Targeting novel molecular networks underlying bladder cancer recurrence and progression

Project

Prof. Camilla Jandus & Prof. Grégory Verdeil

Bladder cancer (BC) is a very significant world public health problem, in terms of prevalence, mortality, clinical management and cost. For most patients (around 70%), the disease is detected as a non-muscle invasive BC (NMIBC) at the surface of the bladder. For many years, it has been treated with BCG instillation and tumor resection within the bladder. This treatment is efficient, but most patients will undergo tumor recurrence and will necessitate several rounds of treatment over the years. The disease can also evolve into muscle invasive bladder cancer (MIBC, 30%). In these cases, the treatment consists in chemotherapy and bladder removal (cystectomy). Despite this radical treatment, the overall survival is low, with half of the patients not surviving beyond five years. Survival does not exceed 15 months when the disease is metastatic. In the last years, the tremendous success of immunotherapy has also led to some success in the treatment of MIBC. Immunotherapy, in this case, will restore the capacity of the immune system to fight the disease. 20 to 30% of the patients treated with antibodies blocking the PD-1/PD-L1 pathway showed a response to the treatment. But this rate of response is lower than in other cancer types and there is a clear need to understand why the patients do not respond to the treatment in order to improve and find new immunotherapeutic treatments.

In this optic, we plan to combine the expertise of our two research teams to decipher the molecular mechanisms driving BC recurrence/progression. We will carry out studies directly in patient samples and in a genetically engineered mouse model (GEMM) of BC that recapitulates the human BC tumor progression stages. Furthermore, we will dissect and validate novel therapeutic axes and biomarkers in this GEMM, in view of phase I/II clinical trials in BC patients to improve patient survival.

Preliminary genetic studies on primary and recurrent tumor tissues of a cohort of 12 BC patients led to the discovery of a gene signature associated with BC progression/recurrence. In our study, we will focus on two pathways found in this signature that can be targeted to improve tumor control/elimination. We validated that these two pathways were higher in recurrent versus non-recurrent tumors in a larger cohort of 36 patients. This same gene signature was also detected in the progressive stage of our BC GEMM, confirming the known clinical relevance of this model. **Based on these findings, we hypothesize the existence of a therapeutically targetable crosstalk between immune and BC cells that involves the studied genes and their regulation.**

Therefore, in the first aim of this project, we will validate the progression/recurrence gene signature at the protein level in BC primary patient samples and in our BC mouse model (tumor sections, fresh tumor tissues). This will allow us to define the cell types expressing the candidate genes, i.e., tumor cells, stromal cells, immune cells (myeloid and lymphoid cells).

In the second aim, we will inactivate our target genes or their ligands in the given cell types. We will monitor the *in vitro* behavior of gene-edited human and murine immune cells (phenotype, cytokine secretion, differentiation stage, plasticity) and BC tumor cells (survival,

invasion, migration, colony formation, epithelial-to-mesenchymal transition). We will assess the *in vivo* progression and microenvironment composition of tumors established by intravesical instillation of wild-type or gene-edited BC cells, as well as animal survival. We will also assess tumor growth dynamics and spread in both wild type and genetically modified mice, as well as animal survival and composition of the tumor microenvironment.

Lastly, we will perform pre-clinical studies using either blocking antibodies, small molecules or miRNA mimics in our BC mouse model to determine how these treatments impact on tumor progression and on the immune response against the tumor. Overall, we expect to identify novel targetable gene pathways to improve our understanding and treatment strategies for recurrent and advanced bladder cancer patients.