Miniaturizing patient-derived organoid screening assays for predictive drug testing

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Abstract 1923748

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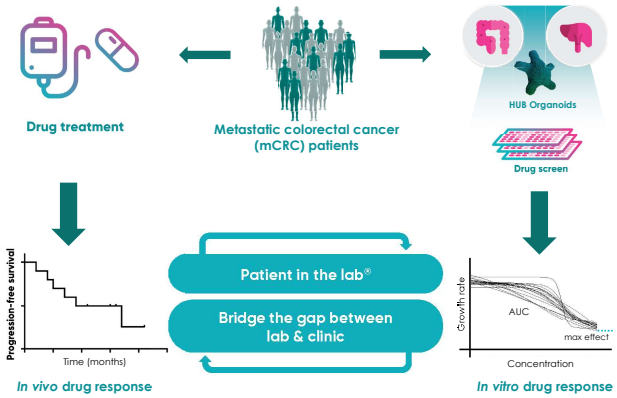
Introduction

Colorectal cancer (CRC) is the third leading cause of cancer incidence and mortality, with treatment options for metastatic patients often giving limited results and significant side effects. There is an urgent need for models that help predict patient response in the clinic. Patient-derived organoids (PDOs or HUB Organoids®) represent a significant breakthrough as they are directly established from patient tissue and accurately recapitulate patient disease. While PDO technology is promising for preclinical drug screening, to benefit patients directly, shortening the turnaround time from diagnosis to delivering PDO-based results is crucial for implementation in the clinic. Through collaboration with Yamaha Motor, an automated transfer system called YAMAHA CELL HANDLER™ (YCH) has been optimized for handling PDOs with enhanced precision and efficiency. An image-based readout system has been developed to quantify organoid numbers to ensure assay quality precisely. A proof-of-concept study on PDO responses to chemotherapy was conducted using this automated platform, demonstrating a strong correlation between PDO and patient responses. This highlights the potential of the developed automated platform for predictive drug testing.

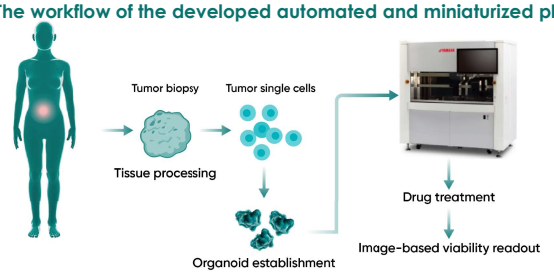
Figure 1. HUB Organoids technology in pre-clinical predictive testing



Methods

- Informed consent was obtained from all patients prior to their inclusion in the clinical study, and samples were collected under the protocols of the OPTIC clinical trial.
- Patient material for the study was acquired, and the procedure to establish PDOs from mCRC small needle biopsies was optimized (**Figure 1**).
- Automated and accurate seeding of organoids in screening plates was achieved using the YAMAHA CELL HANDLER™ to reduce the number of organoids per well (**Figure 2**).

Figure 2. The workflow of the developed automated and miniaturized platform



Results

Figure 3. Transfer efficiency and image-based readout

A: Representative images of organoids 5 days after treatment with DMSO or Staurosporine and stained with CyQuant. B: Organoid number transferred presented as raw counts (top) and % of planned (bottom) 5 days after transfer of 1, 2. 5 or 10 organoids/well.

