Personalised treatment strategies for patients with early-onset metastatic colorectal cancer

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Background: Colorectal cancer (CRC) is huge health burden in Australia. Concerningly, there is an increasing incidence of CRC in patients aged <50 years[1]. These early-onset CRC (EOCRC) patients are more likely to be diagnosed at stage III or IV, where the cancer has spread beyond the bowel wall and is far more difficult to treat. Therefore, there is an urgent need to improve treatment strategies for these patients in order to improve these dismal outcomes. Patient-derived colorectal cancer organoids (PDCOs) represent an innovative approach to personalised cancer medicine, with an opportunity to predict patient response prior to treatment and thus improve both patient outcomes and quality of life. Previous studies have demonstrated the ability of PDCOs to replicate patient response in vitro, however more evidence is required to translate this into clinical care.

Aim: The purpose of this study was to test PDCOs established from tumour tissue of EOCRC patients to determine their utility in personalising cancer treatment. Our aim was to screen the PDCOs against a small library of drug compounds as well as other 'personalised' compounds that were predicted to be responsive based on DNA sequencing analysis of each patient's own PDCO. This will allow us to assess the feasibility and efficiency of both approaches.

Methods: PDCOs were established from CRC tissue obtained from patients undergoing surgical resection at Cabrini Hospital. We assessed treatment response of PDCOs *in vitro,* mimicking patient-matched chemotherapeutic regimes as well as screening against 75 compounds in our custom drug library and the addition of 'personalised' compounds selected on an individual basis. The personalised compounds were predicted based on targetable DNA mutations and gene amplifications[2].

Results: Our previous study has shown that PDCOs exhibit a high level of concordance in histopathological features and key driver mutations when compared to the primary tumour[3]. Recently, we have been investigating the utility of PDCOs for developing personalised treatment strategies for EOCRC patients. Treating patients based on the characteristics of their own tumour holds great promise in improving outcomes as well as quality of life. In this case study, we have examined patient 'ORG64T', a 41 year old female who presented with stage 4 CRC. Following surgery, the patient underwent chemotherapy treatment, FOLFOX, the combination of 5FU and oxaliplatin. Three months after commencing the treatment, the patient had a CT scan which revealed a very poor response to this regimen (Figure 1). We performed genomic analysis on the PDCOs established from this patient's tumour. Using the Cancer Genome Interpreter[2], a number of compounds were predicted to be effective based on the DNA mutations and gene amplifications identified (Figure 2). These included compounds that targeted the *APC* gene mutation and the *AURKA* and *FGFR1* gene amplifications. Combining these with our custom drug library composed of pharmaceuticals currently in clinical trials for the treatment of bowel and other cancers, we screened the PDCOs against a total of 81 compounds. Of the predicted compounds, 3 of 6 were hits. We identified an additional 8 compounds from the library that were also effective in killing the PDCOs. We are in the process of validating these hits through secondary screening, but these preliminary results are very promising.

