survival and induced tumoral and microenvironment remodeling, pointing at its high therapeutic potential and the need for an early clinical trial.

P11.62 BRAIN DISTRIBUTION MODELS TO SELECT POLYMER-DELIVERED DRUGS FOR THE INTRA-CAVITY TREATMENT OF MALIGNANT GLIOMA

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BACKGROUND: Conventional oral or intravenous chemotherapy distributes drugs to the whole body whereby systemic toxicity to healthy parts of the body (e.g. bone marrow failure) limits the maximum dose that can be achieved in the brain. This presents a particular concern for CNS tumours where the blood-brain-barrier (BBB) restricts drug influx from the circulation. The ability to deliver chemotherapy locally at the tumour site offers the opportunity to target residual cancer cells post-surgery whilst minimising systemic toxicity. We have developed a poly(lactic-co-glycolic acid)/poly(ethylene glycol) (PLGA/PEG) polymer matrix that forms a porous paste at room temperature when mixed with chemotherapy-containing saline, solidifying only at body temperature, with close apposition to the irregular surgical cavity. It is important that we can observe whether the drugs released from PLGA/PEG can penetrate brain parenchyma beyond the surgical resection margin at therapeutic doses. Currently the only way to measure the distribution of drugs in the body is to inject radioactive drugs into an animal. We aim to establish drug distribution parameters using label-free mass spectrometry imaging methods, prior to selection of drug formulations for clinically-relevant *in vivo* models. Drugs that penetrate the brain the furthest will be identified as good candidates for localised brain cancer drug delivery using PLGA/PEG paste. **MATERIAL AND METHODS:** Diffusion rates were measured by examining the proportion of olaparib, dasatnib, carboplatin, etoposide, paclitaxel and gemcitabine at 2mg/ml concentration, which passes through 1mm slices of rat brain tissue within Franz cell chambers over a 6 hour period. The spatio-temporal distribution of label-free olaparib and dasatinib within mouse brain homogenate was quantitatively measured using innovative 3D OrbiSIMS, a hybrid time-of-flight / Orbitrap™ secondary ion mass spectrometer. **RESULTS:** Within the Franz cell model, carboplatin and gemcitabine showed the highest diffusion rate diffusion at 16.4 and 6.53 μg/cm^2/h respectively whereas olaparib, etoposide and paclitaxel were relatively poorly diffused at 1.87, 3.82 and 2.27 μg/cm^2/h respectively. The minimum threshold of OrbiSIMS detection for label-free olaparib and dasatinib ions was 0.025 mg/ml and 0.2 mg/ml respectively throughout brain homogenate. **CONCLUSION:** This study demonstrates different diffusion rates through brain tissue, between label-free chemotherapy drugs of distinct chemistries, with highest diffusion rates observed for carboplatin and gemcitabine. We also demonstrate label-free detection of olaparib and dasatinib using the innovative 3D OrbiSIMS method. These models will facilitate the rapid identification of agents most amenable for localised biomaterial-based chemotherapy delivery with high brain penetrance.

P11.63 PI3K INHIBITION IN CONJUNCTION WITH THE KETOGENIC DIET REDUCES GROWTH AND NEUROINFLAMMATION IN PEDIATRIC HIGH-GRADE GLIOMA

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Background: Pediatric high-grade glioma remains a poorly treatable disease with high mortality.Therapeutic advances have lagged behind that of adult glioblastoma, due to small patient numbers, inappropriate generalization from adult tumor types, and unique biology. The use of targeted therapy has recently gained interest in this disease, but efficacy is limited by therapeutic resistance, often as a result of tumor heterogeneity. In the case of phosphatidylinositol 3-kinase (PI3K) inhibition, clinically relevant PI3K inhibitors represent a strong class of drugs for pediatric high-grade glioma, but their use is associated with insulin feedback that reactivates the PI3K pathway and drives therapeutic resistance. Here, we target insulin feedback that is the primary mechanism of PI3K inhibitor-related therapeutic resistance in pediatric high-grade glioma using the ketogenic diet.

