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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-