GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

Les séminaires de la RECHERCHE

UNIVERSITE PARIS SUD – université PARIS-SACLAY

cnrs

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

AVRIL 2016
Salle Roger Monier
Pavillon de Recherche 2

Jeudi 7 avril 2016 - 11h30

Dan LANDAU
Meyer Cancer Center of WCM and New York Genome Center

Invité par Eric Solary, Directeur de la Recherche

« Genetic and epigenetic determinants of CLL evolution »

Cancer progression, relapse and resistance are the result of an evolutionary optimization process. Vast intra-tumoral diversity provides the critical substrate for cancer to evolve and adapt to the selective pressures provided by effective therapy. Thus, understanding intra-tumoral diversity and evolutionary dynamics will be a critical step in the development of effective, curative therapies for cancer.

In order to study these questions, we characterized the intra-tumoral genetic heterogeneity of chronic lymphocytic leukemia (CLL) using massively parallel sequencing of large patient cohorts (Landau et al., Cell, 2013; Nature, 2015). These studies have shown that CLLs contain genetically distinct subpopulations that compete and mold the genetic makeup of the malignancy. Furthermore, we have demonstrated that this heterogeneity can help predict the future evolutionary trajectories of CLL, and that higher intra-tumoral heterogeneity in the pre-treatment sample predicts adverse outcome.

Ongoing efforts are dedicated to studying the quantitative evolutionary dynamics that enable the relapse clone to replace the pre-treatment clone. Using deep sequencing with high temporal resolution we determine the therapy specific clonal fitness with first line chemoimmunotherapy and targeted therapy (Nature Communications, accepted for publication). These investigations offer a novel framework for the study of the evolutionary dynamics that underlie disease relapse, directly in patients.

Additionally, in order to comprehensively study cancer evolution, we developed tools to study intra-tumoral epigenetic heterogeneity, as epigenetic somatic changes are heritable and impact the cellular fitness that is selected in the evolutionary process (Landau et al., Cancer Cell, 2014). With these tools, we uncovered a central feature of the cancer epigenome: massive stochastic disorder in methylation patterns. We have further shown that this stochastic disorder impacts transcription, evolution and clinical outcome. Thus, methylation changes in cancer may be similar to the process of genetic diversification, in which stochastic trial and error leads to rare fitness enhancing events.

Collectively, these studies demonstrate the tremendous degree of intra-tumoral diversity that fuels cancer evolution, and highlight the need to integrate intra-tumoral heterogeneity in the development of the next generation of cancer therapeutics.

Mardi 12 avril 2016 - 11h30

Martin Joseph EDELMAN
University of Maryland - School of Medicine

Invité par Jean-Charles SORIA, Directeur du SIRIC SOCRATE

« Unasked and unanswered questions in lung cancer »

There has been a revolution in the treatment of virtually all stages of lung cancer in the last 10-15 years. Despite this progress, there are many uncertainties, both in how to utilize current therapies as well as questions as to how move forward with newer treatments. In this presentation, I will discuss current status and future directions as well as uncertainties regarding the biology and use of chemotherapy, targeted agents, immunotherapy and radiation in the management of non-small cell lung cancer.

Jeudi 14 avril 2016 - 11h30

Jean-Luc PERFETTINI

Laboratory of Molecular Radiotherapy, INSERM U1030, Gustave Roussy

Invité par Jean Feunteun, CNRS UMR 8200

« Cellular cannibalism, entosis and beyond »

The engulfment of live cells by other live cells, also known as cannibalism, is a cellular process during which internalized cells succumb to a newly described cell death modality called “entosis”. Although cytological evidences of entosis have been widely reported in many physiological and pathological situations, the molecular and cellular basis of this atypical death is still unknown and its biological consequences remains largely enigmatic.

The development of small interfering RNA screening techniques combined to fluorescent confocal microscopy analysis allowed us to *(i)* identify entotic modulators, *(ii)* decipher signaling pathways involved in entotic death and *(iii)* identify unsuspected links between this non-cell autonomous death and other cell death modalities. During our study, we demonstrated that various anticancer treatments that are known to induce typical cell death can also trigger entosis. Moreover, we observed that the frequent detection of entotic death in patient’s samples who received anticancer treatments could predict the efficiency of the therapy. Overall, our work underlines the absolute necessity to tackle and understand the complexity and multiplicity of cell death modalities that occur during physiological and physiopathological situations.

Jeudi 21 avril 2016 - 11h30

Jean-Marc EGLY

Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC) - Illkirch

Invité par Eric Solary, Directeur de la Recherche

« Transcription coupled repair, drugs, mechanism of action »