Since 2016, Paris Descartes University and the Hebrew University of Jerusalem in Israel have been working together, enhancing their partnership and widening the scope of their collaboration. In 2017 a Cooperation Agreement was signed between both Institution, strengthening the links between the Universities and giving a frame to a strong and long-lasting cooperation.

In recent years, cancer immunotherapy is considered as a revolution in the management of cancer patients with more than a dozen approved clinical indications and a dynamic that does not weaken in terms of new molecules in development and therapeutic innovations. Following the initiative of the dean Gerard Friedlander and the international office of Paris Descartes School of Medicine (Manon Xhenseval, Frédéric Batteux), it seemed to us a good time to propose a joint meeting on cancer immunotherapy with the Hebrew University of Jerusalem in Israel (HUJI) for several reasons. The two institutions have a strong involvement in oncology and especially in immuno-oncology even before the recent craze in immunotherapy. They have a fairly close organization with several hospitals on several sites (Ein Kerem and Mt Scoupus for HUJI and Hadassah Hospital) with the Institute of Oncology Sharett integrating the various clinical oncology department. There are 3 hospitals associated with the Paris Descartes Faculty of Medicine (Cochin Hospital, Necker Hospital and Georges Pompidou European Hospital) developing oncology and especially immunotherapy activities.

Translational research occupies a predominant role in these hospitals closely linked to different research centers (Center for Clinical Research and Cancer Research for HUJI; Institut Imagine, Institut Cochin, Cordeliers Institute, PARCC for Paris Descartes University). Clinical Trials Center for Early Stage Drug Development are also present in the two structures.

For Paris Descartes, The ability to bring basic research to bedside has been strongly reinforced by the SIRIC CARPEM program supported by the INCA and coordinated by Pierre Laurent Puig which integrate the various clinical teams and research lab associated with Paris Descartes university.

The valorization of the innovation includes a structure dedicated to Hadassah (Jerusalem Biopark) and a startup incubator, Paris Biotech for Paris Descartes University. Certain clinical specialties such as melanoma, tumors of the digestive tract (hepatocarcinoma, colorectal cancer) have an important patient recruitment and an international visibility both at Hadassah (M Lotem, E Pikarsky) and Paris Descartes (S Aractinghi, J Zucman-Rossi, J Taieb, S Chaussade, C Cellier). They will be the subject of special sessions at this joint symposium.

The Sidney Weiser department of bone marrow transplantation and cancer immunobiology for Hadassah (Pollina Stepensky) and department of hematology at the Cochin hospital (Didier Bouscary, M Fontenay) and Necker (O Hermine) structure onco-hematology and research in immunotherapy for our two institutions. This symposium will discuss the new therapies of CAR T cells in onco-hematology both to speed their transfer to the clinics as well as their optimization.

In terms of cancer immunotherapy, the preparation of this symposium has identified common scientific forces relying on neutrophils and myeloid cells and cancer, as well as translational research programs on the identification of biomarkers and a better understanding of immunomodulation.

We hope that this symposium will be the starting point for a collaboration both clinically by the initiation of common clinical protocols and translationally through the sharing of cutting edge innovative platforms present on our two sites, as well as the development of ambitious research programs around cancer immunotherapy.
**Welcome**

*Introduction: G. Friedlander*, Dean of Paris Descartes Medical School

*F. Batteux*, Vice Dean International Affairs at Paris Descartes Medical School

**9:45**

**Myeloid Suppressive Cells and Neutrophils and Cancer**

*Chairs: M. Wislez & M. Baniyash*

**9:45**

Chronic inflammation, myeloid derived suppressor cells and cancer:
Related complications, biomarkers and treatments

*M. Baniyash*, Hebrew University of Jerusalem in Israel Medical School

**10:05**


*M. Wislez*, Paris Descartes Medical School

**10:20**

Impact of NOS2 and IL-4-induced gene 1 on the tumor microenvironment in melanoma:
Focus on PMN-MDSC

*A. Prevost-Blondel*, Paris Descartes Medical School

**10:35**

Round table and Coffee break

**10:50**

**Oncogenesis and Novel Molecular Targets: Hepatocarcinoma and AML Models**

*Chairs: E. Pikarsky & M. Fontenay*

**10:50**

Pro and Anti tumorigenic functions of ectopic lymphoid like structures

*E. Pikarsky*, Hebrew University of Jerusalem in Israel Medical School

**11:10**

Tumors: from genomics to therapeutic targets

*J. Zucman-Rossi*, Paris Descartes Medical School

**11:30**

Round table

**11:45**

Considering alternatives to targeted cancer therapy

*Y. Ben-Neriah*, Hebrew University of Jerusalem in Israel Medical School

**12:05**

Deciphering the alteration of gene expression co- and post-transcriptional regulations to improve the care of myelodysplastic syndromes

*M. Fontenay*, Paris Descartes Medical School
12:25
Round table

12:45
Lunch break

14:30
Immunotherapy: Clinical Protocols and Immunomonitoring

Chairs: M. Lotem & E. Tartour

14:30
Immunotherapy in Urological tumors
S. Oudard, Paris Descartes Medical School

14:45
Checkpoint Inhibitors for the treatment of advanced skin tumors
S. Guégan, Paris Descartes Medical School

15:00
Immune receptor alternative splicing as a novel regulatory mechanism
M. Lotem, Hebrew University of Jerusalem in Israel Medical School

15:20
Emergent biomarkers derived from the analysis of tumor microenvironment
E. Tartour, Paris Descartes Medical School

15:35
Round table

16:00
Coffee break

16:15
The Consensus immunoscore as predictor of outcome and indicator of response to treatment for patients with colorectal cancers
F. Pagès, Paris Descartes Medical School

16:30
Matrix-localized substrate-level-phosphorylation is critical for mitochondrial remodeling during CD8+ T cell priming
M. Berger, Hebrew University of Jerusalem in Israel Medical School

16:50
Imaging of T Cell success and failure within the tumor microenvironment
E. Donnadieu, Paris Descartes Medical School

17:05
Cardiovascular effect of tyrosine kinase inhibitors in CML patient
E. Messas, Paris Descartes Medical School

17:20
Round table

17:45
End of the meeting

Diner at the restaurant: Ardoise XV, 70 rue Sébastien Mercier, 75015 Paris
July 5, 2019

9:00 - 10:30

Visit of a hospital involved in the management of patients treated with immunotherapy

*Department Medical Oncology Hôpital Cochin*

**F. Goldwasser,**

Main Reception :
Hôpital Cochin
27 rue du Faubourg Saint-Jacques
75014 Paris, France

11:00 - 12:15

Discussion with Member of the Office of International Relations at the Faculty of Medicine Paris Descartes (Frédéric Batteux, Manon Xhenseval, Representant Hadassah France…).

