Séminaire de réflexion nationale

Caractérisation des Lésions pré-néoplasiques

Conference booklet

28 Novembre 2018

Auditorium – Biopark - Aviesan

Caractérisation des lésions pré-néoplasiques

Séminaire de réflexion nationale - 28 novembre 2018
Auditorium du Biopark - Aviesan - 11 rue Watt 75013 Paris

Programme

10h - 10 h 30 **Café d'accueil**

10h30 - 10h55
Introduction
Christine Chomienne *(ITMO Cancer Aviesan/INCa)*
Pierre Saintigny *(CRCL, Lyon)* **et Muriel Altabef** *(ITMO Cancer Aviesan)*

Session 1 : Définition des lésions pré-néoplasiques selon différents points de vue

11h - 11h10
Pascal Ducournau
(Université de Franche Comté, Besançon)
Traiter les pré-néoplasies : quelle prévention pour quelle santé ?

11h10 - 11h20
Virginie Verkarre
(Hôpital Européen Georges Pompidou, Paris)
Comment définir la maladie pré-néoplasique ?

11h20 - 11h30
Cécile Badoual
(Hôpital Européen Georges Pompidou, Paris)
Lésions malpighiennes des VADS de la dysplasie aux carcinomes infiltrants

11h30 - 11h40
Joseph Monsonego
(Institut du Col, Paris)
Dépistage cible du cancer du col utérin : Nouvelles directions

11h40 - 11h50
Virginie Lacronique-Pénard
(Institut Gustave Roussy, Villejuif)
Anomalies de la méthylation de l'ADN dans les étapes pré-leucémiques

11h50 - 12h
Sandrine Roulland
(Centre d'Immunologie Marseille -Luminy, Marseille)
Tracking early steps of follicular lymphoma progression

Session 2 : Genèse des lésions pré-néoplasiques et mécanismes oncogéniques sous-jacents

12h05 - 12h15

Marie-Cécile Michallet

(Centre de Recherche en Cancérologie, Lyon)

Compréhension des mécanismes d'immunosurveillance des lésions pré-néoplasiques pour la découverte de nouvelles cibles d'immunothérapie

12h15 - 12h25

Corinne Abaddie

(Institut Pasteur, Lille)

Genèse des lésions pré-néoplasiques : la sénescence joue-t-elle un rôle ?

12h25 - 12h35

Laurent Bartholin

(Centre de Recherche en Cancérologie, Lyon)

Lésions pré-néoplasiques de l'adénocarcinome du pancréas

12h35 - 12h45

Marie-Dominique Galibert

(Institut de Génétique et Développement de Rennes)

Mélanomes: Modèles d'étude pour l'analyse des états pré-néoplasiques

12h45 - 12h55

Jean-Baptiste Micol

(Institut Gustave Roussy, Villejuif)

CHIP, a preleukemic state ?

13h - 14h15   **Buffet**

Session 3 : Approches innovantes de l'étude des lésions pré-cancéreuses

14h20 - 14h30

Catherine Uzan

(Hôpital Pitié Salpétrière, Paris)

Comment mieux gérer les lésion prénéoplasiques mammaires ? Entre stress et désescalade

14h30 - 14h40

Marie De Tayrac

(CHU de Rennes)

Données bio-cliniques, définition et identification des patients en état précancereux

14h40 -14h50

Mikaël Salson

(Centre de Recherche en Informatique Signal et Automatique de Lille)

Analyse de données omiques de répertoire immunitaire avec Vidjil

14h50 - 15h00

Henri-Alexandre Michaud

(Institut de Recherche en Cancerologie de Montpellier)

Exploration de l'écosystème tumoral par imagerie par cytométrie de masse

15h00 - 15h10

Bruno Cassinat

(Hôpital Saint Louis, Paris)

Les cellules IPS comme modèles d'étude de syndromes pré-néoplasiques

15h10 - 15h40   **Pause**

15h40 - 17h40

Débat sur les thématiques abordées et perspectives

17h40 - 17h50

Clôture

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TEAM *Initiation of Epithelial Cancers*

UMR8161 Institut de Biologie de Lille 59021 Lille cedex

BRIEF BIOGRAPHY

1984-1987:	PhD in Developmental Biology, University Paris 6
1987-1989:	Assistant Professor at University Paris 6
1989-2006:	Assistant Professor at University Lille 1
2000:	HdR at University Lille 1
2006-Present:	Professor at University of Lille
	Manager of the team "Initiation of Epithelial Cancers" in the UMR8161
2008-2012:	Director of the Master Biology and Biotechnology of the Lille 1 University
2012-2016:	Deputy Director of the Biology Department of the Lille 1 University
From October 1st 2018:	Director of the UMR8161

