E. Trapping a somatic endogenous retrovirus into a germline piRNA cluster immunizes the germline against further invasion. Genome Biol. 2019 PMID: 31227013

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Titre du stage :
Optimisation du profil pharmacocinétique de [^{131}I]ICF01012 pour une meilleure prise en charge du mélanome dans un contexte de radiothérapie interne vectorisée.

Laboratoire d'accueil : UMR 1240 INSERM/UCA, Imagerie Moléculaire et Stratégies Théranostiques (IMoST)
Directeur du laboratoire : P^{re} Elisabeth Miot-Noirault
Adresse : 58 Rue Montalembert - 63000 Clermont-Ferrand

Directeur de stage : D^{r} Arnaud Briat-Le Mest
Tel : (+33) (0)473150816
E-mail : arnaud.briat_le_mest@uca.fr

Résumé : Parmi les différentes approches thérapeutiques en cancérologie, le traitement par rayons ionisants peut avoir lieu par radiothérapie interne vectorisée (RIV). Cette méthode utilise une molécule porteuse d'un radionucléide (souvent un émetteur β- : iode 131, lutécium-177, yttrium-90…) qui est administrée par voie systémique au patient. Cette molécule, présentant une forte affinité pour une cible d'intérêt dans la pathologie cancéreuse, va permettre d'adresser spécifiquement la source radioactive à la tumeur, permettant d'induire des cassures simples et/ou doubles brins de l'ADN. Contrairement à la radiothérapie externe, la RIV peut atteindre les petites tumeurs (inaccessibles pour un chirurgien ou des rayons externes) ainsi que les (micro)métastases.
Parmi les nombreuses pistes de recherche explorées, la RIV regagne en intérêt dans le traitement du mélanome, qui représente 10% des cancers de la peau, et qui enregistre un taux d'incidence en constante augmentation ces dernières décennies. Les mélanomes avancés demeurent associés à un sombre pronostic et la recherche de nouvelles thérapies plus efficaces est plus que jamais d'actualité. Un radiotraceur, [^{131}I]ICF01012, en cours d'étude clinique pour la RIV du mélanome, a récemment montré une efficacité prometteuse pour le ciblage des tumeurs pigmentées. Pour une application en RIV, le radiotraceur doit présenter un profil pharmacocinétique optimal (i.e. valeurs de fixations tumorales élevées et durables associées à une élimination rapide des organes non-cibles). La mélanine, cible de ce radiotraceur, est présente dans d'autres tissus, en particulier les yeux. Ce projet a pour objet d'évaluer différentes approches visant à réduire la fixation de la molécule radiomarquée dans ces tissus sains.
Pour mener à bien ce projet, l'étudiant(e) aura en charge l'évaluation (i) de techniques permettant de bloquer les cibles présentes au niveau des tissus sains (yeux) ; (ii) de la distribution biologique *in vivo* de la molécule radiomarquée afin de déterminer la meilleure approche permettant de préserver les tissus sains sans compromettre l'action thérapeutique au niveau tumoral.

Méthodologies envisagées (mots-clés) :
Imagerie préclinique, radiothérapie interne vectorisée, mélanome.

Publications du laboratoire sur le thème proposé (3 max.)

1- Thivat, E.; Rouanet, J.; Auzeloux, P.; Sas, N.; Jouberton, E.; Levesque, S.; Billoux, T.; Mansard, S. et. al. Phase I study of [^{131}I]ICF01012, a targeted radionuclide therapy, in metastatic melanoma: MELRVIV-1 protocol. *BMC Cancer* **2022**, 22, 417.
2- Rouanet, J.; Quintana, M.; Auzeloux, P.; Cachin, F.; Degoul, F. Benzamide derivative radiotracers targeting melanin for melanoma imaging and therapy: Preclinical/clinical development and combination with other treatments. *Pharmacol. Ther.* **2021**, *224*, 107829
3- Michelot, J.M.; Moreau, M.F.C.; Veyre, A.J.; Bonafous, J.F.; Bacin, F.J.; Madelmont, J.C.; Bussière, F.; Souteyrand, P.A. et al. Phase II scintigraphic clinical trial of malignant melanoma and metastases with iodine-123-*N*-(2-diethylaminoethyl-4-iodobenzamide). *J. Nucl. Med.* **1993**, 34, 1260-6.

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : Decipher the role of the GCN2-ATF4 pathway in pancreatic adaptation to sulfur amino acid restriction.

Laboratory : Team PROTEOSTASIS, UMR1019 INRAE/UCA, Human Nutrition Unit
Laboratory director : Didier REMOND
Address : INRAE Research center of Theix – 63122 Saint-Genès-Champanelle, FRANCE

Internship tutor : Alain Bruhat, PhD
Tel : +33 4 73 62 41 50
e-mail : alain.bruhat@inrae.fr

Summary :
The literature indicates that, in rodents, restriction of sulfur amino acids (SAA—methionine and cysteine) extends lifespan, limits body weight gain, and provides protection against metabolic diseases. This dietary restriction activates the eIF2α-ATF4 signaling pathway. However, the specific role of the GCN2 eIF2α kinase, an amino acid sensor responsive to essential amino acid deprivation, remains poorly understood. This signaling pathway can promote survival through autophagy or lead to apoptosis under prolonged or severe stress conditions.
Our preliminary results in mice show that the eIF2α-ATF4 pathway is early induced in the pancreas with a diet devoid of SAA. The aim of this internship is to decipher the role of the GCN2-ATF4 signaling pathway in maintaining proteostasis within the pancreas, a process essential to the proper functioning of this organ. More specifically, the aim will be to determine how this pathway contributes to the adaptation of pancreatic cells to SAA restriction. Two complementary approaches will be implemented: (i) an *in vivo* approach, using a mouse line genetically invalidated for GCN2 (GCN2-KO), to assess the tissue consequences of the absence of this pathway during SAA restriction. (2) an *in vitro* approach, using a pancreatic cell line treated with a specific pharmacological inhibitor of GCN2, to study the cellular and molecular effects in a controlled environment. In both models, activation of the GCN2-ATF4 pathway will be analyzed using transcriptomic (RT-qPCR) and protein (Western blot) approaches to identify the functions and metabolic pathways regulated in response to SAA restriction. In parallel, the potential crosstalk between the GCN2-ATF4 pathway and the mTOR pathway, central to the regulation of metabolism and cell growth, will also be investigated.

Methodologies (key words) : nutritional experiment in mice, cell culture, analysis of gene expression by RT-qPCR and protein expression by western-blot.

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

Carraro *et al.* (2022). Activation of the eIF2α-ATF4 Pathway by Chronic Paracetamol Treatment Is Prevented by Dietary Supplementation with Cysteine. *Int J Mol Sci*. 2022;23(13):7196.

Chaveroux *et al.* (2015). In vivo imaging of the spatiotemporal activity of the eIF2α-ATF4 signaling pathway: insight into stress and related disorders. *Science Signaling*, 28;8 (374):rs5.

B'chir W, et al. (2013). The eIF2α-ATF4 pathway is essential for stress-induced autophagy gene expression. *Nucleic Acids Res*earch, 41(16):7683-99.

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title :
Pathophysiological study of the enteric nervous system in the colonic hypersensitivity associated with chronic abdominal pain in IBS patients and related comorbidities.

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 :
Irritable Bowel Syndrome (IBS) is a common and complex gastrointestinal disorder characterized by chronic abdominal pain and altered bowel habits, often accompanied by comorbidities such as anxiety and depression. One of the hallmark features of IBS is colonic hypersensitivity (CHS), a heightened perception of visceral pain whose pathophysiological mechanisms remain poorly understood. Increasing evidence suggests that dysfunctions of the enteric nervous system (ENS) play a critical role in mediating these symptoms, acting at the interface between the immune system, gut microbiota, and central nervous system. This **M2 internship project** will aim to explore the pathophysiological role of the ENS in relation to CHS and its associated comorbidities using preclinical models that reflect three complementary IBS-related etiologies. Depending on the outcome of ongoing ANR funding evaluations, the student will focus on one of the following topics: (1) the role of the AhR/IL-22/Reg3γ signaling pathway in either maintaining or alleviating CHS; (2) the long-term impact of early-life cross-feeding alterations between microbial communities on visceral pain sensitivity; or (3) the effects of chronic exposure to a chemical mixture mimicking the dietary inorganic exposome on gut physiology and CHS.
The project will integrate multidisciplinary techniques including behavioral pain assays, immunohistochemistry, molecular biology, and microbiota analysis, and will contribute to a better understanding of how environmental, microbial, and immunological factors interact with the ENS to promote chronic abdominal pain. This internship offers the opportunity to work within a collaborative and translational research environment and may serve as a foundation for doctoral training in neurogastroenterology.

