4th Symposium of the Network on Monocytes-Macrophages-Microglies
Bordeaux, 26 Novembre, 2021

**The symposium will be in hybrid format**


Organised with

**4th SYMPOSIUM OF THE OCCITANIE NETWORK ON MONOCYTES – MACROPHAGES – MICROGLIES**

**FRIDAY, 26 NOVEMBER 2021**
**Bordeaux**

# PROGRAMME

**Information and registration :** https://somm2021.sciencesconf.org
aksam.merched@u-bordeaux.fr - florence.ottones@u-bordeaux.fr

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**8h30 – 8h45** ***OPENING OF THE REGISTRATION DESK***

**8h50 – 9h00** ***SYMPOSIUM INTRODUCTION***

Florence OTTONES (CRMSB, BDX) & Aksam MERCHED (BMGIC, BDX)

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| **9h00 – 10h40** | **SESSION 1: Role of lipid mediators in phagocytosis.**<br>Chairs: Pr Aksam MERCHED (BMGIC, BDX) & Dr Florence OTTONES (CRMSB, BDX) |
| 9h00 – 9h30 | **KEYNOTE LECTURE 1 – Pr Magnus BÄCK** (Karolinska, Stockholm)<br>"Macrophages and lipid mediators in the resolution of inflammation in atherosclerosis and aortic valve stenosis." |
| 9h35 – 10h05 | **LECTURE 1 – Pr Agnès NADJAR (Neurocentre Magendie, BDX, France)**<br>"Role of lipid metabolism in microglial function during neurodevelopment." |
| **10h10 – 10h40** | **SESSION 2: Flash Poster Presentation**<br>*10h10 – 10h20: **Julie GIRAUD** (Immunoconcept, UMR 5164, BDX) "Exploiting immunity of hepatocellular carcinoma to improve the treatment of patients."<br>*10h20 – 10h30: **Dr Krisztina NIKOVICS** (Imagery Unit, French Armed Forces Biomedical Research Institut, Brétigny sur Orge) "Non-specific binding, a limitation of immunofluorescence method to study macrophages in situ."<br>*10h30 – 10h40: **Damien LAOUTEOUET** (INSERM U1183, montpellier) "Origin and role of macrophage subsets in the pathophysiology of osteoarthritis." |

**10h40 – 11h00** ***Coffee break / Poster Session***

*(20')* ***Exhibition & Sponsors***

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| **11h00 – 12h20** | **SESSION 3: Monocytes & Macrophages and Cancer.**<br>Chairs: Dr Gabriel COURTIES (IRMB, Montpellier) & Dr Florence APPARAILLY (IRMB, Montpellier) |
| 11h00-11h30 | **KEYNOTE LECTURE 2 – Dr Massimiliano MAZZONE** (VIB-KU, Leuven)<br>"A metabolic cross-talk between cancer cells and TAMs sustains immunosuppression and immunotherapy resistance." |
| 11h35-12h05 | **LECTURE 2 – Dr Pieter GOOSSENS** (MUMC, Maastricht)<br>"Imaging myeloid phenotypes in their tissue micro-environment." |
| 12H10-12H20 | **OSE Immunotherapeutics**<br>"Immune targets in cancer." |

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| **12h20-14h00** | ***Lunch / Networking / Poster Session*** |
| *(1H40)* | ***Exhibition & Sponsors*** |

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| **14:00 - 15:30** | **SESSION 4: Monocytes & Macrophages and metabolism.**<br>Chairs: Dr Anne-Karine BOUZIER (CRMSB, BDX) & Pr Agnès NADJAR (Neurocentre Magendie, BDX) |
| 14h00-14h30 | **KEYNOTE LECTURE 3 – Dr. Laurent YVAN-CHARVET** (UMR INSERM U1065/UNS - C3M, Nice)<br>"Macrophage glutaminolysis in cardiometabolic diseases." |
| 14h35-14h55 | **LECTURE 3 – Dr Johan GARAUDE** (IRMB, Bordeaux)<br>"Innate immune control of mitochondrial metabolism." |
| 15h00-15h25 | **SESSION 4: Flash Oral Presentation**<br>*15h00-15h10: **Dr Florence OTTONES** (CRMSB, BDX) "The specific optical properties of foamy macrophages may be due to their specific metabolism and/or lipid handling."<br>*15h15-15h25: **Janaïna GREVELINGER** (CRMSB, BDX) "Distinct functional phenotypes between major models of foamy macrophages: consequences and impact in the field of therapeutic research." |

