Title

EXTH-71. HYPERPOLARIZED [1-13C] PYRUVATE AS A BIOMARKER FOR TREATMENT MONITORING IN LYMPHOMA MURINE MODELS

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CDK9 may be an actionable therapeutic target in GBM with aberrant MYC signaling and, importantly, the clinical stage oral small molecule, TG02, is an appealing drug candidate for GBM with elevated MYC activity. Ongoing in vivo efficacy studies are evaluating TG02 in clinically relevant MYC-driven GBM mouse models.

EXTH-68. RECURRENT XENOGRAFT TUMORS UPREGULATE EGFR AFTER LENTIVIRAL VECTOR MEDIATED SUICIDE GENE THERAPY FOR GLIOBLASTOMA, BUT ARE RESISTANT TO COMBINATORIAL TREATMENT WITH ERLOTINIB

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BACKGROUND: Lentiviral vector mediated herpes simplex virus thymidine kinase (HSV-Tk)/ ganciclovir (GCV) therapy is a very promising therapeutic option for the treatment of glioblastoma (GBM). Although this therapy leads to complete remission of GBM in an orthotopic PDX model, recurrent tumors are observed, which contain a fraction of surviving Tk-GFP$^+$ cells. Here, we hypothesize that prolonged prodrug treatment could provide a significant survival benefit through killing of these remaining Tk-GFP+ cells. **METHODS:** After intracranial implantation of a patient derived biopsy, tumor growth was monitored by MRI and when the tumors reached a measurable size, lentiviral vectors encoding Tk-GFP were injected intratumorally followed by intraperitoneal GCV administration for 3 weeks or oral Valganciclovir (ValGCV) administration for 3 months. After euthanasia, brains were fixed and paraffin embedded for immunohistochemical analysis and/or snap-frozen for RNA-sequencing. **RESULTS:** Initially, we sorted the remaining Tk-GFP$^+$ glioma cells from recurrent tumors after GCV treatment and showed that these cells retained sensitivity to GCV *in vitro*. Therefore we decided to use prolonged administration (3 months) of valganciclovir (valGCV), which is similar to GCV but tailored for oral administration, and compared it to the 3-week period of GCV administration *in vivo*. Prolonged ValGCV therapy resulted in a significant survival advantage compared to short-term (3 weeks) GCV application. Nonetheless, the majority of animals treated with valGCV also developed recurrent tumors. These were more invasive compared to the primary tumors and showed significant upregulation of the epidermal growth factor receptor (EGFR) warranting for a combinatorial treatment of HSV-Tk/valGCV with an anti-EGFR therapy. However, the combination of suicide gene therapy with erlotinib, a widely used EGFR small molecule inhibitor, failed to provide survival benefit. Currently we are initiating RNA sequencing experiments on recurrent compared to primary tumors to unravel potential changes in glioma cells refractory to suicide gene therapy and/or erlotinib.

EXTH-69. AN ENGINEERED microRNA CLUSTER FOR BROAD TARGETING OF EPIGENETIC COMPLEXES IN GBM

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Epigenetic deregulation is a hallmark of glioblastoma (GBM), causing tumor cells to be refractory to differentiation, hyperproliferative and resistant to multiple genotoxic insults, including radiation and TMZ-induced DNA damage. Analysis of TCGA data revealed a highly significant inverse correlation between the expression of a group of microRNAs belonging to the neural lineage, downregulated in GBM, and several target proteins with epigenetic functions, including EZH2, BMI1 and LSD1, known oncogenes upregulated in the tumor. Consequently, we engineered an artificial DNA sequence encoding 5 of the above microRNAs arranged as a genetic cluster, and delivered to human GBM stem cells by lentiviral infection. The artificial transgene correctly produced all 5 mature microRNAs, and resulted in profound downregulation not only of putative targets, but also of other non-target oncogenes with epigenetic functions like DNMT1 and MYC, suggesting a synergistic effect caused by the combination of microRNAs. This combination determined a much more marked phenotypic effect than each single microRNA, both in vitro, measured as cell proliferation, induction of differentiation and clonogenic capacity, and in vivo, resulting in more than double survival time in mice with intracranial GBM xenografts. After temozolomide treatment, 90% of GBM cells overexpressing the multi-microRNA cluster underwent apoptotic cell death, as compared to 10–15% observed with single microRNA upregulation. Importantly, this effect was independent of MGMT expression status. Finally, co-culture experiments showed that all 5 overexpressed microRNAs were actively transferred from transduced cells to non-transduced ones, retaining their biological function in the acceptor cells. This suggests the potential for a vector-mediated delivery of clustered microRNAs in the clinical setting. In conclusion, we show a new microRNA-based gene therapy approach for GBM, which takes advantage of small size, ease of genetic manipulation, broad molecular targeting and cell-to-cell diffusivity proper of microRNAs.

