treatment of rats bearing orthotopic GBM6 tumors with a combination of 6-thio-dG and V-9302 caused tumor shrinkage, an effect that could be visualized by magnetic resonance imaging by day 21 after treatment. Furthermore, lactate production from hyperpolarized [1-^{13}C]-alanine was significantly reduced at day 7 after treatment with 6-thio-dG and V-9302, when anatomical alterations were absent. Collectively, our results indicate that simultaneously targeting TERT and ASCT2 provides a novel therapeutic opportunity for GBMs and that hyperpolarized [1-^{13}C]-alanine serves as a companion agent for imaging early response to therapy. Our findings pave the way for precision therapy and response assessment for GBM patients.

EXTH-14. INHIBITION OF THE ANGIOTENSIN II TYPE 2 RECEPTOR AT2R IS A NOVEL THERAPEUTIC STRATEGY FOR GLIOBLASTOMA

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Glioblastoma (GBM) is a primary malignant brain tumor with poor clinical outcomes. Standard of care consists of surgical debulking followed by radiation and temozolomide, but the tumor invariably recurs, and median survival is only ~18 months. Repurposing drugs used for the treatment of other diseases is a promising avenue to identify novel treatments for this highly aggressive form of cancer. One such class of compounds is angiotensin II (AngII) receptor blockers, commonly used to control blood pressure. We show that ~80% of primary human GBM express the angiotensin II type 2 receptor (AT2R). In the presence of AngII, inhibition of AT2R using either PD123319 or EMA401 significantly inhibits GBM proliferation. This effect was lost in GBM cells with CRISPR/Cas9 mediated knockdown of AT2R. EMA401 inhibited invasion, angiogenesis, reduced GBM spheroid growth and induced apoptosis through caspase 3/7 activation. Furthermore, EMA401 induced changes in a number of growth regulatory pathways including apoptosis, DNA replication and focal adhesion. The crystal structure of AT2R bound to EMA401 revealed the receptor to be in an active-like conformation with helix-VIII blocking G protein or β-arrestin recruitment. We demonstrate that the architecture and interaction of EMA401 with AT2R differs drastically from complexes of AT2R with other compounds. Conjugation of EMA401 to angiopep-2 enhanced its blood brain barrier passage and reduced tumor volume in an orthotopic xenograft model of GBM. Targeting AT2R is a novel therapeutic strategy to treat GBM that should be explored in patients.

EXTH-15. DRUG SCREENING ON PATIENT GBM CELL CULTURES IDENTIFIES OMACETAXINE MEPESUCCINATE AS A POTENT ANTI-GLIOMA AGENT WITH THE ABILITY TO CROSS THE BLOOD-BRAIN-BARRIER

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INTRODUCTION: Little progress has been made in the development of effective new therapies for glioblastoma (GBM) the past decades. Fresh patient-derived GBM cell culture models have become the gold standard for GBM drug discovery and development. One of the major obstacles in identifying novel candidate drugs against GBM remains the blood-brain barrier (BBB). Therefore, it is crucial to select drugs with favourable physicochemical properties to cross BBB and reach the tumour tissue in therapeutically effective concentrations. In current drug repurposing approach, we evaluated available anti-cancer agents in our patient-derived drug screening platform against GBM. METHODS: The FDA-approved Oncology Drug Set II library was tested on 45 primary GBM cell cultures. We developed a drug shortlisting pipeline combining efficacy data with pharmacodynamic and pharmacokinetic characteristics of each compound. The therapeutic efficacy of the selected agent was assessed in an orthotopic mouse PDX model, while penetration into the CNS by LC/MS/MS. RESULTS: Omacetaxine mepesuccinate (OMA) was ranked as one of the most promising candidates applying our drug selection approach. In vitro, OMA revealed anti-tumour activity at IC50 values well-below reported Cmax plasma values in approximately 80% of GBM cultures. NanoString nCounter analysis, revealed DNA damage repair as the main pathway involved in OMA's anti-tumour effect. Activation of caspase 3/7 activity and decrease of glioma cell invasiveness were also linked to its anti-tumour effect. In vivo, 1mg/kg dose of OMA was found to reach the brain tumour tissue in concentrations similar to the reported IC50 values *in vitro*. No adverse reactions were noted and a survival benefit was observed in a proportion of the treated mice. CONCLUSIONS: At 1 mg/kg, OMA reaches the tumour brain tissue in therapeutically effective concentrations in mice while a moderate therapeutic benefit was observed. Additional in vivo experiments are ongoing investigating higher dosages of OMA and longer exposure.

EXTH-16. THE ORAL IRON-MIMETIC GALLIUM MALTOLATE SUPPRESSES TREATMENT-RESISTANT GLIOBLASTOMA – IN VIVO VALIDATION

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BACKGROUND: We previously reported on our *in vitro* and *in vivo* studies using the metallocompound gallium maltolate (GaM) to target glioblastoma (GBM). We demonstrated a profound cytotoxic effect *in vitrov and in vivo. Additionally, our preliminary in vivo data suggested a substantial inhibitory effect on tumor growth, as well as a significant extension of disease-specific survival (OS). Here, we further validate the inhibitory effects of GaM in vivo.* METHODS: *In vitro irradiated adult GBM U87-MG cells were stereotactically implanted into the right striatum of male and female athymic rats. Advanced MR imaging at 9.4T was carried out weekly starting two weeks after implantation. Daily oral GaM (50 mg/kg) or vehicle were provided on tumor confirmation. Longitudinal advanced MRI parameters were processed for enhancing tumor ROIs in OsiriX 8.5.1 (lite) with Imaging Biometrics Software (Imaging Biometrics LLC,). Statistical analyses included Kaplan-Meier survival plots, linear mixed model (LMM) comparisons, and t-statistic for slopes comparison (as indicator of tumor growth rate).* RESULTS: *Median OS for the male pilot cohort (5 control, 5 GaM) was 28 and 51 days, respectively; 31 and 59 days for the male replication cohort (1 control, 3 GaM); 37 and 48 days for the female replication cohort (6 control, 7 GaM). GaM-treated xenograft tumors grew significantly slower than control tumors with sex and time dependent growth rates. No significant differences were seen between male and female cohorts in both control and treatment groups at all timepoints. Hence, subsequent analyses were performed on pooled data. Median OS was 30.5 days and 48 days for control and GaM groups, respectively ($p < .001$). A strong correlation between treatment and survival ($X2 = 6.238187$; $p = .0125$) and tumor growth suppression (LMM; $p < .0001$) was evident.* CONCLUSION: *We have successfully validated the inhibitory effects of GaM on GBM growth in vivo.*

EXTH-17. COMBINATION OF HDAC INHIBITOR AND PI3K/MTOR INHIBITOR SYNERGISTICALLY INDUCES APOPTOSIS IN DIPG

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Diffuse Intrinsic Pontine Glioma (DIPG) is a pediatric brain tumor characterized by epigenetic dysregulation with median survival of 9-11 months. Currently, radiation is the only therapy option, and therefore calls for a new, effective treatment method. RG2833 is a brain penetrant, selective HDAC 1/3 inhibitor. Western blot confirmed that RG2833 treatment alone downregulates the NFkB pathway in multiple DIPG cell lines. We showed that RG2833 treatment decreases expression of NFkB regulated anti-apoptotic genes XIAP, BCL-2, and BCL-XL in vitro. In vivo results in DIPG flank tumors confirmed that BCL-2 and BCL-XL