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|---|---|
| **15h30-16h00** | ***Coffee break / Poster Session*** |
| *(30')* | ***Exhibition & Sponsors*** |

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| **16h00-16h30** | **SESSION 5: Imaging Macrophages** Chairs: Dr Edouard GERBAUD (CRCTB U1045, BDX) & Dr Gisèle CLOFENT-SANCHEZ (CRMSB, BDX) |
| 16h00-16h30 | **KEYNOTE LECTURE 4 – Dr. Carlos PEREZ-MEDINA** (CNIC, Madrid) "Imaging Macrophages with positron emission tomography." |
| 16h40-17h20 | **SESSION 6: flash oral presentation** *16h40-16h50: **Dr Jan Pieter KONSMAN** (INCIA UMR 5287,BDX) "Brain Perivascular Macrophages Do Not Mediate Interleukin-1-Induced Sickness Behavior in Rats." *16h50-17h00**: Dr Sylvain FRAINEAU** (enVI/UMR U1096, Rouen) "Ezh2 as an epigenetic checkpoint during monocyte differentiation: a potential target for cardiac recovery after myocardial infarction." *17h00-17h10: **Dr Pauline HENROT** (CRCTB, INSERM U1045, BDX) "Muscarinic receptor M3 activation promotes COPD fibrocyte contraction." *17h10-17h20: **Edmée EYRAUD** (CRCTB, INSERM U1045, BDX) "A high probability of short-range interactions between fibrocytes and CD8+ T cells potentiates the inflammatory response in COPD." |

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| **17h30-17h45** | ***Awarding of prizes for the best oral presentation and the best poster*** |
| **17h45-18h00** | ***Concluding remarks*** |
| **18h00-19h00** | ***Cocktail reception with Malikal, afro-tropical rhythms*** |

**19h30-22h30** ***Diner and Networking***

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# Invited speakers

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## KEYNOTE LECTURE 1 – Pr Magnus Bäck (Karolinska, Stockholm)

**Associate Professor Magnus Bäck** is senior consultant in cardiology and research team leader at the Center for Molecular Medicine. The research undertaken has two main focuses: lipid mediators and valvular heart disease.

Lipid mediators can either act as proinflammatory stimuli (e.g. leukotrienes) or participate in the resolution of inflammation (e.g. lipoxins). Our aim is to unravel the role of lipid mediators in cardiovascular inflammation and its resolution, and how these pathways can be targeted as therapeutic interventions in cardiovascular disease. Our research has provided mechanistic insights into the role of leukotriene signaling in atherosclerosis, and through a pharmacoepidemiological approach we translated this into clinical findings, indicating beneficial effects of leukotriene receptor antagonism in terms of reducing cardiovascular risk.

The third most common cardiovascular pathology, after ischemic heart disease and hypertension, is valvular heart disease. We were the first to identify a possible role of leukotriene signaling in the calcification and obstruction of the aortic valve causing aortic stenosis. Since no medical treatment has hitherto proved to be efficacious in slowing down valvular calcification, we are presently further exploring the potential therapeutic role of the lipid mediator (and other) pathways in aortic stenosis.

The group is focusing on translational research, with approaches ranging from clinical epidemiological, echocardiographic and biomarkers studies, through experimental analysis of human tissues and cells, to basic experimental mechanistic studies.

**9:00 – 9:30 “Macrophages and lipid mediators in the resolution of inflammation in atherosclerosis and aortic valve stenosis.”**

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## LECTURE 1 –Agnès Nadjar (Neurocentre Magendie, Bordeaux)

**Professor of neurosciences at the University of Bordeaux, Agnès Nadjar** is a member of the Physiopathology of energy balance and obesity team at the Neurocentre Magendie (Inserm and University of Bordeaux - Bordeaux Neurocampus). Specialist in the interactions between nutrition and the brain, her pioneering work on the effect of lipid nutrients on microglial function and neuroinflammation processes aims to lead to the development of innovative treatments in the fight against obesity.

In a recent study, that she will present during the conference, her team studied the role of polyunsaturated fatty acids (omega-6 and 3) on microglial lipid metabolism and the consequences on the activity of neighboring neurons. Their work has shown that a drop in omega-3 intake during development exacerbates the phagocytic and inflammatory functions of the microglia, leading to neuronal dysfunctions.

