wildtype), and 8 oligodendrogliomas (IDH mutated). The concentrations of glutamine and glycine were both significantly higher in enhancing tumors than in non-enhancing tumors (p=0.001 and 0.0001, respectively). The concentrations of glutamine and glycine were both positively correlated with MIB-1 (p=4E-5 and 1E-7, respectively). The sum of glutamine and glycine levels showed stronger association with MIB-1 (p=5E-10, r=0.89). In the Kaplan-Meier overall survival analysis, the survival was significantly shorter in patients with glutamine levels higher than 4.1 mM than those with concentrations less than 4.1 mM (p=0.02). For glycine, the patients with higher than 2.4 mM showed association with poor survival (p=0.03). The sum of glutamine and glycine levels showed stronger association with overall survival (p=0.008, cutoff 8.5mM). 2HG level greater than 0.5 mM was associated with long survival (p=0.01). We tested metabolic ratios to 2HG, in which 2HG estimates less than 1 mM were put as 1 mM (avoiding infinite ratios arising from null 2HG cases). The glutamine/2HG, glycine/2HG, and (glutamine+glycine)/2HG showed strong association with overall survival (p=2E-4, 2E-5 and 4.5E-7, respectively). Our data suggest that increased metabolism of glutamine and glycine is closely associated with rapid cell proliferation and poor survival, suggesting the metabolites are imaging biomarkers of glioma aggressiveness.

BIMG-10. IDH1 MUTATIONS INDUCE ORGANELLE DEFECTS VIA DYSREGULATED PHOSPHOLIPIDS

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BACKGROUND: Metabolic alterations of lipids have been identified as a hallmark of neoplasms, with the most prevalent being the balance between saturated fatty acid (SFA) and monosaturated fatty acid (MUFA). Stearoyl-CoA desaturase1 (SCD1), converting SFA to MUFA, is increased in many cancers, leading to worse prognosis. In glioma, the role of SCD1 remains unknown. Isocitrate dehydrogenase (IDH) mutations have been most commonly observed in glioma, but the involvement of mutant IDH in SCD1 expression also remains unknown. **METHODS:** We conducted metabolic analysis to examine the alteration of SCD1 expression in genetically engineered glioma cell lines and normal human astrocyte (NHA). Lipid metabolic analysis was conducted by using LC-MS, Raman Imaging Microscopy and SCD1 expression was examined by Western-blotting and RT-PCR method. Electron microscopy was employed for organelle structure and genetic knock-down of SCD1 gene was performed. **RESULT:** Herein, we uncovered increased MUFA and their phospholipids in Endoplasmic Reticulum (ER), generated by IDH1 mutation, that were responsible for Golgi and ER dilation. RNA seq data from The Cancer Genome Atlas, showed that SCD1 expression was significantly higher in IDH mutant gliomas compared with wild-type, and high SCD1 expression was associated with longer survival. Inhibition of IDH1 mutation or SCD1 silencing restored ER and Golgi morphology, while D-2HG and oleic acid induced morphological defects in these organelles. Moreover, addition of oleic acid, which tilts the balance towards elevated levels of MUFA, produced IDH1 mutant-specific cellular apoptosis. **CONCLUSION:** Collectively, our results suggest that IDH1 mutant-induced SCD overexpression can rearrange the distribution of lipids in the organelles of glioma cells, providing a new insight on the link between lipids metabolism and organelle morphology in these cells, with potential and unique therapeutic implications. The results of the present study may also provide novel insights into the discovery of metabolic biomarkers for IDH mutant gliomas.

BIMG-11. PHARMACODYNAMIC EVALUATION OF IDH AND EGFR INHIBITION IN HUMAN GLIOMAS USING MOLECULAR MRI

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Metabolic differences are inherent to specific glioma subtypes and can be altered using targeted treatments, including IDH and EGFR inhibition. Using a large cohort of patients scanned at UCLA and other centers over the last 5 years, we demonstrate that IDH, 1p19q, and EGFR alterations uniquely contribute to alterations in glycolysis and oxygen utilization using a clinically available molecular MRI technique termed amine chemical exchange saturation transfer spin-and-gradient-echo echoplanar imaging (CEST-SAGE-EPI). Our data shows that CEST-SAGE-EPI estimates of tumor acidity are strongly associated with the degree of glycolysis as evaluated with direct pH measurements, quantitative IHC, bioenergetics experiments, and correlations with 18F-FDG PET images. Data further reveals that IDH wild type gliomas have higher acidity and oxygen utilization compared with IDH mutant gliomas, 1p19q non-codeleted gliomas (astrocytomas) have higher tumor acidity compared to 1p19q codeleted gliomas (oligodendrogliomas), and EGFR amplified gliomas have higher oxygen utilization compared with non-amplified gliomas. Additionally, phase II clinical trial data suggests successful IDH inhibition results in an early and measurable increase in tumor acidity and further reduction in oxygen utilization, signifying suppression of oxidative phosphorylation and/or glutaminolysis in favor of glycolysis. Alternatively, phase II clinical trial data suggests successful EGFR inhibition with brain penetrant agents results in early reductions in tumor acidity and 18F-FDG PET uptake, consistent with a reduction in glycolysis. Data also indicates that continual increases in tumor acidity during routine follow-up after initial therapeutic changes results in uniformly worse outcomes in all tumor subtypes under all mentioned treatment scenarios.

