(HER2+) breast cancer, and the unique brain microenvironment contributes to this therapy resistance. Nutrient availability can vary across tissues, therefore metabolic adaptations required for breast cancer growth in the brain microenvironment may also introduce liabilities that can be exploited for therapy. Here, we assessed how metabolism differs between breast tumors growing in the brain versus extracranial sites and found that fatty acid synthesis is elevated in breast tumors growing in the brain. We determine that this phenotype is an adaptation to decreased lipid availability in the brain relative to other tissues, which results in a site-specific dependency on fatty acid synthesis for breast tumors growing at this site. Genetic or pharmacological inhibition of fatty acid synthase (FASN) reduces HER2+ breast tumor growth in the brain, demonstrating that differences in nutrient availability across metastatic sites can result in targetable metabolic dependencies.

DDRE-08. NRF2/GLUTATHIONE METABOLISM AS A NOVEL THERAPEUTIC TARGET FOR IDH1-MUTATED GLIOMA

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BACKGROUND: *IDH1*-mutated glioma is a recently defined disease entity with distinctive patterns of tumor cell biology, metabolism, and resistance to therapy. Although *IDH1* mutations are highly prevalent in patients with WHO II/III glioma, curative molecular targeting approaches remain unavailable for this disease cluster. **METHODS:** In the present study, we investigated the glutathione *de novo* synthesis pathway through the TCGA patient cohort and patient-derived cell lines with *IDH1* mutation. The biologic function of nuclear factor erythroid 2-related factor 2 (NRF2) was analyzed by biochemistry and cell biology assays. Finally, NRF2 inhibitors were evaluated in *IDH1*-mutated cell lines and preclinical models as an experimental therapy. **RESULTS:** *IDH1* mutant neomorphic activity depletes the cellular pools of enzyme cofactors such as nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). The limitation of NAD(P) not only affects the anabolic reactions, but also results in oxidative stress and damages on DNA and protein. Further, we showed that the reprogrammed redox landscape results in constitutive activation of NRF2-governed cytoprotective pathways through the decoupling of NRF2 from its E3 ligase Kelch-like ECH-associated protein 1. NRF2 mediated the transcriptional activation of *GCLC*, *GCLM*, and *SLC7A11*, which not only strengthens the glutathione *de novo* synthesis, but also relieves the metabolic burden in *IDH1*-mutated cells. The importance of the glutathione synthesis is further confirmed through COX regression analysis on lower-grade glioma. Blockade of the NRF2/glutathione metabolic pathway synergizes with the elevated intrinsic oxidative stress, which results in overwhelming oxidative damage, as well as a substantial reduction in tumor cell proliferation and xenograft expansion. **CONCLUSION:** We report that the NRF2-guided cytoprotective pathways play pivotal roles in the disease progression of *IDH1*-mutated glioma. Targeting NRF2 and glutathione metabolism could be novel targeting strategies for *IDH1*-mutated glioma.

DDRE-09. THERAPEUTIC TARGETING OF PURINE METABOLISM IN DIPG

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Diffuse intrinsic pontine glioma (DIPG) is an incurable brainstem malignancy in children with median survival less than 1 year and 5-year overall survival only 2 percent. Little progress has been made in treating this deadly disease due to its inoperable location and treatments aimed at targets defined in adult gliomas. Despite recent advances in genetic characterization of DIPGs there are still no targeted therapies that significantly improve overall survival. We recently generated a metabolic profile for patient-derived DIPG cell lines by integrating an untargeted metabolomics analysis with RNA-sequencing data from the same lines which demonstrated dysregulated purine metabolism in these cells. Furthermore, we have identified putative driver mutations common to DIPG patients as the direct cause for this metabolic alteration. Purine metabolism provides the basic components of nucleotides needed for tumor proliferation and thus considered a high-priority target in cancer treatment. De novo purine biosynthesis (DNPS) is a sequential ten step enzymatic process resulting in the production of inosine monophosphate. The DNPS enzymes co-localize into a metabolon known as the purinosome and our preliminary data demonstrates DIPG cell lines are selectively sensitive to pharmacological and genetic disruption of purinosome formation. Interestingly, antifolate compounds that inhibit DNPS, but do not disrupt purinosome assembly, are cytotoxic to both DIPG cells and normal cell types. Strikingly, cell viability could be rescued by purine supplementation when inhibiting this pathway with antifolates, however inhibition of DNPS by disruption of purinosome assembly could not be rescued. Metabolomics analysis showed DIPGs have a preference for generating GMP over AMP which is exacerbated when purinosome assembly is disrupted. This is likely due to the duel-role of the DNPS enzyme ADSL which is required for AMP production.

