Netherlands. [8]Department of Neurosurgery, Heidelberg University Hospital, Heidelberg, Germany. [9]Pediatric Neurosurgery Division, Department of Neurosurgery, Heidelberg University Hospital, Heidelberg, Germany. [10]Pediatric Glioma Research, German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany. [11]Pediatric Haematology and Oncology, Hannover Medical School, Hannover, Germany

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

Sergio Guadix[1], Brice Martin[1], Madeline Laramee[1], Nadia Dahmane[1], Craig Thomas[2], Mark Souweidane[1,3]; [1]Department of Neurological Surgery, Weill Cornell Medicine, New York, NY, USA. [2]Division of Preclinical Innovation, National Center for Advancing Translational Sciences, National Institutes of Health, Rockville, MD, USA. [3]Department of Neurosurgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

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

Marc Zuckermann[1,2], Chen He[3], Jared Andrews[3], Roketa Sloan-Henry[4], Brandon Bianski[5], Jia Xie[5], Yingzhe Wang[6], Nathaniel Twarog[7], Arzu Onar-Thomas[8], Kati Ernst[1,2], Lei Yang[7], Yong Li[7], James Dalton[9], Xiaoyu Li[9], Divyabharathi Chepyala[7], Xiaoyan Zhu[3], Junyuan Zhang[3], Ke Xu[10,11], Laura Hover[3], Peter J. McKinnon[4], Stefan M. Pfister[1,12], Zoran Rankovic[7], Burgess B. Freeman[6], Anang A. Shelat[7], Jason Chiang[9], David T.W. Jones[1,2], Christopher L. Tinkle[5], Suzanne J. Baker[3]; [1]Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany. [2]Division of Pediatric Glioma Research, German Cancer Research Center (DKFZ), Heidelberg, Germany. [3]Developmental Neurobiology, St. Jude Children's Research Hospital, Memphis, USA. [4]Center for Pediatric Neurological Disease Research, St. Jude Children's Research Hospital, Memphis, USA. [5]Radiation Oncology, St. Jude Children's Research Hospital, Memphis, USA. [6]Preclinical Pharmacokinetics Shared Resource, St. Jude Children's Research Hospital, Memphis, USA. [7]Chemical Biology and Therapeutics, St. Jude Children's Research Hospital, Memphis, USA. [8]Biostatistics, St. Jude Children's Research Hospital, Memphis, USA. [9]Pathology, St. Jude Children's Research Hospital, Memphis, USA. [10]Center for Applied Bioinformatics, St. Jude Children's Research Hospital, Memphis, USA. [11]Computational Biology, St. Jude Children's Research Hospital, Memphis, USA. [12]Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ), Heidelberg, Germany

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

Tuyu Zheng[1,2], Martin Sill[1], Roland Imle[3,4], Ryo Shiraishi[5], Wanchen Wang[5], Alaide Morcavallo[6], Louis Chesler[6], Daisuke Kawauchi[5], Olivier Ayrault[7,8], Lutsik Pavlo[9], Stefan M. Pfister[1,10], Lena M. Kutscher[11], Ana Banito[3], David W. Jones[12], Kristian W. Pajtler[1,10], Marc Zuckermann[1]; [1]Hopp Children's Cancer Center Heidelberg (KiTZ) and Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ), Heidelberg, Germany. [2]Faculty of Biosciences, Heidelberg University, Heidelberg, Germany. [3]Hopp Children's Cancer Center Heidelberg (KiTZ) and Pediatric Soft Tissue Sarcoma Research Group, German Cancer Research Center (DKFZ), Heidelberg, Germany. [4]Department of General, Visceral and Transplantation Surgery, Division of Pediatric Surgery, University Hospital Heidelberg, Heidelberg, Germany. [5]Department of Bicochemistry and Cellular Biology, National Center of Neurology and Psychiatry (NCNP), Tokyo, Japan. [6]Division of Clinical Studies, The Institute of Cancer Research, and The Royal Marsden NHS Trust, Sutton, Surrey, United Kingdom. [7]Institut Curie, PSL Research University, CNRS UMR, INSERM, Orsay, France. [8]Université Paris Sud, Université Paris-Saclay, CNRS UMR 3347, INSERM U1021, Orsay, France. [9]Division of Cancer Epigenomics, German Cancer Research Center (DKFZ), Heidelberg, Germany. [10]Department of Neuropathology, Institute of Pathology, Heidelberg University Hospital, Heidelberg, Germany. [11]Hopp Children's Cancer Center Heidelberg (KiTZ) and Developmental Origins of Pediatric Cancer

Group, German Cancer Research Center (DKFZ), Heidelberg, Germany. [12]Hopp Children's Cancer Center Heidelberg (KiTZ) and Pediatric Glioma Research Group, German Cancer Research Center (DKFZ), Heidelberg, Germany