RESEARCH BRIEF

The team "Initiation of Epithelial cancers" is working since 2002 on how the **molecular mechanisms of cellular aging (senescence) impact on neoplastic transformation. Our main activities are basic research aiming at understanding the mechanisms of senescence, especially that of epithelial cells that are poorly studied compared to fibroblastic models, although much more relevant to cancer.** For that purpose, we are using *in vitro* cultured models of normal human epidermal keratinocytes (NHEKs) and dermal fibroblasts (NHDFs). We have established that both recapitulate senescence in response to normal replication or various inducers but, importantly, only senescent NHEKs recapitulate the early events of cellular transformation by a mechanism of post-senescence emergence. We have evidenced a role for oxidatively-induced DNA damage (single-strand breaks) in both senescence and post-senescence neoplastic emergence. Moreover, we have also evidenced a role for endoplasmic reticulum stress and autophagic activity in the balance senescence/neoplastic escape.

We have also examined whether an alteration of the paracrine interactions between epidermis and dermis during aging could direct the outcome of the cells and impact on cancer initiation. We have characterized the secretome of senescent NHDFs and shown that it enhances an epithelium-to-mesenchyme transition in the post-senescent emergent keratinocytes.

Presently, we are working on the model of second cancers developing after radiotherapy, with the hypothesis that ionizing radiations could recapitulate some oncogenic events occurring with normal aging.

KEY WORDS

• Epithelium	• Oxidative stress
• Senescence	• Endoplasmic reticulum stress
• DNA damage	• Autophagy

Corinne Abbadie
« Genèse de lésions pré-néoplasiques mammaires? Entre stress et désescalade »

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TEAM   *PARCC*

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BRIEF BIOGRAPHY

- Full Professor (PU-PH) at Paris Descartes School of Medicine Paris Descartes Faculty of Medicine.
  Professor of Medicine in the Department of Pathology at the Europeen Georges Pompidou hospital (HEGP), Assistance Publique-Hôpitaux de Paris (AP-HP) (nov 2012-).
- Head of a group in team 10, Inserm UMR970, Paris, France. Co-leader of the digital pathology platform (multiplex automated imaging and translational research) HEGP/Inserm
- Director of the tissue biobanking in the HEGP hospital
- Vice Dean (Education) of the Paris Descartes University of Medicine

RESEARCH BRIEF

The precancer lesion in head and neck cancer correspond to epithelium dysplasia. The squamous cell carcinomas are mostly derived from lesion located in the epithelium. The oropharyngeal cancers have a very specific evolution. Indeed the pre cancer lesions are impossible to be seen, and the majority of the diagnoses are done at the metastatic stage. The understanding of the evolution of the cancers is very difficult. The use of algorithm to predict the evolution of the lesion in virtual slide could help to understand to predict and to diagnose of cancer or prelesions.

KEY WORDS

• Head and neck	• HPV
• Carcinoma	• Immunology
• Precancer lesion	

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TEAM *TGFβ and Pancreatic Cancer*
UMR1052 Inserm, CNRS 5286, CRCL, Université Lyon 1

BRIEF BIOGRAPHY

For the past 16 years, Laurent Bartholin has been studying transforming growth factor beta (TGFβ) signaling. He obtained his PhD in 2002 (INSERM U453, Centre Léon Bérard, Lyon), conducted his postdoctoral training from 2002 to 2006 (University of Virginia, VA, USA), before reintegrating Lyon in 2007 (INSERM U590, Centre Léon Bérard), where he initiated a research program focusing on understanding the role of **TGFβ in Pancreatic Ductal Adenocarcinoma (PDAC)** with the support of the INSERM Young Investigator program (2007), and the INSERM Avenir program (2008). Laurent was then recruited as permanent researcher (CR1) by the INSERM (2009). His team was favorably evaluated by AERES for the creation of the Cancer Research Center of Lyon (2011) and favorably renewed by the HCERES (2016). In 2013, Laurent Bartholin became the deputy director of the Tumoral Escape Signaling department at the CRCL. His scientific production comprises 51 publications in the fields of TGFβ, pancreas or both (H-index=21).

RESEARCH BRIEF

PDAC formation is a multi-step process arising from **three major precursor lesions**: Pancreatic Intraepithelial Neoplasia (PanIN), Intra-ductal Papillary and Mucinous Neoplasia (IPMN) and Mucinous Cystic Neoplasm (MCN). Pre-cancerous lesions of increasing grade are associated with recurrent genetic alterations. For instance, oncogenic KRAS activating mutations are detected in virtually all low-grade PanIN. Higher-grade PanIN and PDAC harbor additional genetic alterations inactivating tumor suppressor genes such as p16/CDKN2A, TP53 or SMAD4. SMAD4 is a key mediator of the tumor suppressive effect of TGFβ on epithelial cells. When SMAD4 is lost as observed in humans and demonstrated in mouse models, TGFβ loses its tumor suppressive function and perniciously acquires oncogenic properties associated with tumor invasion, metastatic dissemination and immune suppression. During the last 15 years, one axis of Laurent's research has been to characterize the precise role of TGFβ signaling in the onset of precursor lesions along with their progression towards aggressive stages.