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.
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.
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.

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Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : Establishment of a preclinical model for ocular rosacea: investigation of pathophysiological mechanisms and exploration of novel therapeutic approaches.

Laboratory : NeuroDol UMR 1107 Inserm UCA - team 1 « Pharmacologie Fondamentale et Clinique de la Douleur » (PFCD)
Laboratory director : Pr Radhouane Dallel
Address : Faculté de Médecine et de Pharmacie, 28 place Henri Dunant 63000 Clermont-Ferrand

Internship tutor : Dr David CIA
Tel : 04 73 17 79 83
e-mail : david.cia@uca.fr

Summary :

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. The intestinal and/or ocular surface microbiota may be a promising therapeutic target, as it could contribute to inflammation and corneal sensitization in ocular rosacea patients. **This internship** is part of a research project aimed at deepening the understanding of the pathophysiological mechanisms involved in inflammation and corneal hypersensitivity associated with ocular rosacea, with the goal of identifying novel therapeutic approaches. Preliminary work has been initiated to develop a preclinical animal model of the disease. Two murine models are currently under development: one based on ocular surface exposure to ultraviolet B (UVB) radiation, and the other on ocular instillation of the antimicrobial peptide LL-37. **Initial data** obtained through ELISA and histological analyses indicate corneal inflammation in both models. This inflammation appears to be accompanied by hypersensitivity of the ocular surface, as evidenced by the behavioral “eye wiping” test. Furthermore, gene expression analyses by quantitative RT-PCR show an overexpression of several genes linked to innate immunity and ocular microbiota regulation. **The main objective of the internship** will be to confirm these preliminary findings and to further characterize the two models. Particular attention will be given to the study of the gut and ocular surface microbiota, with the aim of identifying a microbial signature specific to the pathology and evaluating innovative microbiota-based therapeutic strategies.

Methodologies (key words) : Behavioral assessment of ocular sensitivity in mice (eye-wiping test, von-Frey test, …), ELISA, Histological studies, Immunostaining, RT-qPCR

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

Jacquemot, N., Wersinger, E., Brabet, P., & Cia, D. (2023). Hydrogen Peroxide Affects the Electroretinogram of Isolated Perfused Rat Retina. *Current Eye Research*, *48*(12), 1179-1188.

Hassel, C., Couchet, M., Jacquemot, N., Blavignac, C., Loï, C., Moinard, C., & Cia, D. (2022). Citrulline protects human retinal pigment epithelium from hydrogen peroxide and iron/ascorbate induced damages. *Journal of Cellular and Molecular Medicine*, *26*(10), 2808-2818.

Meynier, M., Daugey, V., Mallaret, G., Gervason, S., Meleine, M., Barbier, J., ... & Carvalho, F. A. (2024). Pasteurized akkermansia muciniphila improves irritable bowel syndrome-like symptoms and related behavioral disorders in mice. *Gut microbes*, 16(1), 2298026.

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : Search for Effectors Modulating TGFβ/BMP Signalling to Preserve Muscle Mass

Laboratory : Unité de Nutrition Humaine, UMR1019, Equipe Proteostasis
Laboratory director : Didier Rémond
Address : INRAE Auvergne Rhone Alpes, Route de Theix, 63122 Saint Genes Champanelle

Internship tutor : Lydie Combaret
Tel : 04 73 62 48 24
e-mail : lydie.combaret@inrae.fr

Summary :

Skeletal muscle atrophy occurs in various physiological (e.g., aging) and pathological conditions (such as cancers and chronic diseases), as well as during physical inactivity. It has detrimental consequences for patients' autonomy, quality of life and treatment efficacy. Muscle atrophy is thus a major public health concern for which no effective treatments currently exist.

Using a comparative physiology approach with murine models of induced atrophy and a model of natural resistance to atrophy, the brown bear during hibernation, a prolonged state of fasting and physical inactivity, we have demonstrated the importance of modulating the balance between the TGFβ and BMP signalling pathways (Cussonneau et al. 2021, Cussonneau et al. 2022). Finally, our research has also suggested the presence of circulating compounds in the serum of hibernating brown bears that may have therapeutic potential against muscle atrophy (Chanon et al. 2018).

In that context, the Master 2 internship aims at further investigating mechanisms that enable the favourable modulation of TGFβ/BMP signalling in muscle cells. For that purpose, we will focus (i) on the possible cross-talk between the TGFβ and BMP signalling with other signalling pathways and (ii) on the role of circulating compound in the serum of brown bears on the regulation of the TGF/BMP signalling pathways.

Located in an attractive setting, our team of approximately 20 people offers a friendly and dynamic environment with strong collaboration between members. This internship is a great opportunity to expand your network, gain valuable experience, and explore the possibility of pursuing a Ph.D.

Methodologies (key words) :
Cell culture, isolated muscle fibers, siRNA, Western blots, RT-qPCR

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

Cussonneau et al. 2021. Concurrent BMP Signaling Maintenance and TGF-β Signaling Inhibition Is a Hallmark of Natural Resistance to Muscle Atrophy in the Hibernating Bear. Cells 10, 1873.

Cussonneau et al. 2023. Induction of ATF4-Regulated Atrogenes Is Uncoupled from Muscle Atrophy during Disuse in Halofuginone-Treated Mice and in Hibernating Brown Bears. Int. J. Mol. Sci. 24, 621.

Chanon et al. 2018. Proteolysis inhibition by hibernating bear serum leads to increased protein content in human muscle cells. Sci Rep. 2018 Apr 3;8(1):5525.

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

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: F. COURT
Tel: 04 73 17 81 78
e-mail: franck.court@uca.fr

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..), CRiSPR-based approaches (CRiSPRi/a…), 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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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : Epigenetic modifications of histone H4 and the maintenance of genome stability in *Arabidopsis thaliana*

Laboratory : Institut GReD
Laboratory director : Dr. Krzysztof JAGLA
Address : Bâtiment CRBC, 5è étage, Faculté de Médecine
28 Place Henri Dunant 63001 Clermont-Ferrand cedex 1

Internship tutor : Olivier DA INES
Tel : 04 73 40 74 04
e-mail : Olivier.da_ines@uca.fr

Summary :
DNA double-strand breaks (DSBs) are among the most deleterious forms of DNA damage, capable of inducing mutations, chromosomal rearrangements, or loss, which can ultimately lead to tumorigenesis or cell death. To preserve genomic integrity, cells have evolved multiple repair pathways, including homologous recombination (HR), which uses a homologous template for error-free repair. While DSBs may arise accidentally from external genotoxic agents or endogenous processes such as replication and transcription, they can also be developmentally programmed, notably during meiosis to ensure fertility and genetic diversity.
Repair of DSBs by HR occurs within a dynamic chromatin environment, where histone modifications regulate DNA accessibility and serve as recruitment platforms for repair factors. The central feature of HR is the search for and invasion of an intact homologous DNA molecule, which is used as a template to restore the original DNA sequence. This step is catalysed by RAD51-family recombinases. Notably, homology search and strand invasion mediated by these recombinases require nucleosome remodelling to allow access to both the broken and intact DNA molecules. Recent structural studies have implicated the N-terminal domain of RAD51 in nucleosome interactions with histone H4. To further investigate this relationship, we will explore the role of histone H4 post-translational modifications in homologous recombination in both mitotic and meiotic cells. For this purpose, we will use a comprehensive set of *Arabidopsis* lines expressing point mutations in H4. The impact on recombination will be assessed through a combination of molecular genetics, cytogenetics, immunofluorescence and cell biology approaches.

