8TH FRENCH-CHINESE SYMPOSIUM ON CANCER RESEARCH

November 12, 2020

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PROGRAM

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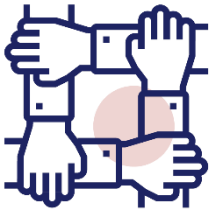
***Prof. Zemin ZHANG**, Professor, Peking University and a principal investigator at BIOPIC, College of Life Sciences of Peking Universities, and Beijing Advanced Innovation Center for Genomics*

12h05 / 19h05

lncRNAs as New Players in Cancer Development

***Prof. Claire VOURC'H**, Professor, University Grenoble-Alpes, INSERM U1209, CNRS UMR 5309*



SPEAKERS / MODERATORS

Dr. Corinne ALBIGES RIZO

Institute for Advanced Biosciences, Grenoble

BIOGRAPHY

Corinne Albiges-Rizo received a PhD in Cellular and Molecular biology from the University of Grenoble in 1990. She worked as a PhD student at EMBL in Grenoble and completed her post-doctoral research as a fellow in HHMI in Chicago. She moved back to Grenoble as a CNRS Scientist. Her team is based within the Institute for Advanced Biosciences (Institut Albert Bonniot) and she also heads the department of microenvironment and cell plasticity. She was President of the French Society for Cell Biology (SBCF). Using transdisciplinary approach, her team is investigating how focal adhesions and invadosomes sense varied external cues to modulate downstream signaling networks and force transmission to elucidate the sensory mechanisms underlying invasion and tissue architecture. The lab is specifically exploring the biological and physiological relevance of integrin activation. The current project is to study how integrins, together or with co-receptors, respond to combination of chemical and physical inputs and then form signaling complexes that are arranged in time and space to specify cell contractility and transcriptional program.

Prof. Liufu DENG

Ph.D., Professor, PI

Shanghai Institute of Immunology

Shanghai Jiao Tong University School of Medicine

BIOGRAPHY

Dr. Deng received his Ph.D. at Institute of Biophysics, Chinese Academy of Sciences in 2010. After that, he obtained postdoc training at the University of Chicago and was promoted to Research Associate (Assistant Professor) at the University of Chicago in 2014. Since 2016, he has been appointed as Professor and PI at Shanghai Institute of Immunology, Shanghai Jiao Tong University School of Medicine. He has committed to putting novel ideas about how to improve cancer care through the interaction of both radiation oncology and immunology. Currently, his research interest focuses on understanding new mechanisms of tumor immune escape in the context of innate immune sensing and T cell stemness programming, and the translation of mechanistic findings into combined cancer therapy strategies.

PRESENTATION SYNOPSIS

Immune escape is a key process of cancer progression and metastatic dissemination and creates spatiotemporal barriers to successful cancer treatment. The quality and quantity of stem cell-like CD8+ T cells is the key to successful immunotherapy, including T cell therapy and immune checkpoint blockade. Understanding the mechanisms of the failure in the formation of stem cell-like CD8+ T cells will provide insight to the development of improved T cell therapy for cancer treatments. His finding uncovers a new mechanism that cGAS-STING cascade plays an unanticipated role in the maintenance of CD8+ T cell stemness in antitumor immunity, given the widespread interest and current develop efforts to use STING agonist in cancer immunotherapy. In addition, he has been developing a new perspective that innate immune sensing evasion is a new modality of the resistance to radiotherapy and the failure of immune surveillance. His findings suggest M-MDSC as a negative feedback circuit of STING signaling mediate radiation resistance, and point out a translational strategy involving anti-CCR2 antibody treatment to improve radiotherapy.

Dr. Aurélie DUTOUR

Researcher, Léon Bérard Cancer Center, Lyon

BIOGRAPHY

Dr Aurélie Dutour, is specialized in translational research of bone sarcomas. After a PhD in molecular and cellular biology, Aurélie Dutour completed a post-doctoral fellowship in immunotherapy for pediatric cancers at Texas Children's Hospital in Houston. Since she joined the Centre Léon Berard in 2007, Aurélie Dutour specializes in the modelisation and evaluation of new therapies for bone sarcomas. She is particularly interested in the interaction of bone tumors with their immune environment in order to identify prognostic factors or new therapeutic targets.

