TUMOR MICROENVIRONMENT & METABOLISM

WORKSHOP

THURSDAY, NOVEMBER 9TH

9 AM - 1:30 PM IUCT-O AMPHITHEATER

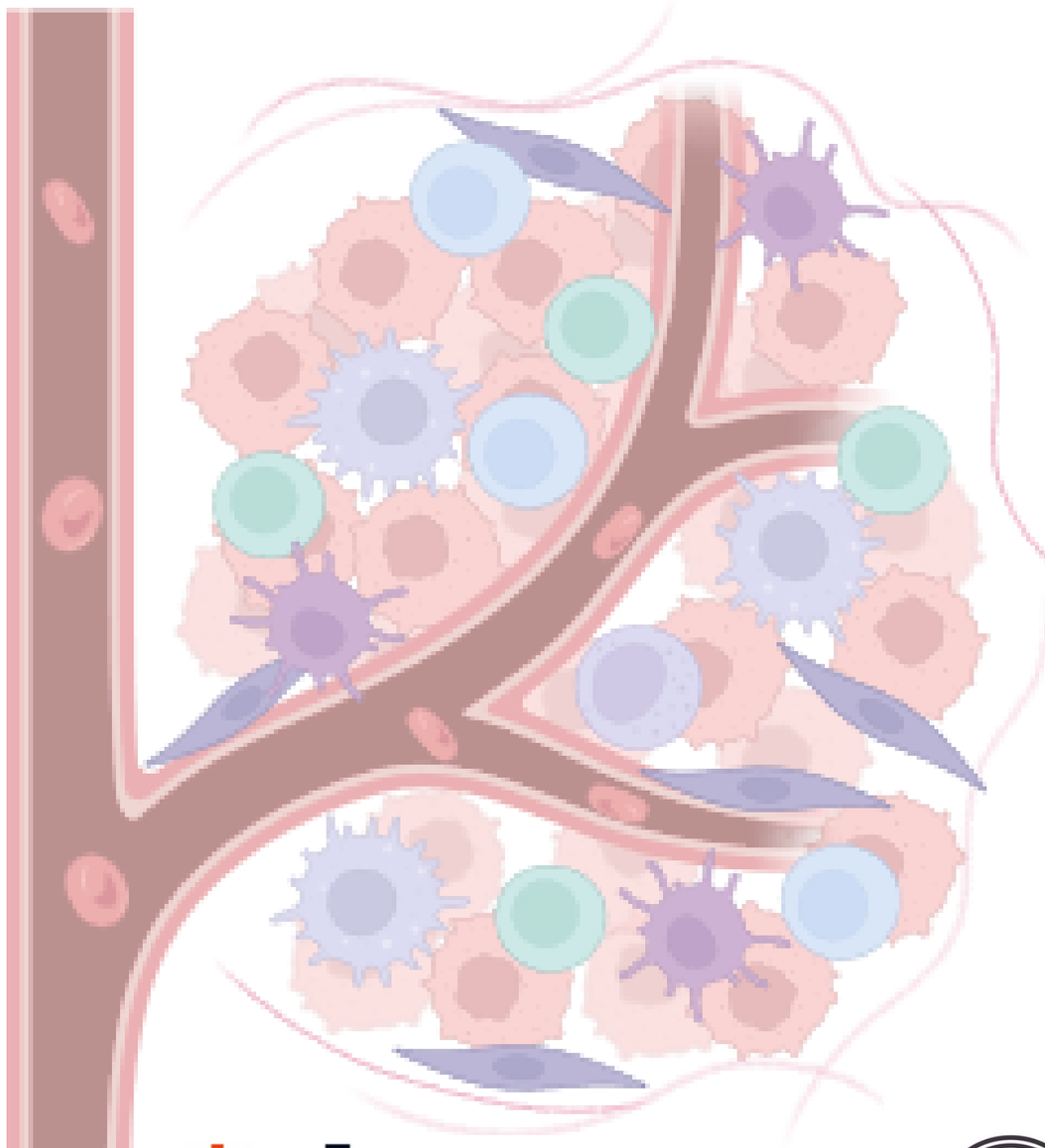
KEYNOTE LECTURES

- **Prof. Richard GROSE :** Barts Cancer Institute, London, UK

Cancer cell communication with neighbouring stromal cells and the extracellular matrix: impact on invasion and response to targeted therapies

