Convection-enhanced delivery (CED), the infusion of drugs under controlled pressure to the brain parenchyma via targeted micro-catheters, allows accurate anatomical targeting and delivery of higher (therapeutic) drug concentrations through clinically relevant volumes of brain tissue or tumor. Histone deacetylase inhibitors have been found in rat and mouse models to be the most active agents against Diffuse Midline Gliomas (DMGs). Using a novel device (implantable subcutaneous pump connected with catheter directly implanted into the pons/medulla) we are performing a Phase I safety study on experimental pediatric tumors to treat. The effects of radiation therapy are temporary, and no chemotherapeutic agent has demonstrated significant efficacy. Intracerebral infusion technique of convection-enhanced delivery (CED) for patients with brain tumors could offer a novel approach for the treatment. We have been working to develop an effective chemotherapy using nimustine hydrochloride (ACNU) with this drug delivery method. After several studies targeting supratentorial recurrent malignant gliomas and recurrent gliomas affecting brainstem, we conducted phase I study to evaluate the safety of combination of convection-enhanced delivery of nimustine hydrochloride and systemic temozolomide against recurrent gliomas affecting brainstem. In this study, we demonstrated the safety and feasibility of CED of ACNU as well as real time monitoring of drug delivery by using a novel device. Additional PK and therapeutic studies are ongoing. We sought to test the hypothesis that panobinostat-loaded CDNs could demonstrate a targeted pharmacokinetic and pharmacodynamic profile comparable to free panobinostat in mice after direct administration to cerebrospinal fluid. METHODS: CDNs were synthesized via Michael addition and engineered to encapsulate a library of HDACi drugs. Nanoparticles were characterized for size, surface charge, loading, controlled release, and stability. CDNs or fluorescent surrogate nanoparticles were administered to the cisterna magna of mice. Tissues were collected for LC-MS/MS (pharmacokinetics [PK]; 1, 4, 8, 24, and 48 hrs) or microscopy [localization: 2, 6, 24, 48, and 72 hrs]. Intravital and confocal microscopy demonstrate that nanoparticles distribute rapidly in subarachnoid space and can localize with metastases, persisting for > 3 weeks. Nanoparticle panobinostat is released over weeks and is better tolerated than free drug. CNP-panobinostat delivery tended to be higher in the cerebellum and lower in the spinal cord at both early and late time points compared to freely administered drug. CONCLUSIONS: We present a nanoparticle platform for HDACi delivery with a differentiated PK profile in the CSF compared to free drug. Additional PK and therapeutic studies are ongoing.
hibitor is a promising strategy to bypass the BBB and to increase the efficacy of an EZH2 inhibitor for the treatment of DIPG.

DDEL-12. NANOPARTICLE DELIVERY OF DOXORUBICIN FOR THE TREATMENT OF DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) Caitlin Ung1, Maria Tsoi1, Jie Liu2, Domenico Cassano2, Danniele Upton1, Anaïd Eftiouta3, Friederike Mansfield1,2, Tim Fair1, Marta Kavallaris1,3, Greg Arndt1, Guy Vitone2,2, Valerio Voltani3,4, Giuseppe Cirillo5,6, and David S. Ziegler1,4,6,1,2,1Children’s Cancer Institute, Lowy Cancer Research Centre, University of New South Wales, Sydney, NSW, Australia, 1ARC Centre of Excellence in Bio-Nano Science and Technology and Australian National University, 1Centre for NanoMedicine, UNSW, Sydney, NSW, Australia, 3ACRF Drug Discovery Centre, Children’s Cancer Institute, Lowy Cancer Research Centre, University of New South Wales, Sydney, NSW, Australia, 4Centre for Nanotechnology Innovation, Instituto Italiano di Tecnologia, Pisa, Italy, 5Department of Pharmacy Health and Nutritional Science, University of Calabria, Calabria, Italy, 6Kids Cancer Centre, Sydney Children’s Hospital, Randwick, NSW, Australia

