Cell-of-origin of prostate cancer and clinical heterogeneity

Personalized treatment for prostate cancer remains a challenge because there are no clear molecular subtypes to guide patient response. Imaging, PSA levels and pathological assessment of biopsies through the Gleason grading system remain the gold standard for diagnosis and risk stratification. Moreover, most genomic campaigns analysed single biopsies with reduce analysis of their cellular landscape, which limit the value of this analysis in what is known to be a multifocal disease. By combining genomic and multiparametric imaging analysis of high-risk prostate cancer patients, we have characterized the radiogenomic landscape of multifocal prostate cancer. Moreover, coupling single-cell profiling and functional characterization by organoid-culture and in situ lineage-tracing analysis in mouse models, we have identified inherently castration-resistant cellular subpopulations in the prostate defined by their unique cell-surface markers. In particular, our studies define LY6D as a marker for prostate progenitors and castration-resistant luminal cells, which may serve as prognostic maker for advanced prostate cancer. Further functional characterisation of the identified therapy-resistant prostate luminal subpopulations will highlight their contribution to tumour subtypes thereby advancing patient stratification and setting a pipeline to develop novel therapeutics.