- **Dr. Jean ALBRENGUES :** Institute for Research on Cancer & Aging, Nice, FR

Young researcher prize awarded by the French cellular biology society
Neutrophil Extracellular Traps formed during chemotherapy confer treatment resistance



Postdoc talks

- Dr Julio Bunay Noboa
- Dr Leila Khajavi

PhD students talks

- Hippolyte Audureau
- Tom Maillet
- Margaux Oberling

ORGANIZED BY: HIPPOLYTE AUDUREAU, MEHDI LIAUZUN, GONCALO-DA-SILVA POMBA DE ALMEIDA, CLAIRE LAC

SUPERVISED BY DR CORINNE BOUSQUET WITH THE SUPPORT OF THE PHD CARE PROGRAM AND THE LABEX TOULOUSE CANCER

THURSDAY, NOVEMBER 9TH

IUCT-O AMPHITHEATER

PROGRAM

9:00 - 9:15 Workshop and axis III presentation by Dr. Corinne Bousquet
CARe presentation by Prof. Bruno SEGUI

9:15-10:00 Prof. Richard Grose : Science at the cutting edge: proteolytic influences in cancer biology

10:00-10:15 Hippolyte Audureau : Acquired chemoresistance in pancreatic adenocarcinoma: mechanism implicating the stromal transcription factor Zbtb16 ?

10:15-10:30 Margaux Oberling : Unraveling the role of PTBP1 in Acute Myeloid Leukemia: shaping proliferation, survival and metabolism

10:30-10:45 Tom Maillet : Metabolic heterogeneity in Glioblastoma, as defined by spectroscopic MRI, drives basal and post-irradiation metabolic profiles of Glioblastoma Stem-like Cells

10:45-11:45 POSTER AND COFFEE BREAK

11:45-12:30 Dr. Jean Albrengues : Neutrophil Extracellular Traps produced during chemotherapy confer treatment resistance

12:30-12:50 Dr. Julio Bunay Noboa : The oxysterol dendrogenin A increases the activation of migratory dendritic cells

12:50-13:10 Dr. Leila Khajavi: Transcriptomics Profiling of the Non-Small Cell Lung Cancer Microenvironment Across Disease Stages Reveals Dual Immune Cell-Type Behaviors

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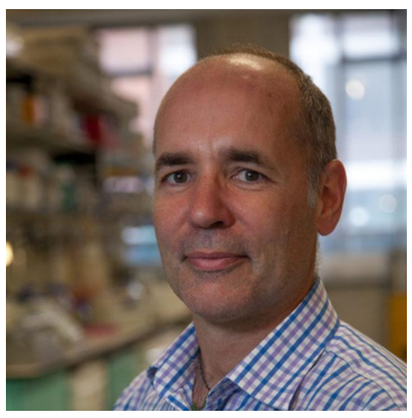
ABSTRACTS

Science at the cutting edge: proteolytic influences in cancer biology



Prof. Pichard GROSE
Professor of Cancer Cell Biology
Deputy Center Lead, Group leader
Barts Cancer Institute, London, UK

Richard Grose is a group leader, Deputy Centre Lead and Professor of Cancer Cell Biology at Barts Cancer Institute, Barts and The London Faculty of Medicine & Dentistry, Queen Mary University of London. His group interrogates cell signalling both in the context of cancer development/progression and in targeted therapies/resistance, focusing on using 3D models to understand the biology of cancer. In addition to an ongoing affinity for RTKs, his group has begun to realise that some multi-transmembrane receptors also play roles in cancer, and recent work has expanded into studying the roles of proteases in cancer, particularly in breast cancer progression and pancreatic cancer invasion.