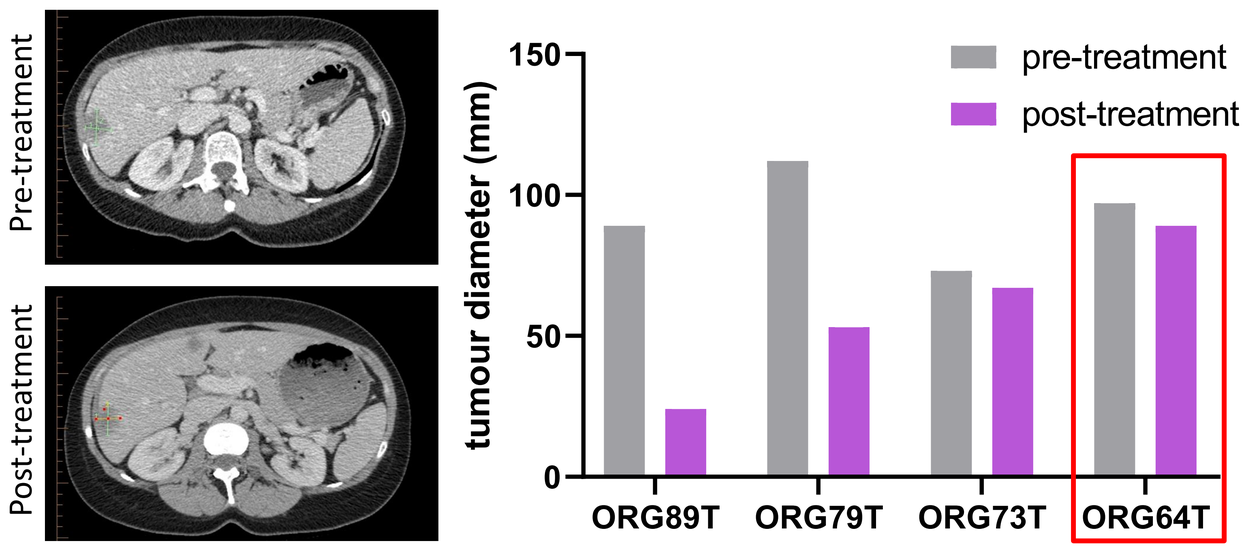

Figure 1a. (top left) Representative images from a patient CT scan (ORG64T) shows minimal response to treatment. **Figure 1b.** (top right) Size of residual tumour lesions for stage IV CRC patients pre and post treatment (diameter, mm).

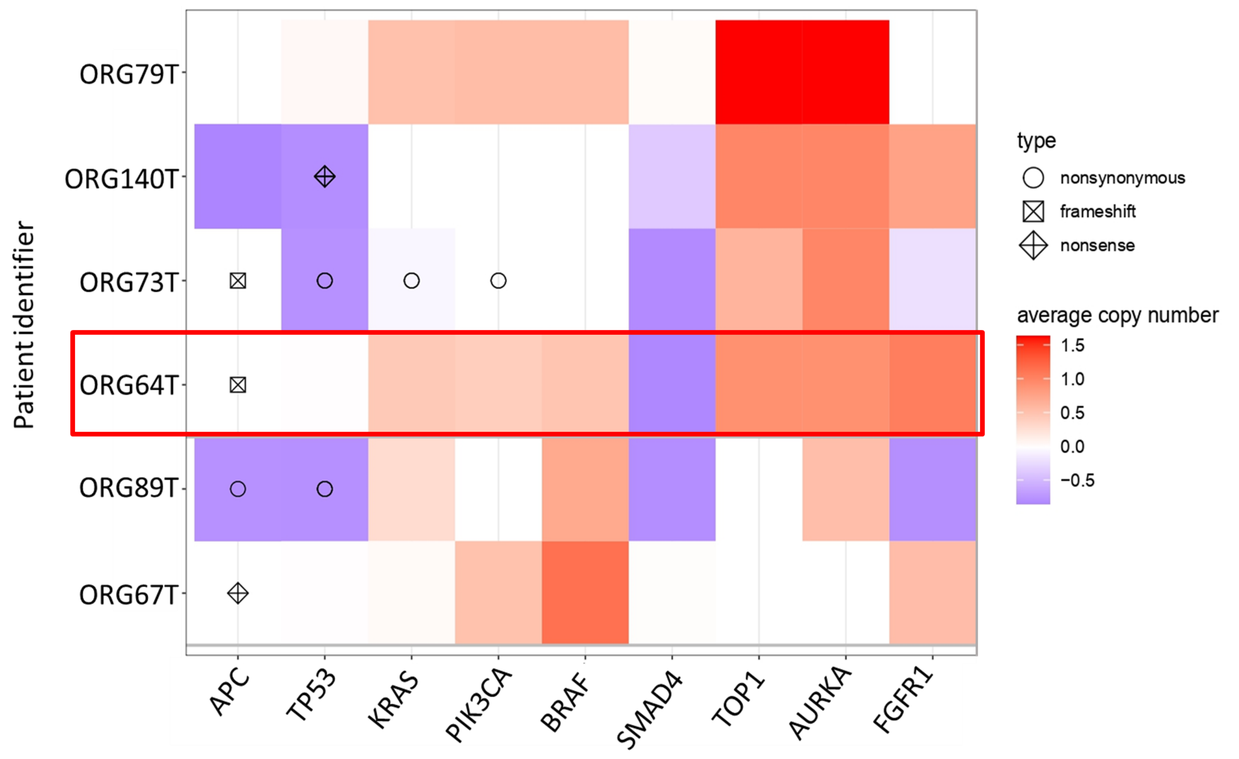

Figure 2. Genomic profiling can be used to identify potential drug targets for personalised treatment of a patient's cancer. This figure shows copy number variations and DNA mutations identified in cancer-associated genes of PDCOs from CRC patients.

Conclusion: Whilst we still have much to learn about the efficacy of utilising PDCOs for guiding personalised cancer treatments, we have shown that we are able to identify alternative therapies that may be effective for treating these patients, both through our targeted genetic screening for predicting compounds and through our custom library screen.

References:

1. Australian Institute of Health and Welfare: *Cancer in Australia 2021*. Australian Government, 2021
2. https://www.cancergenomeinterpreter.org/home
3. Engel R, et al., J Gastroenterol Hepatol. 2022;37:898.

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