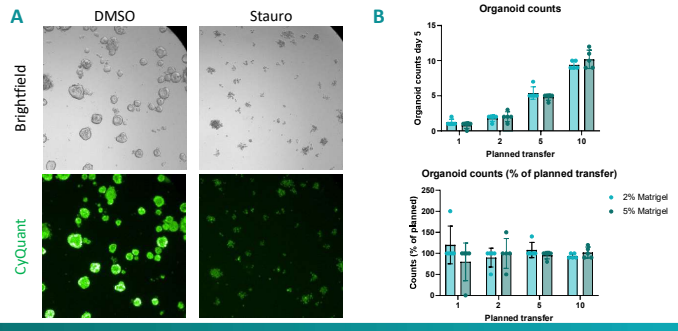


Figure 4. Different organoid responses towards Panitumumab

A Response of KRAS/BRAF WT PDO (PDO 1) and BRAF mutant PDO (PDO 2) towards EGFR inhibitor Panitumumab seeding 10 organoids/well and CyQuant readout (left) or seeding 250 organoids/well and CyQuant readout (middle) or seeding 250 organoids/well and CellTiter-Glo readout (right). Data represents Mean ± SD of technical replicates (n=4). B Correlation of PDO responses to 5-FU and oxaliplatin using 10 PDOs per well and 250 PDOs per well. PDOs are derived from metastases. AUCs for 250 PDOs per well are based on growth rate inhibition (GR) curves. AUCs for 5 and 10 PDOs per well are based on mean intensity drug response curves.

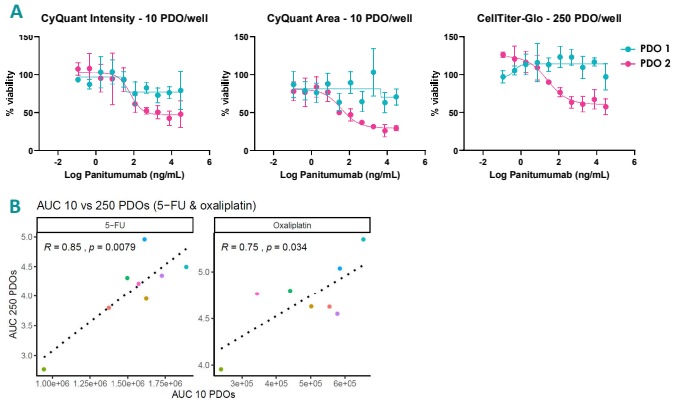


Figure 5. PDO concentration response curves following exposure to 5-FU (left) or Oxaliplatin (right) drug responses.

Each line represents a different PDO, with data points indicating the mean and standard deviation of biological replicates.

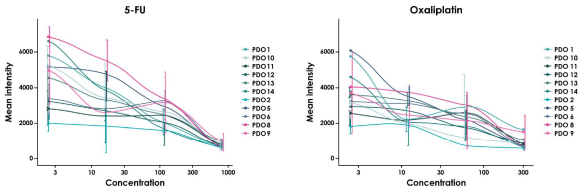
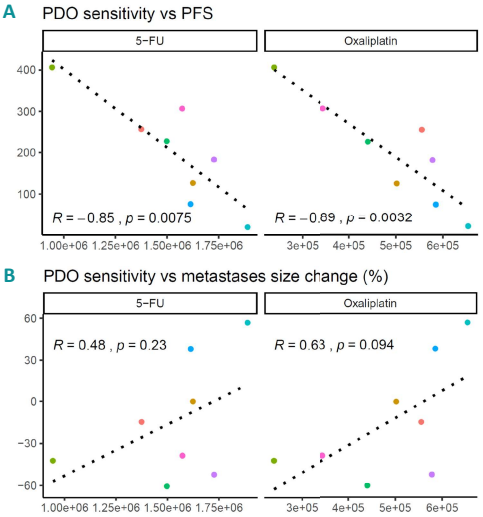


Figure 6. Correlation of PDO responses to PFS and size change metastatic lesions of patients treated with 5-FU/Oxaliplatin combination treatment.

(A) Correlation between patient progression-free survival and CyQuant intensity of PDO responses towards Oxaliplatin and 5-FU single treatments as well as in-silico combination treatment. (B) Correlation between patient size change and intensity of PDO responses towards Oxaliplatin and 5-FU single treatments as well as in-silico combination treatment. Data points represent different PDOs. The measurements shown are the mean of different biological replicates.



Conclusion

In this study, a high-throughput and miniaturized assay to screen tumor PDOs generated from clinical samples was developed. Several parameters, including the size of the organoids, number of organoids, and type of readout, were optimized to develop a PDO-YCH-based predictive assay. Furthermore, a proof-of-concept investigation underscored significant correlations between patient responses and patient-derived organoid (PDO) reactions. This data indicates the potential of predicting patient responses to the 5-FU/Oxaliplatin combination therapy based on PDO behavior. Such predictive capabilities not only streamline the data acquisition process for clinical trials but also highlight the viability of the proposed miniaturized assay in drug screening and clinical diagnostics.

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