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