DDRE-10. METABOLIC TARGETING OF HUMAN GLIOBLASTOMA USING 5-AMINOLEVULINIC ACID (ALA)-MEDIATED SONODYNAMIC THERAPY: A FIRST-IN-HUMAN STUDY.

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Heme biosynthesis is altered in glioblastoma (GBM). Systemic dosing with ALA, the first committed molecule in the heme pathway, results in accumulation of the fluorescent intermediate, protoporphyrin IX (PpIX) only within tumor tissue (Gleolan label, 2019). PpIX is a photosensitizer that is effective in photodynamic therapy (PDT); in recurrent GBM patients, the safety and feasibility of ALA PDT has been demonstrated (Johansson A, et al. Lasers Surg Med 2013;45:225), although the practicality of this strategy in clinical care remains uncertain. Importantly, preclinical models of GBM show that PpIX is also a sonosensitizer and, in combination with transcranial MRI-guided focused ultrasound (MRgFUS), leads to non-ablative cytotoxic effects *in vivo* (Jeong EJ et al, Ultrasound in Medicine and Biology 2013:38;2143, Suehiro S et al, J Neurosurg 2018: 1377, Wu et al Nature Sci Reports 2019: 9;10465). The Ivy Brain Tumor Center is conducting a first-in-human study of 5-ALA sonodynamic therapy (SDT) for recurrent GBM (NCT 04559685). In this Phase 0/1 clinical trial, nontherapeutic, single-treatment SDT is administered prior to planned tumor resection. A Dose-Escalation Arm varies the power/energy of the MRgFUS while using a fixed time-interval from exposure to surgery. A subsequent Time-Escalation Arm varies the interval between MRgFUS and surgical resection, but fixes the power/energy of the delivered ultrasound. In both Arms, patient tumor tissue is assessed for sonodynamic and pharmacodynamic effects. In each patient, half of the tumor volume is not targeted with SDT and serves as an internal control. This first-in-human study will demonstrate the safety and feasibility of ALA sonodynamic therapy in GBM and may provide the first-ever biological evidence of sonosensitization in a brain tumor patient. If successful, this Phase 0 trial will introduce a new, metabolically-driven, GBM treatment modality that may be applicable to any brain tumor that selectively accumulates PpIX after ALA administration.

DDRE-11. TARGETING FATTY ACID BIOSYNTHESIS IN GLIOBLASTOMA

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We recently provided evidence that endoplasmic reticulum (ER) stress promotes fatty acid (FA) biosynthesis in glioblastoma (GBM) cancer stem cells (GSCs). We determined that Stearoyl CoA Desaturase 1 (SCD), a key FA desaturase, is essential for regulating ER homeostasis in GSCs, and showed that these cells are highly susceptible to pharmacological perturbation of SCD activity. An impaired SCD activity leads to the toxic accumulation of saturated FA and activates cell death signaling mediated by the ER sensor Inositol-requiring enzyme 1 (IRE1). This in turn promotes an IRE1-mediated mRNA decay of key DNA damage repair genes and impairs the ability of GSCs to repair DNA damage caused by radiation or chemotherapy. Consequently, combining SCD inhibition with temozolomide (TMZ) leads to major cytotoxicity both in TMZ-sensitive, and TMZ-resistant patient-derived GBM cells. Pharmacological inhibition of SCD delivered through the nasal route in mice, had a remarkable therapeutic benefit in patient-derived orthotopic GSCs mouse models, yet the modest brain permeability of the currently available SCD inhibitors precludes their clinical translation. To overcome this challenge, we have recently acquired a first-in-class, clinically relevant SCD inhibitor. This compound has undergone extensive pharmacokinetic and pharmacodynamic studies which confirmed brain permeability, efficacy, and safety in small animals and non-human primates. We show that the combination of this SCD inhibitor with TMZ is effective both in cultured GSCs, and in preclinical GSCs orthotopic mouse models. Our results support the clinical investigation of this new class of SCD inhibitors, in combination with TMZ, in patients diagnosed with GBM.

DDRE-12. HETEROGENOUS RESPONSE OF IDH-MUTANT AND IDH-WT GLIOMA TO NAMPT INHIBITION

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BACKGROUND: NAD+ is required for cell metabolism and DNA repair. It is generated from nicotinic acid (NA) by NAPRT and from Nicotinamide