Sur invitation du Dr Gilles Pagès :

Nous aurons le plaisir d'accueillir le **Dr Doria FILIPPONI** (Chercheur Postdoctoral, Institut de Recherche sur le Cancer et le Vieillissement - 28, Avenue de Valombrose, 06107 Nice France) qui nous présentera le **Mardi 07 Mai à 11h** en salle de réunion du CSM (2ème étage) un séminaire intitulé :

DNA Damage Signaling-Induced Cancer Cell Reprograming as a Driver of Tumor Relapse

Activation of DNA-damage response (DDR) signaling in response to chemo- and radiotherapy still remains the main efficient route to eliminate cancer cells. However after initial regression following chemotherapy patients often relapse and develop more advanced diseases. The mechanisms of this phenomenon are not completely understood. Recent clinical and pre-clinical data support the view that some cancers are organized hierarchically, with a small number of" dormant" cells capable of clonal long-term repopulation, including Cancer Stem Cells (CSCs). Having low proliferative potential these cells cannot be targeted by chemo- and radiotherapy that only kill active proliferating cells and can be thus functionally linked to cancer relapse. However, the observation that many cancers re-emerge after treatment does not necessarily imply that the cells that survive therapy are intrinsically more resistant than the cells that are killed. To date, it is unclear whether such cells represent a stable cell-type that is intrinsically more resistant, or whether they could reflect a transient state that can be acquired during the course of cancer treatment.

Our work evidenced that in cases where DDR signaling strength is insufficient to eliminate cancer cells, it can drastically favor tumorigenesis by promoting a series of epigenetic reprograming events that can go as far as the re-activation of stem cellspecific and pluripotency genes, including Oct4a. These Oct4a-expressing cancer cells efficiently contributed to tumor relapse both in the mouse and human cancers.

In turn, depletion of OCT4A delays tumor relapse in mice and restores chemosensitivity in human tumors. The reprogramming events induced by cancer treatment mimics some properties ascribed to CSCs, yet without a cancer cell necessarily committing to a CSC model. In particular, we argue that drug resistance and the expression of pluripotency markers, which are considered as some features of CSCs, could also be attributed to the appearance of DDR-induced transient Oct4a-expressing cancer cells. Our work supports a model in which many, if not all, cancer cells independent of hierarchical organization can be challenged by DDR signaling to undergo epigenetic reprograming and provide a new entry point for drug intervention.