Methodologies (key words) : Genetics, Molecular Biology, DNA Damage Sensitivity, Recombination Assay, Cytogenetics, Chromosome Spreads, Immunolocalisation.

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

1. Petiot V., Chéron F., White CI, Da Ines O. Dual role of Arabidopsis SRS2 helicase in meiotic recombination. BioRxiv. (2025). https://doi.org/10.1101/2025.02.26.640294.

2. Petiot V, White CI, Da Ines O. (2024). DNA-binding site II is required for RAD51 recombinogenic activity in Arabidopsis thaliana. **Life Sci Alliance.** 2024 May 20;7(8):e202402701. doi: 10.26508/lsa.202402701.

3. Da Ines O, Bazile J, Gallego ME, White CI. DMC1 attenuates RAD51-mediated recombination in Arabidopsis. (2022). **PLoS Genet.** 2022 Aug 25;18(8):e1010322. doi: 10.1371/journal.pgen.1010322.

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : Deciphering the mechanisms of the active acquisition of epithelial tumor resistance in the drosophila accessory gland.

Laboratory : iGReD, UMR CNRS 6293, INSERM U1103
Laboratory director : Krzysztof Jagla
Address : Centre de Recherche Bio-Clinique, 28 place Henri Dunant, Clermont-Ferrand

Internship tutor : Cyrille de Joussineau
Tel : 04 73 40 53 38
e-mail : cyrille.de_joussineau@uca.fr

Summary : Resistance to treatment is a main cause of death by cancer, as it also often implies more aggressive cells that proliferate at high rate and present increased invasive potential. Rare articles indicate that the exposition to treatment could actively induce the acquisition of resistance. However, there is a lack of simple in vivo model to study the reality of this phenomenon and discover the molecular mechanisms that could govern its attendance. We have developed a new 3R-compatible model of epithelial tumorigenesis in the drosophila accessory gland. There, we can study tumor evolution from initiation to progression (1-2), and gain access to the understanding of steps that are mostly ignored by science due to the absence of adequate tools. We have also been able to genuinely induce resistance and associated aggressiveness by mimicking a treatment that is used against prostate cancer (3). We now want to understand how this active acquisition occurs, in order to be able to block it or even to use discovered mechanisms against tumor progression. In the long term, our goal is so to propose for human purpose strategies to either block resistance induced by usual treatments or select new therapeutic targets that could bring new tools in cancer therapy.
The proposed internship will focus on the relationship between two pathways that seem responsible for acquisition of resistance: Ecdysone Signaling (equivalent to sex steroid signaling that is blocked in prostate and breast cancer), and Notch pathway, which our unpublished results show it could be responsible for the transdifferentiation of tumor cells into resistant/aggressive tumor cells. A Ph.D. internship will be asked to pursue this project in the continuity of the Master 2.

Methodologies (key words) : drosophila genetics, immunohistochemistry, FISH, confocal imaging, use of patients expression data.

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

(1) Sequential Ras/MAPK and PI3K/AKT/mTOR pathways recruitment drives basal extrusion in the prostate-like gland of Drosophila. Rambur et al, Nature Communications, 2020. doi: 10.1038/s41467-020-16123-w
(2) Cholesterol Dietary Intake and Tumor Cell Homeostasis Drive Early Epithelial Tumorigenesis: A Potential Modelization of Early Prostate Tumorigenesis. Vialat et al, Cancers, 2024. doi: 10.3390/cancers16112153
(3) Loss of control of epithelial basal extrusion leads to tumor resistance in drosophila. Vialat et al, preprint, https://doi.org/10.1101/2025.03.18.643888

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : **Study of the Role of Protein Lactylation in the Host Cell Response to Infection and in the Virulence of *E. coli* Associated with Crohn's Disease**

Laboratory :
Laboratory director : Pr. Mathilde Bonnet
Address : CBRV, 28 place Henri Dunant 63001 Clermont-Ferrand

Internship tutor : Dr. Jérémy Denizot
Tel : 0473178346
e-mail : Jeremy.denizot@uca.fr

Summary :

Adherent-invasive Escherichia coli (AIEC) abnormally and persistently colonize the intestinal mucosa of patients with Crohn's disease (CD). The chronic colonization of the intestinal mucosa by AIEC suggests that these bacteria have developed strategies to evade immune defenses and persist in the host over the long term. Our hypothesis is that AIEC may manipulate the host epigenome to promote their own persistence and escape immune defense mechanisms. We have demonstrated that the structure of the epigenome, specifically histone acetylation and lactylation, plays a key role in the interaction between the host and AIEC. The objectives of this internship are: (1) to study the impact of AIEC infection on the lactylation of host cell histones; (2) to identify the molecular mechanisms used by the bacteria to alter histone lactylation; and (3) to analyze the role of bacterial protein lactylation in bacterial virulence. Different approaches will be used: bacteria genetic engineering, bacterial infection of intestinal cell, immunofluorescence/western-blot of histone post-translational modifications, ChIP…
This work will help uncover new molecular mechanisms governing the interaction between AIEC and host cells and characterize the strategies employed by these bacteria to modulate the host epigenome and ensure their persistence in the intestinal mucosa.

Methodologies (key words): *Immunofluorescence (confocal microscopy), western-blot, bacterial genetic engineering, ChIP, cell culture, bacterial infection, ELISA*

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

- Chervy M, Sivignon A, Dambrine F, Buisson A, Sauvanet P, Godfraind C, Allez M, Le Bourhis L, The Remind Group, Barnich N, Denizot J. Epigenetic master regulators HDAC1 and HDAC5 control pathobiont Enterobacteria colonization in ileal mucosa of Crohn's disease patients. Gut Microbes 2022;14:2127444

- Chervy M, Barnich N, Denizot J. Adherent-Invasive E. coli: Update on the Lifestyle of a Troublemaker in Crohn's Disease. Int J Mol Sci;21 . Epub ahead of print May 25, 2020. DOI: 10.3390/ijms21103734.

- Gimier E, Chervy M, Agus A, Sivignon A, Billard E, Privat M, Viala S, Minet-Quinard R, Buisson A, Vazeille E, Barnich N, Denizot J. Methyl-donor supplementation prevents intestinal colonization by Adherent-Invasive E. coli in a mouse model of Crohn's disease. Sci Rep 2020;10:12922.

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : Visualization and quantification of the interplay between TFAM and OGG1 under normal and oxidative conditions

Laboratory : UMR 6533 CNRS-UCA – LPCA - Equipe Santé
Laboratory director : Dominique Pallin
Address : Campus des Cézeaux, Aubière, France

Internship tutor : Géraldine Farge
Tel : +33473405040
e-mail : geraldine.farge@uca.fr

Summary :

Mitochondria are efficient bioenergetic organelles responsible for ATP production via oxidative phosphorylation (OXPHOS). They contain their own DNA (mtDNA), which is exposed to reactive oxygen species (ROS) and other harmful free radicals generated during OXPHOS. Oxidative damage to DNA is primarily repaired through the Base Excision Repair (BER) pathway, in which 8-Oxoguanine DNA glycosylase (OGG1) plays a central role. Mitochondrial transcription factor A (TFAM) organizes and compacts mtDNA into nucleoids within the mitochondrial network. The amount of TFAM determines the balance between active nucleoids, which are involved in transcription or replication, and inactive ones. However, it is not yet known whether this compaction also interferes with DNA repair processes under oxidative stress.

This Master's internship is part of a project aiming to address this question by investigating how oxidative DNA lesions, specifically 8-oxoguanine (8-oxoG), influence the interplay between TFAM and OGG1. During the internship, we will visualize and quantify the interaction between TFAM and OGG1, in the presence or absence of 8-oxoG, to determine whether they compete or cooperate for specific DNA binding sites. These experiments will involve a combination of classical molecular biology and biochemistry techniques, as well as single-molecule visualization methods such as total internal reflection fluorescence microscopy (TIRFm).