Recent advances in molecular profiling methods led to the identification of multiple new molecularly defined tumor types and subtypes, distinguished by distinct molecular markers and characteristic DNA methylation signatures. While the analysis of human methylome using microarrays has become an affordable and a routine in many labs, this technology until recently was not available for murine samples. In the past years, we have successfully generated a variety of mouse models for childhood tumors (e.g brain tumors and sarcomas) using different techniques, most of which faithfully reflect the human tumor counterparts at the histological level. With the recently released Infinium Mouse Methylation BeadChip, we now set out to use our models to generate the first DNA methylation database for murine pediatric tumors. We profiled more than 70 mouse models of pediatric tumors including gliomas, medulloblastomas, ependymomas and sarcomas, as well as 40 normal brain and muscle control tissues. We are currently performing a cross-species comparative analysis of established mouse models and the human counterparts. This will assess, how faithfully each models reflect the human situation and examine the effects of multiple passages of allografting. We will also analyze purified immune cell populations and use the derived methylation signatures to assess the model-specific immune microenvironment. Furthermore, we will investigate the methylomes of multiple putative cells-of-origin, which is hardly possible in the human context due to the lack of purified material. We will correlate these to murine tumor samples and thereby provide novel insights into tumor origins. In summary, our study will generate a validated biobank of murine models for pediatric cancers and provide a valuable resource for future developmental studies and preclinical trials.

MODL-08. CELLULAR YIELD AND XENOGRAFT CREATION FROM PROBE WASHING AFTER STEREOTACTIC BIOPSY OF DEEP-SEATED CNS TUMORS IN CHILDREN

Michael DeCuypere[1,2], Sophie Xiao[1], Yuchen Du[1], Sandi Lam[1,2], Xiao-Nan Li[3]; [1]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA. [2]Northwestern University Feinberg School of Medicine Department of Neurosurgery, Chicago, IL, USA. [3]Ann & Robert H. Lurie Children's Hospital of Chicago, Illinois, Illinois, USA

Intracranial tumors located in otherwise difficult-to-resect regions of the brain are routinely biopsied to obtain tissue diagnosis and guide clinical decision making. However, tissue yield from these stereotactic biopsy samples is limited and leaves little remaining for research purposes or tumor banking. Given the importance of molecular diagnostics and rise of targeted therapies, research into the genetic and immune landscape of these lesions is of paramount importance, especially for inoperable and deep-seated tumors. We sought to obtain viable cellular material from otherwise discarded biopsy probes without visible tumor sample within the probe. Cells were obtained from clinically challenging pediatric tumors of the brainstem, thalamus, and pineal region by washing biopsy probes in FBS media immediately after completion of a stereotactic biopsy. The wash was then filtered and re-suspended in media before evenly distributing in a 24 well plate for culture purposes. A total of 15 samples were collected from probe washes, including 6 diffuse midline gliomas of the brain stem, 7 supratentorial diffuse midline gliomas, and 2 tumors in the pineal region. Viable tumor cells were obtained from 9/15 samples, ranging from 500 to approximately 525,000 cells per sample wash (219,222 ± 181,951). Orthotopic implantation into matching locations was completed with 7 tumor samples. Formation of a patient-derived orthotopic xenograft was confirmed in one thalamic high-grade glioma (165,000 cells). Three of the five diffuse midline gliomas of the brainstem showed early signs of tumor formation (yielding >2 million cells) and will be validated. In conclusion, viable tumor cells can be collected from biopsy probe washes after stereotactic biopsy, without visible tumor within the probe. Tumor cells can be used for patient-derived orthotopic xenograft tumor formation, which allows for new avenues in the development of animal models of difficult to resect brain tumors.

MODL-09. EXPLORING THE ROLE OF MAGMAS (MITOCHONDRIA-ASSOCIATED PROTEIN INVOLVED IN GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR SIGNAL TRANSDUCTION) INHIBITION AS A POTENTIAL THERAPEUTIC INTERVENTION IN MEDULLOBLASTOMA

Clay Hoerig[1,2], Ashley Plant-Fox[3], Kaijun Di[1], Javi Lepe[1], Christopher Douglas[1], Naomi Lomeli[1], Bhaskar Das[4], Daniela Bota[1]; [1]University of California-Irvine, Irvine, CA, USA. [2]Children's Hospital of Orange County, Orange, CA, USA. [3]Ann & Robert H. Lurie Children's Hospital, Chicago, IL, USA. [4]Long Island University, Long Island, NY, USA

