oncology program. Using state of the art molecular assays, INFORM aims for identification of targetable genetic alterations, matching drugs and clinical trials. High evidence targets were associated with doubling of progression free survival when patients received a matching drug. However, the fraction of tumors with high evidence drug targets remains low requiring functional layers of information such as drug sensitivity profiling. The aim of this project is to identify and investigate the role of key pharmacodynamic and pharmacokinetic parameters to improve the predictivity of ex vivo drug response of pediatric tumors. METHODS: Positive control cell lines harboring specific mutations (n=7) and primary tumors (n=121) from INFORM, including 10% ependymomas, 7% high grade gliomas, 5% neuroblastomas and 4% medulloblastomas, were profiled ex vivo using a library of n=76 clinically relevant oncology drugs in a 384 well plate format. Metabolic activity was measured after 72h of treatment. Quality control (QC) was done using the robust z-factor, correlation of replicates and mean negative control. Hit selection was based on maximum percentage inhibition, normalized AUC metric (DSSasym) and maximum serum concentration (Cmax) of the drug. Clinical follow-up was collected using a questionnaire. RESULTS: A linear mixed model revealed the DSSasym to be the strongest pharmacodynamic parameter in drug prediction in cell lines. Drug screens of n=105 INFORM cases passed QC. Application of the filtering parameters resulted in prediction of n=1-16 drugs/case (min-max). A data base of published pediatric pharmacokinetic parameters of the drug library was generated. Analysis of predictive parameters and clinical follow-up of clinical samples is ongoing. CONCLUSION: Including pharmacodynamic as well as clinical pharmacokinetic parameters is paramount to identify potentially clinically active compounds from ex vivo drug screen data. Further algorithm development is warranted.

DDEL-02. INTRA-ARTERIAL DELIVERY FOR NOVEL COMBINATORIAL CHEMOTHERAPIES IN CHOROID PLEXUS CARCINOMA

Brice Martin[1], Tyler Garman[1], Madeline Laramee[1], Amy Wang[2], Natalie Hagen[3], Nadia Dahmane[1], Craig Thomas[2], Mark Souweidane[1]; [1]WCM, New York, NY, USA. [2]NIH, Rockville, MD, USA. [3]NIH, Rockville, USA

Choroid plexus carcinoma (CPC) is a rare infantile brain tumor with an aggressive clinical course that often leaves children with debilitating side effects due to aggressive and toxic chemotherapies. New delivery routes such as intra-arterial (IA) route are being explored to limit toxicity and improve efficacy. To identify novel compounds that may be used in this context, we conducted a high-throughput screen (HTS) informing on the cytotoxicity of 2454 compounds, including some currently approved for IA in other brain tumors, that identified multiple active drugs on a human primary CPC cell line. Key molecular targets previously identified in CPC literature such as mTOR, PDGFR, ATR, CDK, FGFR1 and PI3K were enriched relative to other targets in the screen. Importantly, a combination screen with a wide variety of targets revealed multiple synergistic combinations. We examined two key combinations (topotecan/elimusertib and melphalan/elimusertib) based on mechanistic alignment and translational potential through extended in vitro validation and transcriptome analyses. Pharmacokinetic assays established increased drug brain penetrance with IA delivery when compared with intravenous delivery. Ultimately, a single intra-arterial administration of melphalan combined with systemic administration of elimusertib led to a significant increased survival in a CPC genetic mouse model. This study underscores the efficacy of IA delivery and identifies a promising therapeutic option for the treatment of CPC.

DDEL-03. THE USE OF PROGRAMMABLE VALVES AS A VEHICLE FOR INTRATHECAL CHEMOTHERAPY DELIVERY IN INFANTS WITH CNS TUMORS AND HYDROCEPHALUS.

Rina Dvir[1,2], Tom Rosenberg[1,2], Ronit Elhasid[1,2], Dror Levin[1], Shlomi Constantini[3,2], Jonathan Roth[3,2]; [1]Pediatric Hemato-Oncology ,Dana-Dwek Children's Hospital,Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel. [2]Sackler Medical school,Tel-Aviv University, Tel-Aviv, Israel. [3]Pediatric Neurosurgery, Dana-Dwek Children's Hospital, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel

INTRODUCTION: Current chemotherapy protocols for treatment of embryonal brain tumors in infants recommend administration of intrathecal chemotherapy either by a lumbar tap or via an Ommaya reservoir. Children with concurrent hydrocephalus and shunts may have sub-therapeutic levels of chemotherapy in the CSF due to constant CSF drainage to extra-CNS compartments. We present our experience in delivery of chemotherapy to young children via programmable valves. RESULTS: A retrospective analysis of infants with CNS malignancies and hydrocephalus treated with a shunt and a programmable valve (CERTAS™ Plus Programmable Valves - Integra Life Sciences) was conducted. Five infants 1.1-3 years of age (mean 2) were included. Pathologies included atypical teratoid rhabdoid tumor (ATRT N=2), medulloblastoma (N=2), and metastatic rhabdomyosarcoma(N=1). Intrathecal injections were conducted in an outpatient setting unless hospitalization was required for other reasons. Only one child required sedation due to noncompliance. A total of 61 chemotherapeutic administrations were performed directly through the valve while set on an extremely high opening pressure for several hours(35 with hydrocortisone and cytarabine, 26 with topotecan). There were no infections, leaks or major complications. One child required a wound revision due to exposure of the proximal catheter related to extremely thin skin, one child developed somnolence and fever which were not related to a shunt malfunction or infection, and one child had clinical and radiological shunt over-drainage solved by increasing of valve settings. CONCLUSIONS: Programmable ventriculoperitoneal valves appear to a safe method for delivery of chemotherapy in infants with malignant CNS tumors .This technique may potentially have an added value for children with concurrent shunts, and may also obviate the need for an additional ventricular access device .

