MASTER BIOLOGY and HEALTH SCIENCE of LILLE

Research Projects 2023-2024

The role of the mitochondrial protein CHCHD4 in endothelial cell function	Anna Rita CANTELMO - U1011 - Récepteurs Nucléaires, Maladies Métaboliques et Cardiovasculaires, Institut Pasteur de Lille - Rue du Professeur Calmette - anna-rita.cantelmo@univ-lille.fr	20
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Nouvelles perspectives de traitements des pathologies rares de la glycosylation	François FOULQUIER - UGSF Unité de Glycobiologie Structurale et Fonctionnelle – Univesité de Lille -francois.foulquier@univ-lille.fr	21
A mannose for your antibody : antibody recognition of mannose	Julie BOUCKAERT – UGSF – Bâtiment IRI, Avenue de Halley, Villeneuve dAscq – julie.bouckaert@univ-lille.fr	22
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Role of FAT10/UBD on Mallory Denk Bodies formation in hepatocytes during NASH development	Réjane PAUMELLE-LESTRELIN. UMR1011 « récepteurs nucléaires, maladies métaboliques et cardiovasculaires. rejane.lestrelin@univ-lille.fr	24
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RevErbα & IQGAP2 in the gut: a new axis in dietary lipid handling and in the control of postprandial lipemia?	Olivier BRIAND – INSERM U1011 – EGID - Laboratoire JK, Pôle recherche, Faculté de médecine, Lille - olivier.briand@univ-lille.fr	25
Novel insights into the treatment of rare inborn errors of glycosylation metabolism	François FOULQUIER, UGSF - Unité de Glycobiologie Structurale et Fonctionnelle, francois.foulquier@univ-lille.fr	26
Research into new biomarkers of diabetes complications in nails: development and validation of a liquid chromatography method coupled with mass- and fluorescence spectrometry	Frédéric TESSIER, U1167 RID-AGE, frederic.tessier@univ-lille.fr	26
Study of FAT10/PPARα interaction during NASH development	Audrey HELLEBOID. UMR1011 – Récepteurs nucléaires, maladies métaboliques et cardiovasculaires. audrey.helleboid@univ-lille.fr	27

Cellular Integrative and Translational Neuroscience

Tile: **Therapeutic potential of neuroprotection of anti-ferroptotic drugs in Parkinson's disease.**

Supervisor: **David DEVOS** - Team « Degenerative and Vacular Cognitive disorders », Lille Neuroscience & cognition center, U1172 Inserm, CHU de Lille. David.DEVOS@chu-lille.fr

Neurodegenerative diseases are an upcoming tsunami already affecting millions of people. After 40 years of failure, there is an urgent need of a game changing strategy for neuroprotective treatment. Degeneration occurs in central nervous system regions associated with memory (Alzheimer's disease), automaticity (Parkinson's disease, PD) and motor function (amyotrophic lateral sclerosis), all of which require a high oxygen demand for harnessing neuronal energy. In PD, a progressive degeneration of the substantia nigra pars compacta is associated with the appearance of iron accumulation. At a molecular level, α-synuclein regulates dopamine and iron transport with PD-associated mutations in this protein causing functional disruption to these processes. The molecular pathways that cascade down from such dyshomeostasis still remain to be fully elucidated but strong inroads have been made in recent years. We demonstrated that these alterations can trigger susceptibility to an iron-dependent cell-death pathway with unique lipoperoxidation signatures called ferroptosis.
This project proposes to go further into key modulators of this cell-death pathway that could be new therapeutic targets against ferroptosis. This project will analyse key modulators of this cell-death pathway using human dopaminergic cell culture and unique murin models (GPX4 and ACSL4 KO) with genetic and pharmacologic modulation associated with human dosages coming from large cohorts of patients and clinical trials.
This project will further demonstrate the key modulator of ferroptosis and their therapeutic potential in clinical trials in progress (European clinical trial Fairpark-II) and upcoming (6 new drugs in development).

Title : **Anatomo-radiological correlations in Parkinson's disease models.**

Supervision : **Nacim BETROUNI & Charlotte LALOUX** - INSERM U1172, Lille Neuroscience & cognition center - nacim.betrouni@inserm.fr - Tel 03.20.44.63.54

Animal models of neuro-degenerative diseases play an important role in the understanding of the mechanisms and in therapeutic development. In our team we use three models of Parkinson's disease. They are complementary and model various aspects of the disease at different stages. In previous studies, these models have been explored by different modalities such as magnetic resonance imaging, behavioural analysis and histology. In the present project, we aim to investigate the correlations between imaging markers and those from tissular analysis (neuronal death, protein accumulations, inflammation, etc.), with the intention of highlighting specific signatures of the disease.

Title : **Dissection of Neuroendocrine Determinants of Polycystic Ovary Syndrome**

Tutor: **Paolo GIACOBINI** - Laboratory: Development and Plasticity of the Neuroendocrine Brain, Lille Neuroscience & Cognition, Inserm UMR-S 1172, Bâtiment Biserte - paolo.giacobini@inserm.fr

PCOS is the most common endocrine disorder affecting up to 18% of women worldwide. Current diagnosis is based on the concurrence of at least two of the cardinal clinical findings : hyperandrogenism, irregular menstrual cycles and polycystic ovarian morphology. The syndrome imposes a heavy health burden as it covers also metabolic disturbances including obesity, type 2 diabetes and insulin resistance. The development of treatment options is an urgent need since there isn't currently a cure.

Intrauterine life may be implicated in the origin of PCOS. Among factors that may be at the origin of PCOS are excessive exposure during fetal life to androgens and/or anti-Müllerian hormone (AMH). Exposure of the female fetus to excessive androgens and/or AMH consistently induces PCOS-like traits in female offspring in different animal models, however, a paucity of data exists for equivalent males.

One key neuroendocrine aberration in most women with PCOS is increased luteinizing hormone (LH) pulse frequency. This suggests an increase in activity of gonadotropin-releasing hormone (GnRH) neurons in the hypothalamus. Importantly, we have previously demonstrated that AMH plays unexpected extra-gonadal roles in regulating hypothalamic function, impinging on GnRH neuronal activation. Altogether, these evidences suggest that alterations of GnRH neuronal activity/secretion could be the basis for neuroendocrine anomalies that accompany the reproductive and metabolic disturbances in women with PCOS.