**Working Meeting at Paris Descartes Medical School**

*Dean Office (Office 400, 4th floor)*
15 rue de l'École de Médecine
75006 Paris, France

**G. Friedlander, E. Tartour, M. Xhenseval, D.T. Nguyen,** Paris Descartes Medical School

**E. Messas,** Hadassah France / Hebrew University of Jerusalem in Israel Medical School

**M Lotem,** Hebrew University of Jerusalem in Israel Medical School

12:15

Lunch break at Paris Descartes Medical School *(Office 408, 4th floor)*

End of the meeting
Gérard Friedlander, MD, PhD was born in 1952. He is currently Professor of Physiology at Paris Descartes University School of Medicine, Head of the Department of Physiology at Georges Pompidou Hospital, Paris University Paris Descartes, Paris, France.

He is Dean of Paris Descartes University School of Medicine.

He focused his experimental and clinical research on renal physiology and pathophysiology, water and mineral metabolism, calcium and phosphate homeostasis, chronic kidney diseases, and on the links between ageing, metabolism and homeostasis. He is the author of more than 200 original publications, and of review articles and book chapters.
Professor Frederic BATTEUX, MD, PharmD, PhD, is board certified in clinical pathology and is specialized in Immunology. He holds an MD and a PhD obtained in 2011 and 2008 from Paris Descartes University and Medical School and a PharmD obtained in 2001 from Paris Sud University.

He has a fulltime position as professor in Immunology at Paris Descartes Medical School and is the head of the clinical laboratory of immunology at Cochin Hospital, AP-HP, Paris. He is also the head of the Research Team “Free radicals, inflammation and cancer” at the Cochin Institute, a biomedical research center affiliated to INSERM (Unit 1016), CNRS (UMR 8104) and the University Paris Descartes, UPD (UMR-S1016). Professor Batteux has published over 150 international articles in Pubmed-referenced journals in the fields of systemic autoimmune disorders, inflammation and cancer.

Professor Batteux serves as the Medical Director of the “Hôtel Dieu de Paris”, the oldest hospital in Paris, founded in 651 AD and located in the center of Paris on the Ile de la Cité.
I have a long-term interest in T cell biology and Cancer research. During my Ph.D. studies in the laboratory of Prof. Ygal Haupt I was exploring the mechanisms of cell cycle arrest and programmed cell death controlled by the p53 tumor suppressor protein. Supported by a postdoctoral fellowship from the European Molecular Biology Organization (EMBO), I spent 5.5 years in the laboratory of the 2011 Nobel laureate, Prof. Bruce Beutler, where I employed an in-vivo forward genetic screen in order to find genes that are important to the host resistance to a viral infection. In July 2011 I returned to Israel in order to establish my own laboratory. I have used my expertise in tumor biology and immunology, my successful prior application of both molecular and genetic approaches, as well as the invaluable research tools, to lead my laboratory in research on the role of the quiescence process in T cell – pathogen interactions and leukemia development. Over the past eight years as a PI on ten competitive funding grants, I established a cutting edge laboratory and built an outstanding research group aimed at providing comprehensive and integrative insights into the factors and mechanisms that establish and maintain T cell quiescence, and exploring ways to exploit our findings to better treat cancer and improve T cell function. One of the major fields I have recently developed in the lab is metabolic networks in T cells. Specifically I am interested to exploit our findings to metabolically improve the efficacy of adoptive T cells therapy of solid tumors. In addition, I successfully administered the projects (e.g. staffing, budget), collaborated with other researchers, and produced several peer-reviewed publications from each project.

**Field of Expertise**

- T cell biology, immunometabolism
Matrix-Localized Substrate-Level-Phosphorylation is Critical for Mitochondrial Remodeling During CD8+ T Cell Priming

Oxidative phosphorylation (OXPHOS) is thought to be critical to meet the energetic demand of T cells activation. However, why activated T cells still require OXPHOS in spite a clear "switch" to aerobic glycolysis remains incompletely understood. Here we show the critical role of OXPHOS-coupled matrix substrate-level-phosphorylation in powering mitochondrial remodeling in activated CD8+ T cell.

We demonstrate that shortly upon stimuli, T cell cytoplasmic function becomes independent of mitochondrial ATP out flux. In contrast, OXPHOS restriction leads to arrest of ATP dependent mitochondrial functions, which could be then rescued by restimulation of matrix substrate-level-phosphorylation.

Thus, following the switch to glycolysis, OXPHOS acts as an electron sink, facilitating matrix substrate-level-phosphorylation, a primary ATP source for mitochondrial remodeling during T cell activation. Our study reveals the importance of energetics of the mitochondria as a separate compartment in the capacity of T cells to bypass oxygen deficiency.

Specifically, we demonstrate that mitochondrial matrix-localized substrate level phosphorylation, is central for glycolytic T cell capacity to function under hypoxic conditions.
MARIE WISLEZ

Faculty of Medicine, Paris Descartes University, Paris, France
UMR_S 1138 INSERM, Team « Inflammation, Complement and Cancer », Cordeliers Research Cnter, Paris, France.
Department of Pulmonary Medicine, Thoracic Oncology Unit, Cochin Hospital, AP-HP, Hôpitaux Universitaires Paris Centre, Paris, France.

Biography

MD, PhD, Marie Wislez, is currently Full Professor in Department of Pulmonary Medicine – Medical Chairman of the Thoracic Oncology Unit, in Cochin Hospital.

Pr. Marie Wislez has a well-recognized trajectory in the lung cancer research field, supported by an extensive record of scientific publications.

Following his doctoral degree in tumor biology, she was a postdoctoral fellow during 2 years, in Head and Neck Medical Oncology department in M.D. Anderson Cancer Center Houston, Texas, USA. This research focus on EGFR and K-ras signaling in lung cancer.

