survival of <1 year. The critical location in the brainstem and the often intact blood-brain barrier (BBB) pose significant challenges in the treatment of DIPG. The objective of this study was to demonstrate the potential for focused ultrasound-induced BBB disruption (FUS-BBBD) to improve DIPG treatment by enhancing the safe and efficient delivery of drugs. A genetically engineered mouse model of DIPG was generated using the RCAS (replication-competent avian sarcoma-leucosis virus long-terminal repeat with splice acceptor)/tumor virus A modeling system. A magnetic resonance-guided FUS (MRgFUS) system was used to induce BBB disruption in these mice with the FUS targeted at the center of the tumor. Two radiolabeled agents with different sizes were used to evaluate the delivery efficiency of the FUS-BBBD technique in DIPG mice: a small-molecular radiotracer, ^{68}Ga-DOTA-ECL1i, and a radiolabeled nanoparticle, ^{64}Cu-labeled copper nanoparticles (^{64}Cu-CuNCs, ~ 5 nm in diameter). ^{68}Ga-DOTA-ECL1i (half-life ~ 1 h) and ^{64}Cu-CuNCs (half-life ~13 h) were intravenously injected into the mice after FUS sonication, and microPET/CT imaging was performed at 1 h and 24 h, respectively, to evaluate the spatial-temporal distribution of these two agents in the brain and quantify the delivery outcome. FUS treatment increased the uptake of ^{68}Ga-DOTA-ECL1i and ^{64}Cu-CuNCs to the DIPG tumor by 3.25 folds and 4.07 folds on average, respectively. These findings demonstrated, for the first time, that FUS can increase BBB permeability in a murine model of DIPG and significantly enhance the delivery of agents of different sizes into the DIPG tumor.

HGG-19. 5-AMINOLEVULINIC ACID (5-ALA)-GUIDED RESECTION OF PEDIATRIC BRAIN TUMORS

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Between tumor and normal brain, allowing a higher degree of resection, and improved patient outcomes. In recent years, several reports have emerged regarding the use of 5-ALA in other brain tumor entities, including pediatric brains tumors. Since gross total resection (GTR) of many brain tumors in children is crucial, the role of 5-ALA-guided resection requires elucidation.

Methods: A systematic literature review of EMBASE and MEDLINE/PubMed databases revealed 20 eligible publications encompassing 186 5-ALA-guided operations on pediatric brain tumors. To reduce bias, publications were revised independently by two authors. Results: 5-ALA-guided resection enabled the surgeons to identify the tumor more easily and was considered helpful mainly in cases of glioblastoma (GBM, 21/27, 78%), anaplastic ependymoma WHO grade III (10/14, 71%), and anaplastic astrocytoma (4/6, 67%). In contrast, cases of pilocytic astrocytomas (PAs) and medulloblastomas 5-ALA-guided surgery did not show consistent fluorescent signals and 5-ALA was considered helpful only in 12% and 22% of cases, respectively. Accumulation of fluorescent porphyrins seems to depend on WHO tumor grading. In case fluorescence signal was considered helpful, it was associated with a greater degree of resection. One study showed an association between visible fluoresce signal and concentration of protopophyrin IX (PPIX) concentration. A threshold of 4µg/ml was required in order to visualize the fluorescence signal. The rate of adverse events related to 5-ALA was negligible, especially new postoperative sequelae. Conclusion: 5-ALA could play a role in resection of malignant, contrast enhancing, supratentorial pediatric brain tumors. At present, we are conducting a prospective phase I-II multicenter clinical trial to evaluate side effects and feasibility of 5-ALA guided surgery.

