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

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

Nathan Yuan - Oncoceutics, Schniederjan - Pfister, Hongying, and Charles Vega - Schwalm, Malhotra - Ruff - Emory University, Atlanta, GA; Johns, Eberhart, Lang, and Allen - 1, Jingbo -ponent of polycomb repressive complex (PRC) 1.1. BCOR-ITD exclusively hop to newly effective medulloblastoma treatment. By disrupting their prolonged S-phase, or by disrupting Olig2 function, may lead to an extended period of S-phase and that the fractions of cell expressing the 5 days of treatment, palbociclib altered cell cycle progression to produce compared tumors early and late in the course of therapy. We found that after POx-palbo was clearly effective as a single agent, all mice treated with POx-palbo showed tumor regression and improved the survival of mice with medulloblastoma. While all medulloblastoma subgroups show D-cyclin/CDK4/RB pathway activity, RESISTANCE MODL-03. ADAPTING PALBOCICLIB FOR MEDULLOBLASTOMA THERAPY BY IMPROVING DRUG DELIVERY AND ADDRESSING RESISTANCE Taylor Drumka, 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 for efficacy. To address drug delivery and systemic toxicity limitations, we developed a nanoparticle formulation of CDK 4/6 inhibitor, palbociclib, in poly (2-oxazoline) micelles (POX-palbo). POX-palbo showed reduced systemic toxicity in transgenic mice engineered to develop medulloblastoma, allowing for higher dosing. Pharmacodynamic studies showed POX-palbo suppressed RB phosphorylation acutely and after 24hrs, the effect diminished. This inhibition produced a longer lasting suppression of SHH pathway activity, demonstrated by Gli-luc reporter tumor mice. Importantly, POX-palbo therapy, administered daily, reduced tumor growth and improved the survival of mice with medulloblastoma. While POX-palbo was clearly effective as a single agent, all mice treated with POX-palbo eventually developed progressive disease, as resistant populations of tumor are highly malignant. To understand the mechanisms of resistance, we compared tumors early and late in the course of therapy. We found that 3 days of treatment, palbociclib altered cell cycle progression to produce an extended period of S-phase and that the fractions of cell expressing the stem cell marker Glial were markedly increased. Based on these data, we propose that tumors respond to the initial suppression of palbociclib by increasing the pool of Olig2+ stem cells, that these cells show discernably different cell cycle kinetics and are resistant to CDK4/6 inhibition. Combining POX-palbo with additional therapies that target Olig2+ stem cells, by disrupting their prolonged S-phase, or by disrupting Olig2 function, may lead to newly effective medulloblastoma treatment.

**MODL-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 BCL6-crepressor 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 transcriptional and DNA methylation are poorly under- stood. 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 signature of genes compared to an isogenic model with overexpression of wildtype-BCOR. A similar effect was found in clinical specimens from previous studies. In the murine-cell model, we confirmed increased clonogenicity in soft-agar assays, and tumors developed in nude mice for 3 weeks. Global DNA methylation levels evaluated by ELISA were significantly lower than those of parent cell, and 177 genes were differentially expressed on RNA-seq analysis comparing to 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 change and oncogenic transformation into CNS HGNET-BCOR. More detailed analyses, including methylation arrays comparisons with clinical samples and in-silico drug sensitivity testing, are being performed.

**MODL-06. PRECLINICAL EFFICACY OF THE IMIDOPRIDE ONC-206 AGAINST MEDULLOBLASTOMA**

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Treatment for medulloblastoma (MB) is typically ineffective for MYC amplified or metastatic SHH, Group 3 and 4 subgroups. Promising preclinical data have been obtained in brain xenografts of MB Group 3, MB SHH, ETMR, RELA EPNI, monitored tumor growth via IVIS and randomized the mice into groups (A/B/C). Irinotecan and Irinotecan and in-vitro and in-vivo delivery assays, but treated mice treated with Irinotecan or (ve)ce once per day i.p. and Pamiparib (or vehicle) twice per day per oral gavage. Treatment with Pamiparib did not show any significant benefit, but mice treated with Irinotecan or the combination showed a clear survival benefit. Treatments are ongoing and more results will be presented at the conference.

**MODL-07. OPTIMIZATION OF A NOVEL LOCAL DELIVERY SYSTEM FOR THE TREATMENTS OF SUPRATENTORIAL EPENDYMOMA**

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Ependymomas are the third most common paediatric brain tumour, in curable 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 therapeutics with poor BBB penetration. Using in-vitro and in-vivo assays, we have confirmed and monitored the release of these compounds from the hydrogel. Additionally, we have implemented this delivery system in our preclinical mouse model 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 radiotherapy. 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.