Materials and Methods: Patient-derived pediatric high-grade glioma stem cells were treated with vehicle or the pan-PI3K inhibitor, BKM-120, with glucose deprivation or phenformin to decrease glucose utilization. NSG mice containing patient-derived pediatric high-grade glioma xenografts were treated with vehicle or BKM-120 on a regular or ketogenic diet to determine whether reducing insulin feedback increases BKM-120 efficacy. To determine the effect of glioma cells on neuro-inflammation, we measured pro-inflammatory cytokines in glioma cells treated with BKM-120 and phenformin in comparison to vehicle-treated cells. We then applied conditioned medium from glioma cells treated with BKM-120 and phenformin to cortical neuronal cultures to measure oxidative stress and neuro-inflammation. Results: Pediatric high-grade glioma cells exhibited increased toxicity when exposed to BKM-120 with glucose deprivation or phenformin. Furthermore, mice with intracranial high-grade glioma xenografts survived longer when treated with BKM-120 on the ketogenic diet than with BKM-120 or the ketogenic diet alone. Phenformin reduced the production of pro-inflammatory cytokines by BKM-120-treated glioma cells. Cortical neurons treated with conditioned medium from BKM-120- and phenformin-treated glioma cells exhibited less oxidative stress than those treated with BKM-120 alone. Our results demonstrate that strategies to lower glucose utilization and insulin feedback increase efficacy of BKM-120 and decrease neuro-inflammation.

Conclusions: We show that strategies to lower glucose utilization and insulin feedback increase efficacy of BKM-120. Furthermore, reducing insulin feedback decreases the production of pro-inflammatory cytokines in tumor cells and reduces oxidative stress in neurons treated with conditioned medium from BKM-120-treated glioma cells. By using the ketogenic diet to reduce glucose levels, this strategy may enhance efficacy of PI3K inhibitors in this patient population.

P11.64 SPECIALIZED NEUROONCOLOGIAL BIOREPOSITORY OF THE N.N. BURDENKO NATIONAL MEDICAL RESEARCH CENTER FOR NEUROSURGERY: HIGH-QUALITY TUMOR BANK FOR PERSONALIZED MEDICINE

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BACKGROUND: Specialized biorepositories in neurooncology serve for storage of tissue samples derived from patients with central nervous system (CNS) tumors. In 2016 the new facility was launched for collection of CNS tumor specimens. The principal aim of the repository is preparation of frozen CNS tumor samples accompanied by associated clinical, pathological, molecular, and follow-up data. **MATERIAL AND METHODS:** Each surgical biopsy was divided into several aliquots (usually three), registered, and stored in LN2. Since August 2018 from all aliquots a lesser fragment was separated for paraffin block processing. This histological control was applied for quality assurance of frozen samples. Each specimen record was accompanied with demographic, clinical, perioperative, and histological data. In the follow-up, oncological treatment and response to therapy were added to the databank as well as molecular data. All tumor samples are characterized, passportized, stored, and systemically revised. The following biomarkers were evaluated: Cdk4, Cdk6, FGFR, NANOG, OCT4, SOX2, MELK, Nestin, Notch2, Olig2, GFAP, MAP2, β-III-tubulin, PDGFRA. Dedicated original flexible electronic data storage system was designed for information support of tumor collection. Specimen acquisition, procurement, and storage was encoded using SPREC 2.0 coding system. **RESULTS:** Between March 2016 till January 2019 a total of 596 biopsy samples were stored in the repository. All of them were obtained from the patients operated on in N.N. Burdenko National Medical Research Center for Neurosurgery. Among all entities brain gliomas prevailed and comprised 539 biopsy specimens (90,4%). Specimen quality control using histology, immunohistochemistry, fluorescent in situ hybridization, and molecular methods was performed. The frequency of appropriate aliquots is as high as 83,4%. Tumor sample collection included primary and recurrent cases including those, which underwent primary and secondary in N.N. Burdenko National Medical Research Center for Neurosurgery. **CONCLUSION:** Specialized neurooncological biorepository is advantageous due to possibility of tumor tissue collection at different stages of the disease. The associated databank contains patients' data, tumor tissue data, treatment data, response to treatment, and follow-up data. Further development of the facility will provide collection of the larger spectrum of neurooncological entities, creation of tumor cell culture bank, and experimental therapies for the development of personalized neurooncological treatment.

P11.65 INSIGHTS INTO THE MECHANISMS OF PRIMARY BRAIN TUMOR INVASION

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We have made progress in unravelling the mechanisms of tumor cell invasion by focusing the attention on two molecular pathways including chemokines and extracellular matrix molecules. Chemokines are important mediators of cell signaling that operate both on normal cells and