was 4-years old at diagnosis and received all 3 induction cycles with mg/m2 dosing, developed serious nephrotoxicity during cycle #1 followed by SOS during cycle #3. The HS 4 trial was amended and reopened after external, independent Data Safety Monitoring Board review to dose all chemotherapy drugs in children <6 years old with mg/kg dosing instead of BSA. None of 75 patients enrolled since the amendment developed SOS during induction. These data suggest using caution while dosing young children <6 years of age with intensive induction chemotherapy by BSA.

DDEL-03. LONG-TERM INTRAVENTRICULAR THERAPY ALTERNATING ETOPOSIDE AND LIPOSOMAL CYTARABINE: EXPERIENCE IN 75 CHILDREN AND ADOLESCENTS WITH MALIGNANT BRAIN TUMORS

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BACKGROUND: Malignant brain tumors of childhood carry a high risk for leptomeningeal dissemination and tumor cells floating in the CSF are often not amenable to systemic and/or antiangiogenic chemotherapy. We report on our experience with an intraventricular therapy consisting of alternating cycles of liposomal cytarabine and etoposide. PATIENTS AND METHODS: Between 2004 and 2017, 75 patients aged 0.6 to 22 years (median 11) with various malignant brain tumors received intraventricular etoposide 0.25mg (<1year) - 0.5mg on five consecutive days alternating with liposomal cytarabine at a dose of 25mg (<3 years) - 50mg via an Ommaya reservoir. RESULTS: 5533 doses of etoposide (5–277/patient, median 141) corresponding to 1–56 five-day-cycles/patient alternating with 534 doses of liposomal cytarabine (1–21/patient, median 11) were administered. Treatment was given over a period of 1 – 146 months (median 73.5). Toxicities did occur but were infrequent and mostly mild. Since all patients received some sort of concurrent anti-cancer therapy, the efficacy of intrathecal therapy cannot be assessed independently. However, 29/75 patients are still alive, and none of the patients had tumor cells in the CSF at their last evaluation. CONCLUSION: In conclusion, alternating intraventricular liposomal cytarabine and etoposide produced responses and proved to be an important adjunct for patients receiving drugs with a low penetrance into the CSF. Since production of liposomal cytarabine was discontinued in 2017 it remains to be determined whether substitution of the slow release formulation by aqueous cytarabine on days 1, 4, 8, and 11 may produce similar results.

DDEL-04. ENGINEERED NANOCARRIERS TO ENHANCE DRUG DELIVERY ACROSS THE BLOOD-BRAIN BARRIER

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Pediatric central nervous system tumors are the leading cause of cancer death in children. Promising therapeutics have been identified, but the ability to deliver an effective concentration to the tumor without causing excessive systemic toxicity remains a challenge. To address this, we leveraged a tunable nanocarrier platform to design a brain-penetrant nanocarrier with preferential uptake into tumor cells over healthy brain cells. First, we used the layer-by-layer technique to iteratively coat liposomes with nanometers-thick layers of oppositely charged polyelectrolytes. To investigate the influence of surface chemistry on cellular trafficking, a panel of layered liposomes was tested for interactions with cancer cell lines, identifying poly-L-aspartic acid and hyaluronic acid as the highest-performing formulations across brain tumor lines. To facilitate nanocarrier transit across the blood-brain barrier (BBB), we developed a click chemistry platform to functionalize the nanocarrier with BBB shuttle ligands. To investigate trafficking *in vitro*, we utilized a microfluidic brain microvascular model comprising endothelial cells, astrocytes, pericytes, and glioma cells that self-assemble into a perfusable vascular network. We found that nanocarrier size influenced vascular transport, and the addition of BBB shuttle ligands improved transport in the presence of a glioma spheroid. To investigate *in vivo* nanocarrier trafficking, we performed intravital imaging through a cranial window in anesthetized mice. After intravenous administration, nanocarrier transit across intact brain capillaries was visualized using two photon microscopy, and vessel permeability was quantified over time. Ongoing studies in mice bearing patient-derived xenograft medulloblastoma and glioma tumors are being conducted to further characterize trafficking across tumor-associated vasculature.

DDEL-05. BLOOD-BRAIN BARRIER DISRUPTION AND ENHANCED RADIOSENSITIZERS EXTRAVASATION UPON FOCUSED ULTRASOUND FOR TREATMENT OF DIFFUSE INTRINSIC PONTINE GLIOMA