BIMG-12. [18F]FLUCICLOVINE PET TO DISTINGUISH PSEUDOPROGRESSION FROM TUMOR PROGRESSION IN POST-TREATMENT GLIOBLASTOMA

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PURPOSE: Differentiation of true tumor progression from pseudoprogression (PsP) is a major unmet need in patients with glioblastoma (GBM). [^{18}F]Fluciclovine is a synthetic amino acid PET radiotracer that is FDA approved in the setting of biochemical recurrence in prostate cancer. The aim of this study was to assess the value of [^{18}F]Fluciclovine PET in differentiation of true tumor progression and PsP in post-treatment of glioblastoma. **METHODS:** 15 patients with GBM with new contrast-enhancing lesions or lesions showing increased enhancement (>25% increase) on standard MRI after completion of radiation underwent 60-minutes dynamic [^{18}F]Fluciclovine PET imaging. Patients subsequently (within 1 week) underwent resection of the enhancing lesion and the tumor percentage vs treatment-related changes were quantified on histopathology. Patients were considered true tumor progression if tumor represented ≥ 50% of the resected specimen and considered PsP if treatment-related changes represented ≥70% of the resected specimen. Summed 30- to 40-minute post-injection PET images were used to measure SUV_{peak}, SUV_{max}, and 50% threshold SUV_{mean}. **RESULTS:** 10 patients with true tumor progression and 5 patients with PsP were included. Patients who demonstrated true tumor progression had significantly higher SUV_{peak} compared to patients with PsP (5.3±1.4 vs 3.1± 0.9, p=0.002, AUC=0.92, p<0.0001). SUV_{peak} cut-off of 3.5 provided 100% sensitivity, 80% specificity and 93% accuracy for differentiation of true tumor progression from PsP. There was a moderate to strong correlation between SUV_{peak} and tumor percentage on histopathology (Rho= 0.68, p=0.004). Alternative SUV measures had similar performance. **DISCUSSION:** Our preliminary results indicated that [^{18}F]Fluciclovine PET imaging can accurately differentiate true tumor progression from PsP. Further studies are required to confirm these promising early results and determine the optimal criteria for interpreting [^{18}F]Fluciclovine PET to distinguish PsP from true tumor progression.

BIMG-13. A NOVEL RADIOPHARMACEUTICAL ([^{18}F]DASA-23) TO MONITOR PYRUVATE KINASE M2 INDUCED GLYCOLYTIC REPROGRAMMING IN GLIOBLASTOMA

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BACKGROUND: Pyruvate kinase M2 (PKM2) catalyzes the final step in glycolysis, a key process of cancer metabolism. PKM2 is preferentially expressed by glioblastoma (GBM) cells with minimal expression in healthy brain, making it an important biomarker of cancer glycolytic re-programming. We describe the bench-to-bedside development, validation, and translation of a novel positron emission tomography (PET) tracer to study PKM2 in GBM. Specifically, we evaluated 1-((2-fluoro-6-[^{18}F]fluorophenyl)sulfonyl)-4-((4-methoxyphenyl)sulfonyl)piperazine ([^{18}F]DASA-23) in cell culture, mouse models of GBM, healthy human volunteers, and GBM patients. **METHODS:** [^{18}F]DASA-23 was synthesized with a molar activity of 100.47 ± 29.58 GBq/μmol and radiochemical purity >95%. We performed initial testing of [^{18}F]DASA-23 in GBM cell culture and human GBM xenografts implanted orthotopically into mice. Next we produced [^{18}F]DASA-23 under current Good Manufacturing Practices United States Food and Drug Administration (FDA) oversight, and evaluated it in healthy volunteers and a pilot cohort of patients with gliomas. **RESULTS:** In mouse imaging studies, [^{18}F]DASA-23 clearly delineated the U87 GBM from the surrounding healthy brain tissue and had a tumor-to-brain ratio (TBR) of 3.6 ± 0.5. In human volunteers, [^{18}F]DASA-23 crossed the intact blood-brain barrier and was rapidly cleared. In GBM patients, [^{18}F]DASA-23 successfully

