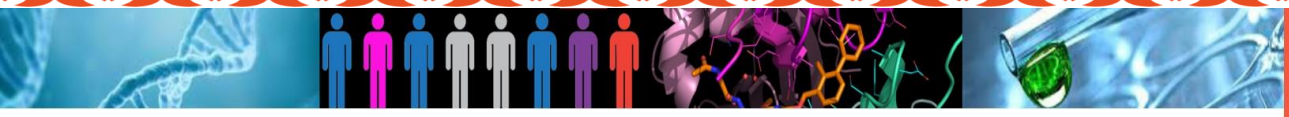
July 3-5, 2023
Lille

# Summer School Graduate Programme "Precision health"



Precision health


## FIRST SUMMER SCHOOL GRADUATE PROGRAMME PRECISION HEALTH

## Breaking Down Barriers: How interdisciplinary approaches shape precision health

how different and complementary disciplines talk to each other to serve precision health, with a particular focus on human and social sciences, the ethical dimension and scientific communication to the public in general.

- Local, national and international speakers,
- Flash talk and poster sessions by students after selection by the scientific comitee (40 seats)
- Social activities, ...

Date:
3-5 July 2023

Location:
Lille

Public:
Students, post-docs, researchers, ingineers, ...

Contact:
graduate-programme-ph@univ-lille.fr

Université de Lille

Egid

PreciDIAB
National Center for Precision Diabetic Medicine

DISTALZ
LABORATOIRE D'EXCELLENCE

FRANCE 2030

## July 3, 2023 → ONCOLille, Bd du Professeur Jules Leclercq, Lille*

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| **14h** | **Welcome Desk & Welcome message** |
| **14h30** | **Discussant: Cyril SOBOLEWSKI, Isabelle WOLOWCZUK**<br>**14h30 – 15h10**<br>**Is predictive medicine raising new ethical challenges?**<br>**Catherine DEKEUWER,** MCU, HDR, Institut de Recherches Philosophiques de Lyon, Univ Lyon<br><br>**15h10 – 15h50**<br>**Shared Responsibilities: Ethical Perspectives on Scientific Communication**<br>**Sébastien CLAEYS,** PU, Sorbonne Université, Espace Ethique île de France<br><br>**15h50-16h - 2 flash talks presented by students**<br>➢ **Dorian MANOUVRIEZ** (PhD student, LIIFE): "*Prediction of the severity in Early-Onset Alzheimer's Disease patients by clustering*"<br>➢ **Valentin LERICQUE** (PhD student, UMR1190 Translational Research for Diabetes): "*Heterogeneity between donors following long-term GABA administration to transdifferentiate human $\alpha$-cells into insulin-secreting $\beta$-cells in vitro and in vivo*" |
| **16h** | **Coffee break** |
| **16h30** | **16h30 – 17h10**<br>**Biologie, médecine, vie : quelles scientificités, quels rapports ?**<br>**Stéphane ZYGART,** PhD teacher in Philosophy, Univ Lille<br><br>**17h10 – 17h50**<br>**Is precision medicine (really) personalized medicine, and what are the ethical issues involved?**<br>**Philippe SABOT,** PU Contemporary philosophy and humanities, Univ Lille<br><br>**17h50-18h - 2 flash talks presented by students**<br>➢ **Emmrich WAKEFORD** (PhD student, UMR1019 Center for Infection and Immunity of Lille): "*Impact of ubiquitination on the propagation of murine Norovirus*"<br>➢ **Emma THEERENS** (PhD student, IMPECS and LilNCog): "*Air pollution-derived ultrafine particles induce ferroptosis in differentiated human dopaminergic neuronal LUHMES cells*" |
| **18h** | **End of conferences** |
| **19h** | **Interdisciplinarity for the taste buds**<br>You are cordially invited to a convivial evening in a restaurant offering typical northern French dishes:<br>**Les 3 Brasseurs - 22 Place de la Gare, 59800 Lille (metro Gare Lille Flandres)** |

## July 4, 2023 → ONCOLille, Bd du Professeur Jules Leclercq*

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| **9h** | **Discussant: Julien CHAPUIS, Martine DUTERQUE**<br>**9h – 9h40**<br>**Multidisciplinary approach to tackle lung cancer**<br>**Alexis CORTOT,** PU, Pneumology and Thoracic Oncology, CANTHER (Efficacy & Resistance to anti-tumor targeted Therapies) CHU Lille, Institut Pasteur de Lille, Univ Lille<br><br>**9h40 – 10h20**<br>**Towards personalized medicine in organe transplantation: focus on the gut microbiome**<br>**Laure BINDELS,** PU, Drug Research Institut Metabolism and Nutrition Research Group UCLouvain, Belgium<br><br>**10h20 – 10h30 - 2 flash talks presented by students**<br>➢ **Marie OOSTERLYNCK** (PhD student, UMR1172 LilNCog): "*Extracellular vesicle-mediated tau propagation: study of extracellular vesicle content and subpopulations*"<br>➢ **Eloïse HAPPERNEGG** (PhD student, IMPECS and LilNCog): "*Role of neurotrophins in triple-negative breast cancer cell adhesion to the Blood-Brain Barrier*" |
| **10h30** | **Coffee break** |
| **11h** | **11h – 11h40**<br>**New Horizons: Gonadotropin-releasing hormone and Cognition**<br>**Vincent PREVOT**, DR1 INSERM, UMR 1172 (Development and Plasticity of the Neuroendocrine Brain), Lille Neuroscience & Cognition, Univ Lille<br><br>**11h40 – 12h20**<br>**Step by step: towards a better understanding of the genetic of Alzheimer's disease**<br>**Jean-Charles LAMBERT,** DR1, Inserm U1167 (Molecular determinants of Alzheimer's disease and relative disorders) Institut Pasteur de Lille<br><br>**12h20 – 12h30 - 2 flash talks presented by students**<br>➢ **Chloé BLONDEL** (PhD student, UMR1011 Nuclear receptors and cardiovascular diseases): "*Regulation of glucose metabolism by the bile acid receptor FXR expressed in the central nervous system*"<br>➢ **Viktor LIENARD** (PhD student, UMR1011 Nuclear receptors and cardiovascular diseases): "*ApoF deficiency is associated with reduced mitochondrial function in the liver*" |

## July 4, 2023→ Science Po Lille, 9 Rue Auguste Angellier**

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| **13h** | **Cocktail lunch** |
| **14h** | **Poster Session**<br>Discussion around posters and evaluation by the committee |
| **17h** | **Debate around the movie " Gattaca " [Andrew Niccol, 1997]**<br>organised by the "Espace de réfléxion éthique des Hauts de France"<br>Screening of the film followed by a debate, round table in public |
| **19h30** | **Cocktail Biers & Cheese** |

## July 5, 2023 → ONCOLille, Bd du Professeur Jules Leclercq*

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| **9h** | **Discussant: Sylvain DUBUCQUOI, Yasmine SEBTI**<br>**9h – 9h40**<br>**A socio-cultural approach to health prevention with vulnerable populations**<br>**Hélène GORGE,** MCU Management Sciences, ILIS, Laboratoire LUMEN (Consumption, Culture and Markets) Univ Lille<br><br>**9h40 – 10h20**<br>**Input of functional genetics into precision medicine in obesity**<br>**Amélie BONNEFOND,** DR2 Inserm, UMR 1283/8199 ((Epi)Functional genomics and Molecular Physiology of Diabetes and Associated Diseases) Univ Lille<br><br>**10h20 – 10h30 - 2 flash talks presented by students**<br>➢ **Bettina RAM** (PhD student, UMR1011 Nuclear receptors and cardiovascular diseases): "*Role of ILc2 in skeletal muscle regeneration*"<br>➢ **Louay BETTAIEB** (PhD student, UMR1011 Nuclear receptors and cardiovascular diseases): "*A novel therapeutic anti-angiogenic strategy targeting dysfunctional CHCHD4/AIF pathway*" |
| **10h30** | **Coffee break** |
| **11h** | **11h – 11h40**<br>**Could there be a mechanical basis of memory and memory loss?**<br>**Ben GOULT,** PU Biochemistry, School of Biosciences, University of Kent, Canterbury, UK<br><br>**11h40 – 12h20**<br>**Stress granules: a new target for hepatocellular carcinoma?**<br>**Cyril SOBOLEWSKI,** CPJ Senior scientist/Team leader BioMedical research. INFINITE Inserm U1286, CHU, Univ Lille |
| **12h20** | **Prizes for bests posters and flash talks** |
| **12h40** | **Lunch / End of the event** |

* Metro line 1, CHR Oscar Lambret
** Metro line 1, République Beaux-Arts

**Contact**: graduate-programme-ph@univ-lille.fr

# SPEAKERS ABSTRACTS

## Catherine DEKEUWER

*MCU, HDR, Institut de Recherches Philosophiques de Lyon, Univ Lyon*

### Is predictive medicine raising new ethical challenges?

NGS were introduced as a « technological revolution ». sequencing the exome is now easier, cheaper and faster. That leads to a « medical revolution »: the goal of genomic medicine is to optimize diagnosis, prevention and therapy by knowledge of the individual genetic variations. I will expose a pluridisciplinary research on the introduction of NGS in Predictive Medicine

## Sébastien CLAEYS

*Adjunct professor at Sorbonne Université, in charge of communication and public debate at Espace éthique Île-de-France (Great Paris Center for Ethics).*

### Shared Responsibilities: Ethical Perspectives on Scientific Communication

We often tend to think that the results of scientific research will be imposed on society and politicians. However, disseminating scientific information requires a mediation process that deserves to be ethically questioned.

