Patient-derived organoids to predict clinical response: *a patient in the lab®*

HUB ORGANOIDS

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Introduction

A large fraction of colorectal cancer (CRC) patients diagnosed with *de novo* metastatic disease do not benefit from standard of care and still experience substantial side effects. Therefore, there is the urgency for a new preclinical model to predict clinical response.

Adult epithelial stem cell-derived organoids are proving to be a breakthrough in preclinical modelling of human cancer. Patient-derived organoids (PDO) – or HUB Organoids® – faithfully recapitulate patient disease *in vitro* and can be propagated for drug testing in a matter of weeks. PDOs bridge the gap between the lab and the clinic and effectively bring a "*patient in the lab*".

In the current study we aimed to 1) validate the predictive value of PDOs in the stratification of metastatic CRC (mCRC) patients for treatment with chemotherapeutic agents and 2) reduce diagnostic turnaround times by using fewer organoids per well which were picked-and-placed by YAMAHA CELL HANDLER™.

Methods

- ✓ Informed consent was obtained from all patients prior to inclusion in the study and samples were obtained under HUB Biobank and/or OPTIC study protocols.
- ✓ Patient material for the study was acquired and the procedure to establish PDOs from mCRC small needle biopsies was optimized (Figure 1).
- ✓ Patient new treatment line started after acquisition of the biopsy for PDO establishment. Information about patient response to systemic treatment was available (Figure 1).
- ✓ PDO sensitivity towards chemotherapeutic agent fluorouracil (5-FU) was evaluated by performing viability screening (Figure 1).
- ✓ Automated and accurate organoid seeding in screening plates was achieved using YAMAHA CELL HANDLER™ to reduce number of organoids/well (Figure 2).
- ✓ Patient response was evaluated by measuring percentage size change of target lesions and progression-free survival (PFS) for each treatment line (Figure 3).
- ✓ Clinical response was compared with PDO drug response and best predicting response parameters (maximum growth rate, or GR_{max} and area under the curve, or AUC) were identified (Figure 4).
- ✓ Results obtained with 250 organoids/well were compared to response data from 10 organoids/well seeded by YAMAHA CELL HANDLER (Figure 5).

Results

Sensitive patients that showed long progression-free survival (PFS) or reduction in metastatic lesion size were very well represented by corresponding PDOs that demonstrated a small area under the curve (AUC) or low growth rate at maximum concentration (GR_{max}).