Agnès Nadjar, was recently appointed junior member of the IUF (University Institute of France).

**9:35-10:05 “Role of lipid metabolism in microglial function during neurodevelopment.”**

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## KEYNOTE LECTURE 2 – Dr Massimiliano Mazzone (VIB-KU Leuven Center for Cancer Biology)


Solid tumors are not simply clones of malignant cells. Instead, they can be considered dysfunctional organs, end-product of the altered interplay, within the **tumor microenvironment (TME)**, among cancer cells and stromal cells (e.g. endothelial cells, macrophages, neutrophils, T cells, etc.). This concept has thrown a spotlight on the **TME** as the central unit governing tumor progression, metastasis and resistance to antitumor therapies.

**Our mission** is to bridge the current gap between **cancer cell biology** - autonomous traits of malignant cells - and **tumor biology** - non-autonomous traits where, the unique features of the TME along with its cellular cross-talks are the main drivers of malignancy. We believe that only a comprehensive understanding of the environmental cues and molecular pathways that participate in the interaction between cancer cells and stromal cells within the harsh TME (at the primary site and metastatic niche) will enable us to **conceive brand new and specific therapeutic strategies**.

*De facto*, the research topics of the lab span the fields of **tumor and inflammation**, focusing on functional characterization of the **hypoxia-response**, a key environmental cue of the TME, on the consequent involvement of **tumor metabolism** in dictating the immune landscape, and on how **immune cell positioning** within the tumor impacts on function and phenotypic skewing of immune cells. To address these points, we take advantage of tissue-specific gene targeting and pharmacologic approaches in mice and combine the phenotype discovery with an extensive phenotypic characterization. In particular, we are using state-of-the-art genetic, cell biological, biochemical and structural methods, all complemented by specific multi-omics profiling and following (meta)-analysis of human and mouse datasets (*i.e*. transcriptomic and metabolomics data). Our investigations will increase the knowledge on the molecular and cellular partners controlling inflammatory cell skewing in the TME and its significance in cancer and those conditions where imbalanced immune response contributes to the pathogenesis of life-threatening disorders (*i.e*. chronic infections and autoimmunity).

**11:00 – 11:30 "A metabolic cross-talk between cancer cells and TAMs sustains immunosuppression and immunotherapy resistance."**

## LECTURE 2– Dr Pieter Goossens (MUNC, Maastricht)

**Pieter Goossens**, PHD, post doc, in the lab of **Prof. Erik Biessen** at the Department of Pathology, studies macrophage phenotypical and functional heterogeneity in the atherosclerosis context. Macrophages display a high degree of phenotypic heterogeneity that reflects the cells' micro-environment. Pieter Goossens combines classical histology with transcriptomics, multi-label fluorescent microscopy and mass spectrometry imaging to study the spatial distribution of macrophage subsets in human and murine atherosclerotic plaques and the impact of local triggers on their phenotype and functions.

**Pr. Erik Biessen's** current passion is to deploy systems medicine approaches, to understand and define critical innate immune pathways in human atherosclerosis and cardiometabolic comorbidities and to validate the relevance of these processes for disease progression by intervention studies in in vitro and in vivo models.

Hereto, the group has developed a new high content microscopy based functionomics platform to measure macrophage functional profile at unprecedented resolution and speed and a technology pipeline for spatial mapping of macrophage phenotype and molecular context.

**11:35 – 12:05 "Imaging myeloid phenotypes in their tissue micro-environment."**

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## KEYNOTE LECTURE 3 – Dr. Laurent YVAN-CHARVET (UMR INSERM U1065/UNS - C3M, Nice)

Doctor in physiology and endocrinology 'summa cum laude' from the University of Paris XI since 2005, specialist in cardiometabolic and inflammatory diseases, his postdoctoral experience, at Columbia University in New York in the United States, opened his themes of research towards understanding the metabolic disturbances that cause inflammation and cardiovascular complications. This work on the role of cholesterol metabolism on hematopoietic stem cells, monocytes and platelets has been awarded numerous international prizes such as the 'Roger Davis Award' from the American Kern Society of Lipidology in 2010, finalist for the prize ' IH Page Investigator Award from the American Association of Cardiology in 2011, the EAS award from the European Atherosclerosis Society in 2013 and most recently the Daniel Steinberg award from the American Society of Atherosclerosis, Thrombosis and Vascular Biology in 2015.

