Prostate cancer (PCa) is the second most common cancer in men worldwide. About 15% of PCa patients are diagnosed with advanced PCa. They have an increased risk of developing a metastatic disease (mPCa) with a five-year survival rate below 30%. The treatment response of mPCa is highly heterogeneous, whereas the therapeutic options and prognostic biomarkers for mPCa are limited.

Our study demonstrated that aldehyde dehydrogenases ALDH1A1 and ALDH1A3 are critical regulators of PCa radioresistance and metastases. The products of the enzymatic activity of ALDH proteins are retinoic acid (RA) isomers serving as ligands for retinoic acid receptors (RARs) and retinoid X receptors (RXRs) that transcriptionally regulate the retinoid-responsive genes. We found that ALDH1A1 and ALDH1A3 genes regulate TGFB1 expression in a RAR- and androgen receptor-dependent manner. TGF-β1 pathway further contributes to the activation of the MMP11 expression in PCa cells. Knockdown of MMP11 in several PCa cell lines increased cell radiosensitivity. Transcription level of MMP11 was identified as a marker of clinical outcomes using independent clinical datasets. The plasma MMP11 levels have shown a potential to differentiate between metastatic and non-metastatic PCa with high specificity and sensitivity. Furthermore, MMP11 plasma levels had a significant association with PSA increase in patients with oligometastatic PCa treated with local ablative external beam radiation therapy.

Based on our findings, we hypothesized that MMP11 contributes to the PCa progression and metastatic dissemination. This study aims to systematically investigate MMP11 for its biological functions, mechanisms of action, potential role as a biomarker in prospective and retrospective clinical trials, and target for inhibition of tumor growth and radio-sensitization. We will decipher the functional role of MMP11 in PCa radioresistance, stemness, migration, invasion, proliferation, and metastatic growth in vivo using murine models. We will analyze exosome-mediated MMP11 delivery, MMP11 interactome, and MMP11-mediated signaling. We will assess the prognostic and predictive value of MMP11 in patients with mPCa using liquid biopsy and tissue samples. Finally, we will develop the MMP11 targeting strategy using patient-derived organoid cultures and in vivo models.

This study will pave the way for future clinical applications of MMP11 as a clinical biomarker for patient stratification and a therapeutic target for combination with other targeted treatments and radiation therapy.