PRESENTATION SYNOPSIS

In many solid tumors, the setting of an immunosuppressive environment regulated by macrophages, cytokines and immune checkpoints (ICP) is often a bad prognosis factor. Thus, targeting this immune environment led to the developments of new immunotherapies that raised high hopes for the treatment of solid tumors.

Immunotherapy for chondrosarcoma (CHS) is comparatively less advanced partly because the immune environment of these rare tumors remains sparsely explored. However, with their high resistance to conventional therapies CHS are typically tumors for which immunotherapies could be a solution.

To get an exhaustive cartography of CHS immune landscape, identify prognosis factors and therapeutic targets, we described the immune populations and the immune checkpoints -of conventional CHS and dedifferentiated CHS one of the rarest and most aggressive subtype of CHS.

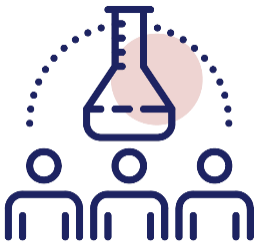
Immunohistochemical methods (IHC) were used to map the expression of immune cells markers (CD3, CD8, CD68, CD163) on a cohort of 27 conventional CHS and 49 dedifferentiated CHS.

RT-qPCR was used to screen the expression of a panel of ICP which expression, for the most promising ones, was confirmed by IHC. The impact of the density of Tumor Infiltrating Lymphocytes (TIL), Tumor Associated Macrophages (TAM) and ICP on clinical outcome were analyzed.

TAM were the main immune population encountered in dedifferentiated and conventional CHS. Immune infiltrate composition was correlated with dedifferentiated CHS' outcome: a high CD68+ TAM density was associated with the presence of metastases at diagnosis ($p<0,05$) and a high CD68+/CD8+ ratio was an independent bad prognosis factor ($p<0.01$).

PDL1 was found to be expressed in 42.6% of dedifferentiated CHS while it was absent in conventional CHS. Of all the ICP tested, CSF1R, B7H3, SIRPA, TIM3 and LAG3 were found to be expressed at mRNA level in both CHS subtypes. The expression of CSF1R by TAM infiltrating CHS was confirmed by IHC in 62.9% of conventional CHS and in 89.7% of dedifferentiated CHS.

By showing that CHS immune environment is mainly composed of macrophages expressing CSF1R and that a high CD68 intratumoral density is correlated with the presence of metastases at diagnosis; our data reinforce the hypothesis of an immunosuppressive environment of this tumor. Our results converge to indicate that an immunomodulation through macrophages could be a promising therapeutic approach for CHS.



Prof. Xin-Hua FENG

Distinguished Professor and Director,

Life Sciences Institute, Zhejiang University, Hangzhou, China

BIOGRAPHY

Education:
1983 B.S., Wuhan University
1986 M.S., Institute of Genetics and University of Chinese Academy of Sciences
1992 Ph.D., University of Maryland, College Park
Research and Professional Held in Chronological Order:
1993-1997 Postdoctoral Researcher, University of California, San Francisco
1997-1999 Research Assistant Professor, University of California, San Francisco
1999-2003 Assistant Professor, Baylor College of Medicine
2003-2007 Associate Professor (Tenured), Baylor College of Medicine; Investigator, Duncan Cancer Center
2007-present Professor (Tenured), Baylor College of Medicine (now part-time/limited effort)
2010-present Distinguished Professor, Life Sciences Institute, Zhejiang University
The research of Feng lab is aimed at elucidating the underlying mechanisms and interplays among protein modifications, signaling pathways and gene transcription as well as understanding their roles in cell proliferation, tissue differentiation and pathogenesis of human diseases. Current research projects focus on the following four areas: (1) TGF-β/BMP signal transduction; (2) Mechanism underlying how cancer escapes from TGF-β anti-growth control and programmed cell death; (3) Noncoding RNA and RNA–binding protein in cancer development and metastasis; (4) Mechanism of stem cell renewal and differentiation. Our ultimate goal is to design better therapeutics in prevention and treatment of human diseases.