After participating in the development of new therapeutic avenues to fight against cardiovascular diseases within the pharmaceutical company Pfizer, he was recruited at Inserm thanks to an excellent funding from Atip-Avenir in 2013 and was promoted to Research Director in 2015. His research work focuses on the identification of new metabolic pathways at the origin of inflammatory and cardiovascular complications with a central aim of proposing new perspectives for the prognosis and treatment of these pathologies. This work was recently funded by a European Consolidator Grant contract in 2017.

**14:00 – 14:30 "Macrophage glutaminolysis in cardiometabolic diseases."**

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## LECTURE 3– Dr Johan Garaude (IRMB, BDX)

**Project description:**

Metabolic reprogramming has recently emerged as a major feature of innate immune cells. At the core of immune cell metabolic reprogramming is the mitochondrion, a bioenergetic organelle that also serves as an immune signaling platform. Our work thus aims at unraveling the structural and functional adaptations of the mitochondrial respiratory chain and metabolism and their relevance for innate immune cells mediated antibacterial immunity. We specifically assess the connection between innate immune receptors engagement by microbial products and the electron transport chain regulation. In turn, we evaluate the innate immune consequences of cellular metabolism dysfunctions and mitochondrial respiratory chain disorders.

**Biosketch:**

Dr Johan Garaude got his Ph.D. in Moleclular Endocrinology in 2007 from the University of Montpellier, France for his work on mitogen-activated protein kinases (MAPK) and activating-protein 1 (AP-1) in leukemogenesis and T cell activation. In 2008, he joined the laboratory of Julie Magarian Blander at the Mount Sinai School of Medicine in New York where he investigated how a dual ligand for innate immune receptors can be used to generate potent antitumor immune responses and contributed to establish that sensing of infected apoptotic cell by dendritic cells is natural inducer of TH17 cell differentiation. In 2011, he got a permanent position at INSERM, France, and started investigating the metabolic adaptations and mitochondrial biology in innate immune cells and how this contributes to antimicrobial responses.

**14:35 – 14:55 "Innate immune control of mitochondrial metabolism."**

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## KEYNOTE LECTURE 4 – Dr. Carlos PEREZ-MEDINA (CNIC, Madrid)

Dr. Carlos Pérez Medina holds a BSc in Chemistry (2003) and a PhD in Organic Chemistry (2008), both obtained in Madrid (Spain). He continued his training as a synthetic chemist during a postdoctoral stay at Trinity College Dublin. In 2009 he joined Dr. Erik Arstad's lab at University College London, where he specialized in radiochemistry and molecular imaging, and continued working on medicinal chemistry. Since then, he has carried out his research in the biomedical sciences with a focus on positron emission tomography (PET) imaging. In 2013 he moved to New York (USA) to join the Nanomedicine lab at Mount Sinai. In collaboration with Drs. Zahi Fayad and Willem Mulder, he worked on the integration of imaging techniques into nanomedicine development. After two years of postdoctoral training, he was hired as junior faculty and later promoted to Assistant Professor. During this time, he also worked on the development of PET tracers for atherosclerosis phenotyping. In November 2018, Dr. Pérez Medina was recruited by CNIC (Madrid, Spain) to lead the Nanomedicine and Molecular Imaging lab. His current research focuses on nanotherapy development for cancer and cardiovascular disease, and radiotracer development for non-invasive phenotyping of cancer and atherosclerosis by PET.

**16:00 – 16:30 "Imaging Macrophages with positron emission tomography."**

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# Selected Presentations

## 10h10 – 10h40 SESSION 2: Flash Poster Presentation

**10h10 – 10h20:**

### Exploiting immunity of hepatocellular carcinoma to improve the treatment of patients.

**Julie Giraud**[1], Domitille Chalopin[1, 2], Laurence Chiche[3], Macha Nikolski[2], Maya Saleh[1, 4]

1 : Immunology from Concept and Experiments to Translation, Université de Bordeaux, Centre National de la Recherche Scientifique : UMR5164
2 : Centre de Bioinformatique de Bordeaux, CGFB
3 : Department of Oncology, CHU de Bordeaux haut Leveque
4 : Research Institute of the McGill University Health Center, Montreal, Quebec, Canada