She has been involved in several clinical trials of perioperative treatment in early stage Non Small Cell Lung Cancer and is actually PI of the Phase II neoadjuvant trial Ionesco (French Intergroup of Thoracic Cancer (IFCT)). She is a member of a network of thoracic clinicians (IFCT and GFPC academic cooperative groups).

In 2018, she joined as a senior researcher, a new team in the Cordeliers Research Center where she leads a group focusing on the mutual interaction between cancer cells and immunes cells deciphering the respective role of cancer cells and individual in the intra-tumor immune environment setting. Her team has expertise on mouse model of lung adenocarcinoma.

Field of Expertise

- Thoracic Oncology
- Immuno-Oncology
- Research Topic: Neutrophils and Lung Cancer
Abstract

Mechanisms of Resistance to Anti-PD-1/Anti-PD-L1 Treatments Related to the Loss of STK11/LKb1 Gene Expression in Lung Cancer: Role of Neutrophils

Scientific background:
Immune check point inhibitors (ICI) such as anti-PD-1 and anti-PD-L1 Abs have been shown to be effective in lung cancer (LC) as monotherapy. Nevertheless, some patients (pts) are resistant or get worse (hyper-progressors) under this treatment. Predictive factors have not yet been fully identified. Our team and others have shown that tumors with mutation (loss of function) of the tumor-suppressor gene STK11/LKb1 do not respond to ICI and that their tumors are highly infiltrated by neutrophils. However, the link between STK11/LKb1 gene mutations, neutrophils and resistance to ICI has not been demonstrated.

Our objectives are:
- to characterize neutrophils (phenotype, function, survival) in circulating blood and within the tumors of pts with LC, with or without STK11/LKB1 gene mutation status and treated or not with ICI;
- to identify mechanisms related to the loss of function of STK11 inducing the recruitment and the modulation of neutrophil functions (co-culture of STK11 mutated or wild-type cell lines with neutrophils);
- to reverse ICI resistance by modulating tumor neutrophil infiltration or neutrophil functions, using genetically modified mouse models for STK11, treated with ICI and/or drugs targeting neutrophils such as STING agonists, Ac antiLOX-1, small molecules (T2AA or peptid p21), Roscovitine (clinical development).

Expected results:
The identification of the mechanisms of neutrophil-related resistance to ICI will provide new therapeutic options that may include current anti-PD1/anti-PD-L1 drugs in combination with other drugs under development that modulate the recruitment or function of neutrophils.
Michal Baniyash is a Full Professor of Immunology and a group leader at the Hebrew University Medical School, training MSc/PhD students, post-docs and teaching immunology. Prof. Baniyash and her team discovered more than a decade ago that chronic inflammation leads to immunosuppression mediated by myeloid derived suppressor cells (MDSCs). They focus on mechanisms underlying the link between inflammatory diseases, immunosuppression and cancer, translating basic research to the clinic. She and her team discovered new biomarkers sensing the host’s immune function and combating modalities that are applied today in the clinic. Prof. Baniyash publishes in peer-reviewed top journals, holds several patents/prizes, invited to meetings, is part of scientific grant and top journals review panels.

Prof. Baniyash’s current research explores the molecular networks controlling MDSCs in chronic inflammatory diseases, their differentiation patterns, their interaction with other immune cells and with the microbiome.

Prof. Baniyash’s research studies deal with a broad spectrum of inflammatory conditions, aiming to combat the deleterious effects of MDSCs and develop novel modalities to better treat patients suffering from such diseases.

Field of Expertise

- Fundamental research on chronic inflammation, immunosuppression, cancer and associated complications, with translational approaches to clinical applications.
Altered myelopoiesis is evident in pathologies characterized by chronic inflammation and is associated with the accumulation of myeloid derived suppressor cells (MDSCs). MDSCs are characterized by diverse phenotypes and functions. They are arrested in their immature state, are polarized towards highly suppressive cells and migrate from the bone marrow to the periphery and site of inflammation.

There they impair effector functions of innate and adaptive immune cells, promote tumor growth, angiogenesis, and cause tissue damage. When reaching new environments, which exhibit a different array of cytokines, chemokines, and pro-inflammatory mediators, MDSCs sense and adapt to the altered micro-environment by changing their cell fate, surface receptors, metabolism and intracellular as well as secreted molecules. Based on the plasticity and biological diversity of MDSCs, they have a dual use: 1) As biomarkers for the evaluation of the hosts’ immune status and the prediction of success rates for immune based therapies, and 2) As targets for treatments aimed at combating them or manipulating their suppressive activity towards preventing associated complications and achieving improved therapies in various pathologies characterized by chronic inflammation.

Examples for the plasticity and biological diversity of MDSCs will be presented and the clinical implications will be highlighted and discussed.
Armelle Prevost-Blondel got her Ph.D. degree in 1996 from the University Paris Descartes, France. She first works on TCR variability in human pathologies (PhD) and then pursued Postdoctoral training on molecular mechanisms of tumor immunosurveillance mediated by CD8 T cells at the Freiburg University, Germany.

Dr. Armelle Prevost-Blondel joined the Cochin Institute as a group leader with a long-standing interest into the role of immune cells and their relationships at the earliest stages of the tumor development in a model of spontaneous melanoma.

Her current research focus on immuno-regulatory properties of enzymes degrading arginine and phenylalanine, inducible nitric oxide synthase (NOS2) and IL4-induced gene 1 (IL4I1), in melanoma as well as at steady state.

Over the years, Armelle Prevost-Blondel and her group have forged relationships with scientists, dermatologists and pathologists in cancer research in Paris.

- **Field of Expertise**
  - Onco-immunology, Melanoma, Immune suppressive enzymes
Impact of NOS2 and IL-4-Included Gene 1 on the Tumor Microenvironment in Melanoma: Focus on PMN-MDSC

Overcoming resistance to checkpoint inhibitor-based immunotherapy, in particular in 40% of patients with metastatic cutaneous melanoma, requires a thorough understanding of the mechanisms underlying immune evasion by tumors. In human primary melanoma, NOS2 is a marker of poor prognosis and IL4I1 is expressed in a large majority of tumors from stage I-III patients and tends to be associated with a poor disease outcome (Ramspott et al 2018).

These enzymes lead to arginine and phenylalanine deficiency and/or toxic metabolite accumulation, but their immuno-regulatory properties in the tumor context remains to be elucidated.