Figure 1. HUB Organoids for clinical predictivity

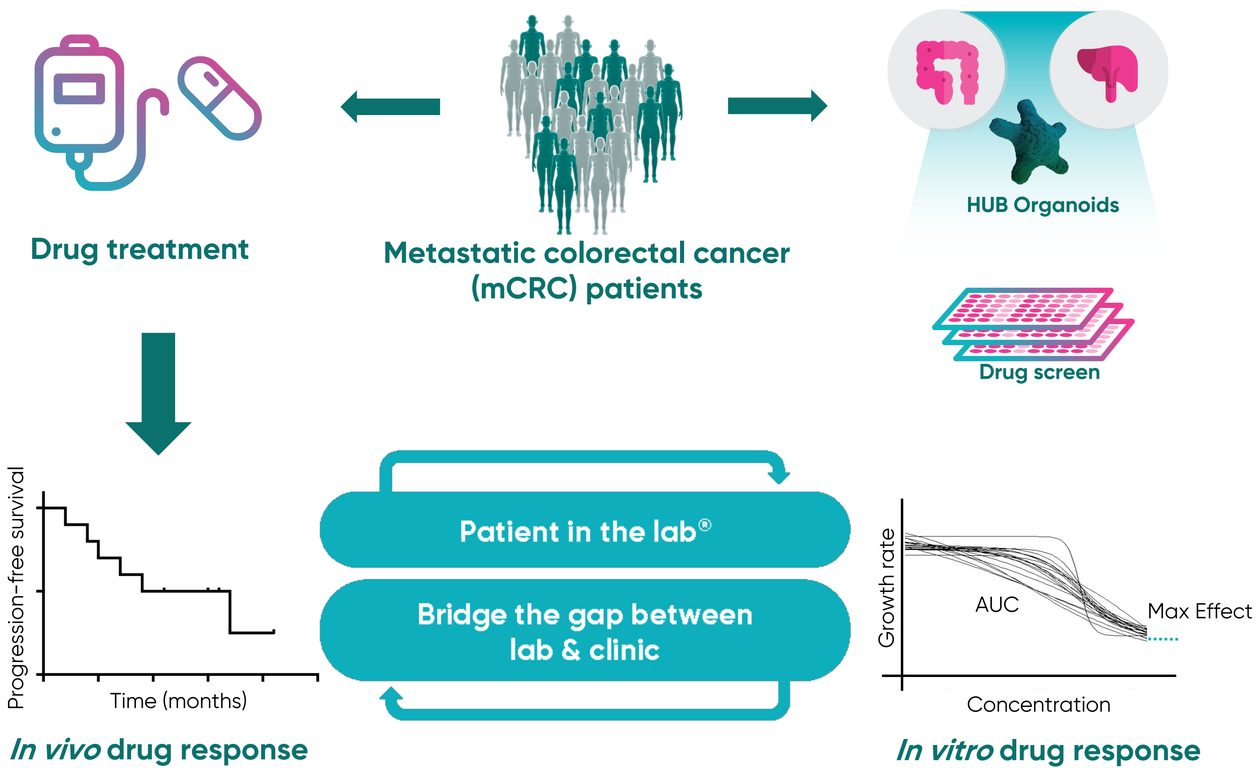


Figure 2. Yamaha CELL HANDLER: an automated system for selecting, picking and placing organoids