## Stéphane ZYGART

*PhD in philosophy, teaches at the University of Lille and at Science Po Lille, associate member of UMR STL and a member of ERER in Hauts-de-France.*

### Biologie, Médecine, vie : quelles scientificités, quels rapports ?

His work focuses on the epistemology of medicine and psychiatry, medical ethics and health policies. His most recent publication is "Vie, activité, handicap : réadaptations et normes médico-sociales" (Éditions de la Sorbonne, 2023). This talk will explore the possible links between medicine and biology in the context of precision health.

## Philippe SABOT

*Professeur de philosophie contemporaine et sciences humaines (U. Lille), UMR 8163 Savoirs, textes, langage, Coordinateur du Hub Société(s) de l'Initiative d'Excellence de l'université de Lille*

### Is precision medicine (really) personalized medicine, and what are the ethical issues involved?

In this presentation, I'd like to discuss some of the ethical issues associated with the development of the paradigm of precision medicine. These issues focus on the personalization dimension that is traditionally attached to this paradigm. In a sense, hasn't precision medicine become impersonal, since the personalization of therapies refers more to the identification of the patient's genetic profile than to the overall consideration of his or her "personality"? There is also the question of what to do with all the data collected and processed, particularly in the context of genome sequencing. Finally, I shall examine the responsibility of patients who are targeted by innovative therapies but who, in return, are required to adapt their lifestyle to their molecular profile.

## Alexis B. CORTOT

*MD, PhD, Head of the Thoracic Oncology Department, CHU Lille ; Professor of Pneumology, University of Lille ; Target team (Efficacy and Resistance to anti-tumor targeted therapies), CANTHER Unit (Cancer heterogeneity, plasticity, and resistance to therapies), ONCOLille Institute*

### Multidisciplinary approach to tackle lung cancer

Lung cancer is a major global health problem, and its management requires the collaboration and expertise of a variety of healthcare professionals from different disciplines. From epidemiology to psychology, from biology to the clinic, major advances have been made in recent years, enabling a quantum leap in lung cancer treatment. Based on concrete projects carried out in Lille and elsewhere, this presentation will show how these seemingly distant approaches have contributed to a better understanding of lung cancer and improved patient care. Special attention will be paid to the role of deregulation of the MET pathway and ways of overcoming it.

## Laure BINDELS

*Prof, Lecturer at the Université catholique de Louvain, WELBIO investigator*

### Towards personalized medicine in organ transplantation: focus on the gut microbiome

The gut microbiome is now heavily explored for its involvement in drug pharmacology, both at pharmacokinetics and pharmacodynamic levels. In this talk, I will introduce key direct and indirect mechanisms by which the gut microbiota can modulate the PK of drugs. I will then present our recent results on the contribution of the gut microbiota to tacrolimus pharmacokinetics. Tacrolimus is a immunosuppressive drug used following transplantation to avoid organ rejection. Clinical use of tacrolimus is complexified by its narrow therapeutic index and a high pharmacokinetic variability (both inter- and intra-patient). I will address two key questions during this talk: (i) does oral TAC administration affect the gut microbiota composition? (ii) does the gut microbiota play a role in TAC PK in vivo, and if yes, how?

## Vincent PREVOT

*Univ. Lille, Inserm, CHU Lille, Laboratory of Development and Plasticity of the Neuroendocrine Brain, Lille Neuroscience & Cognition, UMR_S1172, Lille, France*

### New Horizons: Gonadotropin-releasing hormone and Cognition

Pulsatile secretion of gonadotropin-releasing hormone (GnRH) is essential for activating and maintaining the function of the hypothalamic-pituitary-gonadal (HPG) axis, which controls the onset of puberty and fertility. Two provocative recent studies suggest that, in addition to controlling reproduction, the neurons in the brain that produce GnRH are also involved in the control of postnatal brain maturation, odor discrimination, and adult cognition. I will discuss the development and establishment of the GnRH system, and especially the importance of its first postnatal activation, a phenomenon known as minipuberty, to its later functions, reproductive and non-reproductive. In addition, I will discuss the beneficial effects of restoring physiological, i.e. pulsatile, GnRH levels on olfactory and cognitive alterations in Down syndrome and preclinical models of Alzheimer's disease, as well as the risks associated with long-term continuous, i.e. non-physiological, GnRH administration in certain disorders. Finally, I'll discuss the intriguing possibility that pulsatile GnRH therapy may hold therapeutic potential for the management of some neurodevelopmental cognitive disorders as well as pathological aging in the elderly.

## Jean-Charles LAMBERT

*PhD, Inserm Research Director, Team Leader "Search for molecular determinants of Alzheimer's disease and related disorders" UMR1167, Institut Pasteur de LIlle*

### Step by step: towards a better understanding of the genetic of Alzheimer's disease

Alzheimer's disease (AD) is the first cause of dementia wordwide and already represents a major problem of public health. This disease is characterized by intracellular aggregation of abnormally hyperphosphorylated tau protein and extracellular accumulation of amyloid beta (Aβ) in plaques.

A strong genetic predisposition is present in the common forms of AD, and in view of this major genetic component, identification of genetics of these common forms has been a major objective to better understand the AD pathophysiological processes.

Like most multifactorial diseases, genome-wide association studies (GWASs) and high-throughput sequencing have substantially improved our understanding of the genomics of AD over the last decade. Recently, we completed (via the European Alzheimer's Disease BioBank (EADB) consortium) a discovery meta-analysis of GWASs based on a new large case-control study and previous GWASs. In addition to the 33 known AD loci, we identified 42 new loci associated with the risk of AD. In addition, by an extensive dataset of whole exome sequencing data, we reported a significant association of predicted detrimental rare variants in six AD risk genes which are all GWAS signals. This finding provides further evidence of the crucial role these genes and their associated functions play in the pathophysiological processes of AD. Additionally, these genetic data enabled the development of a genetic risk score, which can differentiate subpopulations at risk of AD/dementia in large population-based studies. Currently, this risk score is being tested in diverse multi-ancestry populations.

## Hélène GORGE

*MCU, HDR, Management sciences, LUMEN research lab (ULR 4999), Univ Lille*

### A socio-cultural approach to health prevention with vulnerable populations

The increasing request for pluridisciplinary health research projects has put forward the importance of including perspectives from social and human sciences into research programs.
In this presentation, we will overview the purposes and outcomes of social and human sciences when studying health and healthcare issues through specific research projects cases.

## Amélie BONNEFOND

*DR2 Inserm - UMR 1283/8199 (Epi) Functional genomics and Molecular Physiology of Diabetes and Associated Diseases Univ Lille.*

### Input of functional genetics into precision medicine in obesity

Obesity, whose prevalence continues to rise, is a multifactorial disease with a strong genetic component. While common obesity is defined as a polygenic disease, monogenic obesity is caused by the presence of a single mutation. Genes related to monogenic forms of obesity are mainly involved in the leptin-melanocortin pathway that regulates appetite. The identification of these genes has led to the development of a new treatment for patients with monogenic obesity, called setmelanotide. Our team has been studying genetic factors associated with obesity for many years. Through recent studies, we have demonstrated the importance of functional genetics, which combines genetic analyses with in vitro functional analyses, in identifying individuals with obesity who may be candidates for precision medicine.

## Ben GOULT

*PU Biochemistry, School of Biosciences, University of Kent, Canterbury, UK.*

### Could there be a mechanical basis of memory and memory loss?

The aim of this talk is to discuss the emerging appreciation that physical forces play a major role in coordinating brain activity. Our research has found that one of the essential synaptic scaffold proteins, talin, which mediates the linkage between the extracellular matrix and the cytoskeleton within the synapse, is mechanosensitive. Here I talk about the ability to experimentally write/store/compute information in the shape of these talin molecules. Talin contains 13 force-dependent switches that are able to store binary information persistently, which can be written/updated using small changes in mechanical force. Having these memory molecules installed in each and every synapse raises the possibility that they might be used to organise the synapse to control the activity in a way that encodes information. Lastly, the talk will discuss the idea that if memories are physical in nature, written in the shape of memory molecules, then this information could be lost if the protein networks get disrupted. Furthermore, as the proteins are located around the edge of the synapse, they might be susceptible to getting clogged up, and any disturbance of switch patterns would corrupt the coding and scramble the information stored, leading to memory loss. Abnormal accumulation of amyloid-β and tau protein is linked to the memory loss and cognitive decline seen in Alzheimer's disease and amyloid-β has been proposed to disrupt the mechanical integrity of synapses leading to loss of memory. Lastly, we have identified a new class of epilepsy which is caused by mutations in talin and the enzymes that interact with it.