Hepatocellular carcinoma (HCC) is among the deadliest cancers worldwide. Environmental risk factors include viral infection, alcohol abuse and the metabolic syndrome. While there is evidence that boosting the activity of tumor-specific T cells might benefit patients with HCC, the underlying liver soil renders the tumor microenvironment of this cancer somewhat unique. Despite a significant therapeutic advance in the treatment of advanced HCC with immune checkpoint inhibitors, ~75% of patients do not respond to these immunotherapies. Such a heterogenous response highlights the need to explore etiology- and organ-specific immunity towards improved patient stratification and the development of new combination therapies. Here, we set to characterize the innate immune landscape of HCC with respect to etiology. We employed single cell RNA-seq to profile CD45+panTCRαβ-CD19- cells in tumoral and adjacent non-tumoral liver from 10 HCC patients with different etiologies and performed spatial transcriptomics (stRNA-seq) (10x Genomics). Analysis of the transcriptomes of 100,000 innate immune cells revealed a remarkable diversity of myeloid cells and natural killer cells and led to the identification of etiology-dependent subsets that were either depleted or enriched in HCC. In particular, we identified novel subsets of tumor-associated macrophages and myeloid-derived suppressor cells with immunosuppressive properties and associated with bad prognosis.The integration of scRNA-seq and stRNA-seq is hoped to elucidate spatial information of the newly characterized clusters and their microenvironmental interactions, with respect to liver zonation, fibrosis and etiology of the disease. Collectively, our work uncovered interesting immunotherapeutic targets as potential novel therapeutic entry points for improved HCC patient care.

**10h20 – 10h30:**

## Non-specific binding, a limitation of immunofluorescence method to study macrophages in situ.

Emma Sicherre[1] , Anne-Laure Favier[1], Diane Riccobono[1] , **Krisztina Nikovics[1]**

1 : Institut de Recherche Biomédicale des Armées
Service de Santé des Armées

Advances in understanding tissue regenerative mechanisms require the characterization of *in vivo* macrophages as those play a fundamental role in this process. This characterization can be approached using immuno-fluorescence method with widely studied and used pan-markers like CD206 protein. This work investigated CD206 expression in an irradiated muscle pig model using three different antibodies. Surprisingly, expression pattern during immunodetection differed depending on the antibody origin and could give some false results. False results are rarely described in the literature but this information is essential for scientists who need to characterize macrophages. In this context, we showed that *in situ* hybridization coupled with hybridization-chain-reaction detection (HCR) is an excellent alternative method to detect macrophages *in situ.*

**10h30 – 10h40:**

## Origin and role of macrophage subsets in the pathophysiology of osteoarthritis.

**Damien Laouteouet**[1], Nicole Hannemann[1], Olivier Bortolotti[1], Manon Chambon[1], Aischa Blömeke-Eiben[1], Julien Delima[2], Frédéric Blanchard[2], Florence Apparailly[1], Gabriel Courties[1]

1 : Institut de Médecine Régénératrice et de Biothérapies (IRMB) - INSERM : U1183, Université de Montpellier, CHU Montpellier Saint Eloi
2 : Sarcomes osseux et remodelage des tissus calcifiés - Phy-Os [Nantes - INSERM U1238], Université Bretagne Loire, Centre Hospitalier Universitaire de Nantes, Université de Nantes

**Background:** Osteoarthritis (OA) is a common form of arthritis characterized by synovitis, cartilage loss and joint dysfunction. Studies indicate a role for chronic, low-grade inflammation in disease pathogenesis with a pivotal contribution of macrophages. Macrophages are essential for tissue homeostasis, but they can also either enhance tissue injury or orchestrate tissue repair. The recently discovered heterogeneity of synovial macrophages raises questions about their ontogeny and contribution to the synovial tissue niche.

**Objectives:** Our goal is to better characterize the macrophage heterogeneity in the knee joint tissue and determine the differential contribution of macrophage subsets in the pathophysiology of OA.

**Methods & Results:** Here, combining sc-RNA sequencing, flow cytometry and confocal imaging with in vivo fate mapping strategies, we show that the healthy joint harbors two macrophage subsets (Lyve1hi and MHCIIhi) with distinct transcriptome, origin, and anatomical location. The Lyve1 cluster represented lining macrophages as revealed by their high expression of *Cx3cr1*, *Timd4* and *Vsig4* whereas the monocyte derived MHCII subset identified interstitial macrophages and was enriched for genes including *Ccr2*, *Cd74* and *Mgl2*. During OA, an additional inflammatory cluster enriched for several genes including *Spp1*, *Ccr2* and *Il1b* populated the interstitial area of the synovial tissue.