•He showed that transcriptional intermediary factor 1gamma (TIF1γ), a repressor of TGFβ signaling, behaves as a tumor suppressor gene in the exocrine pancreas [1]. Indeed, he developed a genetically engineered mouse model and showed that targeted pancreatic conditional inactivation of Tif1γ cooperated with activated Kras to induce IPMN, independently of SMAD4 [2], by controlling the spindle assembly checkpoint to limit chromosomal instability [3].

•He generated LSL-TβR1^{CA} transgenic mice expressing a Cre-inducible constitutively active type I TGFβ receptor (TβRI) [4, 5]. He demonstrated that conditional and inducible expression of TβR1^{CA} in the acinar compartment of murine pancreas induced the transdifferentiation of acinar cells into ductal-like cells (Acinar-to-Ductal Metaplasia, ADM) predisposing them to KRAS^{G12D}-mediated PanIN formation [6].

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2. Vincent, D.F. et al. (2012). Tif1gamma suppresses murine pancreatic tumoral transformation by a smad4-independent pathway. **Am J Pathol** *180*, 2214-2221.
3. Pommier, R.M. et al. (2015). TIF1-gamma Suppresses Tumor Progression by Regulating Mitotic Checkpoints and Chromosomal Stability. **Cancer Res** 20, 4335-4350.
4. Bartholin, L. et al. (2008). Generation of mice with conditionally activated transforming growth factor beta signaling through the TbetaRI/ALK5 receptor. **Genesis** *46*, 724-731.
5. Vincent, D.F. et al (2010). A rapid strategy to detect the recombined allele in LSL-TbetaRI(CA) transgenic mice. **Genesis** *48*, 559-562.
6. Chuvin, N. et al. (2017). Acinar-to-Ductal Metaplasia Induced by Transforming Growth Factor Beta Facilitates KRAS(G12D)-driven Pancreatic Tumorigenesis. **Cell Mol Gastroenterol Hepatol** *4*, 263-282.

KEY WORDS

• Pancreas • TGFbeta • Mouse models	• Pancreatic Intraepithelial Neoplasia (PanIN) • Intra-ductal Papillary and Mucinous Neoplasia (IPMN) • Mucinous Cystic Neoplasm (MCN)

Laurent Bartholin
« Lésions pré-néoplasiques de l'adénocarcinome du pancréas »

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TEAM *Genetics of pathologies related to the development: Bioninformatic & Computational Genetic Unit*

UMR6290 CNRS, IGDR, CHU Pontchaillou, University of Rennes

BRIEF BIOGRAPHY

Marie de Tayrac is Associate Professor at the Medical School of the University of Rennes. She is the head of the Bioinformatic & Computational Genetic Unit of the Rennes University hospital. She is the President of the French BioInfoDiag network and she develops her research activities in the team Genetics of pathologies related to the development at UMR6290 CNRS, IGDR.

After a PhD in Biology and Health on the genetics basis of brain tumors, she made a postdoctoral fellowship in statistical genetics and epidemiology with the Dr E. Genin (Inserm U946). She worked on population genetics and on the identification of hemochromatosis HFE modifier genes. She now coordinates the development and implementation of computational and bioinformatics methods to decipher the genetics architecture of human diseases and to allow routine molecular tests at the Rennes University Hospital.

RESEARCH BRIEF

New methods are needed to decipher the molecular genetics basis of human diseases. My research and medical activities are dedicated to the development of new capabilities to characterize the genetic initiation of disease by the contextual integration of clinical and omic data. In such e context, I am leading with Prof Isabelle Pellier the EXOCARE national project to decipher the basis of cancer and developmental delay in children (INCa PRTK 2016).

KEY WORDS

• Bioinformatics	• Cancer predisposition
• Genomics	• System biology
• Disease initiation	• Pediatric cancer

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TEAM *Normal and pathological Hematopoiesis: Emergence, Environment and Translational Research*
UMRS1131, Institut Universitaire d'Hématologie, APHP, Laboratoire de Biologie cellulaire

BRIEF BIOGRAPHY

Dr Bruno Cassinat is a PharmD, PhD in charge of the cellular and molecular diagnosis of Myeloproliferative Neoplasms (MPN) in Hopital Saint-Louis, Paris. He also co-heads a research team in the UMRS_1131. After several years dedicated to the understanding of leukemogenesis and treatment improvement in Acute Promyelocytic Leukemia he is now fully dedicated to MPN diagnosis, prognosis evaluation and treatment. He participated to the demonstration of molecular responses in patients with MPN treated with Interferon alpha and hence to the development of this novel therapeutic approach in these diseases. He recently highlighted the role of the JAK2^{V617F} mutation in the endothelial compartment. He authored 110 articles in international peer-reviewed journals. He is a Board member of the French Intergroup for MPNs (FIM) and the biological coordinator of the Integrated Center for MPN in Saint-Louis hospital.