BACKGROUND: Brain tumors are the second most common type of pediatric cancer and the leading cause of all cancer-related deaths in children. Medulloblastoma (MB) is the most common type of malignant pediatric brain tumor and has a five-year overall survival ranging from 40-75%, depending on the patient's age and other prognostic features. There are various anti-cancer therapies against medulloblastoma, but the treatment of recurrent and refractory disease remains a challenge. As a result, the need for new and novel therapies remain a top priority. One area of interest in CNS tumors are targets within mitochondria. Magmas overexpression has been reported in multiple types of metabolically active tissue and cancer cells, including prostate cancer, pituitary adenoma, and glioma. Some new data suggest that specific subgroups of medulloblastoma may also overexpress Magmas. This ongoing study aims to examine whether Magmas inhibition by compound "BT9" could be beneficial in the treatment of medulloblastoma. METHODS: We continue to study the ability of a Magmas inhibitor (BT#9) as a therapeutic agent in stable medulloblastoma cell lines and patient-derived primary cultures by performing MTT assays, tunnel assays, flow cytometry, migration assays, and invasion assays. RESULTS: Similar to the adult GBM studies, Magmas inhibition by BT#9 had significant cytotoxic effects, causing both decreased cell proliferation, increased apoptosis, and blocked cell migration in medulloblastoma cell lines DAOY, D283, and D425. IC50s determined for each during different time points demonstrated an average range 2-5μM compared to the average range seen in adult glioblastoma cell cultures which could range up to 10 μM. These findings suggest that the inhibition of Magmas could potentially optimize clinical outcomes in recurrent/refractory medulloblastoma and warrants further investigation. Our future studies will include the determination of IC50s for primary cell cultures and in vitro testing with patient-derived xenograft models.

MODL-10. TUMOR-BRAIN-ORGANOIDS AS A MODEL FOR PEDIATRIC BRAIN TUMORS RESEARCH

Nicole Riedel[1], Flavia W. De Faria[1], Carolin Walter[1,2], Jan M. Bruder[3], Kornelius Kerl[1]; [1]Department of Pediatric Hematology and Oncology, University Children's Hospital Münster, Münster, NRW, Germany. [2]Institute of Medical Informatics, University of Münster, Münster, NRW, Germany. [3]Department for Cell and Developmental Biology, Max Planck Institute for molecular Biomedicine, Münster, NRW, Germany

BACKGROUND: Embryonal brain neoplasms like atypical teratoid rhabdoid tumor (ATRT) or embryonal tumor with multilayered rosettes (ETMR) still have a very poor outcome despite intensive treatment including chemotherapy, irradiation and surgery. To date, precision oncology has identified clinically relevant innovative therapeutic targets only for a minor subpopulation of pediatric brain tumor patients, which may be due to current in vitro screens not recapitulating the cellular heterogeneity and cellular interactions in vivo. As cellular heterogeneity and cellular interactions majorly influence the response of tumor cells to treatment, we established an innovative 3D screening platform that combines human neural tissue surrounding primary tumor tissue. METHODS: We established a model of tumor-brain-organoids (TBO) by incorporating embryonal tumor cells (ATRT and ETMR tumor cells) into hiPSC-derived forebrain organoids. Using whole mount immunostaining (WMI), we evaluated cancer-phenotype, the neuronal and progenitor cell distribution in brain organoids, and we performed drug screening analysis. Furthermore, we used single-cell RNA-sequencing to characterize the cellular heterogeneity and the effect of tumor-organoid cell-cell communication on transcriptional programs. RESULTS: ATRT as well as ETMR tumor cells incorporated extensively into the organoid tissue. We observed remarkable differences in the invasiveness of ATRT-MYC cells into TBO in comparison with ATRT-SHH and ETMR cells via high content imaging. Moreover, tumor cells affected the gene expression of different cell types of the organoid by upregulating genes of important signaling/growth related pathways (e. g. MAP2K2, IGFBP2) and epigenetic regulators (like BRD7). Screening through a 300 compound FDA-approved drug library in these TBO, we identified potential innovative therapeutic approaches against these embryonal tumors. CONCLUSION: Tumor-brain-organoids can be used as a platform to study tumor biology, tumor interactions with its neural tissue microenvironment, as well as for high-throughput drug and toxicity screening in pediatric brain tumor precision oncology.

MODL-11. THE TUMOR SUPPRESSOR CREBBP AND THE ONCOGENE MYCN COOPERATE TO INDUCE MALIGNANT BRAIN TUMORS IN MICE

Schoof Melanie[1,2], Gefion Dorothea Epplen[1], Carolin Walter[3,4], Annika Ballast[4], Dörthe Holdhof[1,2], Carolin Göbel[1,2], Sina Neyazi[1,2], Thomas Albert[4], Kornelius Kerl[4], Ulrich Schüller[2,5]; [1]Research Institute Children's Cancer Center, Hamburg, Germany. [2]Department of Pediatric Hematology and Oncology, University Medical Center, Hamburg-Eppendorf, Hamburg, Germany. [3]Institute of Medical Informatics, University of Münster, [48149] Münster, Germany, and Institute of Molecular Tumorbiology, University of Münster, Muenster, Germany. [4]Pediatric Hematology and Oncology, University Children's Hospital Muenster, Muenster, Germany. [5]Institute of Neuropathology, University Medical Center, Hamburg-Eppendorf, Hamburg, Germany

CREBBP (cAMP response element-binding protein binding protein) and MYCN (v-myc avian myelocytomatosis viral oncogene neuroblastoma