DDRE-30. THERAPEUTIC TARGETING OF DISRUPTED METABOLIC STATE IN DIFFUSE INTRINSIC PONTINE GLIOMA
Nienke Miba1, Amy Myers1, Chan Chung1, Joyce Thompson1, Muthuvarapu Shan1, Yow-Hong Kong1, Karl Koschmann1, Sriram Venkatesh1, Costas Lyssiotis1, 2University of Michigan, Department of Molecular & Integrative Physiology, Ann Arbor, MI, USA, 3University of Michigan, Department of Pathology, Ann Arbor, MI, USA, 4University of Michigan, Department of Surgery, Ann Arbor, MI, USA, 5University of Michigan, Immunology Program, Ann Arbor, MI, USA, 6University of Michigan, Department of Pediatrics, Ann Arbor, MI, USA

BACKGROUND: Diffuse Intrinsic Pontine Glioma (DIPG) is a uniformly fatal pediatric brainstem tumor and the leading cause of brain-tumor related deaths in children. It is therefore imperative to identify novel treatment strategies for this aggressive and devastating disease. Metabolic reprogramming in tumors and in the tumor microenvironment contribute to evasion of therapy and tumor recurrence. The goal of this study was to identify and therapeutically target metabolic vulnerabilities in DIPG that mediate aggressiveness and treatment resistance. METHODS: DIPG tumors are marked by cellular heterogeneity and are driven by a population of cells with stem cell properties. We took a comprehensive metabolomics and transcriptomic screening approach to determine the operative pathways in the tumor driving stem cell compartment. To demonstrate efficacy and potential therapeutic window of activity, we treated DIPG tumors with clinically available and brain-penetrant inhibitors of the identified dysregulated metabolic pathways. RESULTS: Our multi-omics analyses revealed that tumorigenic patient-derived DIPG cells significantly upregulate metabolic programs including cholesterol biosynthesis and mitochondrial oxidative phosphorylation (OXPHOS) compared to DIPG cells. IDH1 mutant tumors induced a unique metabolic profile, characterized by decreased pyrimidine metabolism and mitochondrial oxidative phosphorylation (OXPHOS). The therapeutic targeting of DIPG tumors with clinically available and brain penetrant inhibitors of OXPHOS and cholesterol biosynthesis resulted in tumor cell killing and growth inhibition both in vitro and in vivo. Moreover, there was a therapeutic window of activity in tumorigenic DIPG cells compared with differentiated gliomas and non-malignant cells. CONCLUSION: Our findings demonstrate that DIPG harbors perturbations in metabolic programs that can be exploited for therapeutic benefits. The results from this study defined the metabolic pathways operative in the tumor-driving population in DIPG and demonstrated efficacy of targeting these pathways.

DDRE-31. FEASIBILITY AND BIOLOGIC ACTIVITY OF A KETOGENIC / INTERMITTENT FASTING DIET IN GLIOMA PATIENTS
Karina Schreck1, Fang-Chi Hsu2, Adam Berrington1, Bobbie Henry-Barron1, Diane Vithani1, Lindsay Blom1, Eric Kossoff1, Linda Easter2, Christopher Whittlow1, Mackenzie Cervenka1, Peter Barker1, Jashri Blakeley1, Roy Strowd1, 1Johns Hopkins University School of Medicine, Baltimore, MD, USA, 2Wake Forest School of Medicine, Winston-Salem, NC, USA, 3St. Peter Mansfield Imaging Centre, School of Physics and Astronomy, University of Nottingham, Nottingham, United Kingdom