**Conclusion & perspectives:** Our findings indicate that two distinct macrophage lineages co-exist in the healthy joint and that an osteoarthritic environment is permissive to long-term engraftment of proinflammatory macrophages. Macrophage depletion strategies using CX3CR1CreER/+:R26iDTR/+ and CCR2KO mice are currently underway to determine the role of Lyve1 and Spp1 subsets in the pathophysiology of OA.

## 15h00-15h25 SESSION 4: Flash Oral Presentation

**15h00 - 15h10:**

### The specific optical properties of foamy macrophages may be due to their specific metabolism and/or lipid handling

C. Borowczyk[1], J. Laroche-Traineau[1], J. Grevelinger[1], J. Brevier[2], J.Garaude[3], S. Marais[4], E. Gerbaud[5], M.-J. Jacobin-Valat[1], G. Clofent-Sanchez[1], **F. Ottones[1]**

1 : CRMSB UMR 5536 - CNRS DR15, Bordeaux;
2 : XLIM, Limoges;
3 : MRGM INSERM U1211, Bordeaux;
4 : BIC, Bordeaux;
5 : Centre de Recherche Cardio Thoracique, INSERM U 1045, Bordeaux.

Backgrounds and aims: Various macrophages are implicated in atherosclerosis: dying foamy macrophages (FMs) and inflammatory macrophages (M1) in higher proportion than regulatory macrophages (M2). M1, M2 and FM/Mox models present distinct optical properties in TPEF imaging, with a higher NADH autofluorescence (AF) in M1 and FM/Mox than in M2, and a higher FAD AF in FM/Mox than in M1 and more unexpectedly than in M2 (Borowczyk *et al*. *Atherosclerosis* 2020). We hypothesized that human M1 may use glycolysis and M2 the OXPHOS pathway, while human FMs may use both but mostly the OXPHOS pathway. Methods: Mitochondrial respiration and glycolysis were determined by measuring oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) of live cells and ATP production by these energy pathways using Seahorse XF Analyzer. Results: Human M1 are highly glycolytic but also use the OXPHOS pathway. Human M2 essentially use the OXPHOS pathway, and also glycolysis but to a lesser extent. Human FM/Mox models use glycolysis, and also the mitochondrial respiration at a low level. The level of mitochondrial respiration cannot explain the high AF observed in the spectrum of FAD. Conclusions: The high level of AF in the FM/Mox models may arise from other molecules, such as intracellular ceroids. Our preliminary data showed, a colocalization of the AF in the FAD spectrum with oxLDL coupled to far-red fluorescent DiI. This colocalization suggests a link with the specific handling of lipids by the FM/Mox models.

**15h15 - 15h25:**

## Distinct functional phenotypes between major models of foamy macrophages: consequences and impact in the field of therapeutic research.

J. Brévier[1], E. Gerbaud[2], C. Borowczyk[3], **J. Grevelinger[3]**, J. Laroche-Traineau[3], S. Marais[4], M-J. Jacobin-Valat[3], G. Clofent-Sanchez[3] and F. Ottones[3].

1 : UMR 7252, XLIM, Limoges;
2 : Centre de Recherche Cardio Thoracique, INSERM U 1045, Bordeaux;
3 : CRMSB CNRS UMR5536, INSB, Bordeaux, France ;
4 : Bordeaux Imaging Center, Bordeaux.

**Background and aims.** Macrophages play a central role in atherogenesis. In progressive plaques, they mainly polarized toward inflammatory macrophages or turn into foamy macrophages (FMs) after the phagocytosis of oxidized LDL (oxLDL). Whereas inflammatory are clearly pro-atherogenic, the role of FMs may differ depending on the stage of progression, as the essential anti-atherogenic role of FM, being cholesterol efflux, is altered during plaque progression. Restoring cholesterol efflux as therapeutic approach of atherosclerosis was already envisioned but require further characterization of FM models. To better characterize major *in vitro* models used to mimic plaque FMs, we compared, on the same cells, their level of cell surface expression of different inflammatory and immunoregulatory markers, as well as their optical properties related to energetic metabolism. **Methods.** Different models of human FMs were generated by exposure to acetylated LDL (acLDL) or oxidized LDL (oxLDL) alone or, in an original way, in the presence of a human carotid extract (CE). Their phenotype and optical properties were compared with those of extremely polarized macrophages, inflammatory M1 (MLPS+IFNg) and immunoregulatory M2 (MIL4+IL13) used as reference models. **Results.** Principal Component Analysis (PCA) of the whole data issuing from this study reveals fine phenotypic and optical differences between FM models, according to their lipid content, that may explain functional differences previously described in the literature depending on whether acLDL and oxLDL are used. **Conclusion**. This study underlines the importance of setting up relevant pathophysiological FM models as targets for the development of diagnostic and therapeutic tools.