Methodologies (key words) : Molecular biology, Biochemistry, 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, 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

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : Investigating the emergence of muscle type diversification in vertebrates

Laboratory : iGRED
Laboratory director : Krzysztof Jagla
Address : 28 place Henri Dunant

Internship tutor : Charlene Guillot
Tel :
e-mail : charlene.guillot@uca.fr

Summary : This project investigates how a single pool of neuro-mesodermal progenitors (NMPs) generates diverse axial segments for distinct muscle types using chicken embryos. We performed lineage tracing identifying NMP contributions to cervical , thoracic , and lumbar axial segments. Previous work from our lab showed that NMPs possess a dynamic transcriptomic signature during these axial segment formation , with the CDX (caudal) gene family displaying notable temporal variation (Guillot et al., 2021). As chromatin remodelers, CDX genes are key in spinal cord fate (Metzis et al., 2018), suggesting a possible role in mesodermal regionalization and muscle diversification.

To test this, we analyzed CDX expression and chromatin accessibility in NMPs across developmental stages using HCR-FISH, and qPCR. We found out that CDX expression is dynamic and spatio-temporally heterogeneous within the NMPs. Based on this previously unreported heterogeneity of CDX expression and existing literature, we hypothesize that distinct combinations of CDX genes remodel chromatin to establish specific axial identities.

Using single nuclei Multiomics techniques, we are investigating how CDX heterogeneity influences NMP axial fate by identifying CDX target genes involved in axial specification. During the internship, we will focus on validating the axial specificity of these targets and test their functional roles using CRISPR-Cas9 knockout or targeted overexpression.

Methodologies (key words): CRISPR-Cas9, Sn-Multiomics, CDXs, NMPs, Morphometry, HCR, Imaging

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

Guillot C, Djeffal Y, Michaut A, Rabe BA, Pourquie O: Dynamics of primitive streak regression controls the fate of neuro-mesodermal progenitors in the chicken embryo. eLife 2021;10:e64819

H. Jin, Z. Liu, J. Mou, M. Tang, X. Huang, K. Liu, Q. Zhang, K.O. Lui, & B. Zhou, Dual genetic tracing demonstrates the heterogeneous differentiation and function of neuromesodermal progenitors in vivo, Proc. Natl. Acad. Sci. U.S.A. 122 (14) e2402305122, https://doi.org/10.1073/pnas.2402305122 (2025).

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : **Perivitelline albumen as novel model to study amniotic fluid's influence in epithelial-to-mesenchymal transition during body axis elongation.**

Laboratory : iGReD
Laboratory director : Krzysztof Jagla
Address : 28 place Henri Dunant 63000 Clermont Ferrand

Internship tutor : Charlene Guillot
Tel :
e-mail : charlene.guillot@uca.fr

Summary :

During gastrulation, epiblast cells undergo epithelial-to-mesenchymal transition (EMT), forming the mesenchymal layer. This process continues during body axis extension, where epiblast stem cells (i.e., Neuro Mesodermal Progenitors, NMPs) give rise to neural and mesodermal tissues forming the trunk and tail in vertebrates. Despite growing knowledge of NMP regulation, the role of soluble factors within the amniotic environment, which directly contacts NMPs, remain unexplored, primarily due to accessibility challenges in mammals. This proposal uses *Gallus gallus* embryos as a model system to investigate the influence of amniotic fluid on NMP EMT during body axis elongation. Since amniogenesis occurs later in avian development, the proteome of the perivitelline albumen likely contributes to EMT by acting as a pre-amniotic fluid. By analysing the proteomic composition of the perivitelline albumen and introducing specific modulators into this environment, we aim to assess the responsiveness of NMPs to soluble factors. This approach seeks to uncover novel molecular mechanisms that promote EMT. This study will enhance our understanding of soluble molecules driving EMT during development and provide insights into putative therapeutic targets regulating stem cell differentiation and metastatic transition of cancer cells.

Methodologies (key words) :
Molecular Biology//Proteomic analysis (Western Blot and Mass Spectrometry)//Morphological analysis (Immunofluorescence, HCR, *in-vivo* tracing).

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

1. Chau KF, Springel MW, Broadbelt KG, Park HY, Topal S, Lun MP, Mullan H, Maynard T, Steen H, LaMantia AS, Lehtinen MK. Progressive Differentiation and Instructive Capacities of Amniotic Fluid and Cerebrospinal Fluid Proteomes following Neural Tube Closure. Dev Cell. 2015 Dec 21;35(6):789-802. doi: 10.1016/j.devcel.2015.11.015. PMID: 26702835; PMCID: PMC4691285.
2. Garriock RJ, Chalamalasetty RB, Kennedy MW, Canizales LC, Lewandoski M, Yamaguchi TP. Lineage tracing of neuromesodermal progenitors reveals novel Wnt-dependent roles in trunk progenitor cell maintenance and differentiation. Development. 2015 May 1;142(9):1628-38. doi: 10.1242/dev.111922. PMID: 25922526; PMCID: PMC4419273.
3. Charlene Guillot, Yannis Djeffal, Arthur Michaut, Brian Rabe, Olivier Pourquié (2021) Dynamics of primitive streak regression controls the fate of neuromesodermal progenitors in the chicken embryo eLife 10:e64819.

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title: Exploring How Folate Drives Embryonic Development—From cell fate regulation to Morphogenesis

Laboratory : iGReD
Laboratory director : Krzysztof Jagla
Address : 28 place Henri Dunant 63000 Clermont Ferrand

Internship tutor : Charlene Guillot
Tel :
e-mail : charlene.guillot@uca.fr

Summary :
The vertebrate trunk and tail form through coordinated contributions of mesodermal and neural cells from the tailbud. Disruptions in this process can cause neural tube defects (NTDs), like spina bifida, which are influenced by both genetic and environmental factors. While folic acid (FA) supplementation prevents many NTDs, its role in posterior body axis development remains unclear.
NeuroMesodermal Progenitors (NMPs)—bipotent cells generating both neural and mesodermal tissues—are particularly sensitive to environmental cues, including folate (vitamin B9). Our lab uses avian embryos to model folate deficiency and trace NMP lineages. We've shown that FA deficiency impairs axis elongation, resulting in NTD-like phenotypes marked by neural tube closure defects and mesodermal abnormalities.
Single-cell RNA sequencing revealed reduced NMP proliferation, altered metabolism, and nearly a 50% drop in NMP numbers. To further explore these effects, this internship will induce FA deficiency in NMPs using CRISPR knockout of MTHFD1, a key folate pathway enzyme. We'll investigate axis formation using live imaging, HCR FISH, immunofluorescence, and qPCR to map gene expression changes and cell fate. This project will uncover how folate shapes vertebrate development at the single-cell level, with implications for understanding and preventing NTDs.
If you're curious about how metabolism intersects with development, we invite you to join our research.

Methodologies (key words): Molecular Biology/Morphological analysis
Immunofluorescence, HCR-FISH, *in-vivo* live imaging, single-cell quantitative analysis.

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

1. Guillot C, Djeffal Y, Michaut A, Rabe B, Pourquié O. Dynamics of primitive streak regression controls the fate of neuromesodermal progenitors in the chicken embryo. Elife. 2021 Jul 6;10:e64819. doi: 10.7554/eLife.64819. PMID: 34227938
2. Oginuma M, Moncuquet P, Xiong F, Karoly E, Chal J, Guevorkian K, Pourquié O. A Gradient of Glycolytic Activity Coordinates FGF and Wnt Signaling during Elongation of the Body Axis in Amniote Embryos. Dev Cell. 2017 Feb 27;40(4):342-353.e10. doi: 10.1016/j.devcel.2017.02.001. PMID: 28245921
3. Binagui-Casas A, Dias A, Guillot C, Metzis V, Saunders D. Building consensus in neuromesodermal research: Current advances and future biomedical perspectives. Curr Opin Cell Biol. 2021 Dec;73:133-140. doi: 10.1016/j.ceb.2021.08.003. Epub 2021 Oct 28. PMID: 34717142.

