Advanced *in vitro* models of prostate cancer metastases: unravelling and overcoming ARSI resistance

Project

Prof. Mark Rubin

Prostate cancer is the most common cancer type and the second cause of cancer-related death among the Swiss male population. Current standard treatment for metastatic prostate cancer is based on androgen deprivation therapy and androgen receptor signalling inhibitors (ARSI).

The emergence of resistance to ARSI constitutes a negative turning point in prostate cancer disease course, often leading to a rapidly progressing tumor phenotype. The biological mechanisms driving ARSI resistance are complex and remain not fully understood. Recent evidence points to a critical role of the tumor microenvironment of the metastatic niche in promoting prostate cancer progression and therapy resistance. However, the underlying mechanisms remain understudied.

The overarching goal of this project is to clarify how prostate cancer cells interact with distinct metastatic niches and how this interplay contributes to the emergence of ARSI resistance. We will employ actionable patient- and stem cell-derived models of prostate cancer metastases to establish *in vitro* ARSI resistant tumor clones. We will investigate resistance mechanisms by performing comprehensive genomic and transcriptomic profiling of these tumors. Additionally, we will cross-validate our findings by analyzing metastatic biopsies from patients with ARSI resistant disease. The generated molecular profiling data will serve to direct targeted drug screenings for the development of novel strategies to prevent or overcome ARSI resistance.

In summary, the aim of this project is to improve our understanding of metastatic niche-driven therapy resistance mechanisms in advanced prostate cancer and to uncover novel therapeutic targets and strategies for the personalized management of metastatic prostate cancer.