

## Master 2

Parcours / Track

*Nutrition Health  
and Mobility*

**Propositions de stages**

**Internship proposals**

Année / Year  
2024-2025

**Tableau récapitulatif des propositions de stages (2 pages) /  
Summary table of internship proposals (2 pages)**

**En rouge, les stages proposés également sur le parcours BIP/**

**In red, internships also offered in the BIP Track**

**§ : sujet susceptible d'être retiré / subject likely to be removed**

**\* : fléché pour un étudiant Profession de Santé / \*targeted for a medical student**

	<b>Responsable/ Tutor</b>	<b>Laboratoire / Research Unit</b>	<b>Sujet de stage / Intership's subject</b>
<b>1</b>	<b>Averous J</b>	UNH	Plant protein and health prevention: role of an intermittent amino acid restriction
<b>2</b>	<b>Barnich N</b>	M2ISH	Characterization of new virulence factors of Adherent-Invasive Escherichia coli (AIEC) bacteria using a Tn-Seq approach without a priori.
<b>3</b>	<b>Begou M</b>	NeuroDol	Direct involvement of PLP deregulation in the development of chronic pain symptoms in MS model?
<b>4</b>	<b>Briat-Le Mest A</b>	IMoST	Preclinical relevance of SPECT Imaging with [99mTc]-NTP-15-5 for the evaluation of chondrosarcoma response to immunotherapy.
<b>5</b>	<b>Carvalho F §</b>	NeuroDol	Assessing long-term exposure to a chemical mixture representative of the dietary inorganic exposome on the gut microbiota-immune system and gut-brain axes: toward susceptibility to chronic diseases?
<b>6</b>	<b>Carvalho F §</b>	NeuroDol	Pathological role of d-serine metabolism in microbiota-gut-brain axis dysfunction in intestinal inflammatory disorders
<b>7</b>	<b>Cia D</b>	NeuroDol	Development of a preclinical model of ocular rosacea: study of pathophysiology and development of new treatments
<b>8</b>	<b>Decombat C</b>	UNH	Impact of seaweed extract in inflammation and associated metabolic disorder: application to osteoarthritis
<b>9</b>	<b>Farge G</b>	LPC	Characterization of modulators of mitochondrial replisome activity in healthy individuals or in pathological conditions
<b>10</b>	<b>Kocer A</b>	iGReD	Liver X Receptors acts as a promoter of epithelial-mesenchymal transition in advanced prostate cancer
<b>11</b>	<b>Maurin AC</b>	UNH	Studying the contribution of ATF4 to adaptive changes in amino acid transport and metabolism in the liver during catabolic inflammatory states.
<b>12</b>	<b>Nguyen H</b>	M2ISH	Targeting autophagy by physical activity to attenuate the deleterious effects of Western diet and pathogenic bacteria on intestinal homeostasis and gut microbiota.
<b>13</b>	<b>Pinel A §</b>	UNH	Impact of mechanical load and/or protein supplementation on muscle loss prevention during weight loss in obese rats (MECAPROB)
<b>14</b>	<b>Polge C</b>	UNH	Identification and characterization of a molecule with anti-atrophic potential

<b>15</b>	<b>Ranchon Cole I</b>	NeuroDol	Light and migraine pain
<b>16</b>	<b>Taillandier D</b>	UNH	Evaluation of biomarkers to monitor sarcopenia in intensive care unit patients, a single-center pilot observational study
<b>17</b>	<b>Walrand S*</b>	UNH	Effect of rheumatoid arthritis biotherapies on the muscle secretome and interactions with omega-3 and vitamin D (ERABIO-M3D)
<b>18</b>	<b>Zbili M</b>	NeuroDol	Characterization of cortical homeostatic plasticity associated with facial neuropathic pain in rodent.

#### Laboratoires / Research Units :

<b>iGRéD</b>	institut de Génétique Reproduction et Développement
<b>IMOST</b>	Imagerie Moléculaire et Stratégies Théranostiques
<b>LPC</b>	Laboratoire de Physique de Clermont
<b>M2iSH</b>	Microbes Intestin Inflammation et Susceptibilité de l'Hôte
<b>Neurodol</b>	Neurosciences et Douleur
<b>UNH</b>	Unité de Nutrition Humaine