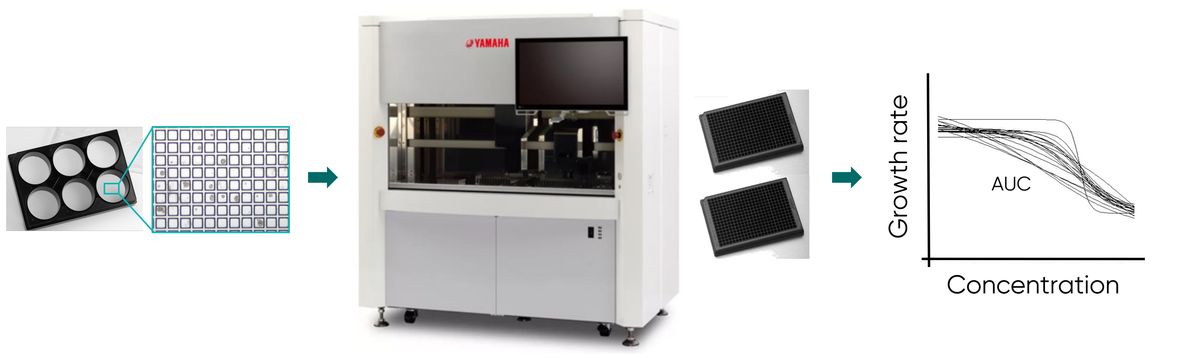


Figure 3. Progression-free survival & size change in metastatic lesions

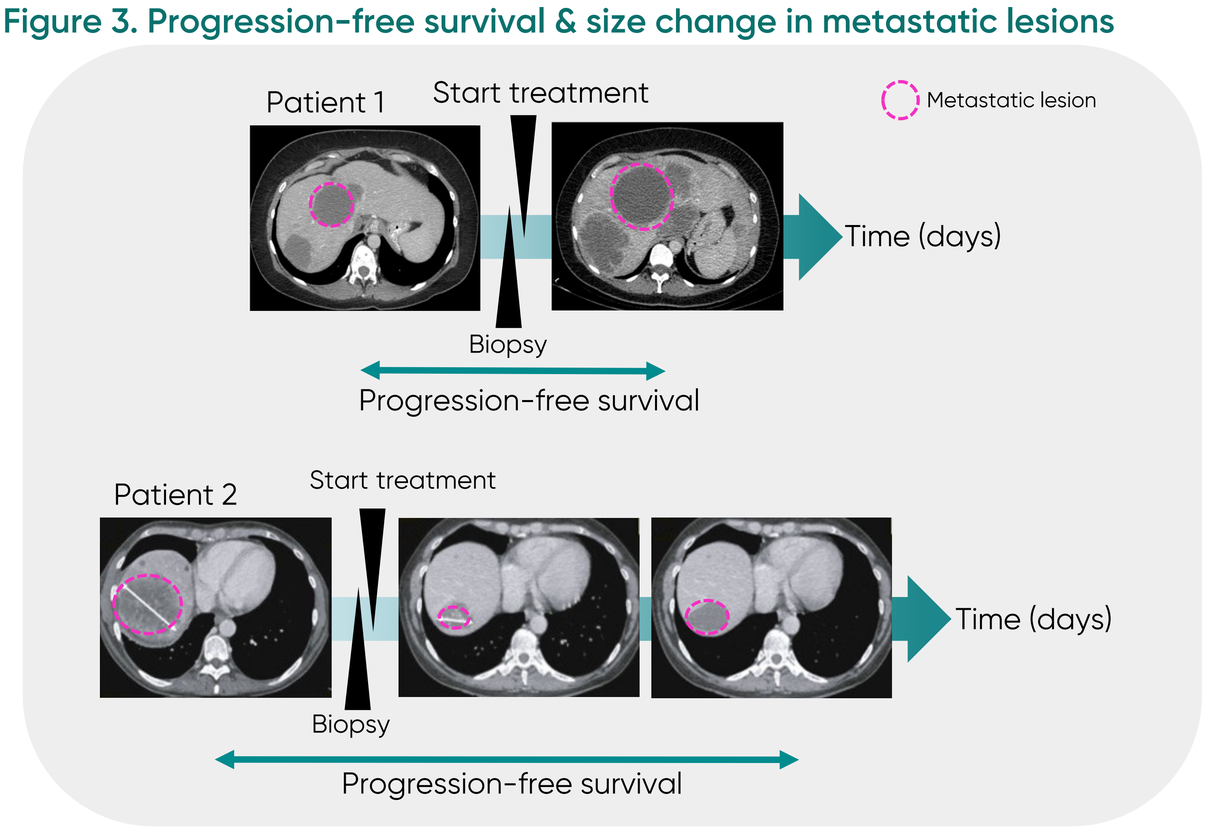


Figure 4. Clinical predictivity for 5-fluorouracil (5-FU) monotherapy

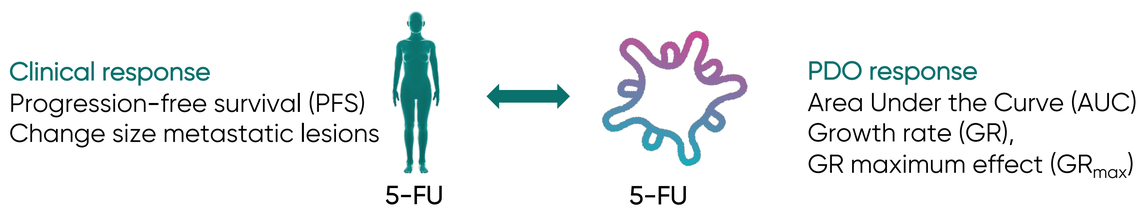
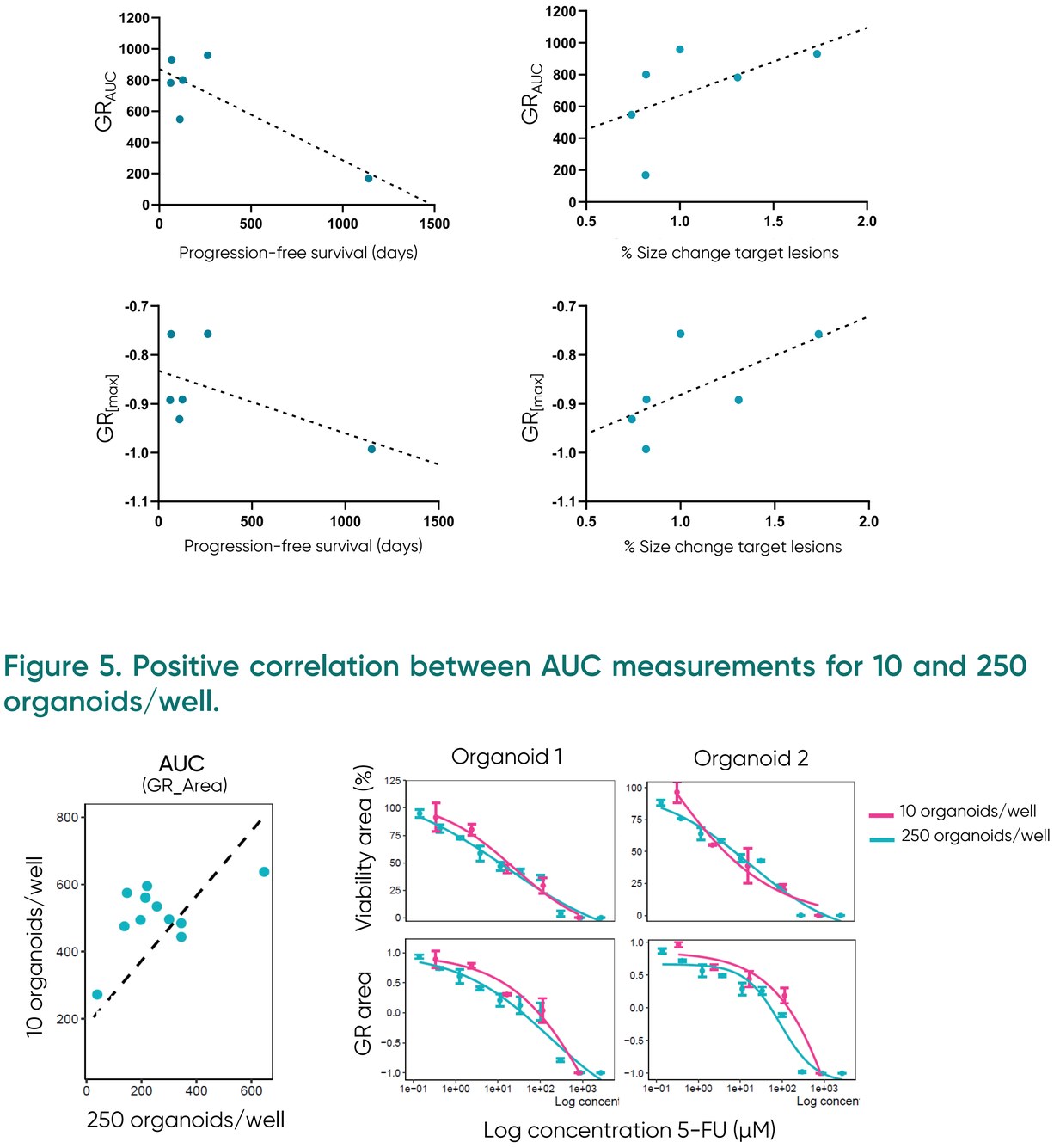


Figure 5. Positive correlation between AUC measurements for 10 and 250 organoids/well.



Conclusion

Our results demonstrate that organoid response correlates with patient response to 5-FU suggesting that organoids can serve as a predictive model and guide personalized cancer treatment. HUB Organids in combination with improved operational efficiency by the YAMAHA CELL HANDLER will enable accurate and fast prediction of treatment response to improve clinical outcome.

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