Patient-Derived Organoids as a Platform for Personalised Medicine in Pancreatic Malignancies: Our experience from a Pilot Study

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Background

- Pancreatic cancer is the most lethal common solid malignancy (Tiriac 2018).
- First-line chemotherapy is chosen empirically. In phase III trials, objective response rates were 31.6% with FOLFIRINOX and 23% with nab-paclitaxel plus gemcitabine (Conroy 2011; Von Hoff 2013).
- Organoids can be generated rapidly from resected pancreatic tumours and biopsies (Boj 2015).
- PDO libraries recapitulate the mutational spectrum and transcriptional subtypes of primary pancreatic cancer, and PDO drug profiles paralleled patient outcomes in case studies (Tiriac 2018). PDOs from pancreatic and distal bile duct tumours have been used for personalised drug screening (Driehuis 2019).

Aim

To assess the feasibility of using patient-derived organoids (PDOs) as patient-specific models for chemosensitivity testing across pancreatic and periampullary tumours.

Methods

1 Resection
Consent to tissue donation at pancreatic resection

2 Derivation within 1 h
Fresh tissue transported on ice and processed within one hour

3 Culture
Daily monitoring; medium changed on alternate days

4 96-well plating
Once sufficient growth was achieved

5 72 h drug exposure
Gemcitabine and 5-fluorouracil (5-FU)

6 Readout
Brightfield imaging and ATP-based viability (CellTiter-Glo)

Concentration ranges for gemcitabine and 5-FU were set using SUIT-2 and MIA-PaCa-2 spheroids.

Results: derivation

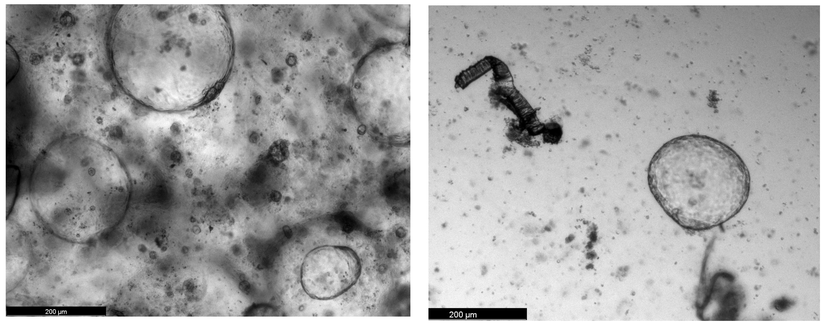
9 patients consented to tissue donation

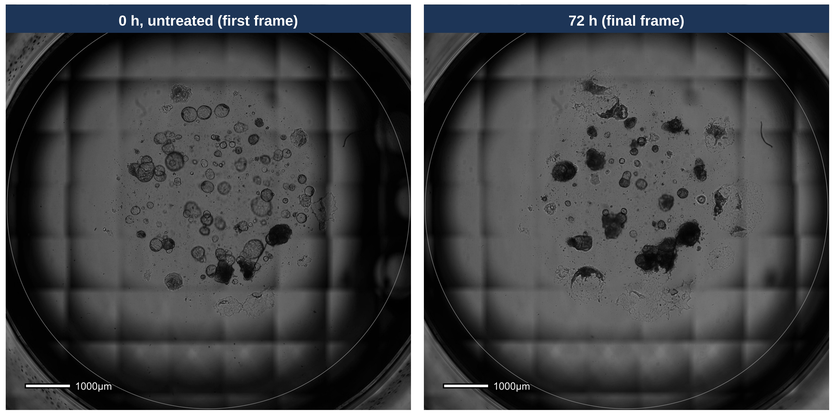
7/9 samples gave organoids that were derived and passaged

4 PDO lines completed chemosensitivity testing

Pathology of the four tested lines
Ampullary adenocarcinoma: 2 (PDO005, PDO007)
PDAC: 1 (PDO006)
Distal cholangiocarcinoma: 1 (PDO009)
All samples included PDAC, distal cholangiocarcinoma, IPMN and ampullary adenocarcinoma

Organoid morphology and drug response

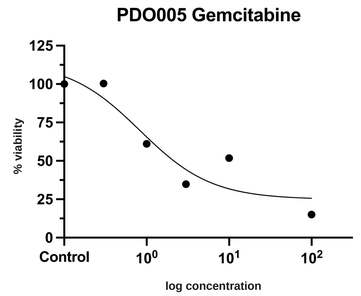


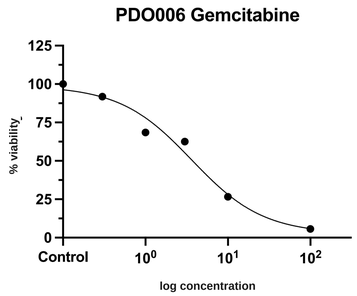


B. The same well at the first and final frames of a time-lapse run. By the final frame the organoids are darker and have lost their cystic outline. Scale bar 1000 µm. **PDO006; gemcitabine-treated**

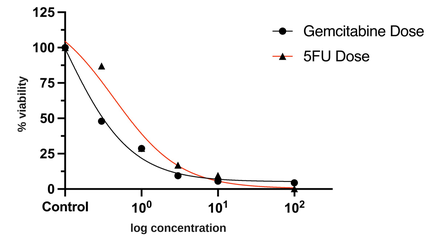
Results: chemosensitivity

All four tested PDO lines (two ampullary, one PDAC, one distal cholangiocarcinoma) showed dose-dependent, measurable changes in morphology and viability 72 h after exposure.



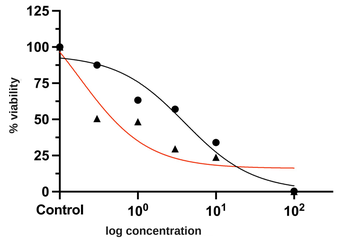


PDO005, ampullary: gemcitabine



PDO007, ampullary: gemcitabine and 5-FU

PDO006, PDAC: gemcitabine



PDO009, distal cholangiocarcinoma: gemcitabine and 5-FU

x axis, log concentration; y axis, % viability by CellTiter-Glo relative to untreated control, 72 h. Curves reproduced unchanged from the Year 2 PGR presentation, slides 34–36; axis titles overlaid.]

Conclusion and future work

- PDOs were established from a range of pancreatic and periampullary tumours, with organoids derived and passaged from seven of nine samples.
- PDOs may provide a feasible high-throughput platform for personalised chemosensitivity testing.
- A larger study is needed to assess interpatient variability and predictive accuracy.

References

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