Barnett S and Goult BT. (2022) The MeshCODE to scale – Visualising synaptic binary information. *Frontiers in Cellular Neuroscience*. 16:1014629 PMID: 36467609
Goult BT (2021) The mechanical basis of memory – the MeshCODE theory. *Frontiers in Molecular Neuroscience* 14:592951 PMID: 3371664

## Cyril SOBOLEWSKI

*Ph.D, Junior Professor (Hub-Precision Health) / team leader, U1286-INFINITE, University of Lille*
*cyril.sobolewski@univ-lille.fr*

### Stress granules: a new target for hepatocellular carcinoma?

Trans-acting factors controlling the fate of mRNAs (e.g, miRNA, RNA-binding proteins) are critical regulators of the expression of oncogenes (ONC) and tumor suppressors (TS) in hepatocellular carcinoma (HCC). Among them, Adenylate-Uridylate-rich elements binding proteins (AUBPs) have been involved in the post-transcriptional regulation of key cancer cell factors. AUBPs bind to the 3'UTR of target mRNAs and control their decay and/or translation through processes involving their recruitment into small cytoplasmic compartments, such as stress granules (SGs). SGs are small membrane-free cytosolic liquid-phase ordered entities in which mRNAs are protected and translationally silenced during cellular adaptation to harmful conditions (e.g, hypoxia, oxidative stress). Increasing evidence indicates that SG assembly may significantly contribute to the development of metabolic and inflammatory diseases, as well as cancers. However, the role of SGs in chronic liver diseases (e.g., Non-Alcoholic Fatty Liver Disease) and HCC remains totally unknown. Our recent work has highlighted that the SG component TIA1, and SG formation are critical features of hepatocarcinogenesis, involved in several cancerous hallmarks, including cancer cells proliferation, migration/invasion and chemoresistance. Modulating SG assembly/disassembly or targeting the expression/activity of specific SG components, may therefore represent an appealing approach to treat hepatic disorders and potentially cancer.

# FLASH TALK N°1 - POSTER N°1

## Prediction of the severity in Early-Onset Alzheimer's Disease patients by clustering

**Dorian Manouvriez**, Vincent Roca, Cécile Bordier, Thibaud Lebouvier, Florence Pasquier, Grégory Kuchcinski, Renaud Lopes

*LIIFE - Lille In vivo Imaging and Functional Exploration, Univ Lille*

**Objective**: BrainAge in Early-Onset Alzheimer's Disease (EOAD) has been shown to be a biomarker associated with the severity of the disease. The aim of this study was to cluster patients according to their BrainAge and show that clusters can distinguish fast and slow decliners.

**Materials and Methods**: 174 participants who met the criteria for EOAD (≤ 65 years) were included at baseline and followed-up each year. Participants were examined neuropsychologically and clinically and got structural magnetic resonance images (MRI). 3D-T1 MRI were fed into a pre-trained BrainAge algorithm in order to perform KMeans Clustering on the last layer (before age prediction). At baseline, intergroup differences were assessed by Wilcoxon rank sum tests or Chi-Squared tests and linear models with covariate corrections were used for neuropsychological scores and brain volumes. Longitudinal analyses were made using linear mixed-effect models. Patient kept same cluster at baseline and during the follow-up.

**Results**: Sex, age and disease duration were correlated with the clusters. Patients among cluster with the higher BrainAge had low Mini-Mental State Examination (MMSE) scores 14.37 ± 7.08 and high Clinical Dementia Rating Sum of Boxes (CDR-SoB) 7.83 ± 4.25 compared to patients from the lower BrainAge Cluster with MMSE at 19.19 ± 4.76 and CDR-SoB at 5.93 ± 3.44. Longitudinal analyses showed that development of the disease was signicatively different between clusters (rate of cognitive decline higher in old BrainAge cluster) and revealed fast and slow decliner patterns.

**Conclusion**: Clustering was able to find out clinical attributes of the severity of the disease and also distinguished fast and slow decliners from participants.

## FLASH TALK N°2 - POSTER N°2

# Heterogeneity between donors following long-term GABA administration to transdifferentiate human α-cells into insulin-secreting β-cells *in vitro* and *in vivo*

**Valentin Lericque**[1], Gianni Pasquetti[1,2], Julien Thévenet[1,2], Nathalie Delalleau[1,2], Valery Gmyr[1,2], Caroline Bonner[1,3], Thomas Hubert[2], François Pattou[1,2,4], Marie-Christine Vantyghem[2,5] and Julie Kerr-Conte[1,2].

*[1]Université de Lille, Lille, France ; [2]INSERM U1190, Translational Research for Diabetes, EGID, Lille, France; [3]Institut Pasteur de Lille, Lille, France ; [4]Service de Chirurgie de l'Obésité, CHU de Lille, Lille, France ; [5]Service d'Endocrinologie, CHU de Lille, Lille, France*

**Background:** treatment against diabetes must be cheap and accessible even to third-world countries. Y-aminobutyric acid (GABA) induces conversion of α-cells to β-cells by nucleocytoplasmic translocation of α-cell transcription factor, Aristaless Related Homeobox (ARX) in murine and human islets *in vitro* and *in vivo*. Murine studies are controversial and only one publication confirms GABA conversion of human studies (n=1). The aim is to confirm the effect of GABA on more human islets *in vitro* and *in vivo* and understand the heterogeneity of response.

**Methods**: Human islets were used in agreement with « Agence de la BioMédecine ». *In vitro*, islets were cultured ± GABA (50µM) in 3D for 15 days (n=6) or 30 days (n=3). *In vivo*, islets (n=7) were transplanted into immunodeficient mice. GABA (20µM) was administered daily by intraperitoneal injection for 28 days (n=6 mice: 3 Control and 3 Treated) with weekly monitoring of blood glucose, weight and human C-peptide levels. Quantifications were performed by immunofluorescence and imaging software.

**Results**: GABA induced a slight conversion of α-cells to human β-cells: *In vitro*, the percentage of conversion represents 5.74% ($p<0.01$) after 15 days and 4.44% ($p<0.01$) after 28 days. *In vivo,* the percentage of conversion represents 3.17% ($p<0.01$). A heterogeneity between donors was observed: 66.66% responders after 15 days, 100% after 28 days *in vitro* and 57.14% *in vivo*. In 1 month, GABA had no impact on blood glucose, weight and human C-peptide levels ($p>0.05$). Moreover, GABA increased the translocation of ARX (2.01%; p=0,2958) and the number of Nkx6.1+β-cells (2.57%; p=0,1858). Finally, GABA could induce α-cells neogenesis in duct cells (in progress).

**Conclusions**: The effect of GABA on the transdifferentiation of α-cells into β-cells in human islets appears moderate and heterogeneous between donors. Future studies will provide more evidence on the biological activity of GABA as well as on the identification of donor characteristics that may influence the response to GABA.

# FLASH TALK N°3 - POSTER N°3

## Impact of ubiquitination on the propagation of murine Norovirus

**Emmrich WAKEFORD**, Frank LAFONT, Ghaffar MUHARRAM

*CIIL - U1019-UMR9017, Institut Pasteur de Lille, team "Cellular Microbiology and Physics of infection" Lille France*

The Norovirus, a small, non-enveloped single stranded RNA (+) member of the Caliciviridae family, is one of the mains causes of gastroenteritis worldwide resulting in a high human and socioeconomic burden. Noroviral infections trigger the activation of the innate immune system. Ubiquitination is an ATP-dependent multistep posttranslational process involved in the regulation of some of these immune responses. Indeed, polyubiquitin chains can be formed on a given target's lysine residue. The fate of those ubiquitinated proteins is determined by the type of chain produced through the addition of successive ubiquitin on the preceding ubiquitin's lysin residue. To assess the impact of polyubiquitination on the viral lifecycle of the murine norovirus (MNoV) in the macrophage cell line Raw264.7, several stable cell lines were generated by transfection of various ubiquitin proteins fused with a YFP tag, followed by FACS and geneticin selection. These cell lines were subsequently infected with the MNoV_S99 strain and multiple analyses were then carried out to study how the alteration of polyubiquitin chain formation via the lysin 29 or 48 or 63 in comparison with WT ubiquitin, where all chains can be formed, affect the noroviral cycle. Using immunofluorescence and western blot techniques, we show a reduced expression of the viral markers VP1, NS5 and double-stranded RNA in cells where the formation of polyubiquitin chains via lysine 48 is abrogated. Using the TCID50 titration method, we further confirmed a dramatic drop of norovirus production in these cells. The inactivating mutation on lysine 29 or 63 have no such impact. Hence, our results suggest a significantly negative effect on the murine norovirus propagation in cells where the polyubiquitin chain formation via the lysine at position 48 of ubiquitin is impeded.

## FLASH TALK N°4 - POSTER N°4

# Air pollution-derived ultrafine particles induce ferroptosis in differentiated human dopaminergic neuronal LUHMES cells

**E. Theerens**[1, 2], O. Simonin[1], H. Bouchaoui[1, 2], A. Jonneaux [2], F. Gouel [2], J.-C. Devedjian[2], J.-M. Lo Guidice[1], D. Devos[2], A.-S. Rolland[2], G. Garçon[1].

[1] *Univ. Lille, CHU Lille, Institut Pasteur de Lille, ULR4483-IMPECS, Lille, France ;* [2]*Univ. Lille, Inserm, CHU Lille, U1172 LilNCog, Lille, France*

**Purpose:** Parkinson's disease (PD) is characterized by a predominant regulated cell death (RCD) of dopaminergic neurons of the Substantia Nigra pars compacta. Several forms of necroptosis have been described including ferroptosis which seems particularly prevalent. This iron-dependent RCD is characterized by high levels of intracellular iron and lipid peroxidation. We assessed whether ultrafine particles (UFP) could induce neuronal cell death.

