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 transplantations. 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 have 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.
link between PDPN expression and platelet aggregation in gliomas and additionally pinpoint the tumour cells as the source of PDPN inducing platelet aggregation. Our data indicate that blocking PDPN specifically on tumour cells could represent a novel strategy in order to prevent platelet aggregation and reduce the risk of VTE in glioma patients.

**PO-200 3D IN VITRO CULTURES OF PDX-DERIVED TUMOUR FOR ANTI-CANCER DRUG DISCOVERY**

1L Price*, 2S Basten, 3K Yan, 4T Giesemann, 4J Schueer, 6B Herpers. 1OcellO BV, Discovery, Leiden, The Netherlands; 2OcellO BV, PDX Services, Leiden, The Netherlands; 3OcellO BV, Bioinformatics, Leiden, The Netherlands; 4Charles River Discovery Research Services Germany GmbH, Discovery Services, Freiburg, Germany; 6OcellO BV, Oncology, Leiden, The Netherlands

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**Introduction** Patient-derived xenograft (PDX) models emulate tumour complexity and heterogeneity, and reflect the variation in pathologic and genetic diversity within the population. As such, these models are a valuable source in preclinical drug development. We employ hydrogel embedding as a 3D culture technique to generate short term cultures of dissociated PDX material. This miniaturised setup allows economical screening of drug libraries, testing of drug combinations and pre-selection of relevant models for in vivo follow up.

**Material and methods** In a high throughput approach, small amounts of tumour material are seeded in 384 well plates. Following exposure to multiple concentrations of standard-of-care chemotherapeutics, small molecules, targeted therapies, antibodies and antibody-drug-conjugate, the cultures are fixed and stained with cellular markers at the experimental endpoint. A 3D stack acquisition of each well is obtained, followed by high content image analysis using an in-house developed analysis platform, Ominer™. This enables measurement of relevant features such as tumour volume, tumour invasion, nucleus size and fraction of apoptotic cells; hence detailed tumour culture responses can be quantified, generating dose-dependent profiles for selected features.

**Results and discussions** We successfully developed >50 cultures derived from breast, stomach, pancreatic, colon, bladder and lung cancer. Each model has unique growth characteristics and morphologic differences are prominent both between the different tissues of origin and similar pathologies. Histologic characterisation of the 3D tumour cultures show hallmarks of the original tumour, such as retention of relevant biomarkers. We present drug response data for various cancer indications, including multiple lung and breast cancer pathologies.

**Conclusion** We demonstrate phenotypic variation amongst different PDX models and differential responses to anti-tumour therapies. This method facilitates the comparison and in depth interrogation of responses to both established, biosimilar and novel cancer drugs - and allows follow up in the same model in vivo.

**PO-201 MUTANT KRAS-DRIVEN CANCERS DEPEND ON PTPN11/SHP2 PHOSPHATASE**

1D Rüss*, 2G Heynen, 3K Ciecielski, 4W Birchmeier, 5R Schmid, 6H Algül. 1Klinikum rechts der Isar-Technische Universität München, Internal Medicine II, Munich, Germany; 2Cancer Research Program- Max Delbrück Center for Molecular Medicine MDC, in the Helmholtz Society, Berlin, Germany

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**Introduction** The ubiquitously expressed non-receptor protein tyrosine phosphatase SHP2, encoded by PTPN11, is involved in signal transduction downstream of multiple growth factor, cytokine and integrin receptors. Its requirement for complete RAS-MAPK activation and its role as a negative regulator of JAK-STAT signalling have established SHP2 as an essential player in oncogenic signalling pathways. Recently, novel potent allosteric SHP2-inhibitors have been presented as a viable therapeutic option for RAS-driven cancers, but were shown to be ineffective in KRAS mutant tumour cell lines in vitro.

**Material and methods** Various mutant KRAS-driven murine models of pancreatic ductal adenocarcinoma (PDAC) and non-small cell lung cancer (NSCLC) were employed to investigate the contribution of Ptpn11/SHP2 to carcinogenesis and tumour maintenance, and to determine its utility as a therapeutic target for treatment of established tumours in vivo. CRISPR/Cas9 mediated knockout of PTPN11 in human PDAC cell lines, drug-synergy screening and human PDAC organoid and tissue xenograft model therapeutic trials substantiated the rationale of dual SHP2/MEK inhibition in a human context.

**Results and discussions** We report a central and indispensable role for SHP2 in oncogenic KRAS-driven tumours. Genetic deletion of Ptpn11 profoundly inhibited tumour development in mutant KRAS-driven murine models PDAC and NSCLC. We provide evidence for a critical dependence of mutant KRAS on SHP2 during carcinogenesis. Deletion or inhibition of SHP2 in established tumours delayed tumour progression but was not sufficient to achieve tumour regression. However, SHP2 was necessary for resistance mechanisms upon blockade of MEK. Synergy was observed when both SHP2 and MEK were targeted, resulting in sustained tumour growth control in murine and human patient-derived organoids and xenograft models of PDAC and NSCLC.

**Conclusion** Our data suggest clinical utility of dual SHP2/MEK inhibition as a targeted therapy approach for KRAS mutant cancers.

**PO-202 PI3K ACTIVATION IN NEURAL STEM CELLS DRIVES TUMOURIGENESIS WHICH CAN BE AMELIORATED BY TARGETING THE CAMP RESPONSE ELEMENT BINDING (CRED) PROTEIN**

1T Mantamadiotis*, 2P Daniel, 1G Filiz, 3M Christie, 4P Waring, 5Y Zhang, 5C Pouton, 6D Flanagan, 7E Vincan, 8W Phillips. 1The University of Melbourne, School of Biomedical Sciences, Melbourne, Australia; 2McGill University, McGill University Health Centre and RI-MUHC, Montreal, Canada; 3Royal Melbourne Hospital, Anatomical Pathology, Melbourne, Australia; 4The University of Melbourne, Clinical Pathology, Melbourne, Australia; 5Monash University, Monash Institute of Pharmaceutical Sciences, Parkville, Australia; 6Peter MacCallum Cancer Centre, Gastrointestinal Cancer Program, Melbourne, Australia

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**Introduction** Hyperactivation of the PI3K signalling is common in cancers but the precise role of the pathway in glioma biology remains to be determined. Some understanding of PI3K signalling mechanisms in brain cancer comes from studies on neural stem/progenitor cells, where signals transmitted via the PI3K pathway cooperate with other intracellular pathways and downstream transcription factors to regulate critical cell functions.

**Material and methods** To investigate the role for the PI3K pathway in glioma initiation and development, we generated a mouse model targeting the inducible expression of a