To gain insight into the role of immune cells at the earliest stages of the tumor development, we set up a model of spontaneous melanoma with Pr Kato (Nagoya, Japan).

RET mice, transgenic for the constitutively activated form of the human RET oncogene, develop a primary uveal melanoma that rapidly disseminate throughout the body. PMN-MDSC drive the metastatic process by inducing cancer cell phenotypic changes typical of EMT.

Interestingly, NOS2, expressed by tumor infiltrating γ δ T cells, supports their IL17 secretion, and the production of IL-8 and G-CSF within the primary RET melanoma leading to PMN-MDSC recruitment and accumulation and subsequently tumor cell dissemination. IL4I1 also contributes to tumor progression via enhanced recruitment of PMN-MDSC and reduced infiltration of B cells, Th1 and cytotoxic T cells at the primary RET melanoma site.

Targeting NOS2 and IL4I1 may improve cancer treatment and help to cure patients resistant to current immunotherapy.
Eli Pikarsky received his MD and PhD from the Hebrew University of Jerusalem. He is a professor of pathology at the Lautenberg center for Immunology and Cancer Research at the Hebrew University Medical School and the chairman of the department of pathology at the Hadassah-Hebrew University Medical Center.

He studies the role of inflammation in liver disease and in liver cancer in particular. His studies focus on how heterotypic cellular interactions shape cellular phenotype along the course of liver disease and how they affect disease progression.

**Field of Expertise**

- Liver cancer, inflammation, molecular pathology
The different roles of the adaptive immune system in cancer are beginning to unfold. The dramatic responses to immune check point drugs in some tumors generated an accelerated need for understanding the complex set of interactions between tumor and immune cells. In view of the major pathophysiological role of immune cells in hepatocellular carcinoma it is not surprising that malignant hepatocytes interact extensively with adaptive immune cells, resulting in both pro-tumor immunopathology and anti-tumor protective immunity.

Identifying potential responders to drugs that target the adaptive immune system, monitoring their immune response to the tumor and devising the best treatment combinations depends on understanding the complex set of interactions taking place within the tumor and in the adjacent hepatic parenchyma.

Cellular infiltration usually entails a diffuse influx of immune cells, scattered throughout the inflamed tissue. However, infiltrating leukocytes often form ectopic lymphoid aggregates or even more complex structures that histologically resemble lymphoid organs.

These structures direct various B and T cell responses and are referred to as ectopic lymphoid-like structures (ELSs). ELSs often develop at sites of chronic inflammation where they can influence the course of disease. In many cancers, the presence of ELSs correlates with a better prognosis and they may coordinate endogenous antitumor immune responses. Surprisingly, in the liver – ELSs have diverse roles – while intratumoral ELS are associated with a good prognosis, the presence of ELSs in the liver parenchyma is positively correlated with HCC.

We are currently dissecting the potential role of immunosuppression in ELS protumorigenic function and aiming to identify ways to restore functional immunity upon ELSs.
Biography

Jessica Zucman-Rossi is Professor of Medicine at University Paris Descartes, within the department of Oncology at the European Hospital Georges Pompidou (AP-HP).

She is the director of the Cordeliers Center of Research and of the team “Functional Genomics of Solid Tumors”, with a focus on liver, mesothelial and renal tumors.

Her team aims to develop basic genomic approaches based on human tumors analyses to identify new mechanisms of tumorigenesis and to transfer this knowledge into biomarkers that could be introduced in clinical care. In particular, the group was pioneer in the elucidation of the molecular classification of benign and malignant liver tumors.

Currently, she is executive secretary of ILCA (International Liver Cancer Association), vice-Chair of the AASLD SIG Hepatobiliary neoplasma, she acts as co-Editor for Journal of Hepatology and Editor in Chief for JHEP Reports.

Field of Expertise

- Genetic of tumors, Liver tumors, Hepatoblastoma, Liver adenoma, Mesothelioma, Renal cancer
Abstract

Liver Tumors: From Genomics to Therapeutic Targets

Hepatocellular carcinoma (HCC) is one of the leading causes of death by cancer worldwide. It is mainly developed on cirrhosis due to chronic hepatitis B and C, metabolic and alcoholic liver diseases in western countries.

Recent advances in molecular classification and dissection of genetic and epigenetic drivers have increased our knowledge of the molecular diversity of malignant liver tumors. Using genomic approaches, we identified several new oncogenes and tumor suppressor genes and we described a molecular classification of hepatocellular carcinoma.

An interesting strategy is to identify genomic defects that occur early during liver tumorigenesis to identify oncogene addiction. Among these alterations, TERT promoter mutation is the most frequent and the earliest recurrent genomic alteration identified during hepatocarcinogenesis in Human. Consequently, telomerase reactivation is the most important mechanism of malignant transformation of cirrhotic nodules in carcinoma but also in the transformation of hepatocellular adenoma in carcinoma.

We also found new mutational signatures in HCC as the result of exposure to specific genotoxic agents and viral insertional mutagenesis (HBV and AAV2 in rare cases of HCC developed in non-cirrhotic liver.

Genomic alterations in HCC are also closely related to tumor phenotype and we identified homogenous sub-groups of HCC defined by pathological features, gene mutations and transcriptomic profile leading to develop new diagnostic tools.

Finally, next generation sequencing was particularly fruitful to identify new drug targets in hepatocellular carcinoma and these finding open new avenues to develop genome based clinical trials.
YINON BEN-NERIAH

Yinon Ben-Neriah, MD, PhD
The Lautenberg Center for Immunology & Cancer Research
Hebrew University-Hadassah Medical School

Biography

MD at Tel Aviv University and PhD at the Weizmann Institute; postdoc with Dr. David Baltimore at MIT, Yinon is a professor of immunology and cancer research and vice dean for research at the faculty of Medicine, at the Hebrew University.

Yinon is an elected EMBO member, recipient of the Teva Founders’ (2007) the Rappaport (2016) and EMET (2019) prizes for biomedical research, co-director of the SignGene German Israeli PhD program and Adjunct Professor in Shanghai Jiao Tong University.

