clinical symptoms of Melanoma Brain Metastases (MBM) typically include headaches, seizures and other neurological deficits, suggesting that MBM disrupt normal brain functions. One of the major cell types that melanoma encounter and interact with during brain metastasis are astrocytes. Astrocytes, the most abundant cell in the brain, interact with neurons and the vasculature, provide trophic and energetic support to neurons, and regulate local blood flow. Metabolic pathways in astrocytes, particularly the glutamate-glutamine cycle, are essential for the recycling and resupply of neurotransmitters needed to maintain the excitation/inhibition balance. We propose that MBM co-opt astrocytic metabolism, fueling MBM growth, and deplete metabolic intermediates crucial for neuronal activity leading to altered neurologic function. We begin to unravel the metabolic interactions between astrocytes and MBM using novel modeling platforms with genetic and pharmacological tools to manipulate the tumor microenvironment. This project investigates the contribution of astrocytic metabolism to MBM growth. We intend on dissecting the distinct metabolic needs of metastatic brain melanoma in the CNS microenvironment and the subsequent neurological consequences. Completion of this project will provide a platform to study MBM and interaction with the local brain microenvironment. Inhibiting metabolic interactions between melanoma and glial cells may provide new avenue for therapeutic targeting of MBM.

FSMP-05. KETOGENIC DIETS FOR HIGH-GRADE GLIOMA

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BACKGROUND: Given therapeutic challenges posed by high-grade glioma (HGG), multiple concomitant therapies, including metabolic adjuncts to standard of care, are warranted. Tumor cells are almost exclusively energy-dependent on glucose. Preclinical data supports the use of ketogenic diets (KDs) in this population to deplete the tumor microenvironment of glucose, thereby exerting anti-tumor effects while the surrounding parenchymal tissue utilizes ketones. **OBJECTIVE:** The aim of this study was to conduct an up-to-date systematic review of the clinical use of ketogenic diets (KD) in the setting of high-grade glioma treatment and compare study designs, outcomes, and challenges in the translation of these methods from bench to bedside. **METHODS:** We conducted comprehensive searches of both the national clinical trials database (clinicaltrials.gov) and pubmed.gov. Trials were included in our review if they were conducted in a patient population with high-grade glioma (either early or refractory) and at least one study arm included the use of a KD. **RESULTS:** The clinicaltrials.gov search yielded 12 studies of which 11 met inclusion criteria. Five of these trials reported results. The PubMed search yielded 2 additional studies. Seven clinical trials with reported results on a total of 69 patients were considered. **CONCLUSIONS:** The use of KD has proven to be safe and tolerable in early trials, however, further studies are warranted to examine efficacy. Challenges to feasibility include low patient enrollment and compliance, as dietary changes were reported to negatively affect quality of life. Additionally, variability between animal and plant-based KDs, duration of KD regimen, carbohydrate: fat ratio, underlying genetic factors that affect the induction of ketosis, and use of steroid therapy in this patient population may all contribute to inconsistent clinical data when compared to preclinical studies. Future larger scale clinical trials and prospective studies are needed to clarify the role of KDs in the treatment of HGG.

FSMP-06. *IN VIVO* MONITORING OF LDHA EXPRESSION IN GLIOBLASTOMA USING QUANTITATIVE EXCHANGED-LABEL TURNOVER ^{1}H MRS TECHNIQUE