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : Deciphering the role of tumour-associated neutrophils (TANs) in a mouse model of metastatic adrenal carcinoma

Laboratory : iGReD, UMR CNRS 6293, INSERM U1103, Clermont Auvergne University Molecular Pathophysiology of Adrenal and Endocrine Tissues team
Laboratory director : Dr Krzysztof JAGLA
Address : Bâtiment CRBC, Faculté de Médecine, 28 Place Henri Dunant, 63001 Clermont-Ferrand

Internship tutor : Dr Rachel GUITON
Tel : 04.73.40.74.10
e-mail : rachel.guiton@uca.fr

Summary :
Adrenocortical carcinoma (ACC) is a rare and aggressive cancer with a poor prognosis. Indeed, many patients already have metastases at the time of diagnosis, and their 5-year survival rate remains under 15%. The currently available treatments, surgery and chemotherapy, are unable to cure ACC, this is why much effort is being made to better understand the pathophysiology of this cancer. Immunotherapies have raised high hopes, especially in treating aggressive melanomas, sometimes leading to tremendous results. Unfortunately, clinical trails aiming at blocking the PD-1/PD-L1 immune checkpoint failed at improving ACC patients' survival, but manipulating the immune cells definitely is a promising challenge to cure aggressive cancers. This needs a better knowledge of the tumour microenvironment. To this end, our team generated a unique mouse model which is based on two major genetic alterations found in patients: the *Trp53/Znrf3* double knockout mice. This model presents aggressive adrenal tumours associated with a significant increase of adrenal weight. Mice die from 16 weeks of age and half of them already show pulmonary metastases. Interestingly, single cell sequencing analyses revealed a huge remodelling of the immune cell populations in the primary tumours of these mice, and especially, an increase in tumour-associated neutrophils (TANs) together with metastatic progression. This internship will aim at confirming the presence of TANs in primary tumours by immunohistology. A deeper analysis of available transcriptomic data will help to identify specific markers of this population, which will be confirmed by spectral flow cytometry. Additionnally, the role of neutrophils in tumour progression will be assessed by *in vivo* depletion in *Trp53/Znrf3* double knockout mice. This may provide novel therapeutic options for a cancer with dismal prognosis.

Methodologies (key words): immunohistochemistry/immunofluorescence, flow cytometry, bioinformatics, cell culture.

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

- Wilmouth JJ Jr, Olabe J, Garcia-Garcia D, Lucas C, Guiton R, Roucher-Boulez F, Dufour D, Damon-Soubeyrand C, Sahut-Barnola I, Pointud JC, Renaud Y, Levasseur A, Tauveron I, Lefrançois-Martinez AM, Martinez A, Val P.
Sexually dimorphic activation of innate antitumor immunity prevents adrenocortical carcinoma development.
Sci Adv. 2022 Oct 14;8(41):eadd0422. doi: 10.1126/sciadv.add0422.
- Basham KJ, Rodriguez S, Turcu AF, Lerario AM, Logan CY, Rysztak MR, Gomez-Sanchez CE, Breault DT, Koo BK, Clevers H, Nusse R, Val P, Hammer GD.
A ZNRF3-dependent Wnt/β-catenin signaling gradient is required for adrenal homeostasis.
Genes Dev. 2019 Feb 1;33(3-4):209-220. doi: 10.1101/gad.317412.118.

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : Role of perineuronal net degradation by activated microglia in the retrospenial cortex in neuropathic pain

Laboratory : Laboratoire de Pharmacologie fondamentale et clinique de la douleur, UMR Inserm 1107 Neuro-Dol
Laboratory director : Pr Radouhane Dallel
Address : Faculté de Médecine, 28 Place Henri Dunant, 63000 Clermont-Ferrand

Internship tutor : Fabien Marchand
Tel : 33-4-73-17-82-31
e-mail : fabien.marchand@uca.fr

Summary : Neuropathic pain affects around 10% of the population worldwide and despite years of research remains difficult to treat. It has been suggested that the degradation of a component of the extracellular matrix, the perineuronal net (PNN) surrounding neurons, by activated microglia at the spinal cord level could played a crucial role in neuropathic pain. We demonstrated that the retrosplenial cortex could play an important role in neuropathic pain (Barriere et al, 2019) and, importantly, that the perineuronal net is also degraded by activated microglia in this brain structure in a neuropathic pain model. However, the type of neurones (inhibitory or excitatory) and the consequences of this degradation on neuronal activity and synaptic structure are not known. In addition, the effect of local microglia inhibition in this brain structure in neuropathic pain is also unknown. The aim of this internship is to better characterize the degradation of the perineuronal net and the type of neurons affected as well as to assess synapses engulfment by microglia in the retrospenial cortex in a neuropathic pain model. Therefore, we will investigate the type of neurons particularly affected and their synaptic structure as well as the effect of microglia inhibition within the retrosplenial cortex on PNN degradation and pain behaviours and associated comorbidities in a neuropathic pain context. To do so, we will use several approaches ranging from behavioural tests, local chemogenetic and pharmacological inhibition of microglia and immunochemistry/RNAscope. This project should help to better understand the role of the perineuronal net and microglia within the retrosplenial cortex in chronic neuropathic pain.

Methodologies (key words) : neuropahic pain, behavioral tests, DREADD virus, RNAscope, Immunohistochemistry

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

Barrière D, Hamieh AM, Magalhães R, Traoré A, Barbier J, Bonny JM, Ardid D, Busserolles J, Mériaux S, Marchand F. Structural and functional alteration in the retrosplenial cortex following neuropathic pain. Pain, 2019; 160(10):2241-2254.

Marchand F, Perretti M, McMahon SB. Role of the immune system in chronic pain. Nat Rev Neurosci. 2005 ;6(7):521-32. doi: 10.1038/nrn1700

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathology »

Proposal for a Master 2 internship – 2025-2026

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

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathology »

Proposal for a Master 2 internship – 2025-2026

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

Laboratory : Institut de Génétique, Reproduction et Développement (iGReD)
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)

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Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

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 deposited 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&TAG

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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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : Impact of the co-infection with microsporidia and colibactin-producing *Escherichia coli* (CoPEC) on colonic carcinogenesis

Laboratory : « Microbes, Intestin, Inflammation et Susceptibilité de l'Hôte (M2iSH) », UMR Inserm/ Université Clermont Auvergne U1071, USC INRAE 1382
Laboratory director : Prof. Mathilde Bonnet
Address : CBRV - 28, place Henri Dunant - 63000 Clermont-Ferrand, France

Internship tutor : Dr. Céline Nourrisson
Tel : +33(0)4.73.95.01.95
e-mail : c_nourrisson@chu-clermontferrand.fr

Summary :
Almost 10 million people die from **cancer** every year, making it the world's leading cause of death. Among environmental factors promoting carcinogenesis, **pathogens** can have a pro-carcinogenic effect. This is the case of certain virulent strains of *Escherichia coli* producing bacterial effectors, such as colibactin (**CoPEC** strains), which have the ability to induce genomic instability. The effect of these pathogens may also be indirect by disrupting the regulations of the host cells. Our team has demonstrated the role of CoPEC in the pathogenesis of **colorectal cancer (CRC)**. **Microsporidia** are obligate intracellular eukaryotes, mainly responsible for intestinal infections, and several studies have shown that they hijack the cellular machinery of the cells they infect. At least 10% of the population exhibit anti-microsporidia antibodies, making it a frequent intestinal pathogen. The role of co-infections by different pathogens in the occurrence of cancer remains little explored. The objective of this project is to investigate the **impact of** a **co-infection with CoPEC and microsporidia on the occurrence of CRC**. The recruited student will work on biological material obtained from a mouse model genetically predisposed to CRC ($Apc^{Min/+}$ mice) co-infected with microsporidia and CoPEC in order to decipher the cellular mechanisms involved. **The student will not have to work on live mice** (material will be sampled before the start of the student's internship). The experiments to perform will aim to: **(i)** detect the presence of microsporidia in tumor tissues (FISH), **(ii)** study cell apoptosis and proliferation by RT-qPCR, Western blot or immunohistochemistry on tissues (Ki67, PCNA, cyclins, p53, …), **(iii)** study inflammation (ELISA to detect pro-inflammatory cytokines secretion: TNF-α, IL-1β, IL-6, IL-12), **(iv)** explore the impact on microbiota (SCFA quantification by gas liquid chromatography).

