According to our results, the TDPI/TOP1 ratio might be a potential predictive indicator for the response of GMB cancer cells to IRT treatment and may further help to optimize the chemotherapeutic treatment protocols for individual patients.

**EXTH-11. PD-1 ANTAGONIST WITH CONCURRENT COMPETITIVE INHIBITION OF PARP PROMOTES REGRESSION OF INTRACRANIAL Glioblastoma**

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**BACKGROUND:** Checkpoint inhibition using monoclonal antibodies against PD-1 is currently under evaluation for treatment of glioblastoma (GBM); Inhibition of protein phosphatase 2A (PP2A) was recently identified as a novel strategy to enhance cancer immunity. We hypothesized that pharmacologic inhibition of PP2A utilizing a novel small-molecule inhibitor, LB100, could enhance the therapeutic effect of anti-PD-1 checkpoint inhibition in a syngeneic murine GBM model. METHODS: C57BL/6 mice were inoculated with 130,000 GL261-Luc cells in their right striatum. When tumors reached a size of 1.3–2.6 million photon/sec*mm2 in the region of interest (ROI) on bioluminescent imaging mice, were randomized into treatment groups: control (PBS), anti-PD-1, LB100, and combination. For in-vitro studies, CD4 and CD8 cells were isolated from mouse splenocytes. FACS analysis was performed. 0.4m polyethylene terephthalate transwell cell culture inserts were utilized for lymphocyte-GL261 co-culture experiments. RESULTS: Mice treated with the combination therapy demonstrated a significantly increased survival rate (p<0.05) compared to the control (p<0.01). A long-term durable cure occurred in 25% of combination treated mice, but not in any other group. In-vitro analysis demonstrated a dose-dependent inhibition of PP2A by LB100 in CD4 and CD8 cells. LB100 increased the proliferation index of activated CD4 and CD8 cells. LB100 treated CD8 cells, but not CD4 cells, induced a higher expression of PDL-1 on CD11b+ cells cultured in transwell cell culture inserts. CONCLUSION: These data suggest that PP2a inhibition and PD-1 mAb checkpoint inhibition act synergistically against intracranial GBM. This finding supports further preclinical investigation of the LB100 and anti-PD-1 combination.

**EXTH-12. REPURPOSING PROPRANOLOL AS AN ANTI-TUMOR AGENT FOR VON HIPPEL-LINDAU DISEASE**

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**INTRODUCTION:** Von Hippel-Lindau disease (VHL) is a tumor predisposition syndrome characterized by the development of CNS hemangioblastomas (VHL-HB) and renal cell carcinomas (RCC) due to hypoxia inducible factor activation. Due to a lack of effective medical therapies for infantile hemangiomas (IH), and possibly VHL-HBs. We investigated whether propranolol has anti-tumor activity against VHL-related HBs/RCCs. METHODS: Patient-derived VHL-HBs or 786-O-VHL-RCCs were treated with clinically relevant concentrations of propranolol in-vitro and assessed with viability assays, flow cytometry, QF PCR and western blots. In-vivo studies demonstrated that propranolol anti-tumor activity was confirmed in athymic nude mice bearing 786-O xenograft tumors. Lastly, patients enrolled in a VHL natural history study (NCT00005902) who were also on propranolol were identified. Propranolol activity against VHL-HBs was assessed retrospectively with volumetric HB growth kinetic analysis. RESULTS: Propranolol decreased HB and RCC viability in-vitro with an IC50 of 100μM and 200μM, respectively. Similar to prior reports in IH, propranolol induced apoptosis and led to increased VEGF-A mRNA expression in patient-derived VHL-HBs and 786-O-VHL cells. Intracellular VEGF-A and VEGF-C promoter region levels were not altered by propranolol. Tumor bearing nude mice exposed to propranolol had slower tumor progression compared to controls (33% volume reduction at 7 days, p < 0.05). Four patients harboring 76 CNC-HBs started propranolol therapy during longitudinal VHL-HB study. HBs in these patients tended to grow slower (m=0.19 versus 0.13, p=0.04) during propranolol treatment. CONCLUSION: Propranolol decreases VHL-HB/RCC viability in-vitro likely by apoptosis and modulation of VEGF expression. Propranolol abrogates 786-O xenograft tumor progression in vivo and retrospective clinical data suggests that propranolol curtails HB growth. These results suggest propranolol may play a role in treatment of VHL-related tumors.