In this project, the PhD candidate will dissect the GnRH-sensitive neuroendocrine pathways underlying the origin of PCOS health-related changes.

Title : **Role of mechanical signaling in synaptic plasticity**

Supervisor : **Devrim KILINC** - Team: Molecular Determinants of Alzheimer's Disease and Related Disorders - Inserm U1167, Risk Factors and Molecular Determinants of Aging-related Diseases - devrim.kilinc@pasteur-lille.fr

Chemical synapses of the nervous system form the basis of learning and memory. Their regulation is a key factor in understanding neuropathological processes leading to cognitive decline and dementia. Accordingly, synapse loss due to the disruption of neuronal plasticity mechanisms is an early event in the Alzheimer's disease (AD) pathogenesis. Synapses undergo activity-dependent structural change, which involves a number of mechanically-relevant processes, including cytoskeleton and cell adhesion molecules (CAMs) (doi.org/10.3389/fncel.2018.00483). However, little is known about the mechanical aspects of synaptic plasticity, and if and how AD genetic risk factors are involved therein. Within this framework, this M2 project aims to develop a model system for the induction of pre- and post-synaptic structures on primary neurons through mechanical stimulation of N-Cadherin (NCad), a transsynaptic CAM, through magnetic tweezers-based force application (doi.org/10.1039/c3ib40185e) in a microfluidic model. We will grow neurons in multi-chamber devices to isolate their dendrites and axons (doi.org/10.1002/adhm.201600895), target them with magnetic particles functionalized against NCad ectodomains, and analyze shape change and synaptic protein accumulation via live microscopy and/or immunocytochemistry. In complementary experiments, we will analyze the synaptic localization of NCad as a function of synaptic potentitation and AD-related synaptotoxicity. This is an ambitious project at the intersection of neurodegenerative diseases and mechanobiology fields that deals with an emerging, yet understudied concept using custom, innovative tools.

Title : **Hormonal control of gestational oligodendrogenesis**

Supervisor : **Ariane SHARIF** - UMR-S1172, Lille Neuroscience & Cognition Research Center - Laboratoire Développement et Plasticité du Cerveau Neuroendocrine - (https://hypothalamus.eu/) - Bâtiment Biserte - 03-20-62-20-65 - ariane.sharif@inserm.fr

A successful gestation requires profound changes in brain function to induce the central and peripheral adaptations underlying the correct completion of pregnancy, delivery, lactation and the onset of maternal behaviour. Previous work from the laboratory has recently revealed a novel process of brain plasticity associated with pregnancy in the rat, showing that gestation promotes the formation of oligodendroglial lineage cells in the hypothalamus, and that the production of these new cells is important for the development of maternal behaviour. However, the mechanisms regulating this gestational oligodendrogenesis in the hypothalamus remain to be explored. Gestation is accompanied by profound changes in the concentrations of several hormones, in particular estrogens, progesterone and prolactin. These hormones are known to promote the development of maternal behaviour via mechanisms that are still incompletely understood, and to regulate oligodendrogenesis in brain regions other than the hypothalamus. We therefore propose the hypothesis that gestational hormones could be the molecular determinants promoting gestational oligodendrogenesis in the hypothalamus.

This project aims to investigate whether oligodendrogenesis in the hypothalamus of the adult female rat is regulated by hormones, in particular reproductive hormones (gonadal steroids, prolactin). It will include in vivo (analysis of hormone receptor expression, hormonal modulations and consequences on cell neogenesis) and in vitro (primary cultures of oligodendroglial cells) experiments in the rat. The completion of this research project will lead to a better understanding of the physiological mechanisms regulating cell plasticity in the adult hypothalamus as well as the neurobiological basis of maternal behaviour.

Diabetes and Cardiovascular diseases

Title: **The molecular clock in liver fibrosis**

Mentor: **Philippe LEFEBVRE**, Univ. Lille, UMR Inserm 1011. philippe-claude.lefebvre@inserm.fr

Our laboratory has a longstanding interest in nonalcoholic steatohepatitis (NASH) and liver fibrosis. We identified altered signaling pathways in humans which may be causal in disease progression (see references below). Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver dysfunctions detected in its mildest form as the build-up of excess fat in the liver. Intimately linked to obesity and type 2 diabetes, the disease progresses within years towards an inflammatory state (NASH) and eventually induces liver fibrosis, a detrimental excess of extracellular matrix deposition that strongly impacts physical and functional properties of this organ. The major contributors in the fibrogenic response to liver damage are hepatic stellate cells (HSCs). During NASH, HSCs undergo a critical 'activation' process characterized notably by massive extracellular matrix component production. The circadian clock (CC) is critical in establishing cellular and tissular homeostasis. Timed by zeitgebers such as light and food intake, organs exhibit cyclic expression of CC mRNA transcripts and of proteins which adjust cellular activities to external cues. Our preliminary data suggest that components of the molecular clock participates into HSC activation. This project will investigate further this relationship.
Upon completion of his/her training in an environment fostering scientific interactions, the candidate is expected to master basic cellular and molecular biology techniques and essential analysis tools, to be able to apprehend the general purpose of his/her research project, and to acquire written and oral presentation skills.

Key references: Berthier, A., et al. (2018). PNAS, 115, E11033-E11042 ; Bobowski-Gerard, M., et al. (2022). Nat. Comm. 13.-33063-9 ; Lefebvre, P., et al. (2017). JCI Insight 2, e92264 ; Margerie, D., et al. (2019). BMC Medical Genomics 12. 10.1186/s12920-019-0536-1 ; Vandel, J., et al. (2021).. Hepatology 73, 920-936.