PRESENTATION SYNOPSIS

Members of TGF-ß superfamily play essential roles in normal development. In physiological settings, strength and duration of TGF-ß signaling are tightly and precisely controlled. Dysregulation or function of TGF-ß signaling is associated with pathogenesis of human diseases. For instance, loss of the antiproliferative response is a hallmark in human cancers. Tumor cells have developed a number of strategies to escape from negative growth control. One major mechanism to resist the cytostatic effect of anti-growth factor such as TGF-ß is through inactivating mutations/deletions in the TGF-ß signaling pathway, which frequently occur in gastrointestinal and pancreatic cancer. For example, tumor suppressor Smad4/DPC4, the central transducer of TGF-ß signaling, is deleted in more than half of pancreatic cancer patients. However, deletion or mutations in the Smad4 gene are rare in other types of cancers. We have taken functional genomic, proteomic and cell biological approaches to study how the tumor suppressor function is regulated in normal and cancer cells. We found that activation of many oncoproteins can cause TGF-ß resistance. Our novel studies gain conceptual insights into the oncoprotein-tumor suppressor interplay in tumorigenesis and provide guidance to logical therapeutic designs in cancer prevention, diagnostics and treatment

Dr. Romain GUIÈZE

Department of Clinical Hematology and Cellular Therapy,

Clermont-Ferrand University Hospital Center

Team EA 7453 - CHELTER (Role of intra-Clonal HEterogeneity and Leukemic environment in ThErapy Resistance of chronic leukemias), Clermont Auvergne University

BIOGRAPHY

A longstanding theme of my studies has been how to take into account the molecular features of leukemia cells to improve patients' management. My first works involved study of normal hematopoiesis (*Blood* 2008) and translational studies on acute myeloid leukemia (*Leukemia* 2010). By joining the Clermont-Ferrand clinical team, my research of interest has focused on chronic lymphocytic leukemia (CLL) and therapeutic resistance. I have notably investigated resistance to cytotoxic agent (*Oncotarget* 2015, *Blood* 2015) and novel agents (*Cancer Cell* 2019). My current works are focusing on how to best benefit from novel agents by using genomic monitoring. With this aim, we are leading studies integrating both clinical questions and cutting-edge technologies in the setting of the FILO group (French innovative leukemia organization) and international collaborations.

PRESENTATION SYNOPSIS

Mitochondrial apoptosis can be effectively targeted in lymphoid malignancies with the FDA-approved B cell lymphoma 2 (BCL-2) inhibitor venetoclax, but resistance to this agent is emerging. We show that venetoclax resistance in chronic lymphocytic leukemia is associated with complex clonal shifts. To identify determinants of resistance, we conducted parallel genome-scale screens of the BCL-2-driven OCI-Ly1 lymphoma cell line after venetoclax exposure along with integrated expression profiling and functional characterization of drug-resistant and engineered cell lines. We identified regulators of lymphoid transcription and cellular energy metabolism as drivers of venetoclax resistance in addition to the known involvement by BCL-2 family members, which were confirmed in patient samples. Our data support the implementation of combinatorial therapy with metabolic modulators to address venetoclax resistance.

Prof. Pierre HAINAUT

Chair, Cancéropôle CLARA Steering Committee

BIOGRAPHY

Pierre Hainaut, PhD in Biological Sciences, is a graduate of the University of Liège in Belgium. After his post-docs in France and the United Kingdom (1988-1994), he joined the International Agency for Research on Cancer (IARC, World Health Organization) in 1994, where he held the position of Head of Molecular Carcinogenesis from 1999.

In 2014, he was appointed Professor of Cancer Biology and holds the Chair of Excellence in Translational Research at the University of Grenoble-Alpes (UGA). As a Practitioner at CHU Grenoble-Alpes, he develops access to therapeutic innovation for the benefit of patients.

Since 2015, he has directed the Institute for Advanced Biosciences (IAB) in Grenoble, a joint research center of the University of Grenoble-Alpes, the French National Institute for Health and Medical Research (Inserm) and the French National Center for Scientific Research (CNRS), which brings together nearly 300 researchers on the theme of "Epigenetics, Environment, Cellular Plasticity and Cancer".

Pierre Hainaut is internationally renowned for his work on mutations in the TP53 gene, the gene most often mutated in cancers. In particular, he is known for his work on the mutagenic effects of tobacco, on liver cancers and on Li-Fraumeni Syndrome, a form of cancer predisposition caused by the hereditary transmission of TP53 mutations. He is the author of more than 400 international publications and several reference works, including a recent Encyclopedia of Cancer.

