Poster Presentation: Tumour Biology
Animal Models of Cancer

**INTRODUCTIVE ANALYSIS OF IN VIVO MODELS OF PANCREATIC CANCER REVEALS COMPLEX MECHANISMS BEHIND TREATMENT FAILURE AND PROVIDES NEW TOOLS FOR EFFECTIVE TARGETING**

**Introduction** Pancreatic cancer remains a highly lethal cancer where response is limited by both intrinsic and acquired chemoresistance. Understanding resistance mechanisms may therefore lead to improved therapeutic strategies. We have recently defined specific molecular subgroups of pancreatic cancer associated with pre-clinical and clinical response to select tailored treatment strategies.1-3

**Material and methods** Using robust patient-derived xenografts (PDXs) of pancreatic cancer, here we generated novel *in vivo* models for the study of intrinsic and acquired chemoresistance mechanisms to clinically-used agents, gemcitabine, mitomycin C, and cisplatin. Here, we used whole genome sequencing (WGS) and microarray analysis to compare gemcitabine-resistant and gemcitabine-sensitive pancreatic tumours to identify relevant resistance mechanisms.

**Results and discussions** Integrative analysis of WGS and microarray profiling of gemcitabine-resistant tumours revealed complex but potentially targetable resistance mechanisms, including increased DNA repair through activation of PARP1, MCM genes and RRM1, and changes within the tumour microenvironment. Importantly, acquired resistance to gemcitabine was effectively reversed by a novel PARP inhibitor, rucaparib, indicating that combination therapy involving this low toxicity agent may be useful in treating gemcitabine-resistant tumours. Both agents together are synergistic for reversing gemcitabine resistance and efficacy testing of novel combination therapy is ongoing.

**Conclusion** Significance our findings demonstrate the promise of patient-derived xenograft models for the study of *in vivo* mechanisms of chemotherapy resistance and efficacy testing of novel agents for the treatment of human pancreatic cancer.

**REFERENCES**
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3. Chou A, et al. *Gut* (2017) pii: gutjnl-2017-315144 (epub ahead of print)
FLAVOPEREIRINE SUPPRESSES COLORECTAL CANCER GROWTH VIA INDUCING CELL CYCLE ARREST AND APOPTOSIS IN P53 SIGNALLING DEPENDENCE

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Introduction High-grade colorectal cancer (CRC) worldwide is of particular importance for brain cancers, as they allow to better recapitulate the brain tumour environment and the blood brain barrier.

Material and methods Glioblastoma PDX models were based on 3D organotypic spheroids, derived from mechanically minced patient material. Spheroids were implanted in the brain of immunodeficient mice and further propagated by serial intracranial transplantation. For detailed molecular characterisation each PDX was compared to its original patient tumour at the genetic, epigenetic and transcriptomic levels and intra-tumoral heterogeneity was addressed at the single cell level. We furthered performed proof-of-concept preclinical studies interfering with angiogenesis and autophagy.

Results and discussions Our glioblastoma PDX models starting with viable patient-derived spheroids has a high tumour take rate and a reproducible phenotype and tumour development time. We observed three distinct histological tumour phenotypes: a highly ‘invasive’, a highly ‘angiogenic’ and an ‘intermediate’ phenotype which combines invasion and vascular abnormalities. Typical glioblastoma characteristics such as pseudopalisading necrosis, invasion or microvascular proliferation we maintained. PDXs retained the genetic and epigenetic profiles of patient tumours through several generations. Transcriptomic profiles of PDXs were similar to patient biopsies and correlated better with TCGA glioblastoma samples than conventional glioma cell lines. In vivo pharmacological inhibition of autophagy significantly increased survival of PDXs and combination treatment with bevacizumab showed a synergistic effect.

Conclusion Here we show that glioblastoma PDXs represent a reliable and clinically-relevant animal model. The model can be applied for analyses at different molecular levels. Importantly, the PDXs can be applied for accurate reproducible pre-clinical trials, including personalised medicine-based treatments. The use of this model should lead to a more realistic evaluation of the efficacy of novel drugs, thereby increasing the success of clinical studies.

PO-199 PLATELET AGGREGATE FORMATION IN A NOVEL MURINE PRECLINICAL GLIOMA MODEL DEPENDS ON PODOPLANIN EXPRESSION ON TUMOUR CELLS

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Introduction The sialomucin-like transmembrane glycoprotein podoplanin (PDPN) is the natural ligand of the platelet receptor C-type lectin-like receptor 2 (CLEC-2). Binding of PDPN to CLEC-2 induces platelet activation and aggregation. PDPN expression is increased both in glioma cells and in tumor-associated astrocytes. In human glioma patients, high expression of PDPN is associated with worse prognosis and has been shown to correlate with intratumoral platelet aggregation and with an increased risk of venous thromboembolism (VTE).

Material and methods To functionally assess a causative link between PDPN and platelet aggregation in vivo we established a syngeneic orthotopic murine glioma model in C57/B16 mice, based on transplantation of p53- and pten-deficient neural stem cells. This model is characterised by the presence of intratumoral platelet aggregates and by the upregulation of PDPN both in glioma cells and in astrocytes.

Results and discussions Deletion of PDPN either in tumour cells or in astrocytes resulted in glioma formation with the same penetrance and grade compared to control mice. Importantly, only the lack of PDPN in tumour cells, but not in astrocytes, caused a significant reduction in intratumoral platelet aggregates.

Conclusion Our results show that the newly developed syngeneic orthotopic murine glioma model faithfully recapitulates human glioma features and is well suited to investigate mechanisms of glioma biology in an immunocompetent environment. PDPN loss-of-function experiments demonstrate a causative