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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-

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)

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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 a novel gold nanoparticle functionalised with human serum albumin (Au-NP, 98.8 ±19 nm) for the delivery of doxorubicin. In this study, we evaluated the cytotoxic efficacy of doxorubicin delivered through gold nanoparticles (Au-NP-Dox). We found that DIPG neurospheres were equally sensitive to doxorubicin and Au-NP-Dox (at equimolar concentration) by alamar blue assay. Colony formation assays 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 apoptotic markers cleaved Parp, caspase 3/7 and phosphorylated H2AX in Au-NP-Dox treated DIPG neurospheres. 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 whether efficacy can be improved using measures to open the BBB transiently. 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

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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 entry of drugs across the cerebrovasculature. Given that the utility of FUS in brainstem tumors remains unknown, the purpose of our study was to determine the safety and feasibility of this technique in a murine pontine glioma model. METHODS: A syngeneic orthotopic model was established by stereotactic injection of PDGF-B^{+}PTEN$^{-/-}$p53$^{-/-}$ murine glioma cells (10,000/1ul) into the pons of B6 albino mice. A single-element, spherical-segment FUS transducer (center frequency=1.5MHz) driven by a function generator through a power amplifier (acoustic pressure=0.7MPa) was used with concurrent intravenous microbubble injection (FUS+MB) to sonicate the tumor on post-injection day 14. BBB opening was confirmed with gadolinium-enhanced MRI and Evans blue. Kondziela inverted screen (KIS) testing was completed to measure motor function. Mice were either immediately sacrificed for histopathological assessment or serially monitored for survival. RESULTS: In mice treated with FUS (n=11), there was no measured deficit in KIS testing. Additionally, the degree of intra-tumoral hemorrhage and inflammation on H&E in control (n=5) and treated mice (n=5) was similar. Lastly, there was no difference in survival between the groups (control, n=6, median=26 days; FUS, n=6, median=25 days, p>0.05). CONCLUSION: FUS+MB is a safe and feasible technique to open the BBB in a preclinical pontine glioma model.

DDEL-14. SAFETY OF INTERVENTRICULAR METHOTREXATE ADMINISTRATION FOLLOWING RADIATION IN PEDIATRIC PATIENTS WITH MALIGNANT BRAIN TUMORS

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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 MRI demyelination or white matter 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 regimen received. Clinical neurological 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. NANOTHERAPEUTIC TARGETING OF TUMOR ENDOTHELIUM FOR ENHANCING DRUG DELIVERY PAST THE BLOOD-BRAIN BARRIER

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OBJECTIVE: The Sonic Hedgehog (SHH) medulloblastoma subgroup accounts for ~25% of all cases and has an intermediate prognosis. Current therapies result in devastating morbidities including intellectual disability and secondary malignancies. Although molecularly targeted agents against the SHH pathway have demonstrated efficacy, on-target bone toxicities suggest new therapeutic approaches are needed. METHODS: We investigated the SHH pathway inhibitor, vismodegib, packaged in a fucoidan-based nanoparticle (Fi-Vis) that targets P-selectin expressed on endothelial cells and induced by low-dose ionizing radiation (XRT) in a time- and dose-dependent manner. This P-selectin targeting nanoparticle shows selectivity toward tumor and not normal brain vasculature in a GEM SHH medulloblastoma model as assessed by *ex vivo* infrared imaging and molecular studies. RESULTS: Quantitative RT-PCR analysis of SHH medulloblastoma following single dose XRT and Fi-Vis treatment (10mg/kg) showed synergistic reduction of Gli1 expression (>90% target inhibition). We demonstrate that low-dose XRT (0.25Gy) can induce P-selectin expression specifically on medulloblastoma tumor endothelium and synergize with low-dose Fi-Vis (10mg/kg) to significantly enhance mouse survival ($p<0.01$) compared to radiation or Fi-Vis alone. Assessment of bone toxicity using micro-CT and histological analysis following Fi-Vis administration in postnatal (P10) mice shows no bone toxicity when compared to free vismodegib. Finally, *in vitro* studies using bEnd.3 brain endothelial cells and *in vivo* studies using *Cav1* 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 BBB EFFLUX PUMPS IN DRUG DISTRIBUTION AND CLEARANCE

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