DIPGs are the most aggressive pediatric brain tumors. Currently, the only treatment is irradiation but due to its palliative nature patients die within 12 months. Effective delivery of chemotherapy across the blood-brain barrier (BBB) has been a key challenge for the eradication of this disease. We have developed and explored novel nanoparticle-based delivery systems to allow systemic delivery of anticancer drugs such as doxorubicin (DOX) to the tumor site. In this study, we evaluated the cytotoxic efficacy of doxorubicin delivered through gold nanoparticles (Au-NP-DOX). We found that AuNP-DOX nanospheres were equally effective to doxorubicin and Au-NP-DOX (at equimolar concentration) by alamar blue assay. Colony formation analysis demonstrated a significantly more potent effect of Au-NP-DOX compared to doxorubicin alone, while the Au-NP had no effect. Furthermore, western blot analysis indicated increased expression of p21 and apoptotic markers cleaved Parp, caspase 3/7 and phosphorylated H2AX in Au-NP-DOX treated DIPG nanospheres. Live cell content and confocal imaging demonstrated significantly higher uptake of Au-NP-DOX compared to doxorubicin alone. Treatment of a DIPG orthotopic mouse model with Au-NP-DOX showed no signs of toxicity with stable weights being maintained during treatment. However, in contrast to the above in vitro findings the in vivo study showed no anti-tumor effect possibly due to poor penetration of Au-NP-DOX into the brain. We are currently evaluating ways to improve this by using different routes to open the BBB consistently. This study highlights the need for rigorous in vivo testing of new treatment strategies before clinical translation to reduce the risk of administration of ineffective treatments.

DDEL-13. FOCUSED ULTRASOUND MEDIATED BLOOD BRAIN BARRIER DISRUPTION IN A MURINE MODEL OF PONTINE GLIOMA: A SAFETY AND FEASIBILITY STUDY Zeynep Emre1,2, Hong-Jian Wang1,2, Anel Pouliopoulos3, Pavan Upadhayayula1, Chia-Inh Jan1, Eleonora Spinazzi1, Peter Canoll1, Jeffrey Bruce1, Neil Feldstein2, Stergos Zacharoulis3, Elisa Konotogou3, and Cheng-Chia Wu1,1,2Department of Neurosurgery, Columbia University Medical Center, New York, NY, USA, 3Department of Neurosurgery, Columbia University Medical Center, New York, New York, USA, 1Department of Biomedical Engineering, Columbia University, New York, New York, USA, 2Department of Pathology, Columbia University Medical Center, New York, New York, USA, 3Department of Pediatrics, Columbia University Medical Center, New York, New York, USA

BACKGROUND: Drug delivery remains a major obstacle in DIPG, as the blood brain barrier (BBB) limits the penetration of systemic therapies to the brainstem. Focused ultrasound (FUS) is an exciting new technology that, when combined with microbubbles, can open the BBB permitting the delivery of drugs into the brain. In this study, we evaluated the safety and feasibility of focused ultrasound with microbubbles to disrupt the BBB in a preclinical pontine glioma model.

OBJECTIVE: The Sonic Hedgehog (SHH) medulloblastoma subgroup accounts for ~25% of all cases and has an intermediate prognosis. Current treatments result in devastating morbidities including intellectual disability and secondary malignancies. Although molecularly targeted agents against the SHH pathway have demonstrated efficacy, off-target bone toxicities suggest new therapeutic approaches are needed. METHODS: We investigated the MRI pathway inhibitor, vismodegib, packaged within liposome-based nanoparticle (viP) that targets P-selectin expressed on endothelial cells and induced by low-dose ionising radiation (XRT) in a time- and dose-dependent manner. This P-selectin targeting nanoparticle shows selectivity toward tumor and not normal brain vasculature. The in vivo S-143 Tumor model was assessed by ex vivo infrared imaging and molecular studies. RESULTS: Quantitative RT-PCR analysis of SHH medulloblastoma following single dose XRT and VisP (10mg/kg) showed synergistic reduction of SHH expression (p<0.05) in viP treatment. Assessment of bone toxicity using micro-CT and histological analysis following VisP administration in postnatal (P10) mice shows no bone toxicity when compared to free vismodegib. Finally, in vivo studies using bEnd.3 brain endothelial cells and in vivo studies using Car.1 knockout mice suggest a caveolin-1 mediated transcytosis mechanism for nanoparticle entry across the blood-brain barrier. CONCLUSIONS: These data suggest applicability of combined XRT and tumor vasculature-targeted nanotherapeutic dose de-escalation strategies for SHH medulloblastoma with implications for other pediatric brain tumors.