Title : **The role of the mitochondrial protein CHCHD4 in endothelial cell function**

Tutor : **Anna Rita CANTELMO** - U1011 - Récepteurs Nucléaires, Maladies Métaboliques et Cardiovasculaires, Institut Pasteur de Lille - Rue du Professeur Calmette - 03 20 33 70 78 - anna-rita.cantelmo@univ-lille.fr

Mitochondria exert central functions in bioenergetics, metabolism, and apoptosis. The correct function of these organelles requires the import of > 1000 nucleus-encoded proteins as the mitochondrial genome provides only 13 proteins. A key component of the mitochondrial protein import machinery is the evolutionarily conserved AIF/CHCHD4 oxidoreductase that catalyzes the oxidative folding of targeted proteins after they cross the outer mitochondrial membrane. This mechanism is finely tuned and it is affected in disease.
Using a multidisciplinary approach, combining molecular and cellular biology, this project aims at i) studying the role and functional relevance of AIF/CHCHD4 in endothelial cells, and ii) characterizing the signaling pathways that impact on AIF/CHCHD4-dependent import pathway in angiogenesis in disease. The working hypothesis is that aberrant activity of this import pathway drives pathological angiogenesis. We will investigate angiogenic responses in healthy endothelial cells overexpressing CHCHD4 mimicking pathological endothelial cells.
The results generated with this project promise to provide unprecedented insights that will be useful for the development of novel therapeutic strategies for a variety of human diseases characterized by dysfunctional vasculature, such as cardiovascular disorders.

Title : **Evaluation of pharmacological therapies for NASH in a new preclinical mouse model of NASH/NAFLD**

Supervisor: **Fanny LALLOYER** - Inserm UMR 1011 - Institut Pasteur of Lille - University of Lille - +33320877996 - fanny.lalloyer@univ-lille.fr

NAFLD (Non-Alcoholic Fatty Liver Disease) is the most common liver disease in the world, with a prevalence estimated at 25% of the general population, but reaching 80-90% in obese adults and 50-70% in patients with type 2 diabetes. This pathology has now become a veritable global “epidemic” whose incidence continues to increase, in parallel with the growing epidemic of obesity and diabetes. NAFLD is the hepatic expression of the metabolic syndrome and is characterized in its first stage by an excessive accumulation of fat in the liver, considered as benign steatosis, in the absence of excessive alcohol consumption. During the progression of NAFLD, simple steatosis can progress to NASH (Non-Alcoholic Steatohepatitis), diagnosed as a combination of steatosis, inflammation and ballooning of hepatocytes. In the worst cases, liver damage can progress to fibrosis, cirrhosis and hepatocellular carcinoma, which can lead to the death of the patient. Currently, there is no approved therapeutic treatment for patients with NAFLD and NASH, the aggressive form of NAFLD.
In the laboratory, we developed a new mouse model which presents all stages of human NAFLD pathology (liver steatosis, inflammation, ballooning and fibrosis) under high fat diet for 12 weeks. The project aims to better understand NASH physiopathology and to test novel therapeutic targets for NASH in this model. Histological, biochemical and molecular analyzes will be carried out on the various technical platforms of the laboratory.

Title : **Metabolic effects of Sodium-Glucose-Co-Transporter-4 Inhibition : From Mouse Studies to Clinical Translation**

Supervisor : **Caroline BONNER** - Institut Pasteur de Lille, Inserm UMR 1190 Translational Research of Diabetes, Faculty of Medicine, Pôle recherche - caroline.bonner@univ-lille.fr

Would inhibiting SGLT4 reverse obesity and prevent the progression to type 2 diabetes (T2D)? Unlike some of its better-known SGLT family members, SGLT4 also exhibits a Na+-dependent alpha-methyl-D-glucopyranoside transport system with a Km of 2.6 mM, suggesting that it is a low affinity-type transporter, similar to that of SGLT2. Studies using radiolabeled mannose suggested that an 'SGLT4-like transport system' might be physiologically relevant for intestinal absorption. But unlike SGLT1 and SGLT2, which transport only glucose, SGLT4 transports naturally occurring sugars with a rank order of mannose, glucose, fructose, 1.5AG (artificial sweeteners), and galactose, all enriched in the Western diet (WD), and dangerously elevated in the blood of obese individuals with and without T2D. We hypothesized that SGLT4 inhibition would lower the serum concentrations of these sugars, which would be a "game-changer" for the treatment of such pathological conditions. To address this, we created a global Sglt4 KO mouse using CRISPR/Cas techniques, allowing us to follow wild-type (WT) and Sglt4 KO mice for several months while they were fed the WD. Intriguingly, we discovered that Sglt4 KO mice were protected against obesity and T2D after only three months of feeding the WD when compared to WT mice fed the same diet. These findings suggest that Sglt4 deficiency slows the onset of obesity and hyperglycemia in mice fed the WD. To examine whether inhibition of SGLT4 substrate absorption can prevent obesity induced by the WD using mouse and human studies in parallel, with adequate experimental design and statistical power.
Methods and assessment: Since Sglt4 is expressed in the intestine and islets in mice and humans, and induced by obesity and hyperglycemia the functional characterization of Sglt4-loss-of-function will be evaluated in both organs in vivo and in vitro using isolated islets and intestinal organoids.
Project outcomes: We will advance our knowledge on SGLT4 substrate transport in the intestine and pancreas.

Title: **Role of FAT10/UBD on Mallory Denk Bodies formation in hepatocytes during NASH development**

Supervisor: **Réjane PAUMELLE-LESTRELIN**. UMR1011 « récepteurs nucléaires, maladies métaboliques et cardiovasculaires. rejane.lestrelin@univ-lille.fr

Non-alcoholic fatty liver disease (NAFLD) affects one third of the general population. NAFLDs are characterized by an intrahepatic accumulation of lipids (steatosis) progressing to non-alcoholic steatohepatitis (NASH) which can lead to the development of cirrhosis and hepatocellular carcinoma (HCC). To date, no effective medical treatment for NASH is available other than lifestyle change or weight loss surgery. Among the various mechanisms involved in the development and progression of NASH, the disruption of degradation pathways leading to the formation of Mallory Denk Bodies (MDB) appears to be a potential mediator of the progression of NASH to cirrhosis and HCC. However, the mechanisms leading to the formation of MDBs during NASH are not yet known. Our transcriptomic analysis of liver biopsies from obese patients with NASH show that the expression of FAT10/UBD correlates positively with the different histological grades of NAFLD. FAT10 is a protein of the "ubiquitin-like" family involved in FATylation processes regulating protein degradation. Interestingly FAT10 play a role in the formation of MDB induced by a chemical agent, DCC, in mice. The Master 2 project therefore aims to determine the role of FAT10 in the formation of Mallory bodies in hepatocytes, in vitro, in models of human hepatocytes and in vivo, in a mouse model developing NASH.

