Introduction Manchester Cancer Research Centre (MCRC) has established an MTB to facilitate precision medicine decision-making within the TARGET trial (Tumour chAracterisation to Guide Experimental Targeted Therapy). The MTB meets monthly to review clinical data and next generation sequencing (NGS) results from tumour tissue and circulating DNA (ctDNA) for patients being considered for early phase clinical trials. Initially the MTB relied on multiple paper reports. Here we present eTARGET, a digital solution developed by the digital Experimental Cancer Medicine Team (digitalECMT), which integrates clinical and genomic NGS data to facilitate decision-making for matching patients with clinical trials.

Material and methods The digitalECMT explored data sources and existing reports to define end-user and data requirements. Following a successful prototype, a beta version was developed. Created in Microsoft Azure, a secure cloud computing platform, components included a storage account for data upload from three different sources, and a database for storing and integrating the data. The solution enabled automated extraction of individual pseudonymised clinical and genomic data. In addition, a web application to view the data was developed with clinical input.

Results and discussions The beta version of eTARGET went online in October 2017 and has been utilised at 5 MTB meetings for 55 patient cases. This portal interface presents patient characteristics, treatment history and genomic data. The portal can be viewed remotely, across multiple locations, where all attendees see the same view. eTARGET has enabled the MTB to review individual patient data in a single portal, capture meeting outcomes in real-time and upload to the electronic patient record. Decisions regarding significant variants, trial matching or requirements for further analytical or translational analyses are captured.

Conclusion eTARGET has shown that a digital solution can be implemented to overcome the challenge of integrating data from disparate sources in different organisations to create a single view of patient clinical and genomic data. We have shown the utility of eTARGET in a hospital setting to support decision-making for an MTB. The eTARGET project opens the possibility of wider MTB participation including cross centre collaboration. Next steps are to enhance the software to visualise the global molecular dataset and serial changes in NGS profiles on treatment.

PO-048 THERAPY RESPONSE TESTING USING A 3D PERFUSED MICROFLUIDIC PLATFORM

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Introduction Breast cancer is the most common invasive cancer among women. Currently, there are only a few models used for therapy selection, and they are often poor predictors of therapeutic response or take months to set up and assay. In this report, we introduce a microfluidic OrganoPlate platform for extracellular matrix (ECM) embedded tumour culture under perfusion as an initial study designed to investigate the feasibility of adapting this technology for therapy selection.

Material and methods The triple negative breast cancer cell lines MDA-MB-453, MDA-MB-231 and HCC1937 were selected based on their different BRCA1 and P53 status, and were seeded in the platform. We evaluate seeding densities, ECM composition (Matrigel, BME2rgf, collagen I) and biomechanical (perfusion vs static) conditions. We then exposed the cells to a series of anti-cancer drugs (paclitaxel, olaparib, cisplatin) and compared their responses to those in 2D cultures. Finally, we generated cisplatin dose responses in 3D cultures of breast cancer cells derived from 2 PDX models.

Results and discussions The microfluidic platform allows the simultaneous culture of 96 perfused micro tissues, using limited amounts of material, enabling drug screening of patient-derived material. 3D cell culture viability is improved by constant perfusion of the medium. Furthermore, the drug response of these triple negative breast cancer cells was attenuated by culture in 3D and differed from that observed in 2D substrates.

Conclusion We have investigated the use of a high-throughput organ-on-a-chip platform to select therapies. Our results have raised the possibility to use this technology in personalised medicine to support selection of appropriate drugs and to predict response to therapy in a real time fashion.

PO-049 EGFR BLOCKADE INDUCES A PANETH CELL-LIKE PHENOTYPE WITH REWIRED SIGNALLING DEPENDENCIES IN CRC TUMOURSAT MAXIMAL RESPONSE

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Introduction Anti-EGFR therapies with the monoclonal antibodies cetuximab and panitumumab have improved survival in colorectal cancer (CRC) patients; nevertheless, incomplete mass obliteration and eventual relapse are a common setback, even after a plateau of maximal response. Preclinical data suggest that tumour recurrence may be fueled by a reservoir of so-called 'drug-tolerant persisters' that engage non-mutational routes of adaptation to therapy. Yet, the molecular underpinnings that sustain residual disease, as well as the strategies to oppose it, are largely unexplored.

Material and methods The effects of targeted therapies were evaluated in patient-derived xenografts. The biochemical and biological consequences of drug exposure were gauged by immunohistochemistry and morphometric analyses (*in vivo*), and by time-lapse imaging, Western Blot, Cell Titer-Glo and Caspase-Glo assays (*in vitro*). Transcriptional perturbations were assessed by microarray analysis and/or RT-qPCR. The activity of transcriptional modulators was measured by reporter assays *in vitro*.