His scientific career began as a research technician, developing HIV ELISAs, before studying Zoology at the University of Bristol, and working in the molecular sciences department at Pfizer. He returned to academia, studying for a PhD in embryonic wound repair with Prof. Paul Martin at UCL, and undertaking postdoctoral research, focusing largely on FGF signalling in cancer, with Prof. Sabine Werner at ETH Zurich and Prof. Clive Dickson at Cancer Research UK London Research Institute. He moved to Queen Mary in 2004 as a lecturer and has been there ever since. Alongside research, he is Dean for Global Engagement within the Faculty of Medicine and Dentistry, a member of flying faculty on the QMUL-Nanchang Joint Programme and Course Director for an MSc in Cancer and Molecular & Cellular Biology.

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ABSTRACTS

Neutrophil Extracellular Traps produced during chemotherapy confer treatment resistance

Dr. Jean Albrengues
Inserm Researcher
Cedric Gaggioli's Team
Institute for Research on Cancer and Aging
Nice, Fr

Metastasis is the major cause of cancer death, and the development of therapy resistance is common. The tumor microenvironment can confer chemotherapy resistance (chemoresistance), but little is known about how specific host cells influence therapy outcome.

We show that chemotherapy induces neutrophil recruitment and neutrophil extracellular trap (NET) formation, which reduces therapy response in mouse models of breast cancer lung metastasis. We reveal that chemotherapy-treated cancer cells secrete IL-1β, which in turn triggers NET formation. Two NET-associated proteins are required to induce chemoresistance: integrin-αvβ1, which traps latent TGF-β, and matrix metalloproteinase 9, which cleaves and activates the trapped latent TGF-β. TGF-β activation causes cancer cells to undergo epithelial-to-mesenchymal transition and correlates with chemoresistance.

Our work demonstrates that NETs regulate the activities of neighboring cells by trapping and activating cytokines and suggests that chemoresistance in the metastatic setting can be reduced or prevented by targeting the IL-1β-NET-TGF-β axis.

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ABSTRACTS

The oxysterol dendrogenin A increases the activation of migratory dendritic cells

Dr. Julio Bunay Noboa
Inserm Researcher
team INOV : Cholesterol Metabolism and Therapeutic Innovations
CRCT, Toulouse, France

Background and aim: Dendritic cells (DC) are antigen-presenting cells with the property to initiate immune responses and anti-tumor activity after their maturation and CC chemokine receptor-7 (CCR7)-dependent migration to lymphoid organs. The activation of DC is often reduced in tumors resistant to immunotherapies, such as immune checkpoint inhibitors (ICI), used in the clinic. Hence, the development of novel therapy that restore or enhance DC function would help to enhance ICI response. Dendrogenin A (DDA), is an endogenous oxysterol and a modulator of the Liver-X receptors (LXRα/β), which induces tumor re-differentiation and growth inhibition in various cancers. These effects were shown associated with DC and T cell infiltration into tumors (de Medina et al, Nature Commun. 2013). In addition, the complex DDA/LXRβ in tumor cells increases the secretion of anti-tumor and immunogenic small extracellular vesicles (exosomes) (Record et al, J. Extracell. Vesicle, 2022), indicating that DDA activates an anti-tumor immune response by targeting the LXRβ present in tumors. Since LXR ligands, such as 22R-hydroxycholesterol, were reported to inhibit the maturation and migration of DC as well as anti-tumor immune response (Villablanca, Nat Med, 2010), we characterized, in the present study, the impact of DDA treatment on DC and the mechanism involved.

Methods and Results: Since previous biodistribution assays indicated that DDA accumulates in bone marrow (Segala et al, Nat Commun, 2017), we studied DC derived from bone marrow precursors (BMDC) from mice. We showed that DDA increased the differentiation of BMDC by increasing the population of Ly6C-Cd62l+ DC precursors along with a decrease in macrophage markers. DDA induced the differentiation of BMDC which were enriched in migratory CCR7+ DC and upregulated the transcription of non-canonical transcriptional factors Id2/E2-2a and Stat3. Furthermore, DDA induced the maturation and the activation of migratory DC by increasing the surface expression of CCR7, MHC class II and costimulatory molecules (CD80, CD86) compared to BMDC challenged with the solvent control. This is followed by functional DC maturation shown by increased mRNA levels of cytokines produced during DC maturation. We also showed that the DDA induced the maturation and the activation of migratory DC through LXRβ activation and characterized the potential mechanism involved.