DDEL-04. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS OF THE DNA METHYLTRANSFERASE INHIBITOR 5-AZACYTIDINE SHOWS ADEQUATE BRAIN TISSUE PENETRATION WITH INTRAVENOUS ADMINISTRATION IN A DIPG MOUSE PATIENT-DERIVED XENOGRAFT MODEL.

Andrew Groves[1], Kristen Jones[2], Amy Cameron[2], Eshini Panditharatna[1], Murry Morrow[2], Brett Mozarsky[3], Cynthia McCully[4], Cody Peer[3], Quang-De Nguyen[2], Mariella Filbin[1], Katherine Warren[1]; [1]Dana-Farber Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA. [2]Lurie Family Imaging Center, Center for Biomedical Imaging in Oncology, Dana-Farber Cancer Institute, Boston, MA, USA. [3]Clinical Pharmacology Program, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. [4]Pediatric Oncology Branch, National Cancer Institute, NIH, Bethesda, MD, USA

One of the biggest obstacles in developing effective therapies for CNS tumors is drug delivery due to the enigmatic challenge of penetrating the blood-brain barrier. 5-azacytidine is a DNA methyltransferase inhibitor which was the first epigenetic targeting chemotherapeutic approved by the FDA. Altered DNA methylation is a hallmark of many cancers, including diffuse intrinsic pontine glioma (DIPG). 5-azacytidine has been shown to be active in DIPG cell lines, with only modest in-vivo activity. We have previously shown in a non-human primate model that intravenous (IV) administration of 5-azacitidine does not result in measurable CSF penetration, while intrathecal (IT) administration does and is well tolerated. To follow up these studies in a tumor-bearing mouse model (HSJD DIPG007), we performed pharmacokinetic (PK) and pharmacodynamic (PD) analysis following IV vs. IT administration. Forty mice were randomized to receive four weekly doses of IV 5-azacytidine (25 mg/kg), IT 5-azacytidine (40 μg), or corresponding vehicle controls. Four mice from each arm were sacrificed 30 minutes after the last dose and brain tissue was collected for PK/PD analysis. Drug concentration was quantified using ultra-high-performance liquid chromatography with tandem mass spectrometric detection, while pharmacodynamic methylation profiling was performed using the Infinium MethylationEPIC BeadChip (850K). Brain tissue concentrations were comparable between IV (7.6-58.0 pg/mg) and IT (6.9-63.9 pg/mg) dosing. Methylation profiling unexpectedly showed a significantly more pronounced pharmacodynamic effect with IV dosing vs. IT, with a mean decrease of 13.6% vs. 2.6% in global DNA methylation score (GDMS = percentage of highly methylated (beta ≥ 0.7) genomic loci) compared to vehicle controls. For the remaining mice, there was no significant difference in survival. Our results are encouraging that phenotypically relevant demethylating effects can be achieved in the CNS with IV 5-azacytidine administration; however, further research is needed to develop promising combination strategies in DIPG.

DDEL-05. INTRAVENTRICULAR THERAPY WITH TOPOTECAN IS FEASIBLE AND SAFE: EXPERIENCE IN 50 PEDIATRIC PATIENTS WITH VARIOUS MALIGNANT BRAIN TUMORS

Andreas Peyrl, Natalia Stepien, Lisa Mayr, Amedeo Azizi, Johannes Gojo, Alicia Baumgartner, Cora Hedrich, Maria Aliotti Lippolis, Irene Slavc; Medical University of Vienna, Vienna, Austria

BACKGROUND: Malignant brain tumors carry a high risk for leptomeningeal dissemination, but the CSF compartment is often not affected by systemic therapy. Intraventricular therapy via an Ommaya reservoir is one possibility to increase the cytotoxic drug concentration in the CSF. Unfortunately, the number of drugs that can be administered directly into the CSF is limited. We report on our experience with topotecan administered via an Ommaya reservoir. PATIENTS AND METHODS: Between 2015 and 2021, 50 patients aged 1 to 22 years (mean and median both 8 years) with various malignant brain tumors received intraventricular topotecan via an Ommaya reservoir. Topotecan was administered at 0.4mg twice a week (>1 and <2 years 0.25mg, >2 and <3 years 0.32mg). RESULTS: In total, 1168