

A novel panel of patient-derived preclinical models of prostate cancer: xenografts and PDX-derived organoids to recapitulate patients disease profiles

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Introduction & Objectives: The treatment of advanced and castration resistant prostate cancer (CRPC) has changed drastically in recent years with novel compounds in the pipeline. Currently, accurate (CR)PC models as patient-derived xenografts (PDXs) are relatively scarce, as they have been proven difficult to establish. To continue to reflect current patients' disease profiles, existing models need updating. In parallel, new 3D culture technologies are aiming to replace traditional PDXs to enable semi-high throughput screening approaches in order to accelerate drug development and implementation in clinical practice. To achieve this aim, we generated 4 novel PDXs from (CR)PC patients and developed a workflow to create in vitro PDX-derived organoids.

Materials & Methods: Tumor tissue was obtained from (CR)PC patients undergoing transurethral resection of the prostate (TURP). Tumor fragments were implanted subcutaneously in male athymic NMRI nude mice. Tumor response to androgen manipulation was assessed by weekly tumor volume measurements. From our existing PDX panel (*Navone et al. Prostate 2018*) and the 4 novel PDXs, we initiated organoid cultures by plating small cell clumps into synthetic hydrogel. Organoids were grown in prostate growth medium (*Marques et al. Int J Cancer 2005*) or medium adapted from Drost et al. (*Nat Protoc 2016*). Growth was monitored over time by bright field microscopy. Tissue morphology and characteristics were assessed by histology and immunohistochemistry (IHC). PSA in culture medium was quantified by ELISA. RNA sequencing was performed on PDX tissue, organoids and original patient samples.

Results: We have established 4 new PDX tumors, 1 from a hormone sensitive patient and 3 from patients progressing on taxane treatment. One PDX was derived from a consecutive TURP of the same patient following progression. Interestingly, all 4 PDXs are hormone sensitive, express the androgen receptor (AR) and produce PSA. Analysis of RNA-seq data was conducted to show clustering of PDXs to their matched patients based on expression profiles of a set of preselected genes. We were able to grow short term organoid cultures in 10 out of 11 PDXs. Speed of organoid formation varied by PDX type, with an outgrowth of organoids within a few days up to several weeks after plating. IHC of organoids derived from androgen sensitive PDXs confirmed preservation of AR expression. Moreover, a progressive increase in PSA production was observed over time and may be used to reflect organoid growth.

Conclusions: We have currently expanded our existing PDX panel with 4 novel PDXs that accurately represent original patient characteristics. Moreover, we have established organoid cultures from these PDXs, both previously established and new. We believe these short term PDX-derived organoids can be of great added value in semi-high throughput drug screens and personalised medicine.