## 16h40-17h20 SESSION 6: flash oral presentation

***16h40 - 16h50:***

### Brain Perivascular Macrophages Do Not Mediate Interleukin-1-Induced Sickness Behavior in Rats.

Konsman Jan Pieter [1]

1 : Insitute for Cognitive and Integrative Neuroscience. CNRS : UMR5287, Université de Bordeaux (Bordeaux, France)

Sickness behavior, characterized by on overall reduction in behavioral activity, is commonly observed after bacterial infection. Sickness behavior can also be induced by the peripheral administration of Gram-negative bacterial lipopolysaccharide (LPS) or interleukin-1beta (IL-1β), a pro-inflammatory cytokine released by LPS-activated macrophages. In addition to the microglia, the brain contains perivascular macrophages, which express the IL-1 type 1 receptor (IL-1R1). In the present study, we assessed the role of brain perivascular macrophages in mediating IL-1β-induced sickness behavior in rats. To do so, we used intracerebroventricular (icv) administration of an IL-1β-saporin conjugate, known to eliminate IL-R1-expressing brain cells, prior to systemic or central IL-1β injection. Icv IL-1β-saporin administration resulted in a reduction in brain perivascular macrophages, without altering subsequent icv or ip IL-1β-induced reductions in food intake, locomotor activity, and social interactions. In conclusion, the present work shows that icv IL-1β-saporin administration is an efficient way to target brain perivascular macrophages, and to determine whether these cells are involved in IL-1β-induced sickness behavior.

***16h50 - 17h00:***

## Ezh2 as an epigenetic checkpoint during monocyte differentiation: a potential target for cardiac recovery after myocardial infarction.

Julie Rondeaux[1], Déborah Groussard[1], Sylvanie Renet[1], Virginie Tardif[1], Anais Dumesnil[1], Alphonse Chu[2], Jean-Paul Henry[1], Zina Badji[1], Claire Vezier[1], Delphine Béziau[1], Dominique Guerrot[1], Marjorie Brand[2], Vincent Richard[3], Eric Durand[1], Ebba Brakenhielm[1], **Sylvain Fraineau[1]**

1 : Normandie Univ, UNIROUEN, INSERM U1096 EnVI & FHU REMOD-VHF
2 : Ottawa Hospital Research Institute [Ottawa]
3 : Service de pharmacologie CHU Rouen, Normandie Université, Université de Rouen Normandie

Monocytes-macrophages play an important role in cardiac repair after Myocardial Infarction (MI). Specifically, M2-like macrophages (M2) modulate inflammation and fibrosis, and promote angiogenesis during cardiac repair post-MI. Interestingly, an epigenetic histone modification: JMJD3-dependent H3K27 demethylation, has been shown to promote M2 polarization.

We hypothesized that JMJD3 antagonistic enzyme EZH2, responsible for H3K27 methylation, could act as an epigenetic checkpoint during monocyte to M2 differentiation regulating cardiac repair post-MI.

We demonstrate for the first time that while Ezh2 is localized in the nucleus of monocytes as well as M0 and M1 macrophages, unexpectedly it translocates to the cytoplasm in M2 polarized cells in both healthy and post-MI mouse hearts *in vivo*. We reproduced this phenomenon *in vitro* in differentiating monocytes. At the chromatin level, ChIP-Sequencing in monocytes revealed that bivalent genes, regulated by EZH2, are implicated in angiogenesis and cardiac repair processes. Gene expression profiling by RNA-Seq performed on monocytes treated with EZH2 inhibitor, GSK-343, allowed identification EZH2-dependent bivalent genes including *DLL1* and *VEGFA*. EZH2 inhibition decreased H3K27me3 level at the promoter of these genes enhancing their expression to promote human monocyte repair functions. mRNA profiling revealed that GSK-343 treatment brings monocytes closer to M2 macrophage profile than to any other myeloid cell lineage. In line with this protective effect, GSK-343 treatment accelerated cardiac inflammatory resolution preventing infarct expansion and subsequent cardiac dysfunction after MI *in vivo*.