outlined tumors visible on contrast-enhanced magnetic resonance imaging (MRI). The uptake of [^{18}F]DASA-23 was markedly elevated in GBMs compared to normal brain, and it was able to identify a metabolic non-responder within 1-week of treatment initiation. **CONCLUSION:** We developed and translated [^{18}F]DASA-23 as a promising new tracer that demonstrated the visualization of aberrantly expressed PKM2 for the first time in human subjects. These encouraging results warrant further clinical evaluation of [^{18}F]DASA-23 to assess its utility for imaging therapy-induced normalization of aberrant cancer metabolism.

BIMG-14. IDENTIFICATION OF IDH MUTATION STATUS USING PROTON MR SPECTROSCOPY AND MASS SPECTROMETRY: A STUDY OF 178 GLIOMAS

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IDH mutation, a key factor in predicting glioma prognosis, alters the levels of some metabolites in brain, including 2-hydroxyglutarate (2HG), glutamine (Gln), and glutathione (GSH). While proton MR spectroscopy (^{1}H-MRS) enables in-vivo detection of these metabolites, liquid chromatography-mass spectrometry (LC-MS/MS) is a sensitive in-vitro method to measure absolute metabolite concentrations. This study aims to examine the correlation of metabolic concentrations measured using ^{1}H-MRS and LC-MS/MS in gliomas, and to detect IDH mutation with machine learning based on ^{1}H-MRS and LC-MS/MS metabolic intensities. The patient cohort included 178 glioma patients (111M/67F, mean age:44.09±13.95 years, 100 IDH-mut, 78 IDH-wt). The patients were scanned pre-surgery by a 3T MR scanner with a 32-channel head coil. ^{1}H-MRS was obtained from a manually placed region of interest with no necrosis, edema, and hemorrhage, using a Point Resolved Spectroscopy (PRESS) sequence (TR/TE=2000/30ms). LCModel software was used for quantification of eighteen metabolites of ^{1}H-MRS data. Metabolite concentrations including creatine (Cr), choline (Cho), Gln, glutamate (Glu), gamma-aminobutyric acid (GABA), N-acetyl aspartate (NAA), myo-inositol (mIns), 2HG, and lactate (Lac) were also determined with LC-MS/MS for surgical specimen of the same patients. Spearman correlation coefficients were calculated between the metabolite concentrations measured with ^{1}H-MRS and LC-MS/MS. Additionally, machine-learning algorithms were used to detect IDH mutation in gliomas based on metabolite concentrations obtained with ^{1}H-MRS and LC-MS/MS. Consequently, there were statistically significant correlations between ^{1}H-MRS and LC-MS/MS results for 2HG (p=0.036), Cr (p=0.009), mIns (p<0.001), Lac (p=0.007) and NAA (p=0.004). IDH mutation was detected with an accuracy of 92.42% (sensitivity=91.70%, specificity=93.46) and 82.94% (sensitivity=84.04, specificity=81.43) based on LC-MS/MS and ^{1}H-MRS metabolic intensities, respectively. In conclusion, ^{1}H-MRS and LC-MS/MS metabolic intensities were highly correlated and these techniques were successful in identifying IDH mutation in gliomas. This study has been supported by TUBITAK 1003 grant 216S432.

BIMG-15. LACTATE AND GLUTATHIONE LEVELS DETECTED WITH PROTON MR SPECTROSCOPY ARE ASSOCIATED WITH POOR SURVIVAL IN IDH WILD TYPE TERTP MUTANT DIFFUSE GLIOMAS.