RESEARCH BRIEF

Myeloproliferative neoplasms (MPNs) are chronic hematopoietic disorders characterized by the accumulation of normal red blood cells (in Polycythemia Vera) or platelets (in Essential thrombocytémie) in the peripheral blood. These diseases are considered to derive from the acquisition of mutations in the hematopoietic stem cell compartment leading to the constitutive activation and proliferation of hematopoietic progenitors. The patients may evolve on a chronic mode for several years but a proportion of them will secondary transform to myelofibrosis or acute myeloid leukemia. Both the clinical evolution and response to therapies are heterogeneous and this variability is considered to be dependent on the type and numbers of somatic mutations acquired by the patients' cells. Furthermore, many of the mutations acquired by these patients are also found in healthy people with the recently described clonal hematopoiesis of indeterminate potential (CHIP) features.

Based on a cohort of more than 2000 patients followed in our institution, our research is dedicated to the understanding of clonal evolution of MPN and its relationship with the microenvironment and therapeutics. We have started to analyse the molecular landscape of these patients through the implementation of a Next generation sequencing panel. We are seeking to describe clonal evolution during disease progression and under treatments. This led us to describe the occurrence of molecular responses (decrease in the allelic burden of mutations in *JAK2* or *CALR* genes) in patients treated with Interferon alpha, and the potential resistance induced by the co-occurrence of additional mutations. We have characterized the efficacy of Interferon alpha at the single cell level through clonogenic assays, and this will be completed soon using more efficient methods. We derived induced pluripotent (iPS) cells from patients in order to better characterize the impact of mutations on cell behavior. This approach allowed us to show that endothelial cells harboring the JAK2^{V617F} mutation have pro-inflammatory and pro-thrombotic features, which is a main characteristic of MPN patients. In the future, and this is the objective of the novel research unit recently created, we aim at deciphering how the microenvironment and the therapeutics participate in or prevent the clonal evolution that could lead from the chronic phase to the leukemic evolution.

Bruno Cassinat
« Les cellules IPS comme modèles d'étude des syndromes pré-néoplasiques »

KEY WORDS

• Myeloproliferative neoplasms • Microenvironment • Leukemia	• Clonal evolution • Therapeutics

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TEAM *Laboratoire de Sociologie et d'Anthropologie*
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BRIEF BIOGRAPHY

My current position in Full Professor of Anthropology and Sociology at the University of Bourgogne Franche-Comté. My background started with philosophy, before to turn on sociology. My PhD thesis was prepared in an inter-disciplary perspective, working inside an INSERM Unit of Epidemiology and Public Health. My main current teaching positions are lectures on the history of sociology and anthropology (Bachelor's level), lectures on sociology of health and environment (Master's level), and lectures on the ethics of research and science/society relations (doctoral's level). In addition, I am developping seminars for the professionals of medicine (Inter-university Diploma in Precision diagnosis and personalised medicine, and Diploma in Ethics and Vulnerability). Previously, I was Vice-President of the Non-Interventional Research Ethics Committee (CERNI) at the Federal University of Toulouse (**2016-2017), and now I am coordinator of doctoral training in Research Ethics and Scientific Integrity, at University of Bourgogne Franche-Comté.**

RESEARCH BRIEF

With various previous studies on the genomic approach of prevention (Ducournau, 2018) and the ethics of research biobanking (Ducournau, 2009), I can bring some expertise to tackle the challenges of precancer characterization.

Three key results emerge from my works :

- Social and ethical acceptability of precancer characterization will be achieved if we prevent to transform everyone in a sick person. This is probably the main issue of precancer characterization : to what extend is this characterization going to "medicalize" healthy people, including with intrusive treatments in the name of the statistical risks ?

- The discourse of risks should be communicated very carefully towards patients. Various profiles of patients must to be considered : some of them won't want to be informed of their risks and others will want to get a translation of the statistic risk for themselves, at their individual level.

- Finally, in a public health perspective, precancer characterization should be considered throught its cost effectiveness to prevent cancers. If biotechnological approaches of illness should be encouraged, environenmental approaches of prevention can also be considered. They have already demonstrated their capacity to reduce mortality and increase life expectancy.