Dr. Carine HALFON DOMENECH

Associate-Professor, Hospital pediatric hematologist,
Institute of Hematology and Oncology Pediatric (IHOPe), Lyon
and Medical Teacher (MCU-PH), University Lyon 1, Lyon, France
Research team "Dependence receptors, cancer and
development", UMR INSERM 1052 - CNRS 5286 –
University Lyon 1- CRCL

BIOGRAPHY

After obtaining my medical degree, specializing in pediatrics, as well as in hematology and oncology in 2009, I performed my Fellowship in pediatric Hematologic and Oncology unit, from 2009 to 2012 at IHOPe, France. Then, I moved to Paris to perform my PhD at the University Pierre and Marie Curie (UPMC), Paris 6, from 2013 to 2016/2017. There, I learned to work on hematopoietic stem cells and engaged hematopoietic cells during fetal life in Fanconi anemia disease with the Dr Michèle Souyri and the Pr Jean Soulier.
Then, I went back to Lyon to take my actual position, and develop my research project on pediatric B-acute lymphoblastic leukemia leukemogenesis in the lab of Dr Patrick Mehlen.

PRESENTATION SYNOPSIS

Acute leukemias are the leading cause of cancer in children and affect particularly young children, with a peak incidence between 2 and 5 years old. In our project, we study mechanisms of resistance to apoptosis in childhood leukemia cells. To do that, we sort blast cells from bone marrow samples at diagnosis, in order to perform RNA-sequencing. We are also working on the residual marrow functionality with hematopoietic differenciation assays on co-culture system. Understanding mechanisms of resistance to apoptosis in leukemia cells also requires study their microenvironment, so we learned to culture mesenchymal stem cells issued from bone marrow samples at diagnosis to further analyses.

Prof. Baiyong SHEN

Ruijin Hospital, Shanghai Jiao Tong University

School of Medicine

BIOGRAPHY

SHEN Baiyong, MD, PhD, FACS, Prof of Surgery. Dr. Shen Baiyong is currently the vice president of Ruijin Hospital, Executive Dean of Sino-French Joint Medical College of Shanghai Jiao Tong University School of Medicine, Director of Pancreatic Disease Institute of Shanghai Jiao Tong University School of Medicine, Executive Director of Institute of Translational Medicine of Shanghai Jiao Tong University, Vice-director of Shanghai Institute of Digestive Surgery and Deputy director of State Key Laboratory of Oncogenes and Related Genes. He received bachelor degree of Clinical Medicine from Shanghai Second Medical University in 1991, a master degree of hygiene management from Hua Xi Medical University in 2002, and a doctor degree of Clinical Medicine from Shanghai Jiao Tong University School of Medicine in 2006. He has been working as a hepatobiliopancreatic surgeon for over 20 years and established one of the largest and most influential medical research centers for diagnosis and treatment of pancreatic disease in China. He and his teammates committed to exploring the pattern of tumorigenesis, development and metastasis in pancreatic cancer, aiming to improve the long-term survival of pancreatic cancer.

Prof. Claire VOURC'H

Professor, University Grenoble-Alpes,

INSERM U1209, CNRS UMR 5309

BIOGRAPHY

Over the years, I have developed a strong interest in the field of chromatin and non-coding RNAs. Using the heat shock (HS) model, allowing rapid and reversible changes in gene expression, I have identified long non-coding RNAs (lncRNA) of centromeric origin, as novel effectors of the HS response, in human cells. At the time of this discovery, André Verdel (the leader of the group RNA and Epigenetics) identified, RNAs of centromeric origin as important new players in the formation and maintenance of heterochromatin in yeast. Within the framework of our recent association, our wish is now to identify new stress-induced lncRNA, and extend this characterization to tumors.

PRESENTATION SYNOPSIS

For many years, the cellular response to stress was essentially described through increased expression of Heat Shock Proteins (HSPs). It now appears that the stress response mediated by the transcription factor Heat Shock Factor 1 (HSF1), also triggers the up-regulation of lncRNA. I will present how these lncRNAs could represent important new players, not only in the heat shock response but also in cancer formation and/or development.

