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

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Pediatric brain tumors harboring amplifications or high overexpression of *MYC-/MYCN* 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 (DDRi) and even more vulnerable to combinations of DDRi 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 inhibitor Irinotecan (SN-38) and Pamiparib (BGB-290), 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 xenograft- (PDX-) cells of various models (MB Group 3, MB SHH, ETMR, RELA EPN), monitored tumor growth via IVIS and randomized the mice into four groups (vehicle, BGB-290, Irinotecan and Irinotecan+Pamiparib) when a predefined threshold of tumor growth was reached. Mice were treated with Irinotecan (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 Irinotecan or the combination showed a clear survival benefit. Treatments are ongoing and more results will be presented at the conference.

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

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CDK4/6 inhibition may be a promising therapy for medulloblastoma. All medulloblastoma subgroups show D-cyclin/CDK4/RB pathway activity, suggesting broad 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 tumors cells emerged. To understand the mechanisms of resistance, we compared tumors early and late in the course of therapy. We found that after 5 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 Olig2 were markedly increased. Based on these data, we propose that tumors respond to the initial suppressive effect 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

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Central nervous system high-grade neuroepithelial tumor with BCL6-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 derepression of PRC2-target genes comparing 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 mice flanks. 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 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 changes 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 IMIPRIDONE 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 and clinical results have been obtained in brain cancers treated with ONC-201, a selective antagonist of DRD2, 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 DRD2, against MB. We treated three different MB cell types representative of SHH- and Group 3-like cells, with varied levels of DRD2 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 ClpP as an additional drug target in MB. ClpP is a mitochondrial protease 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. We observed 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 induced significant cell death of patient-derived SHH, WNT, and Group 3 tumors ex vivo 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.

MODL-08. 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, 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, C11orf95-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 penetrance properties. Using *in-vitro* delivery 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 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 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 in the clinic.