Results and discussions Residual tumours surviving cetuximab treatment exhibited a quiescent, Wnt-high, and secretory/Paneth cell-like state as a distinctive trait. This pattern outlines that of EGFR-inhibited quiescent stem cells of the normal intestine, suggesting that developmental trajectories are somehow coopted by cancer cells to face external insults. Such

phenotype was reversible with drug suspension, pointing to non-genetic plasticity as a determinant of cancer cell reprogramming. Residual tumours also displayed lower expression of EGFR-activating ligands, congruent with reduced EGFR dependency, and showed rewired reliance on compensatory HER2/HER3 activity, as well as persistent PI3K signalling. Mechanistically, the acquisition of Paneth cell-like features was mediated, at least partly, by inactivation of YAP – a key driver of intestinal cell regeneration. Therapeutically, combined blockade of EGFR and PI3K/AKT lessened residual disease burden, but did not lead to long-term disease control. However, treatment with panHER, a mixture of antibodies concurrently targeting EGFR, HER2, and HER3, reduced tumour volumes and delayed tumour relapse after therapy cessation.

Conclusion Drug tolerance in cetuximab-sensitive CRC models involves a switch towards a Paneth-cell like state typified by sustained HER2/HER3 and PI3K signalling. Treatment with panHER effectively exhausted residual tumour burden and impeded/delayed late relapse.

PO-050 A MOLECULARLY ANNOTATED PLATFORM OF PDX-DERIVED CELL LINES MIRRORS THE GENOMIC LANDSCAPE OF COLORECTAL CANCER

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Introduction Progress in the development of effective cancer treatments is limited by the availability of tumour models that accurately reflect patient tumour with regards to histopathology, genomic landscape, and therapeutic response. To accomplish these needs, patient-derived tumour xenografts (PDX) were developed in recent years. Although they closely mirror structural and molecular features of the tumour of origin, PDXs still retain important restrictions related to maintenance costs and large-scale screening. To overcome this issue, we have established a novel platform of 2D cell lines (xeno-cell lines, XL) derived from PDXs of colorectal cancer (CRC) from which patient's germline gDNA was available. We have characterised XL-cells at multiple levels to assess their suitability as patient avatars to interrogate functional networks in colorectal cancer.

Material and methods Exome and expression analysis were performed on the entire xeno-cell line collection. Biomarkers of response and resistance to anti-HER therapy have been annotated in cell lines and pharmacological analysis to validate drug targets has been accordingly completed.

Results and discussions All XL-cells showed an epithelial-like morphology and phenotype, as also confirmed by EMT biomarker analysis. Genetic features (mutation and copy number profiles) were consistently preserved between PDXs and matched cell models, and expression analysis revealed XL-line collection as a significant representative of all CRC subtypes (*CMS* and *CRIS* subgroups). Whole exome and RNA-seq analyses allowed the identification of molecular biomarkers of response and resistance to targeted therapies, including EGFR and HER2 blockade. Genotype-driven responses observed *in vitro* in XL-cells were confirmed *in vivo* in the corresponding PDX.

Conclusion The XL-cell line platform represents a valuable preclinical tool for functional gene validation and proof of concept studies of novel therapeutics in colorectal cancer.

Poster Presentation: Molecular and Genetic Epidemiology

Epidemiology

PO-051 FAMILIAL RISKS AND MORTALITY IN SECOND PRIMARY CANCERS OF OVARIAN CANCER PATIENTS

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Introduction With improving survival in ovarian cancer, second primary cancers (SPCs) and their etiological underpinnings are becoming an issue. How family history may influence the occurrence of SPCs and the related mortality is not well known. We defined familial cancer through identity of cancer in the first-degree relatives (parents or siblings) and patient's SPC, and explored the impact of family history on the risk of SPCs and related mortality.

Material and methods Based on the Swedish Family-Cancer Database, we identified ovarian cancer patients among the 0–83 year old second generation and followed them for diagnoses of SPCs to the end of 2015. Relative risks (RRs) of SPC estimated from Poisson regression in ovarian cancer patients who had first-degree relatives (positive family history) affected by the same cancer were compared to the patients who didn't have (negative family history) with trend test. Causes of death were compared between patients with and without SPC.

Results and discussions A total of 11 300 ovarian cancers were diagnosed among 0–83 year old women of whom 1111 (9.8%) later developed SPC. Accounting for 67.6% of all patients with a SPC diagnosis, 751 had at least one first-degree relative diagnosed with cancer, for 129 of whom it was the same second cancer as in the family member. The trend test for family history of concordant SPC was significant for colon ($RR_{\text{positive family history}}$ *vs.* $RR_{\text{negative family history}}$ 5.00 *vs.* 2.01), lung (3.44 *vs.* 1.46), breast (2.11 *vs.* 1.03) and endometrial (6.56 *vs.* 2.39) cancers. With any family history (concordant or discordant), RR for SPCs was 1.97 in contrast to 1.52 for SPCs without any family history (*p-trend* <0.0001). Accounting for 42.1% of all deaths, SPC was found to be the main cause of death for patients with a second primary.

Conclusion In summary, close to 10% of ovarian cancer patients were diagnosed with SPC, 2/3 of whom had a first-degree relative diagnosed with cancer. Family history contributed to increasing numbers of SPCs and high familial associations were found for cancers that are known to manifest in ovarian cancer-related cancer syndromes. We conclude, considering family history at diagnosis of ovarian cancer may alert