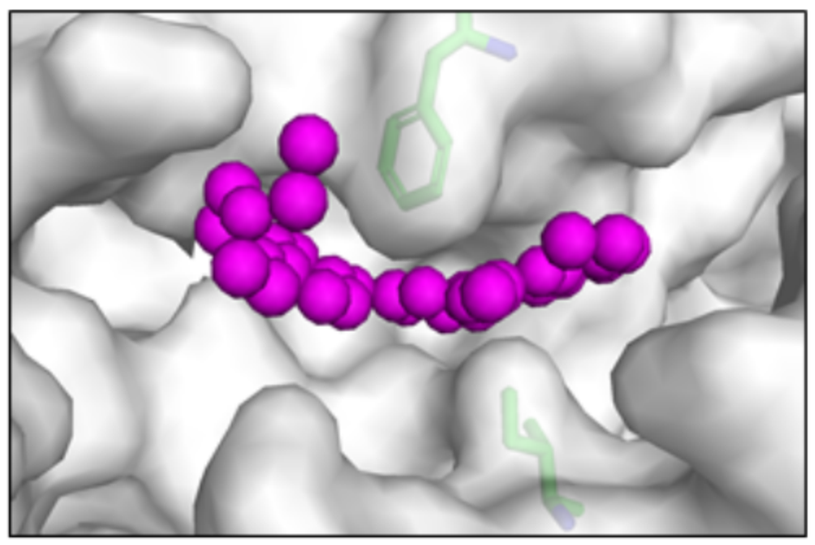
Abstracts

Dr Sandrine Roulland - Tracking early (epi)genetic dysregulation during B cell lymphomagenesis

Dr. Roulland will discuss the natural history of Follicular Lymphoma (FL) progression and describe the mutational landscape of FL precursor cells in prediagnostic blood from healthy individuals' years before disease onset. She will discuss novel insights leveraging single-cell transcriptomics to describe how early FL mutations progressively build-up lymphomagenesis through perturbation of the B cell differentiation dynamics in mouse models phenocopying various stages of FL progression and offering new perspectives of the pathogenesis of this tumor, as well as new possibilitiesfor targeted therapies.

Pr Bart Vanhaesebroeck - In search of novel ways to modulate the PI3K pathway for therapeutic benefit

The PI3K pathway is frequently genetically activated in cancer and is involved in immune dysregulation. The clinical development of PI3K inhibitors has proven challenging, with progress hampered by poor drug tolerance, intrinsic and acquired drug resistance and signalling feedback loops that neutralize PI3K inhibition.



I will provide a general overview of PI3K targeting in disease with a focus on cancer. I will provide an update on our efforts to explore alternative ways to modulate the PI3K pathway, including in cancer immunotherapy, cancer prevention, and the generation of small molecule activators of PI3K.

Abstracts

Dr Romain Baer - Role of RAS/CRAF interaction in RAS-driven lung cancer

The RAF/MAPK pathway is a major RAS effector pathway implicated in RAS oncogenic properties, regulating a diversity of cellular processes. As RAF kinases are thought to be attractive therapeutic targets in RAS-driven cancers, preclinical studies focusing on targeting CRAF in a model of KRAS-driven lung tumour initiation revealed effective inhibition of tumour development without inducing significant systemic toxicities. Recently, Sanclemente et al. further demonstrated that complete ablation of CRAF in established advanced lung tumours (KrasG12V/Trp53) triggers sustainable tumour regression, despite CRAF kinase activity being dispensable. This approach validates CRAF as a therapeutic target for KRAS-driven lung cancer, but also suggests limitations to the use of CRAF kinase specific inhibitors in the clinic.

RAS-GTP strongly interacts with CRAF through its Ras Binding domain (RBD). This interaction is required to activate CRAF. However, disruption of this interaction has never been proven to be a therapeutic target in vivo. Using CRISPR/Cas9 technology, we engineered a new mouse model in which CRAF RBD is constitutively mutated to completely abolish its interaction with RAS GTPases (CRAFR89L). This mouse model recapitulates the embryonic lethal phenotype of the constitutive CRAF KO mouse. Using a combination of murine lung KP (KrasG12D/Trp53) cell lines, either constitutively or conditionally expressing the CRAFR89L allele (CRAFflox/R89L), we show that acute disruption of CRAF/RAS interaction slows cell proliferation. Interestingly, CRAF ablation or RBD disruption minimally affects ERK signalling regardless of an enrichment in GTP-bound RAS, but triggers a PI3K/AKT positive feedback. Disruption of RAS/CRAF interaction also sensitizes cells to anoikis, and is characterized by a significant decrease of E-cadherin at the plasma membrane. Similarly to CRAF ablation, RBD disruption drastically reduces tumour growth in vivo in a syngeneic transplant model. KP lung tumour-bearing mice constitutively expressing one copy of the R89L allele (CRAFflox/R89L) are partially protected against mutant KRAS-induced lung tumourigenesis, showing a gene-dosage effect. RBD disruption recapitulates CRAF ablation and triggers tumour regression in these animals. Our work highlights CRAF interaction with RAS as a therapeutic target for KRAS-driven lung cancer.

