safely across a variety of pediatric nervous tumors. Larger studies are needed to confirm these findings.

**MOID-02. TARGETING REPLICATION STRESS IN PEDIATRIC BRAIN TUMORS**

Krausert1,2, Sander Lambo1,2, Norman Misch1,2, Benjamin Schwalm1,2, Stefan Pfister1,2, Michel BRAOL1,2, (Hopp-Children's Cancer Center Heidelberg; KITZ), Heidelberg, Germany, 2German Cancer Research Center (DKFZ), Heidelberg, Germany

Pediatric brain tumors harboring amplifications or high overexpression of MYC/MYC oncogenes are often associated with poor outcome. High MYC/N expression in these tumors leads to increased transcription, which can be in conflict with DNA replication and subsequently can cause replication stress, R-loops and DNA damage. We hypothesize that high MYC/N expression makes them vulnerable to DNA damage response inhibitors (DDRs) and even more vulnerable to combinations of DDRs and chemotherapeutics. To test this hypothesis we performed in vitro drug experiments using Group 3 medulloblastoma (MB) and ETMR cell lines. IC50-values were evaluated of topoisomerase inhibitors Icruciferin (SN-38) and Pamiparib (RBR290), a brain-penetrant PARP-inhibitor, in monotherapy. All cell lines were sensitive for SN-38 and showed IC50-values in the low nM-range but PARP-inhibitors were ineffective. However, a significant decrease in IC50 can be observed when SN-38 and Pamiparib are used in combination. For in vivo treatments, we injected NSG mice with luciferase labelled patient-derived xenografts (PDX)-cells of various models (MB Group 3, MB SHH, ETMR, RELA EPN), monitored tumor growth via IVIS and randomized the mice into three treatment groups (MB-PAM, ICRU-S3-80, ICRU-P290). When a defined threshold of tumor growth was reached. Mice were treated with Icruciferin (or vehicle) once per day i.p. and Pamiparib (or vehicle) twice per day per oral gavage. Treatment with Pamiparib did not show any survival benefit, but mice treated with Icruciferin or the combination showed a clear survival benefit. Treatments are ongoing and more results will be presented at the conference.

**MOID-03. ADAPTING PALBOCICLIB FOR MEDULLOBLASTOMA THERAPY BY IMPROVING DRUG DELIVERY AND ADDRESSING RESISTANCE**

Taylor Dismuke, and Timothy Gershon; University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

CDK4/6 inhibition may be a promising therapy for medulloblastoma. All medulloblastoma subgroups show D-cyclin/CDK4/6 pathway activity, suggesting potential targets for this drug. In preclinical and normal brain. Efficacy studies of ONC-206 against MB in vivo will be reported in preparation for a planned Phase I study of ONC-206 in children with malignant brain tumors.

**MOID-04. MODELING CNS HGNET-BCOR PATHOGENESIS USING NEURAL STEM CELLS**

Satoshi Nakata, Ming Yuan, Eric Raabe, and Charles Eberhart; Johns Hopkins University, Baltimore, MD, USA

Central nervous system high-grade neuroepithelial tumor with BCOR corepressor alteration (CNS HGNET-BCOR) is a recently identified entity characterized by internal tandem duplication (ITD) of BCOR, a core component of polycomb repressive complex (PRC) 1.1. BCOR-ITD exclusively occurs within an essential binding domain, suggesting aberrant epigenetic activities as a possible mechanism of gliomagenesis; however, the effect of this alteration on the transcriptome and DNA methylation are poorly understood. We have generated new CNS HGNET-BCOR models by lentiviral transduction of the BCOR-ITD into human and murine neural stem cells. In the human model, qRT-PCR and subsequent RNA-seq identified a transient deregulation of PRC2 core components characteristic of models with overexpression of wildtype-BCOR. A similar effect was found in clinical specimens from previous studies. In the murine-model, we confirmed increased clonogenicity in soft-agar assays, and tumors developed in mice faster. Global DNA methylation levels evaluated by ELISA were significantly lower than those of parent cells, and 177 genes were differentially expressed on RNA-seq analysis comparing BCOR-overexpressing control cells, including upregulation of known oncogenes. These results suggest that BCOR-ITD and associated alterations in the function of PRC1.1 affect methylation patterns in neural stem cells, driving transcriptional silence and oncogenic transformation into CNS HGNET-BCOR. More detailed analyses, including methylation array comparisons with clinical samples and in-silico drug sensitivity testing, are being performed.