Among his science achievements are: determination of the structure of the CML oncoprotein and developing a prototype targeted cancer therapy based on Bcr-Abl inhibition; deciphering key components in the NF-κB and Wnt signaling pathway, having a major impact in cancer; identifying NF-κB as the first molecular link between inflammation and cancer; identifying a new type of low grade, smoldering inflammation prevailing in many human cancer types, and the development of a new class of small molecule kinase inhibitors with profound therapeutic effect in a mouse model of aggressive human leukemia, one of which has already been approved for clinical trials.

Field of Expertise

- Molecular cancer research
Considering Alternatives to Targeted Cancer Therapy

Targeted cancer therapies have been introduced 20 years ago and traditionally aim to neutralize oncogenes. With the advance of personalized/precision medicine targeted therapy revolutionized cancer therapy.

However, despite the remarkable success, we learned that, with a few exceptions, any targeted drug has a short half-life and cancer cells quickly learn how to avoid specific drugs. Sometimes, it is possible to overcome specific drug resistance with another, similar, or alternative target drug, but any successive one also has a short half-life.

In addition, many oncogenes, such as Ras are still undruggable; moreover, targeted therapies directed at missing or mutated tumor suppressors are developing very slowly.

I will review the progress, benefits and shortcoming of targeted cancer medicine and will discuss an emerging concept of targeting cancer vulnerabilities instead of traditional cancer drivers. One example to be discussed is targeting the transcriptional addiction of some cancer types.
MICHAËLA FONTENAY

Université Paris Descartes
Institut Cochin INSERM U1016, CNRS UMR 8104
Assistance Publique-Hôpitaux de Paris, Hôpitaux Universitaires Paris Centre
Cochin, Service d’Hématologie Biologique

Biography

MD, PhD, full-Professor in Haematology at Paris Descartes University, head of the laboratory of haematology in Cochin hospital, and director of the research team “Normal and Pathological Haematopoiesis” in Cochin Institute.

She is teaching clinical and biological haematology at Paris Descartes faculty of Medicine. She is the vice president of the Committee for research and innovation in Cochin hospital.

She is the deputy director of CARPEM, a site of integrated cancer research site and vice president of the French Working Group on Myelodysplastic syndromes.

Field of Expertise

- Myeloid malignancies; normal and pathological erythropoiesis
Deciphering the Alterations of Gene Expression Co- and Post-Transcriptional Regulation to Improve the Care of Myelodysplastic Syndromes

Myelodysplastic syndromes are pre-leukemic disorders affecting patients in the elderly. Somatic mutations/deletions accumulate in the hematopoietic stem cell in the context of an inflammatory bone marrow microenvironment. Mutations drive clonal selection at stem and progenitor cell level.

Among MDS subtypes, patients with a 5q- syndrome or an acquired sideroblastic anemia present with a profound anemia and a relatively low propensity to leukemic transformation. Multiple alterations of gene expression co- or post-transcriptional regulation participate in the pathophysiology of these diseases. In acquired sideroblastic anemia, a heterozygous mutation of splicing factor SF3B1 drives the onset of multiple mRNA splicing variants, some of them potentially translated into variant proteins.

We identified one variant protein as a major determinant of the phenotype that represents both a promising therapeutic target and a biomarker of clonal erythropoiesis. In the 5q- syndrome, an interstitial 5q deletion removes one allele of RPS14 gene encoding a ribosomal protein of the small subunit. In this situation, translation becomes selective and contributes to the impairment of erythropoiesis.

Based on a landscape of all human transcripts, we deciphered the common determinants of translation selectivity. Targeting co-transcriptional splicing or translation may improve erythropoiesis and help to cure anemia in patients frequently resistant to erythropoiesis-stimulating agents.
STÉPHANE OUDARD

Stéphane Oudard, MD PhD

Professor of Oncology and Chief of the Oncology Clinical and Translational Research Unit at the Georges Pompidou Hospital in Paris (2011), France.

He is professor in Oncology at the Paris Descartes University, Paris, France.

Biography

He is currently a member of the French Cancer Society, European Society for Medical Oncology (ESMO, scientific committee), and American Society of Clinical Oncology (ASCO).

He integrated the research INSERM Unit UMR-970 Paris Cardiovascular Research Center (directed by Pr Eric TARTOUR) a research team focusing on immunomonitoring and immunotherapy of solid tumours. He is the deputy director of CARPEM, a site of integrated cancer research site. As a clinical researcher, Professor Oudard has served as a Coordinator, Investigator, or Co-Investigator on several phase I–III French, European, and international clinical trials. He is a member of the French GETUG group. He is the principal investigator of the phase III trial on CABASTY and co-leader of the BIONIKK trial on personalized medicine in mRCC.

Professor Oudard has authored 3 educational books, more than 275 scientific articles and 25 literature reviews published in various international journals.

Field of Expertise

- Uro-oncology tumors, angiogenesis, Immuno-Oncology, phase I trials
Immunotherapy in Urological Tumors

Genitourinary (GU) malignancies have a long history of immunotherapeutic approaches to treatment including high-dose interleukin-2 (IL-2) and interferon (IFN) alpha for renal cell carcinoma (RCC), Bacillus Calmette-Guerin for bladder cancer and, most recently, Sipuleucel-T for prostate cancer. Although effective in many patients, these therapies are, in general, not curative. The development of more effective cancer immunotherapy has long been hampered by the multiple strategies that tumors use to evade destruction by the host immune system. One such strategy involves the expression of cell surface molecules, known as immune checkpoints, on tumor-specific lymphocytes.

In kidney cancer, the combination of ipilimumab and nivolumab increase overall survival (OS) especially in intermediate and poor risk mRCC group (MSKCC). Recently, the combination of axitinib and antiPD1 (pembrolizumab) has also demonstrated to increase OS. Sunitinib is no longer the treatment of choice, at least, in intermediate and poor risk group. An ongoing clinical study (BIONIKK trial), based on transcriptomic analysis on frozen metastatic kidney cancer, evaluated prospectively the comparison of TKI and checkpoint inhibitors (CPI).

In bladder cancer, Pembrolizumab has demonstrated its efficacy in post-chemotherapy setting but is not yet available in France. Others CPI have been evaluated in post chemotherapy (CT) as well as in patients unfit for CT. These CPI are also evaluated in combination with CT at different stages of the disease either in neoadjuvant or adjuvant setting. The NEMIO trial investigates, in neoadjuvant, the combination of durvalumab plus tremelimumab with dose dense MVAC chemotherapy. This regimen, may be, in the near future the treatment of choice in invasive non metastatic bladder cancer.
Sarah Guégan obtained her medical degree and her board certification in dermatology from Paris Descartes University. She was a PhD student in INSERM U932, Curie Institute, Paris and obtained a PhD in Immunology. She also has a complementary certification in clinical immunology and medical oncology.