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Telomerase reverse transcriptase promoter (TERTp) mutations in the absence of IDH mutations (TERTp-only) are recently proposed as a characteristic of glioblastoma regardless of the morphological grade. This study aims to analyze metabolic profiles of TERTp-only gliomas using proton magnetic resonance spectroscopy (^{1}H-MRS) and evaluate the effect of metabolite concentrations on progression-free survival (PFS) and overall survival (OS). The patient cohort consisted of 56 TERTp-only gliomas (35M/21F, mean age: 58±10.37 years, 44 glioblastomas (GBM), and 12 lower-grade gliomas with TERTp-mutation but no IDH-mutations). All patients underwent preoperative diagnostic ^{1}H-MRS using a 3T MR scanner with a 32-channel head coil. ^{1}H-MRS was obtained from a manually placed region of interest with no necrosis, edema, and hemorrhage, using a Point Resolved Spectroscopy (PRESS) sequence (TR/TE=2000/30 ms, 1024 points). LCModel spectral fitting program was used for quantification of MR spectroscopic peak concentrations of 17 metabolites. The patients were divided into two groups using median values of the metabolite intensities, and Kaplan-Meier survival analysis followed by a log-rank test was used to determine the effects of metabolite concentrations on OS and PFS. Median PFS and OS of TERTp-only gliomas were 11 and 17 months, respectively. TERTp-only LGG patients had longer OS and PFS than TERTp-only GBM patients (p=0.022 for OS and p=0.018 for PFS). Significantly shorter OS and PFS were identified in TERTp-only gliomas, who had higher GSH/tCr (p=0.011 for OS and p=0.004 for PFS) and higher Lac/tCr (p=0.014 for OS and p=0.012 for PFS). Lactate is a marker of necrosis and a sign of malignancy. On the other hand, both tCr and GSH were lower, which resulted in higher GSH/tCr, in TERTp-only GBM. The results of this study indicate that high Lac/tCr and GSH/tCr might be indicators of poor prognosis in TERTp-only gliomas. This study has been supported by TUBITAK 1003 grant 216S432.

BIMG-16. TRACKING TTFIELDS-INDUCED ALTERATIONS IN GLIOBLASTOMA METABOLISM WITH [18F]DASA-23, A NON-INVASIVE PROBE OF PYRUVATE KINASE M2 (PKM2)

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Despite the anti-proliferative and survival benefits from tumor treating fields (TTFields) in human glioblastoma (hGBM), little is known about the effects of this form of alternating electric fields therapy on the aberrant glycolysis of hGBM. [18F]FDG is the most common radiotracer in cancer metabolic imaging, but its utility in hGBM is impaired due to high glucose uptake in normal brain tissue. With TTFields, radiochemistry, Western blot, and immunofluorescence microscopy, we identified pyruvate kinase M2 (PKM2) as a biomarker of hGBM response to therapeutic TTFields. We used [18F]DASA-23, a novel radiotracer that measures PKM2 expression and which has been shown to be safe in humans, to detect a shift away from hGBM aberrant glycolysis in response to TTFields. Compared to unexposed hGBM, [18F]DASA-23 uptake was reduced in hGBM exposed to TTFields (53%, P< 0.05) or temozolomide chemotherapy (33%, P > 0.05) for 3 d. A 6-d TTFields exposure resulted in a 31% reduction (P = 0.043) in 60-min uptake of [18F]DASA-23. [18F]DASA-23 was retained after a 10 but not 30-min wash-out period. Compared to [18F]FDG, [18F]DASA-23 demonstrated a 4- to 9-fold greater uptake, implying an improved tumor-to-background ratio. Furthermore, compared to no-TTFields exposure, a 6-d TTFields exposure caused a 35% reduction in [18F]DASA-23 30-min uptake compared to only an 8% reduction in [18F]FDG 30-min uptake. Quantitative Western blot analysis and qualitative immunofluorescence for PKM2 confirmed the TTFields-induced reduction in PKM2 expression. This is the first study to demonstrate that TTFields impairs hGBM aberrant glycolytic metabolism through reduced PKM2 expression, which can be non-invasively detected by the [18F]DASA-23 radiotracer.

BIMG-17. EFFECTS OF THE TUMOUR MICROENVIRONMENT ON PROTOPORPHYRIN IX ACCUMULATION IN GLIOBLASTOMA

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Glioblastoma is the most common primary brain tumour and has a poor prognosis. The median survival is less than two years despite clinical intervention that usually involves the resection of the tumour volume, chemotherapy and radiotherapy. Achieving gross-total resection is challenging due to poorly defined boundaries as a result of tumour infiltration. Fluorescence-guided surgery (FGS) utilises an apparently selective accumulation of protoporphyrin IX (PPIX) that occurs in areas of glioblastoma after administration of the metabolite, 5-aminolevulinic acid (5-ALA). 5-ALA and the fluorescent metabolite, PPIX, sit within the endogenous heme biosynthetic pathway, which suggests that FGS is not only an important clinical tool, but also highlights differing metabolic phenotypes naturally present throughout the tumour. Genetic and mechanistic studies into this phenomenon have shown that differential expression of metabolite transporters, altered activity of the heme pathway enzymes and variable nutrient availability are all factors in the accumulation of PPIX. However, little is known about the cellular driving force for the uptake of 5-ALA and subsequent conversion