allows for a high standardisation by reducing operator variability, full reproducibility of data analysis, and future integration into automated workflows.

**Conclusion** Elaborate flow assays specifically designed for CAR T cells, run with high-quality antibodies and fully automated flow analysis, provide a robust assessment of cell manufacturing and patient immunomonitoring. This will help with establishing complex individualised therapies and will allow us to understand from future clinical trials in greater detail the phenotypic changes occurring throughout the life time of a CAR T cell.

---

**Personalised Medicine**

**PO-045 EVALUATING LIQUID BIOPSIES FOR METHYLOMIC PROFILING OF PROSTATE CANCER**

1R Silva*, 1B Moran, 2C Fahy, 2T Vlaginijic, 1DJ Brennan, 1WM Gallagher, 1,2AS Perry, 1University College Dublin, Conway Institute of Biomolecular and Biomedical Research, Dublin, Ireland; 2Trinity College Dublin, Institute of Molecular Medicine, Dublin, Ireland; 3St. James’s Hospital, Department of Histopathology, Dublin, Ireland

10.1136/esmoopen-2018-EACR25.578

**Introduction** Epigenetic modifications, particularly DNA methylation, are centrally involved in prostate cancer (PCa) initiation and progression. Yet, how these alterations unfold and interplay in the progression to the lethal castration resistant phenotype is poorly understood. One reason for this is the difficulty in accessing metastatic tumour deposits for study. Recently, the analysis of liquid biopsies has emerged as a useful and minimally invasive method to study tumour characteristics. The aim of this study is to explore and compare how accurately the DNA methylation patterns of liquid biopsies reflect those of the primary tumour.

**Material and methods** We identified 4 metastatic treatment-naïve PCa patients for whom matched biopsy cores (tumour and histologically matched normal), pre-biopsy urine (≤50 ml), and peripheral blood plasma (3 ml) were available. DNA was isolated from all sample types and quantified using the Qubit Fluorometer. DNA methylation was profiled using the Infinium MethylationEPIC BeadChip (Illumina), and analysed using RnBeads software. Absolute β-values were used to filter the data into probes of interest, with cut-offs for hyper- and hypo-methylation of >0.8, <0.2, respectively.

**Results and discussions** We first considered whether matched normal tissue was epigenetically distinct from tumour by comparing the methylation patterns of several genes (i.e. RARB), for which hypermethylation is considered a hallmark of PCa. Focusing next on the methylation extremes (β >0.8 or β <0.2), we observed that hypermethylation was consistently more prevalent than hypomethylation in both tissue and liquid biopsies. Enumerating these methylation extreme probes revealed that the liquid biopsies contained a higher absolute abundance of hypo- and hypermethylation than the tissue biopsies. We also found that we could detect more hyper- and hypomethylated tumour-specific probes in urine than in plasma (80% vs. 62% and 69% vs. 64%, respectively).

**Conclusion** Liquid biopsies are excellent surrogates for profiling tumour-specific DNA methylation, with urine demonstrating superior sensitivity over blood. Further analysis of differentially methylated regions in the liquid and tissue biopsies, and their relevance is PCa biology, is underway.

---

**Abstracts**

**PO-046 DUAL INHIBITION OF JAK AND SRC: A NOVEL AND PROMISING THERAPEUTIC COMBINATION FOR PANCREATIC CANCER**

1A Parkin*, 1A Steimann, 2D Froio, 1A Drury, 1N Vogel, 1K Murphy, 1N Deng, 2A Gill, 3P Timpson, 1M Pajic, 1The Garvan Institute of Medical Research, Cancer, Sydney, Australia; 2Royal North Shore Hospital, Department of Anatomical Pathology, Sydney, Australia

10.1136/esmoopen-2018-EACR25.579

**Introduction** Pancreatic cancer (PC) has a 5 year survival of only 6%, and persists as the 4th most common cause of cancer-related death in Western societies. A more tailored treatment approach may be beneficial as the current standard-of-care therapies offer only a modest increase in overall patient survival patient overall. Recent large-scale genomic studies have revealed that the Src/JAK/STAT3 signalling pathway is deregulated in up to 35% of PC, and is yet to be systematically examined in this disease. Consequently, we hypothesised that targeting pancreatic tumours with activated JAK/STAT3 signalling with selective JAK1/JAK2 or JAK3 inhibitors and an Src inhibitor represents a promising novel therapeutic strategy for this disease.

**Material and methods** We utilised well-annotated patient-derived cell-line models (ICGC), along with cell-lines generated from the aggressive the KPC mouse model. Using these pre-clinical models we assessed the in vitro efficacy of therapeutic strategies involving Src/JAK/STAT3 inhibition, using cell proliferation assays, 2D-drug synergy screens, and 3D organotypic invasion assays. Extracellular matrix integrity post-treatment was assessed using second-harmonic generation (SHG) imaging and picrosirius staining. To examine in vivo efficacy, we utilised a syngeneic KPC mouse model, and performed both orthotopic and subcutaneous studies.

**Results and discussions** We show that selected JAK and Src-inhibitors inhibit cell proliferation in candidate PDCLs and KPC lines, characterised by activated Src/JAK/STAT3 signalling, with combination therapy being synergistic in the majority of these cell-lines. Cell invasion was significantly inhibited in organotypic matrices, and there was decreased collagen contractility, and reduced fibrillar collagen coverage. We also demonstrate the in vivo efficacy of these therapies, and show their ability to reduce regulatory T-cells, MDSCs and tumour-associated macrophages.

**Conclusion** Our findings demonstrate the potential for tailored therapeutic strategies involving Src/JAK/STAT3 inhibition in PC, and suggest that therapeutic efficacy may be the result of targeting both tumour cells and the tumour microenvironment, as well as by overcoming tumour-induced immunosuppression.

---

**PO-047 ETARGET: A DIGITAL SCIENCE SOLUTION TO INTEGRATE CLINICAL AND GENOMIC DATA FOR THE MANCHESTER MOLECULAR TUMOUR BOARD (MTB)**

1J Stevenson*, 1M Ayub, 2S Dransfield, 2E Shing, 2D Barley, 2R Dunne, 2M Westaway, 1,2O Landers, 1,2M Krebs, 1Cancer Research UK Manchester Institute, Clinical and Experimental Pharmacology, Manchester, UK; 2Christie NHS Foundation Trust, Experimental Cancer Medicine, Manchester, UK; 3Christie NHS Foundation Trust, Biobank, Manchester, UK; 4Manchester University NHS Foundation Trust, Manchester Centre for Genomic Medicine, Manchester, UK; 5The University of Manchester, Research IT, Manchester, UK; 6Microsoft Limited, Customer Success Unit, Manchester, UK; 7AstraZeneca, Early Clinical Development, Cambridge, UK; 8University of Manchester, Division of Cancer Sciences, Manchester, UK

10.1136/esmoopen-2018-EACR25.580
**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**

**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 OrganOn-a-chip 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 TUMOURS AT MAXIMAL RESPONSE**

**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 vitro), 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