HGG-21. MALIGNANT SYNAPTIC PLASTICITY IN PEDIATRIC HIGH-GRADE GLIOMAS

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Pediatric high-grade gliomas (pHGG) are a devastating group of diseases that urgently require novel therapeutic options. We have previously demonstrated that pHGGs directly synapse onto neurons and the subsequent tumor cell depolarization, mediated by calcium-permeable AMPA channels, promotes their proliferation. The regulatory mechanisms governing these postsynaptic connections are unknown. Here, we investigated the role of BDNF-TrkB signaling in modulating the plasticity of the malignant synapse. BDNF ligand activation of its canonical receptor, TrkB (which is encoded for by the gene *NTRK2*), has been shown to be one important modulator of synaptic regulation in the normal setting. Electrophysiological recordings of glioma cell membrane properties, in response to acute neurotransmitter stimulation, demonstrate in an inward current resembling AMPA receptor (AMPAR) mediated excitatory neurotransmission. Extracellular BDNF increases the amplitude of this glutamate-induced tumor cell depolarization and this effect is abrogated in *NTRK2* knockout glioma cells. Upon examining tumor cell excitability using in situ calcium imaging, we found that BDNF increases the intensity of glutamate-evoked calcium transients in GCaMP6s expressing glioma cells. Western blot analysis indicates the tumors AMPAR properties are altered downstream of BDNF induced TrkB activation in glioma. We find that BDNF-TrkB signaling promotes neuron-to-glioma synaptogenesis as measured by high-resolution confocal and electron microscopy in culture and tumor xenografts. Our analysis of published pHGG transcriptomic datasets, together with brain slice conditioned medium experiments in culture, indicate the tumor microenvironment as the chief source of BDNF ligand. Disruption of the BDNF-TrkB pathway in patient-derived orthotopic glioma xenograft models, both genetically and pharmacologically, results in an increased overall survival and reduced tumor proliferation rate. These findings suggest that gliomas leverage mechanisms of plasticity to modulate the excitatory channels involved in synaptic neurotransmission and they reveal the potential to target the regulatory components of glioma circuit dynamics as a therapeutic strategy for these lethal cancers.

HGG-22. EVALUATING THE REGULATION OF BLOOD-BRAIN BARRIER INTEGRITY IN DIPG MOUSE MODELS

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Diffuse intrinsic pontine gliomas (DIPGs) are considered to maintain a fairly intact blood-brain barrier (BBB) based on patient imaging tumor histology. In characterizing recently developed DIPG and HGG mouse models, we identified differences in BBB function and increased Angiopoietin1 (Angpt1) in H3 K27M DIPG models. We hypothesize that H3 K27M mutations promote the maintenance of DIPG BBB integrity through upregulation of Angpt1. To determine DIPG and HGG BBB phenotypes we performed an intergrative analysis of vascular histology and endothelial transcriptomes Ongoing studies using electroporation based DIPG mouse models are being performed examine the regulation and function of Angpt1 in DIPG BBB integrity. We have initiated studies comparing H3 K27M DIPG mouse models to H3 WT and G34R cortical HGG mouse models, demonstrating that DIPG models show minimal changes in vascular phenotype, including vessel density, branching, and diameter compared to cortical HGG models. Comparing DIPG and HGG purified endothelial transcriptomes, HGG ECs displayed enrichments of inflammatory signals and proliferation gene sets, and increased expression of tip cell identity genes. We identified Angpt1 as selectively upregulated in H3 K27M mouse models and derived cell lines. Preliminary data suggests Angpt1 supports the maintenance of BBB integrity in DIPG models. BBB phenotype differences are present in DIPG and HGG mouse models. Uncovering mutation specific mechanisms that regulate BBB function in brain tumors will be critical to advance our understanding of brain tumor pathogenesis and treatment response.

HGG-23. IN VITRO AND IN VIVO PRECLINICAL DRUG SCREENING OF PROMISING THERAPEUTICS FOR DIFFUSE MIDLINE GLIOMA (DMG)

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Introduction: Diffuse midline gliomas (DMGs) are amongst the most unforgiving pediatric brain tumors, characterized by an intrinsic resistance to therapy. Despite major advances in understanding of tumor biology, the prognosis remains exceedingly poor, and treatment options are limited. New therapeutics are being evaluated at a fast rate by different laboratories. In order to prioritize effective drug candidates for DMG treatment, we comprehensively characterized a panel of promising therapeutic agents in in vitro and in different vivo systems. Methods: We determined the sensitivity of primary DMG cell lines to a panel of small molecule inhibitors targeting known DMG targets and pathways. Dose response curves were generated for more than 20 different compounds and possible synergistic effects were investigated by SynergieFinder. In an effort to highlight potential toxicities and associated mechanisms at a large scale, we performed a preclinical toxicity evaluation in zebrafish larvae, with a slightly modified version of the official Fish Embryo Acute Toxicity (FET) test. Drug toxicity was tested by continuous exposure of zebrafish larvae to increasing concentrations of the different compounds. Survival curves, morphological analyses and behavioral tests were performed at a maximum tolerated dose (MTD). To confirm the findings obtained in zebrafish, we further performed in vivo studies in mice for promising candidates. Results: Among the tested drugs in vitro we found 10 drugs showing promising dose- dependent reduction in cell viability with IC_{50} in nM to µM range. These were further evaluated for toxicity in zebrafish. The zebrafish larvae toxicities observations strongly correlated with the findings in murine in vivo studies, reinforcing the importance of