**EXTH-13. IN VIVO THERAPEUTIC POTENTIAL OF IL13-LIPDXR IN A MALIGNANT PERIPHERAL NERVE SHEATH TUMOR MOUSE MODEL**

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Malignant peripheral nerve sheath tumor is a soft tissue sarcoma that poses tremendous challenges for effective therapy. Several therapeutic approaches using drugs such as doxorubicin and rapamycin have been tried in the past with minimum success. Therapeutic resistant property mediated by MDK proteins, in combination with DNA damage repair was proposed as a major cause leading to therapeutic inefficacy of chemotherapeutics in MPNST tumors. To overcome this issue, we encapsulated doxorubicin in lipid nanovesicles and targeted to IL13-Rα2, a receptor that is selectively overexpressed in several malignant peripheral nerve sheath tumor cell lines. In the present study, we developed using STS2Et-Luc cell line stably transfected with luciferase reporter gene. These cells were implanted into the sciatic nerve that could be imaged by Intravital Imaging Spectroscopy (IVIS). After confirming the tumor formation, the mice were injected with 7 μg/kg body weight of (a) IL13 linked liposomal doxorubicin (IL13LIPDXR) (b) unconjugated liposomal doxorubicin (LIPDXR) and (c) control mice injected with equal volume of saline. The mice were treated weekly once for 7 weeks. The mice which received IL13LIPDXR and LIPDXR showed significant reduction in tumor size compared to the control group. Among the targeted and non-targeted liposomes, IL13LIPDXR showed rapid tumor regression. However, beyond 4 weeks, the drug was ineffective in shrinking or maintaining the tumor size. These results suggest that the therapeutic efficacy of doxorubicin seems to be effective initially however in the later course of treatment they are ineffective in controlling the tumor progression. Approaches such as combinatoric doxorubicin with a small molecule Ras inhibitor or other agents in the liposome formulation which are currently underway may help to improve the therapeutic efficacy.

**EXTH-14. THE ALKYLATING CHEMOTHERAPEUTIC TEMOZOLOMIDE INDUCES METABOLIC STRESS AND POTENTIATES NAD+ DEPLETION- MEDIATED CELL DEATH IN IDH1 MUTANT CANCERS**

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Mutant IDH1 suppresses normal IDH1 activity and alters the cellular metabolic microenvironment. We have previously identified that steady-state NAD+ level is decreased in IDH1 mutant cancers. Interestingly, we found that inhibitors of the NAD+ biosynthesis enzyme nicotinamide phosphoribosyltransferase (NAMPT) potently depleted NAD+ and selectively induced cytotoxicity in IDH1 mutant cancers. Here, we investigated strategies to further perturb NAD+ metabolism to enhance NAMPT inhibitor efficacy in IDH1 mutant cancers. One major source of intracellular NAD+ consumption is mediated by distinct enzyme complexes of poly(ADP-ribose) polymerase (PARP). We found that temozolomide (TMZ), a commonly used alkylating agent, transiently and potently reduced NAD+ to enhance NAMPT inhibitor efficacy in IDH1 mutant cancers. One major source of intracellular NAD+ consumption is mediated by distinct enzyme complexes of poly(ADP-ribose) polymerase (PARP). We found that temozolomide (TMZ), a commonly used alkylating agent, transiently and potently reduced NAD+ to enhance NAMPT inhibitor efficacy in IDH1 mutant cancers. Mechanistically, TMZ stimulates an acute burst of NAD+ consumption by PARP via activation of DNA damage repair, and as a consequence, reduces NAD+ levels in IDH1 mutant cells. In an in vivo IDH1 mutant cancer model, combined treatment with TMZ and NAMPT inhibitor enhanced efficacy compared to each agent alone. Thus, we find chemotherapy induces metabolic stress in IDH1 mutant cancers which can be exploited for therapeutic gain. Targeting of NAD+ homeostasis via convergent metabolic pathways could improve responses to metabolic therapy.

**EXTH-15. RADIATION-INDUCED LATE MALIGNANT NEOPLASIA MANAGING TRANSFORMATION: CDK 4/6 INHIBITOR THERAPY**

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