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Prof. Zemin ZHANG

Professor, Peking University and a principal investigator at BIOPIC, College of Life Sciences of Peking Universities, and Beijing Advanced Innovation Center for Genomics

BIOGRAPHY

Dr. Zhang obtained his BS from Nankai University, PhD from Penn State University and postdoctoral trainings at UCSF. Dr. Zhang spent >16 years at Genentech/Roche, leading the cancer genomics and bioinformatics group to discover anticancer targets and biomarkers using cutting technologies such as machine learning and high throughput sequencing. He has pioneered multiple research directions in computational cancer biology and cancer genomics including the first ever whole genome tumor sequencing. He is also an inventor for 60 issued US patents, and has directly contributed to the initial finding of the molecular targets of multiple cancer therapeutic agents in clinical trials. His lab currently focuses on understanding the detailed characteristics of the tumor microenvironment, in particular the interplay between immune and cancer cells using single cell sequencing technologies and novel bioinformatics tools. He is a CUSBEA Scholar as well as Cheung Kong Scholar.

PRESENTATION SYNOPSIS

Understanding tumor immune microenvironments is critical for identifying immune modifiers of cancer progression and developing cancer immunotherapies but it is increasingly evident that different cancer types may harbor distinct characteristics of subtypes, functional states and cell-cell interactions for tumor-infiltrating immune cells. Combining published and newly generated single-cell RNA sequencing (scRNA-seq) data, we performed comprehensive analysis of tumor-infiltrating immune cell sub-populations and delineated their abundance across 21 human cancer types. Such pan-cancer analysis revealed a congruence of major myeloid lineages, dendritic cell (DC) subsets and monocyte subsets, while T cells and macrophage subsets exhibited unique transcriptomic patterns across tumor types. The broadly present *LAMP3*$^{+}$ cDCs could be further characterized according to their different developmental origins, highlighting their differences in transcription factors and external stimulus. We also uncovered the complexity of cDC2s in tumors and identified a pro-inflammatory subset. Tumor-associated macrophages (TAMs) linked with tumor angiogenesis are characterized with diverse markers among different tumor types. Our comprehensive analysis provides deep understanding of the commonalities and differences of the tumor microenvironment across multiple cancers, and some of the feature might shape how different tumors respond to immunotherapies.

Prof. Junke ZHENG

M.D., Ph.D., Professor, PI

Shanghai Jiao Tong University College of Basic Medical Sciences

BIOGRAPHY

M.D., Ph.D., Professor, PI, mainly works on the regulation of stemness of hematopoietic stem cells (HSCs) and leukemia-initiating cells (LICs). Our interest is to understand how bone marrow niche controls the cell fates of HSCs and LICs and dissect the potential niche components that are critical for the maintenance of HSC/LIC activities. Meanwhile, we also study the metabolic control in HSC/LIC stemenss and its interplay with bone marrow niche. We have demonstrated that several niche proteins and metabolic pathways may play important roles in cell fate determinations, which has been published in Nature, Cell Stem Cell, Blood, JCI, Leukemia, EMBO J, Haematologica and Cell Reports.

PRESENTATION SYNOPSIS

Immune checkpoint blockade therapy has been successful in treating some types of cancer but has not shown clinical benefits for treating many types of acute myeloid leukaemia (AML). This result suggests that leukaemia uses unique mechanisms to evade this therapy. Certain immune inhibitory receptors that are expressed by normal immune cells are also present on leukaemia cells. Whether these receptors can initiate immune-related primary signalling in tumour cells remains unknown. We recently revealed unexpected roles of several immune inhibitory receptors (CD244, LILRB2 and LILRB4) in promoting AML development. For example, CD244 co-operates with c-Kit to activate SHP-2 signaling to dephosphorylate p27 and maintain its stability to promote leukemia development. LILRB4 supports tumour cell infiltration into tissues and suppresses T cell activity via a signalling pathway that involves APOE, LILRB4, SHP-2, uPAR and ARG1 in AML cells. Deletion of LILRB4 or the use of antibodies to block LILRB4 signalling impeded AML development. Immune inhibitory receptors may represent a compelling target for the treatment of AML.

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