cover such vulnerabilities, we conducted a chemical synthetic lethality screen using isogenic *IDH1* mutant and *IDH1* wild-type (WT) glioma cell lines and a novel metabolic inhibitor screening platform. We discovered that *IDH1* mutant cells are hypersensitive to drugs targeting enzymes in the de novo pyrimidine nucleotide synthesis pathway, including dihydroorotate dehydrogenase (DHODH). This vulnerability is specific because inhibitors of purine nucleotide metabolism did not score in our screen. We validated that the cytotoxicity of pyrimidine synthesis inhibitors is on-target and showed that *IDH1* mutant patient-derived glioma stem-like cell lines are also hyperdependent on de novo pyrimidine nucleotide synthesis compared to *IDH1* WT lines. To test pyrimidine synthesis dependence of *IDH1* mutant gliomas in vivo, we used a brain-penetrent DHODH inhibitor currently undergoing evaluation in leukemia patients, BAY 2402234. We found that BAY 2402234 displays monotherapy activity against gliomas in an orthotopic xenograft model of *IDH1* mutant glioma, with an effect size that compared favorably with radiotherapy. We also developed novel genetically engineered and allograft mouse models of mutant IDH1-driven anaplastic astrocytoma and showed that BAY 2402234 blocked growth of orthotopic astrocytoma allografts. Our findings bolster rationale to target DHODH in glioma, highlight BAY 2402234 as a clinical-stage drug that can be used to inhibit DHODH in brain tumors, and establish *IDH1* mutations as predictive biomarkers of DHODH inhibitor efficacy.

DDRE-30. THERAPEUTIC TARGETING OF DISRUPTED METABOLIC STATE IN DIFFUSE INTRINSIC PONTINE GLIOMA

Nneka Mbah[1], Amy Myers[1], Chan Chung[2], Joyce Thompson[3], Mengrou Shan[1], Hanna Hong[4], Carl Koschmann[5], Sriram Venneti[2], Costas Lyssiotis[1]; [1]University of Michigan, Department of Molecular & Integrative Physiology, Ann Arbor, MI, USA, [2]University of Michigan, Department of Pathology, Ann Arbor, MI, USA, [3]Univesity of Michigan, Department of Surgery, Ann Arbor, MI, USA, [4]University of Michigan, Immunology Program, Ann Arbor, MI, USA, [5]University 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 that were induced to undergo differentiation (events associated with a loss of tumorigenic capabilities). 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 harbor 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

Karisa Schreck[1], Fang-Chi Hsu[2], Adam Berrington[3], Bobbie Henry-Barron[1], Diane Vizthum[1], Lindsay Blair[1], Eric Kossoff[1], Linda Easter[2], Christopher Whitlow[2], Mackenzie Cervenka[1], Peter Barker[1], Jaishri Blakeley[1], Roy Strowd[1]; [1]Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]Wake Forest School of Medicine, Winston-Salem, NC, USA, [3]Sir 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 astrocytoma 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 gm/day) each week. The primary outcome was dietary adherence by food records. 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 acetoacetate during the study. 48% of patients were adherent by food record. The diet was well-tolerated with two grade 3 adverse events (neutropenia, seizure). Measures of systemic activity including hemoglobin A1c, insulin, and fat body mass decreased significantly, while lean body mass increased. MR spectroscopy demonstrated increased ketone concentrations (β-hydroxybutyrate (bHB) and acetone (Ace)) in both lesional and contralateral brain, compared to baseline. Higher total choline (tCho) and glutamine (Gln) levels 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 Rs0.52, p=0.05). There were no differences in cerebral metabolites in IDH-mutant glioma 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 ketone concentration and appears to be a better indicator of systemic activity than patient-reported food records.

DDRE-32. THERAPEUTIC TARGETING OF A NOVEL METABOLIC ADDICTION IN DIFFUSE MIDLINE GLIOMA

Sharmistha Pal[1], Jakub P. Kaplan[1], Sylwia A. Stopka[2], Michael S Regan[2], Bradley R. Hunsel[1], Benjamin H. Kann[1,2], Nathalie Y. R. Agar[2,3], Charles D. Stiles[1], Tabitha M. Cooney[1,4], Sabine Mueller[5], Dipanjan Chowdhury[1,3], William G. Kaelin Jr.[1], Samuel K. McBrayer[6], Daphne Haas-Kogan[1,2]; [1]Dana Farber Cancer Institute, Boston, MA, USA, [2]Brigham and Women's Hospital, Boston, MA, USA, [3]Harvard Medical School, Boston, MA, USA, [4]Boston Children's Hospital, Boston, MA, USA, [5]University of California, San Francisco, CA, USA, [6]UT Southwestern, Dallas, TX, USA

Diffuse midline glioma (DMG) is a uniformly fatal pediatric cancer that is in need of urgent "outside the box" therapeutic approaches. Recent studies show that tumor 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 CRIPSR knockout 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 rewired such that the cells become dependent on the *de novo* 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* experiment documents 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 orthotopic 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 GLIOBLASTOMA

Beatriz Irene Fernandez-Gil[1], Carla Vazquez-Ramos[1], Alexandra Bechtle[1], Paola Suarez-Meade[1], Neda Qosja[1], Paula Schiapparelli[1], Rachel Sarabia-Estrada[1], Germaine Escames[2], Alfredo Quinones-Hinojosa[1]; [1]Mayo Clinic, Jacksonville, FL, USA, [2]Biomedical Research Center (CIBM). 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