She has a fulltime position as associate professor in Dermatology at Paris Descartes Medical School, University of Paris, and in the Department of Dermatology, Cochin Hospital, AP-HP, in Paris, France. She is the Head of the Referal Center for cutaneous tumors developing on genodermatoses (MAGEC) in Cochin Hospital.

She is also part of the research team “Cutaneous Biology” at Cochin Institute, a biomedical research center affiliated to INSERM (INSERM U1016) and Paris Descartes University, University of Paris. Her research focuses on melanocyte and nevocyte biology, melanocytic tumors such as melanoma and congenital melanocytic nevi, and she has supervised the doctoral training and PhD theses of graduate students in this field.

She is the author of original articles and review articles in international Pubmed-referenced journals, and book chapters in the field of dermato-oncology, melanocytic tumors, and inflammatory cutaneous diseases.

**Field of Expertise**

- Dermato-oncology, cutaneous tumors developing on genodermatoses
- Cutaneous side effects associated with conventional chemotherapy, targeted therapy, immunotherapy
- Skin manifestations in organ transplant recipients
- Skin manifestations associated with inflammatory bowel diseases and inflammatory rheumatism, psoriasis
Checkpoint Inhibitors for the Treatment of Advanced Skin Tumors

Abstract

Checkpoint inhibitors have revolutionized the treatment of metastatic melanoma.

Monotherapy with PD-1 inhibitors or combined immunotherapies associating ipilimumab, an anti-CTLA-4 antibody and a PD-1 inhibitor have shown impressive response rates (ORRs 26-61%) across various different trials, with higher response rates in the case of combined immunotherapy, and durable response after treatment discontinuation in a subset of patients.

Safety profiles compare favorably with chemotherapy, grade ≥ 3 treatment-related adverse events occurring in 10-20% of cases treated with monotherapy, and in 53-61% of cases treated with combined immunotherapy.

Associations of checkpoint inhibitors and targeted therapies are currently being tested in BRAF-mutated advanced melanoma.

More recently, CTLA-4 and PD-1 inhibitors have also been approved in melanoma in the adjuvant setting.

Finally, checkpoint inhibitors such as PD-1 and PD-L1 inhibitors have also been developed in locally advanced and metastatic squamous cell carcinoma, and Merkel cell carcinoma, and are currently tested in other non-melanoma skin cancers.

As other promising immunotherapies for skin cancers proceed through clinical trials, future goals include identifying optimal treatment and combination strategies, and developing reliable predictive biomarkers to guide treatment selection for individual patients.
Michal Lotem, MD
Head, Center for Melanoma and Cancer Immunotherapy
Sharett Institute of Oncology
Hadassah Hebrew University, Medical Center, POB 12000, Jerusalem 91120, Israel

**Biography**

1982-1983  | Internship, Assaf Harofeh Medical Center, Zerifin, Israel.
1986-1993  | Resident, Department of Dermatology, Beilinson Medical Center, Petah Tiqva, Israel
1993-1995  | Resident, Department of Oncology, Beilinson Medical Center, Petah Tiqva, Israel
1995-2002  | Senior Physician, Department of Oncology, Hadassah University Hospital, Ein Karem, Jerusalem, Israel
1997-Present | Senior Physician, Sharett Institute of Oncology, Hadassah University Hospital, Ein Karem, Jerusalem, Israel
2002-2004  | Research fellow, Surgery Branch, NCI, NIH, Bethesda MD. Mentor: Dr. Steven A Rosenberg
2007-Present | Senior lecturer in Clinical and Radiation Oncology, Faculty of Medicine, Hebrew University, Israel
2009-Present | Head, Center of Melanoma and Cancer Immunotherapy, Sharett Institute of Oncology, Hadassah University Hospital, Ein Karem, Jerusalem, Israel
7/2010-1/2011 | Visiting Professor, Stanford University, Faculty of Medicine, Division of Oncology, Prof. Ronald Levy Lab.
1/2013     | Associate Professor of Oncology, Hadassah Hebrew University, Faculty of Medicine

**Field of Expertise**

✓ Melanoma, cancer immunotherapy
The SLAM family of receptors (SFR) is a set of eight receptors and one ligand (CD48) expressed on hematopoietic cells. All SLAM family receptors (SFRs) except 2B4 and CD48 are homotypic binders, i.e. they engage a same ectodomain sequence, either in a cis (same cell) or trans (adjacent cell) configuration. SFR generate signals via a bi-phasic recruitment mechanism to tyrosines in their cytoplasmic part, which are designated immunoreceptor tyrosine-based switch motifs (ITSMs). The small Src homology 2 (SH2)-domain containing adaptor SAP is their default adaptor, interchanging with protein tyrosine phosphatases, mainly SHP-1, but also SHP-2, inositol phosphatase SHIP-1 and protein tyrosine kinase Csk. The interplay between SAP and SHP-1 affects SFR signaling direction.

Hence, SFRs are considered “dual” receptors.

In this talk I will show that the splicing isoforms of a member of the SFR, SLAMF6, is the key to understanding the SLAMs duality phenomenon.
**ÉRIC TARTOUR**

Paris Descartes University, Medical School, Paris, France  
Hôpital Européen Georges Pompidou  
Department of Immunology, Paris, France  
INSERM U970. PARCC: team « Immunotherapy and anti-angiogenic therapy in oncology, 
Paris, France

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**Biography**

Eric Tartour starts his scientific career at Institut Curie (1992-2000) as a senior physician in the clinical immunology lab (Pr WH Fridman). He was in charge of the development of clinical protocols in immunotherapy and of the immunomonitoring of this protocol. Since 2000, he joined the department of Immunology at Hopital Européen Georges Pompidou (HEGP), as senior lecturer and in 2003 as a full professor at Universite Paris Descartes. He is currently responsible of the laboratory of immunology at HEGP belonging to the Assistance Publique-Hôpitaux de Paris. Within this laboratory, an immunomonitoring platform for the follow up of immunotherapy (checkpoint inhibitor blockade and cancer vaccine) has been set up. Eric Tartour is also leading an INSERM team which aims to develop new immunotherapeutic strategies to boost the immune system of cancer patients. He is one of the first group to show the interest of targeting dendritic cells for the induction of CD8+ T cells and the favorable prognostic value of TH1 cell infiltration in cancer (Haicheur et al J Immunol 2000, Tartour et al J Natl Cancer Inst 1998). His current topic relates to the need to induce local mucosal tumor immunity and especially resident memory T cells to control mucosal tumors (Sandoval F Sci Transl Med 2013, Nizard M et al Nat Commun 2017) and the search of biomarker derived from the tumor microenvironment based on innovative technologies (multiplex immunofluorescence in situ technique with digital pathology, single cell analysis…) (Granier C et al Cancer Res 2017) to predict clinical response to immunotherapy.

