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INTRODUCTION: Disorders with Abnormal DNA Damage Response/Repair (DADDRs) are inherited conditions caused by constitutional mutations of DNA damage response and repair genes and are characterized by an increased cancer risk. Furthermore, affected individuals also show an elevated risk of secondary neoplasms as well as excessive toxicity, poor therapy response and increased mortality when treated with standard radiation and chemotherapy regimens. The main aim of this project is to screen for potential novel chemotherapeutic approaches for these cancer entities, and to employ faithful PDX models for *in vivo* validation. METHODS: *In vitro* drug screening was performed using a custom library composed of 345 compounds targeting 61 different proteins. For two specific DADDRs, Li-Fraumeni syndrome (LFS) and Constitutional Mismatch Repair Deficiency (CMMRD), two cancerous (glioblastoma and medulloblastoma) and one non-cancerous cell lines were selected to model each of these conditions. Performance of each drug was assessed based on its efficacy (sensitivity score) and genotoxicity (micronucleus assay). For DADDR PDX model establishment tumor material from DADDR patients is currently being injected orthotopically (brain tumors) or subcutaneously (non-brain tumors) into NSG mice. Following engraftment and expansion, the PDX models will be characterized molecularly and compared with original patient material. RESULTS AND OUTLOOK: *In vitro* screening revealed n=26 drugs that fulfilled the following criteria: a) favorable toxicity in cancerous cell lines compared to non-cancerous cell lines, b) little to no genotoxic effect in non-cancerous cell lines. These characteristics qualify them as potentially suitable candidates for novel therapeutic approaches specifically for DADDR patients. The hits included inhibitors of ATM/ATR, CHK1/CHK2, DHFR, mTOR and PI3K, as well as microtubule-associated compounds. Combination testing and further validation of these hits using disease-specific *in vitro* and *in vivo* PDX models is ongoing.

MODL-05 METRONOMIC INTRATHECAL DELIVERY OF CDK4/6 INHIBITORS IN PRECLINICAL MODELS OF PEDIATRIC BRAIN TUMORS

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INTRODUCTION: CDK4/6 inhibitors have shown promise against central nervous system (CNS) tumors *in vitro*. This class of drugs relies on long-term exposure. Their use in early phase clinical studies in children with CNS tumors has defined dose limitations due to systemic toxicity. We have sought to circumvent these limitations in using CDK4/6 inhibitors for pediatric CNS tumors by first demonstrating enhanced efficiency with long-term administration and exploiting prolonged intrathecal delivery (IT). METHODS: Pediatric CNS tumor cell lines were used for cell viability assays: ATRT (BT-12, BT-16), CPC (CCHE-45), diffuse midline glioma (DIPG-XIII, HSJD-007), and medulloblastoma (DAOY); the assays were conducted at 24h, 72h, and 7d post-administration of CDK4/6 inhibitors (abemaciclib, palbociclib, ribociclib). Half maximal growth inhibitory concentrations (GI50) and areas under the curve (AUC) were compared for short-term (24h, 72h) and long-term (7d) dose-response curves. Toxicity with chronic IT administration was assessed using a neurobehavioral safety profile of 7-day continuous infusion of 2.5mM palbociclib (n = 5) into the mouse lateral ventricle compared with vehicle (n = 4). RESULTS: Our results demonstrate increased CDK4/6 inhibitor potency with longer administration. The greatest reductions in short-term to long-term GI50 were observed in ATRT, CPC, and DIPG across all inhibitors. The most pronounced time-dependent efficacy was observed with palbociclib for ATRT and abemaciclib for CPC and DIPG. AUCs significantly decreased ($P < 0.05$) with increasing drug exposure time across all inhibitors. 7-day intraventricular palbociclib infusion was equivalent in safety to PBS at doses ranging from 1,000 to 10,000-fold the *in vitro* GI50. CONCLUSIONS: The efficiency of CDK4/6 inhibitors in pediatric CNS tumors is enhanced with prolonged exposure. Long-term IT administration can achieve high CNS doses without associated systemic toxicities. Translational efforts using a metronomic IT strategy are logical to explore for pediatric CNS tumors which have potential for a leptomeningeal disease pattern.

MODL-06. TARGETING C-MET IN COMBINATION WITH RADIATION IS EFFECTIVE IN MET-FUSION DRIVEN HIGH-GRADE GLIOMA

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Oncogenic fusion events involving c-MET have been observed in up to 12% of pediatric high-grade glioma (pHGG). MET inhibitors have displayed potent initial responses in MET rearranged tumors but acquired resistance to single agent modalities invariably occurs. To identify new treatment options against these tumors, we established two novel orthotopic mouse models including an immunocompetent, murine allograft and an intracranial patient-derived xenograft (PDX), both harboring distinct MET fusions. We analyzed the pharmacokinetic and pharmacodynamic profiles of two MET inhibitors, crizotinib and capmatinib, and examined their efficacy against tumor cell cultures derived from the aforementioned models. Capmatinib outperformed crizotinib in terms of specificity, potency and brain availability, resulting in a highly differential cellular response compared to crizotinib treatment. We evaluated the efficacy of both compounds in combination with radiotherapy (RT) and found that radiation further potentiated the inhibitory effect of capmatinib on tumor cell growth. We then utilized both models to assess the combinatorial effect of capmatinib and radiation on intracranial tumors in vivo and found that the combination therapy significantly increased overall survival in both cohorts. In the PDX model, the combination, relative to either intervention alone, induced a remarkable decrease of tumor burden, which persisted throughout the observation period in all treated animals. RNA-sequencing of capmatinib-treated tumors and tumor cell cultures revealed impaired expression of DNA repair genes. Further, we showed that capmatinib enhanced radiation-induced DNA damage, as demonstrated by increased γ-H2AX foci in treated cells, providing mechanistic insight for the cooperative effects of the combined treatment. Our results validate capmatinib as an effective inhibitor of MET in pHGG and demonstrate the outstanding efficacy of capmatinib and radiation against MET-driven pHGG in two complementary preclinical models, informing future clinical trials.

MODL-07. DNA METHYLATION-BASED BIOBANK OF MURINE MODELS FOR PEDIATRIC TUMORS

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