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Most cancers, including glioblastomas (GBMs), rely extensively on glycolysis to support growth, proliferation, and survival. A hallmark of this elevated glycolysis is overexpression of Lactate dehydrogenase-A (LDHA) protein leading to increased uptake of glucose and overproduction of lactate. Various clinical trials using LDHA as a target for diagnosis and treatment have yielded encouraging results. However, in vivo monitoring of LDHA expression has been challenging due to either requirement of administration of radioactive substrates or specialized hardware. In this presentation, we will demonstrate a new method-quantitative exchanged-label turnover MRS (QELT, or simply qMRS)-that increases the sensitivity of magnetic resonance-based metabolic mapping without the requirement for specialized hardware. qMRS relies on the administration of deuterated (^{2}H-labeled) substrates to track the production of downstream metabolites. Since ^{2}H is invisible on ^{1}H MRS, replacement of ^{1}H with ^{2}H due to metabolic turnover leads to an overall reduction in ^{1}H MRS signal for the corresponding metabolites. We applied our qMRS technique to monitor the rate of lactate production in a preclinical GBM model. Infusion of [6,6'-$^{2}H_2$]glucose led to downstream deuterium labeling of lactate, thereby resulting in a reduction in the 1.33 ppm lactate-CH_3 peak on ^{1}H MRS over time. The subtraction of post-administration ^{1}H MR spectra from the pre-infusion spectra aided in the determination of the kinetics of the lactate turnover. We believe that the detection and quantification of lactate production kinetics may provide crucial information regarding tumor LDHA expression non-invasively in GBMs without requiring biopsies. Hence, qMRS is expected to open up new opportunities to probe LDHA expression differences in a variety of gliomas, including GBMs and astrocytomas. This method takes advantage of the universal availability and ease of implementation of ^{1}H MRS on all clinical and preclinical magnetic resonance scanners.

FSMP-07. CYSTATHIONINE-Γ-LYASE DRIVES ANTIOXIDANT DEFENSE IN CYSTEINE-RESTRICTED IDH1 MUTANT ASTROCYTOMAS

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Mutations in isocitrate dehydrogenase 1 or 2 (*IDH1/2*) define glioma subtypes and are considered primary events in gliomagenesis, impacting tumor epigenetics and metabolism. IDH enzymes are crucial for the generation of reducing potential, yet the impact of the mutation on the cellular antioxidant system is not understood. Here, we investigate how glutathione (GSH) levels are maintained in IDH1 mutant gliomas, despite an altered NADPH/NADP balance. We find that IDH1 mutant astrocytomas specifically upregulate cystathionine γ-lyase (CSE), the enzyme responsible for cysteine production upstream of GSH biosynthesis. Genetic and chemical interference with CSE in patient-derived glioma cells carrying the endogenous IDH1 mutation, sensitized tumor cells to cysteine depletion, an effect not observed in IDH1 wild-type gliomas. This correlated with reduced GSH synthesis as shown by *in vitro* and *in vivo* serine tracing and led to delayed tumor growth in mice. Thus we show that IDH1 mutant astrocytic gliomas critically rely on NADPH-independent *de novo* GSH synthesis to maintain the antioxidant defense, which uncovers a novel metabolic vulnerability in this dismal disease.

FSMP-08. TARGETING PYRIMIDINE SYNTHESIS ACCENTUATES MOLECULAR THERAPY RESPONSE IN GLIOBLASTOMA STEM CELLS

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Glioblastoma stem cells (GSCs) reprogram glucose metabolism by hijacking high-affinity glucose uptake to survive in a nutritionally dynamic microenvironment. Here, we trace metabolic aberrations in GSCs to link core genetic mutations in glioblastoma to dependency on de novo pyrimidine synthesis. Targeting the pyrimidine synthetic rate-limiting step enzyme carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, dihydroorotase (CAD) or the critical downstream enzyme dihydroorotate dehydrogenase (DHODH) inhibited GSC survival, self-renewal, and in vivo tumor initiation through the depletion of the pyrimidine nucleotide supply in rodent models. Mutations in EGFR or PTEN generated distinct CAD phosphorylation patterns to activate carbon influx through pyrimidine synthesis. Simultaneous abrogation of tumor-specific driver mutations and DHODH activity with clinically approved inhibitors demonstrated sustained inhibition of metabolic activity of pyrimidine synthesis and GSC tumorigenic capacity in vitro. Higher expression of pyrimidine synthesis genes portends poor prognosis of patients with glioblastoma. Collectively, our results demonstrate a therapeutic approach of precision medicine through targeting the nexus between driver mutations and metabolic reprogramming in cancer stem cells.