KEY WORDS

• Sociology	• Genomics
• Anthropology	• Prevention
• Ethics	• Medicalization

Pascal Ducournau
« Traiter les pré-néoplasies: quelle prévention pour quelle santé ? »

Marie-Dominique GALIBERT

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TEAM *Gene Expression & Oncogenesis*
UMR6290 CNRS, IGDR, Univesity of Rennes

BRIEF BIOGRAPHY

Marie-Dominique GALIBERT is Professor at the Medical School of the University of Rennes.
She is the Deputy Director of the Institute of Genetics and Development of Rennes – UMR6290CNRS, where she leads the Gene Expression and Oncogenesis research group. At the Hospital University of Rennes, she is the head of the Somatic Cancer Genetic Unit.

After studying Pharmacy at the University of Paris V - René Descartes, MD GALIBERT, performed a PhD in Human Genetics - at the Institut Pasteur Paris. Her research focused on deciphering transcriptional regulation mechanisms. She persue a post-doctorate in the laboratory of Prof. Colin Goding, in UK thanks to European funds, where she deciphered the biological and pathological processes of melanocytes and melanomas. She focussed on the role of UV irradiation in the melanocytes. Appointed at the Faculty of Medicine of Rennes, she developed her own research group within the Institute of Genetics and Development of Rennes - CNRS UMR6290 (https://igdr.univ-rennes1.fr/index .php) in line with the expertise acquired as a post-doc fellow.

RESEARCH BRIEF

She focuses on understanding the genetic, epigenetic and molecular basis of cancer development, to identify new therapeutic targets and new markers. Recently, the group made important contribution to the field identifying an original mechanism of miRNA sponging promoting melanoma growth (Gilot, Migault et al., *Nat. Cell. Biol.* Nov 2017). They also identified AhR as an upstream regulator of resistance to BRAFi (Corre, Tardif et al., *Nat Commun.* Nov 2018). Together these results give important insights in the underpining mechnisms of melanoma development.

KEY WORDS

• Melanoma	• Initiation
• Genetic and Epigenetic regulations	• Resistance
• Therapeutic target	

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TEAM *Therapeutic targeting of the tumor cells and of their immune stroma*
   UMR1052 Inserm 5286 CNRS, C.Caux Team, CRCL, CLB

BRIEF BIOGRAPHY

I am an **onco-immunologist**. I started my carreer in **1999** in **Pr J.P. Revillard**'s lab (**Ecole Normale Supérieure de Lyon, France**) working on high dose tolerance mechanisms of anti-CD3 antibodies (J *Immunol*) and Thymoglobulin (*Blood*), an immunosuppressive drug widely used in transplantation. I then moved to Pr **J. Tschopp**'s lab (Switzerland) as an **EMBO post-doctoral fellow**. I identified a novel role of the TRADD protein in innate immune responses such as RIG-like helicases (*Immunity*) and TLRs (*Nat Immunol*) pathways. I went back in France and got a position as **CR1 CNRS** in **Dr J. Marvel**'s lab (**CIRI**, **Lyon**) in **2010**. I deciphered a unknown role of RIG-like helicases in immunosurveillance process (*Plos One*), and on the control of microbiota and allergy (*PNAS*). Since 2014, **I am group leader in the team of C Caux at the CRCL /Centre Léon Bérard - Lyon,** to pursue my investigations on the role of innate sensing during early immunosurveillance processes in the tumoral context.

RESEARCH BRIEF

In the Caux lab, we are interested in understanding the **mechanisms of innate immune surveillance during early stages** (oncogenic stress / pre-neoplastic stage) **of tumorigenesis**. Although diverse innate immune cells likely contribute to tumor sensing, it's mainly cellular stress detection by NK cell through NKG2D/NKG2DL interaction that is so far established to mediate tumor recognition. In my group, we will focus on Breast Cancer and Colon carcinoma and use unbiased system biology and biologically-driven approaches, both in human and mice, to identify important mechanisms of immune sensing of the very early stages of cell transformation. To achieve this goal, we will have two complementary approaches:

Understand tumor intrinsic mechanisms leading to early immune detection
Herein we hypothesized that immune surveillance is initiated early during transformation through oncogenic stress. This is supported by the literature and by our data showing that oncogenic stress induced by Sp1 transcription factor accumulation is detected through an innate intrinsic pathway (RIG-like receptors) and results in innate immune cell sensing (*Dupuis-Maurin, Plos One 2015*).
To decipher the underlying mechanisms *in vitro* in human and *in vivo* in mice, we have developed approaches based on **mammary epithelial cell lines expressing an inducible oncogene**, and **co-culture assays with innate immune cells**. Based on our preliminary results, we are currently focusing on **internal stress sensor candidates** and deciphering their contribution in early immune detection by **neutrophils** using pharmacologic inhibitors and genome editing. In complement, in a mouse mammary tumor model where oncogenic stress leads to tumor rejection in immunocompetent (wt) mice but not in immunodeficient mice, an **unbiased genome editing *in vivo* screen** will be performed to select tumor clones developing in wt mice and to discover molecular pathways operating in the tumor cell leading to immune detection.