Methodologies (key words) : *immunohistochemical techniques, Western blot, RT-PCR, FISH, ELISA*

Publications of the research group on the proposed topic (3 max.)
- Increased levels of anti-*Encephalitozoon intestinalis* antibodies in patients with colorectal cancer. Nourrisson C, Moniot M, Vercruysse L, Bonnin V, Pereira B, Barnich N, Bonnet M, Jary M, Pezet D, Gagnière J, Poirier P. *PLoS Negl Trop Dis*. 2024;18(9):e0012459.
-Colibactin-positive *Escherichia coli* induce a procarcinogenic immune environment leading to immunotherapy resistance in colorectal cancer. Lopès A, Billard E, Casse AH, Villéger R, Veziant J, Roche G, Carrier G, Sauvanet P, Briat A, Pagès F, Naimi S, Pezet D, Barnich N, Dumas B, Bonnet M. *Int J Cancer*. 2020;146(11):3147-3159.

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title: **Identification of new therapeutic targets of interest in chondrosarcoma**

Laboratory: UMR IMoST 1240 Inserm/UCA
Laboratory director: Pr Elisabeth Miot-Noirault
Adress : 58 rue Montalembert, BP 184 – 63005 Clermont-Ferrand

Internship tutor: Dr Caroline Peyrode and Dr Emmanuel Chautard
Tel: +33473150825
e-mail: caroline.peyrode@uca.fr

Summary

Background:

Chondrosarcoma (CHS), or malignant cartilage tumor, is considered resistant to both radiotherapy and chemotherapy. To date, surgery remains the only effective treatment, which is often extensive and debilitating, with a 5-year survival rate below 50% in the event of recurrence for the most aggressive forms. There is therefore a real need to improve the therapeutic management of this disease. Since 2021, the UMR1240 Inserm/UCA research unit has been investigating the inflammatory and immune components of chondrosarcoma. Inflammation and immunosuppression appear to play a major role in tumor progression, angiogenesis, and invasion. As part of a project supported by the French League Against Cancer, and in collaboration with the CRLB in Lyon, our unit has identified new immunological targets of interest for the development of innovative therapeutic strategies, using tumor samples from CHS patients. Among these, immune checkpoint inhibitors (ICI) have emerged as a promising avenue that we aim to explore in the context of this internship.

Objective:

The proposed internship aims to evaluate, in preclinical *in vitro* and/or *in vivo* models, the therapeutic potential of these ICIs. In vivo treatment effects will be assessed in a syngeneic rat CHS model (SWARM model), focusing on antitumor efficacy (tumor volume monitoring, histological analyses, etc.). These results will be complemented by *ex vivo* mechanistic analyses, including flow cytometry, immunohistochemistry, and Western blotting. In parallel, *in vitro* studies using human and rat chondrosarcoma cell lines will help to strengthen the functional and mechanistic data.

This internship offers an immersive experience in a translational research project at the interface of tumor immunology, oncology, and preclinical research, centered on a rare and still poorly explored cancer from an immunotherapeutic perspective.

Methodologies (key words) : animal experimentation, Flow cytometry, Immunohistochemistry, Cell culture, Western Blot analysis

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

3D Co-culture between cancer cells and macrophages: From conception to experimentation Quoniou R., Moreau E., Cachin F., Chautard E., Peyrode C. ACS Biomater Sci Eng 2024;10(1):313-325 doi: 10.1021/acsbiomaterials.3c01437

Chondrosarcoma Co-Culture 3D Model─An Insight to Evaluate Drugs Acting on TAMs. Quoniou R., Moreau E., Cachin F., Blavignac C., Bortoli E., Chautard E ; Peyrode C. ACS Biomater Sci Eng 2024; 9;10(9):5832-5843. doi: 10.1021/acsbiomaterials.4c00625.

Peyrode, C.; Weber, V.; Voissière, A.; Maisonial-Besset, A.; Vidal, A.; Auzeloux, P.; Gaumet, V.; Borel, M.; Dauplat, M.-M.; Quintana, M.; Degoul, F.; Rédini, F.; Chezal, J.-M.; Miot-Noirault, E. Proteoglycans as Target for an Innovative Therapeutic Approach in Chondrosarcoma: Preclinical Proof of Concept. *Mol. Cancer Ther.* 2016, *15* (11), 2575–2585. https://doi.org/10.1158/1535-7163.MCT-16-0003.

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : Preclinical development of theranostic radioconjugates for the treatment of cancers resistant to the anti-tumor immune response.

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
e-mail : Aurelien.pommier@uca.fr

Summary :

With unprecedented efficacy observed in some populations, immunotherapy such as adoptive cell therapy, immune checkpoint inhibitors or vaccines has revolutionized the cancer patient's healthcare over the last decade. The efficacy of immunotherapy relies on the generation and stimulation of cytotoxic CD8+ T lymphocytes within the tumor microenvironment which can recognize and kill tumor cells through the recognition of short tumor specific peptides, typically 8–11 aminoacidic residues in length, presented by the Major Histocompatibility Complex (peptide-MHC; pMHC). However, many patients still do not respond to immunotherapies, particularly in solid cancers due to the inability of immune cells to get access to the tumor microenvironment. In this context, the pMHC represent attractive biological targets for the development of alternative therapeutic approaches in immune-depleted tumors often resistant to immunotherapy.

Targeted radiotherapy (TRT) relies on tumor specific vectors to induce cancer cell death through the delivery of radionuclides selectively to the tumor site. The recent approvals of Pluctivo® and Lutathera® for the treatment of prostate cancer and neuroendocrine tumors have proven the efficacy and safety of TRT. However, one of the main challenges in TRT remains the identification and validation of tumor specific targets in other cancer indications. This project aims to develop innovative TRT using pMHC targeting antibodies in musculoskeletal cancers. Our lab identified relevant pMHC through immunopeptidomic analyses in these tumor types. The Master 2 internship will be focused on the target validation steps including the pharmacological studies on cancer models to assess the efficacy of TRT for selected pMHC.

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

Publications of the research group on the proposed topic

Phase I study of 131I-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. Maisonial-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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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title: Chromatin dynamics during the developmental transition from the seed to the seedling

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 is key for epigenetic regulation, helps to compact the genome and contributes to gene expression control. To accommodate the extensive changes in gene expression patterns that occur during developmental transitions, chromatin organization is substantially modified by the addition of histone modification or by the exchange of histone variants. Histone eviction and deposition of new histones is coordinated by a network of specific histone chaperone complexes including HIRA and FACT.

This project will study the dynamics of histones H3 and H2B together with their post-translational modifications during the developmental transition from the seed to the seedling. Using epitope-tagged H3 and H2B histones expressed under the control of developmentally regulated or inducible promoters in the model plant *Arabidopsis thaliana*, the candidate will study the eviction of old and deposition of new histones during the developmental transition in different chromatin contexts. Particular attention will be given to genes that are either induced or repressed during seed germination. To this end, the candidate will use a combination of genomic and microscopic approaches comparing wild type and mutant plants lacking the histone chaperone complexes HIRA and FACT, which show altered seed germination. This comparison will elucidate the respective roles of histone chaperones in histone dynamics, maintenance of histone modifications and transcriptional regulation during developmental transitions.

This project is expected to provide new insights into the mechanisms that ensure inheritance and reprogramming of epigenetic marks during developmental transitions.

Methodologies (key words): *Chromatin Immuno-precipitation coupled to sequencing (ChIP-seq), Histone extraction and Western Blot, confocal microscopy, Immunofluorescence, Image analysis, qRT-PCR, plant phenotyping*

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

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

Layat E, … 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, 22:4031.

Benoit M, …, **Probst AV.** Replication-coupled histone H3.1 deposition determines nucleosome composition and heterochromatin dynamics during Arabidopsis seedling development. *New Phytol.* 2019, 221:385-398.

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2024-2025

Title: "Biological evaluation of vectorized photodynamic therapy (PDT) treatment *in vitro* melanoma model."

Laboratory : Imagerie Moléculaire et Stratégies Théranostiques (IMoST), UMR 1240 Inserm / UCA
Laboratory director: Pr Elisabeth MIOT-NOIRAULT
Address : 58 Rue Montalembert. 63000 Clermont-Ferrand

Internship tutor: Dr Mercedes QUINTANA
Tel: 04 73 15 08 24
E-mail : mercedes.quintana@uca.fr

Summary:

With regard to Dubreuihl's melanoma, surgical excision can be complex, with a risk of functional and/or aesthetic morbidity and high recurrence rates. Therefore, the search for new, minimally invasive treatments is essential. The objective of this internship is to establish in vitro proof of concept for the efficacy of a new nanoplatform targeting MC1R+ cells, which are overexpressed in pigmented melanomas, for photodynamic therapy (PDT).