Title: **Role of Δ9-desaturase activity in the bone loss related to osteoporosis in vivo and in vitro**

Supervisor: **Alexandrine DURING** - Marrow Adiposity and Bone Laboratory - MABLab ULR 4490, Université de Lille - alexandrine.during@univ-lille.fr

Osteoporosis (OP) is a silent and age-related disease characterized by a progressive reduction of bone mass correlated with an increase of bone marrow adiposity. Our hypothesis is that local lipids originated from bone marrow adipocytes might accumulate in the vicinity of bone cells and affect their survival and functions, and thus play a key role in the bone loss during OP development. We reported that the two stearoyl-CoA desaturase indexes (16:1/16:0 and 18:1/18:0) were increased in rat osteoporotic femurs (During et al, 2020 Calcif. Tissue Inter.); data that were recently confirmed at earlier stages of OP development.
This Master's work will be part of the on-going LIPIDOs project and will have to evaluate the contribution of the Δ9-desaturase: 1°) in vivo, by looking at the effects of a Δ9-desaturase activity inhibitor on the bone loss and local lipid profiles in the ovariectomized OVX rat (post-menopausal OP model), and 2°) in vitro, by using an osteoblast culture model capable to produce matrix vesicles and mineral and studying various molecules (lipids, Δ9-desaturase inhibitor, cytokines…) on that process of mineralization. Outcomes of this work should allow to understand better the Δ9-desaturase role in the pathophysiology of OP, knowing that enzyme is a de novo lipogenesis marker which is increased in several metabolic syndromes.
We are looking for a motivated candidate with a solid background in biochemistry, preferably in the lipid area, with an experience in cell culture, aware of good laboratory practices, and with a good English level.

Immunity, Inflammation, Infection

Title : **Dissecting key factors for apicomplexan parasite proliferation using Toxoplasma gondii as a model.**

Tuteur : **Mathieu GISSOT** - CIIL – Equipe BAP - 1, rue du Professeur Calmette, 59000 Lille - mathieu.gissot@pasteur-lille.fr

Toxoplasma gondii is responsible for toxoplasmosis, a disease of importance for pregnant women and immuno-deficient patients. T. gondii is an eucaryotic unicellular pathogen member of the apicomplexa phylum which includes other parasites of medical and veterinary interests. The pathogenesis of these parasites is based on their ability to divide in order to multiply efficiently and rapidly while producing a large number of parasites. The division of these parasites is controlled by the centrosome. However, the composition and centrosome structure of apicomplexes remains largely unknown suggesting the presence of a large number of apicomplex-specific proteins. Using T. gondii as a model Apicomplexa, we propose to dissect the role of new centrosomal proteins that were identified in a previous study [1]. We will produce mutants for centrosomal proteins and inspect their localization together with known markers of the centrosome using state-of-the-art imaging techniques. The consequences of the conditional expression of these proteins will also be examined. The selected trainee will gain significant experience in molecular and cellular biology. In the longer term, this study aims at identifying new therapeutic targets for future therapies against these parasites.

Khelifa AS, Guillen Sanchez C, Lesage KM, Huot L, Mouveaux T, Pericard P, et al. TgAP2IX-5 is a key transcriptional regulator of the asexual cell cycle division in Toxoplasma gondii. Nat Commun. 2021 ; 12 : 116. Doi : 10.1038/s41467-020-20216-x

Title : **Molecular dynamic studies of structure-function relationships of P2X7 modulators**

Tutor : **Nicolas RENAULT** - U1286 Infinite, Université de Lille - 03 62 28 36 69 - nicolas.renault@univ-lille.fr

P2X7 is ligand-gated channel activated by ATP. Its opening induces cell depolarization and new avenues for the treatment of a large group of illnesses from inflammation to diabetes mellitus. It has closed, opened and macropore conformations, which are studied at the lab through in silico methods due to a 3D model built from the crystallography of its panda's homolog. Its trimeric structure makes the choice of a binding site complex because it can induce allosteric cooperativity by modifying the structure of putative binding site in response to the binding of a ligand on the other monomers, but could also explain the varying degrees of opening of the pore.
This project aims at studying positive allosteric modulators by molecular dynamics in order to contribute to the structure-function relationships of these compounds.

Title : **Structure-activity relationships and inverse screening of novel compounds active against Toxoplasma gondii**

Tutor : **Amaury FARCE** - U1286 Infinite, Université de Lille - 03 20 96 49 81 - amaury.farce@univ-lille.fr

Toxoplasma gondii is the causal agent of toxoplasmosis. It is widely spread, and 30-50% of humankind has been infected worldwide. T. gondii has two main forms in its human host: the acute phase tachyzoite and the chronic phase bradyzoite. This last is responsible for the cerebral cysts that may reactivate when the immunity is reduced, either by other illnesses or for therapeutical reasons, with possible lethal consequences. There is currently few if any treatment available against the bradizoite. A collaborative endeavor with a Pasteur Institute team has led to the discovery of such compounds.
This project is built around the elaboration of structure-activity relationships of the series, with QSAR and chemical space analysis methodologies. A secondary target is the assess the off-target potential of the lead compounds by reverse screening.

Title : **Identification of motifs of the membrane protein of the severe acute respiratory syndrome coronavirus-2 involved in viral assembly.**

Tutor : **Sandrine BELOUZARD**, Centre d'Infection et d'Immunité de Lille, Equipe virologie moléculaire et cellulaire. Email : sandrine.belouzard@ibl.cnrs.fr

Coronaviruses are enveloped viruses with a positive single-stranded RNA. Three viral proteins are anchored in the envelope : the spike protein (S), the small envelope protein (E) and the membrane protein (M). The spike protein is involved in viral entry whereas M and E are involved in viral assembly. The M protein is the most abundant component of the viral envelope, it is considered as the motor of viral assembly. Indeed, the M protein has been shown to interact with all the others structural proteins and the co-expression of M and E is sufficient to induce the production of virus-like particles (VLPs). Coronavirus assembly occurs in the intermediate compartment between the endoplasmic reticulum and the Golgi (ERGIC). Knowledges on the mechanisms of coronavirus morphogenesis are still partial. The aim of this project is to better characterize the role of the M protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in viral assembly. More precisely our goal is to identify intracellular trafficking and protein-protein interaction motifs of the SARS-CoV-2 M protein and their importance in viral assembly.