EXTH-71. HYPERPOLARIZED [1-^{13}C] PYRUVATE AS A BIOMARKER FOR TREATMENT MONITORING IN LYMPHOMA MURINE MODELS

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In primary central nervous system lymphoma (PCNSL), L265P mutation of the myeloid differentiation 88 (MYD88) protein is the most common, and induces a constitutive activation of IRAK4 kinase, IRAK1 phosphorylation and increased NF-kB signaling, offering a unique window for therapeutic development. We previously show that AZ1495, a potent inhibitor of IRAK4, significantly delayed progression and improved OS in L265P-mutated PCNSL models [ASH 2016], highlighting the clinical potential of IRAK inhibition. In the clinic however, early monitoring of such targeted therapies remains challenging using conventional imaging, as treatment often results in non-readily detectable anatomical changes. Here, we questioned the potential of a new neuroimaging method, hyperpolarized ^{13}C magnetic resonance spectroscopic imaging (HP-^{13}C MRSI), to non-invasively monitor IRAK inhibition in PCNSL for the first time. Two PCNSL patient-derived xenografts models were studied: one harboring the L265P MYD88 mutation (MYD88mut), and the other, wild type for this protein (MYD88wt). Using HP-^{13}C MRSI, a high production of HP [1-^{13}C] lactate was detected in both MYD88wt and MYD88mut (0.5 ± 0.04, n=2 MYD88wt; 0.61 ± 0.2, n=4 MYD88mut), indicating PCNSL presence throughout the brain. At day 2 and 4 of AZ1495 treatment, the HP [1-^{13}C] lactate-to-pyruvate ratio remains unchanged in MYD88wt animals at all treatment time points (p=0.29 and p=0.29 at day 2 and 4 when compared to baseline, respectively) On the other hand, this ratio significantly decreased in MYD88mut animals at all time points (36.6% at day 2, p=0.07 and 56.3% at day 4, p=0.0006), in line with the previously reported effect of AZ1495 treatment on MYD88mut PCNSL only. To conlude, we showed that HP-^{13}C MRSI can detect MYD88-mutation-specific modulations of HP lactate production following IRAK inhibition. Because HP-^{13}C MRSI is clinically translatable and expanding rapidly, this study is of high significance for future clinical trials, to enhance monitoring of PCNSL progression and response of targeted therapies.

EXTH-72. CELECOXIB INHIBITS PROLIFERATION AND INDUCES APOPTOSIS IN GLIOMA STEM CELLS AND AN ANIMAL MODEL OF GLIOBLASTOMA

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Biological characteristics of glioblastoma multiforme (GBM), such as resistance to chemo- and radiotherapy and their infiltrative and proliferative nature, suggest that these tumors contain cancer stem cells. However, there are few reports of drug treatments for gliomas that specifically target stem cells. Cyclooxygenase (COX)-2 overexpression is associated with increased angiogenesis, tumor invasion, and the development of tumor cell resistance to apoptosis. Celecoxib is a selective COX-2 inhibitor that has shown anti-neoplastic activity in several malignancies, but this has not been investigated in glioma stem cells (GSCs). We addressed this in the