**Methods:** Lund human mesencephalic (LUHMES) cells differentiated into mature dopamine-like neurons were exposed to 2 and 10µg/cm² of UFP for 24h, whereafter intracellular iron storage (ferritin), lipid peroxidation (reactive oxygen species: ROS; 4-hydroxynonenal: 4-HNE, glutathione status, glutathione peroxidase activity: GPx) and protection by some specific inhibitors (liproxstatin-1: LPX, deferiprone: DFP) were investigated, through immunological and biochemical assays. The acquired phenotype was compared to a standard in vitro PD model, i.e., 1-methyl-4 phenylpyridinium (MPP+) inducer. Non-parametric Mann-Whitney U-test was used to look at statistical difference vs negative controls ($p < 0.05$).

**Results:** Our results indicated that LUHMES cells died after UFP exposure with a corresponding lethal dose at 10% of 10 µg/cm². Significant increases in 4-HNE, glutathione oxidation and GPX activity were observed after UFP exposure, thereby reflecting a high level of ROS production and lipid peroxidation. Even more, LPX and DFP prevented lipid peroxidation and neuronal cell death after UFP exposure, thereby reinforcing that these cells mostly died by ferroptosis. To conclude, these results showed that UFP-exposed dopaminergic neurons died by ferroptosis. Interestingly UFP and MPP+-exposures both led to the same results, supporting the hypothesis that UFP could contribute to the development of a PD phenotype in differentiated LUHMES cells. Those results gave perspective for an in vivo study, what is currently being conducted.

# FLASH TALK N°5 - POSTER N°5

## Extracellular vesicle-mediated tau propagation: study of extracellular vesicle content and subpopulations

**Marie Oosterlynck**[1], Elodie Leroux[1], Balasubramaniam Namasivayam[1], Romain Perbet[1], Raphaëlle Caillierez[1], Anne Loyens[1], Elian Dupre[2], Soulaimane Aboulouard[3], Christophe Lefebvre[3], Vincent Deramecourt[1], Susanna Schraen-Maschke[1], Luc Buée[1] and Morvane Colin[1]

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**State of the art:** In Alzheimer's disease (AD), Progressive Supranuclear Palsy (PSP), and Pick's disease (PiD), neurodegeneration progresses in a hierarchical manner specific to the tauopathy, which may be associated with prion-like propagation of seed-competent tau species spreading from cell to cell. Extracellular vesicles (EV) are unique intercellular delivery vehicles. Among tauopathies, it has been demonstrated that brain-derived EV (BD-EV) from AD, PSP and PiD patients have a heterogeneous tau seeding capacity. The BD-EV of AD patients clearly contain pathological tau species that can induce tau seeding *in vitro* and transmit tau pathology *in vivo*[1,2]. This suggest an implication of EV in the prion-like propagation of tau pathology. Hence, our first aim is to identify tau proteoforms inside EV responsible for this tau seeding capacity. In parallel, we aim to define which EV subpopulations contain seed-competent tau. For this, a comparative study between small EV (SEV) and large EV (LEV) was done.

**Methodology**: AD, PSP, PiD and non-demented control brain extracts were obtained from the Lille Neurobank. The brain-derived fluid was obtained by enzymatic brain dissociation, after which size exclusion chromatography allows EV purification. Purified EV were lysed and tau immunocapture followed by mass spectrometry allowed the identification of tau peptides inside EV among tauopathies. While, progressive centrifugation and ultracentrifugation steps enabled the separation of LEV (>150 nm) and SEV (30-150 nm). They were characterized using Nanoparticle Tracking Analysis and mass spectrometry. Their seeding capacity was studied using a FRET based biosensor cell assay[3].

**Results**: All tau isoforms were detected inside EV, with two enriched tau peptides specific to AD. LEV and SEV subpopulations are characterized with specific expressed proteins and related biological pathways. LEV have a higher *in vitro* seeding capacity than SEV, although the heterogeneity of this seeding leads us to further stratify LEV. This will be done based on 19 transmembrane protein markers identified on LEV allowing immunoselection to decipher their seeding capacity *in vitro* and *in vivo*.

**Conclusion & future**: Proteomic of tau inside EV enabled identification of enriched peptides in AD. Next, the seeding capacity of these peptides will be analyzed *in vitro*.
LEV and SEV stratification suggest a differential seeding capacity of EV subpopulations. To further validate the high-seeding capacity of particular EV subpopulations, *in vivo* studies are planned. Additionally, EV stratification based on AD-specific transmembrane marker proteins and the cell type of origin, will provide new insights into the involvement of EV in the propagation of tau pathology.

1- Ruan *et al.,* Alzheimer's disease brain-derived extracellular vesicles spread tau pathology in interneurons. *Brain* ***2021***, 144, 288-309
2- Leroux *et al.,* Extracellular vesicles: Major actors of heterogeneity in tau spreading among human tauopathies. *Mol Ther* **2022**, *30*,782-797
3- Holmes *et al.,* Proteopathic tau seeding predicts tauopathy in vivo. *Proc Natl Acad Sci,* **2014,** 111(41), E4376-E4385

# FLASH TALK N°6 - POSTER N°6

## Role of neurotrophins in triple-negative breast cancer cell adhesion to the Blood-Brain Barrier

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**Scientific context:** With more than two million new cases and 685,000 deaths worldwide in 2020, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women. The majority of these deaths are due to the metastatic progression of the disease, which is associated with a poor prognosis when it occurs in the brain and, unfortunately, remains largely incurable. Patients with triple-negative (TN) breast cancer are at high risk of developing brain metastases, with median survival after diagnosis not exceeding 6 months.

**Objectives:** Due to the lack of targeted therapy and the aggressiveness of the TN subtype, it is necessary to identify the cellular and molecular protagonists involved in the different steps of brain metastasis development. In order to act as early as possible, this work focuses on the earliest step, which is cancer cell adhesion to the BBB.

**Materials & methods:** A human *in vitro* BBB model consisting of brain-like endothelial cells co-cultured with brain pericytes incubated TN breast cancer cells was used to study the adhesion process to the BBB.

**Results & discussion:** Interestingly, using this model, we found that neurotrophin promotes adhesion to the BBB of cancer cells overexpressing neurotrophin receptor (NTR) and it involves NTR co-receptor. Moreover, we found that neurotrophin increases the expression of NTR and its co-receptor on endothelial cells membrane, it remains to determine their involvement in the increase of cancer cell adhesion.

**Conclusion & perspectives:** Overall, these data provide evidence that neurotrophin and its receptor are implicated in TN cancer cell adhesion to the BBB. Elucidate more precisely mechanisms implicated in this process and downstream steps, including protagonists involved at the endothelium level, would help elaborate new therapeutic strategies to prevent cancer cells from reaching the brain and developing brain metastases.

# FLASH TALK N°7 - POSTER N°7

## Regulation of glucose metabolism by the bile acid receptor FXR expressed in the central nervous system

**Chloé Blondel** [1,2,3,4], Emilie Nicolas [1,2,3,4], Emilie Dorchies [1,2,3,4], Emmanuelle Vallez [1,2,3,4], Cyril Bourouh [1,2,3,4], Emilie Caron[5], Bart Staels [1,2,3,4], Kadiombo Bantubungi[1,2,3,4]

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**Scientific context:** Expressed in different peripheral organs, the bile acid (BA) nuclear receptor FXR is known to mediate the BA effects on glucose metabolism, hence impacting type 2 diabetes. For instance, FXR activation, through gene expression, regulates hepatic glucose production (HGP). In addition to its indisputable action on peripheral organs, insulin also acts on several hypothalamic neuronal circuits to control peripheral glucose homeostasis. Indeed, hypothalamic insulin signaling is necessary for optimal suppression of HGP by acting on vagal innervation of the liver.

**Objective:** With our previous data concerning the FXR hypothalamic expression and its activation on brown adipose tissue function, we hypothesize a new role of FXR in hypothalamic insulin signaling through which it impacts peripheral glucose metabolism.

**Materials and methods:** Using a conditional hypothalamic FXR deletion model (MBH-CRE) by the Cre-Lox technology, we will determine the impact of brain FXR deletion on hypothalamic insulin signaling.

**Results and discussion:** Our preliminary results suggest an enhancement of hypothalamic insulin signaling and increased inhibition of gluconeogenesis in the MBH-CRE mice model.

**Conclusion and perspectives:** The results of our project will provide new insights into the control of peripheral glucose metabolism by brain FXR, impacting type 2 diabetes.

# FLASH TALK N°3 - POSTER N°3

## ApoF deficiency is associated with reduced mitochondrial function in the liver

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**Scientific context:** Non-Alcoholic Fatty Liver Disease (NAFLD) is the most common chronic liver disease worldwide, with its prevalence rising in concert with rates of obesity. NAFLD is characterized by hepatic triglyceride (TG) accumulation, called steatosis. Chronic steatosis induces inflammation and leads to non-alcoholic steatohepatitis. Our group recently reported that hepatic *APOF* (encoding Apolipoprotein F) transcript expression inversely correlates with NAFLD severity in humans.

**Objective:** Determine if *ApoF* deficiency impacts NAFLD development in mice.

**Materials & Methods:** We established a new mouse model deficient for *ApoF* (ApoF-KO). ApoF-KO mice and littermate controls were fed a high-fat diet supplemented with sucrose and cholesterol (HFSC diet) for 22 weeks. After sacrifice, hepatic lipids were measured and gene expression was analyzed by RNAseq. We measured mitochondrial function in primary hepatocytes (PH) from chow-fed ApoF-KO mice and littermate controls with Seahorse.