Title: **Role of Δ9-desaturase activity in the bone loss related to osteoporosis in vivo and in vitro**

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We are looking for a motivated candidate with a solid background in biochemistry, preferably in the lipid area, with an experience in cell culture, aware of good laboratory practices, and with a good English level.

Precision Health

Title: **The molecular clock in liver fibrosis**

Mentor: **Philippe LEFEBVRE**, Univ. Lille, UMR Inserm 1011. philippe-claude.lefebvre@inserm.fr

Our laboratory has a longstanding interest in nonalcoholic steatohepatitis (NASH) and liver fibrosis. We identified altered signaling pathways in humans which may be causal in disease progression (see references below). Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver dysfunctions detected in its mildest form as the build-up of excess fat in the liver. Intimately linked to obesity and type 2 diabetes, the disease progresses within years towards an inflammatory state (NASH) and eventually induces liver fibrosis, a detrimental excess of extracellular matrix deposition that strongly impacts physical and functional properties of this organ. The major contributors in the fibrogenic response to liver damage are hepatic stellate cells (HSCs). During NASH, HSCs undergo a critical 'activation' process characterized notably by massive extracellular matrix component production. The circadian clock (CC) is critical in establishing cellular and tissular homeostasis. Timed by zeitgebers such as light and food intake, organs exhibit cyclic expression of CC mRNA transcripts and of proteins which adjust cellular activities to external cues. Our preliminary data suggest that components of the molecular clock participates into HSC activation. This project will investigate further this relationship.
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Supervision : **Nacim BETROUNI & Charlotte LALOUX** - INSERM U1172, Lille Neuroscience & cognition center - nacim.betrouni@inserm.fr - Tel 03.20.44.63.54

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Tutor : **Anna Rita CANTELMO** - U1011 - Récepteurs Nucléaires, Maladies Métaboliques et Cardiovasculaires, Institut Pasteur de Lille - Rue du Professeur Calmette - 03 20 33 70 78 - anna-rita.cantelmo@univ-lille.fr

Mitochondria exert central functions in bioenergetics, metabolism, and apoptosis. The correct function of these organelles requires the import of > 1000 nucleus-encoded proteins as the mitochondrial genome provides only 13 proteins. A key component of the mitochondrial protein import machinery is the evolutionarily conserved AIF/CHCHD4 oxidoreductase that catalyzes the oxidative folding of targeted proteins after they cross the outer mitochondrial membrane. This mechanism is finely tuned and it is affected in disease.
Using a multidisciplinary approach, combining molecular and cellular biology, this project aims at i) studying the role and functional relevance of AIF/CHCHD4 in endothelial cells, and ii) characterizing the signaling pathways that impact on AIF/CHCHD4-dependent import pathway in angiogenesis in disease. The working hypothesis is that aberrant activity of this import pathway drives pathological angiogenesis. We will investigate angiogenic responses in healthy endothelial cells overexpressing CHCHD4 mimicking pathological endothelial cells.
The results generated with this project promise to provide unprecedented insights that will be useful for the development of novel therapeutic strategies for a variety of human diseases characterized by dysfunctional vasculature, such as cardiovascular disorders.

Title : **Evaluation of pharmacological therapies for NASH in a new preclinical mouse model of NASH/NAFLD**

Supervisor: **Fanny LALLOYER** - Inserm UMR 1011 - Institut Pasteur of Lille - University of Lille - +33320877996 - fanny.lalloyer@univ-lille.fr

NAFLD (Non-Alcoholic Fatty Liver Disease) is the most common liver disease in the world, with a prevalence estimated at 25% of the general population, but reaching 80-90% in obese adults and 50-70% in patients with type 2 diabetes. This pathology has now become a veritable global “epidemic” whose incidence continues to increase, in parallel with the growing epidemic of obesity and diabetes. NAFLD is the hepatic expression of the metabolic syndrome and is characterized in its first stage by an excessive accumulation of fat in the liver, considered as benign steatosis, in the absence of excessive alcohol consumption. During the progression of NAFLD, simple steatosis can progress to NASH (Non-Alcoholic Steatohepatitis), diagnosed as a combination of steatosis, inflammation and ballooning of hepatocytes. In the worst cases, liver damage can progress to fibrosis, cirrhosis and hepatocellular carcinoma, which can lead to the death of the patient. Currently, there is no approved therapeutic treatment for patients with NAFLD and NASH, the aggressive form of NAFLD.
In the laboratory, we developed a new mouse model which presents all stages of human NAFLD pathology (liver steatosis, inflammation, ballooning and fibrosis) under high fat diet for 12 weeks. The project aims to better understand NASH physiopathology and to test novel therapeutic targets for NASH in this model. Histological, biochemical and molecular analyzes will be carried out on the various technical platforms of the laboratory.

Title : **Metabolic effects of Sodium-Glucose-Co-Transporter-4 Inhibition : From Mouse Studies to Clinical Translation**

Supervisor : **Caroline BONNER** - Institut Pasteur de Lille, Inserm UMR 1190 Translational Research of Diabetes, Faculty of Medicine, Pôle recherche - caroline.bonner@univ-lille.fr

Would inhibiting SGLT4 reverse obesity and prevent the progression to type 2 diabetes (T2D)? Unlike some of its better-known SGLT family members, SGLT4 also exhibits a Na+-dependent alpha-methyl-D-glucopyranoside transport system with a Km of 2.6 mM, suggesting that it is a low affinity-type transporter, similar to that of SGLT2. Studies using radiolabeled mannose suggested that an 'SGLT4-like transport system' might be physiologically relevant for intestinal absorption. But unlike SGLT1 and SGLT2, which transport only glucose, SGLT4 transports naturally occurring sugars with a rank order of mannose, glucose, fructose, 1.5AG (artificial sweeteners), and galactose, all enriched in the Western diet (WD), and dangerously elevated in the blood of obese individuals with and without T2D. We hypothesized that SGLT4 inhibition would lower the serum concentrations of these sugars, which would be a "game-changer" for the treatment of such pathological conditions. To address this, we created a global Sglt4 KO mouse using CRISPR/Cas techniques, allowing us to follow wild-type (WT) and Sglt4 KO mice for several months while they were fed the WD. Intriguingly, we discovered that Sglt4 KO mice were protected against obesity and T2D after only three months of feeding the WD when compared to WT mice fed the same diet. These findings suggest that Sglt4 deficiency slows the onset of obesity and hyperglycemia in mice fed the WD. To examine whether inhibition of SGLT4 substrate absorption can prevent obesity induced by the WD using mouse and human studies in parallel, with adequate experimental design and statistical power.
Methods and assessment: Since Sglt4 is expressed in the intestine and islets in mice and humans, and induced by obesity and hyperglycemia the functional characterization of Sglt4-loss-of-function will be evaluated in both organs in vivo and in vitro using isolated islets and intestinal organoids.
Project outcomes: We will advance our knowledge on SGLT4 substrate transport in the intestine and pancreas.