**Field of Expertise**

- Cancer Immunotherapy  
- Predictive biomarker of response to immunotherapy  
- Analysis of tumor microenvironment by innovative technologies  
- Cancer Vaccine
Emergent Biomarkers Derived from the Analysis of Tumor Microenvironment

Immunotherapy based on the blocking of the PD-1-PD-L1 pathway is clinically beneficial in 20-25% of cancer patients. A better selection of patients would make it possible to offer a more personalized immunotherapy and to avoid side effects to patients resistant to these treatments.

A new population of CD8\(^+\)T cells expressing CD103 and CD49a called resident memory CD8\(^+\)T cells not recirculating in the body has been recently identified. Different properties of these cells (location in contact with the tumor, expression of inhibitory receptors (PD-1, etc.), high cytotoxicity, ability to be reactivated, etc.) suggest that they constitute one of the effector mechanisms of immunotherapy. Their presence in tumors is associated with a good prognosis even in multivariate analysis.

Nevertheless, different studies have also shown that infiltration with CD8\(^+\)T cells is not sufficient to predict the response to immunotherapy. Different phenomena can explain this observation (tumor resistance to immunological attack, infiltration by suppressor cells such as regulatory T cells and MDSC ...).

Co-expression of inhibitory receptors (PD-1, Tim-3, Lag3 ...) leading to a terminal exhaustion of T cells can also explain this resistance. Multiparametric immunofluorescence techniques with automated cell counting by machine learning allow for in situ cell phenotyping and propose a profile of inhibitory receptors in situ for each patient. The results obtained by these techniques could also help to propose guided therapeutic combinations based on this analysis of the tumor microenvironment.
FRANCK PAGÈS

Professor of Medicine in Immunology, Paris Descartes University, Paris, France (MD, PhD)
Vice-chairman of the Department of Immunology, Hôpital Européen Georges Pompidou, Paris, France
Head of the Immunomonitoring platform, Department of Immunology, Hôpital Européen Georges Pompidou, Paris, France.

Franck Pagès obtained his medical degree and earned board certification in Immunology from the University Paris Descartes, France. Dr. Franck Pagès is a Full Professor of Immunology at the Medical school, University Paris Descartes. He is the vice-chairman of the Department of Immunology at the Hôpital Européen Georges Pompidou in Paris.

Pr. Franck Pagès head the immunomonitoring platform of the Department of Immunology, to assess and quantify the immune infiltrate in tumors. He has developed and is the co-inventor of the test “immunoscore”.

He is a senior researcher and a group leader in the team “Integrative Cancer Immunology Team” headed by J. Galon at the Cordeliers Research Center.

Field of Expertise

- Tumor immunology with a translational approach from fundamental research to immunotherapy of cancer
Abstract

The Consensus Immunoscore as Predictor of Outcome and Indicator of Response to Treatment for Patients with Colorectal Cancers

The predictive accuracy of the traditional staging system assumes that disease progression is a tumour cell-autonomous process, but it fails to incorporate the effects of the host immune response. We demonstrated that the adaptive immune reaction composed of T lymphocytes (CD3+) with cytotoxic (CD8+) and memory (CD45RO+) phenotypes located in both the core of the tumor (CT) and the invasive margin (IM) of colorectal cancers highly predict recurrence and survival and could be superior to AJCC-UICC TNM classification (1).

We developed a scoring system named ‘Immunoscore” derived from the densities of CD3+ and CD8+ cells in tumor regions evaluated by digital pathology. The prognostic power and the robustness of the Immunoscore was recently validated in a multi-institutional study supported by the Society of Immunotherapy for Cancer (SITC), involving 3539 patients in 13 countries (2).

This is the first standardized assessment of the immune component for the prognostic purpose. These results support the implementation of the consensus Immunoscore as a new component of a TNM-Immune classification of cancer.

The prognostic and theranostic values of the IS in colonic and rectal cancers will be discussed in this presentation.

(2) Pagès F et al. The Lancet 2018
Emmanuel Messas M.D, PhD, F.E.S.C is cardiologist specialized in vascular medicine and head of the Vascular department at Hôpital Européen Georges Pompidou. His field of expertise is ultrasound imaging and therapy along with common and rare vascular diseases. His main field of research is to use new technology of imaging to better understand and treat cardiovascular diseases. Using new ultrasound technology as Ultrafastecho and Supersonic Shear wave imaging developed by the Inserm Unit of Michael Tanter called Physics for medicine, he developed with Michael Tanter and Mathieu Pernot an entire program dedicated to cardiovascular disease: Shear wave imaging and Ultrafast Doppler for the carotid plaque evaluation, Contrast echo with micro vessels flow analysis for Inflammatory arterial disease and Ultrafast Doppler for analysis of segmental arterial pulse wave velocity in case of aortic aneurysm associated with bicuspid aortic valve. His clinical responsibility drives him also to take care of rare and common vascular diseases. In 2010 he started a collaboration with Dr Rea Hematologist in Saint Louis hospital on the potential of catastrophic cardiovascular side effect (with amputation in some case) of second generation of tyrosine kinase which are prescribe for lifetime in patient with chronic myeloid leukemia. His department became one of the clinical leading reference in this field and he collaborated with the Phi LMC group of the French Society of Hematology on establishing the recommendation for the management of CV effect of TKI in CML patient. He started recently collaboration with Alain Tedguy team working on animal model of atherosclerosis to better understand the effect of TKI on the arterial wall.