**Results & discussion:** No changes in body weight, plasma lipids and glycemia were observed between ApoF-KO and control mice on HFSC diet. However, hepatic TG content (-57%) and cholesterol content (-25%) was lower in ApoF-KO compared to controls. Liver transcriptomic analysis revealed decreased expression of mitochondrial genes in ApoF-KO mice compared to control mice on HFSC diet. In addition, PH from chow-fed ApoF-KO mice displayed decreased mitochondrial function (notably decreased spare respiratory capacity) compared to littermate controls, further supporting a role for *ApoF* in the control of hepatic mitochondrial metabolism.

**Conclusions & perspectives:** Our results indicate that *ApoF* deficiency impacts hepatic mitochondrial function and lipid storage. These findings suggest that *ApoF* reduction serves to protect the liver from lipid overload in the context of NAFLD. Further studies are necessary to elucidate the link between *ApoF* expression and mitochondrial function.

# FLASH TALK N°9 - POSTER N°9

## Role of ilc2 in skeletal muscle regeneration

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**Scientific context**: The skeletal muscle has a remarkable capacity to regenerate following injury, elicited by satellite cells (SCs) activation, differentiation, and fusion into new fibers. An early period of inflammation is essential to achieve proper muscle healing. Recently discovered innate lymphoid cells (ILCs)1, 2 and 3 are potent cytokine secretors known for rapid sentinel behavior at the organ-environment interface.

**Objectives**: In the light of data characterizing its beneficial role in tissue repair, we hypothesized that ILC2 might control skeletal muscle regeneration through the modulation of inflammatory responses and/or interactions with SCs.

**Material and Methods**: We used C57/Bl/6J wild type (WT) mice injured with $BaCl_2$ to establish the kinetics of ILC2 infiltration during muscle repair through flow cytometry. To determine ILC2 implication during muscle regeneration we used ILC2-deficient mice (*IL7r*$^{cre/+}$*RORα*$^{fl/fl}$) and their control littermates and performed histological and gene-expression analysis.

**Results and Discussion**: Flow cytometry analysis of ILC2 recruitment in WT mice during muscle regeneration highlighted a peak at day 4 post-injury. In addition, global skeletal muscle regeneration showed a delay in fibers maturation and an increase in fibrosis deposit in ILC2-deficient mice compared to control mice. This was further confirmed by a decrease of mature myosin gene expression and an increase in collagen gene expression upon ILC2 deficiency. However, SCs proliferation 2 days post-injury was not affected by ILC2 deletion. A decrease in total leucocytes and Th2 cytokines was also established.

**Conclusion and perspectives**: In conclusion, we demonstrated that ILC2 deletion in the context of acute injury leads to impaired muscle regeneration associated to fibrosis development. Ongoing single-cell RNA sequencing experiments on ILC2 isolated from injured-muscle will help to decipher how ILC2 impact muscle regeneration.

# FLASH TALK N°10 - POSTER N°10

## A novel therapeutic anti-angiogenic strategy targeting dysfunctional CHCHD4/AIF pathway

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**Scientific context:** Besides being the cellular energetic center, mitochondria are a metabolic crossroad that requires the import of most of their proteome. This import is mediated by an import protein machinery, the core component of which is the conserved oxidoreductase CHCHD4. The substrate proteins of CHCHD4 are implicated in many cellular functions including regulation of mitochondrial metabolism, therefore any alteration of this pathway is associated with cellular dysfunction and ultimately disease. Endothelial cells (ECs) lining blood vessels play an indispensable role in all tissues and when dysfunctional contribute to a variety of diseases. Growing evidences suggest aberrant mitochondrial import machinery in different cell types during disease (e.g. neurons, muscle and cancer cells) however so far, it is unknown whether CHCHD4/AIF activity is also associated with EC dysfunction.

**Objectives:** We dissected the role of CHCHD4/AIF in EC biology. We postulated that aberrant activity of CHCHD4/AIF pathway drives pathological angiogenesis by affecting mitochondrial metabolism and cell function, thus contributing to blood vessel abnormalities.

**Materials & methods:** As model system we used human umbilical vein ECs (HUVECs) which express high levels of CHCHD4. We silenced CHCHD4 in HUVECs and investigated the impact on proliferation, adhesion and migration. We also assessed mitochondrial homeostasis and metabolism by measuring mitochondrial respiration and bioenergetics.

**Results:** CHCHD4 silencing significantly reduced EC proliferation by exerting a small yet consistent long-term cytotoxic effect. This was consistent with a significant reduction of mitochondrial oxygen consumption rate as consequence of downregulation of some of the electron transport chain complexes.

**Conclusions:** CHCHD4 plays a key role in EC physiology. Characterizing this pathway in ECs will contribute to identify novel mechanisms which are altered and can be target in dysfunctional blood vessels.

# POSTER N°11

## Study of the effects of jet lag on brown adipose tissue

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**Scientific context:** Obesity is a global health issue which is linked to other metabolic diseases. The discovery of active brown adipose tissue (BAT) in adult humans has renewed interest in its targeting to treat metabolic diseases. BAT activity is inversely correlated with body mass index and is reduced in obese patients. BAT shows circadian activity, leading to 24-h body temperature variations. Circadian rhythm disruption affects metabolism and cardiovascular health. However, the impact of biological clock alterations on BAT is less understood.

**Objective:** This study investigates the jet lag (JL) effects on BAT in mice.

**Materials & methods:** Mice underwent a 12 h JL with phase inversion every week for 14 weeks and were sacrificed every 3 hours for 24 hours or at a single point after 14, 18 and 34 weeks of JL. Gene expression, morphology and BAT activity were analyzed.

**Results & discussion:** Our results show rhythmic changes in lipid droplets size over 24 h in control mice. This rhythm is altered after jet lag, resulting in an increase in lipid droplets size at all times of the circadian cycle. The impact of jet lag on lipid droplets intensifies over time, gradually increasing lipid droplets size during the different JL durations. Moreover, JL alters mRNA expression of genes involved in lipid metabolism and inflammation. Finally, it reduces the uncoupled respiration of BAT, indicating impaired BAT activity in these conditions.

**Conclusion & perspectives:** All our results suggest that JL induces BAT whitening. More analysis at morphological and transcriptional levels will allow to better understand the underlying mechanisms.

# POSTER N°12

## Place of alkaline phosphatase in the diagnosis of Chronic Histiocytic Intervillositis

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**Scientific context:** Chronic histiocytic intervillositis is a rare and severe disease of the placenta, currently diagnosed only after microscopic examination of the placenta following pregnancy.

**Objective**: The aim of the study was to show the place of maternal total alkaline phosphatase in the diagnosis of this pathology.

**Material & Methods:** Total alkaline phosphatase determinations were collected from pregnant women in Lille between 2011 and 2019. Predictive factors for disease were identified by logistic regression and a factor analysis of mixed data was used to explore diagnoses.

**Results & discussion:** Of 6826 women studied, only 28 had the disease (0.4%). The predictive positive value of chronic histiocytic intervillositis rose progressively from 8.7% to 40.0% as the alkaline phosphatase threshold varied between 3 and 7 MoM. 4 variables were significantly associated with the diagnosis of chronic histiocytic intervillositis : the total alkaline phosphatase assay was the most predictive factor (26-fold increase in the risk of disease). Factor analysis showed a clear discrimination of intervillositis.

**Conclusion & perspectives**: The existence of elevated levels of alkaline phosphatase appears to be the most predictive factor of chronic histiocytic intervillositis. Such an assay could enable diagnosis during pregnancy. Future studies should confirm this first finding and investigate the prognostic value of alkaline phosphatase.

# POSTER N°13

## Adipocyte specific RORa invalidation favors adipocyte hypertrophy in obesogenic conditions

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**Scientific context:** The obesity epidemic is a major public health problem. During obesity, excess energy is stored in white adipose tissue (WAT) which expands by increasing adipocyte size (hypertrophy) and/or number (hyperplasia). While hypertrophy favors metabolic complications, hyperplasia seems protective. Heterogeneous responses are also observed depending WAT depots (subcutaneous WAT (scWAT) vs visceral WAT (vWAT)).

**Objectives:** Identifying the factors controlling WAT plasticity is crucial to limit the deleterious effects of obesity. The nuclear receptor ROR alpha (RORa) regulates glucid and lipid metabolism but its role in mature adipocytes is unclear.

**Materials & methods:** Here, we developed mice in which RORa is specifically invalidated in mature adipocyte (*Rora*$^{AdKO}$), and compared them to their RORa$^{fl/fl}$ littermates after low fat (LF) or an obesity-induced high fat (HF) feeding for 16 weeks.

**Results & discussion:** HF-fed RORa$^{AdKO}$ mice displayed increased scWAT without change in vWAT. This scWAT expansion is characterized with increased expression of hypertrophic markers (*Leptin, Mest*), collagen genes (*Col5a3*, *Col6a2*) and altered expression of lipid metabolism genes (*Apoe, Pla2g5*). Histological analyzes confirmed scWAT hypertrophy in HF-fed RORa$^{AdKO}$ mice.

**Conclusion & perspectives:** Overall, our results indicate that adipocyte specific RORa invalidation impacts adipocyte in a depot-specific manner, favoring hypertrophy and adipocyte fat storage in scWAT during obesity. Further studies are needed to dissect the mechanisms of Rora-induced hypertrophy and its metabolic consequences.