Role of neutrophils and other innate immune cell (Dendritic Cell subsets, NK) crosstalk in early tumor immune surveillance

Thanks to a collaboration with the anti-cancer center Léon Bérard, we have access to **human early tumor lesions** (Hyperplasia and *In Situ* Breast Carcinoma, and Colon polyps). We have also acquired a fine knowledge of **pre-neoplastic stages in a spontaneous mouse mammary carcinogenesis model**. Here we plan to perform a **comprehensive analysis of the functional/activation status of neutrophils and other innate immune cells** (collaboration J Valladeau-Guilemond and N Bendriss-Vermare groups) in **early compared to invasive tumors in human and mice** using state-of-the-art technologies: 1) CytOF and deep scRNAseq of **tumor-infiltrating neutrophils** and other innate immune cells, associated to advanced computational and system biology; 2) multi-immunofluorescence of selected early immune surveillance pathway(s); 3) evaluation of their role in *in vitro* models (pre-neoplastic organoids and co-culture assays with innate immune cells) and *in vivo* in mice.

Overall, we expect to generate **novel basic knowledge and concepts on immune sensing mechanisms of early cell transformation** and decipher the cooperation between **neutrophils** and innate immune cell populations. Because these immune surveillance mechanisms are likely to be exceeded in established tumors, we also expect to identify **novel escape/resistance pathways** and **targets for immune intervention**.

KEY WORDS

• Immunosurveillance	• Neutrophils
• Pre-neoplastic stages	• Breast cancer
• Innate immune cells and receptors	• Colon cancer

Marie-Cécile Michallet
« Compréhension des mécanismes d'immunosurveillance des lésions pré-néoplasiques pour la découverte de nouvelles cibles d'immunothérapie »

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TEAM *Immunity and Cancer*

Institut du Cancer de Montpellier, IRCM

BRIEF BIOGRAPHY

After having obtained my Pham.D, I realized a Ph.D focused on the immuno-modulatory effect of monoclonal antibodies in infectious disease treatments in a CNRS-labeled unit (Montpellier). During my first post-doc, I worked on the humoral response targeting human retroviruses (HERVs) in HIV-1 infected patients at the Division of Experimental Medicine (UCSF-San Francisco). We showed that anti-HERVs antibodies recognize and eliminate HIV-1 infected cells through ADCC mechanisms. Then, I joined the Immunity and Cancer team at the IRCM (Montpellier). We showed that the use of immune checkpoint inhibitors potentiates the effect of an anti-tumor monoclonal antibody treatment. My work evolved toward the study of tumoral microenvironment and the immunosuppressive pathways involved in the anti-tumor treatment resistances. We demonstrated that disrupting the CD39/CD73/adenosine pathway improves anti-tumor therapies. In parallel, I supervise different projects about the impact of radiotherapy on the tumoral immune microenvironment. Recently, I was hired as head scientist and operational of the first French platform of mass-cytometry imaging.

RESEARCH BRIEF

Strengthening/reinvigorating the tumor immune surveillance by stimulating rejection-type processes or blocking suppressive pathways is the foundation of new immune-based therapies that allow the development of a long-lasting adaptive immunity, which both counteracts tumor growth and prevents tumor relapse. In this context, the research programs developed in our group aim at a better understanding of the relationships between cancer cells and cells of the immune system, with a specific interest in the contribution of immune effectors to the prevention or treatment of cancer and the role of mediators of inflammation in the development of cancer.

Through a deep and comprehensive analysis of tumor immune microenvironment we search for new immune based combined therapies to improve response to conventional therapies such as targeted therapies or radio- and chemo-therapies.

We described the CD39 ectonucleotidase as a novel immune checkpoint inhibitor and identified CD39 neutralizing antibodies currently under pre-clinical development by Innate Pharma (Manuscript in revision for Immunity).
We demonstrated that some inflammatory cytokines, promotes the polarization of gd T cells into regulatory cells and are currently working at a better characterization and understanding of the regulatory gd T cell subpopulation in cancer (Oncoimmunology 2017).

Using the B16F10 melanoma model in mice, we demonstrated the immunomodulatory potential of the TA99 mAb, an antibody that targets the TYRP-1 surface antigen overexpressed in tumor melanocytes, leading in 30% of treated mice of a complete tumor eradication associated with a long-term protective memory immune response. In this model, we showed that the PD-1 blockade at the time of tumor escape potentiates the immune-mediated antitumor effects of TA99 treatment (Oncoimmunology 2017).