Internship step:

1) Evaluation of the therapeutic efficacy of the nanoplatform in vitro,
2)Evaluation oxidative stress induction by reactive oxygen species (ROS) detection

Methodologies (key words) : cell culture, spectrophotometry, flow cytometry, incucyte, Western Blot.

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

Delorme S, Privat M, Sonnier N, Rouanet J, Witkowski T, Kossai M, Mishellany F, Radosevic-Robin N, Juban G, Molnar I, Quintana M, Degoul F. New insight into the role of ANXA1 in melanoma progression: involvement of stromal expression in dissemination. Am J Cancer Res. 2021 Apr 15;11(4):1600-1615. PMID: 33948376; PMCID: PMC8085877.

Akil, Hussein; Quintana, Mercedes; Raymond, Jérémy H.; Billoux, Tommy; Benboubker, Valentin; Besse, Sophie; Auzeloux, Philippe; Delmas, Véronique; Petit, Valérie; Larue, Lionel; D'Incan, Michel; Degoul, Françoise; Rouanet, Jacques. 2021. "Efficacy of Targeted Radionuclide Therapy Using [131I]ICF01012 in 3D Pigmented BRAF- and NRAS-Mutant Melanoma Models and In Vivo NRAS-Mutated Melanoma" Cancers 13, no. 6: 1421. https://doi.org/10.3390/cancers13061421

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title: Development of a Murine Model to Study Interactions Between CAR-T Cells and Respiratory Pathogens

Laboratory: EA (UR) CHELTER 7453
Laboratory director: Prof. Marc Berger
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Internship tutor: Prof. Paul Rouzaire
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Summary :

Treatment with genetically modified T cells (CAR-T cells) is revolutionizing the management of hematological malignancies. However, the development of respiratory infections is a major complication observed in patients undergoing CAR-T cell therapy, significantly impacting both treatment efficacy and patient prognosis. To date, no experimental studies have been conducted, and the underlying pathophysiological mechanisms remain poorly understood.

The aim of this project is to develop a murine model to study the interactions between CAR-T cells and respiratory pathogens. To achieve this, a lung infection model using *Klebsiella pneumoniae* will be established in mice treated with anti-CD19 CAR-T cells, which specifically target B lymphocytes.

The objectives are: (1) to investigate the impact of CAR-T cell therapy on bacterial colonization and the pulmonary microbiota, and (2) to assess how respiratory infections affect CAR-T cell efficacy. To address this question, animals will receive an injection of CAR-T cells followed by intranasal instillation of *K. pneumoniae* 24 hours later. Pulmonary colonization by the pathogen will be monitored over a 7-day period through bacterial load quantification. The expression of genes encoding key virulence factors of *K. pneumoniae* (capsule, pili, siderophores), as well as the potential emergence of antibiotic resistance genes, will be assessed by RT-qPCR in lung tissues. The in vivo efficacy of CAR-T cells will be evaluated using A20 cells (expressing luciferase). Bioluminescence of the A20 cells will be monitored weekly following inoculation. CAR-T cell proliferation will be assessed in serial blood samples based on EGFP expression. At the end of the experiment, mice will be sacrificed to assess CAR-T cell and A20 cell infiltration in the spleen and lungs.

The knowledge generated from this study will help improve the therapeutic management of patients receiving CAR-T cell treatment.

Methodologies (key words): *in vivo* experimentation (mouse), cell culture, flow cytometry, RT-QPCR

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

- Dougé A, El Ghazzi N, Lemal R, Rouzaire P. Adoptive T Cell Therapy in Solid Tumors: State-of-the Art, Current Challenges, and Upcoming Improvements. Mol Cancer Ther. 2024
- Vareille-Delarbre M, Miquel S, Garcin S, Bertran T, Balestrino D, Evrard B, Forestier C Immunomodulatory Effects of Lactobacillus plantarum on Inflammatory Response Induced by Klebsiella pneumoniae. Infect Immun. 2019

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : Study of the influence of a pollutants cocktail present in the amniotic fluid of pregnant women on the signaling pathways of nuclear receptors in the human fetal membranes.

Laboratory : iGReD, Universite Clermont Auvergne, CNRS, INSERM (team « Translational Approach to Epithelial Injury and Repair »)

Laboratory director : Krzysztof Jagla (team leaders: Pr. Sapin & Dr. Blanchon)

Address : CRBC, UFR de Médecine et des Professions Paramédicales, Place Henri Dunant

Internship tutor : Pr. Vincent Sapin

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Summary : The rupture of fetal membranes (FM) is a physiological phenomenon that is programmed at the end of pregnancy (after 37 weeks of gestation (WG)). It's the consequence of weakening and loss of elasticity of FM resulting from cellular and molecular events such as extracellular matrix degradation, apoptosis and sterile inflammation. Throughout pregnancy, many cellular actors, including the nuclear receptors (NR), are of primary importance for an harmonious gestation in order to prevent a premature rupture of FM (before 37 WG), occurring in 3 to 4% of pregnancies. In September 2019, "Santé Publique France" communicated the results of the Esteban study, which confirms the exposure of the French population, including pregnant women to pollutants such as phthalates (for example MEHP). Up to date, little is known about their potential negative actions on nuclear receptors signalling pathways in such FM context.

This project aims to better understand the potential links between exposure of pregnant women to pollutant and premature rupture of FM. Previous experiments published by the team demonstrate a dysregulation of PPARγ signalling pathway in FM by MEHP but not by an alternative plasticizer MINCH (see below pub 1 and 2). The team has now a precise idea of the pollutants cocktail present in amniotic fluid regarding quantification done in 90 samples. In this project, such cocktail will be used to determine its negative or neutral influence on PPARγ but also on other nuclear receptors pathways such as: Retinoic Acid Receptors (RAR), Vitamin D Receptors (VDR), Liver X Receptors (LXR), Retinoid X Receptor (RXRs, heterodimeric partner of PPARγ, RAR, VDR, LXR), Progesterone Receptor (PR) or AhR (Aryl hydrocarbon Receptor/known as a pollutant receptor). These studies will use all cell types present in the FM to decipher globally the pollutant cocktail influence on FM strength.

Methodologies (key words) : *Cell culture (primary and cell lines), qRT-PCR, Western-blot, luciferase gene reporter, Immunofluorescence, multiplex quantification.*

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

1. Charnay *et al.* (2025) The anti-inflammatory effect of the amniotic PPARγ pathways is not dysregulated by the alternative plasticizer DINCH and its metabolite MINCH in human fetal membranes. *Environ Sci Pollut Res Int*, 32(10):6273-6284

2. Antoine A. *et al.* (2022) Dysregulation of the amniotic PPARγ pathway by phthalates: A new hypothesis to explain the premature rupture of fetal membranes. *Life* 12(4):544.

3. Belville C *et al.* (2022) Physiological TLR4 regulation in human fetal membranes as an explicative mechanism of a pathological preterm case. *Elife*. 11:e71521.

UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : Mechanistic Insights into Gene Expression Control by the Epigenetic Regulator Ten-Eleven Translocation (TET).

Laboratory : iGReD – Institut de Génétique Reproduction et Développement ; UMR6293 CNRS-UCA / UMR1103 Inserm-UCA
Laboratory director : Dr K. Jagla
Address : 28 place Henri Dunant, 63000 Clermont-Ferrand

Internship tutor : Dr Laurence Vandel
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Summary :

Enzymes of the Ten-Eleven Translocation (TET) family play a central role in gene expression regulation and are implicated in various human pathologies, particularly hematopoietic cancers and neurodevelopmental disorders. These enzymes are best known for oxidising and demethylating 5-methylCytosines (5mC) on DNA, a common epigenetic mark that affects transcription. However, beyond 5mC DNA oxidation, these proteins can also act through less well-understood mechanisms: they can interact with other factors that regulate gene expression and/or oxidise methylated cytosines (m5C) on RNA. However, these non-canonical modes of action remain poorly characterised.