# POSTER N°14

## Regulation of Tau protein phosphorylation by kinase O-GlcNAcylation and its implication in fibrillar aggregation

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Two types of lesions describe Alzheimer's disease (AD): the extraneuronal senile plaques made of Aβ peptides and neurofibrillary tangles constituted by intraneuronal inclusions of hyperphosphorylated Tau proteins[1]. Tau is a microtubule-associated protein. It is an intrinsically disordered protein, which makes it prone to posttranslational modifications. The functions of Tau are regulated by phosphorylation. The hyperphosphorylation is also known to play a role in Tau pathogenesis related to fibrillar aggregation in neuronal disorders, but the mechanism of aggregation is not well known yet. The modulation of Tau pathology by the O-β-N-acetylglucosamine (O-GlcNAc) modification is explored as an alternative strategy to kinase inhibitors in neurodegenerative diseases.

In our laboratory, it has been shown that Tau phosphorylation and aggregation were weakly modulated by O-GlcNAcylation of Tau. It only modulates GSK3β-mediated phosphorylation of the pathological PHF-1 epitope (pS396/pS400/ pS404), as shown by using Nuclear Magnetic Resonance (NMR) spectroscopy. S400 O-GlcNAcylation stabilizes the local conformational changes induced by S404phosphorylation, and decreases the aggregation rate, but does not prevent the fibril formation of phosphorylated Tau.

A hypothesis that O-GlcNAcylation could regulate the activity of kinases phosphorylating Tau, is under consideration to explain the benefits of O-GlcNAc hydrolase (OGA) inhibitors on Tau pathology. GSK3β is a good candidate as an AD-related kinase and a substrate of O-GlcNAc transferase (OGT).

We are investigating the O-GlcNAc modification of GSK3β by using enzymatic and protein engineering approaches, and analyses of the O-GlcNAc modification by chemo-enzymatic labelling and MS/MS.

Our preliminary data indicate the O-GlcNAcylation of the C- and N-terminal disordered regions of the kinase. We further aim to extend the characterisation of the O-GlcNAc profile of GSK3β by using NMR that provides structural information on disordered domains to define their role in the regulation of kinase activity. The functional impact and the mechanism of O-GlcNAc-mediated regulation of kinase activity will be evaluated on the GSK3β-mediated phosphorylation of Tau.

# POSTER N°15

## Role of oxidative stress in obesity-induced cardiac remodeling

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**Introduction**: Lifestyle changes, such as obesity, have led to an increase in the prevalence of cardiovascular disease. It is well known that obesity participate in cardiac remodeling, characterized by hypertrophy and fibrosis. Many studies have shown that Reactive Oxygen Species (ROS) production is increased in obese patients and may contribute to cardiac remodeling.

**Objective:** To identify the mechanisms regulating oxidative stress in obesity-induced cardiac remodeling.

**Methods:** Male C57BL6 mice exposed to a high-fat diet (60%) and neonatal rat cardiomyocytes (NCM) exposed to increasing doses of palmitate (PA) were used. Cardiac hypertrophy and fibrosis were studied by measurement of cell area and expression of pro-hypertrophic and fibrotic genes by qPCR. The levels of antioxidant enzymes and pro- and anti-apoptotic proteins were quantified by western blot.

**Results:** Exposure of mice to the HFD diet (60%) induced a significant increase in body weight, cardiac hypertrophy and fibrosis. As expected, the HFD diet significantly increases catalase expression. I showed for the first time that the HFD diet induces a significant increase in the inactive acetylated form of SOD2, a mitochondrial antioxidant enzyme, that could be regulated by sirtuin deacetylase 3 (SIRT3), whose expression is significantly decreased in this model. In vitro, a low dose of PA (25µM) induces hypertrophy of NCMs whereas a high dose (500µM) leads to cell death. Furthermore, exposure of NCMs to 500µM of PA induces a significant increase in catalase and acetylated SOD2 expression and a significant decrease in SIRT3 expression.

**Conclusion:** Taken together, these results showed, that the HFD and PA treatments induce a significant decrease in mitochondrial antioxidant SOD2 activity associated with cell death. Subsequently, it would be interesting to determine whether increased SIRT3 expression could deacetylate SOD2 and activate it to have a beneficial effect on obesity-induced cardiac mortality.

# POSTER N°16

## Understanding the effect of intracellular metabolic reprogramming of dendritic cells on NASH development

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**Context:** Non-alcoholic fatty liver disease (NAFLD) is a significant health problem caused by triglyceride accumulation in hepatocytes, leading to inflammation and non-alcoholic steatohepatitis (NASH). We found that altered hepatic conventional dendritic cell (cDC) populations are associated with NASH in humans and mice. We hypothesize that metabolic changes in obesity impact hepatic cDC function in NAFLD by affecting their intracellular metabolism.

**Objective:** Identify changes in cDC gene expression in NAFLD and the signals driving their expression.

**Materials and methods:** Single cell RNAseq (scRNAseq) was performed on sorted cDC from livers from chow and NASH-diet fed mice. We used bone-marrow derived DC (BMDC) that can be differentiated into cDC1-like or cDC2-like cells submitted to different metabolic and immune treatments. We measured gene expression using RT-qPCR on *purified RNA from BMDC cultures.*

**Results:** Our scRNAseq results identified a NASH-associated cluster of cDC with markers corresponding to mature regulatory DC (mregDC), including Ccr7, IL12b, Ccl5, Ccl22 and Il4i1.

**Discussion:** Previously, we demonstrated that increased extracellular fatty acids profoundly affect DC immune function, by the modification of their metabolism. Moreover, the mregDC program observed in NASH show different regulation between LPS and LPS+Palmitate simulated cDC with a higher expression of Ccr7, Ccl5 and Ccl22.

**Conclusion & Perspectives:** Together, these results highlight the importance of considering the metabolic environment in understanding the hepatic immune system activation in NAFLD**.** Further investigation will seek to identify metabolic pathways required to induce the mregDC gene program in NAFLD.

# POSTER N°17

## Functional analysis of Alzheimer's disease associated PTK2B gene variants

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Alzheimer's disease (AD) is the main cause of dementia. Genome wide association studies identified the PTK2B gene as an AD risk factor. PTK2B encodes Pyk2, a non-receptor tyrosine kinase highly enriched in neurons. Studies of underlying mechanisms suggest a complex contribution with involvement in amyloid toxicity and tauopathy, combined with possible functional deficits in neurons. To date, it has not been determined which variants of the PTK2B gene influence the development of AD. Bioinformatic analyses and luciferase reporter assays in SY5Y cells suggest that both the rs28834970 and rs755951 variants could modify the PTK2B gene expression, by modulating CEBPβ/δ and CTCF binding, respectively.

The objective is to investigate the impact of rs28834970 and rs755951 on (i) the regulation of PTK2B gene expression, (ii) Aβ-induced synapse loss and excitotoxicity and (iii) Tau hyperphosphorylation in isogenic iPSC-derived human neurons carrying the different allele combinations.

We obtained two different isogenic iPSC lines carrying the different genotypes for the rs28834970 variant. Ongoing EMSAs and ChIP-qPCR experiments assess the ability of this variant to promote the binding of CEBPβ and CEBPδ. PTK2B mRNA and Pyk2 protein levels will be compared between the human induced neurons (hiNs) carrying the different genotypes using RT-qPCR and immunoblotting,respectively. Microfluidic devices will be used to analyze synapse density after exposure of hiNs cultures to Aβ1-42 oligomers, and the PTK2B variants effects on Aβ-induced excitotoxicity will be evaluated using electrical activity recording with a multielectrode array system. Lastly, we will assess the impact of the PTK2B variants on the quantity and phosphorylation state of Tau protein in post- synaptic compartments, using immunofluorescence, subcellular fractionation, and immunoblotting.

This project should clarify how the PTK2B genetic risk factor is involved in the etiological mechanisms of AD.

# POSTER N°18

## Study of the interactions between the Alzheimer's disease genetic risk factors BIN1 and PTK2B

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Alzheimer's disease is the first cause of dementia worldwide. It is characterized by synaptic loss and by two lesions composed of amyloid beta peptides and Tau proteins. The most frequent forms are multifactorial with a major effect of the genetic component. Some results from the lab have shown that BIN1 and PTK2B are two genetic risk factors modulating tau toxicity in Drosophila. Moreover, our collaborators have preliminary data showing an in vitro physical interaction between them. So, we wonder if BIN1 and PTK2B participate in a common signaling pathway, potentially central to the disease.

My thesis consists in understanding if/how BIN1 and PTK2B interact and what is the role of this interaction. First, we are testing the genetic interaction between BIN1 and PTK2B in Drosophila. We use two readouts for this purpose: the rough eye induced by Tau protein and the neuromuscular junction. We test whether independent and simultaneous gain or loss of BIN1 and PTK2B modulate Tau toxicity in the eye. Knowing from the literature that PTK2B knockout have a larger neuromuscular junction size we test in double PTK2B-BIN1 knockout if the loss of BIN1 could modulate this phenotype. In addition, to assess functional conservation in Human, we are testing the co-localisation between BIN1 and PTK2B in human induced neurons. We are currently implementing a proximity ligation assay protocol to answer this objective.

This work will provide a better understanding of the genetic risk factors BIN1 and PTK2B, how they interact and contribute to the disease.