Conclusion: Together, these data show that DDA stimulates the differentiation and maturation of migrating BMDC by acting through the LXRβ. Thus, DDA seems to have a dual effect on anti-tumor immunity by acting on LXRβ present in tumors to release anti-tumor and immunogenic exosomes and also on LXRβ present in BMDC to activate their maturation and migration.

ABSTRACTS

Transcriptomics Profiling of the Non-Small Cell Lung Cancer (NSCLC) Microenvironment Across Disease Stages Reveals Dual Immune Cell-Type Behaviors

Dr Leila Khajavi, ,
team NetB(IO)² : Network Biology for Immuno-oncology
CRCT, Toulouse, France

Background: Lung cancer is the leading cause of cancer death worldwide, with a survival rate of 7 (small cell lung cancer) to 28% (non-small cell lung cancer) after 5 years. Our current understanding of the complex processes defining cancer is insufficient to treat a majority of patients effectively.

Methods: We applied a computational immunology approach (involving immune cell proportion estimation by deconvolution, transcription factor inference and immune score estimation) in order to better characterize bulk transcriptomics of primary lung adenocarcinoma (LUAD) samples from patients across disease stages.

Results: Through our methodology and feature integration pipeline, we identified clusters of immune cells corresponding to disease stage as well as potential immune response or evasion. More specifically, we report a duality in the behavior of immune cells, notably natural killer (NK) cells, suggesting a potential association with immune response or dysfunctional/exhausted states.

Conclusion: The dual profile of other immune cells, most notably T-cell populations, have been discussed in the context of disease such as cancer. Here, we report the duality of NK cells which should be taken into account in conjunction with other immune cell populations and behaviors in predicting immune response or evasion. Whether these NK profiles contribute to the prediction of response to therapy will need to be explored.

ABSTRACTS

Acquired chemoresistance in pancreatic adenocarcinoma: mechanism implicating the stromal transcription factor Zbtb16 ?

Hippolyte Audureau, PhD student
team MICROPANC: Microenvironnement and Therapeutic Resistance in Pancreatic Neoplasms
CRCT, Toulouse, France

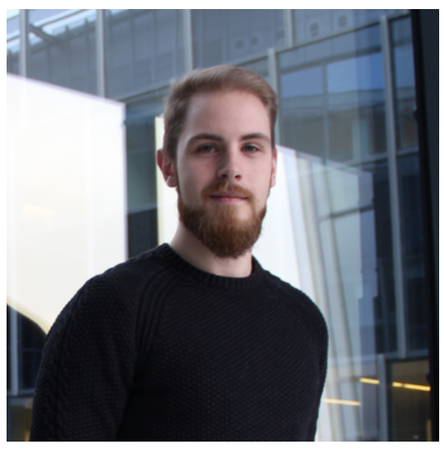
Pancreatic ductal adenocarcinoma (PDAC) is highly lethal. Rich in stroma, it contains a heterogeneous population of cancer-associated fibroblasts (CAFs), key players in chemoresistance, although the underlying mechanisms need to be better identified in order to develop new, more effective drug combinations.

The aim of our project is to identify and characterise stromal targets involved in the relapse of CAFs under chemotherapy. We have developed a patient-derived xenograft model (PDXs) in which tumours have been rendered resistant to Gemcitabine (Gem) by chronic treatment. Analysis of RNA-seq data from these PDXs showed that the stroma of tumours still 'sensitive' to Gem over-expressed a transcription factor not described in the PDAC in response to Gem. A major player in cell identity, we hypothesise that it controls the activation state of CAFs and thus blocks the acquisition of chemoprotective properties. By overexpressing this transcription factor in CAFs in vitro, we confirmed that it inhibited the basal activation state of these cells but also their capacity to activate in the form of pro-tumour and chemoprotective CAFs. In parallel, using multiplexed markers on patient tumours, we are correlating its expression with tumour biological characteristics (cancer cell subtypes and CAFs) and clinical data.

