Decipher the resistance to immune checkpoint inhibitors in advanced bladder cancer to develop new immunotherapeutic strategies

Bladder cancer (BC) represents about 1200 new cases per year in Switzerland (Swiss Cancer League). Most of the BCa are non-muscle-invasive BC (NMIBC) and 25% of them muscle-invasive BC (MIBC) or metastatic disease. Within 5 years, from 50% to 70% of NMIBC will recur and from 10% to 30% of NMIBC will progress towards MIBC or metastatic disease. Despite treatments, the 5-year survival is about 50% and the median survival is around 15 months for MIBC and metastatic disease, respectively. Immune checkpoint inhibitors (ICI) that block the PD-1/PD-L1 axis were successfully introduced in routine medicine. However, only 15 to 25% of patients with MIBC respond to this treatment despite a high level of tumor mutation burden (TMB). For that, it is urgently needed to understand why current therapies fail in most BC patients and find potential combinatorial therapies for patients with MIBC.

We are using an inducible BC mouse model that mimics features of the human MIBC by targeting *Tp53* and *Pten* genes. We published that this MIBC model displayed a strong pro-tumor microenvironment, characterized by a high number of tumor-associated macrophages (TAMs) and a poor number of CD8 T cells, and was resistant to anti-PD-1 treatment. The first aim of this project is to decipher the crosstalk between p53/pten-deleted tumor cells and the immune microenvironment, especially TAMs and CD8 T cells to understand why BC is resistant to ICI compared to other type of tumors. This study will be done in parallel with study of fresh and frozen patient's samples. The second aim of this study is to combine therapies, including radiotherapy and TAMs-targeting therapy, to rescue the anti-PD-1 response in MIBC in pre-clinical settings.

Understanding the mechanisms that induce ICI resistance and develop new therapeutic strategies are key to improve the therapeutic management of BC patients.