Title: **Novel insights into the treatment of rare inborn errors of glycosylation metabolism**

Supervisor: **François FOULQUIER -** UGSF Unité de Glycobiologie Structurale et Fonctionnelle – Univesité de Lille - francois.foulquier@univ-lille.fr

Glycosylation consists in the attachment of glycan structures covalently linked to proteins and lipids. An extreme diversity of attachment and glycan structures are found and define the different types of glycosylation including the N-, O-, glycosaminoglycan (GAG) and glycosylphosphatidylinositol (GPI) glycosylation. The regulation of this process is so complex that the importance of these structures was primarily underestimated, and just considered as decorations. Awareness of the crucial involvement of glycosylation in the intricate design of life came later with the discovery of patients suffering from glycosylation defects. To date, this group of diseases is called Congenital Disorders of Glycosylation (CDG) and represent >160 rare genetic diseases of metabolism (1). Our group has identified several new genes involved in these rare diseases particularly one affecting the Golgi manganese homeostasis called TMEM165. Several new variants have been discovered and need to be fully dissected to discover and explore novel cellular pathways that will constitute the basis of exploring manganese based treatments in CDG subtypes. This project offers a unique opportunity to engage directly with clinical and molecular geneticists to better understand the genetic basis and molecular pathogenesis of inherited disorders. We are seeking a highly motivated individual who can address complex questions regarding disease pathogenesis. Interested applicants should send their cover letter, resume to Dr. François Foulquier.

Title : **A mannose for your antibody : antibody recognition of mannose**

Tutor : **Julie BOUCKAERT** – UGSF – Bâtiment IRI, 50 Avenue de Halley, Villeneuve dAscq – Tel. 03 62 53 17 29 - julie.bouckaert@univ-lille.fr

Protein glycosylation has received much attention due to its many roles in normal physiological and pathological conditions. Paucimannose is the tri- or dimannosyl N-glycan core structure of all eukaryotic organisms, in its unsubstituted form. Paucimannose is expressed abundantly in plants and invertebrates, but has been detected in only very small amounts in normal mammalian tissue. Now it is clearly associated with human brain and blood cancers (Proteomics. e1900010. doi: 10.1002/pmic.201900010). The expression of paucimannose-carrying glycoproteins is upregulated under embryogenic, tumorigenic and inflammatory conditions and an important presence of mannose-recognizing antibodies may be circulating under these same circumstances.
The candidate will examine a new assortment of nanobodies/antibodies for their potential to recognize paucimannosylated glycoproteins. Purification of the antibodies and glycoproteins will make it possible to sequence by peptide mapping, for cloning, expression and structure determination.

Title : **Molecular dynamic studies of structure-function relationships of P2X7 modulators**

Tutor : **Nicolas RENAULT** - U1286 Infinite, Université de Lille - 03 62 28 36 69 - nicolas.renault@univ-lille.fr

P2X7 is ligand-gated channel activated by ATP. Its opening induces cell depolarization and new avenues for the treatment of a large group of illnesses from inflammation to diabetes mellitus. It has closed, opened and macropore conformations, which are studied at the lab through in silico methods due to a 3D model built from the crystallography of its panda's homolog. Its trimeric structure makes the choice of a binding site complex because it can induce allosteric cooperativity by modifying the structure of putative binding site in response to the binding of a ligand on the other monomers, but could also explain the varying degrees of opening of the pore.
This project aims at studying positive allosteric modulators by molecular dynamics in order to contribute to the structure-function relationships of these compounds.

Title : **Structure-activity relationships and inverse screening of novel compounds active against Toxoplasma gondii**

Tutor : **Amaury FARCE** - U1286 Infinite, Université de Lille - 03 20 96 49 81 - amaury.farce@univ-lille.fr

Toxoplasma gondii is the causal agent of toxoplasmosis. It is widely spread, and 30-50% of humankind has been infected worldwide. T. gondii has two main forms in its human host: the acute phase tachyzoite and the chronic phase bradyzoite. This last is responsible for the cerebral cysts that may reactivate when the immunity is reduced, either by other illnesses or for therapeutical reasons, with possible lethal consequences. There is currently few if any treatment available against the bradizoite. A collaborative endeavor with a Pasteur Institute team has led to the discovery of such compounds.
This project is built around the elaboration of structure-activity relationships of the series, with QSAR and chemical space analysis methodologies. A secondary target is the assess the off-target potential of the lead compounds by reverse screening.

Title: **Exploring the Molecular Basis of Tau Protein Aggregation Using Single-Domain Antibodies That Bind Tau Protein**

Supervision: **Isabelle LANDRIEU**, CNRS EMR 9002 Integrative structural Biology – U1167 RID-AGE ULille-Inserm-Institut Pasteur de Lille, Risk Factors and Molecular Determinants of aging related diseases- Isabelle.landrieu@univ-lille.fr

Protein aggregation is a hallmark of age-related neurodegenerative diseases that involves the formation of toxic protein deposits that kill nerve cells and damage the brain. In Alzheimer's disease (AD), this involves the formation of toxic amyloid β aggregates as well as the intra-neuronal accumulation of deposits made by a protein called Tau. Tau is implicated in AD as well as several other dementias collectively referred to as the Tauopathies. Blocking the aggregation of Tau proteins is a valid therapeutic strategy to delay the emergence of the disease. In this project, we will study the formation of Tau fibers and Tau aggregation-modulating proteins in order to dissect the molecular and structural bases of their mode of action. We will evaluate the effect of 6 anti-Tau nanobodies (or small single domain antibodies), which each recognizes a specific Tau epitope on the formation of Tau fibers. Tau aggregation kinetics tests in the presence of these anti-Tau nanobodies (Nbs) will allow a mechanistic analysis of their inhibition activity. We will use in vitro methodologies that allow the formation of fibers whose structure is similar to the structure of Tau present in the human brain. On the other hand, recent studies show the ability of Tau to generate a liquid-liquid phase separation which leads to the formation of “drops”. This could be an early event in the formation of Tau fibers. This condensation effect can be reproduced in vitro by “crowding” agents such as polyethylene glycol. We will test whether the 6 anti-Tau nanobodies we have are able to interfere with this mechanism and reduce the formation of condensates. These experiments will also allow to understand which Tau regions are involved in the formation of its condensates. This project provides information regarding the formation and structure of Tau fibers, which are necessary to consider molecules capable of blocking this process.