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Poor prognosis of diffuse midline glioma, including diffuse intrinsic pontine glioma (DIPG), reflects the low efficacy of current treatment strategies, mainly due to (1) a largely intact blood-brain barrier (BBB) and (2) the proficiency of tumour tissues to upregulate multiple DNA repair genes, resulting into radio-resistance. *In vitro* studies showed therapeutic benefit by combining radiotherapy and radiosensitizers, while pre-clinical and clinical studies evidenced safe and transient opening of the BBB using microbubble mediated focused ultrasound (FUS). Previously, we demonstrated the enhanced extravasation of olaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor in the mouse pons. Local drug delivery was applied using an in-house built X-ray image-guided FUS system with a 1 MHz mono-element transducer delivering a tone-burst pulse with a mechanical index of 0.4. Tissue/blood drug concentrations were analysed by LC-MS/MS, 30 minutes after intraperitoneal injection of 10 mg/kg olaparib. The FUS system allowed for precise treatment of the pons, proven by local extravasation of Evans Blue-conjugated albumin. A significant 5.1 fold median increase was observed in absolute concentrations in the pons after FUS intervention compared to the control and a 4.9 fold increase of the median tissue-blood ratio ($*p<0.05$). No significant differences were detected in brain regions outside the ultrasound focus and other organs, confirming the local intervention. With this, the 299 nM equivalent olaparib concentration found in the pons will facilitate PARP inhibition in future murine patient-derived xenograft tumour models, thus leading to a greater therapeutic effect when in combination with radiotherapy treatment of DIPG.

DDEL-06. DRUG INTERACTION BETWEEN EVEROLIMUS AND CANNABIDIOL IN PEDIATRIC PATIENTS WITH SUBEPENDYMAL GIANT CELL ASTROCYTOMAS: A SINGLE INSTITUTION EXPERIENCE

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Tuberous sclerosis complex (TSC) is an autosomal recessive genetic disorder associated with clinical manifestations including subependymal giant cell astrocytomas (SEGA) and seizures. The combination of everolimus and Epidiolex, a purified form of cannabidiol, has become an increasingly common treatment regimen in this population. Everolimus is primarily metabolized via CYP3A4, which may be inhibited by cannabidiol. We seek to describe our institution's experience with this drug interaction. METHODS: Investigators conducted a retrospective review of neuro-oncology patients with TSC and SEGA who were treated concurrently with everolimus and cannabidiol. Data collected included demographics, body surface area, everolimus dose, everolimus troughs, date of cannabidiol initiation, documented symptoms, liver and renal function tests, and reason for discontinuing therapy. RESULTS: Three patients (ages 11–17 years) met inclusion criteria. All patients were stable on everolimus doses ranging from 6.5 to 9.5 mg/m^2/day and achieving trough goals of 5–10 ng/mL. Two to four weeks after initiating cannabidiol, everolimus trough concentrations rose 200–860% above goal. One patient reported new-onset involuntary movements, but no other toxicities were noted. Cannabidiol was discontinued in all cases due to caregiver concerns regarding drug interactions. All patients were able to achieve goal trough concentrations on previously stable doses of everolimus after discontinuing cannabidiol. CONCLUSIONS: Cannabidiol appears to modulate everolimus metabolism leading to significantly elevated serum concentrations. Additional research is required to determine the need for empiric dose adjustments upon cannabidiol initiation. Patient counseling, frequent trough monitoring, and surveillance for adverse effects are crucial for optimizing outcomes in patients prescribed this regimen.

DDEL-07. A PHASE I STUDY EXAMINING THE FEASIBILITY OF INTERMITTENT CONVECTION-ENHANCED DELIVERY (CED) OF MTX110 FOR THE TREATMENT OF CHILDREN WITH NEWLY DIAGNOSED DIFFUSE MIDLINE GLIOMAS

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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 vitro* 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/thalamus) we are performing a Phase I safety study of repeated infusions of MTX110 (MTX110, Midatech) in a dose escalation manner. Eligible patients include 3–18 years of age with newly diagnosed DMGs following radiation therapy without evidence of hemorrhage or cysts with intact organ function. Patients undergo a tumor biopsy and a single catheter (Spetzler lumbar shunt catheter, Integra, Plainsboro, NJ) is placed stereotactically into the geometric center of the tumor. A second catheter is inserted subcutaneously with the distal tubing connected to the infusion pump, (SynchroMed II (Medtronic)), also inserted subcutaneously. The infusion pump is prefilled with MTX110 and administered using wireless N'Vison Clinical programmer into two 24-hour infusions, consisting of 20 hours of drug infusions at 0.2mL/hr. The pulse is completed 7 days later. This is a dose escalation study with the infusate consisting of gadolinium and MTX110 (30, 60, or 90 microM). The study describing the first use in children of this device for direct-to-tumor drug delivery is open to recruitment (January 2020) and the preliminary data will be available for presentation by June 2020.

DDEL-08. CONVECTION-ENHANCED DELIVERY OF NIMUSTINE HYDROCHLORIDE (ACNU) AGAINST PEDIATRIC DIFFUSE INTRINSIC PONTINE GLIOMAS

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Diffuse intrinsic pontine gliomas (DIPGs) are amongst the most challenging tumors to treat. Surgery is not an option, 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 effective chemotherapy. 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 1 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 distribution by mixing ACNU with contrast agent; Gd-DOTA. We also defined the maximum tolerable concentration in this study and proceeded to phase 2 trial against recurrent gliomas affecting brain stem. However, these trials revealed the difficulty of treating pediatric DIPG at the time of recurrence. Therefore, we decided to treat pediatric DIPG cases at their initial diagnosis in the subsequent study. Aiming at obtaining Shonin approval both for intraparenchymal infusion catheter and drug to infuse into brain parenchyma, we are now conducting Phase II physician-led trial against initially diagnosed pediatric DIPG cases.