In collaboration with the Institut regional du Cancer de Montpellier (ICM) and industrials, we developed different projects aiming to decipher the impact of radiotherapy on the tumoral microenvironment to improve such therapy and identify immune signature that may predict treatment response in the context of the locally advanced cervix cancers.

Under our initiative and with the strong support of the ICM, we will be the first institute in France to propose an imaging mass cytometry platform for the exploration of tissue ecosystem. The Helios/Hyperion system will be installed at IRCM by the end of 2018 and open by the beginning of 2019. Such breakthrough technology allows high multiplexed imaging of tissues (ex: tumor) with subcellular resolution by mass cytometry in spatial context.
Altogether our projects are established on our expertise in onco-immunology with a strong knowledge of preclinical models and a recognized expertise of tumor immune microenvironment analysis. They are developed in close association with clinicians and industrial partners.

KEY WORDS

• Oncoimmunology	• Immunosuppression
• Tumor ecosystem	• Mass Cytometry and Imaging
• CD39/CD73/Adenosine	• Anti-tumor therapy

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TEAM *Team 3 – Normal and Pathological hematopoiesis*
UMR1170 Inserm, IGR, Université Paris Sud

BRIEF BIOGRAPHY

MD graduated in hematology (Lille 2008), assistant-professor in Paris (Saint-Louis Hospital 2008-2011), recruited as a physician in the department of hematology of Gustave Roussy Cancer Center (currently responsible of the Leukemia Unit). Trained to research in onco-hematology in Villejuif under the direction of Dr Vainchenker and Pr Solary (PhD graduate in 2016, University Paris Saclay). Spend 2 years in Dr Abdel-Wahab Lab at MSKCC, New York, working on the role of ASXL2 in haematological malignancies (2013-2016). Selected trainee for the Translational Research Training in Hematology 2015 program and awarded of the SFH Prize in 2016.

RESEARCH BRIEF

Joined UMR1170 in 2017, focusing research in the field of acute myeloid leukemia (AML), especially preleukemic state. Involved in clinical/research project on genetic predisposition leading to AML as RUNX1 and ATG2B/GSKIP germline predisposition and their role in leukemogenesis. Leading project on the role of clonal hematopoiesis in cancer in general and as a potential preleukemic event, especially in therapy related myeloid neoplasm.

KEY WORDS

• Acute Myeloid Leukemia	• Pre Leukemic state
• Clonal hematopoiesis	• TP 53
• Therapy related myeloid neoplasm	

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TEAM *Team 1 – Early step of hematopietic transormation*
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BRIEF BIOGRAPHY

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RESEARCH BRIEF

Virginie Penard-Lacronique is leading the research effort on acute myeloblastic leukemia (AML) in Gustave Roussy Cancer Campus (Villejuif, France). Her recent work focus on IDH-Mutant AMLs and the detailled studies of the recently developed inhibitors of these mutants, which were tested for the Gustave Roussy part in the Department of clinical hematology. She has developed all necessary technics and reagents for this project.

KEY WORDS

• Leukemia, myeloid , acute/genetics • Cell differentiation • Epigenesis	• Hematopiesis

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TEAM *Genomic Instability and Human Hemopathies*
S.Roulland & B. Nadel team, U1104 Inserm, CIML

BRIEF BIOGRAPHY

Sandrine Roulland is a PharmD and a scientist who did a PhD in Molecular Epidemiology and Public Health studying blood biomarkers of environmental exposure at the University of Caen. She joined the Centre d'Immunologie de Marseille Luminy to work on B cell lymphomagenesis and contributed to identify lymphoma precursor cells in 'healthy individuals' years before diagnosis and characterize the immunological processes governing lymphoma progression. She obtained a tenure track position at INSERM in 2009 and received the CNRS Bronze medal in 2015. She recently spent 2 years in Lou Staudt's laboratory at the National Cancer Institute (NIH) to dissect the genetic vulnerabilities of mature B-cell lymphomas using functional screens, identify new targets for therapy and probe lymphoma biology. In 2018, she was appointed group leader at the CIML and co-director of the team 'Genomic Instability and Human Hemopathies' and currently directs research at the frontier of cancer prevention, molecular basis and treatment of B-cell lymphomas.

