Developing PDX-Derived Organoid Models for Efficacy Evaluation of Anticancer Therapies

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ABSTRACT

Developing most fitting models that best reflect real patient tumor system is crucial for advancing cancer mechanistic research and mediating drug discovery. Patient derived xenograft (PDX) models can accurately reflect cancer responses to therapies, thus being recognized as a gold standard in oncology drug development. However, PDX models can be labor intensive, time-consuming and costly. Cancer organoid is 3D infinitesimal derived from patient tumor cells, which can faithfully recapitulate genetic profile, mutational landscape, phenotypic and histo-pathological features and responses to therapies of patient tumors. Organoids derived from PDX tumors, namely PDXOs, are suitable for *in vitro* anticancer drug efficacy evaluation, forming good combinations with their *in vivo* PDX counterparts. By 2025-March, we have established >30 PDXO models from our PDX bio-bank. These models cover different cancer types, including colon cancer, gastric cancer, pancreatic cancer, lung cancer, liver cancer to name a few. Herein we present our latest progress of PDXO model development for anticancer drug efficacy evaluation uses.

METHODS

PDXOs were developed using Matrigel dome embedding approach with fresh cell digests from PDX tumor tissues. The model development included continuous expansion for >3 passages followed with cryopreservation and downstream analysis. The morphology features of each model were assessed using bright field imaging (BFI) and H&E staining. Whole exome sequencing (WES) and mRNAseq profiles were available for each model. Immuno-cytochemical staining (ICC) and flow cytometry were used to assess the biomarker expression. BFI, CellTiter-Glo (CTG) assay, LDH release assay and fluorescence imaging were used for drug efficacy evaluation.

Workflow Scheme

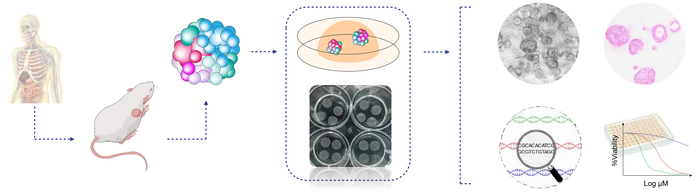

Fig 1. The Workflow of PDXO Model Development from PDX Tumor Tissue and Its Downstream Analysis.

PDX vs PDXO: WES & Drug Response

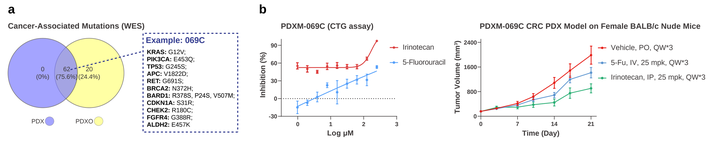

Fig 2. Consistent Genetic Profile and Drug Response Prediction between PDX and PDXO. (a) PDXO of 069C, a colon cancer, well-preserved all cancer-associated exonic mutations of its PDX counterpart. (b) Both *in vitro* efficacy results by PDXO and *in vivo* efficacy results by PDX showed a higher sensitivity to irinotecan over 5-Fluorouracil of 069C.

Characterization of PDXOs: Morphology & Drug Response

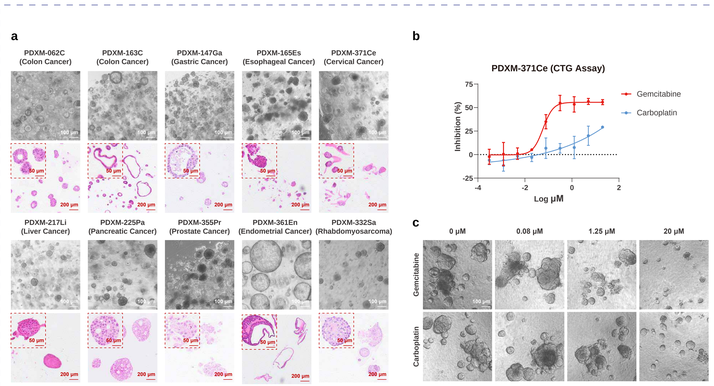

Fig 3. Characterization of PDXOs. BFI and H&E results of PDXOs (a). Efficacy study of standard-of-care anti-cancer drugs, Gemcitabine & Carboplatin, on a Cervical Cancer PDXO: (b) CTG assay results and (c) BFI results.

Mini-Multi-Omics Study: HER2 & EGFR

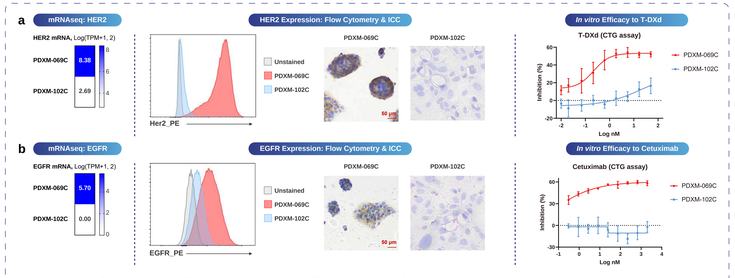

Fig 4. Mini-Multi-Omics Studies on PDXOs with Different Expressions of HER2 and EGFR. 2 Colon Cancer PDXOs, 069C and 102C, were selected based on their different expressions of HER2 (a) and EGFR (b) from mRNAseq results. Their HER2 (a) and EGFR (b) expressions were further assessed using flow cytometry and ICC, showing that 069C was $HER2^{high}EGFR^{high}$ while 102C was $HER2^{low}EGFR^{low}$. This finding was consistent with the downstream *in vitro* efficacy evaluation results to T-DXd (an anti-HER2 ADC drug) and Cetuximab (an EGFR blocker).

Efficacy Evaluation Using Co-Culture of PDXO with PBMCs

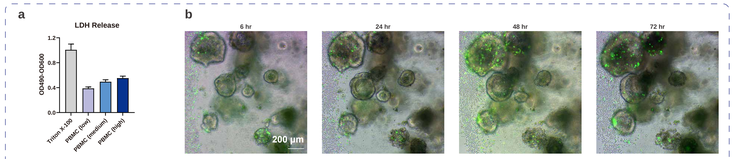

Fig 5. Evaluation of Anti-Cancer Efficacy of PBMCs on PDXO (163C, Colon Cancer) Using A Co-Culture System. (a) LDH release assay showed a dose-responsive effect of PBMCs on PDXO. (b) Time-course analysis using fluorescence imaging showed an enhanced PBMC infiltration and killing performance over time. PBMCs (Green) labeled with DiO.

Acknowledgement

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SUMMARY

- PDXO could well preserve the mutational features of the PDX counterpart and exhibit the same response to therapies as the PDX counterpart.
- The unique 3D morphology features of PDXOs could be assessed using BFI and H&E. Their drug responses could be assessed using CTG assay and BFI.
- PDXOs with particular genetic or protein expression features were suitable for efficacy evaluation of the corresponding targeted therapies.
- *In vitro* efficacy study of immune therapy could be assessed on PDXOs using co-culture system with PBMCs or other immune cells.

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