INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HOPITAL UNIVERSITAIRE DE BERNE
BERN UNIVERSITY HOSPITAL

UNIVERSITÄT BERN

Project funded by Wilhelm Sander Stiftung
Mark Rubin and Irene Paassen

Title: *Unraveling Chromatin Remodeling Mechanisms in Regulating Lineage Plasticity in Metastatic Castration-Resistant Prostate Cancer*

Summary

Under therapeutic conditions, lineage plasticity can cause cancer cells to switch from one committed state to another. The increasing use of targeted therapies for prostate cancer (PCa) has revealed that treatment with androgen-deprivation therapy can lead to the outgrowth of resistant tumors that have changed lineage identity compared to pre-treatment tumors, referred to as lineage plasticity. The cellular and molecular mechanisms that underlie treatment-associated lineage plasticity in PCa remain poorly understood. It is speculated that epigenetic control might play an essential role. One major complex determining cell identity during development and disease is the SWI/SNF chromatin remodeler complex**. In this study, we aim to elucidate the role of the SWI/SNF complex in controlling lineage plasticity in PCa**. We will exploit the RPM PCa xenograft model (RB1$^{-/-}$, TP53$^{-/-}$, MYC^{T58A}), which is proven to undergo lineage transition towards castration-resistant neuroendocrine PCa (CRPC-NE). We will transduce RPM organoids with a barcoded sgRNA library, including guides against subunits or interactors of the SWI/SNF complex. After subcutaneous transplantation of the barcoded organoids into mice, tumors will be extracted at multiple time points and subjected to combined single-cell RNA and ATAC-sequencing, leading to the identification of essential subunits during lineage transition. New insights into the clonal dynamics underlying lineage transitioning in PCa will be formed, ultimately improving strategies to prevent or overcome resistance to targeted therapies and realize their full promise for PCa patients.