**Track « Nutrition, Health, Mobility »**  
**Proposal for a Master 2 internship – 2024-2025**

**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

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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 synthesized 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 propose to set-up an intermittent restriction. For that purpose, it would be interesting to take advantage of specific plant proteins, whose methionine contents are low, instead of using free amino acid diet. The aim of the project will be to evaluate whether this nutritional strategy is able to exert a preventive role in a model of induced obesity. The molecular mechanisms involved in this potential effect will be investigated, the role of the GCN2/ATF4 pathway will be studied 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

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

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

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

**Laboratory director :** Professor Nicolas Barnich

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

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

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**Summary :**

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

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

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

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

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

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

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

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

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**Track « Nutrition, Health, Mobility »**  
**Proposal for a Master 2 internship – 2024-2025**

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

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

**Laboratory director:** Radhouane DALLEL

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

**Internship tutor:** Méлина BEGOU

**Tel:** 04 73 17 81 02

**e-mail:** melina.begou@uca.fr

**Summary :**

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

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

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

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

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

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

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

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**Track « Nutrition, Health, Mobility »**  
**Proposal for a Master 2 internship – 2024-2025**

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

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

**Laboratory director :** Elisabeth Miot-Noirault

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

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

**Tel :** 0473150816

**e-mail :** arnaud.briat\_le\_mest@uca.fr

**Summary :**

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

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

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

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

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

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## Track « Nutrition, Health, Mobility »

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

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

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

**Laboratory director :** Pr Radhouane Dallel

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

**Internship tutor :** Dr Frédéric CARVALHO

**Tel :** 04 73 17 81 03

**e-mail :** [frederic.carvalho@inserm.fr](mailto:frederic.carvalho@inserm.fr) ou [frederic.carvalho@uca.fr](mailto:frederic.carvalho@uca.fr)

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

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

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

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

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## Track « Nutrition Health and Mobility »

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

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

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

**Laboratory director :** Pr Radhouane Dallel

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

**Internship tutor :** Dr Frédéric CARVALHO

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#### **Summary :**

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

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

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

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

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**Track « Nutrition, Health, Mobility »**  
**Proposal for a Master 2 internship – 2024-2025**

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

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## Track « Nutrition, Health, Mobility »

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

**Title :**

Impact of seaweed extract in inflammation and associated metabolic disorder : application to osteoarthritis

**Laboratory :** UMR 1019 Human Nutrition Unit INRAe -UCA (Didier Raymond), équipe ECREIN

**Laboratory director :** Pr Florence Caldefie-Chézet, équipe ECREIN (microEnvironnement CellulaiRE, Immunomodulation et Nutrition)

**Address :** UFR de Pharmacie – 28 place Henri Dunant – 63001 Clermont-Fd cédex 1

**Internship tutor :** Dr Caroline Decombat

**Tel :** 04.73.17.79.93

**e-mail :** caroline.decombat@uca.fr

**Summary :**

Behind today's major public health problems - allergies, osteoarthritis, diabetes, obesity - lies a single physiological problem: inflammation. Inflammation is a first-line defense mechanism of our body in the face of aggression. Nevertheless, inflammation can become persistent and chronic, affecting one or more organs as a result of dysimmune mechanisms.

Man has always been able to use natural products and more particularly plants, to feed and treat himself. Natural matrices are major sources of bioactive metabolites. According to a study published in 2020, over 60% of all approved between 1980 and 2020 were of natural origin. The potential for innovation linked to the biological activities of primary and secondary metabolites derived from natural products is therefore still considerable and very little exploited and it is against this backdrop that the LabCom Phytobio'innov project aims to develop new phyto-probiotics targeting overweight and inflammation, of interest in the medical and cosmetics fields.

Algae represent a major challenge for the planet. Indeed, seaweed is an important resource for the nutrition, pharmaceutical and cosmetics industries. Yet algae remain a largely unexplored and underused resource. It is in this context that, thanks to the Labcom, we are seeking to develop seaweed extracts as innovative products offering considerable medicinal resources, since they have been little investigated chemically and biologically. To begin with, their anti-oxidant and anti-inflammatory effects will be studied., and then more explorations will be carried out to study their role in the management of osteoarthritis, an associated metabolic disorder with the inflammatory process.

This Master 2 internship project aims, therefore, to establish the contribution of several seaweed extracts in the inflammation and associated metabolic disorder such as osteoarthritis.