**MOID-06. PRECLINICAL EFFICACY OF THE IMPRIMONE ONC-206 AGAINST MEDULLOBLASTOMA**

Jose Velazquez Vega1, Matthew Schniederjans2, Varun Prabhu1, Joshua Allen1, and Toheev MacDonald1; 1Emory University, Atlanta, GA, USA, 2Children's Healthcare of Atlanta, Atlanta, GA, USA, 3Oncoceutics, Inc, Philadelphia, PA, USA

Treatment for medulloblastoma (MB) is typically ineffective for MYC amplified or metastatic SHH, Group 3 and 4 subgroups. Promising preclinical data has been obtained in brain tumors. We treated three different MB cell types representative of ONC-201, a selective antagonist of DDR2, a G-protein coupled receptor that regulates prosurvival pathways. Herein, we report the activity of ONC-201 and ONC-206, which has increased non-competitive antagonism of DDR2, against MB. We observed that three different MB cell types representative of SHH- and Group 3-like cells, with varied levels of DDR2 expression, and consistently observed increased cell death in a dose-dependent manner at lower doses of ONC-206 compared to ONC-201. We also evaluated OX-palbo as an additional drug target in MB. Clp is a mitochondrial target that has been shown to directly bind and be activated by ONC-201, and is highly expressed at the protein level across pediatric MB, malignant glioma and ATRT, but not normal brain. Here, we show that similar to ONC-201, ONC-206 treatment of MB cells induces the restoration of mitochondrial membrane potential to the non-proliferative state, degradation of the mitochondrial substrate SDHB, reduction in survivin and elevation in ATF4 (integrated stress response). Importantly, ONC-206 treatment significantly reduced SHH and Group 4 cells in vitro, while having no observable toxicity in normal brain. Efficacy studies of ONC-206 against MB in vivo will be reported in preparation for a planned Phase I study of ONC-206 in children with malignant brain tumors.

**MOID-08. OPTIMIZATION OF A NOVEL LOCAL DELIVERY SYSTEM FOR THE TREATMENTS OF SUPRATENTORIAL EPENDYMOMA**

Lisa Ruff1, Chris Parkins1, Sabrina Terranova1, Erica Nathan1, Paraskevi Kasapidou1, Renata Lang2, Oren Scherman2, and Richard J Gilbertson1; 1Cancer Research UK Cambridge Institute, Cambridge, United Kingdom, 2Melville Laboratory, Department of Chemistry, Cambridge, United Kingdom

Ependymomas are the third most common paediatric brain tumour, incurable in up to 40% of cases. Until recently, ependymomas were regarded as a single disease group with all patients receiving combinations of maximal surgical resection and radiotherapy. Use of chemotherapy has been limited by the resistant nature of the tumour and poor access to tumours behind the blood brain barrier (BBB). It is now known that ependymoma comprises up to nine different molecular subgroups. One subgroup is characterized by a novel fusion protein, C11orf93-RELA, which acts as a potent driver of oncogenesis resulting in a poor prognosis. Here, we present the optimization of a novel drug delivery system that uses biodegradable hydrogels to deliver drugs with potent anti-ependymoma properties into post-resection cavity of supratentorial ependymoma. Our previous high-throughput in-vivo drug screens identified candidate ependymoma therapies with poor BBB penetration. Using improved delivery systems, we have confirmed and monitored the release of these compounds from the hydrogel. Additionally, we have implemented this delivery system in our preclinical mouse hospital in which mice receive standard-of-care surgery and radiotherapy. The efficacy of hydrogel-based delivery of these compounds is now being tested preclinically, in combination with rapamycin. Treatment for ependymoma patients have not changed in the last 30 years and therefore an effective chemotherapy could add a great survival benefit to the clinic.