Precision medicine in prostate cancer: the use patient-derived organoids to predict patient-centric responses to therapy

Mahasha P.J. Perera[1,2,3,4] Patrick B. Thomas[1,2,4], Saeid Alinezhad[1,2], Andre Joshi[3], Alivia R. Calabrese[1,2],,Ian Vela[1,2,3,4], Elizabeth D. Williams[1,2,4]

1. Queensland Bladder Cancer Initiative (QBCI), Institute of Health and Biomedical Innovation, Queensland University of Technology (QUT), Princess Alexandra Hospital, Translational Research Institute, Woolloongabba, Queensland 4102, Australia.
2. Australian Prostate Cancer Research Centre – Queensland, Institute of Health and Biomedical Innovation, Queensland University of Technology (QUT), Princess Alexandra Hospital, Translational Research Institute, Woolloongabba, Queensland 4102, Australia.
3. Centre for Personalised Analysis of Cancers (CPAC), Brisbane, Queensland, Australia.
4. Department of Urology, Princess Alexandra Hospital, Brisbane, Queensland, Australia.

Background

Prostate cancer is the 2nd most commonly diagnosed cancer amongst Australian men. Whilst localised prostate cancer can be curatively treated with radiation or surgical resection, 10-20% of men present with metastatic disease. Individual patient responses to pharmacotherapy vary. We present a pipeline of deriving patient-derived organoids as a tool for predicting patient-centric responses to therapy.

Objective:

1. We aim to generate patient derived organoids (PDOs) from our QLD based prostate cancer biobank.
2. We aim to use our derived PDOs in a preclinical assay to predict patient responses to therapy.

QBCI Prostate Cancer Cohort Demographics

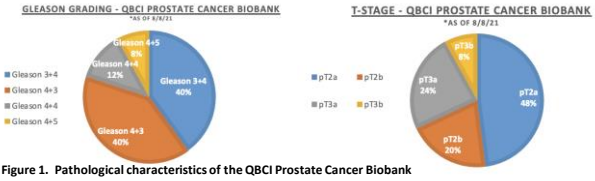
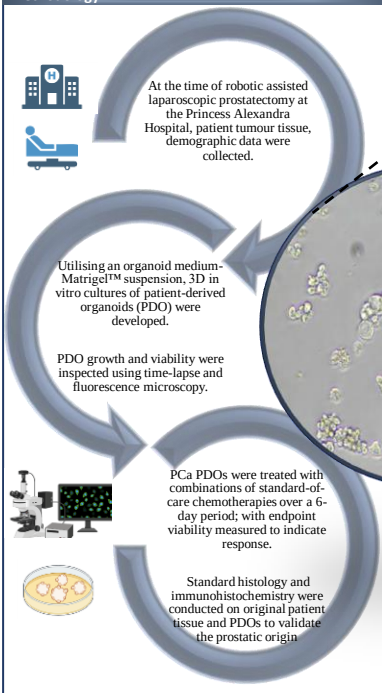


Figure 1. Pathological characteristics of the QBCI Prostate Cancer Biobank

To date, our tissue biobank contains, 25 malignant prostate tumours, 8 samples of benign prostate tissue and one benign lymph node. Ten patients had definitive histology demonstrating intermediate favourable disease (Gleason 3+4=7). The remainder of patients had at least intermediate unfavourable disease or worse (Gleason > 4+4=8). The vast majority of patients had acinar pattern adenocarcinoma, whereas two patients had mixed ductal-acinar adenocarcinoma and intraductal adenocarcinoma.

Methodology



Patient Derived Organoid Development and Drug Treatment Assays

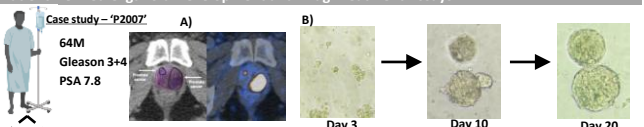


Figure 2. 'P2007' Case study of Gleason 3+4. a) PSMA PET/CT showing avidity corresponding to prostate cancer focus. b) PDOs and proliferation in cell culture.

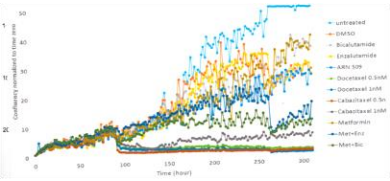


Figure 3. In vitro drug treatments of 'P2007' organoids and confluency analysis over time during drug treatments through the Incucyte.

Limitations

Cost effective
Easy to handle
Established protocol

Spheroid heterogeneity
Lack of quantifiable data

Patient derived organoids are 3-dimensional in vitro models which more readily recapitulate features of primary tumours. PDOs provide a cost-effective preclinical model for predicting patient responses to treatment. PDOs can also be used to examine rare variants of disease which are infrequently encountered clinically.

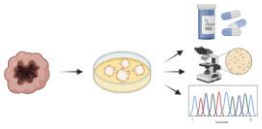


Figure 4. Pipeline of PDO generation and downstream utility of PDOs for the analysis of patient tumours.

Conclusions

- To date, our biobank contains a heterogenous sample of prostate cancer ranging from intermediate favourable grade disease to aggressive unfavourable disease.
- Our organoid generation and drug treatment demonstrates feasibility in generating PDOs for drug screens, however further optimisation of the organoid process is required.
- A major limitation of organoids as a model for drug treatments is heterogeneity between samples.

Future work will seek to add samples with diverse variants of disease and varying disease states including metastatic specimens.

Acknowledgements

This work is supported by the Princess Alexandra Research Foundation, Australian Government Department of Health and Ageing, the MovemberFoundation and the Prostate Cancer Foundation of Australia through a MovemberRevolutionary Team Award, and MetroSouth Health funding