**Methodologies (key words) :** cell culture, ROS, RT-qPCR

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

- *Aspalathus linearis* (Rooibos) Targets Adipocytes and Obesity-Associated Inflammation. Nehme R, Chervet A, Decombat C, Longechamp L, Rossary A, Boutin R, Rousset A, Senejoux F, Vachias C, Auxenfans C, Fraisse D, Guyon JB, Filaire E, Berthon JY, Diab-Assaf M, Delort L, Caldefie-Chezet F. *Nutrients*. 2023 Apr 3;15(7):1751. doi: 10.3390/nu15071751.
- Exploring the Therapeutic Potential of *Ampelopsis grossedentata* Leaf Extract as an Anti-Inflammatory and Antioxidant Agent in Human Immune Cells. Chervet A, Nehme R, Decombat C, Longechamp L, Habanjar O, Rousset A, Fraisse D, Blavignac C, Filaire E, Berthon JY, Delort L, Caldefie-Chezet F. *Int J Mol Sci*. 2023 Dec 28;25(1):416. doi: 10.3390/ijms25010416.

**Track « Nutrition Health, Mobility »**  
**Proposal for a Master 2 internship – 2024-2025**

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

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

**Internship tutor :** Géraldine Farge  
**Tel :** +33473405040  
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**Summary :**

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

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

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

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

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

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

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

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

**Track « Nutrition, Health, Mobility »**  
**Proposal for a Master 2 internship – 2024-2025****Title :**

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

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

**Laboratory director :** Dr Christophe Jagla

**Address :** 28 place Henri Dunand Bat CRBC

**Internship tutor :** Ayhan KOCER

**Tel :** 0473406776

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**Summary :**

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

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

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

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

## Track « Nutrition, Health, Mobility »

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

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

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

**Laboratory director :** Didier Rémond

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

**Internship tutor :** Anne-Catherine Maurin

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

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#### Summary :

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

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

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

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

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

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

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**Track « Nutrition, Health, Mobility »**  
**Proposal for a Master 2 internship – 2024-2025**

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

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

**Laboratory director :** Professor Nicolas Barnich

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

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

**Tel :** 0473178345

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

**Summary :**

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

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

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

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

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

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

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

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

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

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**Track « Nutrition, Health, Mobility »**  
**Proposal for a Master 2 internship – 2024-2025**

**Title:** Impact of mechanical load and/or protein supplementation on muscle loss prevention during weight loss in obese rats (MECAPROB)

**Laboratory:** Human Nutrition Unit, UMR1019 INRAe/ICA

**Laboratory director:** Didier Rémond

**Address:** “Alimentation, Santé Musculaire et Sarcopénie” research team, Université Clermont Auvergne, 28 Place Henri Dunant - TSA 50400, 63001 Clermont-Ferrand Cedex 1

**Internship tutor:** Alexandre Pinel

**Tel:** 0473178283

**e-mail:** alexandre.pinel@uca.fr

**Summary:**

Obesity is a public health concern and bariatric surgery remains, to date, the most effective treatment for reducing associated comorbidities. However, this surgery can lead to an involuntary loss of muscle mass which increases the risk of sarcopenia with age. The aim of the study is to test two methods of muscle loss prevention: (i) by compensating for weight loss by using a weighted vest, (ii) by a protein supplementation, in diet- induced obese rats.

Forty-eight adult rats will be submitted to a high-fat high-sucrose (HF-HS) diet for 9 weeks before induction of caloric restriction (CR) by reducing food intake (50% of daily food intake) for 3 weeks.

During CR, 4 groups (n=12) of rats will be subjected to: i) vest without weights (Control group), ii) vest with incremental loading compensating for weight lost during CR, iii) vest without weights with protein supplementation, iv) vest with incremental loading compensating for weight lost during CR together with protein supplementation. We hypothesize that preservation of mechanical loading via weighted vest and/or protein supplementation will promote an improved muscle anabolism and will help to reduce the loss of lean muscle mass and favor a greater loss of fat mass.

The experiment would be almost completed before the beginning of the internship. The fellow will have to participate to the end of animal experiments (organ and blood harvesting) and in the analysis of the samples obtained by different techniques mentioned below.

**Methodologies (key words):** Animal study, Indirect calorimetry, EchoMRI, Western Blot, RT-qPCR

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

Weight loss does not affect the sit-to-stand metabolic cost in adolescents with obesity. Eur J Appl Physiol. 2023 Nov;123(11):2511-2523. doi: 10.1007/s00421-023-05247-8. Epub 2023 Jun 13. PMID: 37310434.

Adipose Tissue Dysfunctions in Response to an Obesogenic Diet Are Reduced in Mice after Transgenerational Supplementation with Omega 3 Fatty Acids. Metabolites. 2021 Dec 4;11(12):838. doi: 10.3390/metabo11120838. PMID: 34940596; PMCID: PMC8706165.