BACKGROUND: There has been increasing interest in exploring ketogenic diet therapies (KDT) in patients with glioma given the poor prognosis. The purpose of this single-arm, open label phase 2 study was to rigorously examine the feasibility, safety, systemic biological activity, and cerebral activity of a KDT in patients with glioma. METHODS: 25 patients with biopsy-confirmed WHO Grade 2-4 astrocitoma with stable disease following adjuvant chemotherapy were enrolled in an 8-week GLioma Atkins-based Diet (GLAD). GLAD consisted of 2 fasting days (calories<20% calculated estimated needs) interleaved between 5 modified Atkins diet days (net carbohydrates<20 g/day) each week. The primary outcome was dietary adherence by food record. Markers of systemic and cerebral activity included weekly urine ketones, serum insulin, glucose, hemoglobin A1C, IGF-1, and MR spectroscopy at baseline and week 8. RESULTS: 21 patients completed the study. 80% of patients reached ≥40 mg/dL urine acetocacetate during the study. 48% of patients were adherent by food record. The diet was well-tolerated with two grade 3 adverse events (neuropathy, seizure). Markers of systemic activity indicated decreasing hemoglobin A1C, insulin, and fat mass decreased significantly, while lean body mass increased. MR spectroscopy demonstrated increased ketone concentrations (β-hydroxybutyrate (BHB) and acetoacetone (Acetone)) in both lesional and contralateral brain, compared to baseline. Higher total cholesterol and glucose were observed in lesional as compared to contralateral brain at baseline, and both decreased following intervention. Average ketonuria correlated with cerebral ketones in lesional (tumor) and contralateral brain (BHB R<0.52, p=0.05). There were no differences in cerebral metabolites in IDH-mutant glioma patients after controlling for ketonuria. CONCLUSIONS: The GLAD dietary intervention, while demanding, produced meaningful ketonuria, and significant systemic and cerebral metabolic changes in participants. Participant ketonuria correlated with cerebral ketones and may be a better indicator of systemic activity than patient-reported food records.

DDRE-32. THERAPEUTIC TARGETING OF A NOVEL METABOLIC ADDICTION IN DIFFUSE MIDSILINE GLIOMA
Sharmistha Pal1, Jakub P. Kaplan1, Sylwia A. Stopka2, Michael S Regan2, Bradley R. Hunsel1, Benjamin H. Kann1,2, Nathalie Y. R. Agar2,3, Charles D. Stiles1, Tabitha M. Cooney1,4, Sabine Mueller2,3, Djupan Chowdhury1, William L. Everett1,5, Sumed K. McBrayer1, and Daphne Haas-Kogan1,6, 1Dana Farber Cancer Institute, Boston, MA, USA, 2Brigham and Women’s Hospital, Boston, MA, USA, 3Harvard Medical School, Boston, MA, USA, 4Boston Children’s Hospital, Boston, MA, USA, 5University of California, San Francisco, CA, USA, 6UT Southwestern, Dallas, TX, USA

Diffuse midsiline glioma (DMG) is a uniformly fatal pediatric cancer that is in need of urgent “outside the box” therapeutic approaches. Recent studies show that tumors cells adapt to stresses created by oncogenic mutations and these oncogene-induced adaptations create vulnerabilities that can be exploited to therapeutic ends. To uncover these oncogene-induced vulnerabilities in DMGs we conducted a genome-wide CRISPR knock out screen in three DMG lines. The top common DMG dependency pathway that we discovered is de novo pyrimidine biosynthesis. Under normal conditions pyrimidine nucleotide needs are met through the salvage pathway. However, in DMG tumorigenesis, pyrimidine nucleotide synthesis is required such that the cells become dependent on the de novo pyrimidine biosynthesis pathway. De novo pyrimidine synthesis is catalyzed by CAD, DHODH and UMPs; all three genes are identified as dependencies in our screen and have been validated using shRNA mediated gene knockdown. Interestingly, DMG cells did not exhibit a dependency on the de novo purine biosynthesis pathway. Using a small molecule inhibitor of DHODH, BAY2402234 (currently studied in phase I trial for myeloid malignancies (NCT03404726)), we have demonstrated and validated, (i) efficacy and specificity of de novo pyrimidine synthesis inhibition in vitro in DMG cells; (ii) de novo pyrimidine addiction is not attributable to cell proliferation; (iii) DHODH inhibition induces apoptosis by hindering replication and inciting DNA damage; (iv) DHODH and ATR inhibition act synergistically to induce DMG cell death; and (v) critical in vivo efficacy. The in vivo experimental data showing that BAY2402234 crosses the blood-brain barrier, is present in the brain at therapeutically relevant concentrations, suppresses de novo pyrimidine biosynthesis in intracranial DMG tumors in mice, and prolongs survival of recurrent DMG tumor bearing mice. Taken together, our studies have identified a novel metabolic vulnerability that can be translated for the treatment of DMG patients.