**Field of Expertise**

- Cardiovascular diseases, Ultrasound, Arterial thrombosis, Rare vascular disease
Abstract

Cardiovascular Side Effect of Tyrosine Kinase Inhibitor in CML patient

Tyrosine kinase inhibitors targeting the BCR-ABL oncoprotein represent an outstanding progress in chronic myeloid leukemia and long-term progression-free survival has become a reality for a majority of patients. However, tyrosine kinase inhibitors may at best chronicize rather than cure the disease thus current recommendation is to pursue treatment indefinitely. As a consequence, high quality treatment and care must integrate optimal disease control and treatment tolerability.

Tyrosine kinase inhibitors have an overall favorable safety profile in clinical practice since most adverse events are mild to moderate in intensity. However, recent evidence has emerged that new generation tyrosine kinase inhibitors may sometimes damage vital organs and if not adequately managed, morbidity and mortality may increase.

The 2nd generation tyrosine kinase inhibitor nilotinib is licensed for the treatment of chronic myeloid leukemia with resistance or intolerance to imatinib and newly diagnosed chronic phase-chronic myeloid leukemia.

Nilotinib represents an important therapeutic option but it is associated with an increased risk of cardiovascular events. The purpose of this article by the France Intergroupe des Leucémies Myéloïdes Chroniques is to provide an overview of nilotinib efficacy and cardiovascular safety profile and to propose practical recommendations with the goal to minimize the risk and severity of cardiovascular events in nilotinib-treated patients.
Emmanuel Donnadieu, Research director at the CNRS, is currently working at the Cochin Institute where he directs the team “Cancer and Immune Responses” (12 persons).

Working in the field of immunology for more than 15 years, Dr. Donnadieu has now accumulated a thorough experience in cell signaling and cellular imaging related to T cell physiology.

He is particularly well recognized in the field of T cell migration and the role played by external factors controlling this process. He has set up a novel experimental system of tissue slices which, combined to dynamic imaging, enables the visualization and tracking of T cells in murine and human tissues, including tumors.

His major contributions were the demonstrations of, (a) the role of CCL21 in triggering T cell migration within lymph nodes, (b) a defect in T cells to infiltrate human tumors, (c) and the role of macrophages and matrix fibers in this process. He recently moved to cancer immunology and cancer immunotherapy fields and belongs to several national and international networks including a European H2020 consortium on CAR T cells.

Field of Expertise

- T cell activities; Cancer immunotherapy; CAR T cells; Tumor environment; Cell migration; Fluorescent microscopy
Abstract

Imaging of T Cell Success and Failure within the Tumor Microenvironment

Recent years have seen the emergence of novel cancer immunotherapies based on our increasing knowledge of molecules involved in the regulation of T cell responses. This has led to the development of several monoclonal antibody-based therapies such as anti-CTLA-4 or anti-PD-1, which provide clinical benefit in several cancers.

Although some patients show an impressive survival response, response rates usually remain low, and it is now well accepted that multiple mechanism suppressing anti-tumor immune functions take place in the tumor microenvironment. These last few years, our team made significant progress in the understanding of how T cells are blocked in their antitumor activities and identified macrophages, the extracellular matrix, and TGFβ as major obstacles to cancer immunotherapy. We also made important advances on how CAR (chimeric antigen receptors) T cells infiltrate solid tumors.

Several approaches are used to address these issues including an experimental system based on fresh human tumor slices combined with dynamic imaging microscopy.

Our objectives are to pursue the analysis of elements from the tumor microenvironment that may positively and negatively influence immune responses. We foresee that the identification of these regulators can lead to the design of novel diagnostic and therapeutic strategies.
FRANÇOIS GOLDWASSER

Professor of Medicine Oncology, Paris Descartes University, Paris, France (MD, PhD), Cochin Port-Royal Hospital, APHP 5

Biography

Born April 28th, 1966.

• 1993 : MD in Medical Oncology (Paris XI University, France)
• 1993 to 1995 : Guest Researcher in the laboratory of Molecular Pharmacology of Dr Kohn, in the group of Dr Pommier, at the National Cancer Institute (NCI), at the National Institutes of Health (NIH) (Bethesda, Maryland, USA).
• 1995 : Phd in Molecular and Cellular Pharmacology of Anticancer
• Sept 2001 to date: Professor in Medical Oncology at Paris Descartes University, France. Head of the Department of Medical Oncology in Cochin Hospital, Paris, France.

Field of Expertise

✓ Pharmacology of anticancer Agents, Toxicity risk assessment, Immunotherapy, Cachexia, Metastatic cancer diseases, sarcomas
Visit of the Department of Medical Oncology

The department of medical oncology includes:

• An outpatient unit (30 patients per day) dedicated to 4 different programs:

  Anticancer treatment administrations (solid tumors; chemotherapy, targeted therapy, immunotherapy)

  Multidisciplinary risk assessment prior treatment initiation

  Palliative care

  Rehabilitation

• An inpatient unit (27 beds) organized for 3 different programs:

  Chemotherapy of soft-tissue and bone sarcomas and urogenital cancers

  Palliative care

  Oncologic emergencies

A clinical research team organizes 42 clinical studies (early trials, pharmacokinetics, translational, phase II, phase III) in the department.
Manon Xhenseval is the International cooperation coordinator in Paris Descartes University, School of Medicine. As the International cooperation coordinator she organizes the International partnerships for the Faculty Medicine.

She supervises the reception of foreign students and she sends French students abroad for rotation or study period. She is in charge of the reception of foreign delegations, creation of new partnerships and implementation of European projects. She organizes symposiums and international events with partner universities.

As the international cooperation coordinator she works closely with the Professors, the Hospitals and the University.

She worked in the French Erasmus+ Agency as a project Manager for the Euromed + project and in the French Ministry of City, Youth and Sport for the Grande Ecole du Numérique project.
Dan Thanh NGUYEN is an international project manager in Paris Descartes University Medical School. She is in charge of Asian and especially Vietnamese partnership.

She also participates in international partnerships management missions, including monitoring the various partnership agreements and setting up new partnerships; and organizes symposiums and international events with partner universities.

Born and educated in Brussels, she completed a master degree in political sciences and international relations. As part of her studies, she did an internship at the European Parliament and participated in the Model Nato Youth Summit in Montenegro.