An organoid prostate cancer platform to study early disease biology & novel therapies

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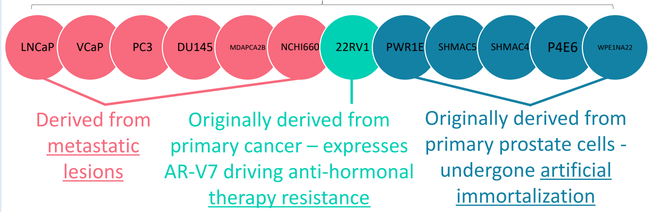
EARLY DETECTION & UROLOGICAL MALIGNANCIES PROGRAMME

Prostate Cancer Research

1 Lack of early disease models impedes cancer research

Commonly used prostate cancer cell models



What about primary prostate cancer models?

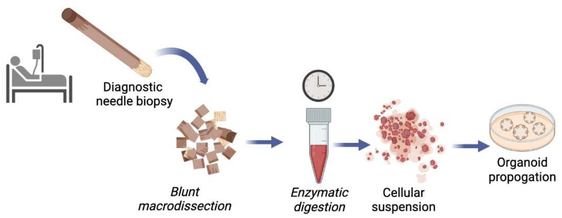
Cellular heterogeneity & 3D structure

Organoids

Inexpensive & quick to establish compared to mouse models

Expandable enabling perturbation & CRISPR screening research

2 Bedside-to-bench *ex vivo* workflow



- The DIAMOND bioethical framework (Study REC 03/018) was used to obtain image-guided prostate diagnostic biopsies from men suspected of high-risk prostate cancer (PSA ≥10, MRI PIRADS ≥4).
- Needle biopsies were preserved in Miltenyi MACS Tissue Storage Solution prior to tissue dissociation via enzymatic digestion. Cells were resuspended in Matrigel prior to plating in published conditions[A] for expansion and growth phase. Alternatively, cells were plated in formulations according to proprietary protocols for maintenance and expansion phase of cellular growth.
- Post-procedure histological evaluation of parallel biopsies was reviewed by a uro-histopathologist to validate histological content.

3 Results

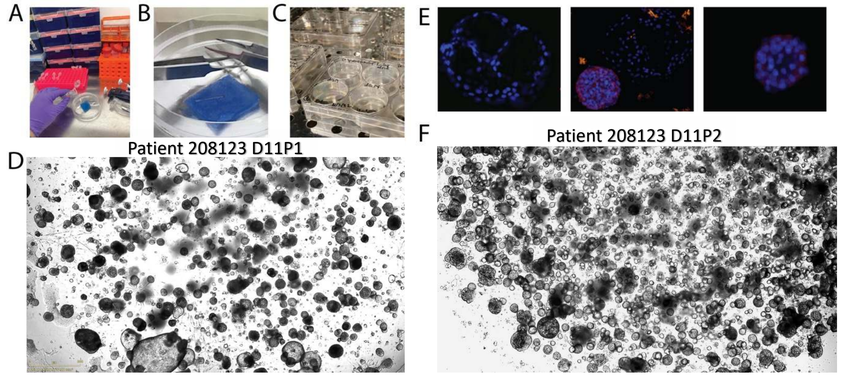


Figure 1 Prostate tissues are brought directly from the clinic to the laboratory (A, B) for culture of primary patient-derived cells as organoids (C). (D) High-magnification of passage 1 organoids in culture using 3D-incucyte, after 11 days of growth. Patient-derived organoids demonstrate cellular variability with cystic and solid appearing structures; (E) Confocal microscopy images with DAPI (blue), cytokeratin 5 basal cell marker (red); (F) White light microscopy demonstrating cellular appearance of passage 2 PDOs after 11 days growth from prostate tissue biopsy of a patient with Grade Group 2 Adenocarcinoma.

