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