RESEARCH BRIEF

The primary focus of our lab is to investigate the pathogenesis of Follicular Lymphoma (FL), an indolent germinal-center (GC)-derived B cell malignancy in adults. Since the seminal discovery of FL precursors in the blood from otherwise healthy individuals and the impact of pesticide-induced lymphoproliferation on those cells, we seek to understand the genetics of premalignant states in FL, its potential as a biomarker for predicting FL risk long before diagnosis, and whether those premalignant states could serve as a cell reservoir seeding relapses and resistance to therapy during FL clinical course. We are using innovative approaches combining genomic and transcriptomic at the single cell resolution to track the 'hidden' yet highly impacting putative cancer precursor cell (CPC) population in 'healthy' and pathological human samples with the goal to identify CPC biomarkers and provide biologic-driven therapeutic rationales to directly target this CPC population and eventually prevent relapse or transformation into aggressive FL disease.

We also develop genetically and pathologically mouse models of premalignant and FL stages to recapitulate FL clonal progression, characterize (epi)genetic, microenvironmental and immunological cues, notably the perturbation of GC/memory B cell dynamics, as drivers of early FL progression that may ultimately serve as an in vivo preclinical tool to validate candidate targets. To develop new treatments for FL, our lab utilizes functional genomic approaches, including CRISPR-based genetic screens, to dissect genetic vulnerabilities in FL. Among others, we showed that FL rely on a B Cell Receptor signaling mode that engage the PI3K/AKT survival pathway thereby suggesting rational therapeutic strategies using proximal BCR inhibitors and PI3K inhibitors. We are pursuing functional genomic studies in t-FL to define mechanisms of response and resistance to targeted drugs with the expectations that it may serve in a near future as a foundation for translational studies to treat this disease.

Sandrine Roulland
« Tracking early steps of follicular lymphoma progression »

KEY WORDS

• Lymphomagenesis • Predictive biomarkers • Lymphoma Precursor cells	• Targeted therapies

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TEAM *Bonsai*

  UMR9189 CNRS, Inria, Univ.Lille - CRIStAL

BRIEF BIOGRAPHY

Mikaël Salson is an associate professor in computer science in the Bonsai bioinformatics group in Lille since 2010. He conceives algorithms and software for processing data from high-throughput sequencers. Together with Mathieu Giraud, he is the co-author of Vidjil, a platform for the analysis of immune repertoire, which is now used in routine practice by several hospitals around the world and which is supported by the VidjilNet consortium. He is also the co-author, with Nicolas Philippe, of CRAC a software for the analysis of RNA-seq data. This software is now transferred via the SeqOne startup. Apart from those practical contributions, Mikaël Salson has also proposed several theoretical contributions in string algorithmics (dynamic indexing and approximate string matching).

RESEARCH BRIEF

Since 2011, we have developed in Lille an open-source software platform designed for the analysis of immune repertoire, Vidjil. This platform was first conceived to identify lymphocytes at diagnosis in leukemia. It is now used in routine clinical practice in several European countries (France, Italy, Czech Republic, United Kingdom) and has analysed immune repertoires of thousands of patients so far. The platform can also have other usages. It is designed to be able to track lymphocytes along the time, making possible to monitor an immune response. The Vidjil platform could also be used to identify or monitor tumor infiltrating lymphocytes.

KEY WORDS

• High-throughput sequencing	• Immune repertoire
• Bioinformatics	• Leukemia
• Tumor infiltrating lymphocytes	

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TEAM *Team 13 – PARCC , Paris Centre de Recherche Cardiovasculaire*
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BRIEF BIOGRAPHY

Pathologist at Necker enfants Malades hospital from 1997 to 2015 and then at European Georges Pompidou hospital (HEGP) from 2015 until now, I had the opportunity to diagnose a broad range of pathology from inflammatory and autoimmune to tumoral lesions, in multiple organs, in pediatric and adult population. In the department of pathology of HEGP, I am responsible for the uropathology sector. Bladder, prostate, kidney and external genital organ offer some various and interesting model of carcinogenesis.

RESEARCH BRIEF

I initially focused my research on intestinal T lymphomagenesis occurring in the context of celiac disease, an autoimmune intestinal disease due to gluten intolerance. Associated to a polyclonal expansion of intra-epithelial T cell lymphocytes, inflammatory infiltrate and villous epithelial atrophy, celiac disease could be considered as a pretumoral lesion being associated to a higher risk of intestinal T cell lymphoma and intestinal adenocarcinoma.
Then, in the field of uropathology, I focused my research on kidney cancers and particularly those occurring in genetically predisposed people which concern 5% of patients developing a renal tumor. As part of the care program, we set up since 2016, easy access to oncogenetic consultations and develop a specific molecular plateform in order to identify patients with a hereditary predisposition to kidney tumors. Interestingly, among the 12 known syndromic forms, some of then are associated with cystic lesions that could evolve into renal cancer, such as cystic lesion and clear cell renal cell carcinoma occurring in the context of Von hippel disease.

KEY WORDS

• Hereditary cancer predisposition	• Celiac disease
• Kidney cancer	• Autoimmune disease
• T cell intestinal lymphoma	