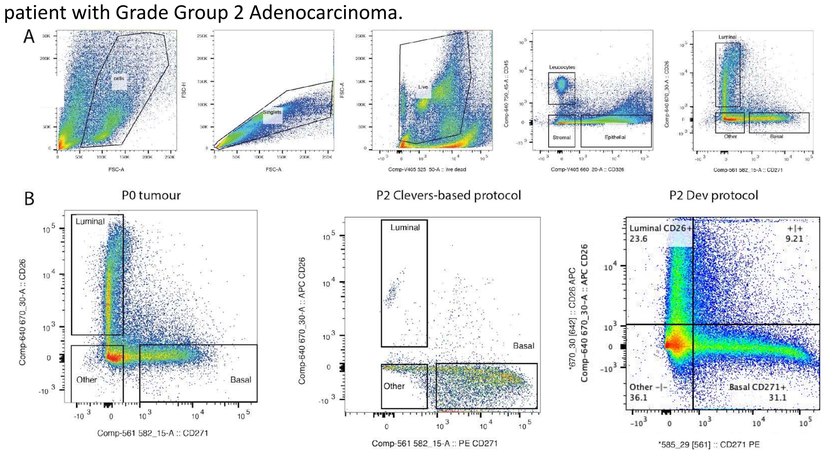


Figure 2 Flow cytometry analysis demonstrates cellular subtypes discernible from prostate tumour tissue after dissociation protocol. (A) Epithelial cell enrichment is used to identify luminal, basal and other epithelial cell type fractions. (B) Epithelial cell content (EpCAM+) at P0 (left), P2 (culture using standard prostate organoid protocols[A]) and P2 (Dev organoid workflows), showing maintenance of non-basal lineages, suggesting a stem-like state is maintained with capacity to maintain luminal-like features.

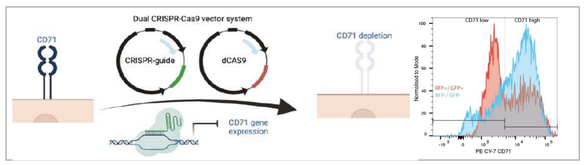
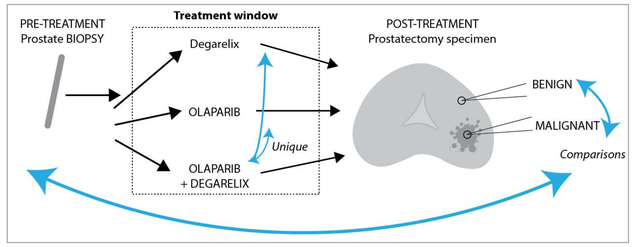


Figure 3 CRISPR-Cas9 lentiviral organoid transduction. Application of the dual vector CRISPRi system[B] demonstrates an ability to perform efficient gene-editing, with >50% efficiency in transduced cells.

4 Next steps

- Further characterise our early models of high-risk localised prostate cancer (bulk genomic, WES, transcriptomic profiling).
- In collaboration with Mohammed lab (OHSU), perform prostate organoid single cell multi-omic profiling to explore the heterogeneity of patient early disease biology
- Leverage prostate organoids in the development of novel therapeutics and treatment selection biomarkers in collaboration with AstraZeneca & STEMCELL Technologies
- Leverage clinical trial specimens to define the molecular response to DNA damaging agents using surgical window trial specimens[C]



5 References

[A] Drost et al. (2016) Organoid culture systems for prostate epithelial and cancer tissue. Nat Protoc. Feb;11(2):347-58.

[B] Sun et al. (2021) A functional genetic toolbox for human tissue-derived organoids. Elife. t 6;10:e67886.

[C] Pacey, et al. Study of Olaparib (± Degarelix) Given to Men With Intermediate/High Risk Prostate Cancer Before Prostatectomy (CaNCaP03). https://clinicaltrials.gov/ct2/show/NCT02324998

The Massie & Dev labs based in the Early Cancer Institute in Cambridge are recruiting. Scan the QR code for more information.