Sur invitation du Dr Gilles Pagès :

Nous aurons le plaisir d'accueillir le **Dr Mélanie TICHET** (PhD, Hanahan Lab, École Polytechnique Fédérale de Lausanne, EPFL-SV-CMSO, Suisse) qui nous présentera le **Lundi 11 Mars à 11h** en salle de réunion du CSM (2ème étage) un séminaire intitulé :

Deciphering the role of tumor-associated macrophages in melanoma - implication in immune suppression and resistance to therapy

Cutaneous melanoma is one of the most aggressive cancers capable of distant and lethal metastatic spread. Recent breakthroughs in the treatment arose from understanding oncogenic signaling and cancer immunobiology. Targeted therapies successfully block MAPK signaling in BRAFV600e mutant melanoma with high clinical responses followed, unfortunately, by rapid relapse, while checkpoint inhibitors activate the immune response inducing long-lasting responses, albeit only in a subset of patients. These limitations have driven interest in understanding the innate and acquired resistances.

We established and investigated a refined immunocompetent genetically engineered mouse model (GEMM) of BRAF driven melanoma (iBIP2), which phenocopies the human disease in his development, histopathology, and response to therapy. Interestingly, our mouse model will respond transiently to drugs targeting the MAPK pathway (BRAFi and MEKi) then relapse due to acquired resistance mechanisms and will exhibit an innate resistance to immune checkpoint inhibitors (PD1 and CTLA4) similar to the human. To better understand the resistance mechanisms occurring in our model, we focused on the tumor microenvironment (TME) and investigated stromal populations including tumor-associated-vasculature, fibroblasts, and macrophages that could lead to new therapeutic strategies.

We uncovered that tumor-associated macrophages (TAMs) were involved both in the tumor development and resistance mechanisms. Indeed, TAMs are known to promote key processes in melanoma progression, like angiogenesis, immunosuppression, invasion, drug resistance, and metastasis. Using in vivo and ex vivo analyses as well as omics data, we characterized this population and shown that TAMs are a major component of the TME and predominantly polarized toward a pro-tumoral "M2-like" phenotype. In our model, TAMs also produce immunosuppressive factors and exhibit extensive immune suppressive abilities arguing that they might be playing a significant role in suppressing immune responses in the melanoma TME.

Furthermore, we performed combinatorial trial using conventional strategies and identified that inhibitory targeting of PI3Kγ, a key macrophage lipid kinase, stimulates antitumor immune responses, leading to improved survival and responsiveness to standard-of-care targeted therapies. Indeed, PI3Kγ selectively drives immunosuppressive transcriptional programming in macrophages that inhibits adaptive immune responses. These data highlight the central role that macrophage plays in melanoma progression and demonstrate that pharmacologic inhibition of PI3Kγ, and more widely TAMs targeting/reprogramming, represents a new therapeutic modality to enable efficient anti-tumor immune responses for this devastating cancer.