DDRE-33. MELATONIN AS A MASTER METABOLIC SWITCH FOR GLOBLASTOMA
Beatriz Irene Fernandez-Gall1, Carla Vazquez-Ramos1, Alexandra Bechtle1, Paola Suarez-Meade1, Neda Qosa1, Paula Schiapparelli2, Raquel Barahona-Estrada1, Genoveva Escache1, Alfredo Quinones-Hinojosa1, 1Mayo Clinic, Jacksonville, FL, USA, 2Biomedical Research Center (IBM), University of Granada, Granada, Granada, Spain

Glioblastoma (GBM) is the most common form of malignant primary brain cancer in adults with a median survival of only 15 months. Therefore, new therapies to suppress malignant brain cancer are needed. Brain Tumor Initiating Cells (BTICs) are a GBM subpopulation of cells with a highly
glycolytic profile that are thought to be responsible of the resistance of GBM to treatments. Metabolic reprogramming allows tumor cells to survive in unsupportive microenvironments. Manipulating tumor metabolism to counteract GBM resistance arises as a powerful approach with minimum effects in normal counterparts. At pharmacological concentrations, melatonin displays oncostatic properties. This is thought to be due to an increase in mitochondrial oxidative phosphorylation through the effects of melatonin in mitochondrial electron organellar fatty acids, which inhibit the proton gradient and thus the formation of ROS (reactive oxygen species). Additionally, these systems are under strong selective pressure divergent in tumors, and even in the absence of metabolic defects, cancer cells can become auxotrophic for particular nutrients or metabolic byproducts generated by other cells in the tumor microenvironment (TME). Conventional cell culture systems do not recapitulate the metabolic heterogeneity of glioblastoma (GBM), while primary cultured cells do not account for the influences of the microenvironment and the blood brain barrier on tumor biology. Additionally, these systems are under strong selective pressure divergent from that in vivo, leading to reduced heterogeneity between cultured tumor cells. Here, we describe a biofilm of direct-from-patient derived orthotopic xenografts (GliomaPDX) and gliomaspheres that reveal a subset of gliomas that, while able to form in vivo, cannot survive in vitro. RNA sequencing of tumors that can form both in vivo and in vitro (termed “TME-Indifferent”) compared to that of tumors that can only form in vivo (termed “TME-Dependent”) revealed transcriptional changes associated with altered nutrient availability, emphasizing the unique metabolic programs impacted by the tumor microenvironment. Furthermore, TME-dependent tumors lack metabolic signatures associated with nutrient biosynthesis, thus indicating a potential dependency of these tumors on scavenging specific nutrients from the extracellular milieu. Collectively, these data support the notion that brain-microenvironment specific metabolic dependencies that can be targeted for therapy.

ETMM-05. CANCER CELLS DEPLOY LIPOCALIN-2 TO COLLECT LIMITING IRON IN LEPTOMENIGEAL METASTASIS
Yudan Chi1, Jan Remski2, Vaidotas Kiselovas3, Camille Derderian1, Ugur Sener1, Majdi Alghader2, Fadi Saadell3, Kate Nikishina1, Teus Bale1, Christin Jacobzou-Donuhue1, Tiffany Thomas1, Dana Peet4, Linas Mazutis5, Adrienne Bourre61, MSKCC, New York, NY, USA, 2CUNY, New York, NY, USA, 3Columbia University, New York, NY, USA

The tumor microenvironment plays a critical regulatory role in cancer progression, especially in central nervous system metastases. Cancer cells within the cerebrospinal fluid (CSF)-filled leptomeninges face substantial microenvironmental challenges including inflammation and spatial micro-nutrients. To investigate the mechanism by which cancer cells in these leptomeningeal metastases (LM) overcome these constraints, we subjected CSF from five patients with LM to single-cell RNA sequencing. We found that cancer cells, but not macrophages within the CSF express the protein lipocalin-2 (LCN2) and its receptor SCL2A17. These macrophages generate inflammatory cytokines that induce cancer cell LCN2 expression but do not generate LCN2 themselves. In mouse models of LM, cancer cell LCN2 expression was supported by the LCN2/SCL2A17 axis and is inhibited by iron chelation therapy. A Phase 1a/1b clinical trial focused on this novel treatment approach is underway.