Abstracts

Coralie Cayron - PI3Kα/γ cooperation : a new target to limit metabolic heterogeneity in pancreatic cancer

Pancreatic cancer (PDAC) patients have a low survival rate; chemotherapy does not cure. PI3K pathway is necessary for PDAC development and targeting PI3Kα and γ isoforms reduces PDAC tumor progression. Moreover, patients with PI3Kα and PI3Kγ high expression levels present higher metabolic flexibility. Inhibition of PI3Ks may be a way to force pancreatic cancer tumor cells into a metabolism that makes them sensitive to combinations of chemotherapy drugs and metabolic inhibitors

Anaïs Cornebois - Development of a versatile intracellular antibody-based approach for targeted protein degradation

The role of proteins is mainly assigned by the phenotypic analysis of their loss or gain of functions. An alternative approach for inhibiting intracellular proteins consists in inducing their targeted degradation, with functionalised antibodies for instance. Two main classes of these protein-based degraders exist, either the tagged or the non-tagged system. While highly convenient to test the degradability of a target, the addition of large tags such as GFP can interfere with protein function. Therefore, my main objective of my thesis project is to develop an alternative tag-based targeted protein degradation system.

Sebastian Castillo - Regulation of the ERK/MAPK signaling by the small GTPase RHOB in non-small-cell lung cancer

Even though the functional consequences of RHOB expression in cancer have been well characterized, the molecular mechanisms by which RHOB opposes tumorigenesis remain unclear. Through a cell-based tripartite split-GFP protein-protein interaction screening, we identified a novel interaction between RHOB and ERK1/ ERK2 kinases of the ERK/MAPK signaling pathway, which is frequently deregulated in cancer. Here we aim at understanding the biological functions of this interaction and the underlying regulatory mechanisms of ERK/MAPK signaling by the small GTPase RHOB.

Abstracts

Ariadna Brito Accurso - Role of cellular fusion in the oncogenesis of Leiomyosarcomas

Leiomyosarcomas (LMS) is one of the most common and aggressive types of soft tissue sarcomas with a very chaotic karyotype. We observed that in a hybrid cell line, formed after the spontaneous cell fusion of smooth muscle cells and fibroblast, a very specific PRKG1 deletion, a gene involved in smooth muscle contractile function. Then, we identified PRKG1 deletion in 14% of LMS (either a break point or an intra chromosomal rearrangement), making PRKG1 among that 5 most altered genes. Moreover, its low expression is a significantly associated with poor prognosis. Cell fusion models are able to mimic the chromosomal alterations found in LMS patients, making these models highly relevant in the field.

Manon Bayet - Modelling B-cell acute lymphoblastic leukemia induced by the PAX5 P80R mutation

B-cell acute lymphoblastic leukemia (B-ALL) is the most common form of pediatric cancer. The transcription factor PAX5 has been described as the guardian of B-cell identity but is also the main target of somatic alterations in B-ALL. In particular, the somatic mutation P80R of PAX5 is the most frequent PAX5 point mutation in B-ALL. I will present you a new strategy to model the multi-step process of B-ALL and I will shed light on the biological mechanisms by which PAX5P80R mutation leads to leukemia.

Alexis Hucteau - Modelling the molecular levels of mIDH AML cancer cell resistance by integrating multi-omics data with multilayer regulatory networks

In mIDH acute myeloid leukemia, widespread dysregulations occur at different molecular scales. Abnormal production of an oncometabolite leads to aberrant methylations around chromatin resulting in transcriptional dysregulations and enhanced mitochondrial metabolism. To model and study the full range of dysregulations that occur at these different levels, we have integrated multi-omics data into multilayer regulatory networks.