## POSTER N°19

# Microfluidic pump systems: a way to replace animal models to study aortic endothelial cells response and viability to high shear stress

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Severe heart failure leads to the implantation of cardiac assist devices in patients waiting for a heart transplant. These pumps induce a change in the blood flow regime: from a physiological and pulsatile flow to a pathological and continuous flow with higher shear stress, provoking bleedings in half of the patients. Animal models to study the response to different types of flow require surgical procedures and thus, additional training in animal experimentation making those procedures inaccessible to some biologists. In addition, these practices require more animals used because of the development of the surgery protocol and the survival rate of these operations. Besides, large surgical animal models used to study cardiac assist devices provide macroscopic information while only few explorations are feasible at the cellular and molecular level. Now, microfluidic pump system can be used to study the flow in vitro and we tested the IBIDI® pump system to study the response of aortic endothelial cells to high shear stress. The cells were subjected to different flow types with a high pathological shear stress. Plasma (with and without platelets) were perfused into this model to check the response of blood elements to high shear stress and see the relevance of the model. Immunofluorescence and qPCR analyses were also performed to study the inflammatory response and cell viability.

# POSTER N°20

## Interaction of Alzheimer's disease genetic risk factors: Characterization of PYK2 AND BIN1 protein-protein interaction

**Lucy Martin** [1,2], Gang Peng[1,2], François-Xavier Cantrelle[1,2], Emmanuelle Bolle[1,2], Elian Dupré[1,2], Clément Danis[3], Pierre Dourlen[2], Isabelle Landrieu[1,2]

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Although most late-onset Alzheimer's disease (AD) is considered sporadic, there is a strong genetic predisposition. The laboratory has identified more than 70 disease-associated loci, including BIN1 and Pyk2, which may participate in the pathogenesis of AD through signaling pathways involving the protein Tau. However, their physiological role and their involvement in the pathology are not yet clear. We have focused on the interaction of Pyk2 with the BIN1-SH3 domain. The latter is a domain known to mediate protein/protein interactions through the recognition of proline-rich motifs. Pyk2 contains such motifs, within a proline-rich flexible linker (LK2), which could constitute anchoring sites for the SH3 domain.

We have used nuclear magnetic resonance spectroscopy (NMR) to map BIN1-SH3 interaction sites, which matched with two proline-rich peptides within Pyk2-LK2. This interaction was also confirmed between these identified peptides and full-length isoforms 1 and 9 of BIN1, using 2 dimensional NMR spectra of the latter proteins. Then, we next used NMR and surface plasmon resonance spectroscopy (SPR) titrations to determine the affinity of these interactions. We observed discrepancies between the interaction of the Pyk2-LK2 or the isolated peptides with BIN1-SH3 that we are still investigating. Pulldown experiments, using several domains of Pyk2 protein fused to GST (glutathione-S-transferase), confirm the interaction of BIN1 with Pyk2-LK2. In parallel, these experiments were carried out with a paralog of Pyk2: Fak1. Comparison is of interest as Fak1 is not a risk factor of AD.

# POSTER N°21

## Effects of characteristics and circumstances of daily physical activity on glycaemia, controlling for food intake and insulin administrated in children and adolescents with type 1 diabetes

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**Scientific context**: In type 1 diabetes, physical activity (PA) of daily life can disrupt blood glucose balance and cause hypoglycaemic but also, in some circumstances, hyperglycaemic excursions, which both represent barriers to PA commitment. **Objectives**: The aim of the study was to understand the influence of the characteristics of daily-life PA sessions and their circumstances on glycaemia.

**Methods**: 58 children (4-18 years) wore a uniaxial accelerometer and a continuous glucose monitoring system for 7 days. Participants fill in a diary with their structured PA sessions, diet and insulin data. Multiple linear and multinomial logistic regressions were used to explore link between characteristics of PA and glycaemia (during PA, 2 hours of recovery and subsequent night), controlling for initial glycaemia, carbohydrate intake, insulin administered, time of the day, and individual characteristics.

**Results**: Time spent in moderate-to-vigorous PA (MVPA, accelerometery) and even more the duration of reported sessions were predictors of increased time <70mg.dL$^{-1}$ during PA. Both exercise duration and MVPA were predictive of increased time <54mg.dL$^{-1}$ during the following night. During early recovery, time <54mg.dL$^{-1}$ was greater for exercises performed in the afternoon vs. morning. Concerning hyperglycaemia, starting PA far away from a bolus or after consuming high glycaemic index carbohydrates in the previous hour were associated with more time > 180mg.dL$^{-1}$ during PA. However, if the children did another session on the same day before the current exercise, this risk of hyperglycaemia was prevented.

**Conclusion**: Compared with objectively measured MVPA, self-reported PA duration was at least as well accurate predictor of the risk of hypoglycaemia during PA and late recovery, which can thus be useful in practice. Besides, postponing exercise later after the last insulin bolus and decreasing high glycaemic index carbohydrates 1 hour before PA might be effective strategies for preventing hyperglycaemia during PA.

# POSTER N°22

## Synthesis and biological evaluation of 6-substituted quinolines as *Escherichia coli* efflux pump inhibitors

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**Scientific context**: Antimicrobial resistance (AMR) has become a major public health priority leading to 4.95 million deaths in 2019 and estimates predict 10 million annual deaths by 2050.[(a)] One of the most common resistance mechanism is the (over)expression of efflux pumps. The active transport of several classes of antibiotics from the bacteria to outside is mediated by these efflux pumps, in particular AcrAB/TolC which is mainly expressed by Enterobacteriaceae such as *Escherichia coli*.

**Objectives**: To overcome AMR, the aim of the project is to develop AcrB inhibitors to potentiate the activity of a panel of antibiotics. For this purpose, a screening of 1280 fragments was performed on *E. coli* in combination with an antibiotic substrate of this pump and allowed the identification of a hit.[(b)]

**Materials & methods**: The compounds were synthetised according to the procedure described in Plé *et al.*[(b)]

**Results & discussion**: The hit was optimized to obtain a more potent analogue which was co-crystallized with AcrB and was shown to bind to a unique site on the transmembrane domain of this protein. The crystallographic structure confirmed that the piperazine at position 2 and the chlorine atom at position 3 of the quinoline ring were essential for activity. An unexploited region was observed at the bottom of the crystallographic structure, therefore, a phenyl ring, diversely substituted by electro-withdrawing or donating groups, as well as pyridine rings were introduced.

**Conclusions & perspectives**: In order to obtain 6-substituted quinolines, a synthetic pathway was developed with good yields. The screening of the compounds on *E. coli* showed that the substitution by an electron-withdrawing or donating group was tolerated. The aim is now to introduce other heterocycles in order to increase the compound potency.

[(a)] Murray, C. *et al. The Lancet*, **2022**
[(b)] Plé, C. *et al.* Nat Commun. **2022**, *13* (1), 115
* Correspondence: virginie.meurillon.etu@univ-lille.fr

# POSTER N°23

## UDP-GlcNAc quantification and analysis of its prognostic value in the colorectal cancer response to FOLFOX therapy

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**Context:** Colorectal cancer (CRC) is the 3rd most common cancer and is the 2nd cause of death from cancer worldwide. CRC risk factor is higher for obese or diabetic patients. 5-Fluorouracile (5-FU) based therapies are the gold standard treatments for this cancer. Resistance is the cause of the failure of theses therapies. A prognostic tool for response to 5-FU based therapies could allow to classify patients and to administrate more accurate treatments. We study the link between chemoresistance and O-GlcNAcylation, a nutrition-dependent post-translational modification deregulated in CRC. The nucleotide sugar UDP-GlcNAc is the sugar donor of this modification. From the literature and due to structural similarities between 5-FU and UDP-GlcNAc, we hypothesize interference between 5-FU metabolism and UDP-GlcNAc synthesis pathway. UDP-GlcNAc cellular level could be a predictive tool of the CRC response to 5-FU based therapies.

**Objectives:** The master objective was to devise a quantification of UDP-GlcNAc in both human CRC cell lines and FFPE CRC tissue sections to establish a proof of concept of this quantification as a prognostic tool to the FOLFOX chemotherapy (Folinic acid, 5-FU, Oxaliplatin).

**Methods:** We quantified UDP-GlcNAc by capillary electrophoresis from metabolites extracted from 5-FU sensitive or resistant HT29 cancer cells. Cell lines were cultivated or not in medium with high Glc concentration to boost the synthesis of UDP-GlcNAc, while adding FOLFOX or not. In the second part, we quantified UDP-GlcNAc on human colon tumor FFPE sections using MALDI-Orbitrap MS-imaging. We proceeded to develop the key elements of the protocol concerning paraffin removal and choice of the most adapted matrix.

**Results:** We separated UDP-GlcNAc in HT29 cell extracts from which we observed that both Glc boost of HBP and FOLFOX treatment increase level of UDP-GlcNAc. The FOLFOX resistance seems to be correlated to low UDP-GlcNAc level. Glc boost of HBP induced an increase of TS, main FOLFOX's target and an increase of double strand breaks in HT29 sensitive cells, suggesting an impact of HBP modulation on cell response to FOLFOX and a predictive value of UDP-GlcNAc regarding the response to FOLFOX. While testing different deparaffinization, matrixes and MS detection modes we did not detect UDP-GlcNAc from FFPE CRC tissues. These experiments are still in progress.