DDEL-14. SAFETY OF INTERVENTRICULAR METHOTREXATE ADMINISTRATION FOLLOWING RADIATION IN PEDIATRIC PATIENTS WITH MALIGNANT BRAIN TUMORS Francisco Rosales, Osanna Maher, Maggie Fader, Natalie Gallegos, Tobi Niazi, John Ragheb, and Ziad Khatib

BACKGROUND: Methotrexate has been used for intrathecal administration in leukemia as well as embryonal CNS tumors in children. Concerns about neurologic side effects including leukoencephalopathy, demyelination, and seizures have limited the use of methotrexate following exposure to focal radiation. OBJECTIVE: To evaluate and determine safety of Intraventricular administration of Methotrexate in pediatric patients with recurrent malignant brain tumors along with systemic Topotecan and Cyclophosphamide after exposure to prior radiation therapy. DESIGN/METHOD: Patients with recurrent cerebellar embryonal tumors after standard treatment that included radiation were enrolled on this IRB approved phase 2 study. An Ommaya reservoir was inserted in the lateral ventricle and used to administer 4 daily doses of methotrexate (2 mg/dose) along with (Topotecan [0.75mg/m2/day] and Cyclophosphamide [250 mg/m2/day]). A neurological evaluation was performed at baseline and daily during the intraventricular administration of the Methotrexate, this evaluation was repeated prior to each subsequent cycle and at completion of the protocol. RESULTS: Three patients (age range 3–20) received 2–3 cycles of intra-Ommaya Methotrexate and Topotecan/Cyclophosphamide. No radiation related changes were seen after completion of the intraventricular Methotrexate therapy. None of the patients enrolled on this trial had adverse effects related to the therapy regimens received. Clinical neurologic status was unchanged during the entire course of the treatment and upon completion of the scheduled therapy. CONCLUSION: Intraventricular administration of daily low dose Methotrexate is well tolerated in children with recurrent embryonal CNS tumors who had prior exposure to radiation.

DDEL-15. NANTHERAPEUTIC TARGETING OF TUMOR VASCULATURE FOR ENHANCING DRUG DELIVERY PAST THE BLOOD-BRAIN BARRIER Hiro Kiguchi1,2, Daniel Tylawsky2,1, Jake Vaynshteyn2, Jeffrey Gerwin2, Mandana Manzari2, Janki Shah1, Na Li1, Yosi Shamsay1, Matthew Greenblatt1, Daniel Heller2, and Praveen Raith3,1,2,4Memorial Sloan Kettering Cancer Center, New York, NY, USA, 1Icahn School of Medicine at Mount Sinai, New York, NY, USA, 2Weill Cornell Medicine, New York, NY, USA

OBJECTIVE: The Sonic Hedgehog (SHH) medulloblastoma subgroup accounts for ~25% of all cases and has an intermediate prognosis. Current treatments result in devastating morbidities including intellectual disability and secondary malignancies. Although molecularly targeted agents against the SHH pathway have demonstrated efficacy, off-target bone toxicities suggest new therapeutic approaches are needed. METHODS: We investigated the MRI pathway inhibitor, vismodegib, packaged within liposome-based nanoparticle (viP) that targets P-selectin expressed on endothelial cells and induced by low-dose ionising radiation (XRT) in a time- and dose-dependent manner. This P-selectin targeting nanoparticle shows selectivity toward tumor and not normal brain vasculature. The in vivo S-143 Tumor model was assessed by ex vivo infrared imaging and molecular studies. RESULTS: Quantitative RT-PCR analysis of SHH medulloblastoma following single dose XRT and VisP (10mg/kg) showed synergistic reduction of SHH expression (p<0.01) in VisP treatment. Assessment of bone toxicity using micro-CT and histological analysis following VisP administration in postnatal (P10) mice shows no bone toxicity when compared to free vismodegib. Finally, in vivo studies using bEnd.3 brain endothelial cells and in vivo studies using Car.1 knockout mice suggest a caveolin-1 mediated transcytosis mechanism for nanoparticle entry across the blood-brain barrier. CONCLUSIONS: These data suggest applicability of combined XRT and tumor vasculature-targeted nanotherapeutic dose de-escalation strategies for SHH medulloblastoma with implications for other pediatric brain tumors.

DDEL-16. UNDERSTANDING OPTIMAL CONVECTION-ENHANCED DELIVERY PHYSICO-CHEMICAL INFUSION PARAMETERS: THE ROLE OF BLOOD-BRAIN BARRIER DISRUPTION AND CLEARANCE Erica Power1,2, Liang Zhang1,2, and David Daniels1,2,1Mayo Clinic Graduate School of Biomedical Sciences, Rochester, MN, USA, 2Mayo Clinic Division of Neurosurgery, Rochester, MN, USA, 3Mayo Clinic Division of Molecular Pharmacology and Experimental Therapeutics, Rochester, MN, USA

BACKGROUND: Diffuse midline gliomas harboring the H3K27M mutation in children are aggressive and universally fatal brain tumors that primarily occur in children. The blood-brain barrier (BBB) prevents many drugs from reaching