Title : **Identification of motifs of the membrane protein of the severe acute respiratory syndrome coronavirus-2 involved in viral assembly.**

Tutor : **Sandrine BELOUZARD**, Centre d'Infection et d'Immunité de Lille, Equipe virologie moléculaire et cellulaire. Email : sandrine.belouzard@ibl.cnrs.fr

Coronaviruses are enveloped viruses with a positive single-stranded RNA. Three viral proteins are anchored in the envelope : the spike protein (S), the small envelope protein (E) and the membrane protein (M). The spike protein is involved in viral entry whereas M and E are involved in viral assembly. The M protein is the most abundant component of the viral envelope, it is considered as the motor of viral assembly. Indeed, the M protein has been shown to interact with all the others structural proteins and the co-expression of M and E is sufficient to induce the production of virus-like particles (VLPs). Coronavirus assembly occurs in the intermediate compartment between the endoplasmic reticulum and the Golgi (ERGIC). Knowledges on the mechanisms of coronavirus morphogenesis are still partial. The aim of this project is to better characterize the role of the M protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in viral assembly. More precisely our goal is to identify intracellular trafficking and protein-protein interaction motifs of the SARS-CoV-2 M protein and their importance in viral assembly.

Title: **Role of FAT10/UBD on Mallory Denk Bodies formation in hepatocytes during NASH development**

Supervisor: **Réjane PAUMELLE-LESTRELIN**. UMR1011 « récepteurs nucléaires, maladies métaboliques et cardiovasculaires. rejane.lestrelin@univ-lille.fr

Non-alcoholic fatty liver disease (NAFLD) affects one third of the general population. NAFLDs are characterized by an intrahepatic accumulation of lipids (steatosis) progressing to non-alcoholic steatohepatitis (NASH) which can lead to the development of cirrhosis and hepatocellular carcinoma (HCC). To date, no effective medical treatment for NASH is available other than lifestyle change or weight loss surgery. Among the various mechanisms involved in the development and progression of NASH, the disruption of degradation pathways leading to the formation of Mallory Denk Bodies (MDB) appears to be a potential mediator of the progression of NASH to cirrhosis and HCC. However, the mechanisms leading to the formation of MDBs during NASH are not yet known. Our transcriptomic analysis of liver biopsies from obese patients with NASH show that the expression of FAT10/UBD correlates positively with the different histological grades of NAFLD. FAT10 is a protein of the "ubiquitin-like" family involved in FATylation processes regulating protein degradation. Interestingly FAT10 play a role in the formation of MDB induced by a chemical agent, DCC, in mice. The Master 2 project therefore aims to determine the role of FAT10 in the formation of Mallory bodies in hepatocytes, in vitro, in models of human hepatocytes and in vivo, in a mouse model developing NASH.

Title: **Role of the nuclear receptor Rev-erbα in angiogenesis**

Supervisor: **Benoit POURCET** – Université de Lille INSERM U1011 Institut Pasteur de Lille CHU Lille EGID – 01 rue du Pr Calmette – 0320877125 benoit.pourcet@univ-lille.fr

Atherosclerosis is a chronic inflammatory disease of large vessels triggered by the accumulation of cholesterol and leukocytes in the vascular wall. During atherogenesis, vascular wall thickening induces local hypoxia and promotes the vasa vasorum expansion by angiogenesis. This neovessels are however immature that promote leakage of lipids and leukocytes and contributes to plaque progression and rupture. The molecular and cellular mechanisms involved in the growth of the perivascular blood network are not known. Reducing its expansion could, however, represent an innovative therapeutic strategy in the treatment of these diseases. Our preliminary data suggest that the nuclear receptor Rev-erb-α controls angiogenesis and intraplaque neovascularization ex vivo and in vivo. This proposal aims to determine the impact of Rev-erb-α in angiogenesis using in vivo and in vitro approaches. For this, angiogenesis will be assessed in vivo by confocal and light sheet microscopy in Rev-erbα-/- mice and their control by analyzing the development of the vascular network of newborn retinas. The role of Rev-erb-α on angiogenic processes will then be analyzed in vitro using 3D spheroid models of cell competition. The pathways involved in angiogenesis will be assessed in tissues and cultured cells by WES and RT-qPCR. This M2R proposal aims to determine the impact of Rev-erb-α in angiogenesis during atherosclerosis and to define the molecular and cellular mechanisms involved.

Title: **RevErbα & IQGAP2 in the gut: a new axis in dietary lipid handling and in the control of postprandial lipemia?**

Supervisor : **Olivier BRIAND** – INSERM U1011 – EGID - Laboratoire JK, Pôle recherche, Faculté de médecine, Lille - 03.20.97.42.11 – olivier.briand@univ-lille.fr