# POSTER N°24

## Development of an *ex vivo* model to study the regional vulnerability in tauopathies

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**Scientific context:** Tauopathies are a heterogeneous group of neurodegenerative diseases whose common feature is the filamentous inclusion of aggregated and abnormally phosphorylated tau protein in brain cells. Experimental evidence suggests that pathological species of tau may act as seeds leading to *de novo* aggregation of endogenous/physiological tau. It is also proposed that in some tauopathies, including Alzheimer disease (AD), tau seeds can be transferred from cell to cell and spread between different brain regions. This would explain the spatial and temporal progression of tau pathology in some tauopathies such as AD. However, the existence of connections between two regions is not always sufficient to explain the spread of tau pathology, suggesting that some brain cells/regions are more vulnerable than others.

**Objective:** In this scientific context, the objective is to develop an *ex vivo* model to assess the vulnerability of certain brain regions to develop but also to propagate distinct tau pathologies.

**Materials & methods:** We prepare organotypic cultures of brain region slices from mice expressing human tau protein and we apply human brain homogenate, prepared from patients with tauopathies or from control subjects, to these regions. We follow the potentiation of tau lesions by immunolabeling and the *de novo* production of tau seeds *via* FRET assay. In parallel, we evaluate their neuronal extracellular activity by using a microelectrode array system.

**Results & discussion:** We are still setting the parameters to get reproducible tau pathology potentiation. Then we expect to observe variable effects between brain regions exposed to the same experimental conditions. Finally, we will evolve our model toward co-culture experiments to evaluate the inter-regional spread of the tau pathology.

**Conclusion & perspectives:** The setting of such an *ex vivo* system will make it possible to assess the intrinsic capacity of different brain regions to develop and propagate different tau pathologies.

# POSTER N°25

## Establishment and characterization of a tumor-on-chip mimicking the DIPG tumor microenvironment

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Pediatric gliomas are the leading cause of cancer death in children under 14 years of age. Among them, DIPG (Diffuse Intrinsic Pontine Glioma), display a very poor prognosis, with a median survival of less than 1 year. Following the discovery of recurrent H3K27M mutation, new strategies targeting epigenetic mechanisms were proposed, with very promising pre-clinical results. Unfortunately, clinical trials with these strategies have so far failed to improve patient survival.

We hypothesized that this discrepancy between pre-clinical and clinical results could be due to the absence in our models of various key elements of the native tumor microenvironment involved in the response to therapies. This is why we aim to reproduce a hypoxia gradient, common in solid tumors and associated with tumor radio- and chemo-resistance, and to integrate a blood-brain barrier (BBB) which is a major obstacle to the treatment of brain tumors by pharmacological agents.

In order to meet this objective, I developed a tumor-on-a-chip design containing DIPG cells cultured in a 3D matrix, connected thanks to a microfluidic circuit to a functional and validated model of the human BBB (collaboration with the Laboratory of the Hemato-Encephalic Barrier of Lens).

The characterization of this model at the phenotypic and molecular levels is performed by videomicroscopy and immunofluorescence respectively. I validated the implementation of a hypoxia gradient in the tumor-on-chip, correlated with a gradient of cell density and proliferation. Preliminary results indicate heterogeneity in response to pharmacological and radiotherapy treatments. The connection with the BBB model could also be recently validated, and the characterization of the impact of this co-culture on the response to treatments will be performed soon.

# POSTER N°26

## Role of the cannabinoid 1 receptor in the crosstalk between islets of Langerhans and immune cells in a human *ex vivo* model of insulitis

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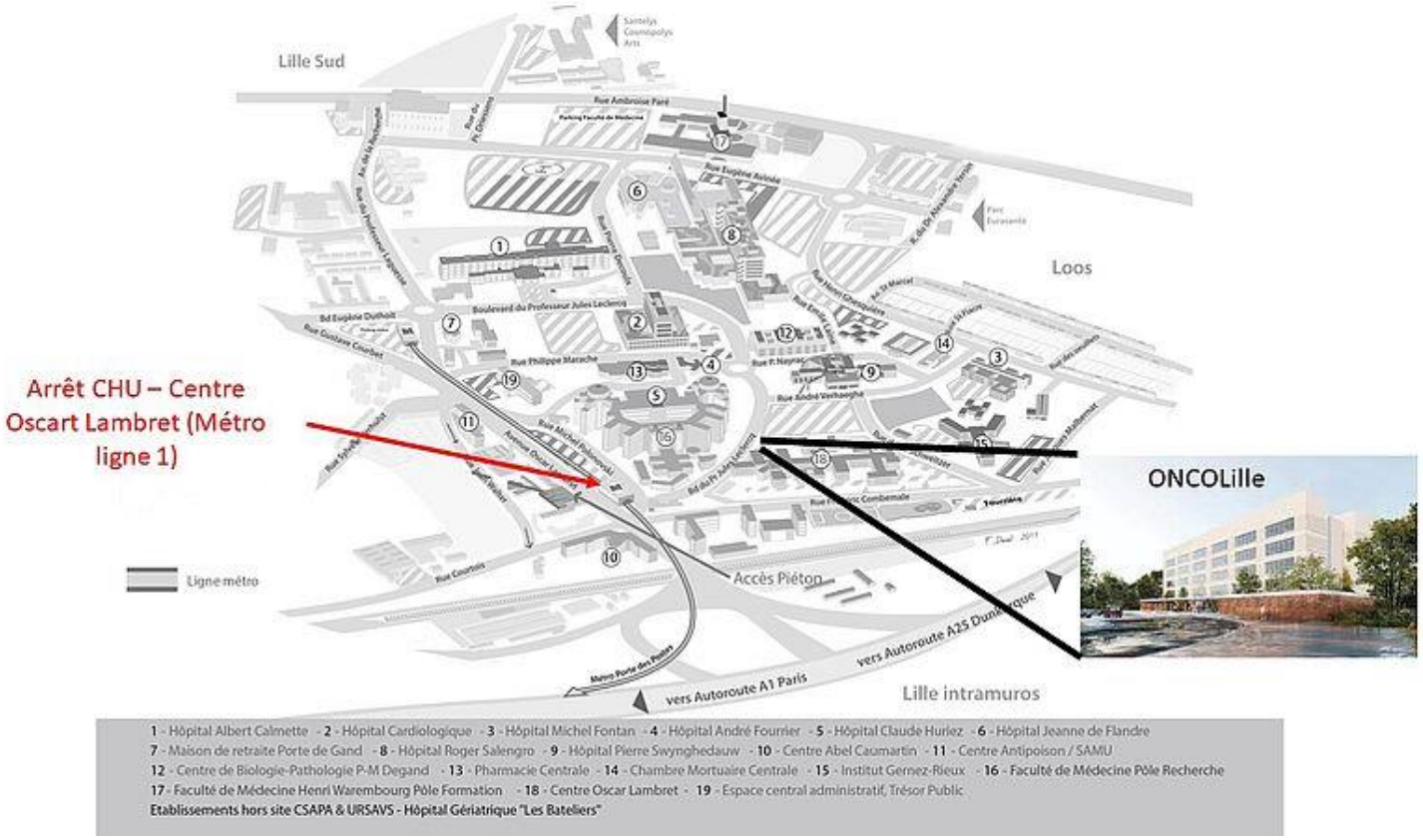
Type 1 diabetes (T1D) is an autoimmune disease, without a cure, affecting mainly children and adolescents. Its pathogenesis results from the progressive infiltration of immune cells into the islets, called insulitis, leading to loss of beta cell (β-cell) mass and insulinodeficiency. However, insulinodeficiency is not due to total loss of β-cell mass, as these cells are still detected many years after onset. Cannabinoid 1 receptor (CB1R) is a G-protein coupled receptor that negatively regulates insulin secretion and activates inflammatory pathways. Immune cells and β-cell express CB1R. Genetic ablation of CB1R in mouse β-cell prevents immune cell infiltration and improves islet viability and function. We hypothesize that CB1R plays a key role in β-cell reactivity to initiate insulitis.

We investigated our hypothesis using a model of human insulitis *ex vivo*: Human islets from cadaveric donors were 3D co-cultured with the same donor's PBMCs and incubated with a mix of cytokines. With this model, we determined islet-cell death, inflammation, function, and immune cell infiltration, in the presence of different concentrations of the CB1R blocker JD-5037 or by transducing islets with AAVs delivering CRISPR-Cas9 targeting *CNR1*(CNR1KD). In another approach, we transfected the PBMCs with control plasmid or plasmid targeting *CNR1* and co-cultured them with 3D cultured islets.

Preliminary data (n = 1-4 donors) showed that pharmacological or genetic ablation of CB1R's function in the islets reduces immune cell infiltration after 2 or 4 days of culture and reduces intra-islet nitric oxide production. Mechanistically, JD-5037 reduced activation of one arm of the unfolded protein response, and the expression of chemokines involved in immune cell attraction. In accordance with pharmacological blockade, genetic ablation of *CNR1* blunted cytokine-induced dysfunction. Our data describe, for the first time, human CB1R as a therapeutic target for T1D.




**1** - Hôpital Albert Calmette - **2** - Hôpital Cardiologique - **3** - Hôpital Michel Fontan - **4** - Hôpital André Fourrier - **5** - Hôpital Claude Huriez - **6** - Hôpital Jeanne de Flandre
**7** - Maison de retraite Porte de Gand - **8** - Hôpital Roger Salengro - **9** - Hôpital Pierre Swynghedauw - **10** - Centre Abel Caumartin - **11** - Centre Antipoison / SAMU
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