Our work highlights the involvement of a transcription factor in the acquisition of stroma-mediated chemoresistance and we hope to be able to propose additional therapies to inhibit therapeutic relapse.

ABSTRACTS

Metabolic heterogeneity in Glioblastoma, as defined by spectroscopic MRI, drives basal and post-irradiation metabolic profiles of Glioblastoma Stem-like Cells



Tom Maillet, PhD Student PhD student
team RADOPT : Radiotherapy Optimising: from molecular signalling pathways to clinical trials
CRCT, Toulouse, France

Glioblastoma (GB) is the most frequent and aggressive primary brain tumor. Standard therapeutic management consists in a surgical resection, combined with radio/chemotherapy.

Despite this treatment, median survival doesn't exceed 15 months, due to the highly invasive nature of these tumors, linked with chemo/radioresistance capacities. This recurrence process is partly explained by the presence of a cellular subpopulation with stem-like cells features (Glioblastoma Stem Cell, GSC) that would facilitate relapse by resistance to conventional treatments. The use of Magnetic Resonance Spectroscopic Imaging (MRSI) in the clinical field allows to highlight the metabolic heterogeneity in GB, notably through the Choline/N-AcetylAspartate Index (CNI) measurement. MRSI analysis identifies two different subtypes of tumor metabolic areas : CNI+ (CNI>2, metabolically active) and CNI- (CNI<2, metabolically inactive). Linked to preoperative MRSI analysis in GB, our previous results demonstrated that CNI+ areas are predictive of post-radiation relapse sites. Moreover, our previous work showed in GB patients a significant GSC enrichment in CNI+ areas compared to CNI-, in the FLAIR anatomic region.

Given the major involvement of GSC in resistance and relapse, and the metabolic adaptation processes considered as a hallmark of cancer, our work is focus on the metabolic characterization of GSC from CNI+ and CNI- areas harvested from patients biopsies, as well as ionizing radiations (IR) impact on the GSC metabolism and resistance capacities, in order to better understand and target the recurrence mechanisms in these metabolically active tumor areas.

ABSTRACTS

Unraveling the role of PTBP1 in Acute Myeloid Leukemia: shaping proliferation, survival and metabolism

Margaux Oberling, PhD student
team METAML : Metabolism and Therapeutic Resistance In Acute Myeloid Leukemia
CRCT, Toulouse, France

PTBP1 is a RNA-binding protein that plays an important role in the regulation of RNA splicing and stability as well as other steps of mRNA processing. It has been linked to tumorigenesis and poor outcome in various cancers. However, its roles in acute myeloid leukemia (AML) biology and response to chemotherapy are still unclear.

Here, we found that PTBP1 played an essential role in the growth and survival of human AML in vitro and in vivo. Furthermore, PTBP1 invalidation affected glycolysis, mitochondrial metabolism and redox homeostasis in vitro. However, in vivo, the impact of PTBP1 on the anti-leukemic effect was uncoupled from its well described action on mitochondrial oxidative phosphorylation. RNA sequencing revealed that PTBP1 has a prevalent effect on alternative splicing while having a little impact on mRNA abundance in AML cells. Interestingly, pathway enrichment analysis indicated that PTBP1 controlled various aspects of AML cell metabolism, extending beyond glycolysis to amino acids, carbohydrates, lipids, and pyrimidines metabolism. Additionally, among the genes differentially expressed or spliced upon PTBP1 modulation we found a strong enrichment in genes involved in DNA damage response and proliferation. These results suggest that, beyond controlling the catabolism of glucose through glycolysis, PTBP1 may also a be key regulator of the major central metabolic pathways that can provide substrates to fuel mitochondrial TCA cycle and oxidative phosphorylation, linking energy metabolism and cell proliferation.

Overall, this research sheds light on a novel role of PTBP1 in AML biology and its potential as a therapeutic target.