Nuclear receptors are transcription factors that modulate the expression of target genes in response to specific ligands. Among these, Rev-Erbα is highly expressed in the body and participates in energy homeostasis coordinating lipid, carbohydrate and bile acid metabolism with the biological clock. Increased magnitude and duration of post-meal hypertriglyceridemia, or postprandial dyslipidemia, is a cardiovascular risk factor because of its pro-atherogenic and inflammatory nature. In diabetic or obese patients, the overproduction of chylomicrons by the intestine is a major contributor of postprandial dyslipidemia. In our work, we demonstrated the control by Rev-Erbα of key steps of chylomicron metabolism in small intestinal epithelial cells (enterocytes). IQGAP2, a player in lipid metabolism in the liver, is the gene most strongly regulated by Rev-Erbα as revealed by transcriptomic analysis in the Caco-2/TC7 cell line. The use of IQGAP2 ko mice and the silencing of IQGAP2 in vitro have shown that deficiency in this gene is associated with a defect in the activation of autophagy in response to a lipid challenge as well as with an exacerbated cellular storage of lipids. These data suggest a role for IQGAP2 in the control exerted by Rev-Erbα in the enterocyte.
The project we propose for an M2 is part of the investigation of the molecular mechanisms by which the nuclear receptor RevErbα and the protein IQGAP2 control lipid turnover and lipophagy in enterocytes. We then plan, for a thesis project, to characterize this process in a genetically altered mouse model (RevErbα ko intestine-specific). The approaches used are based on cellular and molecular biology techniques (gene and protein expression analysis, indirect immunofluorescence and video microscopy, protein half-life, gene invalidation and overexpression ...). This project is based on an important work in cell culture (filter culture of the human enterocyte line Caco-2/TC7 and murine and human intestinal organoids).

Title: **Novel insights into the treatment of rare inborn errors of glycosylation metabolism**

Supervisor : **François FOULQUIER**, UGSF - Unité de Glycobiologie Structurale et Fonctionnelle, francois.foulquier@univ-lille.fr

Glycosylation consists in the attachment of glycan structures covalently linked to proteins and lipids. An extreme diversity of attachment and glycan structures are found and define the different types of glycosylation including the N-, O-, glycosaminoglycan (GAG) and glycosylphosphatidylinositol (GPI) glycosylation. The regulation of this process is so complex that the importance of these structures was primarily underestimated, and just considered as decorations. Awareness of the crucial involvement of glycosylation in the intricate design of life came later with the discovery of patients suffering from glycosylation defects. To date, this group of diseases is called Congenital Disorders of Glycosylation (CDG) and represent >160 rare genetic diseases of metabolism (1). Our group has identified several new genes involved in these rare diseases particularly one affecting the Golgi manganese homeostasis called TMEM165. Several new variants have been discovered and need to be fully dissected to discover and explore novel cellular pathways that will constitute the basis of exploring manganese based treatments in CDG subtypes. This project offers a unique opportunity to engage directly with clinical and molecular geneticists to better understand the genetic basis and molecular pathogenesis of inherited disorders. We are seeking a highly motivated individual who can address complex questions regarding disease pathogenesis. Interested applicants should send their cover letter, resume to Dr. François Foulquier.

Title: **Research into new biomarkers of diabetes complications in nails: development and validation of a liquid chromatography method coupled with mass- and fluorescence spectrometry**

Supervisor : **Frédéric TESSIER**, U1167 RID-AGE, 03.20.62.35.61, frederic.tessier@univ-lille.fr

Worldwide, the prevalence of diabetes continues to rise and could reach 10% of the world's population by 2040. In addition to regular blood glucose monitoring, diabetic patients are advised to have annual tests to monitor the potential development of complications. Unfortunately, the recommended 3 times per year glycated hemoglobin test is only performed on less than half of the patients. Glycation products (AGEs) are good biomarkers for the early identification of potential diabetes-related complications. Various studies have shown that certain AGEs are predictive of diabetic retinopathy and that AGE levels in blood and skin are predictive of microvascular diseases. The currently used analytical methods quantify some AGEs by invasive measurements or measure the fluorescence of some AGEs on the skin.
For this Master 2 project, the student will participate in the development and validation of a liquid chromatography method coupled to mass- and fluorescence spectrometry to quantify several glycation products in nails. Several methodological issues will need to be elucidated, including the maximum duration and optimal conditions for sample storage and preparation. Method validation will involve the following: linearity, precision, accuracy, specificity, repeatability, limits of detection and quantification and robustness. This project will be based on a sample library of nails from healthy and diabetic subjects, already established in the laboratory. The final objective will be the publication of a scientific paper of our novel analytical method for the quantification of AGEs in human nail clippings.
Recent publication of the laboratory: Jaramillo Ortiz et al. (2021) Biomarkers of disease in human nails: a comprehensive review. Critical reviews in clinical laboratory sciences, 1-17

Title: **Study of FAT10/PPARα interaction during NASH development**

Supervisor: **Audrey HELLEBOID**. UMR1011 – Equipe "Récepteurs nucléaires, maladies métaboliques et cardiovasculaires". audrey.helleboid@univ-lille.fr

The prevalence of non-alcoholic fatty liver disease (NAFLD) is on the rise. NAFLDs are initiated by steatosis progressing to non-alcoholic steatohepatitis (NASH) characterized by inflammation, ballooning of hepatocytes, and sometimes fibrosis which can progress to more serious stages ranging from cirrhosis to hepatocellular carcinoma. No pharmacological treatment is currently available. The laboratory has shown that the activation of PPARα, a nuclear receptor strongly expressed in the liver, known for its anti-inflammatory, anti-fibrotic effects and for promoting lipid metabolism, is a promising therapeutic strategy. However, the gene expression of PPARα as well as its activity are reduced in the livers of patients with NASH, partly explaining the ineffectiveness of PPAR agonists in clinical studies treating NASH. It is therefore crucial to better understand the mechanisms underlying this modulation of PPARα during the progression of NASH. Transcriptomic analysis of liver biopsies from obese patients showed that the expression of the FAT10 (UBD) gene, an ubiquitin-like protein, increases during the progression of NASH, and is inversely correlated with the expression of PPARα. FAT10 is known to be responsible for FATylation controlling the stability/degradation and activity of various proteins. Thus, FAT10 could interact with PPARα to modulate its activity during NASH. Our preliminary results show that FAT10 interacts with PPARα in hepatocytes during NASH progression in vivo in murine and human NASH liver biopsies and in vitro in HepG2 cells and contributes to inhibit PPARα activity by its agonist, pemafibrate in vitro and in vivo. FAT10 could therefore promote the progression of NASH by inducing the degradation and/or deactivation of PPARα, making any therapeutic strategy targeting PPAR ineffective. The Master 2 project therefore aims to study the FAT10/PPARα interaction during the development of NASH in vitro and in vivo in order to contribute to the identification of a new therapeutic treatment.