In conclusion, our study reveals that epigenetic modulation of cardiac-infiltrating immune cells may hold promise to limit adverse cardiac remodeling after MI.

***17h00 - 17h10:***

## Muscarinic receptor M3 activation promotes COPD fibrocyte contraction.

**Pauline Henrot**[1], Edmée Eyraud[1], Elise Maurat[1], Sophie Point[1], Guillaume Cardouat[1], Jean-François Quignard[1], Pierre-Olivier Girodet[1], Maéva Zysman[1], Patrick Berger[1], Isabelle Dupin[1]

1 : CRCTB Inserm U1045 - INSERM : U1045

Introduction: Fibrocytes are circulating monocytes-derived cells, able to migrate to injured organs and differentiate into myofibroblasts-like cells. We have previously shown that they are increased in the lungs of Chronic Obstructive Pulmonary Disease (COPD) patients and associated to worse lung function. COPD is characterized by irreversible airflow obstruction, partly due to an increased cholinergic environment activating the muscarinic M3 receptor. Our goal was to investigate the role of fibrocytes in COPD airway contraction.

Methods: Fibrocytes were isolated from COPD patients' blood and cultured for 14 days to reach full differentiation. Presence of M3 receptor was assessed by PCR, flow cytometry and immunocytochemistry. Calcium signalling and contraction experiments were performed in presence of carbachol (cholinergic agonist) +/- tiotropium bromide (M2/M3 antagonist).

Results: PCR showed that differentiated fibrocytes expressed all isoforms of muscarinic receptors. Moreover, 59,7% (±15) of fibrocytes were found to express the M3 receptor by flow cytometry. Immunocytochemistry showed the existence of cytoplasmic and membrane-associated pools of M3. Stimulation with carbachol (10-4M) elicited an intracellular calcium response in 39% (±20) of fibrocytes. Such response was blunted in presence of tiotropium bromide (10-6M). Moreover, carbachol induced a significant contraction of fibrocytes embedded in collagen gels, which was prevented by prior tiotropium bromide addition.

Conclusions: Around 1/3 of COPD patient's fibrocytes express a functional muscarinic M3 receptor. Cholinergic-induced fibrocyte contraction could participate in airway contraction and subsequent increase of airflow resistance in patients with COPD. The inhibition of these processes could participate to the beneficial effects of muscarinic antagonists for COPD treatment.

*17h10 - 17h20:*

## A high probability of short-range interactions between fibrocytes and CD8+ T cells potentiates the inflammatory response in COPD.

**Edmée Eyraud**[1], Elise Maurat[1], Pierre Vallois[2], Jean-Marc Sac-Epee[2], Cecile Contin-Bordes[3], Pierre-Olivier Girodet[1,4], Matthieu Thumerel[1,4], Patrick Berger[1,4], Isabelle Dupin[1]

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**Introduction:** Chronic obstructive pulmonary disease (COPD) is a respiratory disease with chronic inflammation, in which CD8+ T cells play a key role. Since circulating and tissue fibrocytes, respectively, are associated with mortality and bronchial obstruction, we investigated whether tissue fibrocytes can interact with CD8+ T cells, and whether the contact between both cell types could be a cause of chronic immune activation.

**Methods:** Using co-immunostaining of bronchial specimens obtained from surgery in 17 COPD patients and 25 control subjects, and image analysis methods, we quantified the relative distribution of fibrocytes and CD8+ T cells. Direct and indirect co-cultures of fibrocytes and CD8+ T cells, isolated from COPD patients' blood, were performed to test fibrocyte effect on CD8+ T cell proliferation and cytokines secretion profile. We defined a computational model with intercellular interactions which fits to experimental measurements and explains the macroscopic properties of cell populations *in situ*.

**Results:** Fibrocytes density in contact with CD8+ T cells and the minimal distance between both cell types were respectively higher and lower in tissue specimens from COPD patients compared with those from control subjects. We also demonstrated that direct contact between both cell types triggered *in vitro* CD8+ T cell proliferation and cytokines production. Computer modelling predicted that modification in local intercellular interactions induced changes in cell repartitions similar to those measured *in situ*.

**Conclusion:** This study reveals that direct intercellular interactions between fibrocytes and CD8+ T cells can occur *in vivo* and could potentiate the inflammatory response in COPD patients lungs.

# 4th Symposium of the Network on Monocytes-Macrophages-Microglies
# Bordeaux, 26 Novembre, 2021

**The symposium will be in hybrid format**


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