To explore them, we use the fruit fly *Drosophila melanogaster*, a model organism whose genome lacks DNA methyltransferases but still encodes a critical *Tet* gene. This offers a unique opportunity to study TET's function independent of DNA methylation. We have shown that TET is essential for transcription regulation in the Drosophila larval brain and that much of this function does not rely on its enzymatic activity (Gilbert et al. 2024). Still, we also observed TET's catalytic-dependent functions, likely at the post-transcriptional level. In line with these results, this internship will investigate TET's role in both transcriptional and post-transcriptional gene regulation. Specifically, the student will (i) further characterize splicing defects in TET-deficient larval brains that have been observed recently in the team. (ii) help establish a new method for acute TET depletion, enabling the study of its immediate impact on gene expression.

This work will provide deeper insight into new TET's mechanisms of action and, over time, its function in both normal and disease contexts in humans. Of note, all relevant techniques are well-established in the lab. The Master 2 internship can be extended into a PhD project within the team.

Methodologies (keywords) : Transcriptomics, molecular biology, confocal imaging, drosophila genetics, bioinformatics analyses (with the support of the team's bioinformatician).

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), doi: 10.1126/sciadv.adn5861.
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.

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : Interactions between *Klebsiella pneumoniae* and inflammasomes in intestinal epithelial cells

Laboratory : UMR CNRS 6023 Laboratoire Microorganismes : Génome Environnement (LMGE), Equipe CMES : Communautés microbiennes : écotoxicologie-santé
Laboratory director : Didier DEBROAS
Address : UFR de Pharmacie, 28 place Henri Dunant, 63000 Clermont-Ferrand

Internship tutor : Marjolaine VAREILLE-DELARBRE
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Summary :

Klebsiella pneumoniae is a ubiquitous Gram-negative bacterium and a major cause of nosocomial infections. As commensal bacteria of the gut, *K. pneumoniae* colonizes the intestinal microbiota and interacts with immune cells in the intestinal mucosa without triggering a significant inflammatory response. This immune evasion may facilitate bacterial dissemination and the establishment of extra-intestinal infections. However, the mechanisms underlying this ability to avoid inflammation remain poorly understood and are crucial to uncovering how *K. pneumoniae* manipulates the host's intestinal immune responses.

The objective of this internship is to investigate the interactions between *K. pneumoniae* and the NLRP3, NLRP10, and NLRP12 inflammasomes—key components of the innate immune system and potent activators of inflammatory pathways—in human intestinal epithelial cells. The modulation of inflammasome gene and protein expression by *K. pneumoniae* will be assessed using RT-qPCR and western blotting in infected cells. Levels of the pro-inflammatory cytokines IL-1β and IL-18 will be measured by ELISA.

Additionally, the activation of inflammatory caspases, particularly caspase-1, will be analyzed through enzymatic assays, and the induction of pyroptosis, a form of highly inflammatory programmed cell death, will be evaluated via flow cytometry.

The roles of major bacterial factors—such as the capsule, lipopolysaccharide, and siderophores—in modulating host immune responses will be examined using various *K. pneumoniae* mutants available in the laboratory.

This project will contribute to a deeper understanding of the immune evasion strategies employed by *K. pneumoniae* within the intestinal environment and may lead to the identification of novel therapeutic targets.

Methodologies (key words) : cell culture, bacterial infections, RT-QPCR, ELISA, flow cytometry

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

Vareille-Delarbre M, Miquel S, Garcin S, Bertran T, Balestrino D, Evrard B, Forestier C Immunomodulatory Effects of *Lactobacillus plantarum* on Inflammatory Response Induced by *Klebsiella pneumoniae*. Infect Immun. 2019 Oct 18;87(11):e00570-19.

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : Characterization of a Human IPSCs-derived sensory nerve platform to model neuropathic pain associated with cancer treatment

Laboratory : UMR INSERM-UCA 1107 NeuroDol (Team: Fundamental and Clinical Pharmacology of Pain)
Axis: Pain and Cancer (Dr. J. Busserolles)
Laboratory director : Pr Radhouane Dallel
Address : Facultés de Médecine et de Pharmacie- 28 place Henri Dunant - 63001 Clermont-Ferrand (France)

Internship tutor : Eric Wersinger
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Summary :
Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common and potentially permanent side effects of anticancer drugs, with clinical symptoms often including numbness, loss of proprioceptive sense, tingling, hyperalgesia, or allodynia that can lead to dose reduction or cessation of therapy. The mechanisms underlying CIPN are not fully understood but may result from direct and indirect effects on sensory nerves, such as damage to neuronal cell bodies in the dorsal root ganglion, changes in ion channel expression/function, increased neuronal excitability, and mitochondrial dysfunction. To date, neither predictive biomarkers nor preventive treatments for CIPN are available, which is partially due to the lack of 1) fully translational models; 2) an understanding of the molecular and cellular mechanisms that produce CPIN. Recent advances have demonstrated that induced-pluripotent stemcell (iPSC) derived sensory neurons can be used as a preclinical model system to study CIPN. However, a major drawback in the use of such models relates to the restricted modeling of sensory neurons as monocultures, whereas multiple cell types such as glial cells contribute to the onset and maintenance of CIPN through the release of specific mediators. Therefore, in this project, the intern will be involved in the characterization of a new coculture model mimicking the neuron-glia interplay and made of sensory neurons and satellite glial cells both derived from hiPSCs. Using a combination of cellular, molecular, and functional readouts, we will check the effects of anticancer drugs and evaluate the pharmacological efficacy of the compounds currently under preclinical investigation by our team. These experiments will be a prerequisite to go further in the understanding of the neuronal/cancer cells interplay that could be studied using the same model thanks to microfluidic systems.

Methodologies (key words) : Cell culture (differentiation of hiPSC into neuronal and glial cells), Immunocytochemistry, Live cell imaging and Electrophysiology

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

-Patent n°WO2022074313 Inventors Busserolles J, Bourinet E., Taillefumier C., Roy O., Nauton L., Aissouni Y Titre : « Novel peptoids and use thereof for preventing or treating chronic pain».
-Poupon L, …, Busserolles J. Targeting the TREK-1 potassium channel via riluzole to eliminate the neuropathic and depressive-like effects of oxaliplatin. Neuropharmacology. 2018 Sep 15;140:43-61. doi: 10.1016/j.neuropharm.2018.07.026.
-Descoeur J, …, Busserolles J, …, Bourinet E Oxaliplatin-induced cold hypersensitivity is due to remodelling of ion channel expression in nociceptors. EMBO Mol Med. 2011 May;3(5):266-78. doi: 10.1002/emmm.201100134.

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UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2025-2026

Title : In vivo and in vitro characterization of cortical plasticity development in facial neuropathic pain.

Laboratory : Neuro-Dol, Université Clermont-Auvergne, INSERM UMR 1107
Laboratory director : Radhouane Dallel
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Internship tutor : Mickael Zbili
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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 maladaptative neuronal plasticity in cortical sensory networks inducing hyperexcitability of somatosensory cortex. Following this hypothesis, the hyperexcitability of the primary somatosensory cortex (S1) causes a persistent pain sensation.
To explore this hypothesis, we used a rodent model of facial neuropathic pain: the infraorbital nerve ligature (IONL). We showed that IONL induced both a pain development in the vibrissae region an increase of neuronal excitability in the S1BF cortex (primary somatosensory cortex barrel field, the cortex corresponding to vibrissae region). However, to fully understand the link between facial pain and cortical hyperexcitability, we need to know the exact temporal relationship between these modifications. The purpose of this internship will be to combine in vivo calcium imaging (fiber photometry), behavioral measurements (Von Frey pain test) and immunohistochemistry of neuronal axon initial segment (AIS) to decipher the kinectics of pain and cortical hyperexcitability in neuropathic facial pain. This preliminary study will pave the way to the unraveling of new molecular targets for neuropathic pain treatment. In addition, the aim of this internship is to continue the study as part of a three-year PhD program.

Methodologies (key words): Fiber photometry, Calcium imaging, 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 commentary *Revue Neurologique.* doi: 10.1016/j.neurol.2021.07.004.

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