Modulation of Insulin Resistance and the Adipocyte-Skeletal Muscle Cell Cross-Talk by LCn-3PUFA. Int J Mol Sci. 2018 Sep 15;19(9):2778. doi: 10.3390/ijms19092778. PMID: 30223577; PMCID: PMC6164755.

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**Track « Nutrition, Health, Mobility »**  
**Proposal for a Master 2 internship – 2024-2025****Title :**

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

**Laboratory:** Human Nutrition Unit, UMR1019**Laboratory director:** Didier REMOND**Address:** INRAE de Theix – 63122 St Genès Champanelle**Internship tutor:** Cécile POLGE**Tel:** 04 73 62 42 18**e-mail:** cecile.polge@inrae.fr**Summary:**

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

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

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

**Methodologies (key words):** cell culture, cell viability assay, western blot, interactomics**Publications of the research group on the proposed topic (3 max.)**

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

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

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

**Track « Nutrition, Health, Mobility »**  
**Proposal for a Master 2 internship – 2024-2025**

**Title :** Light and migraine pain

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

**Directeur du laboratoire :** R. Dallel

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

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

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

**e-mail :** isabelle.ranchon-cole@uca.fr

**Summary :**

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

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

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

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

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

**Track « Nutrition, Health, Mobility »**  
**Proposal for a Master 2 internship – 2024-2025**

**Title :** Evaluation of biomarkers to monitor sarcopenia in intensive care unit patients, a single-center pilot observational study

**Laboratory :** Unité de Nutrition Humaine - UMR1019  
**Laboratory director :** Didier Rémond  
**Address :** INRAE de Theix - 63122 St Genès Champanelle

**Internship tutor :** Daniel TAILLANDIER  
**Tel :** 0473 62 48 44 / 0782 75 62 44  
**e-mail :** [daniel.taillandier@inrae.fr](mailto:daniel.taillandier@inrae.fr)

**Summary :**

Patients admitted to intensive care units (ICU) are exposed to increased catabolism and undergo muscle wasting. They then become sarcopenic, some of them already being sarcopenic upon admission to ICU. Sarcopenia is a known prognostic factor in ICU patients. Sarcopenia monitoring is essential in diseased patients and its diagnosis is codified and based on imaging and functional tests, which are not always possible in ICU. However, no sarcopenia biomarker has been validated yet. Recently, we discovered 13 mRNA blood biomarkers linked to the activation of proteolytic systems in skeletal muscles from chronic renal failure or cancer patients. As these biomarkers witness muscle atrophy independently of the causal disease, we hypothesize they could be useful for any situation of muscle atrophy like ICU patients.

The aim of this internship is to evaluate the performance of these sarcopenia-linked biomarkers during longitudinal monitoring of ICU patients. Blood samples from ICU patients will be collected at days 3, 7, 10, 14, 28 during ICU care and three months after leaving ICU. Muscle mass will be evaluated the very same days using quadriceps scanning and ultrasound to determine the presence of sarcopenia and the evolution of muscle mass. Muscle surface area and muscle density will be measured by CT scan at L3 and/or T4 on admission, D14 and/or exit from intensive care and 3 months after leaving ICU. In parallel, functional tests will be carried out at the same times using the Hand grip test and the MRC score, and quality of life will be assessed by the EQ-5D questionnaire and the Barthel ADL – IADL scale. Markers related to inflammation (CRP, IL6, I11, I110, mHLA DR), IGF-1 and GDF-15 will also be determined.

**Methodologies (key words):** *Blood RNA purification, Absolute RT-qPCR, dPCR, biostatistics*

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

- [1] Aniert, J., et al. (2019) Muscle wasting in patients with end-stage renal disease or early-stage lung cancer: common mechanisms at work. *J. Cachexia Sarcopenia Muscle*, doi: 10.1002/jesm.12376.
- [2] Aniert, J., et al. (2016). Upregulation of MuRF1 and MAFbx participates to muscle wasting upon gentamicin-induced acute kidney injury. *Int Journal Biochem Cell Biol*, 79, 505-516. DOI : 10.1016/j.biocel.2016.04.006
- [3] Polge, C. et al. (2018). UBE2E1 Is Preferentially Expressed in the Cytoplasm of Slow-Twitch Fibers and Protects Skeletal Muscles from Exacerbated Atrophy upon Dexamethasone Treatment. *Cells*, 7, DOI : 10.3390/cells7110214.