DDEL-09. HIGH DOSE MTX110 (SOLUBLE PANOBINOSTAT) SAFELY ADMINISTERED INTO THE FOURTH VENTRICLE IN A NON-HUMAN PRIMATE MODEL

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OBJECTIVE: This study tested the safety and pharmacokinetics of short-term and long-term administration of MTX110 (soluble panobinostat; Midatech Pharma, UK) into the fourth ventricle of non-human primates. METHODS: Four rhesus macaque monkeys underwent posterior fossa craniectomy and catheter insertion into the fourth ventricle. In Group I (n=2), catheters were externalized and lumbar drain catheters were placed simultaneously to assess cerebrospinal fluid (CSF) distribution after short-term infusions. MTX110 (0.5 ml of 300 μM panobinostat solution) was infused into the fourth ventricle daily for five consecutive days. Serial CSF and serum panobinostat levels were measured. In Group II (n=2), fourth ventricle catheters were connected to a subcutaneously-placed port for subsequent long-term infusions. Four cycles of MTX110, each consisting of 5 daily infusions (0.5 ml of 300 μM panobinostat solution), were administered over 8 weeks. Animals underwent detailed neurological evaluations, MRI scans, and post-mortem histological analysis. RESULTS: Neurological assessments, MRI, and histology confirmed catheter placement and an absence of neurotoxicity. Panobinostat was undetectable in serum collected two and four hours after infusions in all samples in both groups. In Group I, mean peak panobinostat level in fourth ventricle CSF (6242 ng/ml) was significantly higher than in lumbar CSF (9 ng/ml; $p < 0.0001$). In Group II, mean peak CSF panobinostat level (11,042 ng/ml) was significantly higher than mean trough CSF level (33 ng/ml; $p<0.0001$). CONCLUSION: MTX110 can be safely delivered via 4th ventricle at supra-therapeutic doses. These results provide data for a pilot clinical trial in patients with recurrent medulloblastoma.

DDEL-10. A NANOPARTICLE PLATFORM FOR INTRATHECAL DELIVERY OF THE HISTONE DEACETYLASE INHIBITOR (HDACI) PANOBINOSTAT IN METASTATIC OR RECURRENT MEDULLOBLASTOMA

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INTRODUCTION: Panobinostat is a histone deacetylase inhibitor (HDACi) that is a clinical candidate for treatment of pediatric medulloblastoma and diffuse intrinsic pontine glioma. Panobinostat is poorly water-soluble and experiences a number of barriers to effective delivery. Here, we developed a novel drug delivery system consisting of β-cyclodextrin-poly(β-amino ester). These cyclodextrin-networks (CDNs) self-assemble into nanoparticles encapsulating a high quantity of HDACi for slow release. We sought to test the hypothesis that panobinostat-loaded CDNs would demonstrate a differentiated pharmacokinetic profile compared 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, and 48 hrs, 1 and 3 wks). RESULTS: 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. CDN-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.

DDEL-11. CONVECTION-ENHANCED DELIVERY OF EZH2 INHIBITOR FOR THE TREATMENT OF DIFFUSE INTRINSIC PONTINE GLIOMA

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BACKGROUND: Diffuse intrinsic pontine glioma (DIPG) is a fatal childhood brain tumor and the majority of patients die within 2 years after initial diagnosis. Factors that contribute to the dismal prognosis of these patients include the infiltrative nature and anatomic location in an eloquent area of the brain, which precludes total surgical resection, and the presence of the blood-brain barrier (BBB), which reduces the distribution of systemically administered agents. Convection-enhanced delivery (CED) is a direct infusion technique to deliver therapeutic agents into a target site in the brain and able to deliver a high concentration drug to the infusion site without systemic toxicities. OBJECTIVE: This study aims to assess the efficacy of enhancer of zeste homolog-2 (EZH2) inhibitor by CED against human DIPG xenograft models. METHODS: The concentration of EZH2 inhibitor (EPZ-6438) in the brainstem tumor was evaluated by liquid chromatography–mass spectrometry (LC/MS). We treated mice bearing human DIPG xenografts with EPZ-6438 using systemic (intraperitoneal) or CED administration. Intracranial tumor growth was monitored by bioluminescence image and the therapeutic response was evaluated by animal survival. RESULTS: LC/MS analysis showed that the concentration of EPZ-6438 in the brainstem tumor was 3.74% of serum concentration after systemic administration. CED of EPZ-6438 suppressed tumor growth and significantly extended animal survival when compared to systemic administration of EPZ-6438 (P=0.0475). CONCLUSION: Our results indicate that CED of an EZH2 in-