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**Track « Nutrition, Health, Mobility »**  
**Proposal for a Master 2 internship – 2024-2025**

**Title :** Effect of rheumatoid arthritis biotherapies on the muscle secretome and interactions with omega-3 and vitamin D (ERABIO-M3D)

**Laboratory :** Unité de Nutrition Humaine (UNH), Équipe Alimentation, Santé Musculaire et Sarcopénie (ASMS), Unité Mixte de Recherche (UMR) 1019, INRAE/UCA ? UFR de Médecine

**Laboratory director :** Didier Rémond

**Address :** 28 place Henri-Dunant, TSA 50400, 63000 Clermont-Ferrand

**Internship tutor :** Pr Stéphane Walrand / Pr Anne Tournadre / Dr Frédéric Capel

**Tel :**

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**Summary :**

**Rationale:** Rheumatoid arthritis (RA) is a chronic inflammatory disease accompanied by alterations in muscle function and metabolism linked to the level of inflammation. In addition to the pro-inflammatory cytokines (TNF $\alpha$ , IL6) targeted by biotherapies, changes in the myokines produced by skeletal muscles could be both a consequence of the disease and a regulatory mechanism. Remission under biotherapy limits the changes in body composition but does not normalise muscle abnormalities. Furthermore, the effect of biotherapies on myokines is unknown and the combination of nutrients could be beneficial for inflammation, muscle lipotoxicity and cardio-metabolic co-morbidities.

**Aim of the project:** The aim is to understand the mechanisms of muscular alterations in RA, their evolution under biotherapy and the impact of nutritional muscle effectors (polyunsaturated fatty acids PUFAs, vitamin D) by studying changes in myokine secretion, body composition, muscle function and muscle metabolism.

**Expected results:** The aim is to identify a myokine profile linked to sarcopenia in RA, to demonstrate a differential effect of biotherapies on the myokine profile and protein renewal pathways, and to determine the impact of PUFAs and vitamin D.

**Conclusions and outlook:** The identification of biomarkers for monitoring muscle health could be extended to situations of chronic inflammation and would make it possible to offer personalised treatment (orientation of biotherapy according to the myokine profile identified) and multimodal treatment combining targeted nutritional strategies.

**Methodologies (key words) :** RCVRIC database, serum bank, Myokine profile before and after biotherapy introduction, impact of polyunsaturated fatty acids and vitamin D

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

-Vial G, Coudy-Gandilhon C, Pinel A, Wauquier F, Chevenet C, Béchet D, Wittrant Y, Coxam V, Soubrier M, Tournadre A, Capel F. Lipid accumulation and mitochondrial abnormalities are associated with fiber atrophy in the skeletal muscle of rats with collagen-induced arthritis. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2020 Feb;1865(2):158574.

-El Hajj C, Fares S, Chardigny JM, Boirie Y, Walrand S. Vitamin D supplementation and muscle strength in pre-sarcopenic elderly Lebanese people: a randomized controlled trial. *Arch Osteoporos*. 2018 Dec 19;14(1):4.

-Chanet A, Verlaan S, Salles J, Giraudet C, Patrac V, Pidou V, Pouyet C, Hafnaoui N, Blot A, Cano N, Farigon N, Bongers A, Jourdan M, Luiking Y, Walrand S, Boirie Y. Supplementing Breakfast with a Vitamin D and Leucine-Enriched Whey Protein Medical Nutrition Drink Enhances Postprandial Muscle Protein Synthesis and Muscle Mass in Healthy Older Men. *J Nutr*. 2017 Dec;147(12):2262-2271.

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**Track « Nutrition, Health, Mobility »**  
**Proposal for a Master 2 internship – 2024-2025**

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

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

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

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

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

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

1. Moisset X, Lefaucheur J.P (2018) Non pharmacological treatment for neuropathic pain : Invasive and non-invasive cortical stimulation. *Revue Neurologique*. doi: 10.1016/j.neurol.2018.09.014.
2. Zbili M, Rama S, Benitez MJ, Fronzaroli-Molinieres L, Bialowas A, Boumedine-Guignon N, Garrido JJ, Debanne D (2021) Homeostatic regulation of axonal Kv1.1 channels accounts for both synaptic and intrinsic modifications in CA3 circuit. *PNAS*. doi: 10.1073/pnas.2110601118.
3. Moisset X, Bouhassira D, Attal N (2021) French guidelines for neuropathic pain: An update and commentary *Revue Neurologique*. doi: 10.1016/j.neurol.2021.07.004.

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